

**WORKSHOP**  
**ON REYE'S SYNDROME**  
**AND**  
**REYE-LIKE INHERITED METABOLIC**  
**DISORDERS**  
**DONCASTER**  
**MARCH 14-15, 2002**

**A REPORT BASED ON SUBMITTED PAPERS  
AND A TRANSCRIPT OF THE PROCEEDINGS**

***THE WORKSHOP WAS FUNDED BY THE NATIONAL REYE'S SYNDROME  
FOUNDATION OF THE UK.***

**REPORT EDITOR: DR SUSAN HALL, MSc, FFPHM, FRCPCH, FRCP**

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- National Reye's Syndrome Foundation of the UK -

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- ◆ What is the evidence that we have a problem?
- ◆ What is its nature and magnitude? Is it preventable by early diagnosis and appropriate management?

*- COVERS INTRODUCTION AND CASE PRESENTATION BY DR SUE HALL AND WORKSHOP QUESTIONS (see introductory section) 1.1 TO 1.3.2.*

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- ◆ Assuming that there is a problem and that early diagnosis of Reye's syndrome and Reye-like inherited metabolic disorders would contribute to a reduction in early childhood morbidity and mortality and in parental distress, how can this be achieved?

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♦ Professor Stephenson and Dr Lakhanpaul

♦ Dr Baumer

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## **WORKSHOP PROCEEDINGS: PREFACE**

On behalf of the National Reye's Syndrome Foundation of the United Kingdom I am delighted that we were able to support this Workshop in full. This was entirely due to the magnificent fundraising efforts of the Foundation's supporters and the generosity of donors.

The meeting represented a milestone in the history of Reye's syndrome and the Foundation: it was held at a time when, thankfully, the incidence of the "classic" form of the disease had declined dramatically following public warnings about the use of aspirin in children and teenagers. Instead of sitting back on its laurels at this point, the Foundation turned its efforts not only towards maintaining awareness of the warning and of "classic" RS, but also towards tackling the problem of the "Reye-like" inherited metabolic disorders.

It was the first time that the Foundation had funded a meeting involving such a wide range of professional disciplines. It was a pleasure to build on our relationships both with CLIMB, the support group for inherited metabolic diseases, and also with the Royal College of Paediatrics and Child Health. The latter had begun when Reye's syndrome became one of the pioneering conditions to be included in a new national surveillance scheme that ultimately resulted in the highly successful British Paediatric Surveillance Unit, which is part of the College's Research Division.

All aspects of Reye's syndrome and the Reye-like inherited metabolic disorders were addressed in the Workshop. The submitted papers and transcript of the discussion are contained in these Proceedings, which are hosted on the Foundation's website so that they are available to parents and professionals alike. The Foundation is most grateful to the Steering Committee who organised the Workshop, the participants who contributed papers and expertise and Mr Carl Clayton for his assistance with the website production.

I am also delighted to report that, as a direct result of the meeting, a formal two year Guideline Development project on the diagnosis and management of childhood encephalopathies, including Reye's syndrome and the Reye-like inherited metabolic disorders, began in November 2003 at the Queens Medical Centre, Nottingham University under the direction of Professor Terence Stephenson. This project has also been funded by the Foundation.

**Gordon Denney Hon. Administrator, National Reye's Syndrome Foundation of the UK**

## **DEDICATION**

*To all those families who have been directly or indirectly affected by Reye's syndrome or Reye-like inherited metabolic disorders.*

# **WORKSHOP PROCEEDINGS: INTRODUCTORY SECTION**

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## **LIST OF PARTICIPANTS**

## **BACKGROUND: WHY THE NEED FOR THIS WORKSHOP?**

## **LIST OF WORKSHOP QUESTIONS**

## **INTRODUCTION BY MR GORDON DENNEY REPRESENTING THE NATIONAL REYE'S SYNDROME FOUNDATION OF THE UK**

## **PARTICIPANTS**

*Name and designation as at March 2002*

**Dr Harry Baumer**, consultant general paediatrician, Derriford Hospital, Plymouth

**Professor Jem Berry**, emeritus professor of paediatric pathology, Bristol

**Dr Jim Bonham**, consultant biochemist, Sheffield Childrens Hospital

**Dr Andrew Boon**, consultant general paediatrician, Royal Berkshire Hospital, Reading

**Dr Anupam Chakrapani**, \*consultant paediatrician, Birmingham Childrens Hospital

**Dr Mike Champion**, \*consultant paediatrician London (Guys Hospital)

**Dr Jane Collins**, consultant paediatric neurologist, London (Great Ormond Street Hospital);  
(Convener, British Inherited Metabolic Disease Group).

**Dr Neil Dalton**, consultant biochemist, London (Guy's Hospital)

**Mr Gordon Denney**, Honorary Administrator of the National Reye's Syndrome Foundation

**Jane Gick**, nurse specialist in inherited metabolic diseases, London (Guy's Hospital)

**Dr John Glasgow**, consultant paediatrician in Accident and Emergency, with special interest in Reye's syndrome, Queen's University, Belfast

**Dr Anne Green**, consultant biochemist, Birmingham Children's Hospital

**Mrs Lesley Greene**, CLIMB Support Services Director

**Professor David Hall†**, professor of community paediatrics, Dept General Practice, School of Health and Related Research, Sheffield University; President, Royal College of Paediatrics and Child Health

**Dr Sue Hall**, consultant epidemiologist, Dept Child Health, Sheffield Childrens Hospital

**Dr Fenella Kirkham**, senior lecturer in paediatric neurology, London (Institute of Child Health). **Professor James Leonard**, \*professor of paediatric metabolic disease, London (Great Ormond Street Hospital)

**Dr Roddie MacFaul†**, consultant general paediatrician, Pinderfields Hospital, Wakefield

**Dr Marian Malone**, consultant paediatric pathologist, London, (Great Ormond St Hospital)

**Dr Paul Masters**, consultant biochemist, Chesterfield and North Derbyshire Royal Hospital

**Gill Moss**, nurse specialist in inherited metabolic disease, Royal Manchester Childrens Hospital

**Dr Eileen Naughten**, \*consultant paediatrician, Childrens Hospital, Dublin

**Richmal Oates-Whitehead**, guideline methodologist, Royal College of Paediatrics and Child Health, London

**Professor Bernard Portmann**, professor of pathology specialising in liver disease, London, (Kings College Hospital)

**Professor Terence Stephenson**, professor of child health, Queen's Medical Centre, Nottingham

**Professor Stuart Tanner**, professor of child health, paediatric hepatologist, Childrens Hospital, Sheffield

**Dr Rob Tasker**, consultant paediatrician in paediatric intensive care medicine, Addenbrookes Hospital, Cambridge

**Dr John Walter**, \*consultant paediatrician, Willink Biochemical Genetics Unit, Royal Manchester Childrens Hospital

†Moderators

\*IMDspecialists



## 1) BACKGROUND (Dr Susan Hall)

### a) WHY THE NEED FOR THIS WORKSHOP?

#### *Epidemiological considerations*

Reye's syndrome (RS) is an acute encephalopathy associated with liver dysfunction characterised by elevated hepatic serum transaminases and plasma ammonia without hyperbilirubinaemia. There is also hepatic panlobular microvesicular fatty infiltration. It is now recognised that RS is not a single disease entity, but that it includes a range of disorders divisible into two main groups:

- (a) "*Classic*" or "*idiopathic*" or "*North American type*" RS, which typically (although not exclusively) occurs in children over 5 years of age and in teenagers. It is usually associated with an influenza or varicella prodrome and with aspirin ingestion in therapeutic dosage;
- (b) The "*Reye-like*" *inherited metabolic disorders (IMDs)*, the main categories of which are fat oxidation defects, urea cycle disorders and disorders of amino acid metabolism. They are not found in children with "classic" RS and usually first present in infants and children less than 5 years of age.

Classic RS is a condition of substantial public health importance, especially in the setting of influenza epidemics. There are specific preventive interventions: non-use of aspirin in children with feverish illnesses and (in the USA) influenza vaccination for children on long term aspirin therapy. Unlike the Reye-like IMDs, classic RS ideally requires long term epidemiological surveillance to monitor the effectiveness of these interventions and to detect any upsurges which might require further exploration.

The British Reye's Syndrome Surveillance Scheme (BRSSS) was an epidemiological survey of trends in the UK and Ireland, which began in 1981 and ended in 2001. Cases conforming to the standard diagnostic criteria were reported by paediatricians and were also ascertained through death entries. The case definition for reporting stated that the encephalopathy should be "unexplained", which implies that all known causes of the clinical and pathological cluster of abnormalities should be excluded before making a diagnosis of RS. It was important that reports were of valid cases of *classic* RS and paediatricians were asked to inform the scheme if the diagnosis was subsequently revised. All atypical cases were actively followed up by the BRSSS to determine whether the diagnosis had been subsequently changed.

Twenty years' experience with the BRSSS demonstrated that:

1. There was a dramatic decline in classic aspirin-associated RS after warning labelling on aspirin was introduced in 1986;
2. About one quarter of reported cases subsequently had the diagnosis revised;
3. About a half of these revised diagnoses were Reye-like IMDs;
4. There were many cases, in fact a preponderance of all reports after 1990, in whom the diagnosis was *not* revised, but who were nevertheless epidemiologically and clinically *atypical* of "classic" RS.

### *Concerns about Reye-like Disorders*

This last finding prompted concern that infants and children are sub-optimally investigated for IMDs when they present with a Reye-like encephalopathy or when they die suddenly and unexpectedly. In the latter situation the BRSSS findings were that the diagnosis of “RS” would be made at autopsy, usually on the basis of fatty change in the liver and (but not always) cerebral oedema. A review of the BRSSS data showed that, of 54 cases reported between 1992/93 and 1999/00 in whom the diagnosis of RS was *not revised*, 24 fell in this second category. This was in spite of publications in 1992 and 1996, based on the BRSSS, which emphasised the importance of investigating such cases for IMDs (1,2).

Although the number of these cases is relatively small, patients and parents still deserve accurate diagnoses, not least because of the implications for specific treatment, pre-natal diagnosis of future siblings and investigation of existing siblings. In these days of heightened public expectations and of availability of information about medical conditions on the Internet, clinicians and pathologists are under increasing pressure from parents to provide specific diagnostic labels to account for a child’s unexplained illness or death. The frustration, grief and anger of unfulfilled expectations may eventually result in litigation in some cases.

### *Concerns about “Classic” RS*

Some paediatricians have dismissed classic RS as being no longer of any clinical importance because of the action on aspirin which has reduced the incidence of this condition. However, for a disease with the capability of re-emergence during a major influenza epidemic or pandemic, especially if aspirin warnings are disregarded, this could be a dangerously complacent view. The decline of RS means that a new generation of paediatricians in training and young consultants will certainly never have seen or heard about a case and are unlikely to have read about it or had it included in educational materials. Furthermore, it is very likely to be unknown to/under-recognised by, physicians caring for teenagers and older adults. Thus, if there is a resurgence of RS we could return to the “old days” of late diagnosis, late or inappropriate treatment and poor outcome in terms of mortality and brain damaged survivors.

### *The National Reye’s Syndrome Foundation of the UK (NRSF-UK).*

The Foundation, a support group for parents and patients with RS and Reye-like illness, has played a major role in educational initiatives. One of its stated aims is to inform both the public and medical communities. In the 1980s it produced a poster, circulated to paediatric departments throughout the country, which aimed to heighten diagnostic awareness of RS and to outline initial investigation and treatment. The Foundation has also produced leaflets designed to educate and inform both parents and the public and the profession.

In recent years, the children of parents who approach the NRSF UK for support have increasingly been likely to have had a Reye-like illness rather than classic RS. This is not surprising, given the epidemiological trends outlined above. Some of these children have been reported to the BRSSS as having had RS, but have been inadequately investigated for IMDs or not at all, and therefore the Foundation has become interested in widening its educational initiatives to address methods of improving the diagnosis of these disorders.

## *Poster*

The Foundation supported the BRSSS after Public Health Laboratory Service funding ceased in 1995. In 1998 the BRSSS offered to redesign the original NRSF UK poster as it had become out dated. Moreover, there were concerns that RS in teenagers and adults was under ascertained by the survey as it depends mainly on reports from paediatricians. The new poster was to be designed so as to be suitable for placement in adult intensive care units as well as for redistribution to paediatric departments. Although focussing on classic RS, the new poster placed more emphasis on the Reye-like IMDs than the earlier version. It also updated the sections on diagnosis and management.

The task of determining the content of this new poster included a postal consultation exercise involving a number of clinicians and clinical chemists with expertise in the field of RS and Reye-like disorders. The exercise was interesting, if a little frustrating, for two reasons: first, difficulty in establishing a consensus on the content and second, the emergence of a view (not shared by all the experts) that the poster should focus on the Reye-like IMDs *rather than or even to the exclusion of*, classic RS. Given that the production and circulation of the poster was to be funded by the NRSF UK, this shift of emphasis to another group of disorders might not have found favour with that organisation. However, because of the changing trends described above, the Foundation is in fact keen to support educational initiatives which place equal, if not greater, emphasis on the Reye-like IMDs as compared to classic RS, although it will always see the latter as its priority interest because, unlike the IMDs, there is no other lay support group for this condition.

## ***Summary Points from Background***

- 1) There is a pressing need for improvement in the diagnosis of Reye-like IMDs by both clinicians and pathologists.
- 2) There is also a need for continuing diagnostic awareness of classic RS and maintaining a knowledge base about its optimal management.
- 3) The NRSF UK is a parents' organisation with a commitment to supporting educational initiatives designed to achieve 1) and 2).

## ***Proposal***

To set up an educational initiative whose principal goal would be to optimise the diagnosis and management of Reye-like childhood encephalopathies and of classic RS in the UK. The first step would be to hold a multidisciplinary Workshop.

## REFERENCES

1. Green A, Hall SM, 1992, Investigation of metabolic disorders resembling Reye's syndrome. Arch Dis Child 67: 1313-1317
2. Hardie RM, Newton LH, Bruce JC, Glasgow JFT, Mowat AP, Stephenson JBP, Hall SM, 1996, The changing clinical pattern of Reye's syndrome. Arch Dis Child 74: 400-405

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## **b) WORKSHOP BRIEFING PAPER FOR PARTICIPANTS**

### ***Working Hypotheses***

1. There is avoidable morbidity and mortality in infancy and childhood in the UK and Ireland caused by insufficient diagnostic awareness of:

- i) Those inherited metabolic disorders (IMDs) which can present as a Reye-like encephalopathy.
- ii) "Classic" Reye's syndrome (RS).

2. There is imprecise diagnosis of these cases at autopsy which may result in avoidable morbidity and mortality in subsequent children.

3. The morbidity and mortality associated with RS and Reye-like IMDs can be reduced by optimising their early diagnosis and management.

The purpose of the Workshop is to examine the evidence which might or might not support these hypotheses and methods of resolving problems and changing practice.

The output will consist of practical proposals to put existing knowledge and evidence into practice; this is likely to consist of varying forms of educational packages for the relevant professional groups.

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### ***Methods***

1. The Workshop was an expert, consensus-based exercise drawing on participants' knowledge of the literature and on their own clinical and laboratory experience including any unpublished series/surveys with which they had been involved. Approval in principle for this educational initiative was obtained from the Executive Committee of the Royal College of Paediatrics and Child Health. Participants represented the relevant disciplines: metabolists; neurology; A&E medicine; intensive care; genetics; hepatology; clinical chemistry; pathology; general paediatrics; medical education; epidemiology; guideline methodology; they also included nurses and parent representatives.

2. A framework of detailed questions which broke down the basic tenets of the working hypotheses into a series of small steps was devised by a small Steering Group (Drs Baumer, Champion and Hall). Participants were allocated individual questions relevant to their own expertise and were also provided with the whole framework in case there were other areas to which they wished to contribute. They were asked to *support their responses to these questions wherever possible with published case series or trials, but also invited to include unpublished work and personal experience*, as it was probable that many of the questions would not be answerable from the literature. This was because the Workshop was addressing a number of uncommon disorders, some only relatively recently recognised. The literature was therefore likely to consist of many small and essentially anecdotal case series, some experience-based reviews and very few robust studies.

3. Participants were invited to prepare a short paper summarising their responses to their question(s) to be made available at least 2 weeks before the meeting so that they could be circulated to all participants in advance. They were also asked to give a 5 minute presentation at the Workshop and/or lead the discussion at that part in the programme.

4. The Workshop programme reflected the questions framework and the importance of time for discussion. The proceedings were recorded and the transcript typed and amalgamated with the submitted papers to produce the Workshop Proceedings.

## WORKSHOP QUESTIONS

QUESTION	INTRODUCED BY
	MODERATOR: Roddy MacFaul
Welcome and introduction:	Sue Hall & Gordon Denney
<b>WHAT IS THE EVIDENCE THAT WE HAVE A PROBLEM?</b>	Sue Hall
1.1.1 "Classic" or idiopathic Reye's syndrome	
(a) How is it defined -clinically and pathologically; is this definition generally agreed?	Stuart Tanner
What other conditions, apart from RS-like IMDs, have been reporting as satisfying this case definition?	ditto
(b) What is the evidence that it is a specific entity and not simply another IMD where the metabolic defect has not yet been identified?	ditto
1.1.2 Reye-like IMDs: What are the IMDs known to be capable (however rarely) of presenting as a Reye-like illness?	Mike Champion
1.2 Is there difficulty in recognising these conditions, i.e. what is the evidence that::	
(a) Reye-like IMDs are being under-diagnosed or diagnosed too late in living infants and children?	Mike Champion
(b) Reye-like IMDs are being misdiagnosed as RS in living infants and children?	Sue Hall
(c) Classic RS is being under-diagnosed in living infants and children?	Ditto
(d) Reye-like IMDs are under-diagnosed at autopsy in cases of sudden unexpected death or in patients who die from unexplained encephalopathy?	Jem Berry
(e) Reye-like IMDs are misdiagnosed as RS at autopsy in cases of sudden unexpected death or in patients who die from unexplained encephalopathy?	Ditto
(f) Classic RS is being under-diagnosed at autopsy in cases of sudden unexpected death or in patients who die from unexplained encephalopathy?	Ditto
<b>1.3 WHAT IS THE SIZE OF THE PROBLEM?</b>	
1.3.1 Reye-like IMDs	
i) Their frequency	James Leonard
a) What is known about the birth prevalence of each of these IMDs?	Ditto
b) In what proportions of each do patients die in the neonatal period (whether because the diagnosis is missed or because of overwhelming catastrophic illness)?	ditto
c) For each IMD what proportion can present as a Reye-like illness as compared to other manifestations?	Ditto
d) For each IMD what proportion present as sudden unexpected death?	James Leonard
ii) Morbidity and mortality rates if untreated or treated late	Anupam Chakrapani
a) What are the mortality rates for each IMD? What are the morbidity rates and what is the nature of the morbidity?	ditto

b) Is there evidence that there is parental (psychological?) morbidity caused by delayed diagnosis or, in the case of a child who dies, by the absence of a clear cut cause of death?	Ditto with Lesley Greene, Gill Moss, Gordon Denney
iii) Avoidable mortality and morbidity (assuming there is no national screening programme -v.i.)	Anupam Chakrapani
a) What is the evidence for each condition that early diagnosis of the index case and appropriate management reduce or prevent morbidity and mortality? (nb there is some overlap here with Question 4.3 a) on page 11 below).	ditto
b) What is the evidence that prenatal diagnosis (eg resulting from diagnosis of a sib at autopsy) reduces or prevents morbidity and mortality?	ditto
iv) Screening	Anne Green
If routine TMS screening is introduced nationally would we still have a problem? (eg. issues of: whether it is likely to happen at all; if it is, likely timescale; likely coverage both of IMDs and of the neonatal population. Nb the Workshop does not aim to revisit the whole TMS screening debate!)	ditto
1.3.2 Classic RS	
i) Frequency	Sue Hall
a) What is the incidence of RS in 2001?	Ditto
b) Is it likely to change in future?	Ditto
ii) Morbidity and mortality rates if untreated or treated late	John Glasgow
What are the figures and what is the nature of the morbidity?	
Avoidable mortality and morbidity: Is there evidence that early diagnosis of RS and appropriate management reduce or prevent morbidity (including parental psychological morbidity) and mortality? (N.B. there is some overlap here with Question 4.4a)	Ditto
SUMMING UP	MODERATOR
<b>Assuming that there is a problem and that early diagnosis of these disorders would contribute to a reduction in childhood morbidity and mortality and in parental distress, how can this be brought about?</b>	
<b>A) INFANTS AND CHILDREN WHO PRESENT DURING LIFE</b> The problem of detecting the Reye/IMD "needle" in the "haystack" of ill infants and children attending A&E.	
<b>CLINICAL DIAGNOSIS : 2.1 Pointers in the history</b>	
2.1.1 <i>IMDs</i>	
a) What is the age - range, mean and median at first presentation for each IMD?	John Walter
b) Is there a seasonal distribution of acute presentation?	Ditto
c) What proportion has a significant family and/or past medical history, what are the features of these?	Ditto
d) What pre- and peri- admission features have been reported in case series?	Ditto
e) Any other useful pointers?	Ditto
f) How do these features in the history vary according to each IMD/group of IMDs?	Ditto

2.1.2 <i>Classic RS</i>	
a) What is the age - range, mean and median at first presentation?	Stuart Tanner
b) Is there a seasonal distribution?	ditto
c) Should RS still be considered if there is a significant (as in 2.1.1 c) family and/or past history?	Ditto
d) What pre- and peri- admission features have been reported in case series (including Stage 1 RS)?	Ditto
e) Any other useful pointers?	Ditto
f) Should a positive or negative history of aspirin exposure influence the diagnostic likelihood?	Ditto
<b>2.2 Recognition of encephalopathy. What is encephalopathy and how common is it? (2.2.1 - neurologists'/metabolists' view; 2.2.2 - A&amp;E and generalists' view)</b>	
2.2.1. A clinical definition of encephalopathy is important because there may potentially be difficulty in deciding whether the patient has "drowsiness" from other causes or "encephalopathy".	Fenella Kirkham
a) How is encephalopathy defined clinically? Does it depend on age: neonate -teenager?	Ditto
b) How ought it to be distinguished from (for example) the post ictal state, or the irritable drowsiness that often accompanies a high fever in infants?	Ditto
c) How ought we to explain how to recognise encephalopathy to junior medical staff and nurse practitioners? For example, does it depend on positive features that suggest cortical depression – behaviour? eye movements? respiratory function? etc. or on negative features, i.e. a rather non-specific abnormal neurological state not explained by fever, post ictal state etc?	ditto
d) What, in brief, is the best current guidance on the role of lumbar puncture and imaging in the diagnostic process of patients like this?	Fenella Kirkham
e) What proportion of cases of acute encephalopathy has an IMD? Which IMDs have been found in these cases?	Anupam Chakrapani
f) How often in an encephalopathic patient is a Reye-like IMD suspected and fully investigated but the results are, by the criteria of current best practice, truly negative?	Ditto
2.2.2.	
a) What is the incidence, among all patients presenting or referred to A&E, of acute illnesses in which encephalopathy is a feature?	Barbara Phillips
b) And in what proportion of these is an obvious cause quickly apparent after admission? What does quickly mean? (It may be that most children are obviously all right, say, within one hour after arrival as is often the case for feverish infants or post ictal infants.)	ditto
Into what main diagnostic groups do these other causes fall?	
c) How do the clinical and pathological features of that vast majority of infants and children who turn out to have a common and benign illness differ from those ultimately confirmed as having RS/IMD?	Barbara Phillips



2.3 Other acute presenting features - what else to look out for on clinical examination: What is the range of other initial clinical presentations of illnesses that are ultimately diagnosed as:	
a) classic RS (including Stage 1);	John Glasgow
b) Reye-like IMDs? Do they differ for each IMD/group of IMDs?	Graham Shortland
<b>SUMMING UP</b>	<b>MODERATOR</b>
<b>LABORATORY AND PATHOLOGICAL DIAGNOSIS</b> : Investigations ("best" practice - ideal world, no resource constraints)	Moderator: David Hall
3.1. a) What are the optimum initial investigations that should be undertaken in the local laboratory for RS and IMDs:	Neil Dalton
b) Should all of them be undertaken on every suspected case? If not, what are the clinical and pathological criteria?	Ditto
c) What specimens? How taken? How much? At what stage of the illness? Into what containers?	Ditto
3.2 a) Should all suspected RS/Rye-like IMD patients have acute specimens taken for subsequent non-routine investigations at a specialist laboratory? If not, what would be the criteria for taking these specimens?	Ditto
b) If so - what specimens? How taken? How much? At what stage of the illness? Into what containers? How should they be stored? Transported?	Ditto
3.3 a) How should the initial laboratory results be interpreted -what findings would suggest what diagnoses?	Jim Bonham
b) How do levels of plasma ammonia and other initial results affect initial differential diagnosis?	ditto
c) Can there be raised plasma ammonia in ill infants and children who do not have an IMD or RS or obvious liver disease? If so, under what circumstances and what would be the clues that this was not an IMD/RS?	Ditto
3.4 a) Should all patients suspected as having classic RS, irrespective of age, medication history, or clinical features, be fully investigated for IMDs?	Eileen Naughten
b) Should "classic" RS only be diagnosed once every known Reye-like IMD has been excluded?	Ditto
3.5 a) Should liver biopsy be part of investigation of all suspect cases of classic RS? If so, at what stage of the diagnostic process? What are the constraints and contraindications? How useful is histological examination and how should the material be prepared? How specific/ useful/ feasible is electron microscopy? What other investigations should be undertaken on biopsy material?	Bernard Portmann
b) What, if any, is the role of liver biopsy in the investigation of suspected IMDs?	Ditto
c) Do other tissues need to be examined in the acute phase of the illness?	Bernard Portmann
<b>SUMMING UP</b>	<b>MODERATOR</b>
<b>MANAGEMENT</b> ("best" (see 3 above) practice)	Moderator - David Hall
4.1. If an acute IMD- or RS- related encephalopathy is suspected, what is the optimum initial management -	
a) While awaiting results of initial investigations?	Mike Champion

b) If hyperammonaemia is confirmed?	ditto
4.2. Do levels of plasma ammonia or other initial results affect initial management? If so, how?	ditto
4.3.a) What published evidence is there for the effectiveness of optimum management of Reye-like IMDs- (each one) ranging from that of early diagnosis and institution of supportive measures, through to tertiary centre treatment? What outcome measures are used? Are there any RCTs? What unpublished evidence are you aware of?	James Leonard
b) What treatment (other than that in 4.1) should be started locally once initial stabilisation has been undertaken?	Ditto
c) What treatment can only be undertaken at a specialist centre? Can it ever be done locally under telephone supervision from the centre?	Ditto
d) What are the indications for transfer? Are a specialist ambulance and/or support during the journey required? Do the specialist centres have outreach teams?	Rob Tasker
e) How should the patient be stabilised before transport?	Ditto
4.4.a) What published evidence is there for the effectiveness of optimum management of classic RS - ranging from that of early diagnosis and institution of supportive measures, through to tertiary centre treatment.? What outcome measures are used? Are there any RCTs? What unpublished evidence are you aware of?	John Glasgow
b) What treatment should be started locally?	ditto
c) What treatment can only be undertaken at a specialist centre? Can it ever be done locally under telephone supervision from the centre?	Ditto
d) What are the indications for transfer? Are a specialist ambulance and/or support during the journey required? Do the specialist centres have outreach teams?	Rob Tasker
e) How should the patient be stabilised before transport?	Ditto
4.5 How and when is information about the diagnosis (whether classic RS or definite or suspected IMD) best conveyed to parents? What resources are available? Should they always be informed about the relevant support group? If so, what is the best time?	Gordon Denney, Lesley Greene & Gill Moss
<b>SUMMING UP</b>	<b>MODERATOR</b>
<b>B. DIAGNOSIS OF RS/IMDs AT AUTOPSY</b>	Moderator: Anne Green
5.1. a) In what proportion of autopsies of cases of sudden unexplained death in i) infancy, ii) childhood, has an IMD been discovered?	Jem Berry
b) Which IMDs have been found in these cases?	Ditto
5.2.a) In what proportion of autopsies of patients who have died from an unexplained encephalopathy has an IMD been discovered?	Jem Berry
b) Which IMDs have been found in these cases?	Ditto
5.3. In what proportion of autopsies of cases of (i) sudden unexplained death, (ii) death from unexplained encephalopathy is a Reye-like IMD suspected and fully investigated but the results are, by the criteria of current best practice, truly negative?	Ditto
5.4 Have there ever been any well documented cases of "classic" RS presenting as sudden unexpected death in childhood?	Bernard Portman

5.5 What are the pathognomonic features of:	ditto
(a) The Reye-like IMDs? Do they differ one from another?	Ditto
(b) "Classic" RS?	ditto
(c) How useful and feasible is electron microscopy of post mortem liver or other tissue in differentiating RS from an IMD?	Ditto
5.6. In what proportion of autopsies of cases of (i) sudden unexplained death, (ii) death from unexplained encephalopathy in children, are any of the features described in 5.5 seen (regardless of final diagnosis)? If these features are present are there any clues which would suggest an IMD/RS rather than some other cause of the changes?	Ditto
5.7 Best practice	
a) What should be the standard autopsy investigations for IMDs/ "classic" RS and what would be the findings which triggered undertaking these?	Marian Malone
b) Should tissues from these patients be routinely preserved? If so, which ones and how preserved and what are the relevant recommendations regarding parental consent?	Ditto
c) What investigations can usually be done locally?	Ditto
d) What are the specialist investigations and where are they undertaken?	ditto
e) Is it important, and if so why, for clinicians to obtain antemortem pathological specimens from moribund patients with suspected RS or an IMD? What specimens should be taken and how should they be preserved?	Graham Shortland
<b>SUMMING UP</b>	<b>MODERATOR</b>
<b>OBSTACLES TO ACHIEVING "BEST" PRACTICE:</b> Why have we got a problem?	Moderator David Hall
6.1 Professional training/education issues - clinical skills	
a) What are the professional groups towards whom action directed at removing barriers to changing practice should be aimed?	Andrew Boon
b) Why are patients with IMDs under-diagnosed or diagnosed late or misdiagnosed as RS?	Mike Champion
What are the obstacles to best practice?	Ditto
c) WHY might classic RS be under-diagnosed or diagnosed late?	Stuart Tanner
What are the obstacles to best practice?	Ditto
6.2 Laboratory support	
6.2.1 DGH Level	Paul Masters
a) Are the investigations in 3.1a) above, in particular plasma ammonia, routinely available at DGHs?	Ditto
b) What are the geographical variations?	Paul Masters
c) Are local measurements of ammonia reliable? If no, what factors affect reliability?	Ditto
d) How can we ensure reliable, 24 hour available, measurement of ammonia at district level everywhere? is this unrealistic? if so- what alternative?	Ditto
e) What are the obstacles to improving the service at local level? How can they be addressed?	Ditto
6.2.2 Specialist laboratories	
a) Where are the specialist laboratories? Are there enough? What do they offer? Are they all the same?	Anne Green

b) Do resource constraints at district level affect referral to specialist laboratories?	Ditto
c) Do they have the resources for any expansion of investigation of encephalopathic/ SUD cases?	Ditto
d) Are they able to provide 24 hour telephone advice and are the contact details available in all the districts they serve?	Ditto
e) Do stored Guthrie cards have a role in the diagnosis of these patients? If so, is the system for storage, retrieval and analysis satisfactory everywhere?	Ditto
f) What are the obstacles to improving the service of specialist laboratories? How can they be addressed?	Ditto
6.2.3 Specialist Clinical Support	
a) Where are the specialist clinical centres? are there enough? what do they offer? are they all the same?	Jane Collins
b) Do resource constraints at district level affect referral to these centres?	Ditto
c) Are they able to provide 24 hour telephone advice and are the contact details available in all the districts they serve?	Ditto
d) What are the obstacles to improving the service?	Ditto
6.2.4 Pathology Services	
a) In what proportion of autopsies of sudden unexplained death or death following unexplained encephalopathy in children is there: An examination which meets the standards in the response to 5.7 above? Are there geographical variations? Is there a difference in likelihood of investigation between a coroner's and a hospital autopsy? Who pays? Does cost affect likelihood of investigation? Has Alder Hey made any difference?	Marian Malone
b) What are the obstacles to best practice?	Ditto
<b>SUMMING UP</b>	<b>MODERATOR</b>
<b>DISSEMINATION AND IMPLEMENTATION OF THE EDUCATIONAL PACKAGE. What form should the output of the Workshop take? Some of these questions may not be answerable until the final discussion Session of the Workshop</b>	
<b>7.1 Can we start getting existing knowledge and evidence into practice in order to make improvements in patient care? If so -</b>	
a) What are the best methods of alerting the relevant professional groups, identified in 6.1 a) above, to rare disorders with common clinical presentations?	Terence Stephenson, and Jane Gick
b) What are the best methods of educating pathologists -both coroners' and hospital?	Jem Berry
c) How can this knowledge be widely and sustainedly disseminated? For example what are the merits of:- national/local seminars? posters? journal articles? inclusion in specialist training curricula and higher examinations? Websites (College, Lay Support Group, dedicated)? NHS Direct? APLS Course? Interactive CDs? Other methods?	Harry Baumer

7.2 How can parents and support groups participate? Should they be given information via the Parent Held Record? Birth to Five Book? (N.B. if neonatal IMD screening is adopted nationally, presumably information about IMDs will be included in these anyway?) (These would also be useful fora to remind parents about the dangers of aspirin).	Gordon Denney and Lesley Greene
7.3. What are the best methods to measure the impact of any educational initiative resulting from this Workshop? How could audit play a part?	Harry Baumer
<b>SUMMING UP AND CLOSING REMARKS</b>	<b>MODERATOR</b>

## ***WELCOME - MR GORDON DENNEY***

May I begin by extending a very warm welcome to everyone here today. I've had the pleasure of meeting a number of you over my sixteen years as administrator of the charity, but there are many of you I have not met before. I hope we will be able to rectify that in the next couple of days. Likewise I hope this Workshop will provide an opportunity for many of you to get to know one another on a more personal basis.

In recent years the children of parents approaching the Foundation for support have increasingly been likely to have had a Reye-like illness rather than classic Reye's syndrome. Indeed some of these children have been reported over the years to the British Reye's syndrome surveillance scheme of the BPSU, which ceased in April 2001. They had often been inadequately investigated for IMD's or not at all and therefore the Foundation has become interested in widening its education initiatives to address methods of improving the diagnosis of Reye-like disorders, although it will always see Reye's syndrome as its primary function and interest. In these days of heightened expectations and the availability of information on the internet, there is an ever increasing pressure from parents to account for a child's unexplained illness or death. Hence the Foundation is funding this workshop and the initiatives that flow from it. In this connection I'm sure we are all looking forward to the final session on the implementation of the educational package, but much thought has to be given to the questions set out on our programme before we reach that stage tomorrow afternoon.

I would like to say a special thank you to the three members of the Steering Group for all their hard work and meticulous planning of the questions that need to be addressed; also a sincere thank you to each and every one for coming to the Workshop today and thank you in advance, on behalf of the Foundation, for your contributions over the next two days. Finally I would like to pay tribute to CLIMB, the other parent group represented here today, for its accomplishments and achievements.

# WORKSHOP PROCEEDINGS: PART 1

## FIRST SCIENTIFIC SESSION:

**What is the evidence that we have a problem?**

**What is its nature and magnitude? Is it preventable by early diagnosis and appropriate management?**

### Introduction *DR SUE HALL*

The hypotheses to be addressed by this Workshop are:

*First*, that there is avoidable morbidity and mortality in infancy and childhood in the UK and Ireland caused by insufficient diagnostic awareness of the Reye-like IMDs and of classic Reye's syndrome itself.

*Second*, that there is imprecise diagnoses of these cases at autopsy, which may result in avoidable morbidity and mortality in subsequent children.

*Third*, that the morbidity and mortality associated with Reye and Reye-like IMDs can be reduced by optimising their early diagnosis and management.

The purpose of the Workshop is to examine both the evidence which might or might not support these hypotheses and also to review methods of resolving problems and actually changing practice. The output of the Workshop will hopefully consist of practical proposals to put existing knowledge and evidence into practice. These may consist of various forms of educational packages for the relevant professional groups, and may also consist of recommendations for further research.

I will start by presenting a patient who typifies the problems to be addressed by the Workshop.

John (not his real name) was aged one year and eight months. There were no previous medical problems or family history of note. He presented to the accident and emergency

department with a two day history of pyrexia, diarrhoea and vomiting. His parents reported that he was unusually lethargic - they hadn't seen him like this with previous viral-type infections, and they also reported that he wouldn't or couldn't stand.

On examination he was febrile, and was described in the notes as irritable but alert and responsive. The GCS was simply recorded as 14. There were no investigations.

Gastroenteritis was diagnosed and he was prescribed antipyretics. The parents were advised about hydration with clear fluids.

That evening when he was put to bed there was a slight improvement in his condition. Early the next morning he was heard crying or playing in his cot, which was normal behaviour for him, so his parents didn't go in. When they did go in an hour or two later they found him collapsed and unresponsive. He was re-admitted to A & E and found to be in cardio-respiratory arrest. Resuscitation was unsuccessful.

At post mortem the findings of note were: a liver slightly heavier than expected, with histological examination revealing diffuse fine fatty droplet infiltration. The brain was described as being slightly heavier than normal and slightly swollen. Blood toxicology revealed the presence of salicylate.

The first diagnosis, made on the basis of the above autopsy findings, including the presence of salicylate, was classic Reye's syndrome and the patient was reported to the national RS surveillance scheme. RS was recorded as the cause of death. Subsequently it emerged that the salicylate was a false positive finding because of the assay that had been used. The diagnosis was then revised to a Reye-like IMD although the precise nature of it was never actually known. Acyl-carnitine assays on the stored Guthrie card and on post mortem blood showed no evidence of medium chain acyl CoA dehydrogenase deficiency. There were no other investigations.

This patient encapsulates the problems we need to address: he was the unrecognised "needle" with encephalopathy in the "haystack" of sick children presenting to a busy A&E department. Could this death have been prevented? When he was first admitted to A & E could or should something have been noted in the clinical examination or in the history? Should some



investigations have been undertaken? If so, what? At autopsy what further investigations might have been done to give the parents a diagnostic label and enable them to know what to do about future pregnancies?

**Workshop Question. 1.1.1(a): PROFESSOR STUART TANNER**

**Classic or idiopathic Reye's syndrome -**

**How is it defined?**

Reye (1963) described a group of 21 children with “encephalopathy and fatty degeneration of the viscera”.<sup>1</sup> 14 were less than 2 years of age, the youngest 5 months. The other 7 were >5 years. It is worth noting at this stage that the age of the patient is a key factor in deciding the diagnostic likelihood of classic RS versus a Reye-like IMD ( see 1.2 (b) below).

In the two surveillance schemes, US and UK, RS was defined slightly differently.

**US: The Centers for Disease Control (CDC) instituted a National Reye Syndrome Surveillance System in 1973, defining Reye's syndrome as:<sup>2</sup>**

- Acute non-inflammatory encephalopathy documented by the clinical picture of alteration in the level of consciousness and, if available, a record of cerebrospinal fluid containing 8 leucocytes or less per microlitre, or a histological section of the brain demonstrating cerebral oedema without perivascular or meningeal inflammation;
- Fatty metamorphosis of the liver diagnosed by either biopsy or autopsy or a threefold or greater rise in the levels of either serum glutamic oxalacetic transaminase, pyruvic transaminase or serum ammonia;
- No known more reasonable explanation for the cerebral or hepatic abnormalities.

***United Kingdom: A joint voluntary Reye's syndrome reporting scheme started by the British Paediatric Association at the Communicable Disease Surveillance Centre in August 1981 and used the case definition:<sup>3</sup>***

An acute non-inflammatory encephalopathy of uncertain cause with microvesicular fatty infiltration of the liver:-

1. Confirmed by biopsy (histology or ultrastructure or both) or necropsy (macroscopically large, pale and fatty liver and histological or ultrastructural confirmation) or
2. Suggested by a serum aspartate transaminase or alanine transaminase or blood ammonia concentration greater than three times the upper limit of normal for the laboratory.

**.Are these definitions generally agreed?**

No, no-one thought either definition was satisfactory; indeed the only point on which there was general agreement was that the definitions were unsatisfactory. In particular,

1. They were vague.
2. They were modified during the years of the surveys. Thus the CDC definition shifted from “fatty metamorphosis” to “microvesicular fatty metamorphosis” to “hepatopathy documented by either liver biopsy or autopsy considered to be diagnostic of Reye syndrome”.
3. The definition said nothing about age, thus it could include neonates though nobody working in the field would make a diagnosis of Reye's syndrome in a newborn.
4. It supposed that an elevated AST or ALT always suggested liver disease, whereas, of course, we know that both can be derived from muscle.

5. The definitions failed to distinguish between diagnosis made at the time i.e. “suspected Reye’s syndrome” or a final conclusion once all of the data about a particular child was available including, of course in many cases, autopsy data. This led to a large number of children being referred to surveillance schemes with suspected Reye’s.
6. Implicit in the definitions was the exclusion of other causes (“of uncertain cause”).  
Reye’s syndrome was diagnosed when a more satisfactory diagnosis could not be made.
7. They encouraged lumbar puncture, later shown to be harmful

In two studies based on the BPSU scheme<sup>3 4</sup> an attempt to refine the diagnostic accuracy was the “Reye score”. That shown below was used in the Risk Factor Study and subsequently modified for the later study.

- 1) *Clearly defined prodrome*: yes=2, no=0, not recorded = 1
- 2) *Vomiting*: moderate/severe= 2; minimal=1; no=0; not recorded= 1
- 3) *Serum ALT/AST*: raised 3 or more x normal = 3; raised <3 x normal =2; not raised = 0; not measured/recorded = 1
- 4) *Plasma ammonia as (3)*
- 5) *CSF*: WBC count  $\leq 8 \times 10^9/l$ =2;  $\geq 8 \times 10^9/l$ , not examined, or bloody tap, or not recorded = 0
- 6) *Hepatic pathology*: macroscopically fatty but no histological examination = 1;  
histological description: panlobular microvesicular fatty infiltration = 3;  
histological description: ‘typical or suggestive of Reye’s syndrome’ =2;  
histology not recorded or not undertaken =0
- 7) *Investigation to exclude alternative diagnoses*: done =2; not done or not recorded = 0
- 8) *One or more atypical features* (for example family history, history of recurrent episodes, unusual presentation such as sudden death) = -2

Highest possible score = 17

Both studies demonstrated that the higher the score the more likely the child was to have received aspirin. It was not meant to be a definition of RS, but does demonstrate what features the authors regarded as typical of RS. The Reye score was also found to be related to age in both studies. In one of them a Reye score of 12 or more was found in 69% of children aged over 10 years, but in only 33% of children less than 5.

Unsatisfactory as those definitions were, it is hard even now to think of a better one. Pathological descriptions such as “acute mitochondrial injury of unknown cause” accurately reflect our thinking about pathogenesis but say nothing about aetiology.

“Grade 1 Reye’s syndrome”: Lichtenstein et al, 1983, reported 25 children with vomiting, a three-fold or greater elevation in alanine amino transferase and a paucity of neurological signs following a viral upper respiratory tract infection or varicella.<sup>5</sup> Fourteen of 19 biopsy results had ultrastructural features of Reye’s syndrome. The authors regarded this as early (Grade 1) Reye’s syndrome. If they were right, the incidence of Reye’s syndrome in their population was as high as 3.5 per 100,000 children under 17 years of age, 11 times as high as the CDC figures. The obvious question is how many of those children would progress to deeper grades of neurological involvement without treatment and, of course, that answer is impossible to obtain. This data, persuasive at the time, certainly led me to do liver function tests in many children with a suggestive history and, in a number with elevated liver function tests, to do a biopsy and look for microvesicular fat in frozen sections by Oil Red O staining. We often did see fatty change. We treated such children with aggressive intravenous glucose therapy and carnitine. We then realised that even without the biopsy we would have given glucose and I would have given carnitine. All of these children did very well, none progressing to Reye’s syndrome.

Probably the message from this group is that temporary mitochondrial dysfunction may be a part of the hepatic disturbance in many viraemic illnesses of childhood. We will return to this point later when we consider the significance of dicarboxylic aciduria and low plasma free carnitine.

What are the conditions apart from RS-like IMDs that have been reported as satisfying this case definition?

Patients reported to the RS surveillance scheme of the BPSU and subsequently felt not to have Reye's syndrome, had diagnoses which included:<sup>6</sup>

*Sudden Infant Death Syndrome*

*Haemorrhagic Shock Encephalopathy Syndrome*

*Viral and post viral encephalitides*

*Hepatitis*

However, the commonest group of revised diagnoses among cases reported to the BPSU were *inborn errors of metabolism*, particularly MCAD and OTC deficiency.

*Intoxications* which produce a Reye-like illness include:-

*Jamaican vomiting sickness* (poisoning from unripe akee fruit)

*Margosa oil poisoning* (reported from India)

*Multiple hornet stings* (Reye-like hepatic pathology seen at autopsy)

There is also a substantial literature about *valproate toxicity* which can produce microvesicular hepatic fatty change, but very frequently in the context of other features of mitochondrial disease. Many of these cases in fact had Alpers disease and many of them had other, at that time undiagnosed, mitochondrial cytopathies. So valproate toxicity should not now be included as a cause of Reye-like illness.

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## REFERENCES

- 1 Reye, R.D.K., Morgan, G. and Baral, J. 1963, Encephalopathy and fatty degeneration of the viscera. A disease entity in childhood. *Lancet*, **2**: 749–752.
- 2 Belay, E.D., Bresee, J.S., Holman, R.C., Khan, A.S., Shahriari, A. and Schonberger, L.B. 1999, Reye's syndrome in the United States from 1981 through 1997. *New England Journal of Medicine*, **340**: 1377–1382.
- 3 Hardie, R.M., Newton, L.H., Bruce, J.C., Glasgow, J.F.T., Mowat, A.P., Stephenson, J.P.B. and Hall, S.M. 1996, The changing clinical pattern of Reye's syndrome 1982–1990. *Archives of Disease in Childhood*, **74**: 400–405.
- 4 Hall, S.M., Plaster, P.A., Glasgow, J.F. and Hancock, P. 1988, Preadmission antipyretics in Reye's syndrome. *Archives of Disease in Childhood*, **63**: 857–866.

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5. Lichtenstein, P.K., Heubi, J.E., Daugherty, C.C., Farrell, M.K., Sokol, R.J., Rothbaum, R.J., Suchy, F.J. and Balistreri, W.F. 1983, Grade I Reye's syndrome: a frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. *New England Journal of Medicine*, **309**:133–139.

6. Green, A. and Hall, S.M. 1992, Investigation of metabolic disorders resembling Reye's syndrome. *Archives of Disease in Childhood*, **67**: 1313–1317.

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## **DISCUSSION**

**Dr MacFaul.** Do we know how many children coming in with an intercurrent illness, if somebody was vigorous enough to do a liver biopsy on them, might have fatty changes in the liver if they had gastroenteritis?

**Professor Tanner.** No, we don't know that. However, we do know that quite frequently in rotavirus enteritis we will see mildly disturbed liver function tests. They are often done by overenthusiastic house officers who just tick more boxes on the form. We also know that if you look for fat in the liver with oil red O stain you find it not infrequently. There was a very quotable paper from an RAF pathologist who looked for fat in the livers of air crew who died in accidents and usually found it. They spend a lot of time in the mess, I should think, before they go flying!

**Professor James Leonard.** Do you have any more information on the patients reported to the BPSU whose revised diagnosis was hepatitis, was it viral?

**Professor Tanner.** This was a little group of cases submitted to the BPSU where the final conclusion was viral hepatitis. However, I don't think any self respecting paediatric hepatologist would diagnose RS in such cases!

**Dr John Glasgow.** There was a series of three patients from Toronto (I'll describe them in my presentation) who apparently had a mixed pathology -signs of inflammation in the liver as well as fatty infiltration. So perhaps there is a spectrum of changes.

**Professor Tanner.** Perhaps this is an example of the fact that if you specifically look for fat with oil red O staining in liver biopsies from, for example, patients with acute hepatitis or autoimmune hepatitis, you'll find it. Perhaps Professor Portmann would comment.

**Professor Portmann.** We have very much so found this, particularly if you use a frozen section or oil red O. It's always risky to diagnose hepatitis if it has not been actually checked histologically. Patients with viral encephalitis may become shocked and develop ischaemic hepatitis which is very common at the time they die, so if you don't have histology I think it is invalid to say they had true viral hepatitis.

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***Q. 1.1.1 (b) What is the evidence that RS is a specific entity and not simply another IMD where the metabolic defect has not yet been identified?***

***PROFESSOR TANNER***

I think I would wish to set aside the young children from this question because they are the group whose Reye-like illness is most likely to be caused by an IMD. So, considering only those older children with classic Reye's syndrome as used to be seen in the United States post-influenza occurring in February, or post-varicella - was it a specific entity? I think the reasons for thinking it *was* are: first, the clinical homogeneity of that group; second, the fact that it did tend to cluster - for example there was an outbreak of chickenpox in New Mexico, where 2.5 per hundred thousand cases developed classic Reye; and third, the fact that that condition has disappeared - presumably because of aspirin. I've certainly not seen a case of Reye's syndrome since I've moved to Sheffield in 1991. So those are the reasons why I think classic RS *is* a specific entity. As to whether it is just another unrecognised IMD - this is a different question but there are a number of indications that it is not; first, investigation of

survivors of classic RS does not reveal any of the known IMDs; second, there are epidemiological differences between the IMDs and RS in terms of peak age, relation to influenza and varicella, and disappearance since the aspirin warnings; third, survivors go on surviving without further episodes; fourth, the fibroblasts of survivors show normal fat oxidation.

Could classic RS be an entity due to a genetically determined susceptibility to aspirin? Well yes, I think it presumably could be. John Glasgow has undertaken work in cultured skin fibroblasts from RS cases and controls which, to my knowledge, is the only study showing any in vitro abnormality reflecting an effect of salicylates on fatty acid oxidation<sup>1</sup>.

## REFERENCE

1. Glasgow, J.F.T., Middleton, B., Moore, R., Gray, A. and Hill, J. 1999, The mechanism of inhibition of  $\beta$ -oxidation by aspirin metabolites in skin fibroblasts from Reye's syndrome patients and controls. *Biochimica et Biophysica Acta*, **1454**: 115–125.

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### ***Workshop Question 1.1.2 Reye-like IMDs***

***What are the IMDs known to be capable (however rarely) of presenting as a Reye-like illness?***

### ***DR MIKE CHAMPION***

Olpin provides an extensive list of IMDs reported to present with a Reye-like illness on the Reye's syndrome Foundation website<sup>1</sup>. The list includes those IMDs that were originally reported to the British Paediatric Surveillance Unit (BPSU) as cases of Reye's syndrome, but were subsequently diagnosed as IMDs. The commonest revised diagnoses in the 10 year period 1981-1991 were fat oxidation defects 20/115 (17%), organic acidaemias 9/115 (8%), and urea cycle defects 5/115 (4%)<sup>2</sup>. Further IMDs reported to have presented with a Reye-like illness are listed in italics and referenced.



## **Defects in metabolism of lipids:**

### **Disorders of mitochondrial fatty acid oxidation:**

- MCAD
- VLCAD
- LCHAD

### **Defects in electron transfer pathway**

- GA II (severe and mild riboflavin responsive)
- mitochondrial disorders<sup>3</sup>

### **Defects in the carnitine cycle**

- CPT I & II
- carnitine acyl-carnitine translocase deficiency
- carnitine transporter deficiency

## **Defects in metabolism of branched chain amino acids**

- MSUD
- multiple carboxylase deficiency
- IVA
- PA
- MMA
- 3-HMG-CoA lyase deficiency
- $\beta$ -ketothiolase deficiency
- 3-methyl glutaconic aciduria

GA-I <sup>4</sup> (*in Saudubray's review of ten years of reported cases of inborn errors that had been initially diagnosed as Reye's this was the most significant of the organic acidaemias although it's really not the way that we usually think of glutaric aciduria type I presenting*).

## **Defects in metabolism of carbohydrates:**

- hereditary fructose intolerance

**Disorders of gluconeogenesis**

-Fructose-1, 6-bisphosphatase deficiency

**Glycogen storage disorders**

-GSD type I

**Disorders of glycerol metabolism**

-glycerol kinase deficiency

**Disorders of ammonia detoxification-urea cycle defects:**

OTC deficiency

CPS deficiency

ASA

Citrullinaemia

HHH syndrome

**Disorders of amino acids transport:**

LPI

***Others:***

*-porphyria<sup>5</sup>*

*-peroxisomal disorders<sup>6</sup>*

Although comprehensive, the above list does not reflect the relative frequencies with which these disorders present when faced with a Reye-like illness which is an essential requirement for planning key investigations to maximise diagnostic yield when investigating such patients. Saudubray reviewed the incidence of various IMDs presenting as Reye's in the literature<sup>6</sup>. A simplified list would therefore be in order of importance:

**Disorders of fat oxidation (esp. MCAD)**

**Disorders of ureagenesis (esp. OTC deficiency)**

**Organic acidaemias (including GA-I)**

**Others (rare)**

Including mitochondrial disorders, hereditary fructose intolerance, fructose 1, 6-bisphosphatase deficiency, GSD I, glycerol kinase deficiency, peroxisomal disorders, porphyria.

## **References**

1. Olpin S. Inherited metabolic disorders which simulate Reye's syndrome. [www.reyessyndrome.co.uk](http://www.reyessyndrome.co.uk) 2001
2. Green A, Hall SM. Investigation of metabolic disorders resembling Reye's syndrome. Arch Dis child 1992; 67: 1313-1317.
3. Quintilla MJM, Campistol PJ, Boleda VMD, Vilaseca BMA, Artuch IR, Palomeque RA, Briones GP, Ribes RA. Reye-like syndrome as initial manifestation of mitochondrial disease. Anales Espanoles de Pediatria 2000; 52: 479-482.
4. Saudubray JM, Ogier de Baulny H, Charpentier C. Clinical approach to inherited metabolic diseases. In Inborn metabolic diseases: Diagnosis and treatment 3<sup>rd</sup> edn (Eds Fernandes J, Saudubray JM, van den Berghe G) Springer, Berlin 2000; 3-41.
5. Orlowski JP. Whatever happened to Reye's syndrome? Did it really ever exist? Crit Care Med 1999; 27: 1582-1587.
6. Saudubray JM, Charpentier C. Clinical phenotypes: Diagnosis/Algorithms. In The metabolic and molecular bases of inherited disease 8<sup>th</sup> edn. (Eds Scriver CR, Beaudet AL, Valle D, Sly WS) McGraw-Hill 2001; 1327-1403.

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## **DISCUSSION**

**Dr John Walter.** Although I agree with Mike Champion's list, many of those disorders don't always present with hepatic involvement do they, or rarely?

**Dr Mike Champion.** Yes, some may have cardiac presentations for example. But we are taking all those conditions which *can* have a Reye-like presentation, i.e. encephalopathy and liver involvement.

**Dr John Walter.** Well then any metabolic cause of encephalopathy would be included wouldn't it.

**Dr Mike Champion.** Yes, that is why the list can be as long as you like and that is why I think it is important that we try and target our investigations.

**Dr MacFaul.** Just to stay on that one. Say we have a child coming in to A & E with encephalopathy you are not going to immediately do a liver biopsy are you? Clinicians will first of all undertake blood tests to determine whether there might be hepatic involvement. If there is none, and the child doesn't have a very decreased level of consciousness they might be tempted to sit it out without doing a liver biopsy. So what *is* the step which tells us the liver biopsy is necessary?

**Dr Mike Champion.** We shall be addressing the question of investigations, including liver biopsy, in another session but the one front line test that is very rarely done but should be done and regularly available, would be plasma ammonia.

**Dr MacFaul.** But, first, are all the conditions on your list capable of producing an elevated ammonia and second, is it possible to have any of these presenting acutely *without* an elevation of ammonia? Because if that is the case then we have a problem!

**Dr Mike Champion.** The answer to both those questions is yes. So yes we do have a problem but the whole idea of this workshop is to raise diagnostic awareness and determine the best way forward to educate people.

**Dr John Glasgow.** Going back to the possible presentations of MCADD - two out of six cases known to me presented with cardiac arrest (ventricular fibrillation) secondary to profound hypoglycaemia.

**Professor James Leonard.** We need to be clear about our goals at this early stage: whether we are trying to define Reye's syndrome in a very precise way that we might use for epidemiological studies or whether we are trying to help children presenting acutely with broad range of symptoms, of which encephalopathy is probably the most important - they may or may not have an enlarged liver. Then our discussion can be focused and we can produce practical guidelines. I have to say Reye's syndrome as I see it has vanished - it's not a term we use any more.

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## ***1.2 Is there difficulty in recognising these conditions?***

***Is there evidence that:***

***(a) Reye-like IMDs are being underdiagnosed or diagnosed too late in living infants and children?***

***DR MIKE CHAMPION***

The diagnosis of IMDs is reliant on clinical suspicion and the taking of appropriate investigations at the time of decompensation. Delays in diagnosis are common, a combination of failure to consider an underlying IMD, and the difficulty of obtaining certain investigations in the particular hospital where the patient presents.

Evidence for misdiagnosis and delay in diagnosis can be taken from the literature in almost all

IMDs. Considering the two commonest IMDs that may present with a Reye-like illness, MCAD and OTC deficiency:

### MCAD

Evidence for the underdiagnosis of MCAD has been the discrepancy between the number of patients diagnosed compared to the number expected looking at the gene frequency in the population. Seddon reported an expected case load of 86 for 2 health regions over a 7 year period based on carrier frequencies for the common G985 mutation, when the actual number diagnosed was only 32 (37%)<sup>1</sup>. This has been further supported by gene frequency surveys in Switzerland<sup>2</sup> and France<sup>3</sup>. It is likely that many of these undiagnosed patients have clinically significant disease with a high incidence of previous sibling deaths. In one study in 36 pedigrees, 9 out of the 42 siblings had previously died of an illness highly suggestive of MCAD deficiency<sup>4</sup>. Three of these had a diagnosis of Reye's syndrome at the time of death.

In those patients who present and a diagnosis is made, more than one episode may have occurred before a diagnosis is made (11-47% of patients)<sup>4,5,6,7</sup>, and in some individuals there may have been multiple episodes before a diagnosis is finally made. Time from first presentation to diagnosis may be many months, mean 22 months<sup>6</sup>, however in the BPSU study 42/46 presenting with acute symptoms were diagnosed within 30 days<sup>7</sup>.

### OTC

Late diagnosis of OTC is reported. In acute neonatal presenting patients, the symptoms are often misinterpreted as sepsis in up to 50% of patients<sup>8</sup>. Of 29 girls referred to the John Hopkins Hospital with symptomatic partial OTC deficiency, only 10 patients (35%), were diagnosed on first presentation<sup>9</sup>. In the remaining 19, the median delay in diagnosis was 16 months (range 2 months to 12 years). This is likely to have a direct impact on outcome with less morbidity if hyperammonaemia or coma can be reversed within 48 hours of the onset of symptoms<sup>10</sup>.

**In conclusion** -the answer to this question is - yes!

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## References

1. Seddon HR, Green A, Gray RGF, Leonard JV, Pollitt RJ. Regional variations in medium-chain acyl-CoA dehydrogenase deficiency. *Lancet* 1995; 345: 135-136.
2. Cone B, Zuffery R, Belin D. The A985G mutation in the medium-chain acyl-CoA dehydrogenase gene: high prevalence in the Swiss population. *J Inher Metab Dis* 1995; 18: 577-583.
3. Fromenty B, Mansouri A, Bonnefont JP et al. Most cases of medium-chain acyl-CoA dehydrogenase deficiency escape detection in France. *Hum Genet* 1996; 97: 367-8.
4. Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. *Arch Dis Child* 1999, 80:459-462.
5. Wilcken B, Hammond J, Silink M, Morbidity and mortality in medium chain acyl-CoA dehydrogenase deficiency. *Arch Dis Child* 1994; 70: 410-412.
6. Iafolla AK, Thompson RJ, Roe CR. Medium-chain-acyl-CoA-dehydrogenase deficiency-clinical course in 120 affected children. *J Peds* 1994; 124: 409-415.
7. Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the UK. *Arch. Dis. Child.* 1998; 79: 116 – 119.
8. Maestri NE, Clissold D, Brusilow SW. Neonatal onset ornithine transcarbamylase deficiency: A retrospective analysis. *J Peds* 1999; 134: 268-272.
9. Maestri NE, Brusilow SW, Clissold DB, Bassett SS. Long-term treatment of girls with ornithine transcarbamylase deficiency. *NEJM* 1996; 335:855-859.
10. Walter JH. Management and outcome of neonatal hyperammonaemia: How aggressive should we be? *BIMDG Bulletin* 2000; 19:13.

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***1.2(b) Is there evidence that Reye-Like Inherited Metabolic Disorders Are Being Misdiagnosed as Reye's Syndrome in Living Infants and Children?***

***DR SUE HALL***

**Method**

PUBMED search using the terms 'Reye's Syndrome' AND 'Misdiagnosis' AND 'Inherited Metabolic Disorder'. Review of my own literature collection including reference lists of relevant papers. Review of cases reported to the British Reye's Syndrome Surveillance Scheme 1994-2001.

**Findings**

***1. Experience outside UK***

Hurwitz, in reviewing the changing epidemiology of RS in the USA in 1988,<sup>1</sup> and commenting on a paper by Rowe et al in the same journal,<sup>2</sup> states that an "increasing number of patients who present with the clinical and laboratory features of RS may have other disorders that *mimic* this disease". At the time, the declining incidence of RS in the USA had been most dramatic in those children aged 5 years and older, resulting in an increasing proportion of reports of cases under this age. Before 1981, approximately 20% of cases reported each year were children under 5 compared to 53% in this age group in 1987.

Hurwitz points out that the diagnosis of RS in children over 5 had been considered relatively straightforward, with few other diseases mimicking the disorder in this age group, particularly if they occur in an appropriate epidemiologic setting (winter flu months, post-chickenpox) with the appropriate prodromal features followed by protracted vomiting and subsequent encephalopathy.

By contrast, the diagnosis of RS in the under 5's had become more complicated because in the 1980's the Reye-like IMD's began to be recognised and identified and were most likely to present in these younger children with an illness similar to RS.



Evidence for the probable overdiagnosis of classic RS in the USA at that time, especially in children under 5, was provided by the Public Health Service Main Study of RS and medications<sup>3</sup>.

As part of the study a physician expert panel reviewed records of 53 patients reported with RS: they confirmed the diagnosis in 88% of children over 5, compared with only 20% of those under 5 ( $p < .001$ ).

Rowe et al<sup>2</sup> report on 4 children referred to a tertiary centre in the USA with a diagnosis of RS between 1985 and 1987. All were diagnosed with an IMD at this centre – 2 had OTC deficiency, 1 had MCADD and 1 had 3-OH-3 methyl glutaryl-CoA lyase deficiency. Three were under 2 years, but 1 was a 12 year old. Rowe points out that all the patients met the Centers for Disease Control (CDC) criteria for RS and that, as far as the referring physicians were concerned, there was no more reasonable explanation for the illness. He highlights the poor specificity of the case definition (CD) for RS.

This is the nub of the problem – as the incidence of classic RS declines, the positive predictive value (PPV) of the definition also declines. We don't know what the specificity of the CD is, but assuming it to be, say, 50% and the sensitivity to be 100%: - in a situation where the 'true' prevalence of a diagnosis of classic RS among a group of children with illnesses satisfying the CD is, say, 20%, it can be calculated that the PPV of the CD is 33%. However, if the prevalence drops to, say, 4%, the PPV is now only 8%.

Belay et al, reporting in 1999 on the epidemiology of RS in the USA 1981-1997, again emphasise that, as the incidence decreases, manifestations that resemble RS are increasingly likely to be due to IMDs, although they present no evidence to support this<sup>4</sup>.

In 1989, sharing similar concerns, Gauthier et al retrospectively studied the charts of 49 Canadian patients with a discharge diagnosis of RS between 1970 and 1987<sup>5</sup>. A panel of experts agreed a set of clinical, biological and histological criteria and the cases were allotted a category of certain, probable, unlikely, or excluded RS by a panel of 3 clinicians. Only 12 (24%) were considered certain or probable. Among the 15 cases in whom the diagnosis of RS was excluded, 11 were on the grounds of the incompatibility of the liver histology; fat oxidation defects were in fact retrospectively identified in 2 of these because of recurrences. The other 4 patients had

alternative (non IMD) explanations for their illnesses. The authors' criteria for 'certain' RS differed for cases under 12 months compared to those over this age in that former had, in addition to the other requirements, to have 'organic acids compatible with RS' and a normal serum carnitine level. The mean age of the certain/probable group was 6.1 years compared to 2.2 years in the unlikely/excluded group.

In 1991, Forsyth et al <sup>6</sup> drew attention to the risk of misdiagnosing RS in children who in fact have IMDs. This was prompted by the findings of their epidemiologic case control study of the association between aspirin and RS. In that study, potential cases of RS were ascertained from a network of 180 paediatric tertiary care centres in North America. Again, a panel of experts decided whether reported cases were 'definite', 'uncertain', or 'definitely not' RS using predetermined guidelines. Unlike the Gauthier paper details of these guidelines are not specified beyond: 'clinical evidence of encephalopathy, laboratory or biopsy evidence of liver dysfunction, and the pattern of the clinical course of the illness'. Electron micrographs of liver biopsy specimens were also reviewed by an expert. The panel confirmed the diagnosis of definite RS in only 22 (65%) of 34 cases considered definite by the hospital physicians. Differences between the experts and the hospital physicians were related to the age of the patients: there was agreement in 87% of cases over 3 years but only 18% in cases under 3. Of 13 electron micrographs available, 7 of which were considered diagnostic by hospital pathologists, only 2 were confirmed by the experts. The authors comment that the experts were more reluctant than referring physicians to make a diagnosis of RS in the younger patients because of their concern that IMDs had not been excluded as an alternative diagnosis. IMD investigations had been ordered in only 5 of 26 children aged 3 and under who were referred to the study as cases of RS.

In 1999 Orlowski reviewed the charts and interviewed the parents of 26 Australian patients surviving an illness in the 1980s which had been diagnosed at the time as Reye's syndrome<sup>7</sup>. Ten years later, 18 of these (69%) had subsequently been diagnosed as having other disorders, of which 12 were definite IMDs (MCADD 4, adipic aciduria 2, urea cycle defect 1, carnitine deficiency 2, delta-aminolevulinic aciduria 1, parahydroxyphenylacetic acidemia 1, beta-methylglutaconic aciduria 1) and 3 were probable, but undiagnosed, IMDs because of recurrent illnesses. It is of note that of the 49 cases recruited in Orlowski's original study in the 1980s as

having RS, 44 were aged less than 5 years which perhaps explains the high prevalence of IMDs later found among the survivors.

In 1993 deVillemeur et al<sup>8</sup> reported on 30 patients referred to their hospital with a diagnosis of RS in whom they undertook intensive investigations for IMD's – 12 had proven disorders of fatty acid oxidation, 6 had suspected fat oxidation defects and 3 had urea cycle disorders; the remaining 9 (30%) were considered to have 'idiopathic RS' and it is interesting that, in this series, the age range of the latter was only 1-17 months compared to 2-14 months in the IMD group; they were also unable to discern any clinical differences between the 2 groups.

In 2001 Autret-Leca et al<sup>9</sup> undertook extensive metabolic investigations on cases reported as RS to a national epidemiological study in France in 1995-1996. Among 14 cases initially designated as 'probable RS' there were 5 (35%) with confirmed IMDs (2 MCADD, 1 LCHAD, 1 methyl malonic acidemia, 1 OTC deficiency). The mean age of the 9 remaining, who were 'definitely' diagnosed as RS, was 5.9 years; the age of the IMD group unfortunately was not reported.

## ***2. Experience in the UK:***

In 1996 Hardie et al published a study which examines the changing clinical pattern of RS in the UK and Ireland<sup>10</sup>. They highlighted differences in the epidemiological features of RS reported to the British and Irish surveillance scheme as compared to cases reported to the US scheme. Both schemes used essentially the same CD. The main difference was the younger median age of British/Irish cases – 14 months compared to 8-9 years in the US; the clear winter peak of incidence seen in the US was not observed here and there was a less marked association with influenza and chickenpox. They recall that in the British risk factor study of the association between RS and aspirin, a scoring system had been devised in which cases manifesting the most typical features of RS (not only those in the case definition but also those seen in the US cases enrolled in their risk factor studies such as a clear viral prodrome before the onset of profuse vomiting) scored highly. There had been a significant correlation between aspirin exposure and a high 'Reye score'<sup>11</sup>.

Hardie et al tested the hypothesis that patients reported with 'RS' are a heterogeneous group

having a number of disorders and that these conditions include not only the 'Reye-like' disorders, including IMD's, but also a separate subset – idiopathic or classic RS, a disorder of unknown aetiopathogenesis except that usually (though not invariably) it is precipitated by aspirin. A modified version of the "Reye score" was applied to all cases reported as RS between January 1982 and December 1990 and trends and score were analysed. 20% of reported cases had subsequently had their diagnoses revised and these received a score of 0.

They found a wide distribution of scores, suggesting that reported cases of RS in whom the diagnosis was *not* revised were a clinically heterogeneous group. There was a significant independent association between high score and: older age, exposure to aspirin, year of diagnosis.

There had been a selectively and significantly greater decline in high scoring cases in the 4½ year period after the 1986 aspirin warning compared to the 4½ years before, in contrast to the trends in intermediate and low scoring cases. The authors suggested that the trends could be explained by a specific decline in idiopathic, aspirin-associated RS leaving still being reported as RS, cases of Reye-like illnesses.

### **Reports to the British Reye's Syndrome Surveillance Scheme (BRSSS)**

*Are cases reported to the scheme as RS likely to be misdiagnosed Reye-like disorders?*

The BRSSS began in August 1981 and ended in April 2001. Its principal purpose was to monitor long-term trends in RS in the UK and Ireland. Cases conforming to the standard criteria were reported by clinicians; from 1986 onwards this was via the British Paediatric Surveillance Unit (BPSU). Cases were also (and still are) ascertained from death entries. Clinicians were asked to notify the scheme if the diagnosis was subsequently revised and all reported cases where the diagnosis was in doubt or investigations were still in progress, were actively followed up. From 1993 a question asking whether IMD investigations had been undertaken, was added to the standard proforma.

Over the 20 years a total of 614 cases conforming to the case definition of RS were reported; in 164 (27%) the diagnosis was subsequently revised; approximately half of these revised diagnoses were IMDs. This finding was highlighted in a paper published in 1992<sup>12</sup>.

### ***Reviewing the Non-Revised Cases in the Most Recent 6½ Years of Surveillance.***

In the period 1<sup>st</sup> August 1994 to 1<sup>st</sup> April 2001, there were 49 reports where the diagnosis was not revised. The median ages in each year in months were respectively 21, 38, 14, 55, 29, and 14. Fourteen (28.5%) were reported as having a sudden onset of encephalopathy with no prodromal illness. The mean RS scores for each year were 11.6, 12.5, 11.8, 13, 15 and 12 compared to the scores between 1982 and 1986 of 16.4, 14.9, 14.7, 14.5, and 14.1 respectively. There were no clear seasonal peaks. Only 8 of the 49 could be said to be ‘classic’ North American-type RS. All of these were aged over 5 years and all had had aspirin for the prodromal illness.

Twelve of the 49 were reported as not having been investigated at all for IMDs, the ages of these cases ranged between 2 months and 11 years, median 17 months. In 3, there was no information on investigations. 34 had had investigations – the proforma doesn’t seek details, but where this is volunteered, exclusion of MCADD is most frequently mentioned.

### **Conclusion**

I believe that this review provides evidence that some children with Reye-like IMDs are at risk of being misdiagnosed as having Reye's Syndrome. The published evidence demonstrates the *potential* for this to occur. The BRSSS data suggest that this was actually happening in these islands in the 1990s because of the young age of reported cases, the lack of seasonality and the atypical nature of their illnesses (compared to the US cases enrolled into their case control studies and described in their surveillance data in the 1980s) reflected in relatively low mean RS scores compared to cases occurring in the period before the aspirin warning. Just under a ¼ had had no IMD investigations even though two thirds of this group was aged less than 3 years. Among those that had been investigated it was clear that there was substantial variability in the depth of this investigation.

It is notable that this was happening in spite of annual reminders in the BPSU Annual Report as well as the published work highlighting the problem<sup>12</sup>. The problem does appear to be a small one and the decline in annual totals of reported RS probably in part reflects improved recognition

of IMDs in these cases such that they wouldn't be reported as Reye's syndrome. However, it could be argued that the preventable morbidity and mortality associated with these conditions means that even one unrecognised case a year is one too many.

### ***1.2.c What is the Evidence that Classic Reyes Syndrome is being Under- diagnosed in Living Infants and Children?***

**DR SUE HALL**

#### **Method**

Pub Med search using Reye's syndrome AND misdiagnosis; Reye's syndrome AND underdiagnosis. I also reviewed my own collection of literature on RS which includes both published and unpublished material.

#### **Findings**

This question is harder to answer than 1.2b because it requires studies in which very large numbers of medical records are reviewed to find cases who satisfy the diagnostic criteria of RS but who nevertheless have alternative discharge diagnoses. No such study in its own right was found, but there were three relevant papers, none of which involved British/Irish patients. In the case control study of Forsyth et al<sup>13</sup>, one of the methods used to address recruiting bias was to review paediatric admissions to all hospitals in a defined geographic area during the study period (1986-7). Records with selected discharge diagnoses other than RS were reviewed in detail by the expert panel (vs.). Of 150 such *potential* cases there were 2 (1.3%) in whom the diagnosis should have been considered but who weren't appropriately investigated for RS. In the same study the expert panel reviewed 63 cases reported as possible RS. These included 16 where the referring clinician had revised the diagnosis after admission to 'definitely not' RS. The panel agreed in 10, was uncertain in 5 and considered the other a 'definite' case. Among 13 cases where the hospital physician had been uncertain about the diagnosis, 2 were considered definite by the panel.

Autret-Leca et al<sup>9</sup>, in checking completeness of ascertainment of RS in their epidemiologic study, randomly selected 10% of paediatric departments in France and retrospectively checked the records of all children with normal CSF and transaminase or ammonia levels 3 times the upper limit of normal. They found no unrecognised cases of RS.

Lichtenstein et al<sup>14</sup> investigated all children presenting in a one-year period with a prodrome of fever, cough, rhinorrhoea and coryza, or of varicella, *plus* acute onset of recurrent vomiting and absence of jaundice. All such cases had liver function tests measured; those with transaminase levels 3 times the upper limit of normal or more had lumbar punctures. Those with normal CSF had liver biopsies. 31 cases were recruited of whom 25 had only stage 1 (Cincinnati system) illness – i.e. quiet and sleepy but responding to verbal command. Of the 19 who had biopsies, 14 had characteristic histological and ultrastructural changes of RS. Based on these findings, the authors calculated the incidence of RS in children under 17 in Cincinnati and found that it was 11 fold higher than that reported by the National Surveillance Scheme even if they only included the biopsy proven cases. Part of the difference may have been underreporting but the authors also suggested that RS was underdiagnosed at the milder end of its spectrum.

## **Conclusion**

There is evidence that there is *potential* for underdiagnosis of classic RS, especially those cases with grade 1 illness, but no comprehensive studies to document the extent of this in the UK have been published. From the little published evidence there is, it seems likely that it may be less of a problem than that of overdiagnosis. Nevertheless, given the underexposure of paediatricians in training to classic RS because of its decline, it is possible that underdiagnosis will occur in the event of the next influenza pandemic. This is more probable the older the patient as adult physicians will be even less familiar with RS or may consider it solely a childhood disorder.

## **References**

1. Hurwitz ES. The changing epidemiology of Reyes Syndrome in the United States: further evidence for a public health success. JAMA, 1988; 260: 3178-3180
2. Rowe PC et al. Inborn errors of metabolism in children referred with Reyes Syndrome.

JAMA, 1988; 260: 3167-3170

3. Hurwitz ES et al. Public health service study of Reyes Syndrome and medications: report of the main study. JAMA, 1987; 257: 1905-1911

4. Belay ED. Reyes Syndrome in the United States from 1981 through 1997. New England Journal of Medicine, 1999; 340: 1377-1382

5. Gauthier M et al. Reyes Syndrome: reappraisal of diagnosis in 49 presumptive cases. AJDC, 1989; 143: 1181-1185

6. Forsyth VW et al. Misdiagnosis of Reyes-Like illness. AJDC, 1991; 145: 964-966

7. Orlowski JP. What ever happened to Reyes Syndrome? Did it ever really exist? Crit Care Med, 1999; 27: 1582-1587

8. De Villemeur TB et al. Metabolic investigations in Reyes Syndrome and Reye-like Syndrome. In: Management of Digestive and Liver disorders in infants and children. J.P. Buts and E M Sokal editors. 1993. Elsevier Science Publishers BV. Belgium.

9. Autret-Leca, E et al. Incidence of Reyes Syndrome in France: a hospital based survey. J Clin Epidemiology, 2001; 54: 857-862

10. Hardie RM et al. The changing clinical pattern of Reyes Syndrome 1982-1990. Arch Dis Child 1996; 74: 400-405

11. Hall SM et al. Preadmission antipyretics in Reye's syndrome. Arch Dis Child. 1988; 63: 857-866

12. Green A, Hall SM. Investigation of metabolic disorders resembling Reyes Syndrome. Arch Dis Child 1992; 67: 1313-1317



13. Forsyth VW et al. New epidemiological evidence confirming that bias does not explain the aspirin/Reyes Syndrome association. JAMA, 1989; 261: 2517-2524

14. Lichtenstein PK et al. Grade 1 Reyes Syndrome. A frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. New England Journal of Medicine, 1983; 309: 133-9

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#### ***1.2 (d-f) What is the evidence that:***

***Reye –like IMDs are underdiagnosed at autopsy in cases of sudden unexpected death or in patients who die of unexplained encephalopathy.***

***Reye-like IMDs are misdiagnosed as RS at autopsy in cases of sudden unexpected death or in patients who die of unexplained encephalopathy.***

***Classic RS is being underdiagnosed at autopsy in cases of sudden unexpected death or in patients who die of unexplained encephalopathy.***

#### ***PROFESSOR JEM BERRY***

There are few published prospective, population-based series from which to answer the above questions. In retrospective series appropriate investigations were seldom carried out. Most post-mortem series focus on metabolic causes of infant death, rather than Reye's syndrome or Reye-like metabolic disorders.

#### **RS and RLS in Sudden infant death.**

A prospective study of IMDs in 90 consecutive sudden unexpected infant deaths from a

defined geographical area (1) using a variety of techniques detected no cases except one possible case of glycogen storage disorder (in retrospect this diagnosis was almost certainly erroneous).

Anecdotal evidence from pathologists interested in sudden death in infancy indicates that MCAD and other disorders of fatty acid oxidation are by far the commonest IMDs presenting to pathologists as sudden unexpected death in infancy, although many more than 30 IMDs have been suggested as possible causes (2-3). When Reye-like fatty change is seen at PM in unexpected death in infancy, our anecdotal experience is that no biochemical diagnosis is made in about 1/3. This group poses particular problems of management and has been noted by others (4).

Several series have used frozen section of liver as a basic screening test for IBEMs. In the recent CESDI study of Sudden Unexpected Death in Infancy a frozen section of liver stained for neutral lipid was described in 196 of 450 post-mortem reports (5). Marked panlobular fatty change was seen in 5/196. In two of these the diagnosis was later shown to be MCAD deficiency, and in a third case there was previously known galactosaemia. MCAD and other disorders of straight chain fatty acid oxidation were specifically excluded in a fourth. The fifth case was thought to have suffered hyperthermia, and had been maintained on a ventilator. In 3 other cases moderate fatty change was over-interpreted as indicating a Reye-like IMD. Assuming all the frozen sections were reported, this gives an approximate incidence for MCAD of 1.0, undiagnosed Reye-like syndrome of 0.3, over-diagnosis of IMD of 1.5, and a predicted rate of missed Reye-like IMD of 0.5 per 100 unexpected infant deaths. 57 cases had some further biochemical screening, and no other IMDs were detected. These figures are small, but this is the largest study of unexpected infant death in the literature and included a population equivalent to almost all the babies born in England in one year. Other studies have confirmed that fatty acid oxidation defects are rare as a cause of sudden unexpected infant death (6-9).

So the answer to these questions is yes -we are both missing them and overdiagnosing IMDs. From the CESDI study (5) it appears that paediatric pathologists are the best at doing the appropriate investigations, general pathologists are pretty good but not so good, but forensic

pathologists, who undertake about a third of these autopsies, rarely do frozen sections. So they are a group who especially need to be targeted.

### **RS and RLS in older children**

I know of no systematic study looking at Reye-like IMDs or unexplained encephalopathy as a cause of sudden death in older children. Sudden natural death of older children is usually explicable and due to infection or pre-existing disease such as asthma, epilepsy or heart disease. Several studies show a small proportion of unexplained deaths in this age group, but these are rare compared to unexplained deaths in infancy. A retrospective Scottish study (10) found no cases of Reye's syndrome, and that 6.5% of natural deaths between 2 and 20 years were unexplained. A similar Swedish study of deaths aged 1-20 years gave a figure of 13% for natural unexplained deaths in childhood (11). Even the latter higher figure is equivalent to only 0.007 deaths per 1000 live births (compared to about 0.5 per thousand in infancy). It is possible that a few cases of Reye-like disorders are missed in this group, one or two of whom suffered vomiting or convulsions prior to death.

In a retrospective study of all deaths of children aged 1 month – 18 years in Denmark in 1979 (an epidemic year for Influenza B) death certificates and autopsy reports were reviewed for evidence of Reye's syndrome (12). Of 242 deaths in hospital (accidents and malignant disease were excluded) there was one case of RS. Of 105 deaths outside hospital no cases of RS were found on retrospective review. At this time there were 1.1 million children aged 1 month to 14 years in Denmark.

Reports of unsuspected Reye's syndrome diagnosed for the first time at autopsy are few (13).

There are no studies, as far as I am aware, of *encephalopathy* at post mortem, where RS or RS-like IMDs have been sought.

**Comment: Diagnosis of RS at post-mortem examination.**

The thrust of the above questions is that pathologists are missing RS and R-L IMDs at post-mortem examination. This is almost certainly true, although the numbers missed are small. If you look at some of the series of older unexplained childhood deaths, some of them could have had Reye's or a Reye-like IMD. A typical example is the child who is obtunded and or has had convulsions and who is dead on arrival in hospital. No specific cause of death is identified at the post mortem examination, but in fact no appropriate investigations have been done. Interestingly, amongst the undiagnosed so- called metabolic disorders, there are some that we now wouldn't put in that group and I suspect we would put in the non-accidental injury group - unexplained recurrent lactate acidosis and collapse for example.

The problem is, the diagnostic criteria used clinically may not be reliable post-mortem. Hepatic fatty change *indistinguishable from that in Reye's syndrome is said to occur in children with a variety of illnesses*, especially if maintained by intensive care for more than about 48 hours (14). In fact Beckwith says that hepatic fatty change alone could not and should not be used to diagnose RS at autopsy. About 75% of cot deaths have a vitreous glucose  $<0.5$  mmol/l, precluding the reliable diagnosis of hypoglycaemia (5). Ammonia rises quite sharply in blood after about six or eight hours post mortem, transaminases are elevated because liver enzymes leach out of the liver post mortem. Cerebral oedema is extremely common at post-mortem, from deaths of all kinds, but especially after resuscitation. Many biochemical markers change after death (15-16). Post-mortem electron microscopy of liver may be difficult to interpret because of autolysis.

Diagnosis depends on thinking of the diagnosis, an excellent history, sampling of body fluids as soon as possible after death (by the clinician?) and saving appropriate tissue samples.

Some histopathologists are probably confused about Reye's syndrome (where did it go, and whatever happened to carnitine deficiency?). They could be reached by an informative insert in the Bulletin of the Royal College of Pathologists, an update article in a mainstream pathology journal, or a direct mailing to forensic and paediatric pathologists.

Following recent advice from the Chief Medical Officer pathologists are much less likely to retain fibroblasts and fluids for biochemical investigation as a routine in cases of unexpected death in infancy and childhood.

### References

- (1) Holton JB, Allen JT, Green CA, Partington S, Gilbert RE, Berry PJ. Inherited metabolic diseases in the sudden infant death syndrome. *Arch Dis Child* 1991; 66(11):1315-1317.
- (2) Emery JL, Howat AJ, Variend S, Vawter GF. Investigation of inborn errors of metabolism in unexpected infant deaths. *Lancet* 1988; 2(8601):29-31.
- (3) Bonham JR, Downing M. Metabolic deficiencies and SIDS. *J Clin Pathol* 1992; 45(11 Suppl):33-38.
- (4) Norman MG, Taylor GP, Clarke LA. Sudden, unexpected, natural death in childhood. *Pediatr Pathol* 1990; 10(5):769-784.
- (5) Berry PJ, Allibone E, McKeever P, Moore I, Wright C, Fleming P. The pathology study: the contribution of ancillary pathology tests to the investigation of unexpected infant death. In: Fleming P, Blair P, Bacon C, Berry J, editors. *Sudden unexpected deaths in infancy. The CESDI SUDI Studies*. London: The Stationery Office, 2000: 97-112.
- (6) Lundemose JB, Kolvraa S, Gregersen N, Christensen E, Gregersen M. Fatty acid oxidation disorders as primary cause of sudden and unexpected death in infants and young children: an investigation performed on cultured fibroblasts from 79 children who died aged between 0-4 years. *Mol Pathol* 1997; 50(4):212-217.
- (7) Penzien JM, Molz G, Wiesmann UN, Colombo JP, Buhlmann R, Wermuth B. Medium-chain acyl-CoA dehydrogenase deficiency does not correlate with apparent life-threatening events and the sudden infant death syndrome: results from

- phenylpropionate loading tests and DNA analysis. *Eur J Pediatr* 1994; 153(5):352-357.
- (8) Lundemose JB, Gregersen N, Kolvraa S, Norgaard PB, Gregersen M, Helweg-Larsen K et al. The frequency of a disease-causing point mutation in the gene coding for medium-chain acyl-CoA dehydrogenase in sudden infant death syndrome. *Acta Paediatr* 1993; 82(6-7):544-546.
  - (9) Miller ME, Brooks JG, Forbes N, Insel R. Frequency of medium-chain acyl-CoA dehydrogenase deficiency G-985 mutation in sudden infant death syndrome. *Pediatr Res* 1992; 31(4 Pt 1):305-307.
  - (10) Keeling JW, Knowles SA. Sudden death in childhood and adolescence. *J Pathol* 1989; 159(3):221-224.
  - (11) Molander N. Sudden natural death in later childhood and adolescence. *Arch Dis Child* 1982; 57(8):572-576.
  - (12) Daugbjerg P, Ranek L. Reye's syndrome in Denmark. A retrospective study. *Acta Paediatr Scand* 1986; 75(2):313-315.
  - (13) Young TW. Reye's syndrome. A diagnosis occasionally first made at medicolegal autopsy. *Am J Forensic Med Pathol* 1992; 13(1):21-27.
  - (14) Bonnell HJ, Beckwith JB. Fatty liver in sudden childhood death. Implications for Reye's syndrome? *Am J Dis Child* 1986; 140(1):30-33.
  - (15) Coe JI. Postmortem chemistry update. Emphasis on forensic application. *Am J Forensic Med Pathol* 1993; 14(2):91-117.
  - (16) Coe JI. Postmortem chemistry of blood, cerebrospinal fluid, and vitreous humor. *Leg Med Ann.* 1977; 1976:55-92.

## **DISCUSSION**

**Professor Portmann.** You say it is very common to have fat in the liver, but how many of those cases also had fat in the heart or the kidney?

**Professor Berry.** That is less common, I accept that. I am talking about macro and microvesicular fat in the liver, and the particular paper I am citing I don't think looked at the heart or the kidney.

**Dr MacFaul.** Would you expect to find fat in the heart or muscle or other tissues in the Reye-like metabolic disorders, or indeed other conditions?

**Professor Berry.** Certainly in some of the IMDs, MCADD especially, and I suspect it might well be found in tissues other than the liver in the very sick child.

**Professor Stephenson.** You concluded that because 75% of the SUDI post mortems had a low glucose in the vitreous that this makes it difficult to know whether there was hypoglycaemia antemortem. How do you know that 75% of the children did not have hypoglycaemia before they died?

**Professor Berry.** That is a possibility, but what we do know is the blood sugar may shoot up and then fall post mortem and the sugar in the vitreous we presume falls progressively. A proportion of these cases also have extremely low sodium levels in the vitreous.

**Mrs Lesley Greene.** As a lay person can I then summarise that really what you've said is how important it is to take the necessary samples and do the necessary tests when the child is or baby is in crisis, because once the child has died really a lot of your sample taking is of no use?

**Professor Berry.** I agree with that. I was going to save that for the pathology session, but thank you for raising the issue of taking samples, because I think (I suspect the other pathologists here will agree with me) we have a real problem now, since the Chief Medical

Officer's advice on sampling at post mortem, post Alder Hey. Pathologists around the country are simply *not* going to take the relevant samples as a routine. So if the possibility of an IMD is raised in two days' time, a weeks' time, or a years' time and we want to go back and look at them, we now have a real problem. But you're right, the best samples are taken by clinicians as the child comes through casualty or certainly before death ideally.

**Dr MacFaul.** These are important messages for any educational package for the professions.

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### ***1.3 What is the size of the problem?***

#### ***1.3.1 Reye-like IMDs    PROFESSOR JAMES LEONARD***

##### ***i) Their frequency:***

***a) What is known about the birth prevalence of each of these IMDs?***

***b) In what proportions of each do patients die in the neonatal period (whether because the diagnosis is missed or because of overwhelming illness)?***

***c) For each IMD what proportion can present as a Reye-like illness as compared to other manifestations?***

***d) For each IMD what proportion present as sudden unexpected death?***

I have summarised the responses to these questions in the Table below. The first point to make absolutely clear is that the data, even on the birth prevalence of these conditions, are extremely poor, and almost all the figures, with the possible exception of MCAD, are really no more than guesses. I would be quite willing to change these if someone comes up with superior knowledge. I would also come back to the point made by Dr Champion that, for the



purpose of this discussion, two conditions absolutely dominate.

The first is MCAD, which we know from the calculations from the frequency of the heterozygote, is *approximately* 1 in 14 000 births (there are variations); the second is OTC deficiency -studies range between 1 in 14 000 to 1 in 30 000 births. We don't know the exact frequency of this, indeed there are considerable problems because of the lyonisation of the X chromosome in the female. So there is wide variation in phenotype and this leads to considerable problems in diagnosis, and in fact in definition altogether.

Almost all of the other conditions are either extremely rare or very rare.

Looking at the Workshop questions - the proportion who die in the neonatal period, the proportions who might present as Reye's syndrome and sudden unexpected death: first the fat oxidation disorders - we know from the BPSU study (2) that approximately five to 10 percent of babies with MCAD die in the newborn period; approximately 50 percent present as a Reye like illness, and in all the studies throughout the world between 15 and 25 percent will die suddenly and unexpectedly. For very long chain acyl CoA dehydrogenase deficiency, long chain hydroxyacyl CoA dehydrogenase deficiency and all the other fat oxidation defects, the data are very poor. We know they die in the neonatal period, we know they can develop Reye's syndrome and we know they can die suddenly, but the precise data are simply not there.

Second, the urea cycle disorders: about 60 percent of males with OTC deficiency die in the neonatal period. This is much lower than people often think, because mild male phenotypes are really quite common which means that the case fatality rate among affected male neonates is not 100 percent. About 20 percent of females die as neonates. A Reye-like presentation is, paradoxically, commoner in the *mildly* affected patients and it's likely to occur in approximately 30 percent of the males and 40 percent of the females. Sudden unexpected death really does not occur in these disorders (although there may be anecdotal reports) - you need time to become hyperammonaemic and it is clear that the patient is unwell beforehand. The frequency of carbamyl phosphate synthetase deficiency is very difficult to determine. It is probably very rare in this country although it may be more

common in the USA. The majority of such patients present in the newborn period and have a very poor outlook.

Third, the organic acidaemias: in fact methylmalonic, propionic and isovaleric acidaemia don't really present as Reye's syndrome, but clearly we need to incorporate them into our algorithm for identifying the patients. The so-called *mild* organic acidaemias, for example HMG CoA lyase deficiency and 3-methyl crotonyl glycinuria, actually do present with sudden onset of severe encephalopathy and are conditions which we certainly do need to be able to identify.

**TABLE FOLLOWS ON NEXT PAGE:**

Disorder	Birth incidence	Neonatal death	Reye presentation	SUD
<u>Fatty acid oxidation disorders</u>				
MCAD	1: 14,000 (1)	5-10% (2)	50% (2-3)	15 – 25% (2-4)
VLCAD	>1:200,000	+	+	+
LCHAD	1:100,000	+	+	+
MADD	1: 75,000	+	+	+
Other FAO	?	+	+	+
<u>Urea cycle disorders</u>				
OTC	1:14,000 (5)	60% males (5)	(30%)	<2%*
	But in UK? 1:30,000	20% females (5)	(40%)	<2%*
CPS	1:62,000 (5)	(80%)	(10-20%)	<2%
	But in UK? > 1:100,000			

Disorder	Birth incidence	Neonatal death	Reye presentation	SUD
Other urea cycle disorders	?	+	+	<2%
<u>Organic acidaemias</u>				
MMA	1:50,000	10%	(10%)	<2%*
PA	1:100,000	10%	(10%)	<2%*
IVA	>1:100,000	5%	(5%)	<2%
HMG CoA lyase	1:100,000	?	75%	<2%
3-Methy crotonyl glycinuria	>1:100,000	(<5%)	?	<2%
Others	+	+	+	+

\* Note: a very small number of anecdotal case reports + No data

## References

- 1: Seddon HR, Gray G, Pollitt RJ, Iitia A, Green A. Population screening for the common G985 mutation causing medium-chain acyl-CoA dehydrogenase deficiency with Eu-labeled oligonucleotides and the DELFIA system. Clin Chem. 1997 Mar; 43(3):436-42.
- 2: Pollitt RJ, Leonard JV. Prospective surveillance study of medium chain acyl-CoA dehydrogenase deficiency in the UK. Arch Dis Child. 1998 Aug;79(2):116-9.
- 3: Iafolla AK, Thompson RJ Jr, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. J Pediatr. 1994 Mar; 124(3):409-15.
- 4: Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. Arch Dis Child. 1994 May;70(5):410-2.
- 5: Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr. 1996; 43:127-70.

## DISCUSSION

**Dr MacFaul.** What proportion of births would have a metabolic disease? It's been guessed at something like one in fifteen thousand I believe.

**Professor Leonard.** We think it's more frequent than that. It depends again on what you define as a metabolic disease. If you include the peroxisomal, lysosomal and mitochondrial disorders then it comes out at one in two to three thousand.

**Dr MacFaul.** For those of us who are at the front line we have to bear this very much in our minds and the pathologists as well. You need to know from which children do you take the relevant samples and the other question of course is what proportion of sudden deaths should

you be looking for these things?

**Professor Leonard.** We can come back to this when we try to define the clinical pointers - but in my experience in all patients that we have seen with a subsequently diagnosed IMD where the child has died suddenly, there has been a clear history that the child was unwell beforehand. You don't put a child down well and find that child dead ten minutes later; these have *all* been unwell with a clear history, with gastroenteritis being much the commonest. They've been fasted or maybe given a bit of dioralyte or water and then they are put down and later found dead. That's the sort of history you get if taken correctly. I don't think the children with methyl malonic aciduria or propionic aciduria come into this category however - because actually they are ill beforehand and people pick them up for other reasons.

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***Q. 1.3.1 ii) a) If untreated or treated late, what are the mortality rates for each IMD, what are the morbidity rates and what is the nature of the morbidity?***

***DR ANUPAM CHAKRAPANI***

The Table below summarises the available data and is based on the Reye-like IMDs that are listed on the Reye's Syndrome Foundation's website as the cause of Reye-like illnesses. As Professor Leonard has said, unfortunately there is not that much information available for the majority of these conditions. Again breaking them down into the three main categories described by Professor Leonard: first *the fat oxidation defects* - MCAD is the only one where there is really any substantial information at all. The mortality rate is said to be around 20 percent according to published data; the morbidity rate - again that's a guess but there is probably a proportion of patients who don't develop any problems at all. The other fat oxidation defects have substantially higher mortality and morbidity rates which are close to

hundred percent for some of the rarer conditions.

Next, *the organic acidaemias*: again in general these have very high morbidity and mortality rates, close to hundred percent in many cases in the more severe forms especially, leading to early death.

Finally *the urea cycle defects*. These are a slightly more heterogeneous group especially the OTC heterozygotes. Among these the female morbidity rate may be as low as 10 or 20 percent, but in the severe neonatal forms mortality is close to 70 or 80 percent.

Unfortunately for some of the other rarer conditions like some of the rarer fat oxidation defects like carnitine transporter defect or the translocase defect there are very few data available - they are literally based on individual anecdotal cases. In general most patients have high morbidity and mortality rates, again emphasising the need for early diagnosis and treatment.

TABLE FOLLOWS:

CONDITION	MORTALITY RATE	MORBIDITY RATE	NATURE OF MORBIDITY
MCAD deficiency	16-25% <sup>3-6</sup>	70%	Recurrent decompensation, developmental delay (14-38% <sup>3-6</sup> )
LCHAD deficiency	38% <sup>1</sup>	>95% <sup>2</sup>	Recurrent decompensation, muscular pains, FTT, feeding difficulties, developmental delay
VLCAD deficiency	47-50% <sup>7,8</sup>	>95% <sup>2</sup>	Recurrent decompensation, myopathy, cardiomyopathy, rhabdomyolysis
Carnitine transporter defect <sup>9</sup>	?	?	Acute decompensation, hypoglycaemia, cardiomyopathy, liver dysfunction
CPTI deficiency <sup>9</sup>	10%	?	Recurrent decompensation, hypoglycaemia, liver dysfunction
CACT deficiency <sup>9</sup>  Severe  Mild	?100%  ? High (2/3)	?100%  ?	Myopathy, cardiomyopathy, arrhythmias, liver failure, recurrent hypoglycaemia
CPT II deficiency <sup>9</sup>  Mild  Severe	Low  Very high	?  ?	Myoglobinuria, myopathy, renal failure  Hypoglycaemia, myopathy, cardiomyopathy, hepatomegaly
MSUD <sup>10,11,26</sup>	?up to 25-50%	?100%	Recurrent metabolic crises with ketoacidosis, encephalopathy
Multiple carboxylase deficiency	High, esp. HCS <sup>12</sup>	HCS ?100%  Biotinidase 50% <sup>11</sup>	Seizures, acidosis, hypotonia, mental retardation
Propionicacidemia (early onset)	40-100% <sup>13-16</sup>	100% <sup>11</sup>	Recurrent metabolic crises, mental and neurological sequelae



Methylmalonic acidaemia (early onset)	73-87% <sup>17,18</sup>	100% <sup>11</sup>	Recurrent metabolic crises, mental and neurological sequelae
Isovaleric acidaemia	?up to 50% <sup>19</sup>	100% <sup>11</sup>	Recurrent metabolic crises, mental retardation
Urea cycle <sup>20</sup> defects (inc HHH and LPI)	<p>OTC, CPS 70-80%</p> <p>AS, AL ?20%</p> <p>LPI, HHH: unknown</p>	<p>Unknown</p> <p>(OTC heterozygote ?10%<sup>21</sup>)</p> <p>LPI, HHH: unknown</p>	<p>Mental retardation, recurrent crises, neurological sequelae<sup>20</sup></p> <p>LPI: growth failure, SLE-like syndrome, skeletal abnormalities, immune problems, renal &amp; pulmonary problems</p>
HFI	?20% <sup>22,23</sup>	Unknown	Failure to thrive, liver dysfunction & failure, bleeding, drowsiness, apathy
F 1,6 BP <sup>24</sup>	?	?	Recurrent episodes of ketoacidosis, hypoglycaemia, coma
Glycerol kinase <sup>25</sup>	?	?	Recurrent metabolic crises with vomiting, acidosis, hypoglycaemia and encephalopathy

## References:

1. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: clinical presentation and follow-up of 50 patients. Den Boer ME, Wanders RJ, Morris AA, IJlst L, Heymans HS, Wijburg FA. Pediatrics 2002 Jan; 109(1):99-104
2. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, Nicholl J, Nicholson P, Tunaley JR, Virdi NK. Health Technol Assess 1997; 1(7):i-iv, 1-202
3. Prospective surveillance study of medium chain acyl-CoA deficiency in the UK. Pollitt RJ, Leonard JV. Arch Dis Child 1998; 79:116-119

4. Iafolla AK, Thompson RJJ, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. *J Pediatr* 1994; 124:409-415
5. Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. *Arch Dis Child* 1994; 70:410-412
6. Touma EH, Charpentier C. Medium chain acyl-CoA dehydrogenase deficiency. [Review] *Arch Dis Child* 1992; 67:142-145
7. Vianey-Saban c, Divry P, Brivet M et al. Mitochondrial very-long-chain acyl-Coenzyme A dehydrogenase deficiency: clinical characteristics and diagnostic considerations in 30 patients. *Clinica Chimica Acta* 1998; 269:43-62
8. Pons R, Cavadini P, Bratta S et al. Clinical and molecular heterogeneity in very-long-chain acyl-coenzyme A dehydrogenase deficiency. *Pediatr Neurol.* 2000 Feb; 22(2):98-105.
9. Roe CR, Ding J. Mitochondrial fatty acid oxidation disorders. In: *MMBID 2001*: 2279-2326
10. Naughten ER, Jenkins J, Francis DE, Leonard JV. Outcome of maple syrup urine disease. *Arch Dis Child.* 1982 Dec; 57(12):918-21.
11. Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, Nicholl J, Nicholson P, Tunaley JR, Viridi NK. *Health Technol Assess* 1997;1(7):i-iv, 1-202
12. Scriver chapter on Biotin
13. Lenhert W, Sperl W, Suormala T, Baumgartner ER (1994) Propionic acidemia: clinical, biochemical and therapeutic aspects. Experience in 30 patients. *Eur J Pediatr* 153 [Suppl 1]: S68-S80
14. Surtees RAH, Matthews EE, Leonard JV (1992) Neurologic outcome of propionic acidemia. *Pediatr Neurol*;333-337
15. Van der Meer SB, Poggi F, Spada M, Bonnefont JP, Ogier H, Hubert P et al (1996) Clinical outcome and long-term management of 17 patients with propionic acidemia. *Eur J Pediatr* 155:205-210
16. Rousson R, Guibaud P (1984) Long-term outcome of propionic acidemia: survey of 105 French cases (1967-1983). *J Inher Metab Dis* 7 Suppl 1:10-12
17. Nicolaides P, Leonard J, Surtees R. Neurological outcome of methylmalonic acidemia. *Arch Dis Child* 1998 Jun; 78(6):508-12
18. van der Meer SB, Poggi F, Spada M, Bonnefont JP, Ogier H, Hubert P, Depondt E, Rapoport D, Rabier D, Charpentier C, et al. Clinical outcome of long-term management of patients with vitamin B12-unresponsive methylmalonic acidemia. *J Pediatr* 1994 Dec; 125(6 Pt 1):903-8

19. Sweetman L, Williams JC. Branched chain organic acidurias. MMBID 2001:2125-2163
20. Brusilow S, Horwich AL. Urea Cycle Enzymes. MMBID 2001:1909-1963
21. Batshaw ML. Inborn errors of urea synthesis. Ann Neurol 1994; 35:133-141
22. Odievre M, Gentil C, Gautier M, Alagille D. Hereditary fructose intolerance in childhood. Diagnosis, management, and course in 55 patients. Am J Dis Child 1978 Jun; 132(6):605-8
23. Baerlocher K, Gitzelmann R, Steinmann B, Gitzelmann-Cumarasamy N. Hereditary fructose intolerance in early childhood: a major diagnostic challenge. Survey of 20 symptomatic cases. Helv Paediatr Acta 1978 Dec;33(6):465-87
24. Disorders of glycerol metabolism. McCabe ERB. MMBID 2001:2217-2237
25. Disorders of fructose metabolism. Steinmann B, Gitzelmann R, van den Berghe G. MMBID 2001:1489-1520
26. Kaplan P, Mazur A, Field M, Berlin JA, Berry GT, Heidenreich R, Yudkoff M, Segal S. Intellectual outcome in children with maple syrup urine disease J Pediatr 1991 Jul;119(1 ( Pt 1)):46-50

## DISCUSSION

**Dr MacFaul.** So the nature of morbidity from these IMDs is on the whole mostly neurodevelopmental delay?

**Dr Chakrapani.** Well it is quite variable - it's the combination of episodes of decompensation, of neurological problems, hypoglycaemia, some of the conditions can even lead to severe cardiac problems and death, so it's quite a varied combination of things really.

**Dr MacFaul.** So this means they are likely to crash in and out of hospital with their emergency action plans from time to time, and they may have neurodevelopmental delay requiring the whole support services. I think there is no obvious dissent from that in the room.

**Dr MacFaul.** *The next point* then is what is the point in diagnosing these conditions. One of the arguments that we've heard put against neonatal screening for IMDs is that if you correctly identify a biochemical phenotype that's not ever going to decompensate into clinical illness, then those children too will be rushed in and out of hospital for drips and invasive

procedures thereby causing great distress. Equally we have heard of the distress and anguish that is caused by *false* positives, knowing that someone might be sitting on a time bomb but of course they will never decompensate. However, I think you are now going to talk about what happens to the families when the child dies, and where they don't have a clear cut cause of death.

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***1.3.1 ii) b) Is there evidence that there is parental (psychological?) morbidity caused by delayed diagnosis or, in the case of a child who dies, by the absence of a clear cut cause of death?***

***DR ANUPAM CHAKRAPANI, MRS LESLEY GREENE, MR GORDON DENNEY***

**Dr Chakrapani.** I tried a literature search on this topic but unfortunately I couldn't find any specific information that is published on Reye's syndrome. I think Gordon Denney here and Lesley Greene will have substantial experience personally as well as through their organisations. Immediate reactions of parents to sudden infant death include anger, bewilderment, self-blame and guilt. Acute reactions of shock, disbelief and self-reproach have also been observed, as well as severe anxiety, overprotection of siblings and insomnia. One of the major elements of emotional stress is guilt, and the lack of aetiological knowledge about SIDS is believed to be a major contributory factor.

Though normal, uncomplicated grief is the expected reaction to SIDS, a large number of parents undergo extreme, prolonged and suppressed grief reactions with secondary effects on behaviour and interpersonal relationships. Such protracted unresolved grief reactions, particularly parental guilt has been attributed to the unknown cause and unexpected occurrence of SIDS.

It follows that an infant death caused by a disease of an explainable cause helps remove the guilt from the family (and physician).

## **References found:**

**Powell M. Sudden infant death syndrome: A crisis for parents and health professionals. Ir J Med Sci 1991; 160(9):282-285**

40 of 61 SIDS families interviewed (40 mothers, 29 fathers) at home between 13 months and 3 years of the loss (normal, uncomplicated grief may last up to 1 year).

Impact of SIDS on family life assessed according to Holmes and Rahe's Social Readjustment Rating Scale (1967)

Overall, 48% had resolved grief and accepted the loss at mean 2.9 years post SIDS

Long-term psychosocial grief effects found:

21.7% shock

37.7% disbelief

44.8% anger – mostly directed at health professionals for not providing/discussing postmortem results. Few (3/41) of those who had discussed PM results with physician had unresolved guilt. Most (17/19) of those whose feelings of guilt remained unresolved had not received postmortem information.

33.3% guilt

30.4% loss of meaning in life

60.9% anxiety

Such extreme, prolonged and suppressed grief reactions represent an incomplete form of grief adjustment, leading to abnormal behaviour and distorted interpersonal relationships.

Such protracted unresolved grief, particularly parental guilt has been attributed to lack of aetiological knowledge of SIDS.

**Salk L. Sudden Infant Death: Impact on family and physician. Clinical Pediatrics 1971; 10:248-250**

Severe, prolonged grief reactions in parents bereaved by SIDS have been attributed to unknown cause and unexpected occurrence. Perhaps the most pervasive emotional reaction which can develop in those closest to the victim is an intense sense of responsible guilt. The physician is in a crucial position, being expected to provide the answers regarding the cause of death in order to help alleviate the intense feelings of guilt on the part of the parents.

It is noteworthy that an infant death caused by a disease of an explainable cause helps remove

the guilt from both family and the physician.

**Weinstein SE. Sudden infant death syndrome: impact on families and a direction for change. Am J Psych 1978 135:831-834**

**Impact of SIDS on family:**

“They ask the logical question: why did my baby die? They look to the physician for answers but he does not have them. They want to make sense out of nonsense and put the pieces together in a way that will enable them to see a cause and effect.”

“A common denominator of SIDS parents is guilt. The guilt, the grief and the lack of knowledge together constitute major emotional stress for the parents both as individuals and as a couple. Guilt can exacerbate previous psychiatric conditions and marital problems.”

\*\*\*\*\*

***Statement from Gordon Denney (National Reye's Syndrome Foundation of the UK):***

There is a great deal of evidence that delayed diagnosis causes parental (psychological) morbidity.

In the case of a child who survives under the age of five, a situation may arise whereby a parent(s) is told, in due course after diagnosis, that their child has presented with a Reye-like illness which has been specifically identified.

A sense of shock invariably arises if they are told that the illness is a rare inherited metabolic disorder. Their disquiet immediately turns to the children they already have or the family they may be planning for the future. Such advice invariably raises questions about possible tests that can be carried out on their offspring. Incidentally partners, or close family members have been known to take differing views about the need for such tests.

Occasionally in the case of a baby or a young child who survives, the illness has been known to be erroneously described as 'Reye's Syndrome' or indeed as a 'mystery illness'.

In cases where a young child dies, 'Reyes Syndrome' is often incorrectly stated to be the cause of death. Because there has been no aspirin involvement, uncertainty about the cause, as stated on the death certificate, can lead to a desperately worrying situation for a parent(s).

A great deal of concern may also arise where the cause is given as 'sudden infant death syndrome'. In both situations, for the enquiring parent, there is no clear cut cause of death.

\*\*\*\*\*

## **CONTRIBUTION FROM CLIMB**

***1.3.1 ii) b) Is there evidence that there is parental (psychological?) morbidity caused by delayed diagnosis or, in the case of a child who dies, by the absence of a clear cut cause of death?***

**Mrs Lesley Greene**

In order to answer the questions required of the workshop, *Climb* carried out a survey of the sixty-five MCADD families with whom it has regular contact. The information was derived both from a special questionnaire and from the information routinely sought when families first contact us. Fourteen replied to the questionnaire in the time available. We have not, but could, repeat this exercise for other Reye-like disorders but would need extra time and financial resources made available in order to do this.

We have summarised the main presenting symptoms, the number of late diagnoses, those diagnosed as being Reye in the first instance and those suffering brain damage and/or death.

***The most common presenting symptoms were:***

- **Coma**
- **Dehydration**
- **Low blood sugar**
- **Vomiting**
- **Fits**

***Slightly less frequent were:***

- **Cardiac arrest**
- **Breathing problems**
- **Floppiness**
- **Pale**

### ***Delayed diagnosis***

Twenty-seven children of the 65 families included received a delayed diagnosis. Of these, six had a further episode from which they suffered brain damage, six received a diagnosis of Reye syndrome in the first instance and eleven died before the diagnosis was made.

### ***Parental morbidity***

**Ten mothers needed to see a GP within twelve months. Of these, illness or symptoms were:**

- **Unable to sleep**
- **High BP**
- **Mild anaemia**
- **Infections**
- **Depression**
- **Stressed**
- **Hyper alert**
- **Hypothyroidism (x 2)**
- **Anxious**
- **Tearful**
- **Feeling overloaded**
- **Acute appendicitis**
- **Dismissal of symptoms by the doctor increased anxiety etc.**

### ***Medication/treatments given were:***

- **More time given by GP on a one-to-one basis**
- **High blood pressure tablets**
- **Iron**
- **Antibiotics**
- **Prozac**
- **Metoclopramide**



- **Diazepam**
- **Cimetidine**
- **Thyroxin**
- **Counselling**

*Other indicators that stress was increased were:*

- **No sleep**
- **Emotional**
- **Unable to concentrate**
- **Family relations suffered**
- **Breakdown**
- **Mental exhaustion**
- **Poor eating**
- **Physical exhaustion**
- **Guilt owing to self blame for late diagnosis**
- **Heightened sensitivity to noise**
- **Short temper**
- **Started smoking**
- **Started drinking**

## **DISCUSSION**

**Dr John Glasgow.** It is desperately important for these families to have precision in the diagnosis if at all possible.

**Professor Berry.** Although I shouldn't generalise, could I just say that pathologists often use the term "Reye's syndrome" extremely imprecisely. Generally speaking a general pathologist who isn't interested in this area will see a fatty liver and if he hasn't done the inborn errors screens he will call it Reye's syndrome and if he's done them he will call them something else. So we need to educate our colleagues.

\*\*\*\*\*

***1.3.1. (iii) What is the evidence that mortality and morbidity can be avoided with early diagnosis, or prenatal diagnosis following an affected sibling, plus appropriate management (assuming no national screening programme)***

***Dr A CHAKRAPANI***

The Table (below) summarises the again very sketchy data that's been published on most of these conditions. For the most common, MCAD, I think everybody agrees that there have been good published data on that and that there is very, very low mortality after diagnosis. Certainly that is one of the conditions on the agenda for screening in the next few years. For the other disorders unfortunately there's not that much data, but overall I think the kind of conditions that are likely to present with Reye-like illnesses like, for example, the milder forms of the organic acidaemias, certainly would have a relatively low mortality. Unfortunately again there are no specific published figures but some of the conditions certainly are not very amenable to treatment like the severe forms of organic acidaemias and the severe urea cycle defects - they have high mortality and morbidity irrespective of treatment.

TABLE FOLLOWS :

CONDITION	OUTCOME AFTER EARLY/PRENATAL DIAGNOSIS AND TREATMENT
MCAD deficiency	Very low mortality after diagnosis; after 1 <sup>st</sup> presenting episode, developmental delay in 14-38% survivors <sup>1-4</sup>
LCHAD deficiency	14% mortality after diagnosis; high morbidity in survivors (?30%) <sup>5</sup> ; no data on prospective treatment
VLCAD deficiency <sup>5,6</sup>	High mortality and morbidity after diagnosis (no specific figures available); no data on prospective treatment
Carnitine transporter defect <sup>7</sup>	low mortality and morbidity after diagnosis (no specific figures available); no data on prospective treatment, but good outcome likely
CPTI deficiency <sup>7</sup>	Low mortality and morbidity after diagnosis; no data on prospective treatment
CACT deficiency <sup>7</sup>	
Severe	High mortality and morbidity after diagnosis; no data on prospective treatment
Mild	
CPT II deficiency <sup>7</sup>	
Mild	?High morbidity, low mortality following diagnosis; no data on prospective treatment
	High morbidity and mortality following diagnosis; no data on prospective treatment
Severe	
MSUD <sup>8,9</sup>	Normal intellectual outcome with reduced morbidity and mortality if treatment started <10-14 days
Multiple carboxylase deficiency <sup>10</sup>	HCS – Low morbidity and mortality with early and prenatal treatment; exceptions may be partially responsive cases  Biotinidase – very low morbidity and mortality with early treatment
Propionic acidaemia (early onset) <sup>11,12</sup>	High mortality and morbidity despite early diagnosis and treatment (including prenatal diagnosis)
Methylmalonic acidaemia (early onset) <sup>11,12</sup>	High mortality and morbidity despite early diagnosis and treatment (including prenatal diagnosis)
Isovaleric acidaemia <sup>11,12</sup>	Low mortality and morbidity with early or prenatal diagnosis and treatment
Urea cycle <sup>13,14</sup>	Early onset UCDs: High morbidity and mortality despite early diagnosis and treatment, esp. OCT and CPS
defects (inc HHH and LPI)	Prospective treatment: poor outcome for OCT,CPS <sup>15</sup>
HFI <sup>16,17</sup>	Low mortality and morbidity with early diagnosis; no data on prenatal but presumed good outcome
F 1,6 BP <sup>18</sup>	Presumed low morbidity and mortality with early diagnosis; no data on prenatal but presumed good outcome
Glycerol kinase <sup>19</sup>	Presumed low morbidity and mortality with early diagnosis; no data on prenatal but presumed good outcome

## References:

1. Prospective surveillance study of medium chain acyl-CoA deficiency in the UK. Pollitt RJ, Leonard JV. Arch Dis Child 1998; 79:116-119
2. Iafolla AK, Thompson RJJ, Roe CR. Medium-chain acyl-coenzyme A dehydrogenase deficiency: clinical course in 120 affected children. J Pediatr 1994; 124:409-415
3. Wilcken B, Hammond J, Silink M. Morbidity and mortality in medium chain acyl coenzyme A dehydrogenase deficiency. Arch Dis Child 1994; 70:410-412
4. Touma EH, Charpentier C. Medium chain acyl-CoA dehydrogenase deficiency. [Review] Arch Dis Child 1992; 67:142-145
5. Vianey-Saban c, Divry P, Brivet M et al. Mitochondrial very-long-chain acyl-Coenzyme A dehydrogenase deficiency: clinical characteristics and diagnostic considerations in 30 patients. Clinica Chimica Acta 1998; 269:43-62
6. Pons R, Cavadini P, Bratta S et al. Clinical and molecular heterogeneity in very-long-chain acyl-coenzyme A dehydrogenase deficiency. Pediatr Neurol. 2000 Feb; 22(2):98-105.
7. Roe CR, Ding J. Mitochondrial fatty acid oxidation disorders. In: MMBID 2001: 2279-2326
8. Naughten ER, Jenkins J, Francis DE, Leonard JV. Outcome of maple syrup urine disease. Arch Dis Child. 1982 Dec; 57(12):918-21.
9. Kaplan P, Mazur A, Field M, Berlin JA, Berry GT, Heidenreich R, Yudkoff M, Segal S. Intellectual outcome in children with maple syrup urine disease J Pediatr 1991 Jul;119(1 ( Pt 1)):46-50
10. Baumgartner ER, Suormala T. Biotin-responsive multiple carboxylase deficiency. Inborn Metabolic Disease: Diagnosis and treatment. Editors: Fernandes, Saudubray & van den Berghe 2000, pages 277-282
11. Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, Nicholl J, Nicholson P, Tunaley JR, Viridi NK. Health Technol Assess 1997;1(7):i-iv, 1-202
12. Sweetman L, Williams JC. Branched chain organic acidurias. MMBID 2001:2125-2163
13. Brusilow S, Horwich AL. Urea Cycle Enzymes. MMBID 2001:1909-1963
14. Batshaw ML. Inborn errors of urea synthesis. Ann Neurol 1994; 35:133-141
15. Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. J Pediatr 1991 Dec; 119(6):923-8

16. Odievre M, Gentil C, Gautier M, Alagille D. Hereditary fructose intolerance in childhood. Diagnosis, management, and course in 55 patients. Am J Dis Child 1978 Jun; 132(6):605-8
17. Baerlocher K, Gitzelmann R, Steinmann B, Gitzelmann-Cumarasamy N. Hereditary fructose intolerance in early childhood: a major diagnostic challenge. Survey of 20 symptomatic cases. Helv Paediatr Acta 1978 Dec; 33(6):465-87
18. Disorders of fructose metabolism. Steinmann B, Gitzelmann R, van den Berghe G. MMBID 2001:1489-1520
19. Disorders of glycerol metabolism. McCabe ERB. MMBID 2001:2217-2237

## **DISCUSSION**

**Dr Neil Dalton.** In relation to the urea cycle defects I agree that *usually* there is high morbidity and mortality, but particularly with *partial* OTC, which is the one that would present with a Reye-like illness, the outcome is very good if you've made the diagnosis early.

**Professor James Leonard.** Could I just qualify that? Robert Surtees and I have come across some rather worrying, rather subtle, but actually very disabling disorders of executive functions in these patients even if they are prospectively treated. They clearly are a worry so I think while we would have said exactly the same as you, when we came to review them in detail we now think they're just a little bit of a question mark.

**Dr Dalton.** They don't die.

**Professor Leonard.** No, they don't die.

**Dr MacFaul.** So we are preventing death by early diagnosis and treatment in these cases, but is it also possible to modulate the morbidity then with therapy, I think it is, isn't it?

**Professor Leonard.** Yes

**Dr Chakrapani.** I think the same holds true for the late onset organic acidaemias like propionic acidaemia.

\*\*\*\*\*

*Question 1.3.1.(iv) If routine (tandem mass spectrometry) screening is introduced nationally, would we still have a problem?*

*Dr ANNE GREEN*

### **Current UK Position of TMS Screening for IMD**

A recent (2002) survey that I have done shows that several laboratories are now using TMS for PKU screening (Birmingham, Manchester, Sheffield, Leeds, London (GOS and Guys), and Cambridge). This covers approximately 350,000 babies, ~ 50% of UK births. Glasgow are hoping to start soon and others will probably follow in the next 1-2 years (Dublin, Carshalton) so I suspect 60-70% of births will be covered in the very near future.

*PLEASE NOTE* - this is for PKU only and it is extremely unlikely in the short term (i.e. 2002/3) that TMS will be extended to other IMD. The National Screening Committee (NSC) is currently not recommending any additional screening for IMD. Since 1997, efforts to obtain research funding for MCAD have been made. However, it has now been confirmed that the MCAD research project has not been funded.\* An updated HTA (refs <sup>1,2</sup>) is being carried out now by the School for Health and Related Research at Sheffield University with a report date of ? May 2002. It is unclear whether this report is likely to change the 'view' of the child health studies group of the NSC. It is possible that MCAD may be introduced as a service, but other IMD seems less likely in the short term. There is a funding issue for laboratories and metabolic paediatrics if extended screening is to be introduced as a service.

### *TMS Screening for IMD's – World-wide Population*

There are now several reports in the literature from other countries of the potential of TMS for neonatal screening for IMD's (<sup>3,4,5</sup>). The potential for TMS (acyl carnitines and amino acids) for diagnosing Reye-like IMD is summarised in table 1.

In the table below I've taken the list of disorders which are on the Reye's Foundation web site and indicated with ticks and crosses and question marks an assessment of whether they would be

picked up by TMS screening, using acyl carnitine and amino acids. It is clear that it can pick up fat oxidation disorders and the carnitine cycle disorders but is *unlikely* to pick up several of the other disorders, in particular not all the urea cycle disorders. The parts of the world undertaking screening include Sydney, New South Wales; South Australia; Boston in the United States; Pennsylvania; and Bavaria. There are now quite a lot of data from those centres which actually show that you can detect, by real live neonatal screening, certainly the fat oxidation disorders, in particular MCAD, and the carnitine cycle disorders. There's little good evidence at the moment that you would pick up the urea cycle disorders. So that's overall my assessment of the situation.

Data on the experience of diagnosing those IMDs which may present as a Reye-like syndrome from newborn screening is currently being updated for the workshop (6-26).

#### TABLE FOLLOWS:

KEY:

√ = YES

X = NO

? = UNCERTAIN

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\* 2004 update: a pilot study in 6 regions has now been funded (Ed.)

Disorder	Detectable by TMS Acyl carnitine and amino acids	Specific Metabolites
<b>Defects in the <math>\beta</math>-Oxidation Cycle</b>		
Medium-chain acyl-CoA dehydrogenase deficiency	✓	C8, C10, C10:1, C6
Very long chain acyl-CoA dehydrogenase deficiency	✓	C14:2, C14:1, C14, C16
Long chain 3-hydroxy acyl-CoA dehydrogenase deficiency	✓	C16OH, C18:1OH, C18OH
<b>Defects in Electron Transfer Pathway</b>		
Multiple acyl-CoA dehydrogenase deficiency – severe and mild	✓	C4, C5, C8:1, C8, C12, C14, C16, C5DC
Riboflavin responsive multiple acyl-CoA dehydrogenase deficiency	?	
<b>Defects in the Carnitine Cycle</b>		
Carnitine palmitoyl transferase deficiency types I & II (neonatal)	✓	I - Increased Free Carnitine II - C16, C18:1, C18:2
Carnitine acyl-carnitine translocase deficiency	✓	↑ C14, C16, C18:1, C18:2
Carnitine transporter deficiency (primary carnitine deficiency)	✓	Low Free Carnitine + ↓ acyl carnitines
<b>Defects in Metabolism of Branched Chain Amino Acids</b>		
Maple syrup urine disease	✓	Leuc / isoleuc, valine
Multiple carboxylase deficiency	?	C5OH, C3
Isovaleric acidemia	✓	C5
Propionic acidemia	✓	C3
Methylmalonic acidemia	✓	C3
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	?	C5OH
$\beta$ -Ketothiolase deficiency (mitochondrial 3-ketothiolase deficiency)	?	C5:1, C5OH
3-methyl glutacetic aciduria	✓	C5OH



<b>Defect in metabolism of carbohydrates</b>			
Hereditary fructose intolerance	X		
<b>Disorder of Gluconeogenesis</b>			
Fructose – 1,6-bisphosphatase deficiency	X		
<b>Glycogen Storage Disease</b>			
GSD Type 1	X		
<b>Disorders of Glycerol Metabolism</b>			
Glycerol kinase deficiency	?		
<b>Disorders of Ammonia Detoxification – Urea Cycle Defects</b>			
Ornithine transcarbamylase (OTC) deficiency	Probably not??		? ↑ Glutamate / Alanine ↓ cit
Carbamoylphosphate synthetase 1 (CPS) deficiency	Probably not??		? ↑ Glutamate / Alanine ↓ cit
Argininosuccinic aciduria	✓		ASA, Citrulline
Citrullinaemia	✓		Citrulline
HHH syndrome (hyperammonaemia, hyperornithinaemia, homocitrullinuria)	?		ORN, homocitrulline (?)
<b>Disorders of Amino Acids Transport</b>			
Lysinuric protein intolerance (lysine, arginine and ornithine)	?		? ↑ Glutamate / Alanine / Citrulline

## References

1. Pollitt RJ, Green A, McCabe CJ, Booth, Cooper NJ, Leonard JV, Nicholl J, Nicholson P, Tunaley JR, Virdi NK. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. Health Technology Assessment 1997; 1: No.7 .
2. Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, Littlejohns P, Lord J, Wilcox AH. Newborn screening for inborn errors of metabolism: a systematic review. Health Technology Assessment 1997; 1: No. 11.
3. U.S. Department of Health and Human Services, Centre for Disease Control and Prevention (CDC) Atlanta, GA 30333. Using Tandem Mass Spectrometry for Metabolic Disease among Newborns: A Report of a Workgroup. Morbidity and Mortality Weekly Report, April 2001; 50 RR3.
4. Vianey-Saban C, Guffon N, Delone F, Guibaud P, Mathieu M, Diverly P. Diagnosis of inborn errors of metabolism by acyl carnitine profiling in blood using tandem mass spectrometry. J.Inher.Metab.Dis. 1997; 20: 411-414.
5. Vreken P, Van Lint AEM, Bootsma AH, Wanders RJA, Van Gennip AH. Quantitative plasma acyl carnitine analysis using electrospray tandem mass spectrometry for the diagnosis of organic acidemias and fatty acid oxidation defects. J.Inher.Metab.Dis. 1999; 22: 302-306.
6. Abdenur J. E, Chamoles N. A, Schenone A, Guinle A, Fusta M, Gaggioli D. Supplement newborn screening of amino acids (AA) and acyl carnitines by electrospray tandem mass spectrometry (ESI-MS/MS): experience in Argentina. J. Inherit Metab. Dis 23 2000; suppl 1; **026-P**: 13
7. Biberoglu G, Hassanoglu A, Turner L, Ezgu F. S, Genc B. Screening inborn errors of metabolism from dried blood spots using electrospray tandem mass spectrometry. J. Inherit.Metab.Dis. 23 2000; suppl 1; **007-A**: 4

8. Carpenter K, Wiley V, Sim K G, Hammond J, Heath D, Wilcken B. Newborn screening for MCAD deficiency: the New South Wales experience. *J. Inherit. Metab. Dis.* 23 2000; suppl 1; **031-P**: 16
  
9. Carpenter K, Wiley V, Sim K G, Hammond J, Heath D, Wilcken B. Evaluation of newborn screening for Medium chain acyl CoA dehydrogenase deficiency in 275 000 babies. *Arch. Dis. Child. Fetal Neonatal Ed* 2001; F105-F109
  
10. Carpenter K. and Wilcken B. Neonatal diagnosis of long-chain 3-hydroxy-CoA dehydrogenase deficiency and implications for newborn screening by tandem mass spectrometry. *J. Inherit Metab. Dis* 22 1999; suppl 1; 840
  
11. Goyens P, Van Thi HV, Herremans N, Meirleir, Gerlo E, De Laet C, Bourdoux P. Diagnosis of methylmalonic aciduria (MMA) by neonatal screening using tandem mass spectrometry (MS/MS). *J. Inherit Metab. Dis* 23 2000; suppl 1; 014-P: 7
  
12. Marsden D, Zytkevicz T, Larson C, Shih V, Grady G. Prevalence of fatty acid oxidation disorders and organic acidemias in New England newborns screening by tandem mass spectrometry. *J. Inherit Metab. Dis* 23 2000; suppl 1; 029-O: 15
  
131. Marsden D, Zytkevicz T, Larson C, Shih V, Grady G. Spectrum of expression of MCAD and scan detected by newborn screening. *J. Inherit Metab. Dis* 23 2000; suppl 1; 028-P: 14
  
14. Millington D. S. Newborn screening for metabolic diseases. *American Scientist* 2001; **90**: 40-46
  
15. Ranieri E, Gerace R, Bartlett B, Barnard K, Fletcher. The introduction of tandem mass spectrometry into the South Australian neonatal screening programme: benefits and costs. *J. Inherit. Metab. Dis.* 23 2000; suppl 1; 006-P: 3
  
16. Rashed M. S, Rahbeeni Zuhair, Ozmand P. T. Application of electrospray tandem mass spectrometry to neonatal screening. *Seminars in Perinatology* 1999; 23.2: 183 - 193

- 17 Roscher A, Liebl B, Fingerhut R, Olgemöller. Prospective study of MS/MS newborn screening in Bavaria, Germany. Interim Results. J. Inherit.Metab.Dis. 23 2000; suppl 1; 008-P: 4
- 18 Sander S, Janzen N, Janetzky, Scholl S, Steurwald U, Schäfer J, Sander J. Neonatal screening for medium chain acyl CoA deficiency: high incidence in Lower Saxony (northern Germany). ? 2000; 318
- 19 Schulze A, Kohlmüller D, Mayatepek E. Tandem mass spectrometry: first experience in a regional neonatal screening program of Germany. J.Inherit.Metab.Dis 23 2000; suppl 1; **A69**: 143
- 20 Shigematsu Y, Fujisawa K, Hata I, Mayumi M, Tanaka Y, Sudo M. Newborn screening by tandem mass spectrometry; results of pilot study and retrospective analysis in Japan. J.Inherit.Metab.Dis. 23 2000; suppl 1; 012-P: 6
21. Sim K. G, Wiley V, Carpenter K, Wilken B. Carnitine palmitoyltransferase I deficiency in neonate identified by dried blood spot free carnitine and acylcarnitine profile. J. Inherit.Metab.Dis. 24 2001; 51
- 22 Smith W. E, Millington D. S, McDonald K. M, Koeberl D. D. Evaluation of elevated hydroxyisovalerylcarnitine (c5-oh) in the newborn screen by tandem mass spectrometry. J.Inherit.Metab.Dis. 23 2000; suppl 1; 027-P: 14
- 23 Sweetman L. Newborn screening by tandem mass spectrometry: Gaining experience. Clinical Chemistry 2001; 47.11: 1937-1938
- 24 Wilcken B, Wiley V, Sim K G, Carpenter K. Defects in the carnitine cycle detected by newborn screening using tandem mass spectrometry. J.Inherit.Metab.Dis. 23 2000; suppl 1; 030-O: 15
- 25 Wilcken B, Wiley V, Sim K G, Carpenter K. Carnitine transporter defect diagnosed by

newborn screening with electrospray tandem mass spectrometry. The Journal of Paediatrics: 2001; 138 581

- 26 Zyrkovicz T. H, Fitzgerald F, Marsden D, Larson C, Shih V, Johnson D, Strauss A, Comeau A. M, Eaton R, Grady G. Tandem mass spectrometric analysis for amnio organic and fatty acids disorders in newborn dried blood spots: A two year summary from the New England newborn screening program. Clinical Chemistry 2001; 47.11: 1945-1955.

## DISCUSSION

**Dr John Walter.** I've just come back from the United States metabolic disease meeting in California and there's no doubt really that the rest of the civilised world has accepted the need for MCAD screening. I think it's extraordinary that we are still not doing it in this country, particularly when we have the equipment sitting there looking at blood spots on babies for phenylketonuria and at no extra cost we could do the MCADD screening as well. I think there's no doubt from the data that's coming out from other centres that it works, it picks up individuals with MCADD, and it does save lives.

**Mrs Lesley Greene.** Yes, I have to say - to our organisation and our families it beggars belief! We sent out a questionnaire to our MCADD families specifically looking at the questions that apparently were tabled in parliament that screening for MCADD could cause parental anxiety. We asked these parents if they would be made more anxious by a neonatal screen for MCADD and the result was a resounding "no!" - as long as the screening was carried out appropriately with correct follow up procedures. Then now we've done the second survey for this Workshop. The results are those we have just shown (above 1.3.1(ii)b) and as you have seen there are very clear adverse effects on the affected families. I just don't understand why, with all the world evidence that there is, that there is continued delay.

**Professor Leonard.** I support that. I think that one of the messages I would like to come from this group is that MCAD screening needs, at the very least, to be trialled in this country as soon as possible. There are problems because it does identify patients with probable non-disease as we've heard particularly from Bavaria. There is a particular mutation which is never presented clinically which is turning up. But the clear facts emerging are that this is an

important public health measure, and we should remind people that prevention of disease is one of the planks of government policy,

**Dr MacFaul.** I think it was stated in our Workshop programme very carefully that we didn't want to renew the whole TMS screening debate, but it is entirely relevant to what we've been discussing and I think the arguments are heard and they just need to be reiterated repeatedly.

**Dr Neil Dalton.** Just to emphasise a point that Anne Green has made in relation to Reye syndrome: the fact is that with TMS screening, you're unlikely to pick up on the majority of urea cycle defects and particularly will not pick up all of the OTC defects, which are likely to be a significant proportion of the Reye presenters.

**Dr John Glasgow.** Is that because of technological limitations or is it because the patients are not catabolic enough to be able to pick up an abnormal profile?

**Dr Anne Green.** Well, first of all the diagnostic pointers that we would be looking for would be an increase in glutamate, glutamine and alanine that I've indicated in the Table (above) and also citrulline, and there is some uncertainty about whether you could actually set the TMS sufficiently sensitive to actually pick up those levels. Plus there is the fact that this is dried blood spots, as opposed to *plasma* specimens - which are what we are used to looking at, and glutamine is a particularly labile amino acid. So I think there are a number of compounding factors here. Some people have suggested that you could pick up low levels of citrulline - and this has been said by one or two people who are using TMS for screening. I have some concerns about that because it would be extremely difficult, I think, to pick up the subnormal levels of an amino acid that is already pretty low anyway, and the view of the people doing it at the moment is that they think it would be unlikely that you would be able to pick them up.

**Dr Jim Bonham.** The widespread availability of this technology does suggest that, even if we're not permitted to do whole population screening at first, if there's been a previous sudden infant death, especially if there was a fatty liver, it ought to be applied retrospectively to any existing siblings and, perhaps more important, to any newborns coming in to that family.

**Dr Anne Green.** I would welcome that. Certainly in some other parts of the world there is

routine investigation of all sudden unexpected deaths in infancy using dried blood spots or some other material and looking at acyl carnitines.

**Dr MacFaul.** We need to come back to the question posed (1.3.1. iv) *if TMS screening was introduced nationally would we still have a problem - I think the answer is -YES!*

**Dr Anne Green.** Yes we would get the significant fat oxidation disorders like MCAD, but *you wouldn't pick up on all the Reye-like IMDs, in particular OTC deficiency.*

\*\*\*\*\*

### ***1.3.2 (a) What was the Incidence of RS in these islands in 2001?***

#### ***DR SUE HALL***

The Table shows the findings of the British Reye's Syndrome Surveillance Scheme. As the BPSU scheme ended in April 2001, we do not know the incidence in 2001/2. However, no death entries have been received to date since clinical reporting ceased. The numbers of reported cases have declined dramatically since 1986, and the numbers of what we might call "classic" Reye can be counted on the fingers of one hand over the last five or six years.

### ***1.3.2 (b) Is it Likely to Change?***

The following is speculative; I could find no relevant publication.

The incidence could change if:

(a) There is another large influenza epidemic/ pandemic. The last one was in 1977; another was narrowly averted in 1997 when the avian strain H1N5 spread to humans and the entire chicken flock in the vicinity of Hong Kong was slaughtered. It has been observed by Hatta et al<sup>1</sup> that live bird markets in Southern China provide an ideal arena of exchange of genetic material between Influenza A viruses: 'it appears inevitable that novel strains of influenza will continue to emerge and possibly threaten human health'.

(b) In the setting of such an epidemic, warnings about aspirin are forgotten or not heeded.

(c) By contrast, effective immunisation to prevent varicella and influenza would reduce the incidence of RS even further.

Professor Leonard said earlier that his juniors would think he was from another planet if he used the word Reye's syndrome. I understand his reasoning but it's risky in a way to think like that because, as we've seen with diseases like TB and diphtheria, if you think that the conditions have gone away - stop talking about them, stop teaching them, then among people who have never seen them, never heard about them, diagnostic awareness obviously will be low and diagnoses are made too late. I agree that classic RS is extremely uncommon at the moment, but it could resurge if we had a big influenza pandemic (and all the influenza pundits keep on saying this is just around the corner). If, in the setting of an epidemic like that, warnings about aspirin are forgotten or not heeded, or indeed if it is taken by teenagers or young adults then cases will occur and may not be recognised. I think adult physicians may be even less likely to recognise Reye because they possibly perceive it as solely a childhood disorder. I suspect that teenage cases are more likely to be admitted to an adult intensive care unit rather than paediatric.

In the context of prevention of RS it is interesting that, in the United States, one of the indications for routine 'flu immunisation (which is not the case in the UK) is for children on long term aspirin therapy,

**Reference** 1. Hatta M et al. Science 2001; 293: 1840-1842



# **Reye's Syndrome Surveillance in the UK and Ireland 1981/82 - 2000/01†**

Reporting period (August-July)	Total reports from the British Isles	Revised diagnosis (inherited metabolic disorder in brackets)	*Cases of Reye's Syndrome	Number of deaths (of cases)
1981/82	47	7 (3)	40	26
1982/83	69	10 (6)	59	34
1983/84	93	12 (3)	81	36
1984/85	64	8 (2)	56	32
1985/86	53 <sup>1</sup>	13 (4)	39	22
1986/87	47	21 (11)	26	13
1987/88	44	12 (3)	32	19
1988/89	31	13 (6)	18	9
1989/90	24 <sup>1</sup>	8 (5)	15	7
1990/91	25	13 (8)	12	5
1991/92	23 <sup>2</sup>	6 (5)	15	6
1992/93	21 <sup>3</sup>	10 (6)	5	4
1993/94	20 <sup>4</sup>	13 (7)	3	3
1994/95	17 <sup>2</sup>	3 (2)	12	3
1995/96	18 <sup>1</sup>	2 (1)	15	7
1996/97	7	2 (2)	5	4
1997/98	11	4 (2)	7	5
1998/99	11	4 (3)	7	2
1999/00	4	1(1)	3	2
2000/01†	3 <sup>1</sup>	2(1)	0	0
TOTAL	632	164 (81)	450	239

**NOTES TO TABLE** \* Compatible with the diagnosis - see text † to April 01 (provisional data) 1. Follow-up not received for one case 2 Follow-up not received for two cases 3 Follow-up not received for five cases and one case did not meet the case definition 4 Follow-up not received for four cases NOTE: NUMBERS MAY DIFFER FROM PREVIOUS VERSIONS OF THIS TABLE BECAUSE OF LATE ASCERTAINMENT OF CASES AND OF REVISED DIAGNOSES

## **DISCUSSION**

**Dr MacFaul.** And that's an important message isn't it, for the output of this Workshop. I think that clinicians who are treating patients with aspirin for one reason or another wouldn't necessarily have thought about that, so it's a useful practical point.

**Dr Boon.** Is there a potential interaction between the flu vaccine and aspirin?

**Dr Hall.** Well it is a live virus vaccine so I suppose the potential is there, but I've never in all my reading of the Reye literature come across a reported case in a child taking aspirin in association with feeling unwell after 'flu vaccine.

**Dr MacFaul.** I think one of the vaccine methods will be intranasal heat labile vaccine so that it may give a surface immunity and thereby avoid the problem, but it would be interesting to hear an immunologist's views.

**Dr Kirkham.** I have quite a lot of children who have had strokes, on prophylactic low dose aspirin, 1mg per kilogram, and in fact my European colleagues use up to 5 mg per kilogram. It does worry me that the Reye's surveillance has finished although neither I nor my colleagues have ever seen Reye's in association with low dose aspirin. I personally do give them 'flu vaccinations but I can't get varicella vaccine easily at the moment to give to my patients and it does worry me.

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**Question 1.3.2. ii. What are the morbidity and mortality rates of classic RS if it is untreated or treated late? What is the nature of the morbidity?**  
**Is there evidence that early diagnosis of classic RS and appropriate management reduce or prevent morbidity (including parental psychological morbidity) and mortality?**

**DR JOHN GLASGOW**

**Preliminary comments:**

*Precision is needed about the terms RS, classic RS, and Reye-like syndrome.*

- Some of the clinical/ laboratory features of RS can be caused by a variety of disorders – some metabolic, some toxic, others infective. However the term RS should not in my view be applied “willy nilly” to all encephalopathies coming within these categories as some have erroneously attempted.
- Classic RS is I believe strongly associated with the use of aspirin given during the viral prodrome in an individual predisposed in some subtle fashion perhaps along the lines recently suggested by us in an *Archives* annotation.
- RS in the UK differs in some important respects from that in the US, but I believe the classic form (aspirin associated) shows more similarities than differences.
- There can be a fine line between the classic disorder and numerous forms of R-LS, although with proper investigation a distinction can usually be drawn.
- This is the more pressing where there is a first-degree family history, a repetitive history of episodes, aspirin was not used or there are features atypical of classic RS.
- I am not necessarily convinced that age is an important factor in pointing to IMD as so many of our patients were very young (median age 0.75 yr); the majority (46/ 56) had received aspirin [unpublished data].
- We have thoroughly investigated 40 (median age at diagnosis 1.0 yr) of 56 RS patients seen 1979-86 (and 10 sibs of 7 who died), and all of the five RS patients treated after 1986. We have been unable to identify any IMDs (as yet - though we still have our suspicions). Between 1986-1996, quite apart from IMD cases revealed via neonatal screening, 15 *index cases* of IMDs who presented with encephalopathy (R-LS) were recognised, eight of whom had beta-oxidation defects - six with MCADD (unpublished data). The methods used to investigate the RS patients will be outlined if required. None has had a recurrence of RS in a period of 16 – 22 years.
- As far as outcome in RS is concerned, factors that we have shown to be significant are as follows

(numbers are bracketed) – Maximum Lovejoy stage reached (56) (Table1), and maintenance of a cerebral perfusion pressure (CPP) > 40 mm Hg (39) (Jenkins, J.G., Glasgow, J.F.T., Black, G.W., Fannin, T.F., Hicks, E.M. and Keilty, S.R. (1987) Reye's syndrome: assessment of intracranial monitoring. *British Medical Journal* 294, 337-338). Using discriminant function analysis, we have shown that the presence or absence of early seizures in RS predicted outcome in 88% of 48 patients (Glasgow, J.F.T., Jenkins, J.G., Hicks, E.M., Keilty, S.R., Crean, P.M., Black, G.W. and Fannin, T.F. (1986) The prognosis for Reye's syndrome in Ireland can be improved. *Irish Journal of Medical Science* 155, 111-116).

- Patients in Lovejoy stage IV (deeply unconscious) had a significantly shorter mean interval between the prodrome and the neurological phase compared to those in stage I (2.2 v 5.5 days), a higher mean respiratory rate, and higher mean blood ammonia and urea levels (unpublished data).
- It is important in both the classic form and the R-LS to investigate the child rigorously to exclude an IMD.

**Table 1 CLINICAL STAGING BELFAST PATIENTS (Mod. Lovejoy)**

Stage	No of Patients	Full Recovery	%
1	6	6	100
2	18	16	89
3	22	16	73
4	10	3	33
Total	56	41	

The Table might imply that patients are admitted in stage 1, progress to stage 2, and so on. Experience is otherwise - patients appear, having become rapidly unconscious or abruptly develop seizures; the presence of seizures makes the assessment of the Lovejoy stage more difficult, an area that will be alluded to by others (see FK).

## The organisers ask a series of pertinent questions

### 1.3.2. ii) Morbidity and mortality rates if untreated or treated late

*What are the figures and what is the nature of the morbidity?*

In the national BRSSS/ BPSU series to which a total of 632 cases were reported between 01:08:81 – 30:04:01 (full year not completed), 239 died - a mortality rate of 38%; if however, the revised diagnoses (12% IMD) are excluded, mortality is 53% - not surprisingly as survival facilitates further diagnostic study. Approximately half of the mortality occurred during the days of the BRSSS passive-reporting scheme during which mortality (based on deaths/ true cases) was 44%. Under the BPSU from the summer of 1986, there were 119 deaths/ 175 a rate of 68%. In the last 10 years of reporting, mortality was 50%. This would tend to confirm that “we have a problem”.

Over a similar time period in the US using the CDC passive- surveillance system 1<sup>st</sup> Dec 1981 – 30<sup>th</sup> Nov 1997, Belay and colleagues reviewed 1,207 cases among which fatality rate was 31% (Belay, E.D., Bresee, J.S., Holman, R.C., Khan, A.S., Shahriari, A. and Schonberger, L.B. (1999) Reye’s syndrome in the United States from 1981 through 1997. *New England Journal of Medicine* **340**, 1377-1382); complete recovery was 62% in 1,134 patients with RS whose outcomes were known. After logistic regression, mortality was shown to be highest in those < 5 years of age, and in those with a serum ammonia level > 26µmol/ l (P < 0.01). John Partin and others quoted a mortality figure in 1970 of about 70% reducing to one of about 30% in 1986 (Partin, J.C. (1988) General management of Reye’s Syndrome. In Wood, C., (Ed.) *Reye’s syndrome* pp. 156-172. London: Royal Society of Medicine).

In our series of 56 patients seen in 1979-1986, overall mortality was eight cases, or 14% (18% if five further patients seen after 1986, three of whom died, are included). The majority died of brain herniation secondary to uncontrolled/ uncontrollable raised ICP (see below); one developed ARDS and died after a period of prolonged ventilation probably secondary to profound initial hypoxia (Table 1). Partin is not alone in commenting that “there is no truly successful treatment of the comatose case” (Partin, J.C. (1988) General management of Reye’s Syndrome. In Wood, C., (Ed.) *Reye’s syndrome* pp. 156-172. London: Royal Society of Medicine).

Residual neurological complications were present in the CDC series in almost 10%; these were said to be mild in 7%, and severe in almost 3%. Again those with the higher ammonia had a significantly greater risk compared to those with the lower levels (11% v 2.5%). In our series, nine patients are so affected, most with significant permanent neurological disabilities. We have taken the question a step further in those who recovered completely and are attending normal school. Two sibling-controlled studies have been published addressing *first*, intelligence and academic performance, and six years later a *second* on cognitive, emotional and behavioural sequelae. In each study, the two risk factors that appear to significantly influence performance are a) encephalopathy developing in infancy and b) presence of unconsciousness (ie Lovejoy stage III or beyond; see below); factor a) appeared to exert a stronger influence than factor b). Shaywitz and colleagues (Shaywitz SE, Cohen PM, Cohen DJ, Mikkelsen e, Morowitz G, Shaywitz BA. (1982) Long term consequences of Reye's Syndrome. *J. Pediatrics* **100**: 41-46.) attempted a similar study, but were unable to show differences for any of the subtests used.

#### **Psychiatric/ Psychological morbidity**

Psychiatric morbidity was apparent in significantly more of the Shaywitz RS patients compared to controls. These were of two types, a hyperactivity attention deficit disorder or an anxiety reaction apparently generated by the illness. Psychiatric rating (NIMH Children's Psychiatric Rating Scale) seemed to correlate with RS severity as judged by the total dose of mannitol administered. Behaviour after the illness was quite stereotyped with much irritability, and crying; behaviour was described as inattentive, distractible, and impulsive. Most then gradually improved over the next 18 months, although parents did not yet consider them to have returned to normal.

The psychiatric/ psychological consequences of such a life-threatening illness in one child in the family were evident in the parents' perceptions of their "ill child" and the effect of such on the family unit. Increased anxiety frequently emerged often in response to a minor illness. Underlying personality traits were accentuated at least during the acute stages. There was great concern regarding previous speech/ language problems, and the effect of RS on academic performance was always a considerable concern. Sibling jealousy became apparent. There was a variable effect upon family unity/ harmony; this largely depended on the dynamics prior to the RS.

Interestingly, the authors found an unusually large number of children who had experienced a

significant life event within the month *before* development of the encephalopathy. The authors speculate that this unexpected combination of finding may have come about because of an interplay of many neural systems but particularly the brain monoaminergic systems that might play an important role in both life stress events and in the development of the encephalopathic process. Several lines of research seem to support this rather curious interpretation.

Parental and sibling psychological morbidity can be long lasting, and affect all aspects of personal and family life. My source here is not one related specifically to neurological disability or the RS/IMD but to children with cystic fibrosis. The author to whom I make reference is Dr Lindy Burton who was at one time a member of the Dept of Child Health at our University. She conducted a prospective questionnaire study of children and their carers with chronic disability and/ or life-limiting illness over a number of years that resulted in the publication of the book – *The Family Life of Sick Children* (1975); she has also edited the multi-author work – *Care of the Child Facing Death* (1974). The former would richly repay those interested in family morbidity and coping strategies, addressing such issues as - coping with an inherited disease; talking about the disease; changing hopes and expectations for the sick child; brothers and sisters of a sick child; the loss of a child; learning to live with a chronic disease. Each is published by Routledge & Kegan Paul.

## **DISCUSSION**

**Dr MacFaul.** We are dealing with this in more detail later, but do you think that there *is* evidence that early diagnosis reduces or prevents morbidity?

**Dr Glasgow.** I will quote John Partin, from the RSM Round Table Conference on RS in 1986, when he said he has not convincingly been able to show that early treatment prevents brain damage or death in the *deeply unconscious* patient, and that was after managing something like 230 -250 patients over almost two decades a huge experience.

However, I believe early diagnosis of *conscious* patients can prevent morbidity and mortality, but I also believe we've first got to get people to think of this group of diagnoses and that is a big educational challenge for us.

**Dr Dalton.** The main point is that what we are talking about is recognition of hypoglycaemia and hyperammonaemia and there is no doubt that if you diagnose those early, the outcome will be better.

**Dr Glasgow.** Agreed, but with the rider that Daryl Devivo, John Partin and all the celebrated North American "Reyeologists", make - that if you are *unconscious* as a result of these metabolic disturbances, that is a huge challenge and there is no certainty what the outcome will be. So the important thing is to try to establish the diagnosis before the patients become unconscious if at all possible, and enter the three pronged therapeutic attack that we will come onto tomorrow, which has to do with correction of blood glucose and control of intracranial pressure.

**Dr MacFaul - summing up this session.** We have been over a number of questions. Can we identify clearly what Reye's syndrome is - I think we've heard that if we are good *clinicians*, we can certainly pick out the acute encephalopathies and manage those; if they have a metabolic disorder we could identify those probably better with more education. I think we have agreed that Reye's-like inherited metabolic diseases presenting as Reye's syndrome are underdiagnosed. As far as the question of classic Reye's syndrome is concerned the discussions seem to me to hover here. So I think we would have to say there that we are not clear whether classic Reye's syndrome is over or under identified, I think it probably depends, from what we've heard, upon investigation practice and the background epidemiology of classic RS.

We've heard that, as far as the living patients are concerned, cases probably are being missed or diagnosed late, and as far as the children who have died are concerned they may be being missed, underdiagnosed or, possibly more frequently, overdiagnosed because of the frequency of fatty liver. Perhaps this point about the fat being in other tissues is very important. No doubt tomorrow when you come on to how you properly do an autopsy you may consider there is far too much retrograde thinking that an autopsy is what a pathologist does with a body rather than with looking at the over all clinical picture, the history, the samples *and* the autopsy -all have to come into the equation.

James Leonard has given us an over view of the frequency of the IMDs and it seems that for most the birth prevalence is uncertain, but what is more clear is their contribution to deaths and to metabolic presentations.

We've heard there is a need to be very precise if we can about the diagnosis of Reye's syndrome, as opposed to no diagnosis at all, in relation to sudden infant death. The baby may have died but there



are siblings that may be rescued, and there may be need for genetic advice to the families who may then choose not to have additional children.

I think we concluded that for many inherited metabolic diseases it is possible to reduce the mortality and to reduce the morbidity which is good news. We are all agreed that we should be screening for MCADD. We have heard that the incidence of classic Reye's syndrome is falling but if we do encounter an influenza outbreak then it might rise again. There may be ways of preventing Reye's syndrome in people on chronic aspirin therapy, which is an important point.

We have also agreed that tandem mass spectrometry screening will not eliminate the need for diagnosis, for other groups at this stage anyway, of inherited metabolic disease. I think finally what we have agreed is that we need to define Reye's syndrome more clearly against inherited metabolic diseases, and I think that probably tomorrow you will finalise what all this is about in terms of what are the investigation requirements clearly to identify an inherited metabolic disease in terms of the acute presentation clinically, and the appropriate investigations at the time and for those babies and children that die suddenly are similar catechism of investigations and processes to go through.

When it is a case of classic Reye's syndrome John Glasgow has, I think, convinced us that early diagnosis and better management will improve outcome, providing the patient is still conscious on admission.

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## WORKSHOP PROCEEDINGS: PART 2

Assuming that there is a problem and that early diagnosis of Reye's syndrome and Reye-like inherited metabolic disorders would contribute to a reduction in early childhood morbidity and mortality and in parental distress (see Proceedings Part 1), how can this be achieved?

This section will deal with infants and children who present during life and will address the problem of detecting the Reye/IMD "needle" in the "haystack" of ill infants and children attending Accident and Emergency.

### CLINICAL DIAGNOSIS: POINTERS IN THE HISTORY

#### 2.1.1 IMDs

*Questions 2.1.1. a-f What is the age - range, mean and median at first presentation for each IMD?; is there a seasonal distribution of acute presentation?; what proportion have a significant family and/or past medical history, what are the features of these?; what pre and peri-admission features have been reported in case series? any other useful diagnostic pointers?; do these features vary for each group of IMDs?*

**Dr JOHN WALTER**

The Table below includes only fat oxidation defects, so I want to say a bit more about the other disorders that are being discussed as possible conditions that have Reye like features. I suppose that really *any* of the metabolic disorders that presents as an encephalopathy can be included.

Generally, in terms of the *age of presentation*, most severe inborn errors of metabolism that present with a Reye's like illness, would present in the newborn period, and it's only their mild variants that actually present later. For example, **propionic acidaemia** and **methylmalonic acidaemia** - experience is that those disorders mostly present in the newborn period with either severe encephalopathy or severe acidosis, often with hyperammonaemia. But they do also have late onset variants, where there is usually some residual enzyme and these can present at *any* age, but they usually are associated with a clinical history of developmental problems or some other form of illness.

In **ornithine transcarbamylase deficiency** (the urea cycle defect) the milder variants, particularly in females, *can present for the first time at any age* and there are reports in the literature of women presenting with hyperammonaemia for the first time for example after childbirth. So I think that needs to be borne in mind.

There are other conditions that characteristically present after the newborn period - **MCADD** presents usually towards the end of the first year of life or just after, and also following an intercurrent infection, and those children can of course be perfectly normal beforehand. **Glutaric aciduria type 1** can also present towards the second half of the first year of life for the first time with encephalopathy. We have also had children with **fructosaemia** who have been misdiagnosed as having a fat oxidation defect; that is a condition that can present later because obviously it doesn't present before weaning but can manifest at any age after that.

**Turning to the Table**, many of the fat oxidation defects are less well defined in terms of age at presentation because they've been recognised for a relatively short period of time. MCADD has been the most studied and the median age at presentation in one series was eighteen months with a range of six weeks to ten years. We also know that that they can present in the newborn period and may even manifest for the first time in adult life or remain asymptomatic.

For long chain defects - first, LCHAD deficiency, in one series the mean age was 5.8 months at presentation with a range of one day to 26 months. In that series seven of 50 cases, 15 percent, presented in the newborn period. It is difficult to find reliable data on mean and median ages at presentation for some of these disorders. For very long chain acyl-CoA dehydrogenase deficiency the majority present in the first four months of life and half of those are in the newborn period.

For carnitine transporter defects - fifty percent manifested between three months to two and a half years, and fifty percent between one and seven years in a number of series. CPT1 deficiency presented from eight to eighteen months (one of the cases presented as a newborn in the series that I referred to); carnitine acyl-carnitine translocase deficiency presents mainly in the new born period, 15 of 18 in one series; and for CPT2 deficiency, the severe infantile form nearly always presents in the newborn period.

*So with a few exceptions such as MCADD and GAI and some mild forms of OTC, the vast majority of these disorders present in the early months of life.*

I couldn't find any literature on *seasonal distribution*. These disorders are often precipitated by intercurrent infections, so if viral infections are more prevalent in the winter months then a winter peak in presentation for these disorders might be expected. However, this is not something that I have noticed in clinical practice.

In terms of the *past medical history* - as I have already mentioned, for the majority of inborn errors, even those with late presentations, if you go through history reasonably carefully you will find evidence of developmental delay or some illness episodes which have been unexplained.

What proportions have a *significant family history*? Most of these disorders are autosomal recessive conditions and therefore there is sometimes a family history but, as with many autosomal recessive disorders, there may not be.

*Pre- and peri- admission clinical features*: these very much depend on the condition and they all have different phenotypes. In the Table there is some information on the presentation of the different fat oxidation defects. For ornithine transcarbamylase deficiency, where there is marked hyperammonaemia, the main form of presentation is encephalopathy.

## TABLE FOLLOWS

**TABLE**

Enzyme	Age @ presentation	Age @ diagnosis	Mortality and age @ death	Presentation	Diagnosis	Remarks & references
<b>MCAD</b>	6wks-10yr	Median 18m (6w-10.5y)	20-25% (usual -ly at first presentation)	HH*	Acyl carnitines	[4]
<b>LCHAD</b>	Mean:5.8m (1d-26m); 7/50 (15%) in neonatal period		38%, all dying before or within 3m after diagnosis	78% HH; 22% chronic (failure to thrive, feeding difficulties, cholestatic liver disease, and/or hypotonia), Maternal HELLP/FLP	Acyl – carnitines	High morbidity even with treatment [1]
<b>VLCAD</b>	Majority in first 4 months ½ in newborn period		50%  mean age 3m	HH ( with cardiomyopathy in severe neonatal form);isolated rhabdomyolysis (adult milder form)	↑long C14-C18 acylcarnitines; low total carnitine	[3]
<b>CT</b>	50% 3m-2.5y 50% 1-7y			Early onset HH Later onset cardiomyopathy	v.low plasma carnitine	[Scriver]
<b>CPT I</b>	8-18m (1 newborn)			HH, encephalopathy	High or normal plasma carnitine, no Dicarboxylic-aciduria	Hepatic and muscle forms
<b>CAT</b>	Newborn (15/18)		73% (16/22); median 5 1/2m (2d – 3y)	HH in newborn period; liver failure; cardiomyopathy	↑ long chain acylcarnitines; low total carnitine	22 patients in literature. [2]
<b>CPTII</b>	Muscle form: 15-30 years severe infantile: newborn			Episodic myoglobinuria; severe infantile: coma, seizures, HH cardiomyopathy	Acyl carnitines No dicarboxylic aciduria	[Scriver]

\*HH = hypoketotic hypoglycaemia

## References

1. den Boer, M. E., Wanders, R. J., Morris, A. A., Ijlst, L., Heymans, H. S., & Wijburg, F. A. (2002) Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: clinical presentation and follow-up of 50 patients. *Pediatrics*, 109: 99-104.
2. Lopriore, E., Gemke, R. J., Verhoeven, N.M., Jakobs, C., Wanders, R. J., Roeleveld-Versteeg, A. B., & Poll-The BT (2001). Carnitine-acylcarnitine translocase deficiency: phenotype, residual enzyme activity and outcome. *Eur.J.Pediatr.* 160: 101-104.
3. Pons, R., Cavadini, P., Baratta, S., Invernizzi, F., Lamantea, E., Garavaglia, B., & Taroni, F. (2000). Clinical and molecular heterogeneity in very-long-chain acyl-coenzyme A dehydrogenase deficiency. *Pediatr.Neurol.* 22: 98-105.
4. Wilson, C. J., Champion, M. P., Collins, J. E., Clayton, P. T., & Leonard, J. V. (1999) Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. *Arch Dis Child*, 80: 459-462.

## DISCUSSION

**Dr MacFaul.** Regarding the significance of vomiting, is "periodic syndrome" a particular premonitory warning symptom cluster?

**Dr Walter.** I think vomiting is such a non-specific symptom I wouldn't say it was a particularly helpful diagnostic feature especially in the newborns and young infants.

**Professor Leonard.** I've seen quite a number of these query cyclical vomiting, query metabolic disease patients over the years and there are two points which I think help us sort them out. Firstly, the history - in true cyclical vomiting the episodes are quite stupendously stereotyped - they are almost identical every time; and secondly you need to have a standard strategy to get investigations like ammonia, amino acids and organic acids done *when the child is unwell* and then you can exclude virtually all inborn errors.

Can I also just make a point about family history. We've recently had a very good example where someone took what they *thought* was a family history and it didn't look relevant at all. But when someone more experienced took it properly, they discovered the most wonderful sort of "spaghetti-like" family history, with inter-breeding, and it was quite clear that a distant second cousin who had maple syrup urine disease was highly relevant to the case referred. We could have made the diagnosis a lot earlier if somebody had taken a proper history. I think the family history taking often

tends to be - "is your mum ok, is your dad ok, are you first cousins," and that's it. It actually needs to be done *much* more carefully.

**Dr Walter.** That's true, but nevertheless the majority of the children who we see who first presented have *not* had relevant family histories, even with recessive disorders.

**Dr Hall.** Regarding the case I presented earlier, should the fact that there was a history of a sudden death in a first cousin age nine months have been a diagnostic pointer?

**Dr Walter.** It depends on the consanguinity within the family. If there's no consanguinity a cousin dying is probably not relevant, but if there is multiple consanguinity it may be highly relevant.

**Professor Leonard.** I would agree completely. One or two extra questions may settle this very quickly, especially important if the family is from an ethnic minority or are travellers.

**Dr Neil Dalton.** Regarding OTC deficiency the inheritance is X-linked and often there is a good family history that is helpful.

**Dr John Glasgow.** I just wanted to emphasise the point about young age in the presentation of these IMDs. When you look at the review by Saudubray in 1999 of 107 patients with fat oxidation defects - 30 percent, thirty four cases, were diagnosed before one month of age and over sixty percent, were less than one year of age.

**Dr MacFaul.** Regarding peri-admission clinical features - do we gather there's nothing particularly specific here which is a useful diagnostic pointer?

**Dr Walter.** Well there are some features - for example in maple syrup urine disease there may be just ketosis and no hyperammonaemia or significant metabolic acidosis. So if you are experienced in looking at these conditions there may be features that point you to a specific disorder. But that's not particularly relevant to general paediatricians first seeing these children. I think what one needs to have is a sort of "tick list" of investigations that you need to do for *all* children with unexplained encephalopathy and unexplained hypoglycaemia.

**Professor Stephenson.** I agree. The basic objective of this Workshop is to optimise the diagnosis and management of Reye-like childhood encephalopathy. To do this the solution is to optimise the management of *all* children presenting with vomiting and encephalopathy and out of that will come the recognition of the small number of cases of Reye like syndrome. To go for an educational package targeted exclusively at diagnosing IMDs is targeting the needle when it's still buried in the haystack. I think what we want to think about is to optimise the management of children presenting to A&E acutely unwell.

**Dr MacFaul.** That is an important point - how do you recognise the child that is "a bit off it", and about to become seriously ill.

**Dr Glasgow.** Yes- the child that is just slightly out of touch with reality.

#### **2.1.2 CLASSIC RS:**

***a) What is the age -range, mean and median, at first presentation?***

***b) What is the seasonal distribution?***

***c) What proportion has a significant family and/or past medical history? What are the features of these?***

***d) What pre and peri-admission features have been reported in case series?***

***e) Any other useful diagnostic pointers?***

***f) Should a positive or negative history of aspirin exposure influence the diagnostic likelihood?***

#### **PROFESSOR STUART TANNER**

**a) and b).** In the early years of the American survey, 1977 – 1980, a winter peak of incidence was seen in February and years with high influenza activity had high Reye's syndrome incidence<sup>1</sup>. The years 1977 and 1980, years of influenza B outbreaks, showed incidences of 0.71 and 0.88 cases per 100,000 children aged under 18. The mean age of cases was 8 – 9 years. By contrast, the first year of the British study, 1981, showed a lower incidence, 0.21 cases per 100,000 children aged under 16, a much lower mean age (3 years 10 months), no winter peak and a higher case fatality rate (59 per

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<sup>1</sup> Barrett, M.J., Hurwitz, E.S., Schonberger, L.B. and Rogers, M.F. 1986, Changing epidemiology of Reye syndrome in the United States. *Pediatrics*, **77**: 598–602



cent compared with 28 per cent)<sup>2</sup>.

	US 1977-80	UK 1981
Incidence/100K	0.71-0.88	0.21
Winter peak	yes	no
Related to flu, VCZ	yes	no
Mean age	8-9 years	3 years 10 months
Case fatality	28%	59%

c) A significant familial and/or past history obviously increases the chance that the child has an IMD.

However, if classic RS represents a genetic susceptibility to aspirin then familial or recurrent classic RS is possible. So, in my opinion, the answer is "yes".

d) An antecedent illness (influenza B, influenza A, varicella or putative viral gastroenteritis or respiratory infection). This illness is often mild. Its severity bears no relation to the risk of developing RS. Following recovery vomiting occurs followed by changes in neurological status. This may initially be subtle (irritability, being withdrawn) then "combative", and then followed by change in conscious level. Tachypnoea was reported in some series.

e) Raised CK was reported to correlate with severity.

f) Nowadays a history of aspirin exposure is so unusual that no clinician will ignore it.

#### **ADDITIONAL POINTS MADE IN ORAL PRESENTATION**

##### **Professor Tanner**

I wonder if we might agree that Reye's syndrome does not exist. It was a useful concept just like Bright's disease, or Ellis Type 1 nephritis, or Pott's disease of the spine, or lupoid hepatitis, or Pink disease. Those were good concepts in their time, but they don't exist now. What *do* exist now of course, are the young children who present with metabolic disease (and they should never be called Reye-like). There *used* to exist an entity that wasn't diagnosed as a metabolic disease and had some clinical and epidemiological features which are *different* from MCADD. But we don't see it anymore, probably because of the warnings about aspirin. If Dr Hall's nightmare scenario occurs and we have a big 'flu epidemic and see vomiting, encephalopathy and hepatic disturbance in aspirin treated patients, we will say that's like Reye's used to be - but we will find out what is actually the cause of it, and we'll come to a biochemical or cellular explanation.

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<sup>2</sup> Hall, S.M. and Bellman, M.H. 1985, Reye's syndrome in the British Isles. *In*: J.D. Pollack (ed) *Reye's Syndrome*, Vol. IV, pp 32-46 Bryan, Ohio: National Reye's Syndrome Foundation

So what I am reviewing is - what *were* the features of what *used* to be post varicella or post 'flu B or 'flu A encephalopathy and hepatic disturbance. The Table shows an incidence in the late 1970s/early 80s of what was then called Reye's syndrome that was much higher in the United States than the UK, and a *very* striking year on year February peak in the US, not seen in this country.

I think there was a temptation, because RS was known to be associated with varicella, to particularly look for it in these patients. I've already quoted the New Mexico study, which showed an incidence of varicella-associated RS of 2.5 per 100,000. In that series there was a certain clinical stereotypy. They had uncomplicated chickenpox, then began to feel better but then began to vomit. Vomiting was the crucial clinical feature to pick up on, followed by the neurological features which were initially very subtle - combativeness, irritability, change of mood, and then going on to loss of consciousness.

Does a significant familial and/or past history increase the chance/obviate the diagnosis of Reye's? If we are saying that RS may be an as yet uncharacterised biochemical susceptibility to aspirin in the context of an infection, then that *might* be familial. So I suppose the answer would be that a suggestive family or past history should *not* stop us making the diagnosis in the influenza pandemic scenario.

## **DISCUSSION**

**Dr Hall.** We interviewed over 100 families of children with Reye's syndrome during the course of our risk factor study, and one thing that emerged about the vomiting, described almost universally by the parents, was that it was completely effortless. They typically said it just "flowed out" of the child and was perceived by them as different from the heaving vomiting that they had seen before in previous uncomplicated episodes of gastroenteritis. I know effortlessness is said to be typical of the vomiting associated with raised intracranial pressure and I think it is a useful diagnostic point in the history, both for the GP and the A&E clinician.

**Dr MacFaul.** For those of us in the intensive care field - are we seeing the same numbers cases of acute encephalopathy that, in the past, might have been thought to be classic Reye's which actually we now investigate and find are something else?

**Dr Tasker.** I think we do now have a different mind set - I think most people are more inclined to

think, number one, of metabolic disorders rather than entertain a diagnosis of Reye's syndrome. We do not have large enough numbers to see whether there has been a decrease -my impression is that we still get a very small number of children - I've estimated it's something like 1 in 300 critically ill children, that have a metabolic encephalopathy, putting a number of studies together to try and get a ball park figure.

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## **2.2 Recognition of encephalopathy.**

### ***What is encephalopathy and how common is it?***

**DR FENELLA KIRKHAM**

Encephalopathy describes a change in the patient's interaction with his environment, usually reduction in consciousness or abnormal behaviour, with or without focal neurological symptoms and signs.

A recent epidemiological study in Northern region quoted an incidence of non-traumatic coma of 30.8 per 100,000 children under 16 per year, of which 6% were secondary to a metabolic disorder. The incidence is much higher in children < 1 year (160 per 100,000 infants).

Wong CP, Forsyth RJ, Kelly TP, Eyre JA. Incidence, aetiology, and outcome of non-traumatic coma: a population based study. Arch Dis Child. 2001 Mar;84(3):193-9.

**2.2.1 A clinical definition of encephalopathy is important because there may potentially be difficulty in deciding whether the patient has "drowsiness" from other causes or "encephalopathy"**

**a) How is encephalopathy defined clinically? Does it depend on age: neonate-teenager?**

**Methodology:** review of literature under search terms coma or Glasgow coma scale (in collaboration with William Whitehouse)

The British Paediatric Neurology Association and the National Paediatric Neuroscience Benchmarking Group have recently recommended the modified paediatric Glasgow coma scales (modified from James and Trauner 1985) (Child's Glasgow Coma Scale) for use in the United Kingdom (Table below).

### **Child's Glasgow Coma Scale**

*Pain* should be made by pressing hard on the supra-orbital notch (beneath medial end of eyebrow) with your thumb, except for Motor 4, which is tested by pressing hard on the flat finger nail surface with the barrel of a pencil. Toe-nail pressure is likely to elicit spinal withdrawal, especially after 1 or more day's coma.

Score the best response if unclear or asymmetrical. If in doubt repeat after 5 minutes and ask for help.

Score as usual in the presence of possibly sedating drugs. Plot scores over time on a suitable chart.

**TABLE FOLLOWS**

**TABLE: Child's Glasgow Coma Scale**

	<b>&gt;5 Years</b>	<b>&lt;5 Years</b>
<b><i>Eye opening</i></b>		
4		- Spontaneous -
3		- To voice -
2		- To pain -
1		- None -
<b><i>Verbal</i></b>		
5	Oriented	Alert, babbles, coos, words or sentences – normal for age
4	Confused	Less than usual ability, irritable cry
3	Inappropriate words	Cries to pain
2	Incomprehensible words	Moans to pain
1		- No response to pain-
<b><i>Motor</i></b>		
6	Obeys commands	Normal spontaneous movements
5	Localises to supraorbital pain (>9m)	Withdraws to touch
4		- Withdraws from nailbed pain -
3		- Flexion to supraorbital pain -
2		- Extension to supraorbital pain -
1		- No response to supraorbital pain -

The criteria for a useful coma scale are that it should be easily administered, consistent between observers and sufficiently discriminating to identify levels of coma requiring specific interventions. The ideal scale is one that is sensitive enough to pick up important clinical changes, but with sufficiently clear cut categories for most trained observers to be able to agree on the condition of an individual patient. Most scales have also been used in attempts to predict outcome, although this may be a less realistic goal, as interventions used in intensive care may interfere with the accurate assessment of depth of coma at the time points that are discriminatory, and may alter outcome.

In adults, the Glasgow coma scale (Table I) (Teasdale and Jennett 1974, Jennett and Teasdale 1977) has been widely accepted as fulfilling the above requirements (Langfitt 1978). It is the most widely quoted in published series of head injury (Starmark et al. 1988a) and has been used in non-traumatic coma (Teasdale et al. 1983, Sacco et al. 1990). There is, however, a disquieting lack of consistency in reporting (Starmark et al. 1988a). Alternative scales have been advocated for different aetiological groups, for attempting to predict outcome or for improved reliability in collaborative research. The Glasgow scale

does not necessarily compare favourably with the alternatives in terms of the assessment of depth of coma, inter-observer reliability or test-retest variation (Sugiura et al. 1983, Stanczak et al. 1984, Starmark et al. 1988a,b). Many authors have summed the three parts of the Glasgow scale for research purposes, but values in the middle of the range of scores may represent rather different clinical pictures (Sugiura et al. 1983, Starmark et al. 1988b). Therefore, particularly in clinical use, it is always important to quote the eye-opening, verbal and motor scores separately (Teasdale et al. 1979, Teasdale et al. 1983). Most of the problems in recording depth of coma on the Glasgow scale occur in intubated patients or those with severe eyelid swelling, for whom pseudo-scoring systems have evolved (Choi et al. 1983, Marshall et al. 1983), which may underestimate the level of consciousness. Alternative scales e.g. the reaction level scale may actually cover the full range of possibilities more comprehensively (Starmark et al. 1988b), but none have usurped the place of the Glasgow scale either in clinical practice or for research.

The AVPU rapid measure of conscious level is useful for immediate emergency assessment, e.g. by nursing, medical or paramedical staff at the scene of an accident or collapse or in the Resuscitation Room of an Emergency Department as the D part of the “primary assessment”: A airway; B breathing, C circulation, D disability (conscious level / mental status, pupils, posture). Responsiveness is recorded as A Alert; V responds to Voice; P responds to Pain; U Unresponsive. In many countries it is taught as an easily remembered scale e.g. in the Advanced Paediatric Life Support course (Advanced Life Support Group, 2001a). However the Glasgow scale is still recommended for more precise assessment and monitoring of children with an impaired conscious level (Advanced Life Support Group, 2001b).

The unmodified Glasgow scale has been used in several paediatric series of traumatic coma (Bruce et al. 1981, Alberico et al. 1987, Luerksen et al. 1988) and in non-traumatic coma such as Reye’s syndrome (Duncan et al. 1983), but there are considerable difficulties with application in this age group. In particular, the verbal scale is inappropriate in very young children who often do not speak because they cannot or are too frightened, rather than because they are unconscious. There are also difficulties with the motor response. Children under the age of 9 months cannot localise pain and those under 18 months do not reliably obey commands because their receptive language is not sufficiently developed. Several alternative paediatric scales have been designed (Seshia et al. 1977, Simpson and Reilly 1982, Gordon et al. 1983, Raimondi and Hirschauer 1984, Morray et al. 1984, James et al. 1985) but as yet none has been universally adopted.

Two scales designed specifically for infants (Raimondi and Hirschauer 1984, Morray et al. 1984) have

high inter-observer variability (Yager et al. 1990). An alternative to the verbal scale in neonates might be to assess the response to auditory stimuli (Duncan et al. 1981) but the range of clinical problems in this age group is usually quite different and there are arguments for and against using a version of the Glasgow score. Inter-observer variation is least for the Seshia scale (Yager et al. 1990, Newton et al. 1995), probably because there are only 4 levels, and there appears to be a consistent improvement if the choice is less (Newton et al. 1995). Similar remarks apply to the Lovejoy scale developed for the staging of Reye's syndrome and the Blantyre scale (Molyneux et al. 1988), which has been widely used in the developing world for the assessment of tropical CNS infections, such as cerebral malaria (Newton et al. 1997). However, there are advantages in using a scale that is as close as possible to the widely accepted adult Glasgow coma scale, as observations and decisions must often be made quickly by relatively inexperienced Emergency Department staff.

The Glasgow scale is very familiar to nursing staff and casualty officers and works well down to the age of 5. In those below that age, the motor and eye opening scales may be used (except that children below the age of 9 months cannot localise pain), but a modification of the verbal scale is needed. Three of the published scales are paediatric modifications of the Glasgow scale; in each a different approach has been taken to the verbal scoring system for use in children under five, to take into account the development of language in this age group. A group of neurosurgeons in Adelaide developed a scale for use in head injury (Simpson and Reilly 1982, Reilly et al. 1988, Simpson et al. 1991). On the Adelaide scale, only expressive language is assessed so that the maximum score achievable on the verbal scale increases from 2 for a baby of less than 6 months to 5 by the age of 5. In 1983, a scale designed by Jacobi (1982) was endorsed by the European Federation of Child Neurology Societies (Gordon et al. 1983). The Jacobi scale includes an assessment of receptive language (verbal response 5, 4, 3) and a level of motor restlessness (verbal response 2, corresponding to incomprehensible sounds on the adult scale). It is useful to recognise motor restlessness, as deterioration to flaccid coma may occur rapidly. It may be more difficult to be objective when assessing receptive language, but doing so increases the sensitivity of the scale to subtle changes in conscious level that may give early warning of secondary deterioration before irreversible brain damage occurs. Under these circumstances, over-sensitivity may be preferable to over-specificity. Reliability may be improved by defining the stimulus (Sugiura et al. 1983) e.g. for a child a coloured toy, when assessing interaction with the environment. James and Trauner (1985) suggested a "Modified Coma Scale for Infants", in which the number of categories in the verbal scale is the same over the full age range: 5 Coos, Babbles, 4 Irritable cries, 3 Cries to pain, 2 Moans to pain, 1 None and the upper end of the motor scale was also adapted for infants: 6 Normal spontaneous movements, 5

Withdraws to touch, 4 Withdraws to pain, 3 Abnormal flexion, 2 Abnormal extension, 1 None.

The James scale for infants was used and further modified to be applicable to older pre-school children over several years by medical and nursing staff, especially those working on Paediatric Intensive Care units and Emergency Departments in Newcastle-upon-Tyne (Eyre and Sharples, personal communication) and then Birmingham UK . The latest version (Child's Glasgow Coma Scale, Table 1) has been used successfully in many U.K. centres and undergone a rigorous assessment of inter-observer reliability confirming that it can be consistently reproduced between observers. It was formally endorsed by the British Paediatric Neurology Association in 2001.

An identical scale with an additional Grimace scale, as an alternative for the Verbal scale for intubated children on paediatric intensive care units, also exhibits good inter-observer reliability (Tatman et al. 1997). The Grimace scale gives: **5** Spontaneous normal facio/oro-motor activity; **4** Less than usual spontaneous ability; **3** Vigorous grimace to pain; **2** Mild grimace to pain; **1** No response to pain. This version has proved popular with paediatric nurses and has been adopted by the National Paediatric Neuroscience Benchmarking Group, a vigorous United Kingdom-wide paediatric intensive care nurses forum (Warren A., personal communication). However there are no studies yet comparing Grimace with Verbal scores or Grimace with outcome.

The problem of assessing motor response in infants has also been addressed in different ways in the three scales. In the Adelaide and EFCNS scales, there are only 5 categories for the motor scale (Teasdale and Jennett 1974), leaving out withdrawal because of the possibility of confusion with spinal withdrawal in brain stem death. In addition, in the Adelaide scale, the fact that young children, under the age of 9 months, do not localise pain is taken into account so that the maximum motor score possible in a baby of less than 6 months is 3, which increases to 5 for children over 2. The 6 point motor scale (Jennett and Teasdale 1977) has been widely adopted by units caring for adults, however. There is some evidence that withdrawal has a better prognosis than abnormal flexion, for example in children after head injury (Berger et al. 1985), although inter-observer variability is usually greatest for the distinction between abnormal flexion and withdrawal (Braakman et al. 1977, Born et al. 1987). Awake infants usually move all 4 limbs either spontaneously or in response to voice (Murray et al. 1984, Duncan et al. 1981) and it is possible to distinguish between withdrawal and abnormal flexion in this age group. If these four grades are used as the top levels of the infant motor response scale, the grading becomes approximately comparable to the paediatric and adult scales and it may be possible to avoid inflicting pain in fully



conscious babies.

The modification suggested by James and Trauner (1985) and adopted in the Child's Glasgow Coma Scale (Table), which includes withdrawal to touch and to pain, as well as normal spontaneous movements, is preferable to that of the Adelaide scale in which these levels are deleted, thus reducing the total number of categories in very young children. This makes the score easily interpretable and communicable as any given score will imply the same level of conscious level impairment whatever the age of the patient. Furthermore for clinical audit and research, data on pre-school children can be included with data from school-age, adolescent and adult patients without mathematical transformation to accommodate the variable age dependant ceiling effect.

A paediatric coma scale might be used by nurses at the bedside, those best placed to recognise improvement or deterioration in time for action to be taken. It is absolutely vital that such a system should not be confusing and should be validated for inter-observer variability (Teasdale et al. 1978). It is rather disquieting that on the Adelaide scale there was a substantial degree of disagreement between observers for the motor and eye opening scores (Reilly et al. 1988) which should be reasonably objective measures. There may have been more consistency in the scoring of verbal response simply because of the reduction in the number of categories, which may make this scale insensitive to changes in conscious level in young children. These authors emphasized the importance of training staff in reducing inter-observer variability and in fact, in a study comparing a Paediatric Neurology Fellow and an experienced Paediatric Neurologist, inter-observer reliability was shown to be good for both the Adelaide and the Jacobi scales (Yager et al. 1990, Newton et al. 1995), as well as for the 0-IV scale originally proposed by the Winnipeg group (Seshia et al. 1977).

Inter-observer reliability of the Child's Glasgow Coma Score (Table) was assessed by 104 sets of paired blinded observations in 73 paediatric intensive care patients, ages 1 day to 16 years old (median age 73 days). One of 3 investigators (a senior paediatric intensive care nurse, paediatric neurology trainee, paediatric intensive care trainee) assessed the child within 15 minutes of the child's regular bedside intensive care nurse. Both were blind to the other's score, in random order. The level of agreement, assessed by weighted Kappa statistics was: for Eye-opening (n=100) 0.64 (good), Verbal (n=28) 0.49 (moderate), Motor (n=104) 0.49 (moderate), combined (28) 0.57 (moderate). For the Grimace (n=68) weighted Kappa was 0.63 (good). A strength of this study design was that the regular bedside nurse's scores were used: the people who will be making the observations in real clinical settings, not just

specially trained and very experienced medical investigators.

There is a need for a consensus to make teaching and collaborative research easier. Further prospective studies should be undertaken of the inter-observer reliability, predictive value and use in monitoring children of the Child's Glasgow Coma Scale. Clinical scoring systems should probably also be compared with neuroradiological techniques such as CT and MRI scanning and neurophysiological monitoring techniques, such as continuous EEG and multimodal evoked potentials. It is essential that those doctors and nurses who are responsible for children who have suffered a cerebral insult are able to recognise and describe a change in the child's conscious level and there is, therefore, a need for training throughout the medical profession.

### References

- Advanced Life Support Group a. Recognition of the seriously ill child. In Advanced Paediatric Life Support the Practical Approach, BMJ Books, London, 2001, pp 13-18.
- Advanced Life Support Group b. The child with a decreased conscious level. In Advanced Paediatric Life Support the Practical Approach, BMJ Books, London, 2001, pp 127-137.
- Berger, M.S., Pitts, L.H., Lovely, M., Edwards, M.S., and Bartkowski, H.M. Outcome from severe head injury in children and adolescents. *J.Neurosurg.* 62:194-199, 1985.
- Born, J.D. The Glasgow-Liege Scale. Prognostic value and evolution of motor response and brain stem reflexes after severe head injury. *Acta Neurochir.(Wien)*. 91:1-11, 1988.
- Dhellemmes, P., Lejeune, J.P., Christiaens, J.L., and Combelles, G. Traumatic extradural hematomas in infancy and childhood. Experience with 144 cases. *J.Neurosurg.* 62:861-864, 1985.
- Duncan CC, Ment LR, Shaywitz BA. Evaluation of level of consciousness by the Glasgow coma scale in children with Reye's syndrome. *Neurosurgery*. 1983 Dec;13(6):650-3.
- Gordon, N.S., Fois, A., Jacobi, G., Minns, R.A., and Seshia, S.S. The management of the comatose child. *Neuropediatrics* 14:3-5, 1983.
- Hennes, H., Lee, M., Smith, D., Sty, J.R., and Losek, J. Clinical predictors of severe head trauma in children. *Am.J.Dis.Child.* 142:1045-1047, 1988.
- James H.E. and Trauner D.A. The Glasgow Coma Scale. In Brain Insults in infants and children, ed James H.E., Anas N.G., Perkin R.M., Grune and Stratton Inc., Orlando, 1985 pp 179-182.
- Langfitt, T.W. Measuring the outcome from head injuries. *Journal of Neurosurgery* 48:673-678, 1978.
- Lovejoy FH Jr, Smith AL, Bresnan MJ, Wood JN, Victor DI, Adams PC. Clinical staging in Reye syndrome. *Am J Dis Child.* 1974 Jul;128(1):36-41.

Newton, C.R., Pasvol, G., Winstanley, P.A., and Warrell, D.A. Cerebral malaria: what is unarousable coma? [letter; comment]. *Lancet* 335:472, 1990.

Newton, C.R., Kirkham, F.J., Winstanley, P.A., Pasvol, G., Peshu, N., Warrell, D.A., and Marsh, K. Intracranial pressure in African children with cerebral malaria [see comments]. *Lancet* 337:573-576, 1991.

Newton, C.R., Kirkham, F.J., Johnston, B., and Marsh, K. Inter-observer agreement of the assessment of coma scales and brainstem signs in non-traumatic coma. *Developmental Medicine & Child Neurology* 37(9):807-813, 1995.

Marshall, L.F., Toole, B.M., and Bowers, S.A. The National Traumatic Coma Data Bank. Part 2: Patients who talk and deteriorate: implications for treatment. *J.Neurosurg.* 59:285-288, 1983.

Reilly, P.L., Simpson, D.A., Sprod, R., and Thomas, L. Assessing the conscious level in infants and young children: a paediatric version of the Glasgow Coma Scale. *Childs.Nerv.Syst.* 4:30-33, 1988.

Rivara, F., Tanaguchi, D., Parish, R.A., Stimac, G.K., and Mueller, B. Poor prediction of positive computed tomographic scans by clinical criteria in symptomatic pediatric head trauma. *Pediatrics* 80:579-584, 1987.

Sacco RL, VanGool R, Mohr JP, Hauser WA. Non-traumatic coma. Glasgow coma score and coma etiology as predictors of 2-week outcome. *Archives of Neurology* 1990 Nov;47(11):1181-4

Seshia, S.S., Johnston, B., and Kasian, G. Non-traumatic coma in childhood: clinical variables in prediction of outcome. *Dev.Med Child Neurol.* 25:493-501, 1983.

Seshia, S.S., Seshia, M.M., and Sachdeva, R.K. Coma in childhood. *Dev.Med Child Neurol.* 19:614-628, 1977.

Simpson, D. and Reilly, P. Pediatric coma scale [letter]. *Lancet* 2:450, 1982.

Simpson DA, Cockington RA, Hanieh A, Raftos J, Reilly PL. - Head injuries in infants and young children: the value of the Paediatric Coma Scale. Review of literature and report on a study. [Review] [37 refs]. - *Childs Nervous System* 1991 Aug;7(4):183-90

Tatman A, Warren A, Williams A, Powell JE, Whitehouse W. Development of a modified paediatric coma scale in intensive care practice. *Arch Dis Child* 1997; 77: 519-21

Yager, J.Y., Johnston, B., and Seshia, S.S. Coma scales in pediatric practice. *Am.J.Dis.Child* 144:1088-1091, 1990.

Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma [see comments]. *Lancet* 1998 Dec 5;352(9143):1808-12.

**b) How should encephalopathy be distinguished from (for example) the post-ictal state, or the irritable drowsiness that often accompanies a high fever in infants?**

The key here is probably repeat assessment, as the Child's Glasgow coma score of the post-ictal or febrile child should rapidly improve with appropriate treatment, while that of the child with an encephalopathy remains static or deteriorates.

**c) How ought we to explain how to recognise encephalopathy to junior medical staff and nurse practitioners?**

Training is very important and it is useful to have clear descriptions of the different observed responses and their scores on the bed-side chart, particularly if they vary with age. Parental concern about a child's level of consciousness, comparing him with his normal behaviour, must always be taken very seriously. The subtle abnormalities of language function that distinguish between a normal child with a Glasgow score of 15 and one with a score of 11, who requires immediate drainage of his extradural haematoma, for example, are often recognised by those who know the child well. However, it is important, particularly in research studies, that the impressions of those familiar with the child are confirmed by an experienced, unbiased observer and it must be remembered that child abuse is a common cause of head injury in infants. It is sensible for all children in coma to be managed on a children's ward by appropriately trained paediatricians and paediatric nurses, able to call upon other expertise if the child's conscious level deteriorates in any way, even subtly. At initial presentation, it is preferable to err on the side of recording too low a score, since it is easier to withdraw treatment from a child who is improving than to resuscitate one who deteriorates.

The following text is published in the Paediatric Vade Mecum:-

**Settings**

The paediatric coma scale should be used routinely in accident and emergency departments and on wards and intensive care units for the assessment of any child with

**Trauma** (including possible **non-accidental injury**)

**Infection** e.g. **meningitis, encephalitis, cerebral malaria**

**Epileptic seizures**

**Diabetes** or other known underlying **metabolic** abnormality

**Hepatic failure**

**Renal failure** (including **haemolytic-uraemic syndrome**)

## Hypertension

In addition, children at risk of the following complications should be assessed frequently:

**Hypoxic-ischaemic injury** e.g. post-operatively (particularly after **cardiac surgery**)

**Hypotension** e.g. with **shock** (e.g. **meningococcal**) or during **treatment for hypertension** or

**Intracranial hypertension**, e.g. with an **acute encephalopathy**, **diabetic coma**, a **tumour**, or after a **neurosurgical procedure**

## Examination of the child at risk from acute neurological deterioration

### Preliminaries

Check **Airway**

**Breathing**

**Circulation**

Check pupil size, symmetry and reaction to light

### Procedure

It is usually helpful to have the assistance of the child's carer, for example, in speaking to the child or trying to wake him or her up, but the assessment must be performed objectively and it is essential to use a very painful stimulus.

**Step 1** If the child's eyes are open (E4), ask the carer to talk to him or her. Ask the carer to elicit a verbal response appropriate to the child's age e.g.

Babbling for a child < 9 months

Waving bye for a child aged 9-12 months

Putting a hairbrush to the head for a child aged 12-15 months

Pointing to body parts for a child aged 15-24 months

Any words from 12 months

Any sentences from 2 years

Orientation in place and time from 5 years

Decide with the carer whether any verbal response obtained is appropriate for the child's usual ability (V5) or less than the child's usual ability (V4)

If a child appears to understand what is said to him, even if he is not speaking, ask him to obey a simple command e.g. squeeze the carer's finger or squeeze his eyes shut (M6).

If the child does not have any spontaneous speech or eye opening, proceed to step 2.

**Step 2** If the eyes are closed, ask the carer to talk to the child and observe whether the child's eyes open in response (E3). If they do, observe whether the child appears to recognise the carer and understand what is said. If this is the case, ask the carer to elicit a verbal response appropriate to the child's age as for step 1.

If a child appears to understand what is said to him, ask him to obey a simple command e.g. squeeze the carer's finger or squeeze his eyes shut (M6).

If the child's eyes remain closed or he does not obey commands, proceed to step 3

**Step 3.1** Explain to the carer that you are going to press on the child's forehead to see if he will respond to pain as part of your assessment of his level of consciousness. If you are not confident about supraorbital pressure, or nailbed pressure, try the technique on yourself first: press hard enough to elicit a

very focal sharp pain. This feels different to the pressing feeling and stops as soon as you stop pressing. Press firmly on the supraorbital notch (beneath the medial end of the eyebrow) with your thumb (figure 3a).

Observe:

- Whether the eyes open;

- Whether the child cries or moans;

- Whether the child moves his arms:-

  - Above the clavicle (localisation to pain, M5)

  - Below the clavicle but flexing at the elbow (flexion to pain, M3)

  - Below the clavicle without flexion but with rotation at the shoulder (extension, M2)

If the child does not move, press more firmly (as hard as you can) on the supraorbital notch and observe whether there is movement of any body part, including the face (grimace).

If the child flexes but does not localise, press very firmly on the nailbed (flat surface of the nail) of 1 finger with a pencil (figure 3b) and observe whether or not the child moves the finger away (withdrawal to pain, M4).

Observe carefully whether there is any asymmetry of movement, which may mean that the child is at risk of uncal herniation, particularly if the pupils are asymmetrical.

**3.2** When assessing an infant touch and stroke the child on the hand and forearm and note any withdrawal to touch (M5).

**3.3** If you cannot feel one or other supraorbital notch, e.g. because of traumatic facial swelling, apply sternal pressure with the proximal interphalangeal knuckle of your index finger. Alternatively use finger nailbed pressure, as for M4 above. Score localises to pain (M5) if the child brings the *contralateral* arm partly across the body to dislodge the pain or makes a complex purposeful manoeuvre to remove the pain, not just a simple withdrawal (M4).

Observe the eye opening and verbal responses to pain also.

When assessing infants the eye opening score is often E1 (none), even when verbal and motor scores are high e.g. V4, V5, M5 or M6.

#### **Step 4**

Write down the response observed for eye opening, verbal response and motor response. If there is asymmetry e.g. of the motor response, write down the better side.

#### **Footnote: Intubated children**

For intubated patients, score eye opening and motor responses as above and write down VT (for “Tube”) for the verbal score. Many Paediatric Intensive Care Units have adopted the Grimace Scale in place of the Verbal Scale (Tatman et al., 1997). Although there is good inter-observer agreement it has not yet been assessed as a tool for the prediction of outcome and there has not yet been sufficient general paediatric experience in its use to recommend it be generally adopted.

#### **d) What, in brief, is the best current guidance on the role of lumbar puncture and imaging in the diagnostic process of patients like these?**

If the child is **febrile** and is either under the age of 12 months or is older than 12 months and has a Glasgow Coma Score greater than 12-13, undertake a lumbar puncture after checking that the child is not in subtle status (twitching of the arm, leg or face, tonic deviation of the eyes or nystagmus) and does not

have signs of central or uncal herniation. The CSF pressure should be measured with a transducer or a manometer. A dose of Mannitol 0.25 g/Kg should be given if the pressure is greater than 15 cm H<sub>2</sub>O or if there is evidence of deterioration in the Child's Glasgow Coma Score or of the brain stem signs after the lumbar puncture.

If the child is **afebrile** or febrile with a deteriorating level of consciousness, **DO NOT PERFORM A LUMBAR PUNCTURE** but start a 3<sup>rd</sup> generation cephalosporin and acyclovir and ring the nearest PICU with access to a neurosurgical unit to request transfer by their transport team for CT scan and further management

## References

Tasker RC, Matthew DJ, and Kendall B. Computed tomography in the assessment of raised intracranial pressure in non-traumatic coma. *Neuropediatrics* 1990;**21**:91-94,.

Shetty AK, Desselle BC, Craver RD, Steele RW. Fatal cerebral herniation after lumbar puncture in a patient with a normal computed tomography scan. *Pediatrics* 1999;**103**:1284-7.

Horwitz SJ, Boxerbaum B and O'Bell J. Cerebral herniation in bacterial meningitis in childhood. *Ann Neurol* 1980;**7**:524-8.

Rennick, G., Shann, F., and de Campo, J. Cerebral herniation during bacterial meningitis in children. *BMJ* 306:953-955, 1993.

Selby A, Isaacs D, Gillis J, Hanson R, O'Connell A, Schell,D, Van Mai T. Lumbar punctures in suspected bacterial meningitis: too many or too few? *J Paediatr Child Health* 1994;**30**:160-4.

Nadel S, Joarder R, Gibson M, Stevens,J.; Britto,J.; Habibi,P.; Owens,C. Emergency cranial computed tomography in the management of acute febrile encephalopathy in children. *J Accid Emerg Med*

## **Dr Kirkham: Points highlighted in spoken presentation:**

I think one of the problems we have in training nurses and our junior staff is that we may not recognise that children who have still got their eyes open, and are often very irritable - perhaps behaving rather oddly, eating funny things, or very "hyper", as in some of the original descriptions of children with Reye's, are in fact encephalopathic. I remember a patient who turned out to have RS who had a good EEG on admission and was simply very irritable. These children may not have obvious eyes closed reduction in conscious level, but actually they are not interacting with their environment properly and their parents know it. If you go back to the original papers by Loveday and Partin and Devivo, about the epidemics of RS in the US, there are very beautiful descriptions of exactly how these children actually

looked and I think these need revisiting as part of any training initiative.

There is also this issue of vomiting. As a paediatric neurologist the mistakes I see made, are often with vomiting - particularly when there is no accompanying diarrhoea. That always worries me and I don't ever diagnose gastroenteritis if there is no diarrhoea.

We've had two cases recently where a child has had an intracranial lesion (one abscess and one extradural haematoma). In each case the child had been vomiting without diarrhoea and the parents had been reassured by NHS Direct that it was gastroenteritis. So I do think we need to get over the message that *vomiting on its own* is a very serious issue.

Then there's this extremely difficult question of how you try to distinguish children who are asleep or drowsy, from those that have encephalopathy. I've spent about fifteen years addressing this! Part of the difficulty is the issue over which Glasgow Coma Score should we use, or whether we should use the GCS at all. I think there are advantages in trying to use a paediatric modification of it because it is well used in A & E departments. But there are major problems with the verbal scaling in the under fives and that's part of the reason why other scales have been described. There is a good case for a very simple scale such as the AVPU scale, which could be taught to everybody. Nursing colleagues who are looking at this agree, they are trying to convince the profession that there is a problem and there is a need for a very simple scale like the AVPU. It was clear from a study we did in Kenya of cerebral malaria, that the fewer options you give people the better the inter-observer variability. The 15 point Glasgow Coma Scale is fine if you are a distinguished neurosurgeon with 20 years' experience, but if you are a nurse who only qualified last week and who can't quite remember what her text book or her hand written notes said, it is actually very hard to do.

So if we are going to use the modified Glasgow Coma Score we do need to agree it and I would be interested in Dr Tasker's comments, because we have agreed it with the British Paediatric Neurological Association, and the neuroscience nurses are happy with it. There are good inter-observer variability data and also data suggesting it does validly predict outcome. These are powerful arguments for developing its use but I think it should perhaps be as a second level tool. We should be seeing if we can teach everybody to do something simple and everybody to at least learn the Glasgow Coma Scale properly.

Then I come to my next point, which is that although some sort of coma scaling is necessary, it is not sufficient. If you go back to the Lovejoy scaling, what he described is actually what happens in Reye's



syndrome and also in cerebral malaria and other forms of non-traumatic coma. Actually at least two other things happen to encephalopathic children: one is that they fit, and there is nothing about fitting in the Glasgow Coma Scale. It may be very difficult to treat, but it may well make the difference between good and poor outcome. We have data showing that the longer you have electroencephalographic discharges, the more likely you are to be seriously handicapped or in a vegetative state.

The second thing is that these children herniate and they herniate long before you put intracranial pressure monitors into them. They herniate in casualty and recognising the state of herniation is difficult but is another layer of expertise. I have to teach the practical paediatric neurology course and every time I do it I have to remind myself of the stages of herniation, because they are very difficult to remember. There are difficulties, for example you can't do the doll's eye test in a child with a potential neck fracture, so you have to do calorics and people don't do calorics because they are worried about putting cold water into the ears. But I do think that we ought to get better at looking for the herniation syndromes and we have now put them into the Paediatric Vademecum.

*How can encephalopathy be distinguished from the post ictal state or the usual irritable drowsiness accompanying a high fever?* Here **the key is repeat assessment**, because children who aren't encephalopathic get better quickly, usually within half an hour. For example distinguishing febrile convulsions from cerebral malaria is very difficult but the key point is that patients with the former improve very quickly.

*Training is the next question:* I think we have to make training packages with video, and we have to ensure that, from the most junior recently qualified nurse to the most senior just-about-to-retire consultant, health professionals know how to document coma and, more importantly, what to do about it, whether in casualty or in the intensive care unit - long before we are monitoring with fancy equipment. I have just put in the Vademecum a methodology for examining the child at risk from acute neurological deterioration. This is the beginning of a dialogue on how we look at training.

*Next, the question of lumbar puncture:* Whenever I discuss lumbar puncture with groups that I am trying to teach or collaborate with, there is always some argument. Currently, when I talk to junior staff I discover that none of them has lumbar punctured any patients, including neonates for whom there is very little evidence that coning on the end of the needle ever happens. Doctors in the developing world are extremely anxious about the problem of not lumbar puncturing children with fever, because they don't

have enough antibiotics to give to children who in fact have cerebral malaria, and they don't have enough antimalarials to give to children with meningitis - they have to know there and then which one the child has got.

We have to have an approach which is going to be universal. I suggest that if the child is febrile and either a) under the age of twelve months, or b) older than twelve months *and* with a coma score of greater than 12-13, then LP should be performed, with the caveats set out in my paper (above). It's actually 13 in the APLS and 12 is what I propose, but there isn't really very much evidence either way. Nobody has ever done an epidemiological study based on who cones after lumbar puncture. Perhaps that is something the BPSU might consider because it is still happening in the UK. I don't think that any afebrile child who is unconscious should ever be lumbar punctured. Children that I have seen who have coned on the end of a needle have been over the age of twelve months and afebrile. If you *are* going to lumbar puncture and you're uncertain, the other thing I strongly recommend is that you have some mannitol ready to run through the needle. Sometimes when I've been concerned at how much CSF shot out at the top of my manometer I have given mannitol and I haven't yet run into major trouble with coning.

## **DISCUSSION**

**Dr MacFaul.** That's very helpful, practical advice thank you. I think that "state variation" is the terminology used in the USA for this sort of change in behaviour isn't it and there have been various ways of trying to teach it, including video. The Department of Health has just commissioned Fion Davis at the Royal London, who is already doing some video for the APLS course, to capture some with that particularly in mind, i.e. the child with mild, moderate, and severe levels of consciousness change.

**Dr Kirkham.** Yes, there's no doubt video would be the best approach. One of the nurses at Great Ormond Street captured some when she did an inter-observer variation study. There is also some material from Kenya so if we pooled resources to do an educational video I think that would be very helpful.

**Dr Glasgow.** In the RSM Round Table Proceedings of the 1986 conference on RS, John Partin comments on the importance of listening to parents. He says that parents often felt that their child was more ill than the attending doctors accepted [Partin, J.C. (1988) General management of Reye's Syndrome. In Wood, C., (Ed.) *Reye's syndrome* pp. 156-172. London: Royal Society of Medicine] - we need to somehow get that over to junior staff.

**Dr Kirkham.** I think that's still true.

**Professor Leonard.** I completely agree with Dr Glasgow and this problem happens to us just as much with inherited metabolic disease. The families know their children infinitely better than do the admitting doctors and it can be quite difficult for the parents sometimes to persuade them of the importance of doing something *now* and not waiting. Talking to them it is clear that parents recognise the early stages of encephalopathy very well.

We have done a study where one of our nurses has gone out to look at these and see what the very earliest signs are. They are enormously variable, but the families understand the signs very well and I think we do have to build on these observations and on this idea of state variability. The very early symptoms need to be looked at carefully, and they are really no different in an inborn error. We could actually use these to think of these very early signs and symptoms, for example the slightly glazed look, this effortless vomiting - all these can occur.

**Professor Stephenson.** We have studied several hundred children attending Accident and Emergency and selected by triage criteria and I'm afraid parental concern is just not sensitive. If doctors and nurses score the patients on a Lickert scale and also ask the parents to score them, all parents think their child is more unwell than the professionals do. In fact many think their child is strikingly ill, indeed may die soon, with really quite minor complaints.

**Professor Tanner.** The difference is you are talking about acutely sick children previously well, whereas Professor Leonard was talking about patients already known to have an inherited metabolic disorder.

**Professor Leonard.** Yes it is different; I take Terence's point completely.

**Dr Glasgow.** But the reference *I* made was of course to children with classic RS who were ill for the first time, so it is a dilemma.

**Dr MacFaul.** All of this speaks for some form of objective assessment and some of this work on the modified GCS does seem to have advantages; I think it needs testing.

**Dr Kirkham.** Can I just ask, Dr Tasker, what you think from the intensivist's viewpoint?

**Dr Tasker.** I think there are many reasons why one should stick with the Glasgow coma score, or some variant thereof, not least because it's an international standard that is used very commonly and is part of what drives our protocols for head injury and also for children who are decompensating with raised intracranial pressure. I think if you go back in the Reye literature you will find that the Glasgow coma score seemed to be a better correlate of raised intracranial pressure than the other scores. The big problem of course in children is that, unlike the adult population, there were never any validation studies. A lot of scores or variants have been introduced and, apart from the Birmingham grimace score, there are no adequate validation studies. So if we want to look at a score that is going to be applicable to children in the process of decompensation, we need to do large scale validation studies.

Regarding children who have a GCS of greater than 12, the scoring system is a very blunt instrument at detecting subtle clinical signs. It may be that these other things that Dr Kirkham has mentioned may pick them up, but I think we are then down to the issue of sensitivity and specificity. When detecting subtleties with hindsight it always seems as though you made the right choice, but I think looking prospectively you just won't find them.

**Dr Boon.** It's a pity that someone from NHS Direct couldn't be here. I think NHS Direct will become increasingly important, and I would be very interested to know how they set about trying to weed out the child with a potential encephalopathic illness from the thousands of children whose parents are worried about them.

**Dr Tasker.** In our dealing with referrals from all over our Region we just consider the response to eye opening and the motor response and transfer is very much geared towards responses in those two domains.

**Dr Boon.** But does NHS Direct ask those specific questions?

**Dr Tasker.** I don't know.

**Dr MacFaul.** At a recent meeting where the findings of a PhD thesis were presented we heard that what parents want in acute illness is an assessment of the child and the term they usually used was "checked out" by which they meant a "hands on" consultation face to face with a professional. So a telephone call, for small infants particularly, is not necessarily going to solve the problem. I also learned recently that

half of all GP contacts out of hours are dealt with by telephone regardless of age. I think both of those messages are really quite concerning because in the context of acute illness of a non-specific nature in a small child particularly, professionals are challenged and we need to train them up.

**Dr Kirkham.** Can I just say that, as well as the Grimace Score, Tapman et al did look at inter-observer variation in the full and modified Glasgow Coma Score. It wasn't perfect because it was ITU-based, and we need to do it in casualty, but there are some inter- observer data.

**Dr MacFaul.** I want to focus again on how we distinguish, in the child presenting with an acute illness, the one that's got a significant problem. The one that's in coma or has had a fit will clearly get attention, but the question is how we deal with the mild and moderately ill children who may be decompensating as far as metabolic disease is concerned or who may be suffering significant problems with, say, meningitis or compensated shock. How do we do that better?

**Professor Stephenson.** My feeling is that, because Reye's syndrome and the inborn errors generally are less common, in most children presenting with encephalopathy most junior doctors will initially think of either trauma or infection, and they would be particularly anxious about missing meningitis. There's a big culture of litigation around meningitis and I'm not convinced that in children in coma or with altered conscious level we should assume that they will rapidly arrive at these uncommon diagnoses. That's particularly important if there is evidence that early diagnosis alters the outcome. Although I'm sure they get there eventually, when they've had their LP and CT results that show there is no trauma or infection, and someone then says we had better think about inborn errors, but it is now 24/48 hours later.

**Dr MacFaul.** We're talking here about the child with a GCS score say between 11 and 14 where the diagnosis is uncertain. Is it encephalitis? meningitis? trauma? poisoning? hypertension (often missed)? So we need guidance on the management of that particular presentation and that guidance should include not only how we arrive at a metabolic diagnosis eventually but also how we secure the metabolic state in the meantime.

**Dr Walter.** The precise diagnosis is perhaps not the most important initial aspect - the essential thing is to identify a disorder that is treatable and requires urgent treatment. For example meningitis, hyperammonaemia, hypoglycaemia.

**Dr Glasgow.** That's fine twenty minutes from now, but when the doors open and in comes the obtunded patient what you need to know at that point is - is the airway secure? Is the patient shocked? Do I need to give oxygen? Do I need to get an IV line up? For the general paediatricians and A&E doctors at the front door, that is what the story is about. The other important ingredient, to address Professor Stephenson's point, is that the junior doctor needs to know who do I call if I have a sick child, and where is that individual now? The child whose GCS is 12 can be a frightening scenario, so there must be that second tier of cover.

**Dr Tasker.** Most of our juniors are now being taught or coached in the APLS approach and they will know, when they see a child with an altered level of consciousness, that as part of their secondary assessment they will do urea, electrolytes and a blood sugar. But the list in the table in the APLS Book does not mention checking the ammonia. The APLS 'Causes of Coma' has a section for metabolic coma and includes Reye's syndrome. It tells you not to do a lumbar puncture on any child with coma and that if you think the child has raised intracranial pressure, give mannitol.

It then states that after the initial management you then divide your children into those with a coma score between 9 and 12 - who don't get intubated, and those with a score below 9 who do. Then there's this wonderful phrase "then refer for definitive care". I will describe tomorrow the structure that we've set in place in our Region which we want to roll out further to include non-traumatic coma but which we currently have for head injury. In terms of what our juniors are currently being taught - every one of them before getting membership will go on an APLS course. So my view would be: is there something that we can build upon within this current structure? For example should our input be to propose that there ought to be ammonia on that list of investigations of coma, and at what point should it be done. I think those are fairly simple measures that could be then rolled out to every junior doctor who is doing paediatrics in the country,

**Dr MacFaul.** Is everyone agreed that it should be possible, 24 hours a day, to get an ammonia done?

**All.** Yes

**Dr Hall.** Dr Barbara Phillips did send a paper a couple of days ago and she also sent me a letter in which she says " if it's decided by the Workshop that an additional investigation step in the management of the child with a depressed conscious level should be incorporated into the APLS teaching please let me know

and I will discuss it with the International Working Party of which I am chairman".

**Dr MacFaul.** That's very helpful. Is there anything else that should be obtained urgently, liver function tests for example, or is that on the list?

**Dr Tasker.** It isn't on the list but I think one needs to consider the time scale over which you are going to get these results. Where I work I don't get liver function tests back within an hour. So those patients aren't still going to be in A & E - there may be appropriate tests for those patients that are kept on High Dependency Units within the DGH. That's the group of patients who are not intubated but are being kept within the local DGH on the high dependency area which every DGH will have in the future. So I think one might then be talking about a third line assessment, as opposed to the secondary assessment. It may be that you would want to add lactate to the ammonia as part of the secondary assessment - I think there are a number of things to debate.

**Dr Walter.** It's very difficult in some places to get ammonia done out of hours. I know many district general hospitals where you can't get it done and when it is done it's not been very accurate.

**Dr Green.** It should be possible to do - we shouldn't shy away from the recommendations.

**Professor Leonard.** I would support that. Hyperammonaemia is a highly treatable condition and just because they say we can't do it that's not a good enough excuse.

**Dr Masters.** Having surveyed the laboratories around here in Trent, it's available twenty four hours amongst all those who have responded. I can't see why it wouldn't be possible to do that nationally.

**Dr MacFaul.** It looks as though we are signed up to this emergency availability of an ammonia and possibly to liver function tests. Obviously most or all hospitals should have the ability to get glucose done immediately. Is there any other immediate investigation? Is there any possibility of developing a "quick stix" for something - that you just dip in the urine?

**Dr Green.** I don't think there is anything you can do of that type of test that's sensible. I think it can be useful to have clinitests and ketones but that's only to provide clues.

**Dr Bonham.** There is not likely to be a simple stick that can be developed. But Tandem MS is going to be more widely available - although not in your routine DGH - and once we've got a sample we can get a result out within about ten minutes.

Another point is about false positives for hyperammonaemia at the DGH - we do see them. It is important that the assay is repeated in such cases.

**Dr Tasker.** Do false positives matter if the response is going to be to move the child to a centre that is better able to manage the child and get further investigations? The question is - are there false *negatives* with an ammonia test done at a DGH, because you might be lulled into a feeling that we can hang on to this child and not transfer?

**Dr Bonham.** There are. That's an important point. We have to add in that measure of caution that just because we have excluded the possibility of hyperammonaemia -whether falsely or correctly, it doesn't mean we've excluded even these relevant IMDs let alone all IMDs.

Picking up on the other question about which investigations should immediately be undertaken: there are probably two aspects here - one of them is that we should do certain things immediately (for example TMS if we were able, but that's perhaps a little more fanciful). The second is that what we certainly *could* do is to get the *right samples immediately* even if they are analysed subsequently. So for instance you said that virtually everyone has the capacity to do the glucose but of course in doing glucose you take a sample that would enable you subsequently to do free fatty acids and 3-OH butyrate. Some laboratories do have the methods in place to maintain that sample and pass it on automatically and some will not. It is certainly something that should be set in train.

**Dr MacFaul.** Before moving on, we must not lose the point which Dr Kirkham made about the fact that there are other features of encephalopathy as well, like seizures and the emerging signs of herniation, because there is training needed in those too. So can we just underscore that too as part of the acute encephalopathy training pack.

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***Q 2.2.1. e) WHAT PROPORTION OF CASES OF ACUTE ENCEPHALOPATHY HAVE AN IMD and WHICH IMDS HAVE BEEN FOUND IN THESE CASES?***

***Dr ANUPAM CHAKRAPANI***  
***(oral presentation)***

I found a total of five papers in the literature that specifically address this issue. I obtained three - the other two, from the seventies, I couldn't get hold of. There is only one population based study published (Wong et al) which was in 2001 in Archives of Disease in Childhood. It is summarised below. It was done over eighteen months between 1994 and 1995. There were 345 episodes of possible non-traumatic coma. Of the various aetiologies that were determined, infections were by far the most common, contributing nearly 40%, followed by intoxication, about 10%. A total seven patients had a definite or suspected IMD so out of these 278 individuals that's 2.5%. That is the best study that has been published. The two other studies summarised below were both case series of children admitted with coma in the 1970s in Canada. Specific IMD diagnoses were not recorded but about five percent of cases were labelled as having hepatic coma and presumably some of them would have had an IMD.

Dr Kirkham - have you come across any other studies?

**Dr Kirkham.** No - I don't know of any other good data but individual case series from GOS and mine from Guy's have similar findings to the Wong study -2.5% is a reasonable figure.

**Dr Chakrapani.** The next question ( 2.2.1 f) is : **how often in an encephalopathic patient is a Reye-like IMD suspected and fully investigated but the results are, by the criteria of current best practice, truly negative?**

The only British data are from the BPSU (see below) - a total of 71% were actually compatible with the diagnosis of Reye's syndrome. Other series from outside the UK have shown a much higher incidence of false diagnosis of Reye's syndrome (Gauthier et al, Forsyth et al see below).

## FINDINGS (SUBMITTED PAPER)

### Q. 2.2.1.e

#### ***1. Incidence, aetiology and outcome of non traumatic coma: a population based study. Wong et al Archives of Disease in Childhood. 2001; 84:193-199***

Children between 1month and 15yr 11months admitted to hospital or died with a significantly depressed conscious level of non-traumatic aetiology.

Study period July 1994-December 1995

Excluded – SIDS, terminal illness, trauma

345 episodes of possible non traumatic coma

283 fulfilled criteria

278 individuals (155 male, 123 female)

Aetiology:

Infection 37.9%

Epilepsy 9.6%

Accident 6.7%

Congenital 8.2%

Intoxication 10.3%

METABOLIC 5.0% (n=14; 8 had DKA)

Other 7.8%

Of the metabolic causes,

MCADD 3

OTC heterozygote 1

GA I 1

MELAS 1

Additionally, 1 of the unknown group had “undefined” metabolic disorder

**Therefore total 7 children had an IMD (2.5%2.**

**2. Coma in childhood. Seshia SS et al Dev Med Child Neurol 1977; 19:614-628**

75 children admitted to hospital from Sept 1974 to January 1976

Age range 7wk to 16yr

39 male, 36 female

1-12months – 22

13-36 – 26

37-72 – 11

>72 – 16

<b>Aetiology</b>	<b>Number</b>	<b>%</b>
Infection	26	34.7
Septicaemia	3	4.0
Anoxia/diffuse ischaemia	18	24
Epilepsy	11	14.7
“Metabolic”	11	14.7
Vascular lesions	3	4.0
NAI	2	2.6
Histiocytosis	1	1.3

*“Metabolic” included:-*

Gastroenteritis 4

Poisoning 4

Hepatic 3

(Not defined further)

*Spectrum of aetiology classified as metabolic:*

Hepatic

Renal

Pulmonary

IMD

Vitamin deficiency

Fluid/electrolyte imbalance

Poisoning

3. *Non traumatic coma in childhood: clinical variables in prediction of outcome. Seshia SS et al. Dev Med Child Neurol. 1983; 25:493-451*

104 children admitted with coma February 1976-December 1978

Age range 1month – 17 years

57 male, 47 female

Aetiology

Aetiology	Number	%
Infection	24	24
Anoxia/diffuse ischaemia	26	26
Epilepsy	16	16
“Metabolic”	24	24
Poisoning	15	15
Gastroenteritis	4	4
Hepatic	5	5
Unknown	2	2
Vascular/spongiform encephalopathy	12	12

## **Q 2.2.1 f**

### **1. BPSU 1981-1999**

Total 625 cases

161 (26%) had revised diagnosis – of these, 79 (12.6%) had an inherited metabolic disorder.  
447 (71%) were compatible with the diagnosis of Reye syndrome

(See table in BPSU 14<sup>th</sup> Annual Report, 2000, Royal College of Paediatrics and Child health, London 2000)

### **2. *Reye's syndrome. A reappraisal of diagnosis in 49 presumptive cases. Gauthier M et al AJDC 1989; 143:1181-1185***

Retrospective study of 49 patients with presumptive diagnosis of Reye's syndrome

Study period 1970-1987

Patient charts reviewed blindly by 3 clinicians

*Diagnosis of Reye syndrome:*

Certain 1 (2%)

Probable 11 (22%)

Unlikely 21 (43%)

Excluded 15 (31%) – 11 were excluded on histological grounds (of which 2 had “acyl CoA dehydrogenase deficiency”); 4 had other causes identified.

### **3. *Misdiagnosis of Reye's syndrome. Forsyth et al, AJDC 1991;145:964-966***

Retrospective data on patients with possible Reye syndrome reviewed by 3 experts.

Study period January 1986 to July 1987

63 patients fulfilled screening criteria

*Diagnosis* (based on defined clinical, biochemical and histological criteria):

25 (40%) – definite

19 (30%) – uncertain

19 (30%) – excluded

Also – 1/63 had definite IMD; only 5/26 (19%) aged under 3yr had specific investigations for IMD

## DISCUSSION

**Dr MacFaul.** I thought a few minutes ago we said Reye's syndrome didn't exist but clearly there are studies that show *something* exists. Is it an undiagnosed metabolic disorder – “brackets”: inherited or not inherited?

**Dr Glasgow.** It's very difficult to be absolutely sure - even for experts in metabolic disease - that you have investigated the index case thoroughly, and that negative results mean that there is no IMD. For example, I have a patient who came in with classic Reye's syndrome having had aspirin and the parents had already lost an older sib as a sudden infant death syndrome. That child had a fatty liver. We exhaustively investigated this family without coming to a definitive conclusion. Does that mean that there is no inborn error present or does it mean we are not competent enough in our investigations? Does this reflect the non-specificity of fatty liver mentioned earlier? Just to confuse things I have referred elsewhere to another child who came in an obtunded state to A&E with many of the features of RS or a R-L S, but in whom exhaustive tests for an IMD were negative; subsequently, the mother admitted that he had consumed an amount of a cleaning fluid that is a known hepatotoxin.

**Professor Berry.** I didn't intend actually to talk down the fatty liver too much, because when you see the fatty liver of these inborn errors it's quite different to the kind of fat you get non-specifically. I would be interested in the other pathologists' experience of cases in the first year of life when we see what I might call a Reye like liver, absolutely full of microvesicular fat, but we only pin down a metabolic disorder in about two thirds.

**Dr Glasgow.** If we distribute these photographs around - just to illustrate the point Jem Berry has just been making: they are as different as chalk from cheese and one is from a Reye's syndrome patient and the other from an LCHAD deficient individual [latter shows enormously more fatty infiltration than is usual in RS].

**Professor Berry.** When you get a classic Reye or MCADD you don't need to put the oil red -O slide under the microscope it's so red!

**Dr MacFaul.** Easy for you but what about forensic pathologists?

**Professor Berry.** Yes they do tend to call it inborn error even with a small amount of fat.

**Dr MacFaul.** This is a major issue for the investigation of sudden death in infants in this country.

**Dr Sue Hall.** Of cases reported to the BPSU about a quarter hadn't had any metabolic investigations at all and of those that had, although we didn't ask people exactly what investigations they did do, it's clear from what is volunteered that it's mostly exclusion of MCADD. Urea cycle defect investigation for example is very rarely mentioned, so I think the cases that were being reported hadn't had the other disorders excluded properly.

**Dr Glasgow.** How long after your patient has had the acute Reye or Reye like illness or metabolic decompensation, can you go back and hope to create an ethical situation where you can actually investigate such patients and hope to have positive results? There are forty of mine that I think I have investigated very thoroughly but never published and have not found a single case of an IMD.

**Dr Neil Dalton.** As far as disorders like ornithine transcarbamylase deficiency are concerned the allopurinol load is regarded as relatively safe. Whether it's sufficiently specific I would question. As far as fat oxidation is concerned, in most of them it should be possible to make a diagnosis whether they are acute or not. But for those you can't, you have to do some form of prolonged fast in a controlled fashion in order to elucidate the diagnosis.

**Professor Leonard.** This can be subject quite easily to an algorithm which would then take you stepwise through various points. I would always start by going back over the history - was that child completely normal before the attack and so on - and you move on through very straightforward tests like the acyl carnitines and tandem mass spectrometry. You would end up with a fast and allopurinol load. It would be a routine matter for an established metabolic unit and an algorithm could be produced without too much difficulty if it was thought to be needed. But you won't get answers in every case because we haven't yet identified all the metabolic diseases.

**Dr Walter.** Whereas in the past we always used to say you have to investigate during the acute crisis in order to detect MCADD, that's not so true now we've got tandem MS. In my experience the uses of prolonged fast now are very little - we hardly ever make a diagnosis based on this.

**Professor Leonard.** Yes it is well down the algorithm.

**Dr Anne Green.** You've also got available some molecular biology tests now for some of the disorders. So although you may have missed the time window for the acute metabolites, DNA may give you an answer. You can use the dried blood spots. You can pick up MCADD and LCHADD for example.

**Dr Walter.** And for investigation of OCT deficiency we would now look at mutation analysis before undertaking a liver biopsy.

**Dr Baumer.** But whether one needs that algorithm depends who you are writing it for. As a general paediatrician I wouldn't embark on any of that.

**Professor Leonard.** No, it's for the small number of patients like John has described who have had a severe illness, he suspects a metabolic disorder and can't get an answer. It's not for the generalist, we're writing this for ourselves really.

**Dr Bonham.** Near the top of that algorithm - if you do miss that diagnostic window then consider use of the stored dried blood spots from new born screening.

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### ***Question 2.2.2***

- a. ***What is the incidence, among all patients presenting or referred to A&E, of acute illnesses in which encephalopathy is a feature?***

***Dr BARBARA PHILLIPS (not present)***

The majority of children attending an A&E department in the U.K. present to a District General Hospital, which sees patients of all ages. Children make up approximately 25% of the numbers presenting. About 8% of children presenting to A&E departments in the U.K. present to specialist children's emergency departments. There is quite a wide variability in the case mix of children presenting to A&E departments.

This varies with geographical location and the presence of other facilities. In general, in areas where there is good, easily accessible primary care, the children presenting to A&E departments largely have traumatic conditions. Within inner city areas where primary care may be less accessible out of hours or less well regarded by the population, more children with acute illness present to A&E as well as children with trauma. With regards to the departments in specialist children's hospitals that see only children, there is an increased incidence of "medical illness" as there is public perception that these departments are more likely to be appropriate providers of specialist children's care.

It is therefore difficult to give an understanding of the frequency of presentation of encephalopathy within patients presenting to A&E even were this to be a presentation that was generally recorded. There is no universal system of data collection within A&E departments making large scale comparisons difficult.

The vague nature of the presenting symptoms of metabolic conditions makes estimating the incidence of patients presenting with encephalopathy virtually impossible. Such patients will present as "vomiting", "generally unwell", "irritable", etc. I have examined the presentations and final diagnoses in the A&E department at Alder Hey in the first three months of 2002. No patient was designated as attending with "coma". Those known to be unconscious on arrival had presented as "head injury", "diabetic", "? overdose", "generally unwell". The discharge diagnoses from the department reflected the point to which the diagnostic process had proceeded and included "septicaemia", "? meningitis", "epilepsy", "blocked shunt", etc. There were no identified cases of metabolic disease.

The only study of which I am aware which has looked at Question 2.2.2 a, is the prospective population based study reported in the Archives of Disease in Childhood, 2001 March Vol: 84, p. 193-199 by Wong, Forsythe, Kelly and Eyre. "Incidence, aetiology, and outcome of non-traumatic coma: a population based

study. This is quoted in Dr. Tasker's response to you. The other studies of which I am aware are all much earlier than this and occur around the National Childhood Encephalopathy Study, which was a product of the pertussis "scare" in the 1970's.

***2.2.2 b And in what proportion of these is an obvious cause quickly apparent after admission? What does quickly mean? Into what main diagnostic groups do these other causes fall?***

As described in Wong et al's paper meningitis/septicaemia in my experience is the commonest cause of drowsiness/coma with a short term onset of a few hours and in the absence of a history of head injury, intoxication or epilepsy. Intoxication is clearly easy to diagnose where there is a history but in a proportion of cases in both the toddler and teenage age groups there is no history. Physical findings can be helpful but in A&E departments there is a high suspicion of intoxication both with alcohol and other poisons such as methanol and with drug ingestion. APLS and other teaching has emphasised the importance of hypoglycaemia as a cause/concomitant finding in any ill child and this would be done very promptly on presentation of any patient with a depressed conscious level and also any others who were ill, very young, vulnerable, septic, convulsing, etc. "Promptly" I would expect to mean while still within the emergency room of the A&E department, i.e. within an hour or two. These children would either have a diagnosis, a presumed diagnosis, be improving or have required the presence of the paediatric team/intensive care team/telephone advice from specialists because of continued deterioration.

***2.2.2 c How does the clinical and pathological features of that vast majority of infants and children who turn out to have a common and benign illness differ from those ultimately confirmed as having Reye's syndrome/metabolic disease***

I would like to turn this question around and ask how those children with RS/IMD differ from the vast majority of infants and children who turn out to have an alternative diagnosis (many of which will not be common or benign)! The important question is "Is hypoglycaemia an important differentiator between RS/IMD and other conditions" and "Is hypoglycaemia which is difficult to treat/resistant to treatment a good differentiator of RS/IMD from other causes of hypoglycaemia"?

## **DISCUSSION**

**Dr Tasker.** We were involved in a population-based study in the North Thames Region where, over a year, 85 of 86 paediatric provider units contributed to an audit of every child with a North Thames postal code address presenting with preset criteria of critical illness. The incidence of critical illness was 1.8 per thousand child population and it was 13.6 per thousand children under one year. In my paper for this

meeting I've combined those data with the Wong et al data to produce a figure of one in 300 critically ill children who would have a metabolic encephalopathy. It's about one in 60 if you just look at it in terms of all non-traumatic coma.

The North Thames study specifically addressed children that would meet high dependency criteria. Only something like 55-60% of that population ended up being intubated; the remainder were managed without endotracheal tubes. That's the Maybloom study referenced in my paper.

**Dr MacFaul.** That's very interesting. But if we then step a bit further back up the severity scale to the child who is just "starey eyed" and a bit off it, most of whom then get better but some don't - that's the challenge for the A & E doctor isn't it, because only a small subset of those children will actually become critically ill, but they still need assessing. Do we have a handle on the size of that problem presenting to A&E?

**Dr Glasgow.** All I can do is reiterate what's already been said about using the APLS approach bearing in mind that the APLS approach is for the first hour only. Having in that hour corrected metabolic abnormalities, hypoxia, shock, hypoglycaemia, then one has to go on to the next stage in patients who have not responded to any of the aforementioned and who are still obtunded. So it's a step wise progression.

**Dr MacFaul.** But what about the case that Dr Hall presented earlier: they've come up to A & E, they've been sent away. What you have just described is a child whose trajectory of illness is progressive, but there are some who go up and down and perhaps aren't being recognised, are being discharged, and are either dying at home or coming back in more ill because the **state variation** has not been observed over a long enough period. That's an issue isn't it?

*(general murmurs of agreement from participants)*

I don't know how commonly *that* scenario occurs - do we know from the parent support groups?

**Mrs Lesley Greene.** I couldn't give exact numbers but we certainly have cases of parents who have gone with their child to A & E and of course it's usually early in the morning - you know the sort of six o'clock twilight period, and I am aware of families where the parents have been sent away with a child who has subsequently died.

**Dr Glasgow.** We're hoping that the document that the College has produced called "The Designated Liaison Paediatrician" [published by RCPCH 2001] may improve the linkage between acute paediatrics at the DGH level and the Accident and Emergency department which is of course run by a completely different group of people and who are competent to manage people with every condition at every age. There are things that they do better than us and there are things that we think we do better than them - for example the young patient with metabolic or other non-traumatic illness. We need quite a lot of contact so the accident and emergency doctors and paediatricians move their practice closer together.

**Dr MacFaul.** Following up again the same point about children who present with Reye's syndrome or inherited metabolic disease - what proportion of those children do *not* just steadily or progressively become worse? How many are in the mild range and just stay there?

**Dr Glasgow.** Lichtenstein in the US has shown - only 5% or some quite small proportion like that of their Stage I RS patients progressed into deeper levels of the scoring system that they used. [Lichtenstein, P.K., Heubi, J.E., Daugherty, C.C., Farrell, M.K., Sokol, R.J., Rothbaum, R.J., Suchy, F.J. and Balistreri, W.F. (1983) Grade I Reye's syndrome: A frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. *New England Journal of Medicine* **309**, 133-139].

**Dr MacFaul.** Is there a challenge here to pick out the ones that are at the milder end of the spectrum?

**Professor Tanner.** I think there is. I am aware of at least two children with MCADD who have died and who had previously come to an A & E department with nonspecific illness and appeared slightly drowsy with a lowish blood sugar; they had a drip put up and within a couple of hours were described as better - they made a very rapid recovery. The crucial tests i.e. looking for ketones at the time they were hypoglycaemic, measuring the phenylhydroxybutyrate, were never done, and they subsequently died. So I think that's a real problem - the child who gets quickly better is not necessarily *not* suffering from an inborn error.

**Dr Green.** I agree. Anecdotally our observations are we have got quite a few MCADDs that are exactly as you have described. They have not been investigated thoroughly for hypoglycaemia and I think here we need a standard protocol for investigating hypoglycaemia in any A & E department if you haven't got a reason for the hypoglycaemia. They get better, they go home, and we've had cases where they've come back maybe six months later with another episode and that's when the diagnosis has been made. With

urea cycle disorders and the organic acidaemias we've had cases where they've come to A & E (which is in a specialist teaching hospital) vomiting, have been treated symptomatically, gone home but got worse and then come back days later and only then has the diagnosis been made. So that's why I think we should be investigating with proper protocols in A & E departments.

**Dr Glasgow:** But this is really quite different from what Dr MacFaul was asking about earlier regarding the "trajectory of (an) illness" as he called it. This is a "relapse" or "recurrence" of decompensation; do we need to separate the two types where one is a prodrome so to say, and the other is another separate episode entirely?

**Dr Champion.** In casualty, standard treatment for gastroenteritis is appropriate for initial management of the inborn errors so they may get better and the diagnosis isn't made. That's why history taking is so important. Have there been previous episodes, were they were breathing very hard that time etc.

**Dr MacFaul.** There are major training issues here.

**Dr Tasker.** There are a number of parallels I am seeing here with our head injury system. Maybe the line we should take is to have a similar protocol, but for non-traumatic coma. Just as in the head injury patients, in the group that we are sending home we give them a return card - things to look out for. If any of these occur come back straight away. Surely there must be similarity to the issues that you are raising about the child that's coming in a little hypoglycaemic, then seems to be better and you send home.

**Mrs Lesley Greene.** We've had cases where parents have taken their sick child to an increasing number of GPs whose cover overnight is housed within district general hospitals. They've been turned away with dioralyte and of course when the child subsequently dies and they realise that they've actually travelled up once to the hospital where the A & E is on the same site and they haven't even been referred by the GP to the A & E department that has a profound effect on the family sense of guilt.

**Dr MacFaul.** I referred earlier to a PhD student's work on parents' experience of illness. She found that the parents who are seen do not know when to return - they feel really under-confident about when to re-approach health care professionals, so this idea of a return card would resonate very well with that parental need, so that is a very important piece of information.

**Dr Hall.** Coming back to the case that I presented at the beginning again - this child who came to A & E with gastroenteritis and the parents describing her as unusually lethargic. She didn't even get as far as being labelled as hypoglycaemic because she had no investigations whatsoever.

**Dr MacFaul.** There is increasing reluctance to do tests although a lot of patients get oxygen saturation because it's non-invasive.

**Professor Stephenson.** Just to put this needle in a haystack back in context: extrapolating from our data - between 50 and 100 thousand children attend casualty departments every year in the United Kingdom with vomiting and that's not counting the number that just go to the general practitioner or phone NHS Direct. It's the third commonest presenting problem in children without trauma. And the standard treatment for gastroenteritis is not to put a drip up in this country, but to recommend dioralyte or enteral rehydration as the first management. If that is unsuccessful clearly there are other stages. So you've got to see this very big haystack and very small needle. Thirty per hundred thousand will have an inborn error so this approximates to one a year out of every three hospitals.

**Mrs Lesley Greene.** Could I go back to the idea of the call back card? Parents that pitch up in A & E are anxious and once they've said there is nothing wrong you go away really with your tail between your legs, and you are very, very nervous about coming out again. It takes even more courage the second time so I do think that a call back card that is based on the clinical belief that if such and such happens again, or continues to happen, you must return, will give parents more confidence that they are actually doing the right thing and that they are not being fussy and over anxious. *Ninety nine point nine percent of our parents were labelled over anxious.*

**Dr MacFaul.** Clearly the severe end of the spectrum will usually get recognised but these groups that are non-specific in the first couple of presentations are a problem. It does lend an argument very strongly for screening for all of these disorders.

*(General murmurs of agreement).*

**Dr Bonham.** Certainly technologically, even with the very large "haystack" that Professor Stephenson was talking about earlier, it's not impossible to screen all of those children presenting to A&E with a vomiting illness - even if it is say fifty thousand per annum, what we are effectively talking about is five thousand per Region the size of Trent. To do five thousand acyl carnitines a year is not trivial but it is by

no means prohibitive.

**Professor Tanner.** In the context of hypoglycaemia in casualty in small children can I just mention “Ribena Toothkind” and other similar low sugar or no sugar drinks that, in my experience, are increasingly given to children with gastroenteritis. We seem to be seeing more and more hypoglycaemic youngsters who have had drinks like that. Fortunately in Sheffield we do have a system where all the low sugars automatically have intermediary metabolites done, but this must be a real source of confusion in hospitals that are less lucky with their chemical pathology. I guess it might also be dangerous in that casualty officers all say - oh yet another vomiting child with a low sugar - we see so many of those nowadays!

**Dr MacFaul.** What figure for blood glucose do you use as your cutoff for further investigation?

**Dr Bonham.** 2.5

**Dr MacFaul.** Again that’s a useful practical point. Does anything appear in the APLS literature about when to investigate or follow up a glucose found to be at that level?

**Dr Tasker.** It talks about what’s normal and what’s abnormal and then there’s this wonderful phrase “refer for definitive care”. There is an algorithm telling you what you would do and who you would call.

**Dr Glasgow.** We do need to remember that it's talking about resuscitation *in the first hour* of management - it's not a definitive management document.

**Professor Berry.** How many inborn errors do you pick up by doing your screen on all those with blood sugar of less than 2.5?

**Dr Bonham.** I haven’t got the figures but we do find them.

I think it is also important to remember that the BM stix are not an accurate method of determining hypoglycaemia.

**Dr MacFaul.** That's all we've got and we have to live in the real world but I think it's very difficult for us if our immediate instruments are faulty.

**Professor Leonard.** Actually there is some positive predictive value in them, though their limitations must be recognised, but they are actually better than nothing at all.

**Dr Tasker.** Regarding taking APLS beyond the first hour - there are a number of issues that are developing in the paediatric intensive care/high dependency care world. They recognise that there is a group of children that need the APLS-like approach, but extended over a much longer period once these children are on the ward. So I think it is possible potentially to develop protocols to ensure that all the bases are covered; I know that the World Federation of Paediatric Intensive Care Societies is looking into this.

**Dr MacFaul.** From a national perspective there is political concern that children with acute illnesses are not necessarily being recognised as well as they ought to be - that's those with infection as well as metabolic disease. This is evident from CESDI and from the College work on meningococcal disease. So this is a timely topic - what we have heard about encephalopathies we are now also hearing about management of acutely ill children who are "a bit off it" and it does seem that there are a number of messages here which are generalisable to other illnesses as well.

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***Q. 2.3 Other acute presenting features – what else to look out for on clinical examination  
What is the range of other initial clinical presentations of illnesses that are ultimately diagnosed as:***

***a) classic RS (including stage 1)?***

***DR JOHN GLASGOW***

These comments should be seen in context with those in my other papers for this Workshop at paras 2.2.1 (encephalopathy...), 2.2.2 (A&E case mix/ context), and 6.1 c (under/ late diagnosis).

When compared, the nature of the RS prodrome tends to differ significantly from the vast majority of children with viral respiratory infections) - especially as time goes by. There is however much overlap and this is part of the recognition problem. In the one, rhinorrhoea, cough, sneezing are more common whereas in RS, headache, abdominal pain, anorexia and vomiting predominate. This was the case in 6/ 23 (26%) patients I published in 1984 [Glasgow, J.F.T. (1984) Clinical features and prognosis of Reye's syndrome.



*Archives of Disease in Childhood* 59, 230-235] and were accompanied by either restlessness or screaming episodes or both. These were of sufficient severity in five for the GP to have been called – actually twice to three children. *It is the development of (possible) encephalopathic elements that should alert us to the possibility of RS.* At its simplest (this is not a simple area) *encephalopathy is defined as a diffuse disturbance of brain function that results in behavioural changes, reduction in consciousness, or seizures* (JT Parke in Oski FA, 1994).

In RS, we need to ask - is the drowsiness part of an acute feverish illness, or is there sufficient cause for concern because of a greater reduction in consciousness. Behaviour may be altered also. A child's behaviour should make one reflect perhaps more often than it does. Let me explain what I mean; I am always amazed at how willingly young feverish children allow a total stranger to approach/ touch them whilst being held and comforted by a caring parent. Much less often we see those whose experience has sensitised them to clinical examination; they need a break, perhaps anti-pyresis, and a second look. There is a third group where it is impossible to “connect” with a child, a feature confirmed by the parents - these should arouse our suspicion of encephalopathy. Partin makes the perceptive comment that parents have often felt their child was more ill than the attending doctors [Partin, J.C. (1988) General management of Reye's Syndrome. In Wood, C., (Ed.) *Reye's syndrome* pp. 156-172. London: Royal Society of Medicine]. *The question is - are we listening, looking and perceiving as best we can or should?*

### **Vague prodrome**

The characteristic biphasic illness is often less evident, or is even absent, in babies and some toddlers. I reviewed the records of our 56 patients. Although a small series, we think it is the only one of its size and type, carefully contemporaneously documented (and followed), in the UK; however, it cannot represent *current* experience.

[There is an important point to make here. In my view there has been too much emphasis on the stereotypical case that I feel does not represent the whole truth as far as the UK is concerned. No less an authority than Darryl DeVivo (1988), admittedly within the N American context states:

*Most patients present a stereotyped clinical and laboratory profile facilitating the diagnosis in most situations. The diagnostic criteria include several elements....*

*The presence of an antecedent viral illness; a latent interval of several days before the onset of pernicious vomiting.....etc”]*

I have been surprised by the proportion of histories that do not conform to the stereotyped histories much

quoted in textbook and research literature (note the Methods section of the Lichtenstein (1983) stage I study; here the prodrome is defined as an URTI with fever, cough, rhinorrhoea & coryza) [Lichtenstein, P.K., Heubi, J.E., Daugherty, C.C., Farrell, M.K., Sokol, R.J., Rothbaum, R.J., Suchy, F.J. and Balistreri, W.F. (1983) Grade I Reye's syndrome: A frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. *New England Journal of Medicine* 309, 133-139]. Nineteen patients fulfilled the entry criteria of whom 11 were said to have had an URTI and eight, varicella. However, in *our* patients the majority (38 in 56 or 68%) had an URT prodrome; only 3 each (11%) had varicella or diarrhoea as the main prodromal feature. Symptoms in a significant minority (11 of 56 i.e. 20%) were *much more vague and less characteristic*. In some, prodrome and the neurological phases appeared to merge without a distinct latent interval (see below). Here are some examples to illustrate what is meant by *less stereotyped* prodromal symptoms; the parents' histories given to the point of admission are quoted almost verbatim:

*A 5.5-month old girl* was ill for 5 days, crying a lot more than usual, described as being "off colour", with laboured breathing and being limp when handled; there was neither fever, nor other symptoms.

*A 9-month old boy* was ill for two days with afebrile "anorexia, vomiting, lethargy and listlessness".

*An eight-month old* who had had a low grade fever with a non-specific rash for no more than one day and had been seen by their GP, abruptly "collapsed with a seizure".

*Another 5-month old girl* (no salicylates) who was not feverish was refusing feeds and had a fine maculo-papular rash for 24 hours, was admitted at 7 pm. At 2.30 the following morning she became combative & was screaming; she had rather dilated pupils during these outbursts. By 4.00 am, she was not responding to her parents, was very drowsy but responded to voice, she was hyperventilating, the right pupil was slightly larger than that on the left, tone and DTR were increased, with bilateral Babinskis.

*Another afebrile baby* was listless, anorectic, and fretful for less than one day; when the GP saw him at 4.30 pm he sent him to hospital.

*A toddler aged 21-months* was just very irritable and "off colour for 2 – 3 days", had been seen by the GP twice, and had had "one loose stool".

Finally, *an 11-month old* in the course of a six day prodrome, was off feeds for 72 hours and highly irritable. He had seen the GP twice; on admission the anterior fontanelle was thought to be slightly tense.

These histories tend to reinforce the earlier point about the differentiation between the common viral URTI and the child with evolving classic RS. However, a more provocative question can be asked. Have the very narrow or exclusive terms in which some US (? only) authors define/ document their work, and especially the prodromal features, tended to delay diagnosis and management in some cases, and/ or might some cases actually have been missed entirely. My point is that one should think more broadly, and include the *minority* by being prepared to consider RS even when the history is "atypical". This thinking might be uncomfortable but I believe it has to be considered.

### Ultra-short prodrome

Moreover, the prodrome can be very short indeed - not the typical median of 3 days that is again often referred to. For example, in Lichtenstein's stage I study the *minimum* length of prodrome was three days (aver 6.3, max. 16 days) – whereas in 14/ 56 (25%) of our patients this lasted just 24 hours or less. When we compared (univariate analysis) the 13 with a poor outcome with the 35 who made a full recovery in *our first 48 patients* [Glasgow, J.F.T., Jenkins, J.G., Hicks, E.M., Keilty, S.R., Crean, P.M., Black, G.W. and Fannin. T.F. (1986) The prognosis for Reye's syndrome in Ireland can be improved. *Irish Journal of Medical Science* 155, 111-116], an ultra-short prodrome was present in 9/ 13 compared to 5/ 35 ( $P < 0.001$ ). Moreover, in the *total series of 56 patients*, 10 of these 14 with short histories reached the stage of coma III or IV, compared to four who did not lose consciousness (stage II), and made up 7/ 16 with a bad outcome (death/ disability). Hence it seems to be very important to recognise those with very short prodromal histories as these tend rapidly to progress to coma. And, as we will discuss later, management of comatose patients is very challenging.

You may retort that these were not good examples of “classic” RS, but of non-classic RS (what is this?) or of a R-LS/ IMDs; you may be correct – but if that is so the underlying cause has proved extraordinarily difficult to uncover. They all had high levels of blood ammonia and of transaminases, disturbed coagulation, respectably high Reye scores, all but one received aspirin, and, in a number, characteristic liver histology. Not all had electron microscopy done, however. This may in part be immaterial in today's context as all such patients require quality management and thorough further (IMD) investigations. We have investigated these patients and have recently gone through them all again and identified those that had any suspicious feature or family history and carried out tandem MS on blood and *all of these have again been negative*.

### Hepatic signs?

We are often told to feel for an enlarged liver. I have not found this to be helpful and in only two did I contemporaneously record that the liver was somewhat enlarged. In 29, I recorded the consistency of the liver as firmer than normal, in two very firm; but in the rest it felt normal, and in one it is recorded as soft. Although frank jaundice is atypical, we found that sub-clinical icterus ( $> 20 \mu\text{mol/l}$  on admission) was a feature in 7/ 40 in whom bilirubin was tested; four of the seven had a bad outcome.

### ***Differential diagnosis***

This tends to depend upon the age of the child and whether coma is present.

The sequence of events in which a mild viral illness (notwithstanding the vague symptomatology referred to above) is followed by vomiting and selective hepatic dysfunction, agitated delirium and coma is characteristic of RS (but see above comments on non-stereotyped histories).

1. In the **conscious patient**, consideration must be given to common viral URTIs, especially in the pre-school child or infant where vomiting is a prominent feature, as is frequently so in *pharyngo-tonsillitis*; the more so if *delirium is present* (this may extend to older patients also), or those having a *febrile convulsion*; or indeed, any patient with *seizure(s) or status epilepticus*.
2. *Anicteric hepatitis A or B, Epstein-Barr viral hepatitis, cytomegalovirus hepatitis, or  $\alpha_1$ -antitrypsin deficiency* may cause confusion. *Varicella hepatitis* is less likely in the absence of generalized varicella-zoster infection in an immuno-compromised individual (Lichtenstein, et al 1983).
3. *Margosa oil, and hypoglycins* (unripe ackee fruit) are known to cause similar illnesses, and *isopropyl alcohol* has been reported in association with a RS/ Reye-like illness (Glasgow and Ferris, 1969). Drug intoxication with *salicylates or paracetamol*, or anticonvulsant therapy with *sodium valproate* are much more likely possibilities in Western society, where *lead poisoning* is now excessively rare. Another is the admittedly rare child who *ingests some form of hepato-toxin*. In the mid-80s, we treated a boy aged almost four years (DS) who presented with vomiting and agitated delirium and encephalopathy that progressed to stage II. He developed hyperammonaemia, elevated transaminases, and very mild icterus. Time revealed a degree of brain injury and significant learning disability.
4. *Post-infectious encephalopathy*; we have seen this following acute viral infectious diarrhoea managed inappropriately with hypotonic IV fluids; see above).
5. Other disorders in which an abrupt increase in ICP occurs as in acute hydrocephalus, for example, due to a *posterior fossa tumour accompanied by vomiting, agitation caused by pain with or without some decline in consciousness*. Another real possibility is *shaken baby syndrome*, with or without seizures, associated with raised ICP due to *subdural, subarachnoid bleeding, or intracerebral contusion*; or indeed, *subarachnoid bleeding per se* due to rupture of an arterial aneurysm.
6. Occasionally, a primary *intra-abdominal emergency - intussusception or volvulus* - may confuse the unwary as vomiting, confusion and agitation are to the fore.
7. Similarly, those initially thought to have a *primary pulmonary illness* (GPs have often suspected “pneumonia” prior to hospitalisation) may cause initial confusion. There is preceding febrile URTI then the development of rapid breathing (central hyperventilation), and agitation (? hypoxaemia). However, the rapid respiratory rate will

not be associated with increased effort of breathing - such as recession, the  $S_aO_2$  is often normal, and the pH/arterial blood gases ought to show a *respiratory* alkalosis.

#### Differential diagnosis of the comatose Reye syndrome patient\*

Widespread hypoxic/ ischaemic insult - including liver and brain	Intracranial bleeding (eg subarachnoid)
Septicaemic shock	Fulminant hepatitis - especially in early infancy
Severe generalised viral infection - Eg adenovirus, varicella	Haemorrhagic shock encephalopathy syndrome
	Severe dehydration
	Apparent life threatening event
Salmonellosis, shigellosis	Metabolic disorders
Intracranial infection - eg meningitis, encephalitis	Drugs/ toxins (see above)

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\*Implies abnormal liver biochemistry

**2.3 Other acute presenting features –what else to look for on clinical examination: what is the range of other initial clinical presentations of illnesses that are ultimately diagnosed as:**

**b)Reye-like IMDs? Do they differ for each IMD/group of IMDs?**

**DR MIKE CHAMPION**

### **FAT OXIDATION DEFECTS**

Hepatomegaly (acute fatty infiltration)  
Cardiomyopathy [LCHAD & VLCAD]  
Pigmentary retinopathy [LCHAD]

### **UREA CYCLE DEFECTS**

Tachypnoea  
Hepatomegaly  
Trichorrhexis nodosa [ASA]

### **ORGANIC ACIDAEMIAS**

Tachypnoea  
Cardiomyopathy  
Macrocephaly/frontal bossing [GA-1]

### **OTHERS**

*Peroxisomal*: dysmorphic, large fontanelle, jaundice, cataracts, retinitis pigmentosa

*Mitochondrial*: pigmentary retinopathy, cardiomyopathy, cataracts

*GSD*: massive hepatomegaly, no splenomegaly

*LPI*: organomegaly, sparse hair

## **DISCUSSION**

**Dr MacFaul.** You are providing an argument for the existence of a core group of children that develop some kind of metabolic derangement in the context of a viral illness, some of whom go on to develop a serious illness characterised as Reye's syndrome; they don't have any positive results on investigation for an IMD, although this doesn't totally exclude the possibility of some kind of metabolic error, whether it's inborn or acquired or even whether it's induced by aspirin.

**Dr Dalton.** Can I just re-emphasise the point that everybody thinks that acyl carnitine measurement is the answer to this problem. It's not, because it does not rule out ornithine transcarbamylase deficiency, which is going to form a significant part of this group. If we look at the incidence in the literature, OTC deficiency is at least as common as MCADD.

**Dr Walter.** But if the ammonia has been measured and found raised, then this should initiate an algorithm of investigations appropriate to detect urea cycle defects.

**Dr Glasgow.** This is why we urgently need an algorithm that is logical and that is clinician-friendly and worked out by experts. Can I ask laboratory colleagues - is orotic acid measurement a test that can be used as a screening tool in a cohort of patients who have had a metabolic illness of unknown cause and have recovered, or is it only going to be present in large detectable amounts in a decompensation situation?

**Dr Dalton.** It is easier in a decompensated situation, but most of the time it will still be elevated provided you use a sufficiently low cutoff point. But there will be cases from time to time in whom, because they naturally exclude protein themselves, the level will be within the normal range while they are well.

**Dr MacFaul.** Do we reject the notion of Reye's syndrome as an acquired metabolic disease, rather than an inborn weakness of the metabolic system the nature of which

is as yet unearthed?

**Dr Glasgow.** I've always thought that classic Reye's syndrome is an acquired metabolic disorder. It only seems to occur once; I don't understand that, perhaps the biochemists or the geneticists can explain that to us.

**Professor Leonard.** Extrapolating from the examples of Type 1 and Type 2 diabetes I think the distinction is probably artificial because now we realise the importance of genetic polymorphisms in acquired disease.

**Dr MacFaul.** Then perhaps some of these patients may be inherently excessively vulnerable to salicylate or other drug exposures.

**Professor Stephenson.** In the 36 cases of Reye's syndrome reported to the BPSU in the final 6 years of surveillance only 8 were reported as having received aspirin, 13 had received paracetamol and in 10 there was no medication. So the admitting team shouldn't be dissuaded from considering RS in encephalopathic children who have apparently only had paracetamol; ascertainment of aspirin exposure in teenagers is extraordinary difficult because often the packaging doesn't have that name -it's called Anadin or Disprin for example. I think it's important we don't confuse our educational message by deterring people from considering RS because of the medication history.

**Professor Tanner.** I think some of your cases had skin biopsy fibroblasts studied by Dr Middleton to examine long chain fatty acid oxidation in the presence of salicylate. Can you comment on that and say whether the ones with abnormal findings tended to be those with the ultra short prodrome or the younger cases?

**Dr Glasgow.** Yes thank you. With Bruce Middleton and Raymond Moore using cultured skin fibroblasts, we studied the metabolism of labelled palmitate in the presence of aspirin metabolites *in vitro*. (Glasgow, J.F.T., Middleton, B. (2001) Reye syndrome: Insights on causation and prognosis Archives of Disease in Childhood 85; 351-353). We



saw a distinction between the fibroblasts from recovered Reye's syndrome patients (also given aspirin for prodromal symptoms) compared to controls; the latter had skin biopsy taken to exclude an IMD though none had ever been found. Hence they were considered to be "normal". In cells from the latter, two of the principal metabolites - hydroxyhippurate (HHA) and gentisate - were more inhibitory than salicylate at levels below 5mM, but RS cells were equally sensitive to all aspirin metabolites. Thus salicylate below 5mM was a more effective inhibitor of  $\beta$ -oxidation in RS cells than in controls.

Structural similarities between aspirin metabolites and substrates for the mitochondrial trifunctional enzyme (MTE) of  $\beta$ -oxidation prompted us to examine whether the long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) component of MTE was the target for salicylate inhibition. Using fibroblasts from individuals with LCHAD deficiency, it was possible to demonstrate complete absence of inhibition of  $\beta$ -oxidation by salicylate or HHA compared to control cells or RS cells, thus indicating that the LCHAD enzyme is the target for such inhibition.

Our studies have also shown that fibroblasts from RS patients were significantly more sensitive to inhibition of  $\beta$ -oxidation by salicylate than are control cells. The differences were demonstrable at levels well within the therapeutic range of plasma salicylate (see above). In control cells, 1mM salicylate significantly *stimulated* palmitate oxidation, an effect quite opposite to that noted in RS cells; higher concentrations caused increasing inhibition in each group of cells. Stimulatory then inhibitory effects of salicylate on  $\beta$ -oxidation were reported at similar concentrations in rat liver slices [Maddaiah VT, Miller P.S. Effects of ammonium chloride, salicylate, and carnitine on palmitic acid oxidation in rat liver slices. *Pediatric Research* (1989) **25**:119-123.]. Thus stimulatory and inhibitory effects of salicylate were independent; only the latter was due to blocking of LCHAD activity.

How might this stimulation of  $\beta$ -oxidation, at therapeutic salicylate levels, be induced? Salicylate, though not HHA or gentisate, is known to uncouple mitochondrial  $\beta$ -oxidation from phosphorylation. Thus the stimulatory effects in

control cells might be due to the presence of an uncoupling protein. In RS cells, it is possible that salicylate does not uncouple oxidative phosphorylation because a specific target protein is absent. This target protein we suggested is likely one of the family of mitochondrial uncoupler proteins (UCPs) [Ricquier D, Bouillaud F. The uncoupling protein homologues: UCP1, UCP2, UCP3, StUCP and AtUCP. *Biochem J* (2000) **345**:161-179] whose role is still unclear. Their expression is increased under conditions in which long chain fatty acids accumulate, prompting the suggestion that, by stimulating mitochondrial respiration they enhance  $\beta$ -oxidation, thus protecting against apoptosis. Lack of a specific UCP, howsoever caused, might explain the difference in  $\beta$ -oxidation response to low concentrations of salicylate between controls and LCHAD deficient cells on the one hand, and RS cells on the other - a difference that warrants further investigation. This sensitivity of RS cells, if widely expressed in body tissues, could explain the reaction of certain individuals to the action of aspirin on the MTE-LCHAD enzyme system that might contribute to the pathogenesis of RS.

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#### **SUMMING UP Dr MacFaul.**

In an earlier part of this session we heard that a substantial proportion of the inherited metabolic diseases present in the early months of life and whether they are really being managed properly I think requires some kind of evaluation. In older cases many, before they became ill, have developmental problems which is a signal to admitting doctors that if they have an infant or toddler with such problems in the context of an acute illness when they are presenting for the first time, that's a warning flag that there may be other problems here.

Unlike classic Reye's syndrome there doesn't appear to be a seasonal incidence in presentation of IMDs other than their decompensation being associated with viral infections. But it is clear that the majority of the presentations are in infants and young children up to perhaps the age of five. A positive family history is helpful but a negative one is not. But it should be sought, and we need to make sure that

histories are taken properly, even in the course of the busy A & E assessment.

Does Reye's syndrome exist? Some of the discussion we've just had about the notion of acquired illness against a background of predisposition probably provides an answer. But I think what I've heard today suggests that the real characterising features of classic Reye's syndrome are still somewhat fuzzy. The USA cases seem to differ in a number of ways from the British ones.

When we came on to encephalopathy and the management thereof there were a lot of messages there for education and training. In the child with an acute presentation of an encephalopathy how do we identify whether they've got a bacterial illness, whether they've got viral encephalitis or these metabolic diseases. Apart from the resuscitation ABC etc. this does require a standard process of approach - for example the state variation, the use of the GCS and so on.

The point that was made which I am going to emphasise because I think it is so important, is that if you have an acute encephalopathy it is not just the conscious level that needs assessing, it's seeking the other signs of emerging brain herniation which means really immediate therapy where seconds and minutes matter - very important in terms of educational material. We need to study the newly proposed Glasgow coma scale.

As far as the management of acute encephalopathy is concerned and what is done in terms of investigating it - the right samples - guidance is needed on that. One of the eventual outputs of this Workshop hopefully will be - what samples do we collect; how do we store them; and how quickly do we transfer them. That would be very helpful for most hospitals who are dealing with acutely ill children.

We've gone over the recognition of acute illness and the presentation when the child is just not really very well - can we identify the ones with subtle illness who are going to deteriorate, like the case presented at the beginning of the Workshop. I think we need to revisit this altogether.

I think we do need to emphasise how much we need paediatric pathology in this country, and how important it may well be to store some material for later revisiting - not just for the interest in the child who has died, but for the sake of the family for genetic advice. That's a message which needs to be got across but the training of pathologists is clearly an important issue.

When we get a case presenting with a Reye's syndrome-like illness and want to investigate for an IMD we need guidance from our metabolic colleagues and an algorithm would be helpful. We've learned also about the low incidence of IMDs among the large numbers of children presenting to A&E with nontraumatic illness and this does seem to lend an argument for neonatal screening for these conditions. If we can't screen the whole population one alternative that's been proposed is targeted or limited screening of those who have presented acutely. We might take that forward.

The warning sign of hypoglycaemia - never ignore it seems to be a good educational message to get across, always investigate it.

The parent return card is an excellent suggestion and resonates very well with the National Service Framework discussions.

**Dr Walter.** Regarding targeted screening I am worried that that might not be very effective particularly for conditions with significant mortality with the first presentation when clearly it is too late.

**Dr MacFaul.** I think that my own view is the argument for MCADD is clear cut, but how we get that across politically is another issue\*. I think the role of CLIMB and other parental groups exerting their leverage on our political colleagues could be a considerable one.

**Mr Denney.** Are we building up now towards what I call an action sheet?

**Dr McFaul.** I think today we've been characterising many of the problems for potential solutions tomorrow.

**Dr Hall.** So far we have been setting the scene and deciding that, yes, we do have a problem worth addressing and we are beginning to look at how to identify it. In the next sessions we will be getting down to specifics such as exactly what tests are practical and how to teach them. I envisage that we will produce a Proceedings Document out of the transcript of the meeting and submitted papers. A draft will be circulated to participants and you can if you wish contribute further to points that you might agree or disagree with, or want to highlight, or add practical details. The final product should be a useful resource for the development of educational packages or for any systematic review deemed necessary to produce an acceptable evidence base for a formal Guideline\*.

#### **END OF SESSION**

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\* nb. a pilot programme for MCADD screening based on six centres began in 2004 (Ed).

\* Nb Following the Workshop, the Reye's Syndrome Foundation funded a study to produce a formal evidence based guideline; for further information see [www.nottingham.ac.uk/paediatric-guideline](http://www.nottingham.ac.uk/paediatric-guideline). The study began in 2003. (Ed).

## WORKSHOP PROCEEDINGS: PART 3

### LABORATORY AND PATHOLOGICAL DIAGNOSIS: INVESTIGATIONS

#### ("BEST PRACTICE" -IDEAL WORLD - NO RESOURCE CONSTRAINTS)

**Moderator: Professor David Hall**

Dr Neil Dalton begins with the issues of laboratory diagnosis.

*(Workshop Questions 3.1 and 3.2)*

#### DR DALTON

##### Introduction

The laboratory objective in “classic” Reye’s syndrome is to ensure rapid and accurate diagnosis of hyperammonaemia. The inherited metabolic diseases (IMDs) presenting with a Reye-like encephalopathy have been tabulated, with approximate incidences, by Saudubray and Charpentier (Saudubray JM, Charpentier C. Clinical Phenotypes: Diagnosis/Algorithms in The Metabolic & Molecular Bases of Inherited Disease, eighth edition, Chapter 66, 2001). Consideration of the incidences emphasises the importance of inherited defects in the urea cycle and in fat oxidation. The laboratory objectives in this group of disorders are firstly to ensure rapid and accurate diagnosis of hyperammonaemia and/or hypoglycaemia and subsequently to provide a comprehensive differential diagnosis.

***3.1 a) What are the optimal initial investigations that should be undertaken in the local laboratory for:***

***i) RS? ii) IMDs?***

Because encephalopathy is the presenting clinical feature then the initial laboratory tests are the same whether we are considering RS or IMDs.

Plasma ammonia

Plasma glucose

Plasma/serum liver function tests (aminotransferases & bilirubin)

Urine ketones (dipstick)

***b) Should all of them be undertaken on every suspected case? If not, what are the clinical and pathological criteria?***

The tests should be performed on any child/adult with encephalopathy

***c) What specimens? How taken? How much? At what stage of the illness? Into what containers?***

It is essential that all the samples are obtained, and the tests performed, immediately on clinical presentation. The specific logistics and sample tubes will vary between hospitals. The absolute essentials are underlined.

#### **Plasma ammonia**

Inform laboratory that a sample for plasma ammonia is about to be taken, so that they are prepared to receive and analyse the sample stat.

2ml lithium heparin sample tube (batch checked to be ammonia free).

Normal venous/arterial blood sample, 1-2 ml, without constriction.

Sample should be kept on ice for transfer to the laboratory, must be separated immediately on arrival in the laboratory, and then analysed stat.

#### **Plasma glucose**

It is important that hypoglycaemia is recognised and treated rapidly.

A rapid NPT (near patient testing) blood glucose is essential together with a simultaneous sample for laboratory verification.

2ml fluoride-oxalate sample tube, 1-2 ml

Normal venous/arterial blood sample

Sample should be transferred to laboratory at ambient temperature and analysed stat.

Plasma/serum liver function tests

Standard serum separator tube, 5ml

Normal venous/arterial blood sample

Sample should be transferred to laboratory at ambient temperature and analysed stat.

Urine ketones

Dipstix

Fresh urine sample in 25 ml Sterilin container. NPT or preferably laboratory.

***3.2 a) Should all suspected RS/Reye-like IMD patients have acute specimens taken for subsequent non-routine investigations at a specialist laboratory? If not, what would be the criteria for taking these specimens?***

Samples should be taken for subsequent non-routine investigations at a specialist laboratory from any child/adult with encephalopathy. In many instances, but particularly where intensive care retrieval services have been established, the patient may be transferred to a specialist paediatric intensive care for treatment and investigation. However, it is essential that plasma and urine samples are obtained before, or at worst immediately after, treatment has been started.

***b) If so – what specimens? How taken? How much? At what stage of the illness? Into what containers? How should they be stored? Transported?***

In many instances, but particularly where intensive care retrieval services have been established, the patient may be transferred to a specialist paediatric intensive care for treatment and investigation. However, it is essential that plasma and urine samples are obtained at clinical presentation, preferably before, but at worst, immediately after treatment has been started.

### **Plasma**

2ml lithium heparin sample tube

Normal venous/arterial blood sample, 1-2 ml



Sample should be separated quickly and the plasma transferred to a specialist laboratory, preferably the same day, or frozen until dispatch.

Samples can be sent in appropriately sealed containers at ambient temperature by courier or first-class post

**Rapid clinical response to treatment should not prevent the samples being referred.**

*Appropriate tests by the specialist laboratory:*

Quantitative TMS plasma carnitine/acylcarnitine profile/amino acids (particularly basic amino acids)

Quantitative full profile amino acids

Non-esterified fatty acids and 3-hydroxybutyrate

### **Urine**

5-20ml fresh urine, no preservative, in a Sterilin container without preservative

Urine should be transferred to a specialist laboratory, preferably the same day, or frozen until dispatch.

Samples can be sent in appropriately sealed containers at ambient temperature by courier or first-class post

*Appropriate tests by the specialist laboratory*

Organic acids including orotic acid

Amino acids

Sugar chromatography

Referring to Saudubray & Charpentier, the diagnostic preponderance of fat oxidation disorders/organic acidurias means that a plasma acylcarnitine scan has become an essential diagnostic tool. This can be further enhanced to simultaneously include neutral and basic amino acids. The urinary organic acid profile, particularly hexanoylglycine/suberylglycine for MCAD, is also an important diagnostic test. However, I would like to emphasise the incidence of partial OTC and the critical importance of urinary orotic acid in establishing the diagnosis.

## **FURTHER POINTS MADE IN ORAL PRESENTATION**

### **Dr Dalton.**

I don't think we can ask for any more than plasma ammonia, plasma glucose, liver function tests, and urine ketones to be undertaken at the **local** laboratory. In some respects it seems we are asking too much by asking for those four, but actually those are what *should* be done and if they are not provided we have a problem in getting a rapid clue as to what is going on with a patient with encephalopathy.

Should we do these tests on every suspected case? Well, if we mean "best practice, ideal world, no resource constraints", then yes, they *should* be performed on *every* child *or* adult with encephalopathy.

Regarding practicalities of how specimens are taken - as far as plasma ammonia is concerned there is no doubt that if you want it to be done properly it's far better to let the laboratory know before you take the sample, and that you want it done straight away. We still use lithium-heparin sample tubes tested to be ammonia free. We haven't found any that have been ammonia contaminated for years but we still check them, on a batch basis. The essential point is that the sample should be sent to the laboratory *quickly*. If it's on ice it usually gets transferred quicker - it's a constraint that makes people realise that it is important! Even more importantly, it should be separated *immediately*. The main reason for a false rise in the plasma ammonia in a sample is lack of separation.

The main problem with measurement of plasma ammonia is that we do not have an adequate quality control system. If ammonia-based samples are sent out they *have* to be stable and, as a consequence of that, there is no test of anything other than the actual analytical system. So as far as that's concerned, the assays work. The problem lies in the pre-analytical phase, and we haven't as a profession addressed that.

*Plasma glucose:* In relation to what Dr Bonham said earlier, which we haven't put into place but have thought about it- *that* sample is a critical one because it allows you insight at the moment that the glucose may be abnormal, so if you can use it to subsequently measure the intermediary metabolites, the amino acids and acyl carnitines, this can be extremely informative.

Should *all* suspected patients have samples taken for non-routine specialist investigations? If a patient has encephalopathy I think we *should*. However, that could be a significant workload, and has to be thought through. But for the patient with severe encephalopathy who is likely to be for retrieval by a PICU team, then it is *absolutely essential* that they are taken. At the lower grades I don't know where you put the cut offs, as I'm not a clinician - that's a point for others. It is *essential that plasma and urine* samples are obtained *at clinical presentation*, preferably before, but at worse immediately after, treatment has been started.

I re-emphasise here that *a rapid clinical response by the patient to treatment should not prevent samples being referred to a specialist laboratory*. This is because this response can often be so quick - even with encephalopathy caused by an inherited metabolic disease - that the patient may be sent home without a diagnosis, only to return next time they decompensate.

Although it was not part of the brief, my paper does include what I think are the appropriate tests, certainly in the first instance, that should be done by the *specialist* laboratory on these samples. Can I emphasise to clinical colleagues regarding urine organic acids that they need to *specify inclusion of orotic acid* otherwise they are not necessarily going to get it, although they should do.

I want to make a couple of points about best practice.

First, regarding urine organic acids. If you look at the three disorders that come top of Saudubray's list, there is partial ornithine transcarbamylase deficiency - so we need orotic acid; next, MCAD - so we need hexanoyl glycine; finally, type 1 glutaric aciduria - 3 hydroxy-glutarate. Now the first two of these cause problems on the external quality assessment scheme and in order to ensure that they are done properly one *should* actually add in stable isotopes, so that it tells you - that you have extracted, that you have derivatised, that it's got through the liner and that you've detected it properly. It's relatively easy to do but often not done, yet the cost to add in those two internal standards is less than 5 pence.

Second, to emphasise the difficulty with 3 hydroxy-glutarate I am showing you a chromatogram from a patient who died with severe brain swelling with hyperammonaemia – a level of over two hundred. The chromatogram is not spectacular - there is virtually no glutaric acid in there at all, so even in the acute phase the diagnosis is not easy and could be missed. We haven't got an internal standard for this at present.

## **DISCUSSION**

**Professor Leonard.** Is it really necessary to use stable isotope dilution with the hexanoyl glycine assay if you look at the acyl carnitines?

**Dr Dalton.** The fact is that at the moment you are not necessarily going to get both and the assumption of most physicians if they send an organic acid, is that they will definitely have that discrimination.

**Dr Bonham.** I think it *is* necessary, because we've got good evidence that in a carnitine depleted patient you might not get octanoyl carnitine but you tend to get hexanoyl glycine.

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**3.3 a) How should the initial laboratory results be interpreted -what findings would suggest what diagnoses?**

**b) How do levels of plasma ammonia and other initial results affect initial differential diagnosis?**

**c) Can there be raised plasma ammonia in ill infants and children who do not have an IMD or RS or obvious liver disease? if so under what circumstances and what would be the clues that this was not an IMD/RS?**

#### **DR JIM BONHAM**

I have treated these aspects together by evaluating our own experience of hyperammonaemia over a seven year period 1993-2000 and by a ten year retrospective look at the literature to identify other secondary causes of hyperammonaemia. I have attempted to grade the degree of hyperammonaemia seen in association with various IMD's. Part of the information to support this is in the literature and part is gained from informal discussions with colleagues.

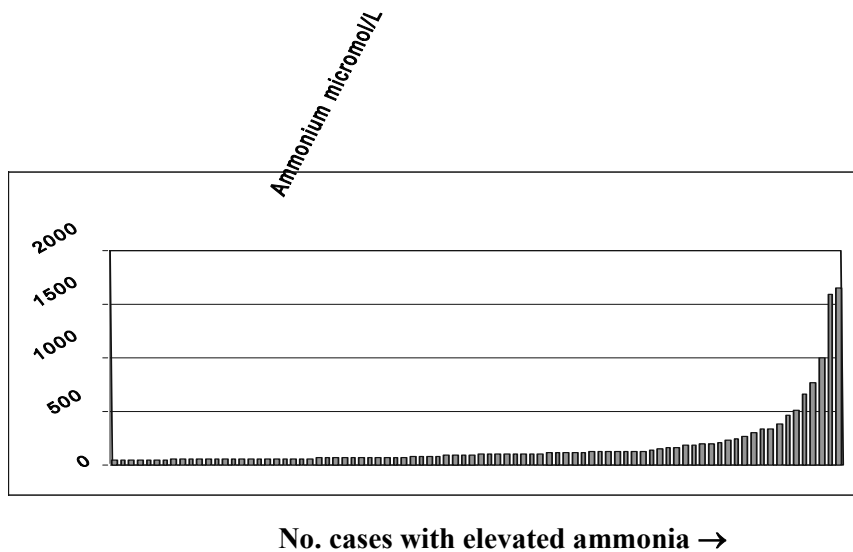
#### **Interpretation and investigation of elevated plasma ammonium**

##### **Reference ranges**

Child/adult	<50 $\mu\text{mol/L}$
Neonate	<100 $\mu\text{mol/L}$
Sick neonate	<150 $\mu\text{mol/L}$

##### **Sheffield Children's Hospital experience (1993-2000)**

- Measured ammonia on 673 occasions (approx 100/year)
- Elevated on 206 occasions (see Figure below)
- Representing 86 new patients with hyperammonaemia
- 16 of these >200  $\mu\text{mol/L}$  (see Figure below)
- 5/16 had features of mitochondrial disease
- 1 PDH, 1 GA2, 2 OTC
- 4/16 liver disease
- 1 contamination, 1 urease organism, 1 perimortem



### Causes of hyperammonaemia (experience and literature search)

- -Liver disease
- -Secondary causes without obvious liver dysfunction
  - Bone marrow transplant
    - *Davies, Bone Marrow Transplant, 1996;17:1119-25*
  - Valproate therapy
    - *Barrueto, Ann Emerg Med, 2001;8: 999-1001*
  - TPN and short bowel
    - *Kapild, JPEN, 2001; 25:286-8*
  - UTI and urease organism
    - *Cheang, Ped Nephrol, 1998; 12:658-9*
  - Multiple myeloma
    - *Martinelli, Ann Oncol, 1997; 8:811*
  - Ribavirin therapy
    - *Bertrand, Pharmacotherapy, 2000; 20:1216-20*
  - 5-fluorouracil toxicity
    - *Valik, Br J Cancer, 1998; 77:1710-2*
  - Portosystemic shunting
    - *Plauth, Gut, 2000; 46:849-55*

- Haemorrhage in GI tract
- *Dejong, Ned Tijdschr aeneeskd, 1998; 142:2558-62*
- RTA type 1
- *Millo, Arch Dis Childh, 1997; 77:441-4*
- Increased ethanol intake and starvation
- *Yuzuriha, Alcohol, 1997; 32:745-52*

•Inherited metabolic disorders

- |                            |   |
|----------------------------|---|
| - Urea cycle defects:      | OTC, CPS, ASAuria, citrullinaemia, arginase, HHH syndrome, LPI  |
| - FAO defects:             | LCHAD, CATR, vLCAD, MCADD, GA2, CPT <sub>1</sub> , carnitine transporter  |
| - Organic acidaemias:      | PA, MMA, IVA, HMG CoA lyase, holocarboxylase synthetase   |
| - Mitochondrial disorders: | Respiratory chain, HSP60  |
| - Others:                  | NKH, P5CS def <sup>n</sup> , PDH, hypoglycaemia/hyperammonaemia syndrome, combinations (drugs and mild disorders) |

## Grading and interpretation of ammonia levels (experience, discussion and literature search)

+++ (> 600 $\mu\text{mol/L}$ )	Urea cycle, disorder (except arginase deficiency), PDH, PA, GA2
++ (300-600 $\mu\text{mol/L}$ )	CATR, LCHAD, VLCAD, MMA, arginase deficiency
+ (50-300 $\mu\text{mol/L}$ )	MCAD, CPT <sub>1</sub> , carnitine trans, MMA, IVA, HMG CoA lyase, holocarboxylase, respiratory chain, NKH, pyruvate carboxylase

## FURTHER POINTS IN ORAL PRESENTATION

### Dr Bonham.

I was asked to say how should the initial laboratory results be interpreted - I think the answer is - with caution! Our experience from the Quality Assurance scheme, which is operated throughout Europe and which covers about 130 laboratories, is that if, for instance, a urine sample from a patient who is known to have MCADD but who is not in crisis, is sent out, it is missed by about 30% of specialist laboratories within Europe as a whole. So we do have problems with interpretation.

We also have problems with some of the initial basic investigations such as glucose. Dr Walter has already mentioned the problematic use of BM stix in A & E. I think in fact that was actually contraindicated by a Medical Devices Agency letter that was sent out three or four years ago. Many A & E departments, including our own, have abandoned the use of BM stix in ICU and in A & E, but nevertheless we know that they are still in use in other places and they can certainly both overestimate and underestimate results. We also know that hemocue technology is problematic and can overestimate by one or two millimoles per litre consistently in some, though not all, patients.

One of the interesting observations that arose from this review of our experience in Sheffield with measuring plasma ammonia 1993 -2000 was that we don't do that many and we probably do too few. Currently we do about 200 a year but during that period the annual average was about 100. The



reason for the recent increase is that, compared to the previous more demanding assay, it's now easier to do - we are using a dry strip technology using Vitros analysers.

Among the 16 cases reported in my paper with an ammonia greater than 200, seven were aged one month to five years, the rest were neonates. It is interesting that "query" mitochondrial disorders featured quite highly in this group and then, in addition to liver disease, there was the scattering of other conditions such as glutaric aciduria type 2 and multiple acyl CoA dehydrogenase deficiency which can sometimes present with severe hyperammonaemia. One of those was up to almost 800  $\mu\text{MOL/l}$ ; PDH deficiency can present with very high ammonia levels and in this series the one case was a little girl with an ammonia of over 1500 $\mu\text{MOL/l}$ .

The second question I was asked to address was - are there *other* potential causes of increased ammonia that are not caused by an IMD or Reye's syndrome. The answer is yes - if nitrogen load is excessive as, for example, might occur with bone marrow transplant or myeloma or haemorrhage, then a modest or even moderate hyperammonaemia can be generated. Anything which creates a secondary interference, particularly in patients who may already be vulnerable, for example valproate therapy, fluorouracil toxicity, sometimes precipitates the recognition of an unidentified inborn error of metabolism, sometimes quite late in life as described in one of the above references for a girl with OTC deficiency. Most alternative causes of hyperammonaemia will be obvious, but clearly there is a need to take a careful history. One that can be misleading is urinary tract infection with a urease-producing organism which can produce quite significant hyperammonaemia.

Regarding the inherited metabolic disorders - just one point about the mitochondrial disorders: we did some work looking at the specificity of the allopurinol loading test and we found a lot of false positives. We found a significant group within that cohort of patients with a positive allopurinol loading test who had moderate hyperammonaemia, some times up to 3-400  $\mu\text{mol/L}$ .

In attempting to get some feel for interpretation I graded the severity of the hyperammonaemia seen in some of these disorders. It is a debatable list, taken from my own experience, looking through case reports over the past 10 years and talking to colleagues. Most of us would agree that the urea cycle disorders - particularly CPS deficiency and OTC deficiency produce some of the highest ammonia concentrations especially in the neonatal period. They don't necessarily produce those kinds of concentrations in a late presenting OTC. One of our cases was a girl who presented at two

years of age, and her ammonia was, relatively speaking, modest at around 300  $\mu\text{mol/L}$ .

I think what is always relevant is that if the biochemical machinery is “broken”, then you get more heterogeneity than when the biochemical machinery is not broken. So because the normal homeostatic mechanisms don’t work there can be a lot of variability. So certainly there *are* LCHAD patients described who have had ammonias over 1000 $\mu\text{mol/L}$ , but in general the fatty acid oxidation defects produce mid-range ammonia levels. Finally there are a number that produce generally speaking more modest hyperammonaemia, some of which would nevertheless creep into the level where it would be treatable of itself rather than just useful as a diagnostic indicator.

## **DISCUSSION**

**Dr Glasgow.** How useful is the prothrombin time or INR as an initial investigation? I do think it can be useful in differentiating some of these disorders particularly classic Reye’s syndrome, although the urea cycle defects will show a problem here too.

**Dr Dalton.** I agree entirely - it is useful.

**Professor Leonard.** The problem of the interpretation of the actual value of the plasma ammonia can cause *real* difficulty - not those over 200  $\mu\text{mol/L}$ , but those of 80 to 100 because it’s very difficult to know just what these mean. We see a lot of values in this sort of range. In a child who is unwell (and the problem really gets worse if that child’s already been on no protein and a glucose drip for twenty four hours), it really becomes extremely difficult to interpret. This is where the initial admission specimen is so useful if it can be retrieved. We *must* emphasise this point about storing specimens and try to persuade chemical pathology departments to do this even if only for a few days.

**Professor Hall.** Can I ask Dr Dalton about the direction of error in the ammonia result which will occur as a result of not following your careful protocol. Is it likely to go too high or too low or can you get errors in both directions?

**Dr Dalton.** It’s predominantly false positive. You could argue that that’s not a problem because the children were then being further investigated, but my own experience is that if you have a

significant number of false positives you lose the confidence of the clinicians doing the requesting and your work load will drop as a consequence.

**Dr Walter.** We should add blood gas analysis to your list of initial tests as we have got no measure of acid-base status. Also, regarding false positives and false negatives of hyperammonaemia - we have had children referred to us who have ammonias reported as being about  $287\mu\text{mol/L}$ , which I think was the cutoff for a “kit” used at the DGH, but when we did it, it was several thousand.

**Dr Champion.** It is important to teach junior doctors to try to reduce false positives caused by squeezing or using capillary samples, because there are difficulties getting ammonia done at local laboratories which isn't helped if you're having to ask for repeats because the level is raised on the first sample.

**Professor Leonard.** A problem that we also see is that people don't believe their first result if it's very high. They then repeat it and so by the time they refer, there is a real problem. So there's an important balance to be found to get it right.

**Professor Hall.** Can we also just clarify whether you should take a venous versus an arterial sample for ammonia?

**Dr Bonham.** It doesn't really matter.

**Dr Anne Green.** I think any guidance that is produced about the quality of the sample for ammonia must advise against capillary specimens and also emphasise that haemolysis can cause artificially elevated results which sometimes still isn't appreciated.

The “kit” that Dr Walter referred to is a meter device. We've had similar incidents in the West Midlands where its upper limit of, I think, 296 was obtained but we found concentrations of over  $1000\mu\text{mol/L}$ . The problem is the local hospital may believe it is  $296\mu\text{mol/L}$  when actually it is much more.

My other point is we do provide a service for ammonia measurement for some local hospitals that aren't far away. We find it satisfactory, providing they separate the specimen *immediately* at their

end and send the frozen plasma to us *immediately*, we get reliable results.

**Dr Bonham.** We've had the same experience with people using this meter: three or four instances with "this topping out" of this set level, sometimes repeated serially throughout the day and then when we eventually receive a sample the ammonia has been perhaps 800-900  $\mu\text{mol/L}$ . What we also often find - and I don't think we can emphasise this too much - is *variability* between ammonia concentrations recorded in the first hospital, and then perhaps a sample frozen and sent to another hospital, and then checked by us. They are very often quite different, particularly in the kind of levels that Professor Leonard was talking about as being problematic for interpretation.

**Professor Hall.** So - as far as getting an accurate measure of the ammonia level goes, there is not only a problem in getting a suitably taken sample to the laboratory, but equally there is also a problem of quality control in the laboratory itself?

**Dr Bonham.** Well there is, and it's very difficult to do external Quality Assessment.

**Professor Leonard.** I think what accounts for a lot of the variability is what happens to the sample *before* it gets to the laboratory. It's very difficult to get a perfect sample from a child who is thrashing around.

**Professor Stephenson.** I would like to bring this discussion back to reality. If I could just reiterate some of the very important statements we had yesterday: Dr Kirkham said that encephalopathy is any change in a child's interaction, reduction in consciousness or abnormal behaviour. That covers tens of thousands of children coming to hospital in the UK each year. We were also told that the incidence of an inborn error of metabolism *within* that presentation is about 30 per 100,000. Now we are having the suggestion that in *all* of those children, at least six tests are done immediately: ammonia, glucose, liver function, a urine sample (which is incredibly difficult to obtain in the middle of the night), a prothrombin time, an arterial blood gas, and a sample stored over the next few days. The blood must be obtained without venous constriction.

If you asked any junior doctors could they conceivably do all that under the conditions you are describing they will say you've lost the plot! The majority of these children - 40 percent we were told yesterday, will have possible infection and a further large number of cases of possible

encephalopathy will in fact be post ictal. But you won't know, as Dr Kirkham said, whether they *are* post ictal for another 30 minutes. Furthermore, they are all going to have venous constriction and it's very difficult to get a cannula in at two am to a one year old without this.

So I think we need to think about some more *practical* advice about a more *selective* approach, rather than just saying every adult and child with encephalopathy - as defined at this meeting, is going to have *all* these tests.

**Dr Champion.** Just tackling this problem the other way round, I think the frustration as a metabolic paediatrician, is that you see children who have been in intensive care for a day or more unconscious, and an ammonia has never been done. One isn't advocating *every* patient - you have to say when is your degree of encephalopathy severe enough to do these tests. But you *would* expect that a child who is in coma should have an ammonia done, which often isn't happening at the moment.

**Professor Stephenson.** I think that's constructive – to target a group where you think the risk of an IMD is much greater and *not* investigating is much more risky, is more sensible than saying that everyone who comes in with encephalopathy should have all these tests done.

**Professor Hall.** This problem extends to the more general context of A & E standards - the art of acute paediatrics is "smelling rats" - it's the case that's that little bit different that makes you think there is something going on and it's very difficult to teach that to junior staff.

**Dr Bonham.** At times people suggest that glutamine would be an alternative to ammonia. It's even been suggested that it's potentially been more sensitive. I was interested to know what others felt about that. We've looked at it and found very poor correlation. Certainly in a hyperammonaemic child you do see high glutamines, but it certainly can't be used, in our experience, as a surrogate for measuring ammonia if you've missed doing the ammonia but you have a plasma sample for amino acids.

**Dr Glasgow.** Regarding the observation about the need to be practical just made by Professor Stephenson - we have for some years had this idea that you need a *marker* to get these patients into the multiple test algorithm and the very important differentials. The marker we have used is

hypoglycaemia. That's not a catch all but hypoglycaemia *and/or* encephalopathy should be a catch all.

I want to ask colleagues here in how many regions have they tried to simplify the biochemical investigations? We have a pre-packed plastic bag of pre-labelled bottles with simple clear instructions prioritising tests according to the clinical situation and what, for example, to do if you can only obtain one ml of blood. We have found this very helpful for junior doctors.

**Dr Green.** We have a similar approach for investigating sudden unexpected death, where we have a kit in appropriate places. We haven't yet got anything along similar lines for encephalopathy or other query IMD but I think it's a good idea.

**Dr Bonham.** We have a similar approach for patients with suspected IMD.

It is essential that we set out a **manageable minimum sample set**, focusing on the need to do a laboratory glucose and then picking up that fluoride blood sample to do, for example, acyl carnitine analysis, free carnitines, free fatty acids, 3 hydroxybutyrate, and lactate. All of that can be done with less than one ml of whole blood, so it's not necessarily a counsel of perfection.

**Professor Hall.** What about the unreliability of the readings of glucose stix in both directions? Is this a good standard of practice or should we be getting rid of stix in A & E and should the standard be, as Dr Bonham suggests, to expect an accurate laboratory blood glucose within X minutes in any hospital seeing children?

**Dr Baumer.** In an A & E department with a large number of staff taking samples, it's really impossible to get the method to its optimum. I see these as screening tests and I would very much endorse the need to back it up with laboratory blood glucose.

**Professor Stephenson.** I think the stix probably need to be retained because of the large numbers of patients involved - our practice is that if the stix indicate a low blood sugar it must be confirmed with a proper laboratory sample in a fluoride tube. But the child with encephalopathy or seizures will *always* have a sample sent to the laboratory.

**Professor Hall.** But Dr Glasgow was suggesting there should be two ways into the diagnostic

algorithm - encephalopathy and hypoglycaemia. That means you want to trust your initial assessment of blood glucose.

**Dr Glasgow.** One other point about the taking of the sample for hypoglycaemia - I'm concerned that so many poorly perfused cold little digits are pricked in patients who are likely to be shocked and I have always questioned does this affect the accuracy of the result and why do we use them rather than earlobes or is that an unnecessary assault?

**Professor Hall.** It sounds to me there is need for an evidence review regarding these questions about what we really know about near patient testing for low glucose levels.

**Professor Leonard.** Coming back to Professor Stephenson's point about the need for practicality in A&E - I think we all accept that you cannot have all the patients having all the tests done. What we need to agree is that if the patient is still encephalopathic, say, three hours or four hours after admission or *certainly* if the child is admitted to PICU, then all the tests are needed. I don't know whether there's an evidence base for saying that if the patient is still unwell after a period of observation of x hours, then you need all the tests done, but that would surely cut the number down.

**Professor Hall.** That sounds deliverable and reasonable although turning it into reality on the ground might be a more difficult.

**Dr Bonham.** It is achievable to do better than stick technology in A & E. There are cheap alternative methodologies that wouldn't be out of the reach of any DGH or teaching hospital and there is good evidence to suggest that they perform much better. I'd be interested to know what others thought about that. Certainly we've abandoned stick technology at Sheffield.

**Professor Hall.** There seems to be quite a lot of *opinion* about all this and perhaps not a huge amount of *evidence*. It might be something we need to take further subsequent to this meeting. It's a very important issue.

**Professor Leonard.** Near patient testing must get the same sort of quality control that laboratories do. There's often a gap in quality control between what happens on the ward normally and what happens in the laboratories.

**Dr Tasker.** The definition of encephalopathy in the Wong paper on non-traumatic coma was a Glasgow coma score less than 12 for longer than four hours. Maybe *that's* a definition that could be used as a marker for undertaking the more in depth investigations. It doesn't deal with the child who is a bit vacant and not responding normally as per Dr Kirkham's definition, but it does take you to a smaller, more severe group.

**Dr Green.** Following on the issue of quality assurance of point of care testing - the way to improve this is to ensure that your point of care testing is included and complies with the accreditation process.

**Dr Walter.** A note of caution about recommending a period of observation before investigation:- in children who do have hyperammonaemic coma, if you wait four hours before you make a diagnosis, you are not going to get treatment in for another hour or so and that's a long period to be hyperammonaemic when it's a treatable condition.

**Professor Leonard.** Clearly those who are comatose are tested immediately. The problem lies in those in whom we are not sure whether or not they are deteriorating.

**Dr Naughten.** I would like to ask Professor Stephenson how good he thinks junior staff are nowadays at picking up big livers. No one has yet mentioned the clinical examination of the child and the fact that there may be a liver which is altering over a short period of time.

**Professor Stephenson.** There is no evidence base but I think with the shortening of doctors' hours and of training, people are probably less adept both at clinical examination of sick children and at taking good histories.

**Dr Glasgow.** In cases of classic Reye's syndrome, even with myself examining every one of the patients in my own series, I was not impressed with the size of the liver and in very few with the consistency of the liver.

**Professor Hall.** This discussion has generated a lot to think about, from the point of view of what the Royal College of Paediatrics and Child Health ought to be doing on what's really a very



common issue about the assessment of the acutely ill child. Particularly the place of doing blood sugars and what we mean by that and what the standards should be.

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**3.4 a) Should all patients suspected as having classic RS, irrespective of age, medication history, or clinical features, be fully investigated for IMDs?**

**b) Should classic RS *only* be diagnosed once every known Reye-like IMD has been excluded?**

***DR EILEEN NAUGHTEN***

**3.4a) YES**, but how far?

**Urine:** organic acids; orotic acid; toxicology

**Blood:** amino acids; ammonia; acyl carnitine; carnitine -total and free; **Beutler test**

**Skin** fibroblast culture

**3.4b)**

It is probably not possible to exclude everything or to say that someone has not got a metabolic problem. "Classic RS" will continue to be eroded into as other pathologies and mechanisms are identified.

#### **ADDITIONAL POINTS IN ORAL PRESENTATION**

**Dr Naughten.** I think we should drop the term "classic Reye's syndrome", because we are talking about a heterogeneous group of conditions. The main problem for all of us is - where and when do we draw the line and *stop* looking, as much as where do we *start*. Dr Glasgow has already said that he has reviewed his own cases but he still can't find a metabolic explanation even with the most thorough modern look at them.

There are a few Reye-like disorders that haven't yet been referred to: we recently reviewed a family

where one child had died of an illness we had called Reye's; one was a cot death; and then there was a boy who subsequently went blind. We eventually found that they all had a Complex I Respiratory Chain Disorder. It took years to find that.

The real difficulty for the busy casualty is - which ones do you look at in more depth? We teach our junior staff that no neonate should have ketones in its urine and I think in general paediatricians all agree that every sick baby should have its urine looked at whether you're looking for infection or ketones or toxicology. We have had maple syrup urine disease picked up in neonates on about the fourth day of life because of ketones detected in the urine - in two cases just a trace.

In terms of blood samples we haven't yet mentioned the Beutler test. It's a screening test for galactosaemia which you can do on whole blood or dried blood spots measuring galactose 1 phosphate uridyl transferase and I certainly think that all pathologists examining dead children should be doing this.

Finally, fibroblast culture may be necessary to help confirm the diagnosis.

## ***DISCUSSION***

**Dr Bonham.** Just commenting on the galactosaemia screening test: I think in practice very few galactosaemics would turn up beyond one month of age undiagnosed. Our experience is that although we don't formally screen for galactosaemia, virtually all of the ones that we've seen in the Trent Region over the last ten years have had elevated phenylalanine that we've detected from the normal Guthrie testing regime. But of course that result may not be back if the child presents with symptoms under one week of age.

**Professor Hall.** Dr Naughten made the important point that, in contrast to investigating all these cases up to the hilt, sometimes the problem is knowing when to *stop*. Because it's always the case that someone's just described yet another condition that this just might be, and presumably the laboratory could go on and on doing tests for ever. Do other people share that perspective - it's not something I'd thought of before. It's a question not of whether you start but when you stop.

**Dr Green.** One of the practical issues from the laboratory perspective is that we need to know from

the clinician *as soon as possible* if the clinical picture changes such that the diagnosis of RS or an IMD is now less likely. We don't always get that message back, and if we have to investigate all suspected cases all the way through, it would become an impossible work load. There is a happy medium but it needs good communication.

**Dr Bonham.** That is absolutely true. Also, picking up Professor Leonard's earlier point about storing samples - I agree it is crucial to get samples at the right time, crucial to store them, but one of the reasons why laboratories are very loathe to do this is that whilst doctors are very happy to *send* us samples for storage, they rarely ring us up and say "now you can throw that sample out"!

**Professor Tanner.** One particular group where it's difficult to know where to stop investigating is the putative mitochondrial disorders. Once one's done muscle enzymes, muscle biopsy, CSF lactate and particularly if there is a continuing hepatic disorder, the question arises - what should you further go on and do?

**Dr Naughten.** I have had two babies referred to me drowsy and with big livers who turned out to be HIV positive and not in high risk groups. I'm all for going back on mystery cases and applying new techniques and that's why I feel that classic Reye's will be eroded into and disappear as we unravel all these explanations.

**Dr Glasgow.** When we investigated our RS cases in depth for IMDs we thought they would all turn up positive and all these children's illnesses would be explained. But we didn't find a single case. So where do you stop, do you ever stop, and what would I say to a mother or father (and they'd be grandparents now) when I go back to them and say - by the way do you remember in 1980 or whenever your child was admitted to hospital, I want to tell you something we've just discovered that might have changed your life then. There are huge ethical issues here as well.

\*\*\*\*\*

**3.5 a) Should liver biopsy be part of investigation of all suspect cases of classic Reye's syndrome (RS)? If so, at what time, stage of the diagnostic process? How useful is histological examination and how should the material be prepared? How specific / useful / feasible is electron microscopy? What other investigations should be undertaken on biopsy material? b) What, if any, is the role of liver biopsy in the investigation of suspected inherited metabolic disease (IMDs)? c) Do other tissues need to be examined in the acute phase of the illness?**

**PROFESSOR PORTMANN**

My remarks deal more specifically with liver biopsy, but many aspects can be extended to autopsy liver tissue which will be discussed by Dr M Malone (see **Proceedings, Part 5**).

The liver morphology of RS includes <sup>1,2</sup>

- Hepatocytes swelling due to multiple small cytoplasmic vacuoles (neutral lipid content demonstrable in *frozen sections* stained with oil red-O or Sudan black B) and centrally located, enlarged hepatocyte nuclei
- Generally slight or absent necrosis and inflammation
- Severely reduced or absent *succinic dehydrogenase* (or cytochrome c oxidase) activity (demonstrable by enzymatic staining of *frozen tissue* embedded in rat kidney, which acts as control).
- And at the *ultrastructural (EM)* level,<sup>6,7</sup> markedly enlarged and misshapen mitochondria (amoeboid mitochondria) with matrix lucency, loss of dense bodies, detachment and fragmentation of cristae
  - numerous small lipid droplets and depletion of glycogen are confirmed.

The light microscopy features are considered pathognomonic, **the EM mitochondrial changes virtually diagnostic of RS, which in my view cannot be diagnosed without liver morphology.**

*The answer to question 3.5a is 'yes', a liver biopsy (or autopsy liver tissue) is indispensable to achieve a diagnosis.*

The 'vanishing' of RS during the late 1980s, has been followed by a sharp drop in liver biopsy specimens being submitted to our laboratory as potential RS. As a consequence fat staining on

frozen sections and succinic dehydrogenase histochemistry have been largely abandoned. Microvesicular steatosis, spotted on H&E stained sections as a microvesiculation or foamy clarification of hepatocyte cytoplasm without nuclear displacement, remains a feature now mostly associated with inherited metabolic or acquired defects of mitochondrial function, in particular that of fatty acid beta-oxidation.<sup>5</sup> In these conditions, which have been the object of isolated case reports or small series of patients, light microscopy and EM liver findings are inconsistently reported, although microvesicular steatosis remains the most consistent feature recorded, alone or in combination with other features which clearly depart from the morphology of classical RS. To complicate the issue, microvesicular steatosis has been found incidentally at autopsy without any specific connotation.<sup>6</sup> However, irrespective of the lack of specificity of the changes, liver tissue is often essential for enzymatic assay or other techniques which are often indispensable to make a specific diagnosis in IMDs.<sup>7</sup>

*Potential Reye's syndrome and Reye-like IMDs cannot be dissociated with regard to the need for a liver biopsy to be taken, and this is indeed a clinical decision, which must be guided according to circumstances. Liver biopsy being an invasive procedure, with a risk of morbidity, and, however low, of mortality, the risk has to be weighed against the potential diagnostic yield.*

Below is a brief review of morphological data in selected IMDs that may present with RS-like features.

### ***Congenital hyperammonaemia syndromes***

These rare and heterogeneous disorders result from defective enzymes of the *urea cycles*, in particular the cytosolic *arginosuccinate synthetase (AS)*, *arginosuccinate lyase (AL)* and *arginase* or the mitochondrial *ornithine transcarbamylase (OTC)* and *carbamoyl phosphate synthetase (CPS)*.<sup>7</sup>

***Argininosuccinic aciduria*** seems the one defect in which significant liver disease is present with severe fibrosis,<sup>8,9</sup> and marked macrovesicular steatosis in some case.<sup>9</sup> Ultrastructural changes include dilatation of the rough or smooth endoplasmic reticulum,<sup>8-10</sup> and the presence of megamitochondria in zones affected by steatosis.<sup>9</sup> The enzyme protein may be absent in the liver;<sup>11</sup> *OTC* deficiency: liver histology generally normal in males. Occasional case reports suggest some mitochondrial and peroxisomal changes.<sup>12</sup> Acquired abnormalities are documented in females at a more advanced age: changes are mild and include steatosis, inflammation, periportal necrosis and fibrosis. Organelles in the hepatocytes are usually normal.<sup>13</sup>

One series including 6 OTC, and 3 CPS deficiencies has revealed, in addition to diffuse microvesicular steatosis with variable portal fibrosis, foci of nonvacuolated clear hepatocytes in both OCT and CPS cases,<sup>14</sup> and these were confirmed on EM to have little/no neutral fat and excessive free glycogen.<sup>14</sup>

In these disorders, both light microscopy and ultrastructural changes are non-specific, and may at times mimic RS. Liver tissue is required for enzyme assay.<sup>7</sup>

### **Mitochondrial cytopathies**

Functional disorders of mitochondria comprise a broad range of diseases affecting multiple organ systems,<sup>15-17</sup> and result in a combination of many diverse symptoms, hepatic failure, or cholestasis with preserved liver function, cardiomyopathy, myoclonic seizures, hypotonia, proximal tubular disorder, endocrinopathies, or pancytopenia. Disease severity, time of presentation and progression are highly variable, and the neuromuscular system may be affected without known hepatic involvement.<sup>18</sup>

The mitochondriopathies can be classified by the genetic defect (i.e. autosomal or mitochondrial) or by the defective enzymatic system (oxidative phosphorylation or fatty acid oxidation). A severe neonatal presentation and a delayed onset (2-18 months) are distinguished,<sup>19, 20</sup> the latter including *Alpers progressive infantile poliodystrophy*.<sup>21</sup>

Confirming the diagnosis of a mitochondriopathy can be difficult. Histopathologic study of liver and muscle, with electron microscopy, may reveal characteristic abnormalities.<sup>15</sup> Some respiratory chain subunits can be detected by immunohistochemistry (cryostat sections). Molecular biologic techniques permit quantitation of mitochondrial DNA as well as detection of some deletions and/or mutations in either nuclear or mitochondrial DNA. Some centres have developed polarographic (requires rather large amount of tissue) or enzymatic methods of measuring respiratory chain activity (requires snap frozen tissue stored at  $-70^{\circ}\text{C}$ ). These diagnostic modalities have been reviewed.<sup>22-24</sup>

*Fatty acid oxidation disorders (medium chain (MCAD) and long chain (LCAD) acyl-CoA dehydrogenase).* Microvesicular steatosis has been the main liver abnormality in a series of 9 patients.<sup>25</sup> Later, fatty infiltration becomes macrovesicular and cirrhosis may develop. Severe ballooning degeneration of liver cells, mild cholestasis and marked bridging fibrosis have been

reported in one case,<sup>26</sup> which ultrastructurally revealed large, membrane-bound vesicles containing a loose, flocculent material and irregular internal membrane profiles. Histology and ultrastructure are informative, not specific; metabolic analysis of postmortem liver tissue has allowed a diagnosis, which can be achieved during life by urine and blood analyses.<sup>15</sup>

*Mitochondrial oxidative phosphorylation disorders.* Histopathologic changes have been described by numerous investigators.<sup>20, 27-33</sup> All have been characterized by microvesicular steatosis, variable cholestasis, ductular proliferation, and sometimes progressive fibrosis and cirrhosis. Light microscopic and ultrastructural descriptions were reported in 2 series totalling 15 cases.<sup>29,32</sup> An oncocytic appearance of liver cells due to mitochondrial crowding is occasionally observed.<sup>33</sup> Ultrastructurally, changes include pleomorphic mitochondria with few or no cristae and a granular fluffy matrix.<sup>34,35</sup> Similar changes have been described in Alpers syndrome, now known to be a mitochondrial disorder involving complex I of the respiratory chain.<sup>28</sup> Liver and/or muscle biopsy is essential for diagnosis.

### ***Drug related RS-like changes***

In both children and adults, a number of drugs have been occasionally associated with clinical features and liver changes resembling RS, an inhibition of mitochondrial beta-oxidation being the likely mechanism of hepatotoxicity. In most instances, detailed metabolic work up is not available, and the extent to which the drug has unmasked an underlying IMD, or produced a ‘genuine’ RS is uncertain.

*Valproic acid (VA).* In cases of acute liver failure ascribed to VA toxicity, the liver has showed RS-like features, necrosis or both.<sup>34</sup> At times, another member of the family had died following seizures suggesting that the patient may have been unduly susceptible to the drug due to an underlying IMD. Ornithine carbamyl transferase deficiency has been demonstrated in at least one patient,<sup>35</sup> and others have been suffering of Alpers’ syndrome, now recognised as a mitochondrial cytopathy.<sup>36</sup>

*Nucleoside analogs.* Rare cases of hepatic toxicity are reported, related to a drug-induced inhibition of mitochondrial DNA polymerase.<sup>37,38</sup> Microvesicular steatosis, giant mitochondria and intrahepatic cholestasis is reported;<sup>38,39</sup> enlarged mitochondria with low matriceal density and occasional vacuoles is found by electron microscopy.<sup>38</sup>

*Ecstasy.* At least, one anecdotal patient has developed liver failure following exposure to ecstasy, with clinical features mimicking RS and liver histology indistinguishable from that of RS.<sup>40</sup>

### Conclusion/Answer to specific questions:

- **Liver biopsy** should be part of investigation of suspect cases of *classic Reye's syndrome* and of *suspected inherited metabolic disease (IMDs)* with evidence of liver involvement (site of enzymatic defect and/or target of the injury). Exception would be those cases in which a diagnosis is achievable e.g. by urine and/ or blood analyses, or on tissue accessible by a less invasive technique than a percutaneous liver biopsy (eg skin fibroblasts, skeletal muscle).
- If feasible (no contraindications), the biopsy should be performed as soon as possible as changes may be transient, particularly in 'mild' forms.
- In all instances, a substantial portion of the biopsy specimen should be **held fresh or snap frozen** (-70<sup>0</sup> C) depending on the requirements of the centre which will carry on the special investigations, some listed above (to be discussed prior to biopsy). A limited number of laboratories are providing specific diagnostic service for IMDs; the list and their areas of interest are generally known to paediatricians. A comprehensive list could be made more widely available.

**Histopathologic changes** are rarely specific, but light microscopy may allow to place the lesion in a restricted category (normal liver, micro- macrovesicular steatosis, parenchymal necrosis and loss, fibrosis, cirrhosis) and provide information on severity and stage of the changes (prognosis value).

**Electron microscopy** provides additional evidence supporting a mitochondrial disorder, but specificity is similarly lacking and ultrastructure study should not represent the prime indication for performing a biopsy. If a liver biopsy is indicated, it is highly recommended to save 1-2 mm of the specimen in EM fixative. This can be plastic embedded and held for any length of time, prior to thin sectioning and EM examination, locally or at a specialist centre. The technique of epon embedding is of relatively low cost and not really time consuming; full EM examination requires extra funding. The value of EM on post mortem material limited. Performing a needle liver puncture as soon as possible after death can provide better preserved tissue for light microscopy, EM and indeed enzyme assays or other specialised techniques.



## REFERENCES

1. Bove KE, McAdams AJ, Partin JC, Partin JS, Hug G, Schubert WK. The hepatic lesion in Reye's syndrome. *Gastroenterology* 1975; 69:605-697
2. Kimura S, Kobayashi T, Tanaka Y, Sasaki Y. Liver histopathology in clinical Reye syndrome. *Brain Dev* 1991;13:95-100
3. Phillips MJ, Poucell S, Patterson J, Valencia P. The liver. An atlas and text of ultrastructural pathology. New York: Raven Press, 1987
4. Partin JC, Schubert WK, Partin JS. Mitochondrial ultrastructure in Reye's syndrome (encephalopathy and fatty degeneration of the viscera). *N Engl J Med* 1971; 285: 1339-1343
5. Fromenty B, Berson A, Pessayre D. Microvesicular steatosis and steatohepatitis: role of mitochondrial dysfunction and lipid peroxidation. *J Hepatol* 1997;26 (Suppl 1):13-22
6. Fraser JL, Antonioli DA, Chopra S, Wang HH. Prevalence and nonspecificity of microvesicular fatty change in the liver. *Mod Pathol* 1995;1:65-70
7. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. *Adv Pediatr* 1996; 43:127-170
8. Zimmermann A, Bachmann C, Baumgartner R. Severe liver fibrosis in argininosuccinic aciduria. *Arch Pathol Lab Med* 1986; 110:136-140
9. Jorda A, Portoles M, Rubio V. Liver fibrosis in arginase deficiency. *Arch Pathol Lab Med* 1987; 111: 691-692
10. Travers H, Reed JS, Kennedy JA. Ultrastructural study of the liver in argininosuccinase deficiency. *Pediatr Pathol* 1986; 5: 307-318
11. Kobayashi K, Itakura Y, Saheki T et al. Absence of argininosuccinate lyase protein in the liver of two patients with argininosuccinic aciduria. *Clin Chim Acta* 1986; 159:59-67
12. Tallen H, Schaffner F, Taffet S, Schneidman K, Gaul G. Ornithine carbamyl-1 transferase deficiency in an adult male patient: significance of hepatic ultrastructure in clinical diagnosis. *Pediatr Res* 1983; 71: 224-232
13. Aida S, Ogata T, Kamoto, Nakamura N. Primary ornithine transcarbamylase deficiency. A case report and electron microscopic study. *Acta Pathol Jpn* 1985; 39: 451-456
14. Badizadegan K, Perez-Atayde AR. Focal glycogenosis on the liver in disorders of ureagenesis: its occurrence and diagnostic significance. *Hepatology* 1997;26:365-373
15. Treem WR, Sokol RJ. Disorders of the mitochondria. *Semin Liver Dis* 1998; 18:237-253

16. Sokol RJ, Treem WR. Mitochondria and childhood liver diseases. *J Pediatr Gastroenterol Nutr* 1999; 28:4-16
17. Morris AAM. Mitochondrial respiratory chain disorders and the liver. *Liver* 1999; 19:337-368
18. Munnich A, Rotig A, Chretien D et al. Clinical presentation of mitochondrial disorders in childhood. *J Inher Metab Dis* 1996; 19:521-527
19. Cormier-Daire V, Chretien D, Rustin P et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. *J Pediatr* 1997; 130:817-822
20. Cormier V, Rustin P, Bonnefont JP et al. Hepatic failure in disorders of oxidative phosphorylation with neonatal onset. *J Pediatr* 1991; 119:951-954
21. Saudubray J, Martin D, Poggi-Travert F et al. Clinical presentations of inherited mitochondrial fatty acid oxidation disorders: An update. *Int Pediatr* 1997; 12:34-40
22. Narkewicz MR, Sokol RJ, Beckwith B, Sondheimer J, Silverman A. Liver involvement in Alpers disease. *J Pediatr* 1991; 119:260-267
23. Munnich A, Rotig A, Chretien D, Saudubray JM, Cormier V, Rustin P. Clinical presentations and laboratory investigations in respiratory chain deficiency. *Eur J Pediatr* 1996; 155:262-274
24. Rustin P, Chretien D, Bourgeron T et al. Biochemical and molecular investigations in respiratory chain deficiencies. *Clin Chim Acta* 1994; 228:35-51
25. Boles RG, Martin SK, Blitzer MG, Rinaldo P. Biochemical diagnosis of fatty oxidation disorders by metabolite analysis of postmortem liver. *Hum Pathol* 1994; 25: 733-741
26. Amirkhan RH, Timmons CF, Brown KO, Weinberger MJ, Bennett MJ. Clinical, biochemical, and morphologic investigations of a case of long-chain 3-hydroxyacyl-Co A dehydrogenase deficiency. *Arch Pathol Lab Med* 1997; 121:730-734
27. Boustany RN, Aprille JR, Halperin J, Levy H, DeLong GR. Mitochondrial cytochrome deficiency presenting as a myopathy with hypotonic, external ophthalmoplegia, and lactic acidosis in an infant and as fatal hepatopathy in second cousin. *Ann Neurol* 1983; 14: 462-470
28. Fayon M, Lamireau T, Bioulac-Sage P, et al. Fatal neonatal liver failure and mitochondrial cytopathy: an observation with antenatal ascites. *Gastroenterology* 1992; 103: 1332-1335
29. Bioulac-Sage P, Parrot-Rouland F, Mazat J P et al. Fatal neonatal liver failure and mitochondrial cytopathy (oxidative phosphorylation deficiency): a light and electron microscopic study of the liver. *Hepatology* 1993; 18:839-846

30. Goncalves I, Hermans D, Chretien D et al. Mitochondrial respiratory chain defect: a new etiology for neonatal cholestasis and early liver insufficiency. *J Hepatol* 1995; 23:290-294
31. Mazzella M, Cerone R, Bonacci W et al. Severe complex I deficiency in a case of neonatal-onset lactic acidosis and fatal liver failure. *Acta Paediatr* 1997; 86:326-329
32. Morris AAM, Taanmen J-W, Blake J et al. Liver failure associated with mitochondrial DNA depletion. *J Hepatol* 1998; 28:556-563
33. Ducluzeau P-H, Lachaux A, Bouvier R, Streichenberger N, Stepien G, Mousson B. Depletion of mitochondrial DNA associated with infantile cholestasis and progressive liver fibrosis. *J Hepatol* 1999; 30:149-155
34. Zimmerman HJ, Ishak KG. Valproate-induced hepatic injury. Analysis of 23 fatal cases. *Hepatology* 1982;2:591-597
35. Tripp JH, Hargreaves T, Anthony PP et al. Sodium valproate and ornithine carbamyl transferase deficiency. *Lancet* 1981;1:1165-1166
36. Krähenbühl S, Brander S, Klienle S et al. Mitochondrial diseases represent a risk factor for valproate-induced liver failure. *Liver* 2000;346-348
37. Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. *Nat Med* 1995;1:417-422
38. Spengler U, Lichterfeld M, Rockstroh K. Antiretroviral drug toxicity – a challenge for the hepatologist? *J Hepatol* 2002;36:283-294
39. Clark SJ, Creighton S, Portmann B, et al. Acute liver failure associated with antiretroviral treatment for HIV: a report of six cases. *J Hepatol* 2002;36:295-301
40. Ellis A, Wendon J A, Portmann B, Williams R. Acute liver damage and ecstasy ingestion. *Gut* 1996;38:454-458

***PROFESSOR PORTMANN : ADDITIONAL POINTS IN ORAL AND SLIDE PRESENTATION***

I don't believe you can definitively diagnose classical Reye's syndrome without liver morphology. In the few metabolic disorders like OTC which I have examined under the electron microscope there was some mild modification of the mitochondria, but nothing like those huge mitochondria that are sometimes described as amoeboid with lucency of the matrix and loss of dense bodies and disruption of the cristae that are said to be specific to classical RS. I don't know whether, in the IMDs, there is the same depletion of succinic dehydrogenase as you see in classic RS.

Pure aspirin toxicity doesn't look like Reye's syndrome. You see *macrovesicular* fatty tissue and you don't see the mitochondrial changes.

## **DISCUSSION**

**Dr Glasgow.** Can I just ask everybody if *all* of the inherited metabolic disorders can be diagnosed by other means or are there any that can *only* be identified by examining liver tissue? Because one issue is the patient who is going to die in whom you don't have a diagnosis and from whom there is the need to take and save tissue.

**Dr Dalton.** The point about *any* metabolite is that it is an *indication* of a disorder - it is not a diagnosis. The diagnosis comes from enzymology or DNA confirmation. So there are disorders that do need liver biopsy to make the diagnosis.

**Dr Green.** For the majority, confirmation will be possible with fibroblast enzymology, but there will be a few in whom you can't get molecular confirmation (urea cycle defects for example), where you *will* need liver.

**Professor Leonard.** If you're faced with this problem of a child about to die then it's very important to have a liver biopsy because even with modern techniques in only 80% of cases of OTC deficiency do we get a molecular diagnosis. Confirmation is only possible with liver biopsy.

**Dr Green.** It may be that you are actually going down the route of, say, fat oxidation and your metabolites are saying that looks likely in which case your fibroblast culture will give you the answer and you won't need a liver biopsy. So I think it needs to be assessed on a case by case basis rather than a carte blanche everyone should have a liver biopsy.

**Mrs Greene.** When you were talking about taking the liver biopsies presumably consent forms are signed? Perhaps that's the wrong presumption, but if that's the case how wide ranging do you make your explanation for tests that are going to be done? From a parental or patient point of view I think if it's *clearly* explained in the light of problems we've had at Bristol and Alder Hey, that would be acceptable.

**Professor Hall.** The important thing is that there is very clear guidance coming from the profession on this, and the view is that this is not about the shape of the consent form but it is about involving

parents in the discussion and, as everyone had been saying, this may well be a multi-step process which may take a long time. The important thing is the involvement of the parents and the family in the whole process. I don't think anyone these days would expect any parents to sign a blanket consent form simply saying this is a liver biopsy for investigation. Everyone agrees that the consent form is merely a vehicle for proper sharing of information.

**Mrs Greene.** Parents and patients welcome that. I think there is shared alarm by patients and support groups that the impact of Alder Hey and Bristol could in fact seriously damage the progress of research. We're not saying you mustn't do anything, quite the reverse.

**Professor Hall.** The Colleges of Paediatrics and of Pathology have been very conscious of this and are about to publish a report on exactly this theme, which is undertaken with a group of parent organisations, particularly those involved in Alder Hey.<sup>1</sup> The theme is very much along the lines you're saying - that most parents do not want to see research and progress on the investigation of their own children impeded by the collapse of paediatric pathology. I'm sure everyone here agrees there is also a massive shortage of paediatric pathologists and that's part of the problem as well.

## **END OF SESSION**

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<sup>1</sup> The Future of Paediatric Pathology Services. March 2002 Royal College of Paediatrics and Child Health. London ISBN 1- 900954-65-6

## WORKSHOP PROCEEDINGS: PART 4

### Management of Reye's syndrome and "Reye-like" encephalopathy

– "best" (ideal world, no resource constraints) practice

MODERATOR: PROFESSOR DAVID HALL

#### **4.1 If an acute IMD – or RS-related encephalopathy is suspected, what is the optimum initial management –**

##### **a) While awaiting initial investigations?**

**DR MIKE CHAMPION**

*Manage patient along APLS guidelines<sup>1</sup>*

Airway

Breathing

Circulation

Disability

assess conscious level

seek evidence for raised intracranial pressure

##### *Specific to IMDs*

Stop feeds

Promote anabolism; 10% dextrose IV at maintenance rates with appropriate electrolyte additives. Aim for glucose 4-8 mmol/l

Add insulin infusion 0.05u/kg/hr if blood glucose >10mmol/l

(Correct metabolic disturbance)

Nb mild acidosis protects against ammonium dissociation

##### **a) If hyperammonaemia confirmed?**

If available, supplement arginine 100mg/kg/day if urea cycle disorder (UCD) suspected given as an infusion over 24 hours.

**Pointers** Ammonia >1000 $\mu$ mol/l  $\Delta\Delta$  urea cycle defect, (organic acidaemia rarely)  
(minimal rise does not exclude)

Respiratory alkalosis (respiratory stimulant)

History: ?protein avoidance, ? development? FH

Absence of: marked ketosis  
hypoglycaemia  
marked acidosis  
lactic acidosis  
leucopaenia  
hypocalcaemia

Consider alternate pathway treatment (sodium benzoate, sodium phenylbutyrate)

#### **4.2 Do levels of plasma ammonia or other initial results affect initial management? If so how?**

##### **Hyperammonaemia**

Indication for referral and transfer to Specialist Centre/PICU:

Ammonia >150 $\mu$ mol/l

Give alternate pathway drugs if UCD or organic acidaemia (OA) suspected, if available at presenting hospital (in practice have been sent by courier in acute situations if delay in transfer likely).

Sodium benzoate 250mg/kg/day and sodium phenylbutyrate 250mg/kg/day are given as continuous infusions. Loading is not recommended. Higher doses up to 500mg/kg/day have been used in resistant hyperammonaemia.

Ammonia >300 $\mu$ mol/l and rising:

Dialysis indicated.

Neonate <2.5kg	peritoneal dialysis
Infant >2.5kg	continuous veno-venous haemofiltration (CVVH)

Monitor ammonia 4 hourly.



## **Results of other initial investigations**

Rapid acute metabolic Tandem Mass Spectrometry (TMS) screening allows rapid diagnosis, whilst awaiting formal organic acid and amino acid analysis, facilitating earlier definitive management. Specimens may be couriered to the metabolic lab from the presenting hospital.

Conditions screened at present include:

- fat oxidation defects
- urea cycle disorders
- propionic, methylmalonic and isovaleric acidaemias
- MSUD

## **Reference**

1. Advanced Paediatric Life Support Group In Advanced Paediatric Life Support: The Practical Approach BMJ Books 2001

BIMDG hyperammonaemia guideline currently (March 2002) under construction.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

### **Dr Champion**

#### ***4.1 a) Management while awaiting results of initial investigations***

As with any acutely ill child we start with the ABC, and of course the assessment of conscious level is very important and looking for evidence of raised intracranial pressure.

But what about whilst we are waiting for investigations and the question of an inborn error has been brought up? As a basic premise we stop feeds whilst we try to find out what's going on, but we don't want to leave the child bereft of calories. We want to promote anabolism and avoid catabolism so we would use 10 percent dextrose as the baseline fluid with appropriate electrolytes added and we would aim to keep the glucose in the region of 4-8 mmol/L.

There will often be argument about how much fluid should be given - some people suggest fluid restriction to protect a potentially swelling brain, but then we see children who are becoming hypoglycaemic because they are severely fluid restricted - even though that fluid has a higher percentage of dextrose. Another problem that can be created is caused by not putting additives into that 10 percent dextrose. For example sodium - so you will then have children who are fitting because they've been left on this drip overnight and then have become hyponatremic.

Another basic practice within the "metabolic community" is that if the patient is becoming hyperglycaemic we add in insulin rather than reduce the amount of dextrose i.e. we are trying to promote anabolism. In the paper above it says "correct the metabolic disturbance" and by that I mean - if the sodium is very low; or if the calcium needs correcting; or the acid base - but you don't want to *over* correct the acid base status, because ammonia diffuses through the cell wall far more effectively than ammonium - so as the ammonia rises it actually increases its own toxicity and so if you correct the pH you are going to make that toxicity more likely. So it may be that a mild degree of acidosis will be protective.

#### **4.1b) If hyperammonaemia has been confirmed then what should one do?**

This is where the metabolic centres have an important role with regards to advice and liaison. It is *essential* that we have good lines of communication, so that we can help not only to direct what investigations are done (because we can often reduce the number of these) but also to direct treatment. If for example we had the patient in front of us and were thinking about a urea cycle defect because there is confirmed hyperammonaemia, then we would be putting arginine into the mix to try and improve the flux through the urea cycle. But arginine is not likely to be available in the local district general hospital. There have been times when the transfer to intensive care or the metabolic centre was going to be delayed for some hours, so we have put the arginine in a taxi and sent it out.

#### ***4.2 Does the level of ammonia influence what you are going to do?***

Yes it does. Once there is a significantly elevated ( $>150\mu\text{mol/L}$ ) ammonia then you need to refer the child for intensive care and management in one of the metabolic centres. If the level is  $>300\mu\text{mol/L}$  and rising then no matter what the cause is, that's an indication for sending the child in for urgent dialysis. The method is determined by the size of the child. So if it's  $<2.5\text{ kg}$  we do peritoneal dialysis. There has been some work - but no randomised controlled trials, just case reports - on what is the most efficient. Haemodialysis is more efficient than haemofiltration but the systemic upset is less, with continuous veno-venous haemofiltration, so that is what we would do in the larger patient.

#### **DISCUSSION**

**Professor Hall.** Could I ask a practical question about one of your first recommendations regarding the ABC and the question of intubation? I am hearing increasingly that smaller hospitals are really struggling to get anaesthetic support from people who are prepared to intervene in any way with small children, because their college has told them they are not supposed to do it unless they are doing 'x' amount of paediatric anaesthesia. Also, while there are some paediatricians who are happy to intubate a child other than a neonate, there are many who are not. If the child has had a cardiac arrest it may be different, but for a child who is breathing it's often not so easy to intubate. So I think we need to address reality - this is becoming a problematic issue in the smaller units.

**Dr Champion.** Yes, I think there has been some deskilling as paediatricians get super specialised.

**Dr Tasker.** Yes, there is a reluctance about intubation but I think the only solution is to have *local* people do it - what we have organised in our own Region is that the local anaesthetists are responsible for intubation if it is required. I think once you take intubation and those other procedures out of the responsibility of the local hospital

offering the service, then you have a situation where you are trying to create a mobile resuscitation unit which, dependent on the size of your Region, is just not going to work.

**Dr Bonham.** There has been no mention so far of carnitine, which has been suggested to be protective, and certainly may well be in the fatty acid oxidation defects, but may also well be in hyperammonaemia per se.

**Dr Champion.** Carnitine is something that I don't give routinely in my practice. Professor Leonard do you use carnitine acutely in an undiagnosed patient?

**Professor Leonard.** It's difficult for me to comment, because we're in a very privileged position at Great Ormond Street. The answer is probably strictly no, we do not. We're not great fans of carnitine.

**Professor Tanner.** On this question of availability of arginine, benzoate etc., in district general hospitals: I appreciate that if every DGH with an A&E where patients like this would come, kept these drugs, they would largely be wasted. But they are not expensive - surely it's worth trying to ensure that they are available in the centres that children might go to. Because to get them out, even by taxi in the evening, can take an hour or two in Trent.

**Dr Champion.** There is great reluctance to consider these as being of relevance to the acute paediatric units, some of whom even have difficulty measuring ammonia. We did a survey with laboratories in South Thames. There was one district general hospital that has a neonatal unit, an A & E, a paediatric unit, but they could not get an ammonia done and there was no mechanism for even sending it out to another laboratory elsewhere. So if you can't even get ammonia measurement into each district general hospital, it's even harder for their pharmacies to be stocking drugs that they may never use, because they are always looking for ways to save money and simplify procedures.

**Professor Leonard.** Furthermore, they have a limited shelf life which is particularly short. It's better to have a *really good* retrieval service and possibly a motor cycle courier system to take these agents out when needed.

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**Question 4.3a) What published evidence is there for the effectiveness of optimum management of each Reye-like IMD, ranging from that of early diagnosis and institution of supportive measures through to tertiary centre treatment? What outcome measures are used? Are there any randomised controlled trials? What unpublished evidence are you aware of?**

**4.3b) What treatment (other than that in 4.1 above) should be started locally once initial stabilization has been undertaken?**

**4.3c) What treatment can only be undertaken at a specialist centre? Can it ever be done locally under specialist supervision from the centre?**

**PROFESSOR LEONARD: POINTS MADE IN ORAL PRESENTATION (Table follows)**

I would like to make three points: *firstly*, there are no controlled trials at all, of the treatment of these conditions. So there are, for example, no controlled trials of the treatment of hypoglycaemia. *Secondly*, we are simply treating the biochemistry and that is difficult - we don't have thresholds, we don't have decision points. *Thirdly*, I think we would all agree that early intervention is the key, so the treatment decisions have to be made at relatively imprecise points.

Regarding local DGH treatment - these patients all need glucose; the role of carnitine is uncertain at present and of course medicines for reducing ammonia, although well tried and tested, have never been subjected to a controlled trial. As for the indications for transferring to a specialist unit, the first is any child who needs PICU, intubation etc or who has a GCS score of 12 or 11 depending on your cut-off. Clearly the major complications I've listed may need further specialist management.

<b>Disorder</b>	<b>Effectiveness Of Acute Treatment</b>	<b>Local treatment</b>	<b>Acute Specialist Treatment</b>
<u>Fatty acid oxidation</u>			
MCADD	yes (1)	glucose	PICU – cerebral oedema
VLCAD ) LCHAD) Other FAO)	early + late ±	glucose ?carnitine	PICU - cerebral oedema - cardiomyopathy (-hepatic disease)
<u>Urea cycle disorders</u>			
All except arginase deficiency	yes	glucose sodium benzoate* (3,8) sodium phenylbutyrate* (5-8) arginine* (4,7,8)	PICU - cerebral oedema - haemofiltration (2)
Arginase deficiency	yes	glucose sodium benzoate*(3,8) sodium phenylbutyrate*(5-8)	PICU
<u>Organic acidaemias</u>			
All	yes	glucose carnitine	PICU - haemofiltration -cardiomyopathy - pancreatitis

\* if available. Can be given orally or intravenously depending on patient's status

Comment: There are no controlled trials of therapy in any of these disorders. The one reference is a historical comparison of haemofiltration and peritoneal dialysis.

## References

- 1: Wilson CJ, Champion MP, Collins JE, Clayton PT, Leonard JV. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. Arch Dis Child. 1999 May;80(5):459-62.
- 2: Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E. Dialysis in neonates with inborn errors of metabolism. Nephrol Dial Transplant. 1999 Apr;14(4):910-8.
- 3: Brusilow SW, Valle DL, Batshaw ML. New pathways of nitrogen excretion in inborn errors of urea synthesis. Lancet 1979; II:452-454.
4. Brusilow SW. Arginine,an indispensable aminoacid for patients with inborn errors of urea synthesis. J Clin Invest 1984; 74:2144-2148.
5. Brusilow SW. Phenylacetylglutamine may replace urea as a vehicle for waste nitrogen excretion. Pediatr Res 1991; 29:147-150.
6. Maestri NE, Hauser ER, Bartholomew D, Brusilow SW. Prospective treatment of urea cycle disorders. J Pediatr 1991; 119:923-928.
- 7: Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr. 1996;43:127-70.
8. Feillet F,Leonard JV..Alternative pathway therapy for urea cycle disorders. J Inherit Metab Dis 1998;21 suppl 1:101 - 111

## DISCUSSION

**Dr Naughten.** When people are saying plasma ammonia isn't available in their hospital, I wonder what has happened to the fear of litigation. In the seventies it was at the top of our list, and colleagues were standing up in court cases saying it should be available at all DGHs.

**Professor Hall.** Yes, I would have thought that DGH adult medicine departments would be demanding ammonias for a whole range of reasons. Can anyone comment from an

adult medicine perspective - are they bothered about not being able to get ammonia measured?

**Dr Bonham.** At Sheffield Childrens Hospital we do the ammonias for a large 8-900 bedded DGH nearby. Surprisingly, they don't have a method to do their own. In total we do about 220 ammonias a year, of which about six are from the DGH.

**Dr Naughten.** Our experience in Dublin is the same.

**Dr Champion.** I think with adult practice in this country there is a belief that inborn errors are solely a paediatric issue. In Europe, particularly Holland, each of the big centres has an adult physician specialising in inborn errors and they are inundated with patients. So it's a case of awareness.

**Professor Hall.** But my point was that in adult medicine most high ammonias will be nothing to do with inherited metabolic disorders, they would be due to liver disease of various kinds. It seems to me one of the points to follow up after this meeting is to talk to a few adult physicians and see why ammonia seems to have dropped off the shopping list, because if the adult physicians were arguing for ammonias in every hospital to be available and done properly then obviously our problem would be simplified as well. So we might try and find out more about that.

**Dr Baumer.** Regarding the importance of rapid therapeutic arginine for this situation and the concept of it being held by the regional centre and sent by motor bike: it is two hours' travelling time from our regional centre, which presumably is not rapid enough. Isn't there a possibility that the shelf life of these products might be extended if somebody did the work to demonstrate their stability?



**Professor Leonard.** The shelf life of arginine may be known because it's been around a long time and pharmacies often do keep it. But they don't keep benzoate or phenyl butyrate.

**Dr Bonham.** I would be surprised if the shelf life of benzoate is problematic because its major use is as a preservative in fizzy drinks.

**Professor Stephenson.** This has opened up quite a wide issue: we have been pushing for the last five years to improve the licensing of medicines, but the bigger area which the *pharmacists* have been pushing, is that of formulations, dispensation, excipients, shelf life, vehicles, quality control. The problem occurs when a company has gone through this process then suddenly agents like arginine and benzoates go from costing a few pence to some phenomenal sum. We must be very careful not to shoot ourselves in the foot!

**Dr Bonham.** I take Professor Leonard's point about retrieval of these patients perhaps being the better option, but we've seen benzoate being dramatically effective in some children in a very short time, ammonia levels going from 750 to under 200 in under three hours, without dialysis or haemofiltration. So I think where ammonia *is* available locally, as it is within the DGHs within the Trent Region, if you get a very high ammonia then it's terribly frustrating to know that that child is a couple of hours return journey away and there's no benzoate locally.,

**Professor Hall.** Do we actually *know* these shelf lives or are we just *speculating* that this is a problem? Do we know how often pharmacies would throw it away?

**Professor Leonard.** Unless it's been formally tested, companies are obliged to put in a rather limited one. The default is something like a year at maximum I believe but would have to check.

**Professor Hall.** Surely it should be possible for a pharmacy to store these three or four compounds and refresh them once a year.

**Professor Leonard.** I think what you need is to have a sensible *advance plan* of management of patients with a high ammonia which is tailored to the local situation - proximity to a major centre etc.

**Dr Baumer.** There is also the point that if you keep your benzoate in the local pharmacy and it's out of hours it may take an hour or two to find it!

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**QUESTIONS 4.3 a-e AND 4.4 a-e**

**4.3/4.4 (a)** *What published evidence is there for the effectiveness of optimum management of Reye-like IMDS ranging from that of early diagnosis and institution of supportive measures through to tertiary centre treatment?*

**4.3/4.4(b)** *What treatment should be started locally once initial stabilisation has been undertaken?*

**4.3/4.4(c)** *What treatment can only be undertaken at a specialist centre? Can it ever be done locally under telephone supervision from the centre?*

**4.3/4.4(d)** *What are the indications for transfer?*

**4.3/4.4 (e)** *How should the patient be stabilized before transport?*

**Dr ROBERT C TASKER**

**Introduction to Comments**

There is no Class I evidence that would help in answering questions 4.3a-e and 4.4.a-e. Therefore, I have tried to provide answers using current national standards for acute paediatric care. I have made no distinction between the answers to questions 4.3 or 4.4. At the end of these answers there is a list of recommendations for discussion and possible action.

## Answers

### **4.3/4.4 (a) What published evidence is there for the effectiveness of optimum management of Reye-like IMDS ranging from that of early diagnosis and institution of supportive measures through to tertiary centre treatment?**

All of the evidence is largely anecdotal or case series management reviews (1). The intensive care reports of the critically ill are primarily concerned with endpoints such as 'toxin' removal and level of intracranial pressure.

### **4.3/4.4(b) What treatment should be started locally once initial stabilisation has been undertaken?**

The majority of children with Reye syndrome will come to medical attention via the emergency services.

#### *How do these patients present?*

In 1996/7 a study in the Thames Regions (paediatric population 3,103,523 children under 16 years) found that the incidence of 'critical illness' was 180 per 100,000 paediatric population per year (2). In the Northern Region, Wong and colleagues found that the incidence of non-traumatic encephalopathy Glasgow coma score <12 for at least 6 hours)

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1 For example, see: Huttenlocher PR (1972) *Reye's syndrome: Relation of outcome to therapy*. Pediatric Pharmacology and Therapeutics 80:845-850; DeVivo DC et al (1975) *Reye syndrome: Results of intensive supportive care*. Journal of Pediatrics 87:875-880; Mickell JJ et al (1977) *Intracranial pressure: Monitoring and normalization therapy in children*. Pediatrics 59:606-613; Duncan CC et al (1987) *Evaluation of level of consciousness by the Glasgow Coma Scale in children with Reye's syndrome*. Neurosurgery 13:650-653.

2 Maybloom B, Chapple J for the Steering Group (1999) *The use of hospital services in North and South Thames for the care of critically-ill children*. ISBN 0 9535150 01. Kensington & Chelsea and Westminster Health Authority.

was 30.8 per 100,000 paediatric population per year (3). And, of these, 38% of the encephalopathic episodes were due to infection and 6% to a metabolic disorder.

Taken together, the following estimates seem likely: ~1/6 children with critical illness have non-traumatic encephalopathy; ~1/16 children with critical illness have encephalopathy related to infection; and, ~1/90 children with critical illness have encephalopathy related to metabolic disease.

***[What proportion of these children have Reye syndrome?]***

*Who sees these patients?*

The majority, if not all, such children are managed initially by casualty officers and junior paediatricians attending casualty.

*What is the initial treatment?*

All of the above individuals will/should/could have received training in the following: Pediatric Advanced Life Support (PALS endorsed by the American Academy of Pediatrics and the American Heart Association); Regional Paediatric Resuscitation Guidelines (derived from PALS and taught by regional resuscitation officers); and Advanced Paediatric Life Support (APLS endorsed by the UK Advanced Life Support Group, the European Resuscitation Council, the Resuscitation Council of Southern Africa, and the APLS Group of Australia and New Zealand).

The PALS curriculum and text is primarily concerned with cardiovascular and trauma resuscitation. There is no reference to non-traumatic coma.

In contrast, the APLS curriculum and text (4) covers the care of the seriously ill child with an impaired level of consciousness in its sections on ‘The structured approach to the

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3 Wong CP et al (2001) *Incidence, aetiology, and outcome of non-traumatic coma: a population based study*. Archives of Disease in Childhood 84:193-199.

seriously ill child' (Chapter 8) and 'The child with a decreased conscious level' (Chapter 12).

In these sections, the text states that:

- i) Investigations during secondary assessment should include blood urea and electrolytes and blood sugar (p.77). *There is no mention of checking the ammonia.*
- ii) Treatment when raised intracranial pressure is suspected could include mannitol 0.5 g/kg intravenously (p.77)
- iii) Reye's syndrome is a metabolic cause of coma (p. 127)
- iv) Lumbar puncture should not be performed in a child in coma (p. 132)
- v) After initial management of coma the child should be referred for 'definitive care' (p.136).

An individual following the APLS approach will probably intubate and ventilate a child with a Glasgow Coma Score (GCS) <9 and then refer the child for intensive care. A child with a GCS 9-12 will be referred for further general paediatric advice.

***[Should an ammonia test be part of the APLS protocol?]***

#### **4.3/4.4(c) What treatment can only be undertaken at a specialist centre?**

Based on the above approach to care, a child could be intubated and referred for intensive care on a paediatric intensive care unit (PICU) or be managed locally in a high dependency (HD) area.

*Intubated children with GCS <9*

All intubated children will be referred to the regional 'lead' centre for intensive care (5). Under the current organisation all District General Hospitals should be able to initiate paediatric intensive care and then refer on to the 'lead centre' which is involved with transport and intensive care protocols. In the framework document the centres which provide general paediatric intensive care are:

Addenbrooke's, Cambridge	Manchester
Birmingham	Newcastle
Bristol	North Staffordshire
Great Ormond Street	Nottingham
Guy's	Oxford
Kings	St George's, London
Leeds	St Mary's, London
Leicester	Sheffield
Liverpool	Southampton

The Paediatric Intensive Care Society (PICS, 470 members) has recently produced a 'Standards Document' (2001) which defines the service, management, and medical and nursing criteria/requirements for lead centres(6). In regard to procedures that might be needed in children with Reye syndrome, it is worth noting that PICS considers the following "procedures" as being "intensive care dependent". Under normal circumstances, when required, they should usually be performed on children within a paediatric intensive care environment:

- i) Acute renal support (e.g., haemodialysis, haemofiltration, and peritoneal dialysis)
- ii) Intracranial pressure monitoring

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5 Paediatric Intensive Care (July 1997) *"A Framework for the Future"*. NHS Executive.

6 Paediatric Intensive Care Society (2001) *Standards Document*. Contact secretary Dr C Stack, Sheffield Children's Hospital.

It would be most appropriate for the child with Reye syndrome or inherited metabolic disease to be referred to a general PICU which could also offer:

- i) Extracorporeal renal support for individuals <10 kg
- ii) Laboratory diagnostic facilities for metabolic disease
- iii) (24-hour?) advice and expertise from a specialist in paediatric metabolic disease

#### *Children with GCS 9-12*

These children are in a HD category. The Department of Health has had an expert advisory group working on NHS standards for provision of HD care in children (7). The expectation is that all DGHs will be able to support such a service. The advisory group have generated a list of conditions and medical/surgical problems that warrant such supervision.

In children with neurological problems, the following placements are recommended:

- i) ***GCS 8-12:*** Children who could be cared for on children's wards in a DGH either in HD unit or identified beds/cots
- ii) ***Possibility of progressive deterioration to the point of needing ventilation:*** Children who need care on a HD unit which is attached to a PICU (i.e., if these children are in a DGH they should be referred to a PICU)
- iii) ***Central nervous system depression sufficient to compromise the airway protective reflexes/respiratory drive or potential to progress:*** Children who need care on a PICU

The place of management will be best determined by the problems that develop e.g. hyperammonaemia, altered level of consciousness, and raised intracranial pressure.

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7 Department of Health (2001) *High dependency care for children*. HDU300501 document, 06/06/01.

**Can it ever be done locally under telephone supervision from the centre?**

- i) *Intensive care:* No
- ii) *HD without the need for extracorporeal renal support therapy or likely intervention with endotracheal intubation:* Possibly

**4.3/4.4(d) What are the indications for transfer?**

*Paediatric Intensive Care*

GCS <9

**and/or** intubation and mechanical ventilation

**and/or** biochemistry necessitating extracorporeal renal support

*High Dependency Care*

GCS 9-12

**and** Specialist metabolic advice

**and/or** frequent neurological observations and scoring

**Is a specialist ambulance and/or support during the journey required? Do the specialist centres have outreach teams?**

Regional guidelines for transfer of the intensive care patient are already in place.

**4.3/4.4(e) How should the patient be stabilised before transport?**

After the publication of the 'framework' document each of the NHS regions were directed to produce regional protocols for the acute management of seriously ill children with head injury, meningococcal disease, and acute respiratory failure. These protocols



had to include information about how and to whom the referral should be made; how the child should be transferred, and what initial management should be undertaken. The APLS course and text (8) includes a section on transport (Chapter 26).

### **Recommendations for discussion and possible action**

1. To endorse the APLS curriculum as the standard for acute emergency paediatric care.
2. To approach the UK Advanced Life Support Group with a protocol/guidelines for 'The Child with a Decreased Conscious Level'. For example, to suggest that plasma ammonia (9) is part of the secondary assessment in children with unexplained GCS<12
3. To investigate which PICUs in England can offer all the services required for the treatment of Reye syndrome and to designate these as specialist centres.
4. To approach the PICS/DoH and suggest that non-traumatic coma be added to the list of protocol requiring regional guidelines.
5. To draw up a framework for a regional guideline (see 2 and 4 above)
6. To 'mail shot' all acute paediatricians with a reminder of Reye syndrome and the non-traumatic coma guideline (see 2, 4 and 5).

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8 Advanced Life Support Group (2001) *Advanced Paediatric Life Support*. ISBN 0 7279 1554 1, BMJ Books.

9 Kirkham FJ (2001) *Non-traumatic coma in children*. Archives of Disease in Childhood 85:303-312.

## POINTS HIGHLIGHTED IN ORAL PRESENTATION

### Dr Tasker

Although I was asked just to address the two questions - "what are the indications for transfer and how should the patient be stabilised for transport?", I want to go back a couple of steps, take in some of the points made earlier, and show some of *our* approaches with what I think is a parallel problem - that of head injury.

From the perspective of the A & E doctors and the paediatric SHOs, who are clerking these patients in the front line, there is already a training structure for them within both specialties. They have a choice as to what curriculum they go through before membership: either the American Pediatric Advanced Life Support, which focuses predominantly on cardiovascular events and trauma, or there is the European approach - the Advanced Paediatric Life Support curriculum. This has more paediatrics in it; there is a section on the comatose child and it includes diabetic ketoacidosis, so this is what a paediatrician in training is more likely to have done. An A & E junior may do both.

The APLS has management guidelines for non-traumatic coma in a child with a GCS <12 and in the secondary assessment these mention urea and electrolytes but there *is no mention of ammonia* and the question is - *could or should that be incorporated there* and what is the feasibility of that?

Within the current system of management, there are two groups of children - the high dependency-type child and the child that is going to be referred to ICU. So what happens now in the UK if a child needs ICU? In my paper I have referred to what is often called The Framework Document - the Troop report. This only addresses England. Essentially it says that for each Region there needs to be a lead centre which serves as the hub, with the spokes out to the district general hospitals within that region.

The Paediatric Intensive Care Society 2001 Standards Document states that a paediatric intensive care unit should be able to provide acute renal support and be able to undertake intracranial pressure monitoring. But what type of additional specialist expertise are we expecting for the Reye/Reye-like group of children? Not all of the centres on the list in my paper will be able to offer 24/7 coverage by a specialist paediatric metabolic physician.

The Standards Document also states that there should be a transport service so that the child can be brought to the centre. That would serve children with a coma score  $\leq 9$  well, but what about the child in the coma score range 9-12 that is not being transferred out? There is another committee looking at the issue of high dependency that should be provided at all district general hospitals and at the criteria for moving these children on if their airway is not safe. The high dependency document is still in evolution and hopefully will come out in 2003.

If ever there was a re-emergence of Reye's syndrome I believe we would approach the management of cases differently from the 1970s and '80s. We have very different tools now. We are now able to do microdialysis in the brain, we now have MR spectroscopy - so we would be trying to work out what was going on in the brain.

Now I want to run the parallel with head injury. As a consequence of the Troop Report and three other reports: the Royal College of Surgeons on the management of patients with head injury; the Society of British Neurological Surgeons on safe neurosurgery; and the Royal college of Surgeons and the British Orthopaedic Association on better care for the severely injured, there were three conclusions. There needs to be a system of care for head injury such that anyone with a subdural effusion or haemorrhage can get surgical evacuation within four hours; the receiving hospital needs to be able to provide ventilation and have an on-call radiologist who could give an opinion; there needs to be image transfer facility and criteria in place for transfer to the neurosurgical ICU.

So we were charged by the Department of Health to assess the practicalities of coming up with a protocol that worked in our Regions. We had a round table meeting with representatives from all 21 of the provider units that we serve, to come up with the means by which we would get imaging done; what the criteria for that would be; who should be consulted; what phone numbers should be available, if there was no answer what the second phone number should be; the referral process; pre-transfer care criteria and management guidelines for each clinical situation, that would work in every DGH.

I suspect that every Region that you work in could use this mechanism as well to put in place some non-trauma coma protocol.

Finally, I wonder how many of you got a letter called "Left Heart Matters", with the little credit cards. I think non-traumatic coma is a much more common situation. I just can't throw it away because it seems so nice and you could actually produce this for non-traumatic coma rather than posters and it could very easily fit in with your credit cards!

## **DISCUSSION**

**Dr Naughten.** Does your initial assessment include measures of coagulation?

I think this has to be very high on the list before transfer because whatever the clinical problem, a pothole in the road on the way to the referral centre can cause an intracranial bleed - we've had that experience. Stabilising clotting first is such an obvious thing.

**Dr Tasker.** It's not part of the secondary assessment in the APLS.

**Dr Naughten.** I think it should be.

**Professor Stephenson.** On your Point 1 for discussion in your paper – the APLS doesn't currently recommend measuring ammonia or coagulation screening. I think what we need is a body of work first to find out the evidence and do it in a systematic way.

**Dr Glasgow.** May I just say two things in response to that? Firstly, much of the third edition of APLS, particularly with respect to cardiovascular resuscitation, *is* based on published evidence although I agree that there often isn't evidence to support *some* of its contentions. Second, we do need to remember that the APLS document is produced for the "golden hour". It's not a definitive management for the first twenty four hours. The ABCD approach is a process rather than an event and I think that possibly ammonia comes after that. However, I absolutely agree with Terrence's point - it needs to be in the document.

**Dr Baumer.** I would like to point out that a document which may have references within it is not an evidenced based guideline. An evidence-based guideline I would see as explicitly linking the evidence to individual recommendations, the level of evidence leading to a grading of that recommendation so that we know where the evidence lies and where it doesn't lie for each individual item. I agree with Professor Stephenson that the APLS document is part of a dissemination strategy that *should* follow from an evidence based piece of work about that area of practice. I would also agree that clearly the APLS is there to do a specific job, and is not going to be able to cover *all* of the things that we are discussing at this meeting.

**Professor Hall.** I think there are probably two strands to that. One is an evidence base for whether the APLS approach *as a whole* improves health care and the other is the evidence for each individual item within it. But does anybody think that there is anything *better* than APLS? My feeling is it's probably the best that we have at the moment. The endorsement is not of every word written within it but of the fact that it's an approach that we are going to continue working with.

**Dr Baumer.** I think that what has always seemed appropriate and logical about having something like an APLS document, where we don't have a well produced piece of work about the evidence, is that you've got to have people doing the same thing and getting on

with it. But for the sort of "hinterland" behind that first golden hour, I think we should be taking a more measured approach.

**Dr Tasker.** To a certain extent the College already partly endorses it by expecting paediatric trainees to have done it prior to being examined for membership. Surely it would be more efficient to work with a structure that's in place rather than try to recreate some parallel.

**Professor Hall.** Yes I would agree with that. I think Professor Stephenson was saying that endorsement should not be taken to indicate that we think every word in the APLS is actually scientific truth - it's a consensus that stops people fighting over what to do in an emergency situation.

**Professor Stephenson.** I agree. I want our junior and senior staff who are attending resuscitation to all be singing from the same hymn sheet. But as an interactive process, for every statement in that APLS booklet, people should be thinking about - what is the evidence to support that; if there's not evidence who should we ask to get the best judgment? It shouldn't just be taken as something handed down on tablets of stone that cannot be questioned, criticised or changed with time. For example, arising from Dr Tasker's presentation and this discussion it is clear that clotting screen and ammonia are first hour investigations which are not included but which probably should be.

**Professor Hall.** I know Dr Barbara Phillips, who couldn't come, was very keen to pick up any messages of that sort. As you say, it is an iterative process with constant improvement, so we have two points to convey to her.

**Dr Glasgow.** The fact that there is a lack of evidence doesn't necessarily imply that a particular therapy doesn't work - it may very well work, but nobody has actually looked at the evidence.

**Dr Baumer.** Two points: First - one of the consequences of putting blood ammonia into the APLS would be a dramatic rise in the number of blood ammonias done. Second - the point about the lack of evidence of benefit not being evidence of lack of benefit: until you have looked carefully and rigorously at the literature how do you know there is a lack of evidence of benefit? You have to do that step first.

**Professor Stephenson.** I just want to clarify how common this problem is. As I understand it from the Wong study, which you cited in your paper, if you've a population of 100,000 children under the age of 16 for one year, 30 will present with non-traumatic encephalopathy, six percent of whom will have a metabolic disorder, over half of whom have ketoacidosis, leaving about two percent with an IMD. So two percent of 30 per 100,000 now becomes point six per 100,000. In your paper you cite the figure of one in 300 critically ill children but I'm more interested in the general population. So taking point six per 100,000 and applying it to the 10 million children under 16 in the United Kingdom, 60 patients with IMDs per year throughout the whole of the UK would present to casualty as a non-traumatic encephalopathy. So the "haystack" is now getting bigger and the "needle" smaller. Whereas if they are already on PICU that's different because that suggests the penny has already dropped and all these samples are quite likely to be taken. Nevertheless, having said that, we have heard anecdotally from Dr Champion about patients on PICU for twenty four, forty eight hours who have never had an ammonia sent.

**Professor Hall.** I think that this sort of analysis is helpful because inevitably parents feel aggrieved when there is some delay in making diagnoses, and having some comprehension of the size of the haystack and the rarity of the needle may be of some help in understanding why.

We should also note that some of the thinking behind this workshop was about children who present to casualty with very minor illnesses and then *subsequently* deteriorate, which is a different aspect of the problem.

**Richmal Oates-Whitehead.** Just further to Dr Baumer's earlier point about the need to *systematically* check to see if the evidence is there. A systematic method does have to be put in place which includes reviewing numerous databases such as Medline, Embase, and the Cochrane register of databases. The method also includes going through references in papers and finding unpublished work.

**Professor Hall.** I'm sure that's right. Enshrined in this workshop there must be about fifty questions each of which could be attacked in that way and part of the art is selecting a question where that approach is likely to produce data that really will affect policy and teaching. Not even Mr Denney with all his generosity is going to fund us to do a systematic review of that scale on all these fifty questions.

**Dr Baumer.** I agree we need to find the key questions but I think a single approach of the sort we are talking about will identify anything that impinges on those fifty questions, because they are all related to the same sort of subject.

**Mr Denney.** Are the protocols described by Dr Tasker in place in most Regions?

**Dr Tasker.** I can only speak for Anglia. We were instructed by the Department of Health to come up with those three protocols, but we were also told that that was the expectation for all Regions. They were all supposed to be done by April 2001, so I assume that they are all in place around the country.

**Professor Hall.** There has been a very big investment in paediatric intensive care and the standards for the high dependency end of it, which is what would happen at the large DGHs, are going to be released soon.

**Dr Tasker.** The approach for the high dependency standards regarding the neurologically affected child divides it by coma score, but also there's a separate condition-based approach and it may be that in trying to find the needle in the haystack you're



concentrating on that group. For example there's going to be a protocol for the child with coma of unknown aetiology.

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***4.4 a) What evidence – published or unpublished – is there for the effectiveness of optimum management of classic RS? And by implication what is optimum therapy?***

***DR JOHN GLASGOW***

### **Management of Reye syndrome (RS)**

Evidence for the efficacy of one therapy, or a group of therapies, over another may exist at various levels from double blind randomised controlled trials down to anecdotal sketches with diminishing powers to commend the practice to others. In **classic RS**, RCTs have not as far as we were aware been published although they have often been called for, most notably in the UK by the late Professor Alex Mowat and Professor Brian Neville in a letter to the BMJ in 1975; Stumpf in an editorial in *Brain & Development* (1995) concurs. Partin echoed the same point in a Workshop on Reye's syndrome held in 1986. In reviewing nearly two decades of therapeutic experience, he said he used the word "opinion" with precision... in that "scientifically sound studies of treatments have not been possible and most reports of treatment schemes represent uncontrolled claims" (Partin 1988).

However, to be certain that this was still the case, a thorough search was made using the Cochrane Library and MEDLINE beginning from 1987. This date was chosen as it was assumed that the Round Table Conference on RS (November 1986) at the Royal Society of Medicine at which invited individuals discussed a wide range of issues including pathological mechanisms, aetiology, prodromal features, diagnosis, and treatment and would likely have identified significant literature published earlier. Several N American authorities presented their experiences; however, the meeting format fell short of a

consensus process, as one would understand the term today. Incidentally, three of the fifteen present then are participating in this Workshop.

### **Literature searching**

Text words terms used to search the literature were – RS, child/ children, metabolic encephalopathy (metabolic brain disease), therapy, hospital management, intensive therapy, and a range of specific treatments including – fluid management, mannitol, hypertonic fluids, hypertonic saline, osmolar therapy, airway management, mechanical ventilation, hypothermia, body temperature control, barbiturates, calcium-channel blockers, corticosteroids, ICP monitors/ -ing, ICP control, ventricular drainage, craniectomy. Outcome was searched using the additional terms – follow up studies, case - control studies, comparison studies, psychometric assessment. Less than one dozen significant papers additional to those of which I was already aware were unearthed by this process. I am indebted to Mr Daimuid Kennedy (librarian) for assisting me.

### **Does early diagnosis help?**

My overall instinct is that it may in some instances; proving this is another matter. We were unable to show in 56 cases using parametric statistics, for example, that the neurological stage at presentation differed significantly over the time period 1979-86. One should add that it was only in May 1985 that our multi-disciplinary RS group in Belfast produced a best practice document on early recognition, investigation and management that was circulated to each A&E and paediatric units throughout the Region in hope of improving outcome (Glasgow JFT 1986). Nor were we able to find an improved morbidity or mortality over the time period, and, although ours is probably the largest single centre series outside the US, we are dealing with relatively small numbers. John Partin addressing the same issue (1988) says that in the late 1960s and early 1970s most comatose cases were recognised very late, and were often undiagnosed in hospital for periods of up to 48 hours.

In the US, it was the sheer volume of the 1974-75 influenza outbreak that improved RS recognition through the efforts of professionals, the media and lay pressure groups. By 1979 Partin found that the duration of “vomiting time” had shortened by some 40% to a mean of 33 hours; a similar figure was quoted by Lichtenstein and colleagues (1983) for the 19 patients in their stage I study. I am interested that even with an experience of hundreds of cases seen over nearly two decades, Partin was unable to demonstrate in those with a range of severities that early diagnosis could reduce the number of those progressing to coma, sustaining brain damage, or the number of deaths. De Vivo and colleagues (1975) reported in 36 patients (seen 1966-75) that case fatality fell after 1971. They attributed this to earlier recognition (milder cases), and more intensive medical management.

The three elements that seem to have stood the test of time and are set out below – continuous use of a hypertonic glucose infusion, intermittent use of hypertonic mannitol and early elective endotracheal intubation combined within a full intensive care setting. Among stage I patients seen at a teaching centre in Cincinnati (Heubi et al, 1984) – only 5% (of 83 all biopsy-proven) progressed to agitated delirium or coma; one was brain damaged (no deaths). This, the authors point out contrasts with those of the Centers for Disease Control (CDC) statistics 1973-80 when the mortality was 10 - 22% (stage I – difficult to arouse/ sleepy), and rate of disease progression was 34%. Reporting bias may have coloured the CDC data in favour of those that progressed to more advanced stages. Furthermore, it was not always clear the degree to which patients in that reporting scheme had received early active intervention therapy with IV glucose etc.

Heubi concludes that early diagnosis is best achieved by the coordinated education of parents, doctors, those in public health, nurses (health visitors) and the media. Somehow I feel that there is a lesson for the UK to take onboard – and shall return to this later.

#### 4.4 a) Effective optimum management?

##### **APLS approach**

I am assuming that all sick/ ill patients will be admitted to hospital (a high dependency environment), the APLS structured approach followed – A, B, C, D – monitors positioned and basic IV lines placed (additional lines will be needed later). I also take it as read that an initial battery of biochemistries and other investigations have been initiated (see monitoring below), and that the diagnosis is at least suspected. *Pari passu*, hypoxia, shock, acid-base disturbance, seizures, hypoglycaemia and excessive body temperature ( $>38.5^{\circ}\text{C}$ ) must be controlled/ corrected against a background of continuous clinical (ABCD) and electro-physiological monitoring (heart rate(HR), ECG, respiratory rate (RR), blood pressure,  $\text{S}_a\text{O}_2$ ). Assuming that shock and moderate to severe dehydration have been corrected, it is prudent during initial resuscitation, to restrict crystalloids to 60% of requirements; hypo-osmolar must fluids be avoided.

##### **Definitive management**

Thereafter management of the individual is determined by the neurological stage indicated by a patient's clinical signs. A number of staging criteria have been published over the years but that of Lovejoy and colleagues (1974) appears to have gained most acceptance. This 5-stage scheme focuses upon respiration, level of consciousness, the pupillary light reflex and response to pain. Any of the schemes are satisfactory provided the medical/ nursing team are trained in its use and apply it consistently. Alternatively an age-adapted GCS can identify the level of consciousness.

**TABLE 1 CNS STAGING (Lovejoy et al, 1974)**

Stage	Level of Consciousness	Respiration	Response to pain	Pupils	Approx GCS
1	Drowsy	Normal	Appropriate	Normal	12
2	Restless/agitated	Rapid	Appropriate	Normal	10
3	Light coma	Rapid	Decorticate	Normal	8
4	Deeper coma	Variable	Decerebrate	Fixed, dilated	3
5	Deeper coma	Apnoeic	Flaccid	Fixed, dilated	

### **Advanced CNS assessment**

However, as Plum & Posner taught us 35 years ago, and Kirkham (2001) has recently reminded us, for those in coma (stages > II), there are additional hazards. It is essential to carry out specific tests of brain stem function and its reflexes that allow an assessment of the level and possible type of impairment that may be occurring at sub-cortical levels. In consultation with neurological colleagues, regular serial examinations can detect herniation syndromes that can be life saving or prevent brain damage. It is clear that some older ideas will have to be revised and possibly reversed.

### *Management according to CNS level*

Those deemed to be in **Lovejoy stage I** (Table) – six patients in our series - must be closely monitored (see above); although only 5% are said to progress and require intensive care management. They should be managed with **IV (re)hydration** judged according to standard clinical signs and the volume/ type of fluid therapy received elsewhere taken into account; careful fluid balance is critical. The N Americans recommend use of a **10-15% hypertonic glucose-multielectrolyte solution**, volume being provided at normal maintenance requirements - 70 ml/ kg/ day (1,600 – 1,800 ml/ m<sup>2</sup>/ day). Sodium content is used at a concentration of 40 mmol/ l (with 30 mmol/ l of potassium). In the early days, we tended to fluid restrict the maintenance volume of many patients (sodium 75 mmol/ l, adding potassium as required), whereas today there seems

little doubt that this policy is contra-indicated. In the early stages other things being equal, glucose given in this type of solution may be the most crucial therapy. John Partin (1988) states that “glucose infusion must be pursued aggressively because a certain but unknown number of non-comatose cases may suddenly advance to delirium (stage II) and coma”. The considerable advantages of infused hypertonic glucose are shown in Table 2 below. Should hypoglycaemia (present in half our patients) prove persistent or recurrent, a 20% solution may be needed although such patients are usually beyond stage I.

In any child showing signs of raised or rising ICP (also likely beyond stage I), **mannitol IV** (0.25 – 0.5 g/ kg) can improve the level of consciousness and should be given immediately. Hypo-osmolar fluids should be avoided. Vitamin K<sub>1</sub> 1 mg is given IV on a daily basis.

### **Monitoring by clinical & laboratory means**

Throughout, patients must be regularly reassessed bearing in mind the inherent risks consequent upon the (widespread) mitochondrial patho-physiological abnormalities and their implications. **Vital signs** (HR, RR, BP, CRT, body temp) and neurological reassessments are central to understanding evolution of the natural history. The level of consciousness must be carefully assessed, using an age-appropriate GCS accompanied by examination of the pupils and assessment of posture, response to pain, and the full range of brain stem tests. This is much more straight-forward in the conscious child.

Regular (4 – 6 hourly) **monitoring of the blood chemistries**, etc are essential also - especially blood glucose, electrolytes, urea, creatinine, calcium, inorganic phosphate, osmolality, haematocrit; urine output, osmolality, etc should also be monitored.

Repeating blood ammonia and transaminases can probably be done somewhat less frequently, although the timing of invasive procedures (biopsy/ insertion of intra-cranial pressure monitor) will require that any abnormality in coagulation (eg INR/ PT %) be corrected. Depending upon circumstances or the possibility of complications, other investigations such as amylase might be essential. Microbiological investigations should be done at the outset.

IMDs will have to be considered also, but it is for others to provide specific detail.

**Radiological assessments** such as CT of the brain may contribute to management once stability of the patient has been achieved, especially where there is doubt about the diagnosis - particularly if a localised lesion is questioned. However, in RS the scan appearance does not correlate with the presence of cerebral oedema or an increase in ICP. (The place and timing of lumbar puncture is referred to below). In a recent Archives review, Kirkham (2001) sets radiological imaging within the contexts of the differential diagnosis and management of the comatose child. *Close monitoring and regular reassessment must be seen as of equal importance to all aspect of therapeutic provision in RS because it is upon these findings – clinical, (including physiological measures mentioned) and laboratory investigations - that therapeutic adjustments and/ or additions will depend.*

This represents the most basic level of safe management.

## **Lovejoy stage II**

Those thought to be at a more advanced stage - (18/ 56 patients in our series) - typified by marked restlessness and/ or agitation and a raised respiratory rate (toxic delirium) - should be resuscitated and stabilised as above. Following admission to PICU a number of additional measures thought to represent best practice can be initiated. The aim is to protect the brain from a range of escalating insults that may culminate in an increased brain volume and possible increased intra-cranial pressure (ICP) that might result in coning, etc. The following are thought advisable at this stage:

- **General anaesthesia** (thiopentone) and neuromuscular blocking drugs administered; Use of propofol is contra-indicated for maintenance of anaesthesia in a children's intensive care setting, and one is aware of a number of child deaths have following its use in RS. IV opiates or similar medications will also be required.

- This allows **endotracheal intubation**, and respiration can now be controlled and the  $P_aCO_2$  maintained around the (low side of) normal range; somewhat higher than was our practice in 1985 (see below). This is the time for **other painful or unpleasant procedures** to be carried out such as central venous cannula insertion, intra-arterial lines for BP monitoring; arterial blood gases/ pH, and nasogastric tube placement, etc.
- If there is significant fever, **temperature control**, use a servo-controlled cooling blanket, or rectal paracetamol and fan.
- **Care of the head/ neck** - during all procedures, care is taken to minimise compression of neck veins and retain the neck in the neutral midline position with a 30° head-up tilt.
- Patients should be **handled a little as possible** and ought not be repeatedly examined unnecessarily by many individuals.
- In the past, **lumbar puncture** was often done where it was thought likely to contribute to management. Increasingly over the years one has tended to avoid this procedure because of likely increased ICP, but nevertheless to treat possible bacterial meningitis and herpes simplex encephalitis de novo. Newer methods of laboratory diagnosis using PCR on a blood samples have now made it less necessary to obtain an early CSF specimen for confirmation purposes. Moreover, even if LP is delayed, useful information may be gleaned later from this source.
- **Liver biopsy** may now be performed. This might be more important in the atypical RS case, or those in whom a snap frozen tissue sample is crucial for diagnostic enzymology, such as OTC deficiency (others can comment). Before this procedure is done a prolonged prothrombin time/ low INR or will need to be corrected using FFP and Vitamin K<sub>1</sub>. In our series, biopsy was carried out in 28/ 56 patients (in 7 others autopsy material); histopathology was therefore available in 35.



**Table 2 ADVANTAGES OF HYPERGLYCAEMIA (from DeVivo, 1988)**

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Cerebral Fuel
Increased transport across blood brain barrier
Increased substrate for glycolysis
Osmotic agent
Lower brain water content
Decreases need for hypertonic mannitol
Insulin secretion
Insulin effect opposes lipolysis, lowering free fatty acids
Insulin effect opposes protein degradation lowering ammonia, amino acids, lactate
Tissue glycogen repletion
Improves cerebral energy reserve
Facilitates organ recovery

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- **Maintenance of hyperglycaemia** is thought to be crucial. It is also assumed, but has not been proven, that brain glucose requirements are increased. It has been shown that cerebral blood flow and cerebral metabolic rate for oxygen are decreased by 75-80% in comatose children with RS (unpublished data quoted by De Vivo, 1988). Our practice is therefore to infuse glucose at a concentration of 10-15% in order to maintain the blood level in the range of 8 - 10 mmol/ l (Table 2). This is roughly in line with the thinking of N American colleagues (Round Table Meeting, 1988, for reference see DeVivo or Partin 1988), although De Vivo tends beyond stage I initially to use 20% glucose. This if given in the daily volume quoted above produces hyperglycaemia (14 – 19 mmol/ l) and provides 500-600 mg /kg /hour; a 10% solution yields 300 mg/ kg/ hour. Provided a constant infusion rate is maintained, this approach has multi-dimensional advantages as set out in Table 2. This establishes continuing metabolic stability of the patient, avoids fluctuating or low blood levels and the associated changes in osmolality observed in some patients treated years ago.

- **Seizures** may be of various types and degrees and must be treated immediately as they are often associated with an increase in ICP and may thus result in cerebral herniation. Status is a particularly worrying accompaniment. The British Association for Paediatric Neurology and APLS have published similar management protocols. Fever should be controlled as it tends to lower seizure threshold. A reduction in body temperature by 1°C may reduce cerebral metabolic rate significantly, and research from other areas suggests that either this or maintenance of normothermia may be helpful.
- We also used oral (via nasogastric tube) lactulose/ neomycin to interrupt ammonia production/ absorption, but whether this is still regarded as essential in classic RS, I doubt.

### **Lovejoy stage III and beyond**

Patients in coma on arrival – (32/ 56 our series; 22 stage III) – but not yet subject to neuromuscular blockade will require all of the above management, and in addition very careful attention to the CNS assessment - the level of consciousness, pupillary examination, actively searching for abnormal brain stem signs. The features of any form of impending brain herniation need to be detected and managed promptly. The assumption is that ICP is raised in all such patients – even though CT scanning might not reflect this – bearing in mind the exponential shape of the relationship between intracranial volume and ICP. These parameters may abruptly increase (further) leading to herniation, brain damage and/ or brain stem death. Unconscious patients give these assessments an added urgency.

Such patients must therefore be admitted at once to a PICU, be anaesthetised and so on as set out above for stage II. Additional modalities of management also need to be considered.

### **Intracranial pressure (ICP) monitoring**

This approach remains controversial. It should not be seen as a substitute for meticulous, regular clinical monitoring by well-trained staff. A variety of devices have been used in the past. Our experience of 39 patients utilised the ventricular catheter (in 3), Richmond bolt (12), and the Ladd epidural fibre optic sensor (24) (Jenkins et al 1987). It was not the presence of a raised ICP that was found to be associated with a poor outcome, nor did this correlate with the CNS stage, or the initial glucose in blood or CSF. Mean cerebral perfusion pressure (CPP) that at insertion was 67 mm Hg fell during management to 49 mm Hg ( $p < 0.001$ ). There was a tendency for lower minimum CPPs to be recorded in the more advanced Lovejoy stages – stage II, 53 mm Hg; III, 47; and IV, 42. *However, it was the minimum CPP that in our hands distinguished between those with a poor and those with a satisfactory outcome (56 vs. 32 mm Hg;  $P < 0.001$ ). The relationship between minimum CPP and outcome was striking in that all 10 patients with a CPP of  $< 40$  mm Hg had a poor outcome compared with two of 29 whose minimum CPP was 40 mm Hg or greater ( $P < 0.001$ ).* Our results had not been biased by the duration of monitoring in the two groups ( $P = 0.075$ ).

Similar findings have been reported in several other groups with non-traumatic coma. Throughout it is important to sustain the systemic arterial BP with fluid boluses as required; central venous pressure will guide titration. Inotrope use is often also necessary and presents its own challenges. It is interesting that in spite of maintaining our patients in the past on the lower side of daily fluid requirements (approx two-thirds) and ventilating to a  $P_aCO_2$  (lower than recommended today), each of which may have been thought adverse in sustaining the CPP, those having a minimum CPP as low as 40 mm Hg (in eight 50 mm Hg or less) in our hands appeared to do well – i.e. at a lower level than reported by others (65 – 70 mm Hg).

### **PICU and (normo) ventilation**

We believe that elective nasotracheal intubation on admission to ICU ensures control of the patient's airway, making respiratory compromise less likely, may reduce IC blood

volume (10% of IC volume), and allows painful and unpleasant manipulations that would tend to increase ICP, to be carried out. There seems little reason today to opt for what 15 years ago we called “controlled hyperventilation”, and most patients today would be maintained in a (low) or normal range of  $P_a\text{CO}_2$  and  $P_a\text{O}_2$  between 14 – 21 kPa - at least initially. Many of those in stage II – early stage III are already hyperventilating and can maintain these values spontaneously while breathing humidified oxygen through a T tube adapted to the endotracheal airway. Alternatively, ventilatory assistance in the IMV mode is necessary particularly if a patient has an altered respiratory pattern such as hypoventilation or periodic breathing. Evidence that “prophylactic hyperventilation” prevents the ICP from escaping to higher levels is lacking. Indeed, overzealous use of IPPV can reduce CBF below an ischaemic threshold in comatose patients, and may do more harm than good. Today’s recommendation is to ventilate to normocapnia, with actual hyperventilation or bagging reserved for abrupt increases of ICP.

### **Intermittent ICP increases or persistently high ICP**

First it is important to state that due care should be taken to ensure that complications such as **seizures** are well controlled by conventional means. In the past we have used prophylactic parenteral *phenytoin* - rectal *paraldehyde* is another option; in the circumstances this seems logical. **Airway suctioning** needs to be carried out with care and possibly coordinated with the use of mannitol or after the administration of IV anaesthesia and neuromuscular blocking drugs when these are indicated for other reasons. Repeated and **unnecessary examinations and excessive handling** may also tend to raise ICP and should be minimised.

Controlling spikes of ICP can often be achieved very rapidly using **mannitol**, bearing in mind the comments made earlier about the use of **hypertonic glucose** that tends to reduce the need for mannitol – a view supported by De Vivo (1988). Mannitol decreases the haematocrit and blood viscosity, and increases CBF and cerebral oxygen metabolism; it may reduce ICP spikes via its action as an osmotic diuretic or by reducing cerebral blood volume. Daily doses up to a maximum of 4 – 6 g/ kg are usually sufficient to control

cerebral oedema, although much more modest amounts are usually sufficient; this presupposes renal function is normal. It can be “piggy-backed” onto a central IV infusion line as need requires. However, prophylactic use does not seem to be beneficial. Examples during therapy of hyperosmolality are seldom encountered bearing in mind that glucose and mannitol have similar molecular weights; a blood glucose of 10 mmol/ l is equivalent to 10 mOsm/ l. In most patients our experience and that of others is that osmolality ranges between 290 – 310 mOsm/ l.

An alternative means of controlling demonstrable spikes of increased ICP would be to **hand bag the child or initiate a (short) period of hyperventilation (IPPV).**

The use of **barbiturates** to reduce ICP is controversial and adds to the difficulty of maintaining normal BP. High drug levels may delay recovery and can pose problems in the respiratory system especially in those who require longer ventilatory support.

A **mild reduction in body temperature** might have some benefit in persistently raised ICP; we have not used this approach.

**Fluid restriction** and the problems this may create have been dealt with above.

Hypovolaemia should not be allowed to develop, nor should hypo-osmolar solutions be infused.

There should be **careful monitoring** of vital signs, including arterial BP, central venous pressure, urine output, body weight, core and peripheral temperature, plasma and urine electrolytes and osmolality every 5- 6 *hours* as a means of judging the need for alterations in fluid or other modalities of management.

Use of **glucocorticoids** is not thought to be of any therapeutic aid, whatsoever the stage, and the risk of developing pancreatitis is increased.

More radical approaches, reported in the early 1970s such as **exchange transfusion**/ total body washout, several of which we undertook at that time, are of historical interest only.

### **Management of seizures – overt/ occult**

We always found it very difficult to know whether comatose patients with RS who are paralysed/ ventilated are having seizures, or if status was present. Our experience in using a cerebral function monitor was rather crude and uncritical. In the past it was said also that such indices as heart rate, BP and pupillary dilatation could provide an indication of seizure activity. Kirkham (2001) has commented on a more sophisticated approach, and on the need for more research. If seizures had been present earlier in the course of the illness logic would seem to dictate that prophylactic, long-acting anticonvulsants be continued.

### ***Have RCTs been carried out?***

These have not to our knowledge been done; others may know of disorders where the patho-physiology is similar and allow such approaches to be used as a surrogate for the metabolic disturbances and encephalopathy of classic RS – though I doubt it. The Cincinnati group (Heubi et al 1984) comments however, that -

*“studies in which patients are randomly assigned to various regimens, including fluids versus no fluids or fluids that contain glucose versus fluids that do not will be necessary to test this hypothesis (i.e. the main managements)...adequately. However, these studies may be difficult to justify on ethical grounds”*

We echo this view, and in any case patient numbers are now so small it would seem that such work is unlikely to be carried out in the foreseeable future.

#### **4.4. a) Outcome measures**

At the most basic level one could look at what one might call intact survival. We have taken this one stage further as outlined earlier in relation to cognitive function etc in those who survived to attend normal school (see 1.3.2.ii in Part 1 of the Workshop Proceedings).

#### **4.4 b) What treatment can be undertaken/ started locally?**

My view is that all children with RS (or those in whom this diagnosis is being considered) should be first discussed with the relevant personnel at the Regional centre and transferred for definitive management as soon as is reasonably possible. This has two aspects – 1) intensive care depending on the stage and progression, and 2) more wide ranging metabolic investigations. I can see no good reason to retain such patients in a DGH. A full battery of bloods should be withdrawn and the processing begun locally (although this will depend on whether such tests as ammonia can be performed at the DGH). Hypoglycaemia should obviously be corrected, and the ABCD assessed according to the APLS approach.

#### **Do we have a Plan of Action?**

*Each region should have a written, multi-disciplinary, agreed strategy in place on how to manage the child with (suspected) metabolic disease including those with encephalopathy, unexplained hypoglycaemia, hyperammonaemia, lactic acidosis, etc.*

Many of these are very young/ tiny babies. There must be clear lines of communication/ authority and it needs to be led by probably two senior consultants (say, one metabolic disease or paediatrician with an interest/ one PICU). If such has been agreed some of the ad hoc difficulties that tend to arise can be circumvented. I can say this in that we had a sort of early model (mid-1980s) that we thought was beginning to work for RS but with the decline in RS it was never tested properly.

My question is -*Does such exist in the Regions/ any area – or nation(s) wide - is it written down, has it been mutually agreed, is it working, or is it now time to begin/ improve/ tighten-up this approach?*

### **The transfer**

In transferring such vulnerable patients, it is important to adhere to the principles and practice set out by in the APLS Manual – of good communication between the DGH and the Regional centre, of physiological stabilisation of the patient (see above) under advice from the centre (according to the agreed Regional referral plan - see above). Those in stage I, in my view should be transferred also as well as all in the more advanced stages. How the transfer should be carried out may depend upon local arrangements, but proper care of the ABCD, and all that this implies, must be provided together with at least two secure IV lines to administer **hypertonic glucose-multielectrolyte solution** (see above), and if necessary **mannitol** *en route*. Seizures may also need to be controlled. Depending on the stage, an **ET airway** under general anaesthetic etc may or may not have been placed prior to departure. Senior staff will need to accompany the child with the full array of equipment that would be available for short term intensive management as required *en route*; complications will need to have been anticipated and prepared for. Some centres may be able to use their Retrieval Team - that has considerable advantages.

### **c) What treatment can only be undertaken at a specialist centre?**

The simple answer is - full PIC in a Regional Unit. Having said that, one is conscious that those thought to have RS, even those < stage II, should be transferred after initial resuscitation and stabilisation. This is an unpredictable and unforgiving disorder. We have always followed this practice, and in N Ireland all those with RS (or likely so) have been referred to the Regional PICU; they ought not to be sent first to the DGH from an Area hospital, but routed *directly* to PICU. Advice initially should be given regarding the three pillars of RS management – as mentioned above– it is here that the value of an agreed Regional referral plan will be demonstrated.



However, where a child arrives already in an advanced stage (say, > stage II)/ comatose, all the more reason for careful liaison with the centre, institution of the full range of monitoring/ management options set out above (see 4.4 a), with transfer being accompanied by senior anaesthetic and paediatric staff, or after a request to the Retrieval team, etc.

## Summary

**The nine-fold rule for the successful management of RS by any physician – all aspects apply to a Regional/ Teaching centre; some to DGH staff –**

- 1) To think about and seriously **consider the diagnosis of RS**, even when clinical features are atypical ;
- 2) To be aware of the full **range of symptomatology** (much of the Workshop directed to this end), as well as the diagnostic criteria;
- 3) To be aware of the **nature and range of patho-physiological** disturbances that can ensue;
- 4) To reflect broadly about diagnosis (and differential) in such a way that embraces the **real possibility of a IMD (R-LS)**, and that urgent **laboratory specimens** are collected expeditiously.
- 5) **Contact local experts** both in the field of laboratory diagnoses (RS/ IMD) and acute paediatrics/ PICU; but with those immediately available to help, either transfer the child to the appropriate centre in company of suitably trained personnel, or await arrival of the recovery team.
- 6) Be able to **begin resuscitation** immediately – APLS approach; discussed specific **transfer/ transport details with the receiving team according to the regional referral plan** (see above), and following appropriate **stabilisation** of the patient in concert with those immediately available to help, either transfer the child to the appropriate centre in company of suitably trained personnel, or await arrival of the recovery team.

- 7) Arrival at the centre is followed by further assessments, and, if necessary, **more advanced resuscitation and specific lines of management in a high dependency/ PICU setting.**
  - 8) **Parental support** by delegating team member should be a part of any protocol.
  - 9) **Follow up** (multi-disciplinary team approach as required) and ongoing support.
- Be able to **begin resuscitation** immediately – APLS approach; discuss specific **transfer/ transport details with the receiving team according to the regional referral plan** (see above), and following appropriate **stabilisation** of the patient in concert.

## REFERENCES

- DeVivo, D 1975, Reye's syndrome: results of intensive supportive care. *J. Pediatr.* **87**: 875-880
- DeVivo, D 1988, Treatment of Reye's syndrome: consensus and controversy. In: *C.Wood (Ed), Reye's Syndrome*, pp 133-150. London: Royal Society of Medicine.
- Glasgow, J.F.T., Jenkins, J.G., Hicks, E.M., Keilty, S.R., Crean, P.M., Black, G.W. and Fannin, T.F. 1986, The prognosis for Reye's syndrome in Ireland can be improved. *Irish Journal of Medical Science*, **155**: 111-116.
- Heubi, J.E., Daugherty, C.C., Partin, J.S., Partin, J.C. and Schubert, W.K. 1984, Grade I Reye's syndrome – outcome and predictors of progression to deeper coma grades. *New England Journal of Medicine*, **311**: 1539-1542.
- Jenkins, J.G., Glasgow, J.F.T., Black, G.W., Fannin, T.F., Hicks, E.M. and Keilty, S.R. 1987, Reye's syndrome: assessment of intracranial monitoring. *British Medical Journal*, **294**: 337-338.
- Kirkham FJ, 2001, Non-traumatic coma in children. *Arch Dis Child*, **85**:303-312
- Lichtenstein, P.K., Heubi, J.E., Daugherty, C.C., Farrell, M.K., Sokol, R.J., Rothbaum, R.J., Suchy, F.J. and Balistreri, W.F. 1983, Grade I Reye's syndrome: a frequent cause of vomiting and liver dysfunction after varicella and upper respiratory tract infection. *New England Journal of Medicine*, **309**:133-139.
- Lovejoy, F.H., Smith, A.L., Bresnan, M.J., Wood, J.N., Victor, D.I. and Adams, P.C. 1974, Clinical staging in Reye syndrome. *American Journal of Diseases of Children*, **128**: 36-41.

Partin, J.C. 1988, General management of Reye's syndrome. *In*: C. Wood (ed.), *Reye's Syndrome*, pp. 156–172. London: Royal Society of Medicine.

Plum, F. and Posner, J.B. 1966, *Diagnosis of Stupor and Coma*, pp. 56–67. Philadelphia: F.A. Davis Co.

Stumpf, D.A. 1995, Reye syndrome: an international perspective. *Brain and Development*, **17 (Suppl.)**: 77–78

## **DISCUSSION**

**Professor Tanner.** I think we need to be cautious about the efficacy of treating Grade 1 RS -the work from Cincinnati, the Heubi paper. They did treat cases aggressively and they had a very good outcome. However, the number of cases they identified suggested a very much higher incidence of Reye's than was generally thought. Maybe they didn't all have Reye or maybe they all had Reye but they wouldn't have progressed to more severe disease anyway. I don't think that the fact that those patients had a good outcome can be taken as proof that treating Grade 1 aggressively is necessarily effective.

**Dr Tasker.** As I said earlier, from the point of view of paediatric intensivists, we would approach this problem very differently now. Glucose has had a bad press recently. For example the New England Journal papers on the randomised controlled trial of insulin in critically ill adults showed that if patients have a glucose in the range of eight to ten during their critical illness, there is excess mortality. So we would need a very good reason to drive patients' glucose up to that level. In the setting of brain injury, like stroke, - whether it's the stress response or hyperglycaemia there seems to be a worsening of stroke outcome and also worsening of outcome post cardiac arrest resuscitation. So again there would have to be a very good reason to adopt that strategy.

We now have other techniques like magnetic resonance spectroscopy to actually *look* at what is happening to cerebral lactate whilst you are giving all this glucose, so I think

there would be a number of research approaches that would be taken if these patients ever presented again.

**Professor Hall.** That is an interesting point. One hopes that this condition won't come back but there may well be another pandemic of 'flu sooner or later and if the public health message about aspirin has been forgotten or if it's ignored, this disease will return. So it would be interesting for someone to just think about that and consider what research steps might be initiated if this was to suddenly reappear.

**Dr Tasker.** Another point is that what we are bringing into head injury practice now is in vivo microdialysis - actually putting catheters into the brain and monitoring chemicals. For example glucose, lactate, pyruvate to get a lactate-pyruvate ratio; glycerol, glutamate. It would be possible to get glutamine and GABA. So these techniques could actually broaden out an understanding of what's actually going on in the brains of these patients.

**Professor Hall.** I wonder if this glucose story is like the old story of bicarbonate and acidosis and whether it seemed like a good thing to do.

**Dr Glasgow.** I accept that new techniques like microdialysis might provide a new approach to the management of RS. However, we need to bear in mind (and our experience supports this) that if one isn't quite aggressive with the concentrations and the amount of glucose (in my paper I've given the recommended figures that were current at that time) and if you are not monitoring carefully and using a high enough concentration, the glucose plummets down again. Then you have to correct it again and DeVivo makes the point that one of the things that you should *never* do is to halt the infusion.

I hope we don't have to go back through this story again, but if we do there will be new approaches. The problem is I can't think of appropriate surrogate conditions for RS that could be studied, before that happens, in some prospective randomised way.

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#### **CONTRIBUTION FROM CLIMB AND NRSF UK**

**Question 4.5 How and when is information about the diagnosis best conveyed to parents?**

**What resources are available? Should they always be informed about a relevant support group and if so, what is the best time?**

How, by whom and when is information best conveyed?

##### How?

Face to face followed by a written summary to both parents. A follow up meeting if needed.

##### By whom?

By a consultant who will look after the child with the right knowledge and who can answer questions or by a health visitor; by the GP; by *Climb* (nb *Climb* would not agree with the organisation being the first to convey the information)).

##### When?

At the time of diagnosis or as soon as possible was the response from 100% of parents.

##### What resources are available?

The doctor, the internet, leaflets, emergency protocols and diet information as soon as possible. Voluntary organisations with specialist knowledge with access to a support network of experienced families with practical solutions, specialist clinical liaison nurses, written documents of similar cases, helpline (not an impenetrable photocopy from a medical journal), should always be informed of the relevant support group. Response was 100 % to this but is hardly surprising as it is *Climb's* members and we would have been disappointed with any other response!

They should be informed of the relevant group as soon as the diagnosis is made with an introductory leaflet only to avoid overload and this information repeated a few

weeks later so parents can decide for themselves when and if to approach the organisation.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

### **Mrs Greene**

The responses above, to the Workshop questions obtained by the CLIMB survey, are from our “captive audience” of parents of children with MCAD. We accept that the responses are from the 14 families who were both motivated to get in touch with a support group in the first place, and were further motivated to respond to the survey. We haven’t got a control sample. It would be interesting to take families or patients who were going through the paediatric process anyway, to see in theory about how *they* would feel about these questions.

From the responses that CLIMB had, it was overwhelmingly felt - regarding *how* the information should be given - that it should definitely be person-orientated, face to face. It should be with the consultant with whom you have the best relationship, who is probably going to be the specialist, but might be the consultant paediatrician from the local district general hospital, or the community paediatrician. One respondent felt that the best person to give the information was the health visitor and another, the general practitioner. One person said CLIMB should convey the information about the diagnosis. We actually totally disagree with that - we think it's completely wrong that CLIMB should be the one that gives the diagnosis and if they came to us we would refer them straight back to the consultant.

The diagnosis should be given face to face with plenty of opportunity for the family to ask questions both immediately and also to go away and consider what’s been said and have the opportunity to return with further questions at a later stage. From CLIMB's experience this is usually about four weeks later.

There also should be a written summary in as “lay friendly” terms as possible, as I believe it is the practice for geneticists to provide, so that the family can have this to refer to. It's also useful to send this to the general practitioner because they might find

this useful as well, and families I am sure would find a written summary helpful when they have to convey the news to relatives.

Information about the condition should be given at the time of diagnosis, or as soon as is practicably possible was the response by a hundred percent of the parents.

Regarding what resources are available to convey the information: obviously the doctor in our view should be the primary source of information, and available to go back to again and again. That is the advice that is given by CLIMB if parents come to us for clarification - we say go back and ask your consultant that question. They are often quite surprised by this reply! Also the internet, but with a "health warning", because there are many things on the internet that are not standardised, not quality checked, and can cause a great deal of anxiety. Leaflets that are appropriately written for the lay person are useful and that is where CLIMB and the Reye's Syndrome Foundation contribute. We like to and must work in partnership with yourselves to get everything accurate.

Talking specifically about MCADD, there are emergency protocols so that families feel reassured, that they won't allow the disease to take control of their lives, they are in charge of this condition, the condition is not in charge of them, they must go out and live as normal a life as possible. If they are going abroad, we also can investigate specialists who might be available. Also important is a letter that explains in the language of the country that they are going to, the basics of the condition, so that if they arrive at an A & E in a district hospital in the middle of Provence or something, then that can fast track getting advice from the right person.

Voluntary organisations have got a lot more to offer than is immediately obvious. For example in relation to opening up networks of support that are not immediately evident, such as the one I've just described, and also with families across the country who have been there already and can provide practical information and support and confidence building.

All respondents said that parents *should* be informed about the relevant support group by the doctor giving the diagnosis. Regarding when and how - we hope that the

person giving the diagnosis would have relevant leaflets available of whatever the appropriate support group is. They should for example say to the parents - if you want to have a bit more information and local networking as well, there is this support group, no pressure. Then in the written summary that goes out to parents, mention the support group again in that. If there is a follow up meeting it could be checked out once more, but at the end of the day it's the choice of the family, whether or not they pursue this.

Sometimes CLIMB has been asked by physicians to contact families that they have seen, and we are very reluctant to do that, because in our view part of the process of coming to terms with the fact that you are now dealing with a child with a chronic illness is to reach that point where you feel - right, we know this is occurring, we think we would like to have a little bit of help here so we'll go to this support group. Of course they can't do that if they don't know the name of the support group, but if they suddenly get a letter out of the blue from ourselves for example, they are perhaps going to feel that they've had the control of the situation taken away from them and perhaps they've been moved forward in this process further or faster than they should have been. We very much respect the fact that the parents or the patient must reach that point themselves rather than feel coerced to do it. In fact where we have, as requested by the consultant, contacted a family, we write in very general terms and say it has been suggested to us by Dr Bloggs that you would like to know about our organisation - here is the leaflet, contact us if you want to. The return I think is zero; they don't come back to us.

**Mr Denney.** The Reye's Syndrome Foundation does make a special point of placing leaflets with hospitals and checking from time to time that they are still available for parents' information. The other point I would make is that some of the parents that have come to the Reye's Syndrome Foundation have done so via the organisation "Contact a Family".

## **DISCUSSION**

**Professor Leonard.** I respect Lesley very much for her contribution; it reminds us of how important it is to give the family appropriate information and in writing as well



of course. But with the vast number of conditions we see it's actually very demanding to do that. We do need to recognise just how long it takes to write parent information leaflets. I have found it really quite difficult to get it exactly right.

We recently did an audit of our emergency regimes and it was very illuminating. Amongst the many questions we looked at was whether families felt they got the right amount of information, and most thought that it was evenly balanced, but some said they got too much and some, too little. It's a difficult problem to get that balance exactly right. We need to recognise that sometimes parents are quite overloaded, they weren't ready for this, they didn't want vast quantities of information at an early stage and needed time to take it all in. I think we have to be very sensitive to what the family's needs are at any one given moment.

**Dr Baumer.** Four points: First, from my experience people want to be told about their child's condition by somebody who is both familiar and can tell them what they need to know. That's a very difficult position for a general paediatrician to be in when you are talking to parents about a condition that you have never met in your professional life. What I need in that situation is the support of specialists, who may even be two hundred miles away on the phone, but who can help me to give that information.

Second, I think that the question of how and when information is given is a very generic one and is not specific to this group of conditions. Indeed it's relevant to surgeons who have to tell patients that they've got cancer and so on. I do think that the training of professionals - doctors, nurses and others, in breaking bad news is something that we as paediatricians need to make sure that we do for ourselves. I've been breaking bad news for twenty years and I went on one of these courses and learnt a structure that helped me.

Third, one of the problems, I suspect, for CLIMB is the heterogeneity of disorders that sit under its umbrella. Parents often want *specific* information about *their* child and *their* condition. What I find difficult is keeping a myriad of different leaflets in any sense or order. Something that I could download from the CLIMB website would be a much better way of being able to do that.

The last point is that support is a two way process. I do warn parents about the fact that they may find the family they contact actually needs more support from them than the other way round.

**Mr Denney.** I am a little concerned that, when a parent gets in contact with the Reye's Syndrome Foundation, after asking questions about the particular case, I find that they are in a complaints situation. This is increasing more and more and I am worried about this. I feel their faith in doctors has been destroyed or minimised.

**Dr Bonham.** We do attempt to keep leaflets and advice sheets as a resource for our Region. But the difficulty of this cannot be emphasised too much because of the heterogeneity of the disorders. You are almost in a situation where you specifically write a leaflet per family. Even in the cases where there's a relatively late onset and "milder" illness, it's still a difficult concept to have a mild disorder that can nevertheless kill you - difficult to explain.

**Mrs Greene.** We are very conscious of that. I say to a new family - do recognise that there is always a different degree of severity. Also, we don't just hand out lists of names. We have our family support service, we have a parent contact network and because we get to *know* the families, we enter into a dialogue with them, that's where we provide the added value over and above just the internet and visiting a website. We are developing a website with information on each specific metabolic disease. At the moment we have files on 549 different metabolic diseases so it will be a major undertaking.

**Professor Tanner.** Mr Denney mentioned parents' anger. It is really hard, when you sit with parents whose child has died or been damaged and tell them that we actually confirmed the diagnosis on their child on the neonatal blood spot; that we have a machine that did it in sixty seconds; and try and answer their question as to why that sample wasn't analysed at birth. I think there is potentially a huge pool of anger in this context.

**Professor Hall.** Some of the people that I have visited over the last few months as part of the National Service Framework have one or more specialist outreach nurses who act in all sorts of ways as part of the support team, talking to parents, dealing with problems, giving advice when the child is unwell, a whole host of things. It seems to me that it enormously enhances the quality of care, but I am not specifically sure how much this applies in the field of IMDs.

Does anyone have a view on that because I imagine from CLIMB's perspective if parents had that sort of intermediary person between them and the busy medical team that would greatly enhance the sort of the experience that the parents have.

**Gill Moss.** I certainly am in that position of being in the middle ground, as regards the parents' access to the hospital and being able to get situations sorted out for them.

**Professor Hall.** The National Service Framework is not going to give us a vast amount of money, but what it might do is enable us to score what the politicians cynically call quick wins, where there are relatively simple things that could be done to improve services enormously at fairly modest cost. It seems to me this is one of those sort of things.

**Mrs Greene.** I endorse that. In our experience clinical liaison nurse specialists are absolute gold dust -they are wonderful and need to be cloned!

**Dr Bonham.** I support that. We have a nurse who works with PKU but also will pick up some of the others. Also we should not forget the role of the dieticians in this, because they can be invaluable intermediary link.

**Professor Hall.** The employment of liaison or specialist nurses is patchy across the country - both between specialties and geographically, but it would seem a very good thing to be going for.

**END OF SESSION**

## WORKSHOP PROCEEDINGS: PART 5

### DIAGNOSIS AT AUTOPSY

**MODERATOR: DR ANNE GREEN**

#### **MODERATOR'S INTRODUCTION**

This session is on the diagnosis of Reye's syndrome and RS-like metabolic disorders at autopsy. What we are being asked to address is - which metabolic disorders are we looking for, i.e. what is the evidence from both investigation of sudden unexpected death in infancy, and from the investigation of encephalopathy, as to *what* we are looking for, and *how* do we look; are there any specific indications that give us the clues to what we should be doing; what investigation and sampling requirements should we be taking heed of and, in addition, the issues of consent and tissue storage.

#### ***QUESTIONS 5.1- 5.3***

***In what proportion of autopsies of cases of sudden unexplained death i) in infancy, ii) childhood has an IMD been discovered?***

***Which IMDs have been found in these cases?***

***In what proportion of autopsies of patients who have died from an unexplained encephalopathy has an IMD been discovered?***

***In what proportion of autopsy cases of i) sudden unexplained death , ii) death from unexplained encephalopathy is a Reye-like IMD suspected and fully investigated but the results are by the criteria of current best practice, truly negative?***

#### **PROFESSOR JEM BERRY**

There are few published prospective, population-based series from which to answer the above questions. In retrospective series appropriate investigations were seldom carried out. Most post-mortem series focus on metabolic causes of infant death, rather than Reye's syndrome or Reye-like metabolic disorders.

### RS and RLS in Sudden infant death.

A prospective study of IMDs in 90 consecutive sudden unexpected infant deaths from a defined geographical area (1) using a variety of techniques detected no cases except one possible case of glycogen storage disorder (in retrospect this diagnosis was almost certainly erroneous).

Anecdotal evidence from pathologists interested in sudden death in infancy indicates that MCAD and other disorders of fatty acid oxidation are by far the commonest IMDs presenting to pathologists as sudden unexpected death in infancy, although many more than 30 IMDs have been suggested as possible causes (2-5). When Reye-like fatty change is seen at PM in unexpected death in infancy, our anecdotal experience is that no biochemical diagnosis is made in about 1/3. This group poses particular problems of management and has been noted by others (6).

Several series have used frozen section of liver as a basic screening test for inherited metabolic disorders. In the recent Confidential Enquiry into Sudden death in Infancy (CESDI) study of Sudden Unexpected Death in Infancy (SUDI), a frozen section of liver stained for neutral lipid was described in 196 of 450 post-mortem reports (7). Marked fatty change was seen in 5/196. In two of these the diagnosis was later shown to be MCAD deficiency, and in a third case there was previously known galactosaemia. MCAD was specifically excluded in a fourth. The fifth case was thought to have suffered hyperthermia, and had been maintained on a ventilator. In 3 other cases moderate fatty change was over-interpreted as indicating a Reye-like IMD. Assuming all the frozen sections were reported, this gives an approximate incidence for MCAD of 1.0, undiagnosed Reye-like syndrome of 0.3, over-diagnosis IMD of 1.5, and a predicted rate of missed Reye-like IMD of 0.5 per 100 unexpected infant deaths. 57 cases had some further biochemical screening, and no other IMDs were detected. These figures are small, but this is the largest study of unexpected infant death in the literature and included a population equivalent to almost all the babies born in England in one year. Other studies have confirmed that fatty acid oxidation defects are rare as a cause of sudden unexpected infant death (8-11)(6-9).

### RS and RLS in older children

I know of no systematic study looking at Reye-like IMDs or unexplained encephalopathy as a cause of sudden death in older children. Sudden natural death of older children is usually explicable and due to infection or pre-existing disease such as asthma, epilepsy or heart disease. Several studies show a small proportion of unexplained deaths in this age group, but these are rare compared to unexplained deaths in infancy. A retrospective Scottish study (12) found no cases of Reye's syndrome, and that 6.5% of natural deaths between 2 and 20 years were unexplained. A similar Swedish study of deaths aged 1-20 years gave a figure of 13% for natural unexplained deaths in childhood (13). Even the latter higher figure is equivalent to only 0.007 deaths per 1000 live births. It is possible that a few cases of Reye-like disorders are missed in this group, one or two of whom suffered vomiting or convulsions prior to death.

In a retrospective study of all deaths of children aged 1 month – 18 years in Denmark in 1979 (an epidemic year for Influenza B) death certificates and autopsy reports were reviewed for evidence of Reye's syndrome (14). Of 242 deaths in hospital (accidents and malignant disease were excluded) there was one case of RS. Of 105 deaths outside hospital no cases of RS were found on retrospective review. At this time there were 1.1 million children aged 1 month to 14 years in Denmark.

Reports of unsuspected Reye's syndrome diagnosed for the first time at autopsy are few (15).

### Comment: Diagnosis of RS at post-mortem examination.

The thrust of the above questions is that pathologists are missing RS and R-L IMDs at post-mortem examination. This is almost certainly true, although the numbers missed are small. However, the diagnostic criteria used clinically may not be reliable post-mortem. Hepatic fatty change indistinguishable from that in Reye's syndrome is said to occur in children with a variety of illnesses, especially if maintained by intensive care for more than about 48 hours (16). About 75% of cot deaths have a vitreous glucose  $<0.5$  mmol/l, precluding the reliable diagnosis of hypoglycaemia (7). Cerebral oedema is common at post-mortem, especially after

resuscitation. Many biochemical markers change after death (17;18). Post-mortem electron microscopy of liver may be difficult to interpret because of autolysis.

Diagnosis depends on thinking of the diagnosis, an excellent history, sampling of body fluids as soon as possible after death (by the clinician?) and saving appropriate tissue samples.

Some histopathologists are probably confused about Reye's syndrome (where did it go, and whatever happened to carnitine deficiency?). They could be reached by an informative insert in the Bulletin of the Royal College of Pathologists, an update article in a mainstream pathology journal, or a direct mailing to forensic and paediatric pathologists.

Following recent advice from the Chief Medical Officer, pathologists are much less likely to retain fibroblasts and fluids for biochemical investigation as a routine in cases of unexpected death in infancy and childhood.

#### *References*

- (1) Holton JB, Allen JT, Green CA, Partington S, Gilbert RE, Berry PJ. Inherited metabolic diseases in the sudden infant death syndrome. *Arch Dis Child* 1991; 66(11):1315-1317.
- (2) Emery JL, Howat AJ, Variend S, Vawter GF. Investigation of inborn errors of metabolism in unexpected infant deaths. *Lancet* 1988; 2(8601):29-31.
- (3) Bonham JR, Downing M. Metabolic deficiencies and SIDS. *J Clin Pathol* 1992; 45(11 Suppl):33-38.
- (4) Norman MG, Taylor GP, Clarke LA. Sudden, unexpected, natural death in childhood. *Pediatr Pathol* 1990; 10(5):769-784.
- (5) Berry PJ, Allibone E, McKeever P, Moore I, Wright C, Fleming P. The pathology study: the contribution of ancillary pathology tests to the investigation of unexpected infant death. In: Fleming P, Blair P, Bacon C, Berry J, editors. Sudden unexpected deaths in infancy. The CESDI SUDI Studies. London: The Stationery Office, 2000: 97-112.
- (6) Lundemose JB, Kolvraa S, Gregersen N, Christensen E, Gregersen M. Fatty acid oxidation disorders as primary cause of sudden and unexpected death in infants and young children: an investigation performed on cultured fibroblasts from 79 children who died aged between 0-4 years. *Mol Pathol* 1997; 50(4):212-217.
- (7) Penzien JM, Molz G, Wiesmann UN, Colombo JP, Buhlmann R, Wermuth B. Medium-chain acyl-CoA dehydrogenase deficiency does not correlate with apparent life-

threatening events and the sudden infant death syndrome: results from phenylpropionate loading tests and DNA analysis. *Eur J Pediatr* 1994; 153(5):352-357.

- (8) Lundemose JB, Gregersen N, Kolvraa S, Norgaard PB, Gregersen M, Helweg-Larsen K et al. The frequency of a disease-causing point mutation in the gene coding for medium-chain acyl-CoA dehydrogenase in sudden infant death syndrome. *Acta Paediatr* 1993; 82(6-7):544-546.
- (9) Miller ME, Brooks JG, Forbes N, Insel R. Frequency of medium-chain acyl-CoA dehydrogenase deficiency G-985 mutation in sudden infant death syndrome. *Pediatr Res* 1992; 31(4 Pt 1):305-307.
- (10) Keeling JW, Knowles SA. Sudden death in childhood and adolescence. *J Pathol* 1989; 159(3):221-224.
- (11) Molander N. Sudden natural death in later childhood and adolescence. *Arch Dis Child* 1982; 57(8):572-576.
- (12) Daugbjerg P, Ranek L. Reye's syndrome in Denmark. A retrospective study. *Acta Paediatr Scand* 1986; 75(2):313-315.
- (13) Young TW. Reye's syndrome. A diagnosis occasionally first made at medicolegal autopsy. *Am J Forensic Med Pathol* 1992; 13(1):21-27.
- (14) Bonnell HJ, Beckwith JB. Fatty liver in sudden childhood death. Implications for Reye's syndrome? *Am J Dis Child* 1986; 140(1):30-33.
- (15) Coe JI. Postmortem chemistry update. Emphasis on forensic application. *Am J Forensic Med Pathol* 1993; 14(2):91-117.
- (16) Coe JI. Postmortem chemistry of blood, cerebrospinal fluid, and vitreous humor. *Leg Med Annu* 1977; 1976:55-92.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

### **Professor Berry**

In what proportion of autopsy cases of sudden unexplained death in infancy has an IMD been discovered? - I would say it's about one percent. As for childhood - I can't answer that question; in some studies a small proportion of unexplained sudden unexpected childhood deaths have been ascribed to metabolic causes, although the precise metabolic disorder has never been identified.



Which IMDs have been found in these sudden deaths? - pathologists know about MCAD and there are couple of cases of OTC in the literature but I think it's chemical pathology and IMD specialists who can answer that better than I can.

In what proportion of autopsies of patients who have died from an unexplained encephalopathy has an IMD been discovered? - there is no literature that I am aware of that answers that question from a pathologist's point of view. I think the reason is that patients don't usually die suddenly from an encephalopathy but survive long enough to have investigations.

In what proportion of these autopsies do we suspect an IMD, fully investigate, but find nothing? In infants when we find hepatic panlobular microvesicular fatty change, often with fatty change in the proximal tubules of the kidney and we think it ought to be metabolic, there are perhaps a third in whom we don't get an answer. However both our and others' experience is small and anecdotal.

Straying on to the next question, which is Professor Portmann's, as to whether there have ever been any well documented cases of "classic" RS presenting as sudden unexpected death in childhood, I found one report describing four or six such cases from a medical examiner in the United States, claiming to have identified RS as the cause. However, as I read it, it became less like RS as there was no encephalopathy and they died suddenly. I suspect these people were just finding fatty change in children who died of other causes. This paper is cited in my handout.

## **DISCUSSION**

**Dr Green.** So the answer is probably none then.

**Professor Berry.** Agreed and it brings us back to the question how do you define classic Reye's syndrome at post mortem when you've got no preceding history.

**Professor Portmann.** What proportion of your SIDS cases have microvesicular fat in the liver?

**Professor Berry.** The CESDI study found five in 196.

**Dr Malone.** I would be very loathe to diagnose Reye's syndrome at all in these cases; it would be better to call them unexplained probable inherited metabolic disease.

**Professor Berry.** We need to discuss the terminology that pathologists should be using, because it's clearly a potential cause of great distress to parents.

**Dr Green.** Our experience is from a limited study we've been doing, which is a comprehensive look for inborn errors (IMD) in sudden unexpected infant deaths (SUDI) in the city of Birmingham, over the last two years. So far we've investigated about 78 cases and we've had four metabolic disorders, which suggests IMD may contribute four or five percent of SUDI cases. There was one case of LCHAD, one carnitine transporter defect, one citrullinaemia and one outstanding fibroblast study to do, a propionic or methylmalonic acidaemia. These were all babies found dead at home, or dead on arrival in A & E, and all were within two years of age.

**Professor Berry.** In the late eighties to early nineties with John Holton in Bristol we looked at ninety sudden unexpected deaths - population-based consecutive cases. The technology might have been different then, but we looked as hard as we could, including fibroblast culture, and found one case of glycogen storage disorder and nothing else. Even the glycogen storage disorder I am quite certain was artefactual. There was a paper in the Lancet about glycogen storage being responsible for twenty five percent of SIDS but it was all an artefact due to abnormal enzymes in preterm babies.

**Dr Dalton.** The Americans have gone in for this in a big way because of the new technology - and certainly in many of the big centres it seems to be routine for *any* childhood death, that a sample is obtained for plasma acyl carnitine and amino acid analysis. It is being pushed because there are a significant number of cases being found.

**Professor Berry.** Yes but there is a risk if you look too hard you will find abnormalities whose clinical significance is uncertain. This comes up with population studies of

mutations - you will find cases with mutations of various sorts which may actually not be related to sudden unexpected death. But I agree that every child that dies suddenly and unexpectedly without an obvious cause should have a metabolic workup. And perhaps those that have an apparent obvious cause of death should *also* have one, because why does that child with bronchiolitis actually curl up its toes and die at home, possibly there was a predisposing condition.

**Dr Green.** So are you suggesting that all unexplained infant deaths should have a metabolic workup?

**Professor Berry.** I think ideally yes they should and from what you are telling us and from what I have been learning, it's not actually an expensive undertaking to undertake screening for the commoner disorders that present in this way. At least the appropriate samples should be taken.

**Dr Hall.** Would you set an age limit on that strategy, because we have sudden unexpected deaths, labelled as RS, reported to the RS surveillance scheme in children aged five and upwards.

**Professor Berry.** No age limit because unexpected unexplained deaths in older children are so uncommon. There are four, maybe five, hundred cases in England a year among infants and perhaps only fifty, if that, in older children.

**Dr Green.** So that's an important proposal - all unexpected unexplained deaths, whatever age, should have samples taken which would provide the potential for a metabolic work up.

Moving on to the question about deaths from encephalopathy, Professor Berry said that from the pathologist's perspective there's very little to say. Is there anything from the paediatrician's perspective?

**Dr Chakrapani.** I could find nothing in the literature.

**Professor Berry.** I think there is a point we can take away. Pathologists sometimes have the experience of receiving cases from the ITU that are diagnosed in life as having encephalitis. But at post mortem there is no evidence of the encephalitis at all. So perhaps such cases should also have appropriate samples taken.

**Dr Boon.** What about the investigation of children who have died of prolonged seizures? I've had a couple of such children under my care and the post mortem was unrewarding. Do they yield many IMDs? It's a small number but it is certainly a well recognised cause of death in childhood.

**Professor Berry.** Yes, we could make a shopping list of types of cases that should be investigated. Another would be unexplained cardiomyopathy. We sometimes autopsy children with big hearts diagnosed in life as having myocarditis, but again there is no post mortem evidence of this.

**Dr. Walter.** We've seen children with carnitine transporter defects die suddenly from cardiomyopathy, the metabolic defect not having been diagnosed beforehand.

**Dr Dalton.** We recently had a case of another enzyme deficiency in which the patient died of cardiomyopathy and we first made the diagnosis from the post mortem samples.

**Professor Berry.** Pathologists don't actually want to know what the chemical defects that you are looking for are, we just want to take the right samples in the right way for given antemortem clinical scenarios.

**Dr Green.** So one could envisage a protocol for post mortem investigation of, say, sudden unexplained deaths, cardiomyopathy, maybe unexplained seizures and maybe unexplained encephalitis. So we need to determine what are the investigations or samples that need to be taken in those situations.

**Dr Dalton.** Another point: in my experience it's very unusual for an autopsy to help with the diagnosis if the patient has already been investigated *before* death for metabolic disease.

**Professor Berry.** The point has been raised as to whether pathologists should be available at all hours to conduct post mortems so that samples can be taken as soon after death as possible. Apart from being unrealistic, if for example you get the samples out at 2am there's no one to take them from you! Taking a perimortem liver and skin biopsy and saving some CSF and blood and urine is a good alternative.

**Dr Green.** At Birmingham we have a system whereby if a child is either brought in dead to A & E, or dies unexpectedly in A & E, the medical A & E staff take the appropriate specimens, which include blood, urine (bladder stab) and skin. The box of sample tubes sits in A & E and so when that situation presents, everything is ready to take all these samples and then they are able to be processed and stored frozen by the 'out-of-hours' clinical service.

**Dr Malone.** We have the same system at Great Ormond Street for children who come in to PICU and collapse and die.

**Dr Green.** So we are we saying that system is something that should be provided at DGH level? Is that realistic?

**Dr Masters.** The problem is it's to do with a rare event and people forget there's a protocol there.

**Dr Chakrapani.** From my experience, I think to get a perimortem skin biopsy done in the middle of the night in DGHs is not possible and liver biopsy is probably even more difficult.

**Dr Green.** You could get away with getting the blood and the urine at the time and then taking the skin biopsy the following day, because you have several hours to get a skin biopsy that's going to be growable. So that is a practical point that would be useful - it doesn't have to be a middle of the night job.

**Dr Walter.** Not only is it difficult to get done but often we find skin biopsies taken after death have been contaminated and don't grow.

**Dr Malone.** We don't find that.

**Professor Berry.** Neither do we. We take post mortem biopsies with no sterile precautions at all, and drop them in a bottle and they virtually all grow, and this is days after death.

**Dr Green.** We say up to forty eight hours, but ideally within twenty four hours.

**Professor Berry.** I would say longer, particularly if it's the last examination of the child its worth trying for up to three or four days although after this the yield falls. It also depends where you take the biopsy from. Anywhere near the abdomen is bad news post mortem - much better from a chest incision.

**Dr Chakrapani.** Are there any tissues useful for obtaining fibroblasts other than the skin?

**Professor Berry.** Yes people have favourites - some prefer fascia lata, some use tunica vaginalis, some use Achilles tendon, others use pericardium.

**Dr Green.** Any further points on question 5.3 which is what proportion of autopsies of cases of either SUD or encephalopathy, is a Reye like IMD suspected and fully investigated, but not found?

**Professor Berry.** I put forward the figure of 30 -33% as a challenge. We are increasingly seeing *first week* deaths at home that are almost certainly metabolic, with grossly fatty livers and a proportion of those are unexplained in spite of full investigation.

**Dr Walter.** There have been a few cases of MCADD presenting in the first week. It seems that breast feeding is a risk factor - if the milk is not established quickly enough then it's a fasting stress which does make sense.

**Professor Berry.** Yes, we've had at least one if not two MCADDs presenting as sudden deaths in the first week

**Dr Green.** This was also reported by the Australian group, Bridget Wilkin and colleagues in Sydney; they reported quite a few neonatal MCADD diagnoses, where breast feeding hadn't been established properly, or sufficiently.

\*\*\*\*\*

#### **Questions 5.4, 5.5 and 5.6**

**5.4 Have there ever been any well documented cases of "Classic RS" presenting as sudden unexpected death in childhood?**

**5.5 What are the pathognomic features of:**

**a) The Reye-like IMDs? Do they differ from one another?**

**b) "Classic" RS**

**c) How useful and feasible is electron microscopy of post mortem liver or other tissue in differentiating RS from an IMD?**

**5.6 In what proportion of autopsies of cases of (i) sudden unexplained death, (ii) death from unexplained encephalopathy in children, are any of the features described in 5.5 seen (regardless of final diagnosis)? If these features are present are there any clues which would suggest an IMD/RS rather than some other cause of the changes?**

#### **PROFESSOR PORTMANN**

**Dr Green.** These questions were covered in Professor Portmann's paper presented in the earlier session and have also partly been covered by Professor Berry.

[SEE part 3, but also reproduced below for convenience]

### **PROFESSOR PORTMANN**

My remarks deal more specifically with liver biopsy, but many aspects can be extended to autopsy liver tissue which will be discussed by Dr M Malone (**see Proceedings, Part 5**).

The liver morphology of RS includes <sup>1,2</sup>

- Hepatocytes swelling due to multiple small cytoplasmic vacuoles (neutral lipid content demonstrable in *frozen sections* stained with oil red-O or Sudan black B) and centrally located, enlarged hepatocyte nuclei
- Generally slight or absent necrosis and inflammation
- Severely reduced or absent *succinic dehydrogenase* (or cytochrome c oxidase) activity (demonstrable by enzymatic staining of *frozen tissue* embedded in rat kidney, which acts as control).
- And at the *ultrastructural (EM)* level,<sup>6,7</sup> markedly enlarged and misshapen mitochondria (amoeboid mitochondria) with matrix lucency, loss of dense bodies, detachment and fragmentation of cristae
  - numerous small lipid droplets and depletion of glycogen are confirmed.

The light microscopy features are considered pathognomonic, **the EM mitochondrial changes virtually diagnostic of RS, which in my view cannot be diagnosed without liver morphology**. *The answer to question 3.5a is 'yes', a liver biopsy (or autopsy liver tissue) is indispensable to achieve a diagnosis.*

The 'vanishing' of RS during the late 1980s, has been followed by a sharp drop in liver biopsy specimens being submitted to our laboratory as potential RS. As a consequence fat staining on frozen sections and succinic dehydrogenase histochemistry have been largely abandoned. Microvesicular steatosis, spotted on H&E stained sections as a microvesiculation or foamy clarification of hepatocyte cytoplasm without nuclear displacement, remains a feature now mostly associated with inherited metabolic or



acquired defects of mitochondrial function, in particular that of fatty acid beta-oxidation.<sup>5</sup> In these conditions, which have been the object of isolated case reports or small series of patients, light microscopy and EM liver findings are inconsistently reported, although microvesicular steatosis remains the most consistent feature recorded, alone or in combination with other features which clearly depart from the morphology of classical RS. To complicate the issue, microvesicular steatosis has been found incidentally at autopsy without any specific connotation.<sup>6</sup> However, irrespective of the lack of specificity of the changes, liver tissue is often essential for enzymatic assay or other techniques which are often indispensable to make a specific diagnosis in IMDs.<sup>7</sup>

*Potential Reye's syndrome and Reye-like IMDs cannot be dissociated with regard to the need for a liver biopsy to be taken, and this is indeed a clinical decision, which must be guided according to circumstances. Liver biopsy being an invasive procedure, with a risk of morbidity, and, however low, of mortality, the risk has to be weighed against the potential diagnostic yield.*

Below is a brief review of morphological data in selected IMDs that may present with RS-like features.

### ***Congenital hyperammonaemia syndromes***

These rare and heterogeneous disorders result from defective enzymes of the *urea cycles*, in particular the cytosolic *arginosuccininate synthetase (AS)*, *arginosuccinate lyase (AL)* and *arginase* or the mitochondrial *ornithine transcarbamylase (OTC)* and *carbamoyl phosphate synthetase (CPS)*.<sup>7</sup>

***Argininosuccinic aciduria*** seems the one defect in which significant liver disease is present with severe fibrosis,<sup>8,9</sup> and marked macrovesicular steatosis in some case.<sup>9</sup> Ultrastructural changes include dilatation of the rough or smooth endoplasmic reticulum,<sup>8-10</sup> and the presence of megamitochondria in zones affected by steatosis.<sup>9</sup> The enzyme protein may be absent in the liver;<sup>11</sup>

*OTC* deficiency: liver histology generally normal in males. Occasional case reports suggest some mitochondrial and peroxisomal changes.<sup>12</sup> Acquired abnormalities are documented in females at a more advanced age: changes are mild and include steatosis, inflammation, periportal necrosis and fibrosis. Organelles in the hepatocytes are usually normal.<sup>13</sup>

One series including 6 OTC, and 3 CPS deficiencies has revealed, in addition to diffuse microvesicular steatosis with variable portal fibrosis, foci of nonvacuolated clear hepatocytes in both OCT and CPS cases,<sup>14</sup> and these were confirmed on EM to have little/no neutral fat and excessive free glycogen.<sup>14</sup>

In these disorders, both light microscopy and ultrastructural changes are non-specific, and may at times mimic RS. Liver tissue is required for enzyme assay.<sup>7</sup>

### **Mitochondrial cytopathies**

Functional disorders of mitochondria comprise a broad range of diseases affecting multiple organ systems,<sup>15-17</sup> and result in a combination of many diverse symptoms, hepatic failure, or cholestasis with preserved liver function, cardiomyopathy, myoclonic seizures, hypotonia, proximal tubular disorder, endocrinopathies, or pancytopenia. Disease severity, time of presentation and progression are highly variable, and the neuromuscular system may be affected without known hepatic involvement.<sup>18</sup> The mitochondriopathies can be classified by the genetic defect (i.e. autosomal or mitochondrial) or by the defective enzymatic system (oxidative phosphorylation or fatty acid oxidation). A severe neonatal presentation and a delayed onset (2-18 months) are distinguished,<sup>19, 20</sup> the latter including *Alpers progressive infantile poliodystrophy*.<sup>21</sup>

Confirming the diagnosis of a mitochondriopathy can be difficult. Histopathologic study of liver and muscle, with electron microscopy, may reveal characteristic abnormalities.<sup>15</sup> Some respiratory chain subunits can be detected by immunohistochemistry (cryostat sections). Molecular biologic techniques permit quantitation of mitochondrial DNA as well as detection of some deletions and/or mutations in either nuclear or mitochondrial DNA. Some centres have developed polarographic (requires rather large amount of tissue) or enzymatic methods of measuring respiratory chain activity (requires snap frozen tissue stored at  $-70^{\circ}\text{C}$ ). These diagnostic modalities have been reviewed.<sup>22-24</sup>

*Fatty acid oxidation disorders (medium chain (MCAD) and long chain (LCAD) acyl-CoA dehydrogenase).* Microvesicular steatosis has been the main liver abnormality in a

series of 9 patients.<sup>25</sup> Later, fatty infiltration becomes macrovesicular and cirrhosis may develop. Severe ballooning degeneration of liver cells, mild cholestasis and marked bridging fibrosis have been reported in one case,<sup>26</sup> which ultrastructurally revealed large, membrane-bound vesicles containing a loose, flocculent material and irregular internal membrane profiles.

Histology and ultrastructure are informative, not specific; metabolic analysis of postmortem liver tissue has allowed a diagnosis, which can be achieved during life by urine and blood analyses.<sup>15</sup>

*Mitochondrial oxidative phosphorylation disorders.* Histopathologic changes have been described by numerous investigators.<sup>20, 27-33</sup> All have been characterized by microvesicular steatosis, variable cholestasis, ductular proliferation, and sometimes progressive fibrosis and cirrhosis. Light microscopic and ultrastructural descriptions were reported in 2 series totalling 15 cases.<sup>29,32</sup> An oncocytic appearance of liver cells due to mitochondrial crowding is occasionally observed.<sup>33</sup> Ultrastructurally, changes include pleomorphic mitochondria with few or no cristae and a granular fluffy matrix.<sup>34, 35</sup> Similar changes have been described in Alpers syndrome, now known to be a mitochondrial disorder involving complex I of the respiratory chain.<sup>28</sup> Liver and/or muscle biopsy is essential for diagnosis.

### ***Drug related RS-like changes***

In both children and adults, a number of drugs have been occasionally associated with clinical features and liver changes resembling RS, an inhibition of mitochondrial beta-oxidation being the likely mechanism of hepatotoxicity. In most instances, detailed metabolic work up is not available, and the extent to which the drug has unmasked an underlying IMD, or produced a 'genuine' RS is uncertain.

*Valproic acid (VA).* In cases of acute liver failure ascribed to VA toxicity, the liver has showed RS-like features, necrosis or both.<sup>34</sup> At times, another member of the family had died following seizures suggesting that the patient may have been unduly susceptible to the drug due to an underlying IMD. Ornithine carbamyl transferase deficiency has been demonstrated in at least one patient,<sup>35</sup> and others have been suffering of Alpers' syndrome, now recognised as a mitochondrial cytopathy.<sup>36</sup>

*Nucleoside analogs.* Rare cases of hepatic toxicity are reported, related to a drug-induced inhibition of mitochondrial DNA polymerase.<sup>37,38</sup> Microvesicular steatosis, giant mitochondria and intrahepatic cholestasis is reported;<sup>38,39</sup> enlarged mitochondria with low matriceal density and occasional vacuoles is found by electron microscopy.<sup>38</sup>

*Ecstasy.* At least, one anecdotal patient has developed liver failure following exposure to ecstasy, with clinical features mimicking RS and liver histology indistinguishable from that of RS.<sup>40</sup>

### **Conclusion/Answer to specific questions:**

- **Liver biopsy** should be part of investigation of suspect cases of *classic Reye's syndrome* and of *suspected inherited metabolic disease (IMDs)* with evidence of liver involvement (site of enzymatic defect and/or target of the injury). Exception would be those cases in which a diagnosis is achievable e.g. by urine and/ or blood analyses, or on tissue accessible by a less invasive technique than a percutaneous liver biopsy (eg skin fibroblasts, skeletal muscle).
- If feasible (no contraindications), the biopsy should be performed as soon as possible as changes may be transient, particularly in 'mild' forms.
- In all instances, a substantial portion of the biopsy specimen should be **held fresh or snap frozen** (-70<sup>0</sup> C) depending on the requirements of the centre which will carry on the special investigations, some listed above (to be discussed prior to biopsy). A limited number of laboratories are providing specific diagnostic service for IMDs; the list and their areas of interest are generally known to paediatricians. A comprehensive list could be made more widely available.

**Histopathologic changes** are rarely specific, but light microscopy may allow to place the lesion in a restricted category (normal liver, micro- macrovesicular steatosis, parenchymal necrosis and loss, fibrosis, cirrhosis) and provide information on severity and stage of the changes (prognosis value).

**Electron microscopy** provides additional evidence supporting a mitochondrial disorder, but specificity is similarly lacking and ultrastructure study should not represent the prime indication for performing a biopsy. If a liver biopsy is indicated, it is highly recommended to save 1-2 mm of the specimen in EM fixative. This can be

plastic embedded and held for any length of time, prior to thin sectioning and EM examination, locally or at a specialist centre. The technique of epon embedding is of relatively low cost and not really time consuming; full EM examination requires extra funding. The value of EM on post mortem material limited. Performing a needle liver puncture as soon as possible after death can provide better preserved tissue for light microscopy, EM and indeed enzyme assays or other specialised techniques.

## REFERENCES

1. Bove KE, McAdams AJ, Partin JC, Partin JS, Hug G, Schubert WK. The hepatic lesion in Reye's syndrome. *Gastroenterology* 1975; 69:605-697
2. Kimura S, Kobayashi T, Tanaka Y, Sasaki Y. Liver histopathology in clinical Reye syndrome. *Brain Dev* 1991;13:95-100
3. Phillips MJ, Poucell S, Patterson J, Valencia P. The liver. An atlas and text of ultrastructural pathology. New York: Raven Press, 1987
4. Partin JC, Schubert WK, Partin JS. Mitochondrial ultrastructure in Reye's syndrome (encephalopathy and fatty degeneration of the viscera). *N Engl J Med* 1971; 285: 1339-1343
5. Fromenty B, Berson A, Pessayre D. Microvesicular steatosis and steatohepatitis: role of mitochondrial dysfunction and lipid peroxidation. *J Hepatol* 1997;26 (Suppl 1):13-22
6. Fraser JL, Antonioli DA, Chopra S, Wang HH. Prevalence and nonspecificity of microvesicular fatty change in the liver. *Mod Pathol* 1995;1:65-70
7. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. *Adv Pediatr* 1996; 43:127-170
8. Zimmermann A, Bachmann C, Baumgartner R. Severe liver fibrosis in argininosuccinic aciduria. *Arch Pathol Lab Med* 1986; 110:136-140
9. Jorda A, Portoles M, Rubio V. Liver fibrosis in arginase deficiency. *Arch Pathol Lab Med* 1987; 111: 691-692
10. Travers H, Reed JS, Kennedy JA. Ultrastructural study of the liver in argininosuccinase deficiency. *Pediatr Pathol* 1986; 5: 307-318

11. Kobayashi K, Itakura Y, Saheki T et al. Absence of argininosuccinate lyase protein in the liver of two patients with argininosuccinic aciduria. *Clin Chim Acta* 1986; 159:59-67
12. Tallen H, Schaffner F, Taffet S, Schneidman K, Gaul G. Ornithine carbamyl-1 transferase deficiency in an adult male patient: significance of hepatic ultrastructure in clinical diagnosis. *Pediatr Res* 1983; 71: 224-232
13. Aida S, Ogata T, Kamoto, Nakamura N. Primary ornithine transcarbamylase deficiency. A case report and electron microscopic study. *Acta Pathol Jpn* 1985; 39: 451-456
14. Badizadegan K, Perez-Atayde AR. Focal glycogenosis on the liver in disorders of ureagenesis: its occurrence and diagnostic significance. *Hepatology* 1997; 26:365-373
15. Treem WR, Sokol RJ. Disorders of the mitochondria. *Semin Liver Dis* 1998; 18:237-253
16. Sokol RJ, Treem WR. Mitochondria and childhood liver diseases. *J Pediatr Gastroenterol Nutr* 1999; 28:4-16
17. Morris AAM. Mitochondrial respiratory chain disorders and the liver. *Liver* 1999; 19:337-368
18. Munnich A, Rotig A, Chretien D et al. Clinical presentation of mitochondrial disorders in childhood. *J Inher Metab Dis* 1996; 19:521-527
19. Cormier-Daire V, Chretien D, Rustin P et al. Neonatal and delayed-onset liver involvement in disorders of oxidative phosphorylation. *J Pediatr* 1997; 130:817-822
20. Cormier V, Rustin P, Bonnefont JP et al. Hepatic failure in disorders of oxidative phosphorylation with neonatal onset. *J Pediatr* 1991; 119:951-954
21. Saudubray J, Martin D, Poggi-Travert F et al. Clinical presentations of inherited mitochondrial fatty acid oxidation disorders: An update. *Int Pediatr* 1997; 12:34-40
22. Narkewicz MR, Sokol RJ, Beckwith B, Sondheimer J, Silverman A. Liver involvement in Alpers disease. *J Pediatr* 1991; 119:260-267
23. Munnich A, Rotig A, Chretien D, Saudubray JM, Cormier V, Rustin P. Clinical presentations and laboratory investigations in respiratory chain deficiency. *Eur J Pediatr* 1996; 155:262-274

24. Rustin P, Chretien D, Bourgeron T et al. Biochemical and molecular investigations in respiratory chain deficiencies. *Clin Chim Acta* 1994; 228:35-51
25. Boles RG, Martin SK, Blitzer MG, Rinaldo P. Biochemical diagnosis of fatty oxidation disorders by metabolite analysis of postmortem liver. *Hum Pathol* 1994; 25: 733-741
26. Amirkhan RH, Timmons CF, Brown KO, Weinberger MJ, Bennett MJ. Clinical, biochemical, and morphologic investigations of a case of long-chain 3-hydroxyacyl-Co A dehydrogenase deficiency. *Arch Pathol Lab Med* 1997; 121:730-734
27. Boustany RN, Aprille JR, Halperin J, Levy H, DeLong GR. Mitochondrial cytochrome deficiency presenting as a myopathy with hypotonic, external ophthalmoplegia, and lactic acidosis in an infant and as fatal hepatopathy in second cousin. *Ann Neurol* 1983; 14: 462-470
28. Fayon M, Lamireau T, Bioulac-Sage P, et al. Fatal neonatal liver failure and mitochondrial cytopathy: an observation with antenatal ascites. *Gastroenterology* 1992; 103: 1332-1335
29. Bioulac-Sage P, Parrot-Rouland F, Mazat J P et al. Fatal neonatal liver failure and mitochondrial cytopathy (oxidative phosphorylation deficiency): a light and electron microscopic study of the liver. *Hepatology* 1993; 18:839-846
30. Goncalves I, Hermans D, Chretien D et al. Mitochondrial respiratory chain defect: a new etiology for neonatal cholestasis and early liver insufficiency. *J Hepatol* 1995; 23:290-294
31. Mazzella M, Cerone R, Bonacci W et al. Severe complex I deficiency in a case of neonatal-onset lactic acidosis and fatal liver failure. *Acta Paediatr* 1997; 86:326-329
32. Morris AAM, Taanmen J-W, Blake J et al. Liver failure associated with mitochondrial DNA depletion. *J Hepatol* 1998; 28:556-563
33. Ducluzeau P-H, Lachaux A, Bouvier R, Streichenberger N, Stepien G, Mousson B. Depletion of mitochondrial DNA associated with infantile cholestasis and progressive liver fibrosis. *J Hepatol* 1999; 30:149-155
34. Zimmerman HJ, Ishak KG. Valproate-induced hepatic injury. Analysis of 23 fatal cases. *Hepatology* 1982;2:591-597
35. Tripp JH, Hargreaves T, Anthony PP et al. Sodium valproate and ornithine

- carbamyl transferase deficiency. Lancet 1981;1:1165-1166
36. Krähenbühl S, Brander S, Klienle S et al. Mitochondrial diseases represent a risk factor for valproate-induced liver failure. Liver 2000;346-348
37. Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med 1995;1:417-422
38. Spengler U, Lichterfeld M, Rockstroh K. Antiretroviral drug toxicity – a challenge for the hepatologist? J Hepatol 2002;36:283-294
39. Clark SJ, Creighton S, Portmann B, et al. Acute liver failure associated with antiretroviral treatment for HIV: a report of six cases. J Hepatol 2002;36:295-301
40. Ellis A, Wendon J A, Portmann B, Williams R. Acute liver damage and ecstasy ingestion. Gut 1996;38:454-458

**PROFESSOR PORTMANN : ADDITIONAL POINTS IN ORAL AND SLIDE PRESENTATION**

I don't believe you can definitively diagnose classical Reye's syndrome without liver morphology. In the few metabolic disorders like OTC which I have examined under the electron microscope there was some mild modification of the mitochondria, but nothing like those huge mitochondria that are sometimes described as amoeboid with lucency of the matrix and loss of dense bodies and disruption of the cristae that are said to be specific to classical RS. I don't know whether, in the IMDs, there is the same depletion of succinic dehydrogenase as you see in classic RS.

Pure aspirin toxicity doesn't look like Reye's syndrome. You see *macrovesicular* fatty tissue and you don't see the mitochondrial changes.

**DISCUSSION**

**Dr Hall.** How available around the country is electron microscopy, and how much is it used?

**Professor Portmann.** Electron microscopy is very demanding and there is not much interest in its use as a diagnostic tool. It can be valuable when you have a specific



question for example if you want to see the mitochondria. We do provide this service at Kings College Hospital where there is an interest in looking at ultrastructural changes in inborn errors of metabolism. But I don't think anybody provides a *routine* service for electron microscopy.

**Dr Malone.** I am certainly looking at mitochondrial morphology, but it is a waste of time, unless the post mortem is undertaken within half an hour of death. Ultrastructure is always the first thing to deteriorate.

**Professor Portmann.** Yes you do need fresh tissue properly processed. In classic Reye's the ultrastructural changes were always said to be transient.

**Dr Malone.** Yes that was our experience. If the patient recovered the mitochondria went back to normal afterwards.

**Dr Dalton.** If there *is* such an entity as classical Reye's syndrome it must have a mitochondrion-based pathology and yet what we are saying here is that there is no real mechanism available to look at mitochondria properly.

**Dr Malone.** But the reason *why* there's nothing set up is because you don't get your post mortems within half an hour of death.

**Professor Berry.** That's an important point to make in order to avoid unrealistic aspirations.

On another issue regarding diagnosing Reye's at post mortem, the absence of glycogen is common also to MCADD – strikingly so in their livers, but for succinic dehydrogenase the literature implies that its absence is specific to classic Reye's. Is that other people's experience?

**Professor Portmann.** I agree it's in the literature, but we don't do it.

**Dr Dalton.** In terms of future research you can argue that, given that the literature is suggesting that loss of succinic dehydrogenase is specific to classic RS, there should be

some proper study done on the specimens we see now. Here is the potential means of definitely diagnosing or excluding classic RS.

**Dr Green.** How in practice could that work?

**Dr Malone.** We have it set up at Great Ormond Street. We do it on muscle but not routinely on liver unless it is a query mitochondrial disorder when we do it on a live liver biopsy. It is never done on our frozen livers, but we could do it.

**Professor Berry.** And around the country there will be quite a lot of frozen livers but it's completely unethical to contemplate as a research project now because we can't use any of our post mortem tissue. Any ethics committee would say you've got to go back to the families for permission.

**Dr Green.** But you *could* do it prospectively?

**Dr Hall.** Are there the same problems with histochemistry as with electron microscopy in terms of needing to receive specimens quickly after death?

**Dr Malone.** No, the enzyme is preserved for quite a while.

**Dr Green.** So that's a useful practical point that perhaps could be taken forward within paediatric histopathology circles.

**Dr Malone.** Most specialist paediatric pathology and neuropathology departments would be doing histochemistry.

**Dr Green.** What about the terminology of Reye's in the context of recording the cause of death?

**Professor Berry.** From the point of view of families it seems to me we shouldn't be using the term Reye's syndrome post mortem when there is no classic antemortem history; we should be calling it a presumed, but unidentified, inborn error of metabolism.

**Dr Malone.** We tend to put it forward as a presumed metabolic disorder, and then list all the negative investigations.

**Professor Berry.** Reye's syndrome is a diagnosis of exclusion and you can't always do all the exclusions post mortem. What we are trying to do is to stop pathologists who, on just seeing a fatty liver, not having done any tests, call it Reye's syndrome.

**Dr Boon.** From the clinician's point of view, if you see Reye's syndrome on the PM report and you are counselling the parents, there is a risk that you are going to say – well don't worry this is a one off. It will probably never happen again and if you are thinking about having any other children or already have other children, they're not at risk. Whereas if the cause of death is recorded as an IMD, we will start thinking more, it will trigger a different response in us. So I think from that point of view it's very important. We would prefer an honest "I don't know" to a "definite" label that closes off thought.

**Dr Hall.** As part of the national Reye surveillance scheme I receive copies of all death entries where there is mention of Reye's syndrome or Reye-like illness as a cause of death. In a few cases these will be children who in life apparently clinically had classic Reye's, but the majority of them in the last decade or so are cases of sudden unexpected death with exactly the scenario described by **Professor Berry**. The post mortems are usually done by coroners' pathologists and it is often difficult to discern from the post mortem report what the features are that led to a diagnosis of Reye's syndrome. For example it is often not clear that there was cerebral oedema as only the brain weight is recorded and in the liver the phrase "fatty change" is often used, without describing whether it is the typical panlobular microvesicular fat of Reye's (and indeed of some of the IMDs). Typically there are no investigations for IMDs in these cases and I understand that in some areas this is due to cost constraints as the cost has to come out of the coroner's budget.

**Professor Berry.** I suspect general pathologists might not appreciate just how rare Reye's syndrome has become. They are still applying a diagnosis to their findings which would

have been appropriate in the late 1970s / early 1980s. There is a case for some re-education.

**Dr Green.** So are we suggesting that the term Reye's syndrome shouldn't be used at all as an autopsy diagnosis?

**Professor Berry.** Presumably it *should* be used in cases who in life had all the classic epidemiological, clinical and pathological features, assuming no other cause emerges at autopsy.

But it *is* an important point about leaving minds open to other possibilities. We're doing the same with Sudden Infant Death – using that term less and putting “unascertained”. We need a phrase that flags cases up in the Reye's surveillance death entry searches and also leaves paediatricians still thinking of inborn errors. So maybe one should put “probable IMD/ Reye-like illness”.

**Dr Boon.** But what would the coroners feel about “woolly” diagnoses? I know that they don't really like “unascertained death in infancy” from speaking to our local coroner who is a little unhappy about the way that pathologists are recording this diagnosis or leaving the diagnosis open. Has anybody had any feedback from coroners about what they feel about not giving a firm diagnosis?

**Professor Portmann.** I feel they don't like it.

**Professor Berry.** Coroners' pathologists in the past existed to keep the coroner happy! What one is trying to do *now* is much more parent and patient orientated and trying to do what is best for them and their other children.

**Dr Hall.** From an epidemiologist's and a public health point of view I wouldn't want the term Reye's syndrome to be lost completely. We need to know if, especially in the event of another influenza pandemic, it is on the increase again. As we no longer have a clinical reporting scheme for Reye's syndrome we are dependent on ascertaining cases via death entries as a warning of any resurgence which might indicate measures to remind the public about the risk of giving children aspirin for flu symptoms.

**Dr Malone.** Must there be a history of aspirin exposure before you can call it classic RS?

**Dr Hall.** No, that is not part of the case definition.

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### **5.7 Best Practice.**

**a) What should be the standard autopsy investigations for IMDs/"classic" RS and what would be the findings which triggered undertaking these?**

**b) Should tissues from these patients be routinely preserved? If so which ones and how preserved and what are the relevant recommendations regarding parental consent?**

**c) What investigations can usually be done locally?**

**d) What are the specialist investigations and where are they undertaken?**

### **Dr MARIAN MALONE**

#### *Best practice*

a) RS/IMDs present to the pathologist at autopsy as sudden unexpected death in infancy  
Thus, the investigation is part of a wider investigation which should include the following procedures:

#### At the time of post mortem:

Full skeletal survey, X-rays to be reported by a radiologist with expertise in non-accidental injury (NAI)

Snap freeze a small sample (about 1cc) of heart, kidney, liver and muscle in liquid nitrogen

Take samples of blood and bile on Guthrie cards

Take a sample of skin in tissue culture medium

Take specimens for virology and microbiology

Take standard samples of all organs for histology

Retain the brain for neuropathological examination?

### After the post mortem

Document virology and microbiology results

Perform an oil red O stain on frozen sections of heart, kidney, liver, and muscle and examine for microvesicular fat

Blood and bile to Chemical Pathology for mass spectrometry for acylcarnitine and fatty acid oxidation

Skin to Enzymology for cultured fibroblasts and storage in liquid nitrogen

Report on paraffin sections of samples for histology

Neuropathological examination of the brain after a week and samples taken for microscopy. (The brain can then be returned to the body in time for the funeral).

b) Since most of these post mortems are performed under the Coroner's system, parental consent is not usually an issue. The issue is persuading the Coroner that such investigations are indicated and need funding. Ideally, such post mortems should only be carried out by specialist paediatric pathologists attached to specialist units where these investigations are available. In practice, many are carried out by general pathologists or forensic pathologists. The Coroner's remit is to establish that a death is from natural causes, and for these purposes an assignation of "inherited metabolic disease" will suffice. Full investigation of these cases is expensive and the local authorities who employ the Coroners do not see it as a priority. In addition, with the recent difficulties surrounding organs and tissues, many Coroners will not allow the pathologist to retain any specimen that is not directly related to establishing the cause of death. Some Coroners take the view that detailed investigation and diagnosis of a specific inherited metabolic disease is outside their remit, and they will not grant such permission.

c) Depending on the pathologist, their expertise, commitment and their place of work, different levels of investigation can be undertaken. Many paediatric pathologists or general pathologists with a special interest in paediatrics send bile for mass spectrometry. Most DGH pathologists can arrange for tissue to be frozen and stained for fat. If no microvesicular fat is detected it is not worth proceeding with further investigations. Forensic pathologists generally do not carry out any special investigations.

d) If the frozen tissue is transported on Cardice by courier to a specialist paediatric laboratory enzymology studies can be performed on the liver and DNA can be extracted. It is not reasonable to expect a local non-expert pathologist to do more than this.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

### **Dr Malone.**

The context in which the pathologist sees these children is that of a child in the first year of life who dies suddenly and unexpectedly. It's a bit like the child coming into casualty - we have a series of causes of death that we must consider in every case, of which inherited metabolic disease is actually quite far down the list.

The first, very important cause that you have to exclude is homicide - either the shaken baby or the child who has been asphyxiated. It's very important that we keep that in mind because we don't know how many of these children are the subject of homicide - 10 -30% according to which series you read. You get a history but you learn to be sceptical of some accounts, for example a story like "I was pushing my baby in the buggy and he just rolled up his eyes and died". It's about "smelling rats" - when you do enough of these cases you begin to get a feel for what's a genuine case and also for the case that's likely to be suspicious because the story doesn't make sense. The story of the child who dies in bed in the early hours of the morning while apparently asleep is much less suspicious. Then there's overheating and then there's asphyxiation. There are the children who are co-sleeping with large parents in bed who may have taken alcohol and also the child who is co-sleeping on a sofa with a parent, again often having taken alcohol, when the child's face gets pushed against the back of the sofa.

Then we have to rule out infection but if we find it we don't conclude that that is necessarily the only problem - in at least one of our cases there was evidence of infection and we subsequently also identified an IMD. Equally important we look for evidence of congenital abnormalities particularly undiagnosed congenital heart disease.

Finally we come to looking for evidence of an inherited metabolic disorder and there is also a group which is interested in the possibility of an inherent brain stem abnormality as a cause of some of these deaths.

Because homicide is top of our list of possible causes of death the very first investigation that we do is a skeletal survey and our policy is not to proceed with the post mortem until the radiologist has seen the films. Then we take specimens for microbiology - CSF, blood, spleen (the same organism recovered from both blood and spleen is considered significant) and lung (for virology). Blood and bile are collected on Guthrie cards for mass spectrometry and blood for toxicology is spun and frozen. Samples of liver, heart, kidney and muscle are snap frozen in one block for possible later cutting and staining with Oil-Red-O. Skin for culture of fibroblasts is taken into culture medium and stored until an alternative cause of death is found.

Ideally, the brain should be retained in all cases, but this has become a problem since the recent concerns with organ retention following Alder Hey. At Great Ormond Street we undertake about 150 of these post mortems annually, from eight coroners.

We ask them to inform the family that we are keeping the brain for one week (in order to formalin fix it), that then thin sections will be taken and the brain will then be reunited with the body. Recently some of the coroners have been resistant to this and we have had to cut the brain fresh which is not ideal. We are currently considering whether, because it is so important to look at the brain properly, we should refuse to undertake the post mortem in these circumstances. This is up for discussion.

Investigation for IMDs in a coroner's post mortem is also problematic because coroners do not see it as their remit to order detailed investigations. For many, "presumed IMD" as a cause of death is sufficient. They are not interested in going further and this attitude gains support from the problems with retained organs.

New legislation is being drafted and is currently (March 2002) out for consultation. (*See also Dr Malone's oral presentation in Proceedings Part 6, Ed.*). It proposes that once the coroner has finished with the case, the parents' wishes concerning the fate of any stored samples should be sought and if this includes destroying them this should be respected. We feel that this is unacceptable because if there was a homicide, the perpetrators are



being given the opportunity to destroy the evidence! It also has implications for investigation of IMDs. We have had a case where there were three SIDS in a family and the parents were under police investigation. We undertook just the third post mortem and found an IMD which had not been found at the previous two infants' autopsies.

## **DISCUSSION**

**Dr Walter.** Presumably you could still retain specimens under this proposed legislation if the parents consent?

**Dr Malone.** Yes but the way parents are thinking at the moment a lot of them won't.

**Professor Berry.** Also, it is a logistic nightmare getting back from a pathology department to parents. Dr Malone's cases come from all over London and we take ours from as far as 300 miles away.

**Dr Green.** I notice you don't include urine in your list of specimens to be taken or investigated?

**Dr Malone.** That is because in most of these babies you can't get a urine.

**Dr Dalton.** That means you wouldn't easily be able to diagnose the ornithine transcarbamylase deficiency (OTC) cases. Although we probably can if the orotic acid is definitely elevated in plasma, but it's not easy to get via the probe technology that we currently have.

**Dr Green.** In what percentage of your autopsies *can* you get urine? I think in our study we are getting urine from 50-70% of cases.

**Professor Berry.** Is that because they take it in casualty?

**Dr Green.** Yes.

**Professor Berry.** Well that's ideal, but I have been told that if you can obtain a useful sample if you just get two drops out of the renal pelvis with a syringe. But how much does it matter if the urine is contaminated with cells?

**Dr Green.** If it's just cells you can spin them out. It's more worrying if there's haemolysis. We've tried both spinning and syringing the nappy but it's not something people find easy to do. I do feel, though, that we should at least be *aspiring* to get a urine sample from these cases because there's the organic acids to look at, as well as orotic acid. They might be helpful in diagnosing some disorders. So we should suggest that urine for orotic and organic acids is added to the list of post mortem samples when possible.

(General murmurs of agreement.)

**Dr Dalton.** Another point to make is that blood TMS (Tandem mass Spectrometry) after death is often very difficult to interpret.

**Dr Malone.** That's why we take bile as well.

**Dr Green.** One observation that we have made is that dried blood spots aren't as good as plasma, for some disorders -particularly for the long chain defects. The extent of the abnormality can sometimes be very tricky to assess in dried blood spots compared to plasma.

**Dr Malone.** Have you tried using bile?

**Dr Green.** We haven't.

**Dr Dalton.** Can you get the same sort of results from bile?

**Dr Malone.** Yes, and it's easy to obtain at post mortem.

**Dr Green.** I think there would need to be an educational exercise for laboratories because I don't think anybody else is looking at bile. Is this something pathologists would be comfortable about collecting?

**Professor Berry.** Yes, we save it for toxicology too; it is quite good for some of those assays.

Also - pathologists need to know where to send it. Dr Malone can just send it upstairs at Great Ormond Street, but most forensic pathologists, who do take some of these things, put them in the fridge but then they sit there because they don't know what to do next. We haven't yet got to the stage as to how we educate pathologists but simply providing a list of where the labs are that will deal with these samples would be helpful.

Another point on who pays for any metabolic investigations - there is actually an official letter (it's not an executive letter) from the Department of Health saying that if, at a coroner's post mortem, investigations are done for *medical* purposes - as opposed to the *coroner's* purpose - then the costs of those investigations falls on the Health Authority from which the child came.

**Dr Boon.** How does one draw the line between so called medical and coroners' reasons? Surely the whole point of a post mortem is to try and ascertain the cause of death, and therefore that would include everything wouldn't it?

**Professor Berry.** The coroner is supposed to establish the medical cause of death, but they differ very widely in what they consider to *be* a medical cause of death, there is no guidance on it that I am aware of. Some virtually just want you to say it was natural, whereas some say they expect you to follow it right down to the genetic level.

**Dr Hall.** Do we know around the country what is the average interval for coroners' cases between the death and the autopsy and what effect does the interval have on the validity of the findings?

**Dr Malone.** Sometimes ours are two to three days but this doesn't seem to affect validity.

**Professor Berry.** I agree. The interval is in the CESDI Report but I can't recall the details. There was one case where the post mortem was done I think twelve or thirteen days after the child died. They didn't do any metabolic investigations but they still obtained a pure culture of staphylococci from the lungs.

**Dr Green.** But I think there might be a problem with the interpretation of some of the metabolic tests. We've only got data from this small study of ours. The free carnitine levels go up dramatically with autolysis so you could miss a depletion. And the long chain acyl carnitines in particular go up, so in our experience we could have great difficulty diagnosing them - but we've need more hard evidence as there has been no large systematic study published. I am also concerned about the other urea cycle disorders - how would we identify those from the samples and investigations we've discussed so far?

**Dr Dalton.** You should be able to do that from the amino acids.

**Dr Green.** Yes but the amino acids are more difficult to interpret the longer the specimen has deteriorated because of autolysis.

**Professor Berry.** As pathologists we can say what samples we can provide, but it's down to your group to say what you can and should be doing with them.

**Dr Green.** We suggest that ideally we want specimens taken within four hours of death and that is done in our A & E. That may be difficult in some places but we believe it is best practice and something to aspire to round the country.

**Dr Dalton.** When this technology became available in the USA some people set up a private forensic metabolic disease investigation service. Don Chase has a lot of experience of what is actually happening as time passes after death, and will be publishing his data soon.

**Professor Berry.** It is a worry that occasional children will throw up abnormal amino acid patterns because of post mortem change, since that's moderately common and inborn errors are extremely rare. So you may make more errors than accurate diagnoses.

**Dr Green.** In our study we had a total of approximately 10 or 12 cases which looked suspicious requiring further investigation - i.e. detailed studies on skin fibroblasts. But of those we only had the three definite IMD diagnoses and one possible, so we had three times as many false positives from the metabolites.

**Professor Portmann.** Another factor which varies and which will affect autolysis is the time between death and the body being refrigerated.

**Professor Berry.** Yes that is a particular problem with SIDS where they die in the night and are not found for some hours.

**Dr Malone.** What about going back to the neonatal blood spots if the post mortem investigations are suspicious of an IMD?

**Dr Green.** Yes that can be helpful. But I think there needs to be an understanding that the metabolites in the initial samples may show up potential abnormalities which may be false positive indicators of an IMD. Therefore having obtained and stored tissues is going to be very important to getting to an end point in terms of whether this is or isn't a "real" diagnosis.

**Dr Dalton.** It is important to make the point that metabolites provide a suspicion and an indicator which allows you to *target* the enzymology that you do, or the DNA.

**Dr Malone.** If you had frozen liver you could undertake enzymology.

**Dr Green.** Yes, except that enzymology might be very tricky if the material is taken more than a few hours after death because if it's many days old it's not going to be useful.

**Dr Dalton.** When you take liver heart and muscle samples for freezing you said you did a block for histology and histochemistry, but do you then keep any samples?

**Dr Malone.** We always freeze separate pieces of heart, liver, muscle and kidney. We use one for the frozen section, just for a quick screen, and then there are the other pieces which we can use for enzymology if that shows anything. You don't need to take a huge amount.

**Dr Dalton.** Can I just ask where vitreous humour fits into all this?

**Dr Malone.** We don't examine it routinely.

**Professor Berry.** The evidence from CESDI from 450 cases where it was taken to investigate sodium poisoning or dehydration, was that there wasn't a single case where it was constructive. It showed minor abnormalities in children who were clinically severely ill for other reasons. Also, if you have a suspected shaken baby and you insert a needle in the eye, although the procedure doesn't create retinal haemorrhage, a barrister will say it does.

**Dr Green.** So it's not something that we want to recommend or that you think people are doing in many centres?

**Professor Berry.** No and I think parents wouldn't like the thought of us sticking needles in their babies' eyes even though we actually would re-inflate them afterwards. I think it's become less useful than it was, but it may perhaps provide a useful sample for toxicology.

**Dr Hall.** Could I ask the pathologists about diagnosis and recognition of cerebral oedema at autopsy? When the Reye surveillance scheme ascertains cases through a death entry and the autopsy report is obtained, we often find that the diagnosis has been based solely on the post mortem findings of cerebral oedema and a fatty liver. (These are usually sudden unexpected deaths and not all are infants). Sometimes the only evidence given in the report to support the finding of cerebral oedema is the brain weight which is frustrating as the normal range is not provided.

**Professor Berry.** I wouldn't diagnose cerebral oedema unless it was absolutely gross. It's very common in babies that have been resuscitated because the venous pressure in resuscitation is about the same as the arterial and you take the brain out and it shows uncinar grooving and tonsillar prominence. You put it aside to complete your post mortem but then find the changes have gone because the brain is so soft. You *can* diagnose cerebral oedema at post mortem - you get a characteristic opacity of the meninges and flattening of the gyri and tonsillar herniation but unless these features are gross one would be loathe to attribute any diagnostic significance to it. Brain weights are difficult - there are tables and we would routinely put the normal weight, but the brain is *often* very heavy, particularly in SIDS and there is literature to support this.

**Dr Green.** Returning to the last part of this Workshop Question (5.7 c) and d)), what is the balance, do you feel, between investigations that can or should be done at local level versus those that require specialist units?

**Professor Berry.** I think what pathologists would like to do is just send the samples off to the department of paediatric biochemistry and wait for the answer to come - the idea of sending half of them to once place or following some algorithm is too difficult for them, they haven't got time. They need a one-stop shop!

**Dr Boon.** Do we know what percentage of post mortems of sudden infant deaths are done by DGH (District General Hospital) general pathologists as compared to paediatric pathologists?

**Professor Berry.** It's changing - the proportion done by paediatric pathologists increased over the three years of the CESDI study. It was about 40% paediatric pathologists, 30% generalists, 30% forensic pathologists over the five health care regions in the study.

**Dr Green.** Just to be clear, are you recommending that *all* of these investigations should be done on *all* infants who have died suddenly and unexpectedly even though there may be no particular circumstances such as consanguinity or a similar sibling death to point to a possible inherited metabolic disease?

**Professor Berry.** Up to now it's not been the practice to do this in every case but maybe it's something that should be recommended particularly as the laboratory technology has evolved. For the record - the current recommendation of the Royal College of Pathologists is that post mortems on children who die suddenly and unexpectedly should *only* be carried out by paediatric pathologists or by somebody with special interest and experience in diseases in young children.

**Dr Boon.** What happens in practice in investigating these cases at the average DGH?

**Dr Masters.** Certainly the investigations that you are talking about wouldn't be available at a DGH chemistry department so they would need to be sent away to a reference laboratory.

**Dr Green.** So it would be important for the local DGH to have a sampling protocol so that when the situation arises they know exactly what to do and where to send it.

**Professor Berry.** When we did the study sampling for antimony and the heavy metals we gave each participating place a box containing precise instructions which worked well. I should like to emphasize that there are some adult and some forensic pathologists who do excellent post mortems in this field, although it has to be said there are others who just believe their job is simply to establish whether or not the death was natural.

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**5.7 e) *Is it important, and if so why, for clinicians to obtain antemortem pathological specimens from moribund patients with suspected RS or IMD?***

**ii) *What specimens should be taken and how should they be preserved?***

**DR GRAHAM SHORTLAND (in absentia)**

i) It is important in making the diagnosis of possible IMD and future investigation of the patient, to obtain appropriate specimens antemortem. Investigations for laboratory (and



storage details) will previously have been discussed (Workshop Question 3.1, see PROCEEDINGS, PART 3).

Obtaining pathological tissue is important and skin fibroblast culture could routinely be collected in most situations (see below). The performance of acute liver biopsy and storage is going to be problematic in most clinical areas. More important is close liaison with pathology services if the child does not survive for an appropriate post mortem examination.

ii) Suggested samples that are practical in settings where the moribund child is likely to present, e.g. accident and emergency departments, admissions departments and paediatric wards, are as follows

*(Based on personal practice and this answer assumes that the clinician is excluding other causes such as sepsis and relates only to RS and IMDs)*

### **Laboratory Tests**

#### **Blood**

*Standard Laboratory Investigation – DGH:-*

Acid base analysis

Anion gap calculation

U&E, Creatinine

Blood glucose

Liver function (AST, Bilirubin, Albumin, ALP,GGT)

Bone profile (Calcium, Phosphate)

Ammonia

Lactate

Clotting screen

*Specialist Laboratory:-*

Toxicology-drug levels

Amino acids

Carnitine – total, free and acylcarnitine

Blood spot on Guthrie card – acylcarnitine analysis

EDTA sample for DNA extraction and analysis

## **Urine**

*Note in moribund child it is important to catheterise or perform supra-pubic aspiration, if less than 6 months old, to obtain appropriate urine sample at the time of presentation.*

*DGH:-*

Dipstix analysis – for glucose, ketones

Urine toxicology, drugs

*Specialist Laboratory:-*

Organic acids

Amino acids

Urine carnitine analysis

## **Other Specimens.**

1) EDTA blood sample for DNA extraction and analysis.

2) Skin fibroblast culture.

Consideration should be given to use of local anaesthetic if child aware of procedures.

Obtain small skin ellipse (0.5cm x 0.5cm is adequate) from buttock or under arm, **under sterile conditions, area must be cleaned thoroughly prior to sample being taken.**

If specific fibroblast culture medium not available may be placed in sterile container with 0.9% normal saline and placed in fridge (4°C) before transfer to local genetics laboratory for culture. Fibroblast culture may be collected after death up to 48 hours later at post mortem.

## **Further Questions for Discussion**

Consent issues for samples not routinely taken (e.g. skin biopsy). This will involve parents and also in the taking of samples immediately after death the role of the Coroner needs to be considered.

## **DISCUSSION**

**Professor Berry.** I support all of these recommendations, but I should point out that it is actually an offence to take a sample from a case that is known to be within the

jurisdiction of Her Majesty's Coroner without his express consent, so one does need to be careful.

**Dr Green.** But we are talking about the situation where a child has been investigated in casualty or intensive care and has then died. These are the very valuable specimens that will *complement* what will be taken at post mortem.

**Professor Berry.** Yes but it's a fine divide if the child is moribund - the antemortem period runs on into the post mortem period.

**Dr Green.** I suggest that urine carnitine *shouldn't* be included, because I wouldn't know how to interpret it. As part of the death process I think you might find there is high carnitine in the urine anyway. Do we agree that is taken off?

*[General murmurs of agreement].*

**Dr Walter.** Orotic acid needs to be added to the list of tests on urine. We should also add antemortem liver biopsy and muscle biopsy.

*[General murmurs of agreement].*

**Dr Boon.** Microbiological investigations are not included and I think if we are going to have a *full* list it should include for example blood and urine for culture, as well as samples for virology.

**Dr Masters.** What about adding surface swabs for microbiology?

**Dr Boon.** They are of dubious value, we certainly don't take them.

**Dr Masters.** Can they not be useful in neonates with suspected Group B streptococcal infection?

**Dr Boon.** I think that the correlation between the superficial swabs and the findings in blood and tissue is not good so we have abandoned them – most neonatal units have.

**Dr Masters.** Whose responsibility should it be to follow up the results of all these tests and collect them altogether finally? This is a problem we have had.

**Dr Walter.** It should be the paediatrician if the patient was admitted while still alive.

**Dr Masters.** But what if the patient had got no further than A&E?

**Professor Berry.** There is a suggestion, coming from multiple directions now, that *all* unexpected childhood deaths should be subject to a formal multidisciplinary case review and that would be one place where all of this could be summated. I think it would be something that would be supported by the Reye's Syndrome Foundation - that proper reviews of such deaths should take place.

**Dr Walter.** It's not only to do with reviewing laboratory results; it's also about proper counselling for the parents.

**Dr Boon.** I agree. I fully support what Professor Berry said, but we include *all* childhood deaths in our clinical governance meetings - after all there not very many of them fortunately.

**Dr Green.** So we should recommend that as best practice.

*[General murmurs of agreement]*

**Dr Boon.** Following on from Professor Berry's earlier remarks about taking samples from Coroners' cases, the last sentence of the document probably needs strengthening.

**Professor Berry.** Yes, furthermore one could imagine the situation where rather robust sampling is done antemortem and then a forensic pathologist comes along and takes exception to finding blood in body cavities that shouldn't be there.

**Dr Chakrapani.** Does this relate to patients who are in hospital who die after treatment or does it only relate to unexpected deaths at home?

**Professor Berry.** It relates to any patient who you or who the person taking the samples knows is going to be, or should be, reported to the coroner. Because the body then becomes the property of, or the responsibility of, the coroner until his investigations are completed.

**Dr Green.** Returning to the problem of coordination - the best antemortem specimens may be taken at the DGH, the child may then have been transferred say to a PICU at another hospital or dies on arrival there, so there needs to be some good way of co-ordinating with the local DGH to get those critical first antemortem samples for specialist investigation. That in our experience is sometimes a problem, and I don't know how one can improve it. It's about having a DGH laboratory that is prepared to separate off the samples, possibly store them and send them to the reference laboratory.

**Dr Masters.** The time for which most DGH laboratories keep specimens is progressively getting shorter because of limited storage space and an increase in the number of requests.

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**Dr Green.** I should like to sum up this session now:

*First*, what proportion of unexpected and/or unexplained deaths in infancy are associated with IMDs – it's probably somewhere between about 1 – 5% depending on the populations examined.

*Second*, we agree and recommend that there should be appropriate samples taken in *all* of these cases to allow a metabolic work up, and there should be *no age limit* on that.

*Third*, regarding a “best practice” protocol - we have agreed a suggested list of investigations that should be undertaken in a systematic way and that include routine tissue sampling and also routine skin biopsy for fibroblast culture. We appreciate that

there are problems with the Coroner system and that there may currently be circumstances where a post mortem won't include these investigations, but hope that the relevant Enquiries will lead to an improvement.

*Fourth*, although there are no good data on investigation of deaths following an episode of unexplained encephalopathy, "encephalitis", seizures, or other possible manifestations of a Reye-like IMD, such as cardiomyopathy, it would nevertheless be useful to have protocols that highlight certain investigations which would be valuable to look for metabolic disease, particularly if it has not been considered antemortem and there has not been a full clinical investigation.

*Fifth*, regarding the terminology for Reye's syndrome as a diagnosis made for the first time at post mortem without any antemortem clinical or biochemical features of this condition - we concluded that the term *should no longer be used* but be replaced by a statement such as "presumed IMD". The term Reye's syndrome should, however, not be completely abandoned, but left in the context of a *clinical*, not an autopsy diagnosis, except where the post mortem findings confirmed the clinical diagnosis.

*Sixth*, regarding antemortem sampling of moribund patients, again, we have agreed on a list of important investigations. A key point is to ensure that there is proper follow up on these cases - perhaps as part of best practice discussion in the clinical governance arena to ensure that all childhood deaths are fully debated and all the investigations pulled together.

*Finally* we recognise that there are associated issues arising from all of these recommendations, not least of which will be funding, as well as educational issues for paediatric pathologists, for district general hospitals, for chemical pathology locally as well as specialist services.

**Professor Berry.** If all these perimortem samples have been taken, does the pathologist still need to take post mortem samples?

**Dr Green.** If you've got a good antemortem specimen then it's far better than a post mortem specimen.

**Professor Berry.** As we are obsessional we probably still would take the samples!

The pathologist does have to be responsible for the diagnosis they've made, sometimes in a court of law or Coroner's court, but if you haven't taken the samples yourself that's much harder.

**Dr Hall.** Can I ask Professor Berry if we are just reinventing a wheel that's already been invented by the CESDI recommendations?

**Professor Berry.** No I don't think so, because there wasn't routine biochemical screening although there were routine frozen sections. One CESDI finding was the strong background of drug abuse amongst parents who suffer sudden unexpected infant deaths, so maybe toxicology is something we should be thinking about more strongly. It also concluded that diagnoses were being missed because appropriate tests were not being done. So here we are just carrying on from their recommendations.

**Professor Portmann.** Do you hold your report to the coroner until you get the tissue samples test results?

**Dr Malone.** We explain to them that the cause of death is unascertained pending investigations which probably won't be back for a week or a fortnight, but it's natural and they can release the body.

**END OF SESSION**

## WORKSHOP PROCEEDINGS: PART 6

### OBSTACLES TO ACHIEVING “BEST” PRACTICE: WHY HAVE WE GOT A PROBLEM?

MODERATOR PROFESSOR DAVID HALL

#### *Question 6.1 Professional training/educational skills*

- a) *What are the professional groups towards whom action directed at removing barriers to changing practice should be aimed?*

**Dr ANDREW BOON**

1. *Paediatric Trainees/Junior Consultant Paediatricians*

Many of these doctors may never have seen a child with Reye’s syndrome.

Suggested target group - RCPCH (the College’s General Paediatric Specialty Advisory Committee).

? Inclusion in the syllabus for core training in paediatrics.

2. *Adult Physicians and A&E consultants*

These doctors are unlikely to have received training about Reye’s syndrome and may be unaware of its occurrence in teenagers and adults.

Suggested target - the RCP

3. *Pathologists*

Reye’s syndrome and inherited metabolic disorders are under-diagnosed or misdiagnosed at autopsy.

Suggest target group - The Royal College of Pathologists

4. *General Practitioners*

Although there is now widespread knowledge about the potential hazards of aspirin under the age of 12 many doctors working in primary care may be unaware of the potential hazards of aspirin in older children. *[Update(Ed.): nb. this may no longer hold true given the change in the upper age limit on the warning to 16 years in October 2003].*



Suggested target - The RCGP

#### 5. Pharmacists

This group of professionals may also be unaware of the potential hazards of aspirin over the age of 12.*[Update(Ed.): nb. this may no longer hold true given the change in the upper age limit on the warning to 16 years in October 2003].*

Suggested target - The Royal Pharmaceutical Society of Great Britain

#### 6. Coroners

References:

1. McGovern MC, Glasgow JFT and Stewart MC - Reye's syndrome and aspirin: lest we forget, BMJ 2001 322 1591 - 1592
2. Belay ED, Bresee JS, Holman RC et al - Reye's syndrome in the United States from 1981 through 1997, NEJM 1999 340 1377 - 82.

### **ADDITIONAL POINTS HIGHLIGHTED IN ORAL PRESENTATION**

**Dr Boon**

I have had a few more thoughts since I wrote this - coming out of the discussions we have been having over the last two days.

I still feel that the main target group is paediatricians. We are going to be the people largely to whom these children present, yet quite clearly, whether or not there is such an entity as classic Reye's syndrome, most junior doctors will never have seen a child with encephalopathy caused by an IMD. Even some young consultant paediatricians may not have come across this during their training. So I think it is important that there is some training on this included in the core training in paediatrics and I thought that the target group would be the general paediatric advisory committee of the Royal College of Paediatrics and Child Health.

As we have also heard, many of these patients may present to adult physicians or to the A & E departments, so in my paper I include both adult physicians **and** A & E consultants. Many of these doctors will not have received any training about Reye's syndrome or IMDs. They might have done a bit of reading for the Membership, but certainly they may be unaware that this can be a problem in teenagers and young adults. So the Royal College of Physicians is another target group.

Pathologists, and here we should also include chemical pathologists, are another important

group to be targeting. We heard this morning about the problems of making the diagnosis at autopsy and also the difficulty in getting the appropriate samples, particularly in a DGH. So the Royal College of Pathologists might be the correct group here.

GPs are also an important group to whom these children may present, although hopefully most GPs will recognise that the child is sick and will refer them in. I think it would be no bad thing just to remind GPs about the hazards of aspirin particularly in slightly older children and the RCGP would be the correct target group.

Similarly with pharmacists, perhaps the message needs to be promulgated that aspirin may be a problem in older children as well and the Royal Pharmaceutical Society of Great Britain would be the appropriate target group.

The final one, which came out as a result of discussion over the last couple of days, is coroners. In some way we need to target them and increase their awareness of IMDs and try to make them aware that a coroner's post mortem should be doing more than simply saying whether the death occurred due to natural causes or not.

#### ***6.1b Why are patients with IMDs underdiagnosed or diagnosed late or misdiagnosed as RS?***

***DR MIKE CHAMPION***

There are many inter-related reasons why IMDs are missed.

These include:-

IMDs mimic other commoner conditions. Presentation is often non-specific.

Lack of awareness of IMDs (many doctors no exposure)

May recover on standard treatment if mild episode in spite of wrong diagnosis (IV dextrose whilst off feeds).

Differing availability of investigations in hospitals

Inappropriate / delayed sampling (i.e. not acute samples)

Delay in results from specialist centres

## **What are the obstacles to best practice?**

Lack of awareness of IMDs

Only a few centres where exposure to these patients can occur on a regular basis.

Considered so rare that unlikely to be seen anyway.

Degree of knowledge promoted for Membership exam minimal. Revision books often accept “inborn error of metabolism” as the answer. Like listening to the heart and saying it is “cardiological”.

Poor understanding of outcomes, therefore less important if late diagnosis or missed.

Fear of the conditions. Avoidance of getting involved with IMD patients by health professionals.

Appropriate investigations unavailable

One centre in South Thames does not have facilities to measure ammonia, and many juniors report grave difficulties out of hours in other centres requesting ammonias.

Hassle compared to normal blood test if has to be run to lab or sent on ice. Deterrent to requesting in the first place.

Often a very long delay in receiving back results from the local specialist laboratory because workloads ever increasing.

Variable practice in analyses undertaken and expertise in interpretation.

Lack of specialist laboratories

Lack of career structure and failure to recognise paediatrics as a specialty of chemical pathology, has severely restricted the number of biochemists entering the field.

Clinical governance and risk management may promote status quo rather than pushing for new developments that will directly benefit patients.

Failure to embrace preventive medicine

Screening for MCADD “delayed” once more. Health Technology Assessment recommendation for trial of MCADD screening published 5 years ago and still no closer to proceeding. *[Update(Ed.): trial/rolling out of service began March 2004. 6 centres covering half the population to be screened, remainder unscreened; comparison of outcomes in the 2 groups.]*

Lack of evidence base to practice

Rarity a problem

Limited resources, not a high priority compared to many other health issues.

Limited number of specialists available [*Updated by Dr Champion, January 2004*]: 14 Paediatric clinical centres in UK and Eire sharing 17 consultants. All single-handed except Great Ormond Street Hospital (3+1), Manchester (3) and Dublin (2). Currently 4 posts advertised chasing 1 trainee, 2 of these services currently single-handed but needing to expand due to patient numbers/clinical demand.

Only 2 recognised training posts nationally, currently reclaimed by regional post-graduate deans

Insufficient manpower to generate the information that is required for fellow professionals and parents.

Lack of metabolic and Paediatric Intensive Care Unit beds.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

### **Dr Champion**

Considering missed diagnoses I think the major problem is lack of experience. These are very rare problems which can mimic other, commoner conditions - we’ve been talking about the “needle in the haystack” and there are lots of “needles” competing for a diagnosis in any particular patient. For example sepsis could be a very reasonable alternative diagnosis to

consider - we've seen a number of IMD patients who have presented before with previous episodes, but following empiric treatment with drips, stopping feeds, and antibiotics, they have recovered, so the diagnosis wasn't made on that occasion.

That also goes hand in hand with lack of specific training. If I look at the core curriculum at Guys Hospital, inborn errors are not considered important enough to be included, so as an undergraduate you will not get exposure. One of the biggest boosts to knowledge is the Membership exam. Metabolic questions written by metabolic specialists are now included, so there is a new desire to learn about these conditions!

Turning to the APLS, which we talked about in the session on management, the instructions for non-traumatic coma state that if there is hypoglycaemia and hepatomegaly "think Reye's". So the APLS doesn't mention inborn errors of metabolism in this context.

*So the two main obstacles to clinical diagnosis are the "needle in a haystack" phenomenon coupled with a lack of specific training.*

If you look at the obstacles to *obtaining* the necessary experience the problem is that it is only to be found by working in those tertiary centres that offer these services, which is not all of them. I had not been exposed to IMDs to any great degree until I went to Guy's, and then I suddenly met all these patients and realised how rewarding and challenging the specialty could be. I would also say having a clinical nurse specialist who facilitates the transfer of patients back to their local service, shared care, has been a major boon to our practice.

Regarding training problems, there are general perceptions that I come up against with the juniors rotating through the hospital, in that they perceive these conditions as an oddity collected by this hospital and not really going to bear a great relevance to their practice in subsequent years. This whole message of not particularly being important has carried on from undergraduate through to post graduate training, and I think that's where we can have an influence.

There is also a perception that outcomes are very poor and these children all die or are all damaged and there's not really anything we can do. But there is progress in enzyme replacement therapy for some conditions, such as Pompe's, which we used to consider incurable, and there are more and more technologies that we are going to be able to use.

The other problem is lack of teachers and in Dr Collins' paper she points out that there are currently only two IMD centres in Great Britain where there is more than one consultant. In

Dublin they are up to three now, and going for a fourth. There are plans for another two centres within the next eighteen months to increase to two consultants, but it makes it very difficult for training of juniors.

With regard to training the new teachers there are only two recognised “Calman posts” -one at Manchester and one at Great Ormond Street. We need to step back to set out a national plan as to what we need to sort out the country as a whole. At present it’s very much down to a local level and individuals.

The last point to make is that you can’t have a metabolic centre without laboratories -they go hand in hand. Yet there is no career structure, no training, paediatric chemical pathology is not even recognised as a specialty, let alone inborn errors. We are looking rather anxiously around the country at the number of specialists who are approaching retirement in the next five to ten years and with no successions!

***(c) Why might classic RS be under-diagnosed or diagnosed late? What are the obstacles to best practice?***

***PROFESSOR STUART TANNER***

- Failure to think of diagnosis
- Belief that RS is a disease of the past
- Initial illness was mild
- Parents were reprimanded for troubling GP with antecedent illness
- Failure of primary care services
- Telephone prescription of anti-emetics
- Ammonia measurements unavailable
- Wrongly thought to be meningitis, encephalitis
- Thought not to be a disease of teenagers/adults
- Early neurological features unrecognised
- Atypical cases
- Prompt early treatment aborts full-blown RS.

## ADDITIONAL POINTS HIGHLIGHTED IN ORAL PRESENTATION

### Professor Tanner

We referred several times yesterday to Dr Hall's nightmare scenario of another influenza epidemic bringing a crop of what used to be called Reye's syndrome. If that occurred who would it affect? Not children under twelve if the aspirin hypothesis is right (we believe it to be); probably not teenagers if the Medicines Control Agency does indeed issue new guidance that aspirin should not be given to teenagers. *[Update(Ed.): the upper age limit on the warning was increased to 16 years in October 2003].*

We now have sixteen years during which we have not given aspirin to under twelve year olds. If indeed, as we speculated yesterday, what we called Reye's was a genetic susceptibility to aspirin, then there's a vulnerable cohort and these are youngsters growing up who presumably will start taking low dose aspirin in adult life to prevent coronary vascular disease.

So I think the situation that we could be anticipating, is a group of middle aged men, presenting with what used to be called Reye's syndrome. And they won't be diagnosed promptly because nobody will be thinking of Reye's. They won't even have heard about it, because we're not talking now, we are probably talking ten years hence. But all of the reasons that used to contribute to late diagnosis of what we then called Reye's syndrome will operate again. The fact that the initial illness is mild; the significance of the vomiting is not recognised - the GP hears about the vomiting down the telephone and just gives an antiemetic by telephone prescription; ammonia is not measured etc, - all the factors that we talked about in the earlier session.

So that's what lies ahead, in about ten years!

## DISCUSSION ON QUESTIONS 6.1 a) – c)

**Professor Hall.** The crucial question is how to get out the key messages and of course that raises the question - what *are* the key messages? The big issue here in this discussion is about the messages to front line staff, the "golden hour" staff. The first most obvious thing to extract is that exams will drive learning more effectively than anything else - so including some metabolic questions in the exam and having some metabolic flow charts in APLS is the single most potent method of getting this into peoples' intellect. Whether it gets into their practice is another matter.

**Dr Champion.** The most successful intervention that I have managed to set up at Guy's, is

teaching on Membership courses. I've had a number of very good referrals made by new registrars who have had some teaching at Membership level and have spotted diagnoses. On one occasion I had a letter from a very good consultant who said "you know I didn't think this was MCADD, didn't even think of it, and the junior was right!". So the exams *can* make a difference particularly if the syllabus is explicit as to what we expect people to know.

**Dr Glasgow.** To what extent in medical schools around the country is APLS taken by senior medical students? Should we have a whole day on the recognition and management of a very ill child really focusing on the ABCD approach? What is likely to be wrong with the sick neonate, with the very sick infant? Is that something that should be in all undergraduate curricula? And to what extent should it be taken further up, maybe for the house officer years?

**Professor Hall.** Basic Life Support (BLS) training at Sheffield is about two sessions with couple of hours in each and I think to extend it beyond that would be enormously difficult for most places.

**Professor Tanner.** Certainly undergraduates don't have APLS at Sheffield.

**Dr Tasker.** We give ours an afternoon of paediatric basic life support with mannikins and other aids.

**Dr Glasgow.** This is what we do in Belfast.

**Professor Hall.** I doubt it would go beyond that and probably would not be profitable. It's probably the SHO level where you invest the energy.

**Professor Leonard.** I just want to point out that any improvement in the training prospects and the organisation of training of consultants in a very small specialty *must* be dealt with nationally. We *cannot* have this regional business, it's utterly chaotic. I think that one of our recommendations should be that we need to have a *unified* system. The current manpower arrangement is impossible.

**Professor Hall.** I agree. We are addressing this through all possible channels. This is politics again, but I believe that getting the commissioning of the specialties right, is absolutely fundamental. There are 15 medical and 9 surgical specialties in paediatrics, and about three or four others not recognised. To think that PCTs can handle all that is totally mistaken, but ministers only listen when a disaster happens - so we need a few disasters perhaps!



To sum up: –we have said that it's up to the IMD group to squeeze a few more questions into the Membership exam; we will talk to Dr Phillips about the APLS; they are probably the two main action messages. There's the slightly more difficult question of A & E medicine, where we have less influence, but if it's in the APLS programme anyone who is seriously doing paediatric A & E would be doing that as well, so at least they would have some exposure. As for adult medicine - there was once a symposium on inherited metabolic disease with the Royal College of Physicians which put it on the map a bit several years ago. Maybe it's time that that is repeated. Perhaps the IMD group might talk to the College of Physicians to suggest a joint symposium.

How many physicians are there in adult medicine who specialise in IMDs - is it one? two?

**Professor Leonard.** One, plus a few with an interest. [*nb as at March 2002*]

**Professor Hall.** Adult physicians have now taken on board the concept of grown-up congenital heart disease so why can't we develop the same thing with IMDs?

**Professor Leonard.** There is now this RCP initiative for a joint training in chemical pathology and metabolic medicine which will have a paediatric component, but it's not yet clear whether we are to train them.

**Dr Green.** We've already been approached in Birmingham to contribute to the syllabus but we can't because we've only got one metabolic consultant. There needs to be some joined up thinking about the training for adult metabolic medicine, and the fact that you *need* the paediatric end of it.

**Professor Hall.** This is not within the remit of the meeting but I think **we will make a note** that some further pursuit of this with the College of Physicians would be helpful.

**Dr Baumer.** The other thought I had, concerned continuing professional development for people who need reminding from time to time about these things. I've certainly got in my personal development plan the need to do some sort of metabolic course to bring me up to date. Also, we haven't really done very much in paediatrics of the self directed learning process of, say, reading something, answering a few questions and getting the CPD point.

**Professor Hall.** The RCPCH Clinical Effectiveness Unit might take a lead on this perhaps.

**Professor Leonard.** There is a one day course that is called "Metabolic disease for the

General Paediatrician”, run every other year and it’s proved extremely popular. It’s problem, not disease orientated - hypoglycaemia, encephalopathy and so on.

**Professor Hall.** That is a very good point and we need to think about how this sort of information is got out to people. This is something that the RCPCH academic vice president might be interested in pursuing.

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### **6.2.1 BIOCHEMICAL INVESTIGATIONS AT DGH LEVEL**

- a) Are the investigations for IMDs, in particular plasma ammonia, routinely available at DGHs?***
- b) What are the geographical variations?***
- c) Are local measurements of ammonia reliable? If no, what factors affect reliability?***
- d) How can we ensure reliable, 24 hour available, measurement of ammonia at district level everywhere? Is this unrealistic? If so – what alternative?***
- e) What are the obstacles to improving the service at local level? How can they be addressed?***

#### **DR PAUL MASTERS**

a) Laboratory practice in DGH biochemistry has moved towards the utilisation of main analysers on a 24 hour/7 days basis and away from separate equipment used out of hours. This means the same repertoire of tests is available at all times. Liver function tests, which previously may have needed to wait until office hours, are now analysed at the time of receipt.

Plasma ammonia measurement is now provided in most DGH laboratories. This differs from the situation in 1988 when few laboratories had a method available<sup>1</sup>. Commercial kits with applications on most clinical chemistry analysers are easily available and have replaced manual techniques.

b) Geographical variations are difficult to determine. However, I am auditing the provision of ammonia assays within the Trent Region and hope to have some data available at the time of the meeting (*see below under oral presentation*).

c) Reliable measurement of ammonia is less of an analytical issue than a pre-analytical one. Analysis is straightforward, but infrequent requests mean that the shelf life of kits may be exceeded unless

procedures are in place to monitor this. Numerous factors may spuriously raise plasma ammonia, including sample tube contamination, haemolysis, inadequate skin cleansing, delayed separation of plasma and erythrocytes.

d) Laboratories which do not, themselves, provide on-site ammonia assay on a 24 hour basis (the minority) must be able to send separated plasma urgently to a facility nearby. Transport time is crucial and should not exceed 30 minutes.

e) There are numerous obstacles to improving local services. Because of the pre-analytical factors in (c) and the relative infrequency of requests, the assay is seen as a difficult one. The laboratory may reject sub-optimal samples without analysis. Any individual biomedical scientists (BMS) may only deal with one request per year or less, and will be unfamiliar with the test. The reagents are unlikely to be onboard the analyser and need to be reconstituted and loaded. Detailed Standard Operating Procedures (SOPs) must be available for the BMS to follow. A national template may be helpful in detailing pre- and post-analytical factors, rather than the analysis itself.

Out of hours requests may be referred to a consultant or other medical or clinical scientist, either to authorise the test to be done or to interpret results. This may tend to deter clinicians from requesting ammonia.

Quality control is difficult due to the instability of ammonia. There is no external quality assessment (EQA) scheme, which reduces confidence in results.

More frequent ammonia assays would tend to improve the service overall, but this is dependent on clinicians requesting them. The pre-analytical factors above all raise ammonia, so that measurement of sub-optimal samples will lead to over-diagnosis of hyperammonaemia, not missed cases. High results can always be checked using an optimally-collected sample. The laboratory threshold should be lowered so that all requests are assayed and appropriate action taken if results are high, rather than initial rejection of apparently unsuitable samples.

## REFERENCE

1. Green A. When and how should we measure plasma ammonia? *Ann Clin Biochem* 1988;25:199-209.

## POINTS HIGHLIGHTED IN ORAL PRESENTATION

### Dr Masters

I am here as a jobbing chemical pathologist from a DGH lab to cover some of the things which we have talked about as being the key investigations of these children. The key ones in the early stages are plasma glucose, liver function tests and ammonia.

Certainly the glucose is a standard test and not subject to any particular problems. I think that's increasingly likely also to be the case for liver function tests. Where I work in Chesterfield and in other places where I've worked, the general trend is towards offering liver function tests on a relatively twenty four / seven basis, simply because of the way that laboratories are organised now. They tend to use the same analytical equipment throughout the twenty four hours rather than just on a nine to five basis. Regarding ammonia measurement, it is difficult to talk about the country as a whole, but within Trent Region I was quite encouraged from a survey I've done locally, to find ammonia is virtually universally available in district and teaching hospital laboratories, again on a twenty four hour basis.

I've had ten replies to a survey of fifteen labs and each of those has said that the ammonia assays are available on a twenty four hour basis. Two of them are using the ammonia checker which has already been mentioned at this meeting as potentially giving spurious results. But I know at least one laboratory is aware of the potential problems with that and is set up to dilute samples where they get high results.

The test is usually available without having to consult with somebody more senior and it's considered to be an urgent investigation, so when an ammonia sample arrives, laboratories will normally expect to turn it round quickly and telephone the result back and discuss its significance with the requesting clinician.

There seems to be good agreement between the laboratories on what they would consider a normal level of ammonia - the reference ranges that Dr Bonham mentioned earlier are pretty much standard. There aren't really aren't outliers amongst the labs on that. But where there *is* some vagueness is in the interpretation of *high* levels, in terms of trying to determine the seriousness of particular levels which are outside of the reference limits. There is certainly scope for education of general chemical pathologists and clinical biochemists on how to interpret high levels of ammonia and what sort of levels ought to be triggering advice to lead

on to the next part of the patient's care.

Another finding from this survey is that the numbers which labs are doing generally is quite small - of the order of between 15 and 60 ammonia samples per year in a district hospital covering a population of two to three hundred thousand. This is less, in some cases, than one ammonia request a week, and that obviously is potentially a problem because unless the test is being done frequently people may lose confidence in their ability to provide it to a high quality.

The reliability of results was touched on in the earlier session. We know that there are a number of factors which affect the results which you get, and we know that most of those are *pre-analytical* rather than analytical factors. Most of those will tend to raise ammonia levels - things like contaminated tubes, haemolysis, delays in the separation, inadequate cleansing of the skin before the sample is sent down, and laboratories are well aware of these pre-analytical factors. In fact it may be that they are so aware of them that they have a fairly low threshold of rejecting samples from analysis in the first place, and that is something that we ought to think about - is it better to analyse the suboptimal sample and follow up those with high levels, or is it better to try and hold out for the appropriate sample that may never come.

Regarding obstacles and overcoming them we discussed earlier whether there might be scope for a national standard operating procedure to deal with the pre-analytical and interpretative aspects of the ammonia requests. Also there are issues with quality control - because of the inherent instability of ammonia, both internal and external quality control is quite difficult and that tends to reduce the confidence that laboratories have in their results. It may mean that people are less willing to accept high results as a genuine problem.

### **6.2.2 SPECIALIST LABORATORIES**

- a) Where are the specialist laboratories? Are there enough? What do they offer? Are they all the same?*
- b) Do resource constraints at district level affect referral to specialist laboratories?*
- c) Do they have the resources for any expansion of investigation of cases of encephalopathy/SUD?*
- d) Are they able to provide 24 hour telephone advice and are the contact details available in all the districts they serve?*
- e) Do stored Guthrie cards have a role in the diagnosis of these patients? If so, is the system for storage, retrieval and analysis satisfactory everywhere?*
- f) What are the obstacles to improving the service of specialist laboratories? How can they be addressed?*

**DR ANNE GREEN**

#### **a) Specialist Laboratories in the UK**

##### **- Location and Service Provision**

There are 20 specialist laboratories listed in the British Inherited Metabolic Disease Group Directory. Most laboratories service a 'regional' population (2-5 million).

In order to try to answer the questions about service provision, a questionnaire was circulated in February 2002. 15 (75%) laboratories responded, and the data are presented below (Tables 1 and 2).

The tests required to provide first line diagnosis of the Reye-like Inherited Metabolic Disease are summarised in Table 3. It is assumed that ammonia and lactate will be provided at local DGH level.

All laboratories provided amino acid (blood and urine) analyses.

TABLE 1

	% total (15 respondents)	Workload range (tests/annum) per lab
Organic acids	14/15 (93%)	570-2099
Acyl carnitines	6/15 (40%)	200-1500
Orotic acid	9/15 (56%)	12-100
Mono/Disacchs	14/15 (93%)	10-900

### Conclusions

Wide variation in workload for some tests taking into account population size.

- Is there under/over requesting?
- What is the 'correct' level of requesting?

Need for audit and evidence based protocols?

### b) Funding/Resource constraints

Most laboratories are funded by contracts for 'regional work' with charging cost/test for ex Regional work. Only 1 laboratory stated that limited resources restricted referrals.

### c) Resources required for expansion/improvements

6 laboratories highlighted the need for services for acyl carnitine analysis. Other improvements required:-

- Improved turnaround times (1)
- Orotic acid service (1)
- Fibroblast culture service (1)

Other issues raised:-

- Impact of working time directive on the service
- Need for standardized protocols for investigation

**d) Provision of 24 hour telephone advice to District and Clinical Protocols.**

Only 3 laboratories (20%) had a protocol for the investigation of acute encephalopathy. 11 laboratories (73%) had a protocol for investigation of SUDI.

11 laboratories (73%) had a 24 hour advice service, although in many cases this was 'ad hoc' and dependent on very few (sometimes only 1 person!) individuals.

Issues raised:-

- 24 hour service was not paid for (no remuneration for staff)
- Dependent on very few specialists/and, in some cases, links with neighbouring services
- 

**e) Storage of Guthrie cards**

- Do they have a role?

*Acyl Carnitines*

There is good evidence that diagnosis of MCAD can be made retrospectively on stored dried blood spots; except in cases where the infant is severely ill and carnitine depleted (refs 1 and 2). Evidence for other disorders is less clear; short chain acyl carnitines are the least stable.

*Amino Acids*

- **Is the system of storage, retrieval and analysis satisfactory everywhere?**

The UK National Screening Laboratory Network (NSLN) undertook a survey of UK laboratories in 2000 (ref 3). This is summarised as follows:

- National practice is very variable

A small number of laboratories have kept cards since screening commenced.



Most laboratories have collections for 5-20 years with a median of 10 years.

A small number store for less than 2 years due to local circumstances.

- Recommendation is for storage for 20 years (Royal College of Pathologists).

Most laboratories want to do this, but there is a problem of identifiable sources.

- Storage conditions are variable and for many laboratories are unsatisfactory (issue of what temperature to store at)
- Only 2 laboratories had a written policy
- *Recommendations of the NSLN survey:*
  1. The NHS Executive (? through the National Screening Committee) should issue instructions on the retention and storage of neonatal screening cards. This should identify who is responsible for the provision of the facilities and funding.
  2. Guidelines should be issued on the use of neonatal blood spots in research. These guidelines should be compatible with other population or family based genetic studies.
  3. A national register of research programmes using neonatal blood spots should be set up with some form of assessing and approving research proposals to conserve a finite resource.

The report provoked a number of discussions and was also submitted to the House of Lords Scientific Committee looking into genetic databases, and was published in their 2001 report as an addendum.

#### **f) Service Limitation**

Limitations of laboratory services are currently as follows:-

TABLE 2

Equipment needs	7 (47%) especially Tandem Mass Spectrometry
MLSOs	7 (47%)
Clinical Scientists	10 (67%)
Funding for staff	10 (67%)
Non-pay	4 (27%)

*Particular issues of concern(see also oral presentation below):*

- Services are vulnerable and ‘near the edge’
- Insufficient skills and expertise
- Recruitment difficulties
- Concern about succession planning/staffing for the future
- Need for equipment replacement strategy
  - Specialisation versus general clinical chemistry
    - training needs
    - ‘conflict’ of priorities
    - how to attract specialist clinical scientists

### References Q 6.2.2

1. Pourfarzam M, Morris A, Appleton M, Craft A, Bartlett K. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. The Lancet, Research letters, September 2001; 358: 1063-1064.
2. Wilcken B, Carpenter K, Wiley V. Neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency. Letter in The Lancet, February 2002; 359: 627.
3. Addison MG, chairman of the UKNSLN. Report on storage and use of Guthrie cards.

Table 3 Q 6.2.2

Disorder	NH <sub>3</sub>	Lactate	Amino Acids	Organic Acids	Acyl Carnitines	Other
<b>Defects in the <math>\beta</math>-Oxidation Cycle</b>						
Medium-chain acyl-CoA dehydrogenase deficiency				✓	✓	
Very long chain acyl-CoA dehydrogenase deficiency				✓	✓	
Long chain 3-hydroxy acyl-CoA dehydrogenase deficiency				✓	✓	
<b>Defects in Electron Transfer Pathway</b>						
Multiple acyl-CoA dehydrogenase deficiency – severe and mild				✓	✓	
Riboflavin responsive multiple acyl-CoA dehydrogenase deficiency	✓			✓	✓	
<b>Defects in the Carnitine Cycle</b>						
Carnitine palmitoyl transferase deficiency types I & II				✓	✓	
Carnitine acyl-carnitine translocase deficiency	✓			✓	✓	
Carnitine transporter deficiency (primary carnitine deficiency)				✓	✓	
<b>Defects in Metabolism of Branched Chain Amino Acids</b>						
Maple syrup urine disease			✓	✓		
Multiple carboxylase deficiency Isovaleric acidemia	✓			✓	✓	
Propionic acidemias	✓			✓	✓	
Methylmalonic acidemia	✓			✓	✓	
3-Hydroxy-3-methylglutaryl-CoA lyase deficiency				✓	✓	
$\beta$ -Ketothiolase deficiency (mitochondrial 3-ketothiolase deficiency)				✓	✓	
3-methyl glutaconic aciduria				✓	✓	
<b>Defects in Metabolism of Carbohydrates</b>						Sugars DNA enzyme
Hereditary fructose intolerance						
<b>Disorder of Gluconeogenesis</b>						
Fructose – 1,6-bisphosphatase deficiency	✓			+/- lactate glycerol		enzyme
<b>Glycogen Storage Disease</b>						
GSD Type I	✓			+/- lactate		enzyme
<b>Disorders of Glycerol Metabolism</b>						
Glycerol kinase deficiency				✓		
<b>Disorders of Ammonia Detoxification – Urea Cycle Defects</b>						
Ornithine transcarbamylase (OTC) deficiency						
Carbamoylphosphate synthetase I (CPS) deficiency	✓		✓	✓		orotic
Argininosuccinic aciduria	✓		✓			orotic
Citrullinaemia	✓		✓			
HHH syndrome (hyperammonaemia, hyperornithinaemia, homocitrullinuria)	✓		✓			
<b>Disorders of Amino Acids Transport</b>						
Lysinuric protein intolerance (lysine, arginine and ornithine)	✓		✓	✓		orotic

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

**Dr Green**

This paper represents the analysis of the questionnaire that I circulated to specialist laboratories over the last few weeks, to try and answer the questions that were posed.

First, I looked at what tests would be required to diagnose the conditions of interest. The Table summarises the investigations such as ammonia, lactate, amino acids, organic acids, acyl carnitines, needed to make the first line diagnosis for this group of disorders. It was against that background that I sent out this questionnaire to the laboratories which are those listed in the British Inherited Metabolic Disease Group circulation which, although a little old, reflects the current position regarding specialised labs in the United Kingdom. There are 20 such laboratories across the UK, most of them serving a regional population somewhere between two and five million people. Fifteen of the 20 laboratories returned the questionnaire.

All 15 are providing a comprehensive blood and urine amino acid service; 14 are providing organic acids; only 40 percent are providing acyl carnitines, and only 56 percent are specifically looking for orotic acid. Most of them provide sugar chromatography.

There is also a huge variation in work load. The work load ranges listed in the paper are per laboratory, but I tried to relate that to the population size that they were actually serving. Even with that there are wide ranges in the order of five to ten fold. This poses the question - is there over- or under-requesting going on, in certain parts of the UK?

In terms of funding (question b), only one laboratory said that they thought that resources actually restricted referrals. All the other laboratories felt that there was no restriction on their service caused by this.

Regarding expansion and improvements needed (question c), six laboratories highlighted the need for services for acyl carnitines, which they currently did not have. In other cases an orotic acid service was needed in one, fibroblast culture in another, and improved turn around in another.

Another issue raised was the fact that the impact of the European Working Time Directive has impacted quite a lot on some laboratories and their ability to provide the required turnaround time.

Question d) was about twenty four hour advice and clinical protocols: only three of the

laboratories had a protocol for the investigation of acute encephalopathy, whereas 11 had a protocol for the investigation of sudden unexpected deaths. Eleven had a twenty four hour advice service although many of them commented that this was very “ad hoc” and it depended on one or two people, at best, being available if they could be contacted over weekends and in the evenings. The fact that it is not a paid service was reported by some people - they were doing it because of a feeling of responsibility. Also, in many places there were links with other specialist laboratories, maybe a hundred miles away, to help out because it was a “one man band” in terms of out of hours work.

The next question, e), is about Guthrie cards. First, do they have a role? I think the answer is, yes they do. There is now very good evidence that MCAD can be diagnosed retrospectively on stored dried blood specimens, except where the child has been severely ill and there has been carnitine depletion - that might be a difficult situation. Evidence for the other disorders is less clear and particularly with the short chain defects there may be problems with the stability of the short chain acyl carnitine. Amino acids - we’ve got no good data to say one way or the other. Theoretically it should be possible.

Regarding the system of storage and retrieval of the cards, I have summarised a survey that was undertaken by the UK Screening Directors in 2000. I’m grateful to Dr Addison from Manchester Children’s Hospital for this work. The situation is extremely unsatisfactory and various recommendations were made. I hope that these might be recommendations that can be taken up by the new Programme Centre, because these are really pressing issues in terms of needing direction and help as to how we store cards.

The final question f), was about service limitation and I asked all the laboratories what the limitations were. You’ll see from Table 2 that there that there is real concern from a large number of laboratories. The numbers shown are the numbers of laboratories out of the 15, who had got problems. I want to highlight the clinical scientists issue: 10 of the 15 laboratories felt that they had real problems with appropriate skills and expertise *now*. The issue of concern that I have bullet pointed are that the service is dependent on very few people, many of whom are reaching the latter years of their career. Dr Bonham and I have undertaken a manpower survey across the UK and we’ve discovered that about 25 posts are required in the next five years for either grade C or high grade B posts. It is a real and difficult problem that the laboratories are facing *now* and real worries for the future.

**Professor Hall.** On a point of clarification – will the scientists who are urgently needed to make the service work be the same scientists needed to run the TMS programme? Because one of the issues that was talked about in screening was the need to make maximum use of

these scarce people by not having machines scattered all round the country.

**Dr Green.** The TMS laboratories would be providing the screening *and* the diagnostic service, so they are not duplicating but actually consolidating them into the same centres.

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### **6.2.3 SPECIALIST CLINICAL SUPPORT**

- a) *Where are the specialist clinical centres? Are there enough? What do they offer? Are they all the same?***
- b) *Do resource constraints at district level affect referral to these centres?***
- c) *Are they able to provide 24 hour telephone advice and are the contact details available in all the districts they serve?***
- d) *What are the obstacles to improving the service?***

**Dr Jane Collins**

It is impossible for professionals working in a metabolic centre to know how many patients are not diagnosed or diagnosed late when they present with a Reye-like illness - without a register there is no way of gathering this information. The definition of a late diagnosis needs to be clarified as it could reasonably be stated that any child with a Reye-like illnesses due to an IMD is diagnosed late i.e. they have already suffered an event associated with significant morbidity and mortality.

Once a diagnosis is made, specialist clinical support is provided in a variety of ways, depending on where the child lives in the UK. There are two major paediatric metabolic centres in the UK – London (Great Ormond Street - GOS) and Manchester. Both have close links with adult services or provide them themselves (Manchester). There are a number of smaller services, which vary from having a single metabolic paediatrician (London – Guy’s, Cardiff, Birmingham and Glasgow) to others with a paediatrician spending a variable proportion of sessions providing the metabolic service (Sheffield, Cambridge, and Bristol). In other paediatric centres there are individuals who take ‘the lead’ for such patients, supported by colleagues from their nearest centre. It can be argued that the two major centres are the only ones able to provide a comprehensive range of services for patients and families 24 hours a day, 7 days a week.

I have been asked whether resource constraints at 'district' level (soon to be replaced by PCTs effectively) affect referral to centres. I am not aware that this is the case. The changes in the NHS may make it harder to develop services, although specialist commissioning may redress that balance or even improve it. There are issues of equity of access, which need to be addressed. As far as I am aware, secondary services know who to contact when they suspect a metabolic problem, although these arrangements are not always formally set out.

Obstacles to improving the service are:

1. A four country (i.e. UK) strategic plan of what services are required and how best provide them eg. Hub and spoke model or a 'network'
2. Insufficient opportunities for training clinical staff (medical, nursing and dietetics) and a sufficiently unclear career path which discourages trainees to choose a metabolic career
3. Recognition of the importance of these disorders in relation to what are perceived as more common ones

But:

- Compared with ten years ago the provision has dramatically improved with ten new consultant appointments not all full time.
- Awareness of metabolic diseases has undoubtedly increased. This is based on anecdotal accounts but also increased interest in organisations such as the BIMDG.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

**Dr Collins**

It wasn't in my brief but I thought it would be helpful to say a little more about the Programme Centre to which Dr Green has just referred. The Department of Health tendered for a UK national and newborn screening Programme Centre, which was awarded in July 2001 to Professor Carol Dezateux and myself at Great Ormond Street Hospital and Sandy Oliver at the Institution of Education. We are starting this April (2002) and will cover all four countries of the UK, but not southern Ireland.

One of the issues that we see as a high priority is that of Guthrie cards. There is a lot of interest in this and we need to set standards. Our role will be to develop a performance management framework and quality assurance for the blood spot screening programme.

Regarding my paper, I think that the issue of knowing the size of the unmet need in metabolic diseases is very important and when I talk about the obstacles I've put this as number three.

Because we don't know how much unmet need there is, it's very difficult to make people recognise how important metabolic disorders are. Some of this may be overcome by developing registers, but we still haven't got any registers other than for a limited number of disorders. I think it is a very difficult thing to overcome and I see that as a major obstacle.

For so many of the issues to do with inborn errors the problem is the lack of a plan. I feel that what we need is a *four country strategic plan* to develop what we need in metabolic medicine. This would obviously encompass all the aspects - from making the diagnosis, providing the treatment, providing the support in relation to specialist nurses, and obviously also, metabolic consultants. If we had that sort of plan then we should in theory be able to right-size it. I think the situation is a lot better than it was five or ten years ago, but there is still this need to have more staff in chemical pathology, in metabolic medicine, medics, nurses etc.. But until there is a clear commitment to developing that infrastructure and those services, we won't be able to attract people into training. Until people feel comfortable that there are going to be jobs to go into, particularly given the fact that Calman training is much less flexible than it was in days past, then I think it's going to be very difficult to attract people into metabolic medicine.

I think those are the main obstacles and I wanted to particularly highlight those. I should also say when I was talking about resource constraints at the district level in my paper, I was thinking of financial resource and about the new NHS as it develops. I think there is also the issue of resource in a much broader sense of *knowledge* at district level which has already been alluded to by Dr Champion and Dr Baumer. Working at a tertiary centre I think we do feel that people do look out for metabolic diseases but then we see it only from the perspective of having the phone calls coming in, so it is a very slanted view. Otherwise, what I put in the paper is how I see things at the moment.

## DISCUSSION

**Professor Leonard.** How does the proposal for a four country programme - the plan for metabolic disease, fit in with the National Service Framework?

**Professor Hall.** What we are arguing for in the NSF is that there should be a statement to the effect that *any* child who has a disorder recognised as being "specialised" - and there are definitions of that - should have access to an appropriate specialty care service. I think it will be difficult to get ministers to sign up to this because it's going to cost money, but if we can get to that point, that's the first step. The second step is then to describe the pattern of service which will deliver that. The four country plan though is more difficult because the NSF does not include Scotland.



**Dr Collins.** I think another point is that in the metabolic world we ought to work more closely with other rare disorder groups, because it seems to me that there is a lot of parent power in rare disorders and their recognition that there is inequity in services. Inequity is a very important way to open doors at the moment.

**Mrs Greene.** I agree and not everybody may know that there is now a coalition of groups that represent rare diseases across the UK called the UK rare disorders alliance. It feeds into an even wider pan-European alliance, an alliance of alliances, called Eurordis. I have further details available.

**Dr Bonham.** A small piece of good news is that we have been awarded £50,000 a year for the next couple of years by the Department of Health, to form a biochemical genetics laboratory network. Just picking up on that last point, one of the things that we will be looking at is equity of access of provision, for diagnostic services.

**Professor Hall.** That will be most useful to the NSF because anything we can say about inequity is likely to bring about improvements. The cystic fibrosis screening story was driven largely by inequity and “post code screening” so where we can demonstrate there is major inequity across the country, it gives opportunities to improve services.

**Dr Baumer.** It is appalling to me in this day and age, that patients that I look after have to go to London to see a specialist. For some of them it's a whole day out. I think it is not acceptable to live in a region that has no effective regional service and what I am ultimately hoping to see is *combined* clinics in DGHs - particularly for people who live in far flung places. This is also good way of getting the education to happen.

**Professor Hall.** The whole theme of what we are arguing for is that we need proper commissioning of tertiary care and by that we mean sufficient staffing to provide exactly what you are describing, managed networks and outreach services.

**Professor Leonard.** Can I just make the point that we must be clear that there will be an adequate amount of work for the specialist consultants who travel out to DGHs.

**Professor Hall.** As we discussed earlier, the nurse specialist would have a role in this.

**Dr Baumer.** Admittedly I work in a large district, but I have about 12-15 children with PKU and another five or more with other rare conditions. I could entertain somebody easily for a

day and I think in far flung places you can often bring them together into one session.

**Professor Hall.** This is a general issue about specialty care and it's a question of numbers and balance but I think the principle is important.

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#### **6.2.4 Pathology services**

***a) In what proportion of autopsies of sudden unexplained death or death following unexplained encephalopathy is there:***

***An examination which meets the "Best Practice" standards in the response to Question 5.7(see PROCEEDINGS PART 5)?***

***Are there geographical variations?***

***Is there a difference in the likelihood of investigation between a coroner's and a hospital autopsy? Who pays? Does cost affect the likelihood of investigation?***

***Has Alder Hey made any difference?***

***b) What are the obstacles to best practice?***

#### **DR MARIAN MALONE**

- a) It is not known in what proportion of autopsies of sudden unexplained death or death following unexplained encephalopathy in children that a satisfactory examination is carried out.

There is no evidence that there are geographical variations.

A hospital investigation is more likely to be properly investigated than a Coroner's autopsy, but as noted above (in Proceedings, Part 5, question 5.7b) there are so few hospital investigations that for practical purposes, the numbers are negligible.

For a hospital investigation, either the Histopathology Dept pays from its hospital budget, or, if a pathology recharging system is in operation in the hospital, the costs are recharged to the clinical unit requesting the autopsy. In a Coroner's autopsy, the costs are met by the Coroner, whose budget in turn is set by the local authority. At Great Ormond Street, we charge £395.00 (nb as at March 2002) for a full investigation of a sudden unexpected death in infancy which includes all the investigations listed under 5.7(a) above (see Proceedings, Part 5).

Cost undoubtedly affects the likelihood of investigation.

As noted above in 5.7(b) issues surrounding organ and tissue retention since the Bristol Inquiry and Alder Hey have had a major influence on the degree to which Coroners will allow investigation of these cases.

b) The obstacles to best practice are

- ☐ Issues surrounding retention of specimens following the Bristol Inquiry.
- ☐ Cost
- ☐ A system whereby, while it is recommended following the Allitt Inquiry that all paediatric autopsies for the Coroner be performed by a specialist paediatric pathologist or a pathologist with a special interest in paediatrics (or in a forensic paediatric case, a forensic pathologist together with a paediatric pathologist), in practice such is not always the case. In particular, cases of sudden unexpected death in infancy are frequently performed by forensic pathologists with no specialist knowledge or commitment who fail to carry out the appropriate investigations.

#### **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

##### **Dr Malone**

We were asked in what proportion of autopsies of sudden unexplained death or death following unexplained encephalopathy in children is a satisfactory examination carried out? “We don’t know” is the answer, from talking to colleagues.

There’s no evidence that there are geographical variations.

Most of these cases are investigated under the auspices of the coroners’ system. The proportion which are investigated as hospital post mortems are probably mainly children dying suddenly in PICU. They are likely to be better investigated, broadly speaking, than those investigated under the coroners’ system. I think that would be true to say.

Funding: for those cases investigated in hospital, the histopathology department of that hospital will fund the post mortem examination. For those under the coroner the costs are met by the coroner, whose budget is set by the local authority. So coroners vary in how much they are prepared to pay for the investigation of these cases.

At Great Ormond Street we provide a paediatric forensic service for children dying suddenly and unexpectedly in London and the Home Counties. We serve between eight and ten coroners, and we do about 150 of these post mortems a year. The cases are brought in from quite a distance - down to the south coast and up as far as St Albans. We charge £395 (March 2002) for the full investigation which I outlined in the previous session. This is actually under- pricing the service, but the coroners we serve are willing to pay that amount for these investigations.

Does cost affect the likelihood of investigation? I think it does, for some coroners, particularly some of the investigations, and certainly issues surrounding organ and tissue retention since Bristol and Alder Hey have had a major influence on the degree to which coroners will allow investigation of these cases.

*<sup>1</sup>There are two separate consultation exercises taking place at the moment, one is by the Department of Health into issues surrounding consent. There have been a few draft proposals sent out already, and some are recommending that after a coroner's investigation is complete, families should be asked if they wish any specimens which have been retained, to be disposed of. Bearing in mind that there will be a proportion of those cases of unexplained death in which it is probable or possible that they're a case of homicide, which is difficult to absolutely determine, those cases will be recorded as unascertained. If there is a future death in the family, it's very important that those specimens are available to go back to and be re-examined. There's also the other side of the coin, exemplified by a family I dealt with where three children had died suddenly and unexpectedly. Only in the third case (which was the post mortem that I performed) were we able to identify an inherited metabolic disorder. That family was under police investigation, and at the inquest the father stood up and thanked us for explaining why his child had died. So I would urge you to contribute to the consultation.*

*Second, the whole coroner system is also being reviewed. The only pathologist representation on that review body is Sir Colin Berry at the London Hospital and he has said if people write to him individually or as a group, he will bring those concerns to the review body.*

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<sup>1</sup> The italicised section is left in for completeness recognising that, while it applied at the time of the meeting (March 2002), matters relating to this issue have now moved on, so some of the remarks will now be out of date. For update see: Milroy CM, Whitwell HL. Reforming the Coroner's service. *BMJ* 2003; **327**: 175-176. and Furness P, Sullivan R. The Human Tissue Bill. *BMJ* 2004; **328**: 533-4 (Ed. June 2004).

Regarding obstacles to best practice, certainly this applies to issues surrounding retention of specimens, because the problem is that “organs” and “specimens” have become confused with each other. Of course parents should consent to retention of *organs*, but as pathologists we feel that retention of *specimens* should be regarded as an inherent part of a pathology examination and that those specimens should be retained as part of the medical archive of that child. There are child protection issues in this as well. Cost is certainly an issue and how this could be funded maybe could be addressed as well.

The Clothier report, following the Allitt enquiry, recommended that paediatric post mortems should ideally be performed by a paediatric pathologist, or a pathologist with a special interest in paediatrics, and certainly that paediatric forensic cases should be performed by a forensic pathologist in association with a paediatric pathologist. That is now happening increasingly, but there are still cases that are being done by forensic pathologists alone. Some perform very good investigations but some don't, and there's no quality control or audit of that system.

## DISCUSSION

**Dr Hall.** On the issue of inequity and, if demonstrated, its power to get things achieved - you said that coroners' budgets are set by the local authorities, and are likely to be variable. Is there any way to obtain the information to demonstrate what inequity there might be in the budgets that they are given, around the country and how it would affect the quality of the post mortems resulting?

**Dr Malone.** The coroner uses his budget at his discretion, so different coroners would use their budget in different ways I think.

**Professor Hall.** So does he receive a single lump sum budget to pay his officer and run his mortuary and everything else?

**Dr Malone.** Yes.

**Professor Berry.** I did once survey paediatric pathologists asking what they were getting paid by their coroners and it ranged from nothing in Bristol (the Bristol coroner never paid for a single investigation in the twenty years I was working there!) to, I think, Manchester where he pays the top fee for chemistry and all the rest of it as well. So there is a huge range.

**Professor Hall.** Does that reflect differences in what the local authority gives them?

**Professor Berry.** Yes I think it's historical budgeting. I should add - the Department of Health is quite clear that, for investigations that are done for *medical reasons over and above what the coroner requires* (and it's now questionable whether it is possible to do those), the cost should fall on the *health authority*. There's no question about that – it's in an official directive like an Executive Letter.

**Professor Hall.** In the situations we are talking about it's hard to distinguish them isn't it, because the coroner's job is to establish the cause of death or at least to exclude unnatural death.

**Professor Berry.** Yes but unfortunately coroners take very different views as to what constitutes a medical cause of death. It varies from "is it natural or not", to "what's the gene defect"!

**Professor Hall.** But if you have no clear evidence as to why a baby has died, then the possibility that it's an unnatural death will remain until you've established a definite cause. So it's a slightly artificial distinction in this particular situation. That sounds like an area for further enquiry.

**END OF SESSION**

## **WORKSHOP PROCEEDINGS: PART 7**

### **DISSEMINATION AND IMPLEMENTATION OF THE EDUCATIONAL PACKAGE**

**MODERATOR PROFESSOR DAVID HALL**

*7.1 Can we start getting existing knowledge and evidence into practice in order to make improvements in patient care?*

*a) What are the best methods of alerting relevant professional groups, identified in 6.1 a) above (see Proceedings, Part 6), to rare disorders with clinical presentations?*

**NURSE SPECIALIST JANE GICK, DR MONICA LAKHANPAUL AND PROFESSOR TERENCE STEPHENSON**

#### **Part 1) Jane Gick**

How do we encourage health professionals to think about rare disorders?

Maybe by reviewing the pathway that has led to a patient being referred to a specialist, we could address some of the obstacles.

In the first instance, it is not unusual for a patient to have had opinions from many specialists before a diagnosis is made.

From the family perspective it comes as a huge relief that someone has been able to pinpoint exactly what the problem is. The realisation then develops as to the rarity of such a disorder. The patient becomes very special and can only be cared for by “specialists”.

What in-put could we expect from teams locally?

Would it be useful to develop outreach services and shared care if the resources were available?

How would this improve patient care?

### **What about shared care?**

“Specialist centres provide excellent treatment and expert care, but the best interests of children may not be served if they must always attend a hospital far from home.”

(L.Hooker & J. Williams BJN 1996 Vol 5, No12.)

Relevant professional groups rarely get the opportunity to learn about patients with rare disorders because they are usually seen by specialists and cared for in specialist centres.

A shared care practice would involve the use of patient held record and communication networks with the patient’s local hospital and the specialist centre.

Would it work?

This has been the practice for many years within the field of oncology. There is an element of risk, however with the instigation of nurse specialists; support for local hospitals is likely to be greater than in the past and the risk much reduced.

How would this improve patient care?

If patients are only ever exposed to specialists within their own field, it makes it very difficult for those not involved with the speciality to learn about these rare problems.

When demand for hospital beds becomes an ever-increasing issue, the ability to treat these patients at a “specialist centre” is not always an option.

The aim of shared care would be to **routinely** expect these patients to be seen and treated at their local hospital during episodes of minor decompensation requiring minimal support.

To ensure this method will work safely and effectively, planning beforehand is essential.

How could this be safely managed?

A sample patient is described

### **Example**

Child retrieved from a district general, acutely unwell requiring ventilatory support. On arrival thorough investigation reveals the child to have MCADD.



During treatment and recovery phase local physicians and nursing teams are informed of diagnosis and progress being made. They are also informed that the child will return when well enough to do so, in order to complete a convalescing period prior to discharge home.

Information on the condition and treatment is faxed to that team. All the other relevant health professionals are made aware of the child. This will include G.P, health visitor, community nurse's etc. They in turn extend the involvement of other health care professionals that are likely to be required e.g. physiotherapist, occupational therapist. (In most instances, there is a huge interest in the individual patient and a majority of professionals want to learn key aspects of the condition, thus instigating an interest with regard to rare conditions).

Prior to discharge the nurse specialist has offered to meet with any of these teams to discuss future care, teaching or any other type of support that is required to ensure adequate care from local services is established prior to transfer.

A discharge package is in place that incorporates a full summary of the child's particular needs and dietary advice. A system has already been agreed by the local team that allows the child emergency access to the hospital following discharge either by "green card" access directly to the paediatric unit or via casualty and seen immediately upon arrival.

Parents are given hand held documentation that advises all of procedure to follow if illness and decompensation is suspected. The documentation also encourages health professionals to contact the specialist teams for advice and support. Parents are asked to inform the metabolic team if using the emergency regimen, even if the child does not require hospital admission.

**Communication** is essential to the smooth transition from one team to another.

### Does it work?

Having a care package in place is certainly reassuring for families involved. The reassurance also extends to health professionals who may never have met with such cases.

By allowing involvement at a local level, health care professionals have a desire to learn as much as possible if they have agreed to take on a degree of responsibility. Thus access to a wide range of people has been instigated.

Sending children back to their local communities meets the requirements of children as

individuals. It is a family centred approach that is less disruptive to the unity of a family.

As a specialist nurse you are an ambassador who is able to follow the child, offering support to the family at home as well as being an educational resource to health care professionals locally.

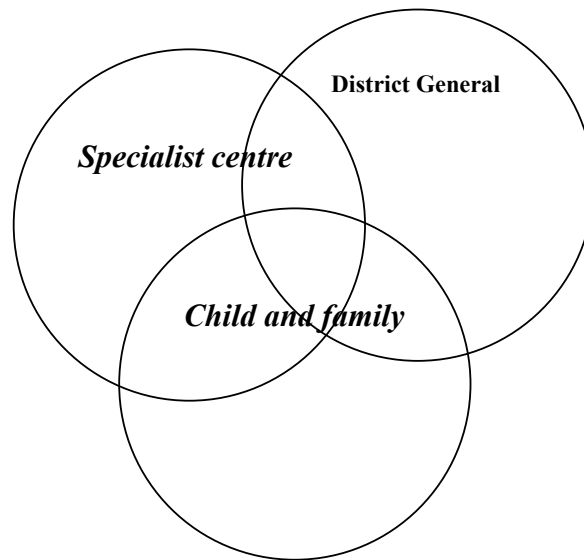
It will often transpire that once people are aware of a service, it is more likely to be utilised.

What evidence supports this?

As a specialist nurse in post invitations to teach have included:

- Paediatric intensive care course
- All grades of paediatric nurse within the trust
- Physiotherapists within the trust.
- District general hospitals receiving patients with inborn error of metabolism
- Community paediatric nurses
- School nurses
- Health visitors
- Midwives & neonatal nurses

### Models of care.



#### **Aim - Simplify management**

- **Working with families**
- **Multidisciplinary team work**
- **Communication between service providers.**

**“Accurate documentation may enhance the care provided”**

(L.Hooker et al BNJ 1996 vol 15 No12)

“Parent held records embrace the concept of partnership and professional working in an open and participative way with clients”.

(R.Charles. Health visitor Vol67 No: 8 Aug 94)

## **Education for the Nursing profession**

Would study days benefit?

From a nursing perspective, study days can prove to be an excellent forum for improving knowledge however what will the response rates be?

Most nurses have to justify their need when applying for study time. There is usually a limit to the amount of days allowed for study. Would rare disorders be a priority?

From personal experience, raising the interest is very difficult. Who would be appropriate to target?

What methods have been used previously?

At Guys the screening laboratory set up a study programme to raise issues relevant to the neonatal screening programme. The aim being to improve the service and to ensure the heel prick blood test is performed on every eligible baby within our region. It was also aimed at increasing existing knowledge and raise awareness of the potential for screening for other conditions.

In the first instance an invitation to a study day at Guys for all those involved in the screening programme was posted out to all the regional hospitals. Response rate from midwives, the main target group was very poor.

A second approach was to go to the appropriate hospitals offering a free study session. This proved a little more successful. The Southeast region covers sixteen acute trust providers, of these only six took up the offer, the rest did not respond. The letters were sent at a six-month interval, those that did not respond in the first instance received a second letter.

A key issue was to improve the screening service from the aspect of frequently requiring repeat samples due to poor standards on first tests. The second was to educate and raise awareness to the possibility of adding further screening tests to that which are already performed.

Of those that responded, the welcoming committees were variable. In some instances the turnout was excellent and interest on the subject matter was well received. However the absolute opposite could be said of some other venues.

It was also a revelation to discover some of the thoughts generated from these visits.

For example:

“I thought PKU is now cured. Having screened for many years, I have never met a positive result”.

My conclusion from this very small study group is that general improvement in the screening process needs to be addressed in the first instance. If the neonatal screening service were allowed to accommodate further diagnostic testing a drastic improvement would be essential to safeguard all involved.

Is there support to make these changes?

### **The NHS Plan**

5. NHS will work continuously to improve quality services and to minimise errors

- Introduction of screening programmes for women & children.

1.13 electronic patient records (maintaining continuity of care.)

6.8 Working with patients and professionals to develop national standards of care. (National service framework)

9:16 Radical reform is required in NHS education and training to reshape care around the patient

### Applying knowledge management within a primary care trust: One approach

KM* 'drivers'	Key activities	Examples
Understanding what patients want to know	Public involvement	Patient satisfaction surveys Providing information on services, complaints procedures etc. Providing patient information as leaflets, or as link to websites
Understanding what staff need to know to support their: <ul style="list-style-type: none"> <li>• Work</li> <li>• Professional development</li> <li>• Research</li> </ul>	Ensuring access to: <ul style="list-style-type: none"> <li>• services</li> <li>• skills</li> <li>• resources</li> </ul>	Peripatetic knowledge management service. Service-level agreements with library services, information technology etc. Support from colleagues with expertise in audit, research, information analysis Access to bibliographic databases
Using knowledge to inform health-care policy	Managing the dissemination of evidence guidelines promoting best practice. Exploiting information management data	NICE guidelines review group Desktop access to evidence Evidence-based commissioning Information management technology policy Audit cycle
Keeping up to date with changing policy, trends and clinical evidence	Updating services	Communications policy Print and e-newsletters Use of bulletin boards 'Alerting' services (e.g. ZETOC)
Developing an organisational 'memory'	Ensuring access to: <ul style="list-style-type: none"> <li>• directories</li> <li>• databases</li> <li>• documents</li> </ul>	Contacts lists, distribution labels Best practice database, HIMP resources catalogue E-access to PCT policy, protocols, referral guidelines
Embedding best evidence into practice	Collaboration with suppliers and other services Implementing guidelines and promoting best practice	Decision support: Protocol and automatic reminders within computer systems Roving primary care development team
Making implicit knowledge explicit	Initiatives to share knowledge	Skills audit; expertise database Special-Interest groups, e-for a

\* KM = knowledge management.

**S.Bryant Putting the knowledge base at work.**

Clinical Governance Bulletin Vol.2, No.5

Suggestions would be...

- Clinical Governance.

Review of midwifery training. Ensuring midwives are informed and up to date with the screening services. It is essential that information to the client group is accurate and up to date.

Accountability has to improve with regard to collection of the sample and ensuring a result has been documented.

## **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

**Jane Gick**

I have looked at how we get education across from a nursing perspective. As far as nurses are concerned, we have tried study days but the people who turn up for anything to do with inherited metabolic disorders are usually those already working in the area and they might not necessarily be the group we are specifically targeting.

I have also taught midwives on neonatal screening to try and improve the service. I heard some bizarre comments like 'I thought PKU did not exist anymore, it's cured', so there is obviously an educational need there.

So now I'm here really to sell my job as a Nurse Specialist, because the only way I have found to be really affective is by undertaking a "shared care system". We cannot possibly *always* accommodate children in a crisis with their IMDs, although we hope always to get beds for them at the time of first onset when we first diagnose the illness. Where I have found I have been most useful in getting education across is if they go through periods when they are unwell and they need a short stop at their local hospital. So initially, once a diagnosis has been made, we try if possible to send them back to their local hospital to convalesce and that gives time for as many people as possible to get to know what the condition is, what it's all about, and how we should care for them. So far this has been quite effective but it is a relatively new service so there may be a few hiccups to come!

When the patient goes back to local hospital to convalesce, I aim to go there the day following. Then I can speak with nurses, doctors, community nurses and community

paediatric nurses who have been of fantastic benefit. Years ago children were looked after by adult district general nurses, but we now have specifically trained paediatric nurses.

When I go back to the District General Hospital we have a system of “hand held” records. That’s an excellent policy to ensure that local people know how this child needs to be looked after in a crisis. However in a crisis parents often forget to bring these with them so if you have your care set up well in advance and try and anticipate all the obstacles that may occur, this does have its benefits.

In respect of teaching I have been asked back to District General Hospitals - they have had the crisis, the crisis is dealt with, the child diagnosed and then people do say ‘ well tell me what this is all about, I want to learn about it’ . So it has been a good teaching forum.

Regarding trying to get the message across about potential neonatal screening for the future, I have approached 16 DGHs to say there is a possibility of an expanded programme which carries educational implications. The people at first hand to be educated are midwives, who want to improve the way that they collect the sample and also expand their knowledge if we did bring in MCADD on to the screen and improve methods of obtaining informed consent. The approach was not well received in some areas, although in others the response was very positive. Midwives just have a task to get a blood spot and their interest in metabolic diseases is not necessarily there and when it comes to positive tests we always ask our patients what information were they given and it is still very limited.

Another system we have set up for the acutely sick children is Green Card Access. Most of the DGHs allow the children to go in, some of them directly to the ward with a doctor there to meet them if they are unwell. Others do it via Casualty. The aim is to try and prevent the problems that have happened in the past when parents turn up, they have got the hand held record, but nobody else knows about them. Maybe the Paediatrician knows but is not in Casualty at the time they turn up.

As far as the government is concerned, nurses are in the same position as doctors, they do want to go for training, and they do want more education but are not always supported. At a recent course I was involved with, two of the girls did not show up for their class on one day and it was because their ward was short staffed. So they are not being protected as far as education is concerned. There are lots of obstacles along the way but as a specialist nurse I am up there and I am also known in my centre as the Roving Ambassador! I hope you all



appreciate that we are trying to do a service, we are a minority and I hope in the future there will be more people in our position.

***7.1 a) What are the best methods of alerting the professional groups to rare disorders with common clinical presentations?***

***Part 2) Dr Monica Lakhanpaul & Professor Terence Stephenson, Nottingham***

**Basic premise**

There is no point in having a guideline (= ‘an educational package’) on Reye’s syndrome if practitioners don’t think of Reye’s syndrome as a possible diagnosis when faced personally with an ill child. There is no point in starting the guideline from ‘raised ammonia’ or ‘abnormal liver function tests’ if practitioners don’t think to perform these tests. Therefore, the educational message should be incorporated into a guideline which starts from the common presenting problems with which Reye’s Syndrome manifests (e.g. a guideline on ‘altered consciousness’ or ‘coma’, ‘seizures’, ‘vomiting’ etc.).

**Introduction**

“As you know, educational initiatives carry more credence and are more likely to be taken up if, as far as possible, they are evidence based.” “So please would you support your responses wherever possible with published evidence (including the references).”

Sue Hall, personal communication, 30<sup>th</sup> November 2001.

- Do I know this? “Do I not know this?” (Graham Taylor, ex-England football manager)
- For the public and health professionals (dealing with an illness perceived as common & minor), MMR suggests the evidence base is not as influential as suggested.
- Do Posh & Becks, or Tony Blair, or royalty carry more credence? Are ‘The SUN’ and ‘Cosmopolitan’ magazine the best current routes to public information? What about ‘BMA NEWS’, or ‘Dr Foster’ for medical practitioners? Should the Reye’s Syndrome Foundation employ a Sun journalist or Alastair Campbell?
- Most educational initiatives in schools, universities and health education are not evidence based (sex education, SATs, MCQs, “don’t die of ignorance” campaign against HIV, league tables in newspapers etc.)

- Despite this, non-evidence based educational initiatives may (HIV – dramatic fall in gay community in 1990's) or may not (sex education – UK still has double the teenage pregnancy rate of most other western European countries) appear to be effective
- But association does not = causality

### **Why guidelines?**

(And not textbooks, speakers, journals, the press etc.)

‘All patients in the NHS are entitled to high quality care. This should not depend on the geographic accident of where they happen to live’.

[A First Class Service: Quality in the NHS 1998)

- Research has shown that if properly developed, communicated and implemented, guidelines can improve patient care [National Institute for Clinical Excellence (NICE)]
- Clinical guidelines help to address all these issues by 'closing the gap between what clinicians do and what scientific evidence supports' [Eccles and Mason 2001] and therefore reducing variations in practice and promoting clinical effectiveness. If introduced with careful evaluation, they have been shown to improve clinical practice [Grimshaw and Russell 1993].
- Armon et al [2001b] have shown that the introduction of guidelines into the emergency department in Nottingham was able to reduce waiting times in the department and reduce the number of invasive tests performed.
- In North American guidelines are often viewed by insurers as a way to reduce mistakes (even though not proven) [Bauchner 1997].
- The increasing number of publications makes it unrealistic for busy clinicians to have the time to read every piece of new evidence available and to incorporate it in their daily practice. Despite agreeing with current evidence, clinicians may not use it in their daily schedule. A number of ways have therefore been sought by which evidence-based medicine (EBM) can be made easily accessible and implemented into busy practice (Gilbert and Logan 1996). Guidelines are one way clinicians can use to keep up to date with the increasing evidence available. The interest in the development of guidelines in the health service in the U.K and internationally continues because guidelines are viewed as

one tool that can be used to improve clinical practice. (Woolf et al 1999). Their purpose is 'to make explicit recommendations with a definite intent to influence what clinicians do' [Hayward et al 1995].

- The Scottish Intercollegiate Guideline Network [SIGN 1999], the Royal College of Paediatrics and Child Health [RCPCH 1998], the National Health and Medical Research Council [NHMRC 1998] and the NHS Executive [1996] are just some examples of established organisations who have written documents on the development and implementation of guidelines. These documents have followed literature and reviews on guideline development [Grimshaw et al 1995, Farmer 1993 and Eccles et al 1996]. Other organisations nationally and internationally have developed tools for appraising guidelines. Cluzeau et al (1997) have developed an appraisal instrument that has been recognised by the RCPCH. More recently, there has been an international collaboration to produce an appraisal instrument which can be used across Europe. The aim of the collaboration was to develop a generic tool called the Appraisal of Guidelines for Research and Evaluation Instrument [AGREE 2001], that can be used to assess the quality and validity of guidelines. It is also envisaged that this tool could be used during the development itself so that a high quality guideline is produced.
- Grimshaw et al (1995) identify 3 factors that contribute to the validity of a guideline:
  1. guideline panel members
  2. the evidence identified
  3. the methodology of the development of the guideline.
- Field and Lohr in 1990 identified 9 key criteria that a high quality guideline should fulfil.
  1. Valid
  2. Reliable
  3. Reproducible
  4. Applicable to the defined population it refers to
  5. Flexible
  6. Clear
  7. Scheduled review
  8. Good documentation
  9. Multidisciplinary review

[MJ Field K N Lohr 1990]

### **Auditing Current Practices**

Audit is an integral part of guideline development. Part of the process of selecting a guideline topic includes auditing current practices and identifying areas in which improvements can be made. The cycle is then completed by auditing any changes that have been brought about by the implementation of the guideline. Armon et al (2001) decided on the development of two guidelines, for seizure and for diarrhoea after auditing paediatric medical attendances presenting to the A and E department and finding that 21% were due to these two presenting problems.

### **Incorporating EBM into guideline development**

Sackett [2000] and Margolis and Cretin [1999] has stated that guideline development should be a combination of evidence and clinical experience. Organisations such as SIGN [1999], NHMRCH [1998], RCPCH [1998] and the NHS executive [1996c] have developed guidance on the methodology required to produce high quality guidelines. Most of this literature places most emphasis on the rigorous and systematic procedure used to identify and assess the available evidence but Sackett makes it very clear that good doctors need to use **both** clinical expertise and best available evidence to make appropriate decisions. Clinical practice needs to be kept up to date with current evidence but we must realise that evidence is not available for every scenario nor is it applicable to all patients. Margolis and Cretin [1999] have developed six steps which provide an outline necessary for the development of a quality clinical guideline and take into account the position of consensus and experience within the process:

1. Generate/choose the seed algorithm
2. Marshal the evidence
3. Perform consensus processing
4. Write the first revision of the algorithm seed
5. Repeat iterations of steps 3 and 4
6. Produce the penultimate draft

A step omitted above but essential is the selection of a guideline development group.

## **Consensus Methods**

The three main consensus methods used in health services research, by doctors and nurses include Delphi method, nominal group technique (NGT) and consensus development conference. The aim of all three is to identify the extent of agreement within a panel and to identify areas of disagreement.

### **1. Delphi**

This method was named after the Greek oracle thought to have the power to predict the future [Murphy et al 1998]. It was initially developed as a research technique by the RAND Corporation in the 1950's to synthesise expert opinion on new technologies [Murphy et al 1998]. The method is now much more widely used but is still more commonly by nurses than by doctors. With the increasing interest in improving quality of care and clinical guidelines, the Delphi method is being adopted as a way to combine evidence with expert opinion and experience [Naylor 1998], [Armon et al 2001].

The technique can be used to deal with a complex problem by a multiple iteration survey [Duffield 1988], [N Bowles 1999]. The key features of this procedure include anonymity, iteration, controlled feedback and statistical group response [Pill 1971].

The first round of the Delphi consists of a group of invited individuals being presented with information in the form of statements [Duffield 1988]. The relevant individuals then provide an opinion on this information based on their own knowledge and experience [Jones and Hunter 1995]. In the second round the questionnaire is mailed out to the respondents again but this time the panel are able to alter their judgment in light of the group's responses. The panel rank the level of agreement or disagreement with each of the statements after receiving feedback on the group's responses. This process continues and the participants continue to re-rank their agreement or disagreement with the statements until an accepted degree of consensus is reached. [Jones and Hunter 1995, Duffield 1988]. Finally, the responses are statistically analysed to determine which statements reached consensus of agreement or disagreement [Murphy et al 1998]. At no time does the group meet and therefore this method allows access to a large number of people and maintains anonymity. The

Delphi method has however been adopted and altered over the years so that the technique can be used in a number of different circumstances [Crisp et al 1997].

## **2. Nominal technique [NGT]**

Delbecq and Van de Ven developed this technique in 1971 for use in committee decision-making [Murphy et al 1998]. The process involves generating ideas and gathering information about an issue or problem from 9 to 12 experts at a structured meeting [Mays and Pope 1996]. The purpose of this process is to define problems in a specific area. The steps involved are outlined below:

The individuals independently and privately record their ideas

Each individual in turn provides one idea to the facilitator and these are listed on a flip chart until all the ideas have been collected.

The group then discusses the ideas and again records their judgements

This may continue and further discussion may take place.

The group judgement is derived after statistically analysing the individual judgements

As with the Delphi process, the NGT can be modified and adapted for individual situations. In some situations literature is provided as a background to the topic under discussion. This method has been favoured because it promotes the development and discussion of ideas. [Murphy et al 1998][Margolis and Cretin 1998][Mays and Pope 1996].

## **3. Consensus development conference (= this Doncaster meeting?)**

Consensus development conferences have been used in the health field in a number of countries such as the United States, Canada, UK and Sweden. This process takes a few days and involves a small group of selected (approximately 10) individuals. The aim is for the group to come to a consensus in a private meeting after having considered evidence presented to them by other experts or interest groups in an open meeting[Mays and Pope 1996]. This consensus method is expensive due to the period over which it takes place, the requirement to involve experts in the field to present

evidence and because it involves participation by the public and other interested parties in an open meeting. After the open meeting a private meeting also takes place for a consensus to be achieved. It requires resources that only large organisations such as the US National Institutes of Health and the King's Fund can provide. The Delphi technique and NGT do not have this disadvantage and are affordable to individual research groups [Mays and Pope 1996].

### **Implementation of clinical guidelines**

Clinical guidelines are currently being produced at an increasing rate not only across the world but also in the U.K. The guidelines are often produced at a national level and subsequently implemented at the local NHS trust level. The developers of the guideline do not always bring about the implementation of the guidelines and the development process often demands vast amount of resources. If clinicians fail to use the guideline, then the guideline has failed. Failure of its implementation, therefore, entails colossal wastage of money unless equivalent attention is given to encouraging health care professionals to use the guidelines and to bring about a change in their behaviour.

Passive dissemination of information is not sufficient to bring about a change in behaviour. Health professionals must be aware that a guideline exists (dissemination), decide to adopt it and then regularly use it (implementation). A more active process is required to encourage this change.

A systematic review by Grimshaw and Russell (1993) concluded that despite the development of clinical guidelines, performance can only be improved if guidelines are developed, disseminated and implemented in an appropriate manner and as part of this process they must be rigorously evaluated. If this process is undertaken, they found that clinical practice is improved.

The aim of this section is to provide an outline of key components of the implementation strategy that need to be considered. In order to identify the key components essential to the successful implementation of the guideline a management tool called forced field analysis developed by Kurt Lewin can be used [Margolis and Cretin 1999]

### **Force Field Analysis (Kurt Lewin)**

This process involves the identification of potential barriers (restraining forces) to the implementation of a guideline and incentives that may encourage it (driving forces).

The guideline development group can generate ideas about the barriers to the implementation process and incentives for adoption of a guideline. They can then develop a strategy to determine how to deflect the restraining forces and utilise the driving forces [Margolis and Cretin 1999]. Examples of categories of driving and restraining forces are provided in the table below. Individual factors contributing to each category must be considered. For example, when considering economic influences restraining factors of implementation may include more expensive treatments being included in the guideline, and driving factors may include less patients requiring admission following the implementation of a guideline and therefore more efficient use of resources.

<b>Driving and Restraining Force Categories</b>
Patient Influences
Sociolegal Influences
Education and Skills
Economic Influences
Administrative Factors

Table adapted from Margolis and Cretin 1999

### **A systematic strategy for disseminating and implementing clinical guidelines**

#### **1. Evaluating current practice**

Health care professionals are often reluctant to alter their practice when there is no perceived necessity for change. The guidelines should be able to demonstrate a tangible improvement in practice once implemented. Current practices may be audited to highlight deficiencies and scope for improvement, which could benefit from the implementation of a relevant guideline.



## **2. Systematic approach**

In order for the process to be successful it must be strategically planned. The strategies to be adopted need to be decided, time frame set, potential participating professionals approached and potential barriers identified.

## **3. Key workers/Facilitator**

An individual who will be available throughout the implementation process and ideally during the follow up period should facilitate the process, provide support to the staff involved and be available to provide on-going education and advice. They must remain focused and be clear about the key recommendations to be implemented.

## **4. Stakeholders**

Stakeholders include anyone who will need to be influenced in order for the desired change to be possible. They should be identified and involved in the development and implementation process to provide them with a sense of ownership. Paediatrics is a multi-disciplinary specialty, therefore, multi-professional collaboration is more likely to promote success. Primary care representatives should be involved in implementation of the guidelines of the paediatric patient whenever possible, this will consequently strengthen the primary/secondary care interface. Some of the other groups to consider include administrators, audit and information technologists and members of the public health team.

## **5. Patients/Consumers of Health Services**

The White Paper places great emphasis on the identification and inclusion of patient preferences when considering decisions regarding treatment and management of patients. Patients have also been shown to have an effect on the decision making process of clinicians (Bauchner 2001). It is therefore becoming increasingly important to involve a patient or their representative (Bauchner 2001) when considering strategies for implementation of guidelines.

## **6. Preparing the environment**

The stakeholders need to be informed of the potential introduction of the guideline. The stakeholder's current level of knowledge about any relevant clinical area can be assessed. Resources necessary for implementation of guidelines can be identified and potential barriers may be tackled.

## **7. The guideline**

### ***Presentation***

Guidelines need to be easily accessible and presented with clarity. The actual format in which the guideline is presented is extremely important if implementation is to be successful. They may be presented as key recommendations, algorithms, care-pathways and increasingly on hospital intranet systems where they are readily available, cannot be mislaid and can easily be updated.

Nottingham Health Authority has adopted a three part guideline format:

- Flow chart summary

A short summary of the guideline which is quick to refer to

- Explanatory Note

Detailed information about the whole guideline development process and the key recommendations made

- Patient Leaflet

Information for the patients

### ***Quality***

The adoption of a guideline will depend on the trust clinicians have in its quality and relevance. The guideline must be evidence-based wherever possible and the methodology used for its development must be rigorous and transparent. The professionals expecting to use them must find them useful, relevant to their practice and flexible allowing them to be adopted to local requirements, and patient needs.

## **8. Dissemination and implementation techniques**

### ***Education and Communication***

Health professionals are unlikely to use guidelines that they are unaware of. Lack of familiarity appears to be one of the main reasons why guidelines are not used. Information can be transferred in 3 different ways.

- Passive diffusion of information, e.g. by publishing in a journal, has not been found effective; however, raising the awareness about the guideline is still an important part of the process.
- Dissemination is a more active process and makes use of different strategies so that all stakeholders are aware of the existence of the guideline and its content. The stakeholders need to have access to the information, know how to use it and the reasons for using it. The type of training may be variable depending on the time and resources available e.g. individual training, small group seminars, to larger conferences. This may be delivered by experts in guideline methodology or by leaders in the relevant clinical fields. Guidelines that are endorsed by an authoritative body e.g. the Royal College may have more credibility and therefore help in their acceptance and implementation. The media may also be employed as a tool for disseminating information. The PIER website (Paediatric Information and Education Resource) is an example of a web site being used to disseminate information, allow access to peer reviewed information and guidelines.
- Implementation is an even more active process and aims to use the resources and skills available to bring about a change in behaviour. In a busy clinical practice, professionals are more likely to need reinforcement of their knowledge of new recommendations. Training is required, not only to inform professionals about the existence of the guideline but also how to use it. Computer decision support systems are increasingly being purchased and can be used to remind professionals to perform a particular action. Other techniques adopted include:
  1. Care-pathways to implement the guideline and improve documentation.
  2. Audit and feedback to inform professionals about the outcomes of implementation. This information can be used to motivate people and encourage the continued use of the guideline.
  3. Involving local opinion leaders who are able to influence other professionals.

## **9. Guideline evaluation**

Adherence to recommendations provided in a guideline need to be monitored. Local researchers and the audit departments can collaborate with other professionals to develop accurate and effective methods for the evaluation of the guideline. This is important so that a

positive change can be identified and the results used to sustain the use of the guideline. Deficiencies in the guideline can be identified and the findings used to improve and update it.

### **Are paediatricians different?**

There has been an increasing trend for the development of guidelines in all disciplines including paediatrics, and an increasing effort to make clinicians adhere to them [Bauchner et al 1997]. Guidelines have been shown to change clinical practice and patient outcome if attention is given to methods used to develop, implement, and monitor them [NHS Centre for Reviews and Dissemination 1994]. In order to implement evidence based medicine and guidelines effectively evidence based methods on implementation should ideally be followed [Grol 1997]. However, a recent Cochrane review [Thomas et al 2000], concluded that at present there is 'insufficient evidence to make firm conclusions about the effectiveness of the different dissemination and implementation strategies'. Flores et al in their study about paediatricians' perceptions of guidelines found that, despite paediatricians being aware of the existence of clinical practice guidelines, they only really used the asthma guideline repeatedly. Not surprisingly, doctors were more likely to follow the guidelines if they were evidence based and were shown to improve outcomes. Until evidence is available about the most effective strategies to change clinical behaviour, it is necessary to employ a variety of strategies for the dissemination, and implementation process.

### **Summary**

Clinical guidelines are more likely to be used if they are evidence-based, simple, flexible, rigorously produced and perceived to improve quality of care. It is important to use a systematic approach that employs different strategies. Professionals will have different views about guidelines and may need to be approached and influenced by adopting different strategies. The implementation process is a state of continuum and will require ongoing evaluation.

**'There are many approaches to changing clinical care for patients and implementing guidelines, all of which have some value and may be useful and effective, depending on the changes aimed at, the target group, the clinical setting, and the barriers and facilitators found there'**

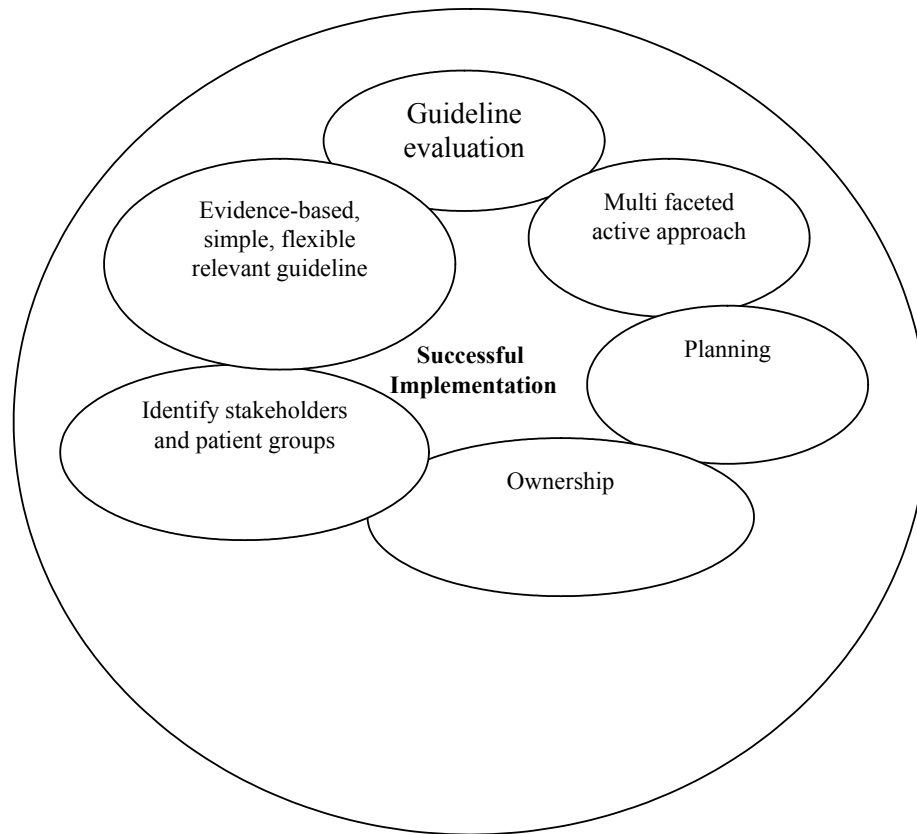
**[Grol 1997]**

## References:

1. Department of Health. (1998) *A First Class Service: Quality in the NHS*. London: DOH.
2. National Institute for Clinical Excellence. (2001). Department of Health.
3. Grimshaw, J M and Russell, I T. (1993) Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* **342**, 1317-1322.
4. Armon, K. (2001) Evidence based and consensus refined guidelines for acute childhood illness. Department of Department of child health. Nottingham: Nottingham.
5. Armon, K, Stephenson, T J, MacFaul, R, Eccleston, P, Werneke, U and Gabriel, V. (2001) Determining the common presenting problems to paediatric accident and emergency. *Archives of Disease in Childhood* **84**, 390-392.
6. Bauchner, H. (2001) Changing physician behaviour. *Archives of Disease in Childhood* **84**, 459-462.
7. Gilbert, R and Logan, S. (1996) Future prospects for evidence-based child health. *Archives of disease in childhood* **75**, 465-468.
8. Woolf, S H, Grol, R, Hutchinson, A, Eccles, J M and Grimshaw, J. (1999) Clinical Guidelines: Potential benefits, limitations, and harms of clinical guidelines. *British Medical Journal* **318**, 527-530.
9. Hayward, R S A, Wilson, M, Tunis, S R, Bass, E B, Guyatt, G and Group, f t E-B W. (1995) User's guides to the Medical Literature. VIII. How to Use Clinical Practice Guidelines. A. Are the Recommendations Valid? *Journal of American Medical Association* **274**, 570-574.
10. Scottish Intercollegiate Guideline Network. (1999) *SIGN Guidelines, An introduction to SIGN methodology for the development of evidence-based guidelines*. Edinburgh: SIGN.
11. National Health and Medical Research Council, A. (1998) *A guide to the development, implementation and evaluation of clinical practice guidelines*. Canberra: Australian Government Publishing Service.
12. Royal, C, of, Paediatrics and Child Health. (2001) Standards for Development of Clinical Guidelines in Paediatrics and Child Health. Department of. Royal College of Paediatrics and Child Health.
13. Grimshaw, J M, Eccles, M and Russell, I T. (1995) Developing clinically valid guidelines. *Journal of evaluation in clinical practice* **1**, 37-48.
14. Farmer, A. (1993) Medical practice guidelines: lessons from the United States. *British Medical Journal* **307**, 313-317.
15. Eccles, M. (1996) North of England evidence based guidelines project: methods of guideline development. *British Medical Journal* **312**, 760-762
16. Cluzeau, F, Littlejohns, P, Grimshaw, J and Feder, G. (1997) Appraisal instrument for clinical guidelines. Department of. St George's Hospital Medical School: London.
17. Field, M J and Lohr, K N. (1992) *Guidelines for clinical practice: from development to use*. Washington DC: Institute of medicine/national academy press.
18. Sackett, D L, Sackett, S E, Richardson, W S, Rosenberg, W and Haynes, R B. (2000) *Evidence-Based Medicine, how to practice and teach EBM*. London: Churchill Livingstone.
19. Margolis, C Z and Cretin, S (ed.) (1999) *Implementing Clinical Practice Guidelines*. Chicago: American Hospital Association Press.
20. Murphy, M, Black, N, Lamping, D, McKee, C, Sanderson, C, Askham, J and Marteau, T. (1998) Consensus development methods, and their use in clinical guideline development. *Health Technology Assessment. NHS R&D HTA Programme* **2**
21. Naylor, C. (1998) What is Appropriate Care? *The New England Journal of Medicine* **338**, 1918-1920.
22. Duffield, C. (1988) The Delphi technique. *The Australian Journal of Advanced Nursing* **6**, 41-45.
23. Bowles, N. (1999) The Delphi technique. *Nursing Standard* **13**, 32-36.
24. Pill, J. (1971) The Delphi Method: Substance, Context, A Critique And An Annotated Bibliography. *Socio-Economic Planning Science* **5**, 51-71.
25. Jones, J and Hunter, D. (1995) Consensus methods for medical health and health services research. *British Medical Journal* **311**, 376-380
26. Crisp, J, Pelletier, D, Duffield, C, Adams, A and Nagy, S. (1997) The Delphi Method? *Nursing Research* **46**, 116-118.
27. Mays, N and Pope, C (ed.) (1996) *Qualitative Research in Health Care*. London: BMJ Publishing group.

28. NHS Centre for reviews and dissemination. (1994) Implementing clinical practice guidelines: Can guidelines be used to improve clinical practice? Department of Effective Health Care. Royal Society of Medicine: London.
29. Department of Health. (1996c) *Clinical guidelines: Using clinical practice guidelines to improve patient care within the NHS*. Leeds: Department of Health
30. NHS Centre For Reviews and Dissemination. (1999) Getting evidence into practice. Department of Effective Health Care, vol. 5. Royal Society of Medicine: London.

## Key points for successful implementation



## **POINTS HIGHLIGHTED IN ORAL PRESENTATION\***

### **Professor Stephenson**

I would like to start by acknowledging my colleague Dr Lakhanpaul from whose thesis most of these observations have been derived.

I have two “take home messages”. The first is that it is my belief that if we are to improve the diagnosis and treatment of Reyes Syndrome, which is what the mission statement of this meeting was, we have to come up with an educational package which generically improves the diagnosis and care of inborn metabolic disease. The second is that we in Nottingham have the expertise and the experience to help you develop and deliver that educational package!<sup>1</sup>

Why do we want to develop guide lines for acute emergencies? Ninety two per cent of all children attending with non traumatic medical problems as an acute emergency do not attend any of the institutions represented by any of the people here, except Dr Baumer, Dr Boon and myself. They attend A & E departments at District General Hospitals. What’s more, only about a fifth of those units have A & E departments where the children are seen separately, so four fifths of them are seen in the chaos, at night, of large adult A & E departments. If they were all in together, you can imagine, alcoholics, trauma, road traffic accidents, parents, tiny children largely seen by doctors training to be surgeons or general practitioners, who are casualty officers doing a job between demonstrating anatomy and cutting some abdomens in the next job. They have a six month casualty job in the middle and they are not particularly temperamentally or emotionally geared towards children and certainly not children’s metabolic disorders.

I think you really have to keep that uppermost in your mind. This is the target group we are talking about. This is why we try to develop some guidelines that ultimately would be two or three sheets or maybe one sheet of a laminated A4 algorithm that they could not miss. If the fire alarm went off in this room now none of you would move, that’s common experience, you would all wait some time. So the method of alerting is relevant. If the fire alarm went off and then a speaker said there is a fire in this building, it is not a test, the fire is 100 metres

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\* See also Professor Stephenson’s powerpoint presentation (Workshop Proceedings Part 9)

<sup>1</sup> Professor Stephenson and his team subsequently successfully applied to the National Reye’s Syndrome Foundation for a grant to develop a formal guideline on the diagnosis and management of acute childhood encephalopathy including Reye’s syndrome and Reye-like IMDs. The project began in November 2003 (Ed.).



from you and is advancing at 3 metres per second, you would be out of here like a shot!

The method of alert is irrelevant if what you are telling people is boring, so you must think in your educational package not just about how you are going to disseminate but the content of the dissemination must be exciting, interesting, visual, pictograms, algorithms, colours, shading, it must have all of those things, not just 'here's a sort of photocopy of a bit of text'.

My grandfather served at the Somme and if you found that the guns were repeatedly jamming in the trenches who would you ask about the problem? You could ask the people firing the guns but they would be like my grandfather- 18 or 19 year olds, seen active service for sixteen days out of four years. So they did not have great personal experience of firing a gun in anger. The NCOs would have done it before and might also have experience of the guns seizing. Front line officers would have a greater over view, staff officers were pretty remote but they probably trained or were responsible for the training process that we just heard about, you might want to ask them. Some might ask the manufacturers because it might not be the gun, it might be the ammunition, it might be the oil used to clean the gun, it might be how it is stored, and it might be a whole range of other things. You might not have addressed the problem at all. You would certainly consult the history books because this might have happened in the Boer War, before the Somme, if you are using the same rifle. That's who you would consult about *why* it is happening but if you actually want the gun to go off and kill the enemy, there's really only one group of people to target and they are the people who fire the guns. If you have identified the problem there is no point in telling the staff officers because they are not going to be in there firing the gun. You have got to tell the troops and the troops are these junior doctors.

The nine to five week only covers 40 out of 168 hours, so you have got to target the people who are on the ground. Our hospital functions as a District General Hospital, there is no other acute admitting hospital and we showed in a prospective study that 80% of children attending as emergencies without trauma are initially seen by someone no more senior than house officer. Of course if they are *admitted* they are seen by someone more senior but the key first decisions are - are they admitted or discharged and were the investigations done in the first hour. This is largely going to be decided by these people.

Now there will be exceptions, but I think generally that's still true for the UK National Health Service that the gatekeeper is the senior house officer. So if you now take my analogy of the Somme, the senior house officers are the troops, the SpRs are the NCOs, the DGH consultants are the front line officers because they are often going to be in at night and the weekends. Once you've got through the net someone's already thinking of the diagnosis and they already

know a great deal so most of the people in this room are really fairly irrelevant to the dissemination process. If you look through the list of attendees the people we really don't have are the troops, we don't have any SHOs or registrars here saying "well that's a very fine idea but when I was on call last weekend we had a locum SHO, we had a registrar who started yesterday and we had great difficulty in getting blood out of this baby, we had four attempts."

Furthermore coming over the horizon are dependent and independent prescribing, and then there's NHS Direct. With our current problems with reaching doctors' hours requirements I think we have got to think in the longer term about rolling whatever educational package we come out with, to nurses and to pharmacists; particularly pharmacists in the light of the Reye-aspirin story.

You *could* use some tactics other than guidelines. However, the journals are read by ivory tower academics but no one else really; text books are out of date by the time they come; things from the Colleges go in the bin; mail separate from the Colleges' packages *may* be read, because it has a rather more impact than something that is imposed with a lot of other material.

In order for guidelines to work they have to be disseminated to everyone. There's the RCPCH membership of course but as a minimum you would also need to send your package to every clinical director of every A&E department in the United Kingdom and also, I suggest, to every Chief Executive of every Trust alerting them to clinical governance issues. Press campaigns can be helpful but they're not really under your control. Probably the reality is, you've got to use all of these.

What has become very clear over these two days of the Workshop is that there are some areas where there is very good evidence - which is what a systematic review will demonstrate. That is what I call the "concrete path", very secure, it shows that under these circumstances a randomised trial has shown we should do this. The trouble for the SHOs at night is that you walk along this concrete path and then you get to a river and there is no way you can get to the other side. This is the whole part of the management which has no evidence and for that you've got to have some consensus method to develop what I would call rope bridges, to allow you to get from the concrete path this side of the river to the other. Rope bridges aren't perfect, they're a bit shaky, you might fall off them, they might need to be rebuilt, but they're better than standing on this side saying I don't know how to get to the path on the other side of the river so I'll do nothing. So you do need some... what I call the "glue" to glue the systematic reviews together and that makes it a practical tool that can be used by practitioners

in casualty. If you only include grade one, grade A evidence you don't really have a usable guideline, so systematic reviews are just where we should *start* from.

In developing a guideline the panel's composition is key. You would really need to involve children's nurses who work in A&E, *not* their managers, *not* the Royal College of Nursing. The actual people who do day to day shifts in A&E – they're the people you need to talk to, the SHOs, the registrars. Also we must include parents and teenagers themselves possibly. To make it work, ownership is absolutely key. What we've got here is a kind of consensus conference where experts sit round a table and say "what we think is best". But we are rather removed from the reality and what you really want is to involve these people, use anonymity so they're not influenced by the wise old men, because they would be intimidated if they were here! It doesn't cost much to send out material by post so you can do it three or four times, get their views, change it, tinker with it, send it back again.

A Guideline would have to be rolled out nationally and the key thing about ownership is you say to the local people when you send it to Reading or Truro, this is what we have arrived at but by all means amend it locally to suit your particular problems. If your lab is twenty miles away or you have actually got an inborn errors doctor or you have a casualty consultant who sees everyone, you are going to have to change it, so it becomes yours, we just give you the template.

## DISCUSSION ON SPECIFIC POINTS

**Dr Boon.** I think a golden opportunity is to try and get guide lines incorporated when we have electronic patient records and electronic systems in all hospitals with integrated care pathways. If you could then just "slot in" the child with, say, coma or impaired consciousness, then hopefully the junior doctor will be led along the right pathway in a very simple way.

**Professor Stephenson.** I think that is true of the *longer* term. People still currently like to use a pen and a piece of paper, but I think if the technology could come and it was portable and not wired in and everyone carried one in their pocket, if it had this blue chip wireless communication, then yes I do think that is the way forward but I think that is a stage beyond us. I suspect you will have to influence the current cohort of junior doctors, who are still largely writing notes by hand in old fashioned medical records.

We are going to launch three guidelines this June (2002) nationally and they will go on an electronic web site, so you will be able to pull them down. But the next stage beyond that will be the kind of thing you are talking about which is much more interactive. In fact you will

only have one single record and as you use the guide line you actually fill in the medical details and you put the results in. I have seen that sort of work in New Zealand. They had consoles on every wall in the new A&E building. You did not have to go to a desk, you could just go to the wall and dial up a patient's details and anything you did you could type it in walking between walls. I think this is quite a long way off in the UK NHS!

### **7.1 b) What are the best methods of educating pathologists – both coroners' and hospital?**

**PROFESSOR JEM BERRY**

We have learnt a lot over these two days and various ways of getting educational messages across. I understand what Professor Stephenson was saying about only academics reading journals, but paediatric pathologists are, I think, reasonably academic and *do* read journals! We were wondering about something in our own professional journal entitled 'Whatever Happened to Reye's Syndrome' because I think as a group we are a bit vague about Reye's Syndrome and where it went and whatever happened to carnitine deficiency and all of these kind of things - just to bring people up to date. That's a general approach.

Possibly the most useful thing we could do is to develop a new practice guideline for investigating *all* unexpected death in infancy and childhood. It would have to be under the auspices of the Royal College of Pathologists to have any authority. If it included the *routine* metabolic investigation of all children who die unexpectedly without a clear cause that would cover a lot of the issues we have discussed.

The kind of thing that could be in the work sheet would be indications for doing a metabolic work up, not only unexplained death but encephalopathy, cardiomyopathy, myopathies etc.; what specimens to take - blood spots, fluids, tissue, frozen sections, and saving what's in the laboratory already, from before the child died. There would need to be very clear instructions on what to do with them, right down to addresses, eg which is the chemical pathologist in your region to send them to. I suspect there *are* people taking the right samples, they put them in their freezer and then they move on to the next case. They sit in the freezer and they are never properly investigated. In very small writing – what actually the common inborn errors are, that turn up as unexpected death. We do not need to understand them we just need to know what to do.

I think we need recommendations about terminology and this is particularly relevant to Reye's syndrome. Can a pathologist make a diagnosis of Reye's syndrome *ab initio* at post-

mortem without any previous investigations or history? We think not and we think it would be preferable to say “probable inborn error of metabolism” or maybe even “Reye-like” but they should avoid actually making a diagnosis of Reye’s syndrome in these circumstances. We need to explain to people what is classical Reye’s syndrome, what are the Reye like illnesses and so on.

Finally, we liked the idea of kits. I think we could also recommend in these practice guide lines what kit the apocryphal forensic pathologist we have been talking about, who is not interested in investigating these things, can use so he just puts samples in the relevant bottles and sends them to somebody.

So that would be a practice guide line. We could mailshot paediatric and forensic pathologists who actually cover perhaps two thirds or more of these cases, to bring them up to speed. We also thought that a question in the MRCPath examination, on Reye’s syndrome, would be a good idea. It would put the wind up everybody the first time it came, but, the candidates would know all about it for the next five years! So those are the kind of things we were thinking about.

We have been fairly hard on pathologists, I think rightly so, standards in post-mortem need to rise, but I should emphasise that people have come a very long way in ten years in raising standards, doing genetic tests, growing fibroblasts, doing their frozen sections and so on. So there are some excellent people out there trying to do their best as well.

## **DISCUSSION**

**Professor Hall.** I think the precise nature of what might be published in which journal, we need to think about, but it sounds a very good way especially if you think your colleagues really will pick it up and read it. That together with a mail shot, I imagine, would be of interest to Mr Denney.

**Professor Berry.** I think in contrast to paediatricians perhaps, that pathologists do read what comes with their journal because there is usually so little! If Mr Denney wanted something specifically on Reye’s syndrome and Reye-like syndromes, I think a sheet of A4 could be tucked in with the bulletin - we do put in things by other organisations. However, I do not think it would have the same effect on practice as having a proper, College endorsed, practice guideline for the investigation of all unexpected deaths in childhood.

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**7.1 c) How can this knowledge be widely and sustainedly disseminated? For example what are the merits of – national/local seminars? posters? journal articles? inclusion in specialist training curricula and higher examinations? websites ( College, Lay Support Group, dedicated)? NHS Direct? APLS course? interactive CDs? other methods?**

**7.3 What are the best methods to measure the impact of any educational initiative resulting from this Workshop? How could audit play a part?**

### **DR HARRY BAUMER**

\* I am going to start by addressing something that has already been touched on, that perhaps we have not really thought through methodically. What do children who attend a District General Hospital that does not have a specialised service on site, actually *need*? We have already covered most of these things –

- We need access to 24 hour emergency advice from specialists and that is something that obviously in this day and age should be deliverable.
- We have heard that we need a rapid method easily available for blood ammonia.
- We need access to specialist diagnostic facilities. We need to get children seen - this is not only about initial diagnosis but also about subsequent management. That is part of, I think, how people like me can hope to keep ourselves educated because we meet face to face with people who can put us right. It also creates opportunities for getting somebody who comes down to give us a talk about something. It's just not one person but the whole department, maybe the A&E department, who may need to have such a session.
- We need expertise in breaking bad news, not only for this but for many other things. During this Workshop I have discovered that we need benzoate and arginine!
- We have also said we need access to information for families.
- We also probably need a paediatrician in the DGH to take a lead role in this area.
- We need dietetic input.
- We need specialist nursing help.

So there's quite a long list of things that we need, for what will be collectively quite a small group of children.

*Coming on to evidence into practice: where are we?* We have had a meeting, we have talked

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\* See also, Dr Baumer's powerpoint presentation (Workshop Proceedings Part 9)

around a variety of different aspects of the subject. I believe we need to make sure that our next step is to identify what the evidence is, in the way described by Professor Stephenson. Let us imagine that he has come to us, he has got some money and he can create this evidence based guide line for us. I want you to write down what you think this should be about, what is its title, what's the scope of what we are going to ask him to do. I think we as a group should think about this. So spend one minute writing down what you think the title is and then we'll go round and see what people think.....

**Dr Hall.** I suggest "How to recognise children who may be developing encephalopathy caused by an inherited metabolic disorder or Reye's syndrome and what to do next."

**Dr Champion.** I was tempted to follow a similar line, but considering the discussions we had this morning, am aiming to broaden it slightly to "the child with non-traumatic coma or encephalopathy - investigation and management thereof", because that's the problem that you are faced with in casualty.

**Dr Glasgow.** "Approach to the child with non-traumatic reduction in consciousness or significant behavioural disturbance", something like that.

**Dr Boon.** "Management of non-traumatic childhood coma".

**Dr Tasker.** "The investigation of children in coma."

**Dr Masters.** "The identification and early management of metabolic disease."

**Professor Berry.** "A practice guide line for the investigation of children dying unexpectedly and without clear explanation."

**Dr Chakrapani.** Should we broaden it to include acutely ill children?

**Dr Baumer.** That is quite broad. It does encompass some of the areas that Professor Stephenson's group has already done some work on.

**Dr Walter.** "Initial investigation and management of infants and children with encephalopathy."

**Professor Hall.** The words "non-traumatic" and "encephalopathy" were in mine.

**Professor Stephenson.** Mine is the same as Dr Walter's except I've used the words "altered consciousness" instead of encephalopathy.

**Mrs Greene.** "Signs and symptoms to suspect metabolic disease and first steps to confirmation of diagnosis and management."

**Dr Hall.** Surely the *first* step is to learn to know how to recognise that the child is actually encephalopathic. In a sense, coma is "easy" - it's the sort of case that I presented right back at the beginning of the Workshop that presents the difficulty.

**Professor Hall.** That's why the word encephalopathy in this group captures what we are talking about. One of the tasks of turning this into an educational programme would be to think about the title. It should not be coma, I agree, because coma is just one end and it is not just altered consciousness, because it's also the altered behavioural phenomena which might be what presents itself rather than the consciousness. So I think we all know what we mean but it's the job of whoever wins the contract to decide on the precise wording! .

**Dr Baumer.** I think it was important just to do that one thing before thinking about how to disseminate the messages from such a guideline. We have already heard about the importance of thinking about who your target group will be. There is a long list and I think if we put together the two lists that Professor Stephenson and I have drawn up, one has to see *all* of those people, plus of course parents and families, as being key stake holders in the thinking behind the guideline to make sure there is a sense of ownership across the wide spectrum of groups.

An important point is that it has to be a multi-faceted approach. My slide (see Dr Baumer's Powerpoint presentation) outlines just some preliminary ideas to get people thinking about some better ideas. This is called "changing paediatric practice". As a paediatrician I do think we are an important group and clearly our change in practice will influence other groups as well. The first point is that the messages need to be clear and one of the problems about thinking about something as complex as what we have here is that there are lots of messages. We have to think what the *key* issues are and I do think there are some key messages that have emerged during the Workshop and I think that has been most useful.

If the Royal College of Paediatrics and Child Health is going to take an active part in this, we have to have an evidence based approach. I am confident that the Nottingham group are producing Guidelines in a way that the College is going to be able to endorse. That in turn means that we have a number of ways of potentially influencing our members. We send out a



summary of these guidelines with College Newsletters; we make them available and tell people where they are, on the College website; we are experimenting with spending some time in our Annual Meeting showcasing the guidelines that we are in the process of appraising, but look superficially to be well produced, and I hope that that is going to turn out to be another way of raising people's awareness.

I do think that one of the messages that we will want to get across is - that it's all very well to see that the College may have done something, or the Nottingham group may have done something, but you have to do something about your *own* locality, work out how it is that you are going complete a *local* guideline.

We've talked about journal articles - it is a useful way to point people who might not otherwise have been aware of it, to the *existence* of an evidence based guideline. But on its own it's not going to do the job.

We've mentioned a care pathway: it doesn't have to be electronic, it can be paper based such as a structured set of notes that mean you are reminded, for example, "blood ammonia now", or what ever the message may be. This also provides the means for auditing the management of children.

There have been examples, particularly selling the messages about retinopathy, where an educational road show by leaders in the field who had trained themselves in effective methods of getting messages across, went round to different localities and spread the message. Even if you are doing a local guideline and you bring somebody in from a neighbouring Trust to do it with you, it just changes the whole dynamics of it.

We've talked about incorporation into the exam and I do agree that that is the key way to get doctors in training to focus their minds on the issues.

We've also talked about incorporation into the APLS which I entirely agree with and it would be very nice for APLS to gradually incorporate evidence based material.

We've mentioned Continuing Professional Development - two points there: one is a method for self assessment and for self education and the second is go and learn about how to break bad news.

Audit has a bad name amongst the medical profession. It is a weak driver for change, but it is another way of encouraging people to change practice.

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## **7.2 How can parents and support groups participate? Should they be given information via the Parent held Record and/or the Birth to Five Book?**

### **MRS LESLEY GREENE AND MR GORDON DENNEY**

By being allowed to speak out as parent representatives, by distributing information, by giving presentations as parent voices to medical meetings, by emphasising the uniqueness of each child. There are no text book cases despite the common presenting symptoms. By giving evidence; by displaying the reality of living with a metabolic disease; by being involved in discussion groups; by involving the GPs at primary care level who could be the first to see the presenting symptoms and need to be made aware.

Should parents receive information via the parent held records, etc? In our survey for this meeting it was felt unanimously that early testing or screening would be the best solution and then the information should be given in these documents, in addition to that about the two disorders currently screened for. One parent was concerned that without screening being available, information in this manner might cause undue anxiety.

#### **Conclusions**

Early diagnosis is essential to maximise the health of the child and the family as well as preventing significant injury and possible death. While the process of neonatal screening could cause appropriate concern, the consequences of late diagnosis and subsequent damage or death have a higher ill health effect on the parents.

Parents wish to be told the diagnosis as soon as possible by a knowledgeable doctor, face to face with whom they have a good relationship and with whom they can refer again. A written summary helps their understanding and (although not mentioned by anyone in the survey) would probably help them to explain their child's condition to concerned relatives.

Resources would include leaflets, specifically written information for parents, websites for further information and voluntary organisations with e-mail and chat facilities, emerging protocols, contact with liaison nurse specialists, access to support groups with a helpline who can network them with other families as needed because it is these families who bring them out of isolation and provide practical solutions. They can give backup to other families in their perceived times of crisis (times that a medical professional might not see as being

critical but which are having significant impact for whatever reason on a family blighted by the illness and its consequences).

One hundred percent of our MCADD respondents felt immediate information regarding support groups should be given and it was felt that parents were important representatives and should be a voice at conferences and workshops providing practical evidence around MCADD and the reality of living with a diagnosis. The majority believe early information linked to neonatal screening should be included in the relevant documents mentioned.

The overall view was that knowledge is power because it will lead to swift diagnosis and appropriate management. Furthermore parents can help make that knowledge focused and relevant, bringing out the commonality of the symptoms suffered while emphasising the uniqueness of each child.

#### **POINTS HIGHLIGHTED IN ORAL PRESENTATION**

##### **Mrs Greene**

I just want to begin by saying that I know you would all agree that the initiative that Gordon has supported through the National Rye's Syndrome Foundation – the proceedings of today and yesterday - is to be applauded and, I am sure, will lead to great things.

What can parents do, how can they participate, and how can support groups participate? I would like to go back to the training and the education side, because our organisation - either as the Research Trust for Metabolic Diseases in Children or as CLIMB - has been working for 21 years, trying to raise the profile of the inborn errors. As some of you know, we hold an annual conference and one of our concerns has always been to have greater participation from the medical profession, both specialist and non-specialist, to increase their awareness of inborn errors. We do have accreditation for our conferences and we are about to embark on a new programme of education. From 2002 we are having two conferences - we are moving round the country because our stakeholders have said that travel is expensive.

We are also attaching to the second one this year (2002) a training day on the day before. I think that it is very important to emphasise shared issues. So within the training day that is held, hopefully with health visitors and social workers, we can talk around the isolation that is felt by any parent who has a child diagnosed with a chronic disease. It doesn't need to be rare. Also the anticipatory grief, the grief that you have at the time of diagnosis, and then if you know it's going to be a chronic, fatal disease, the anticipatory grief that you can feel for weeks or months or years and years, the knowledge you live under the shadow of knowing

your child will die before you. Also the shared issue of access to services - you're into a whole world of welfare rights and so on.

So there is a whole area that you can hopefully attract diverse groups to, because those are all shared problems. Then while you have a captive audience, you can provide, in a very colourful fashion of course, information on metabolic diseases! CLIMB has also had a tradition over the years of having parent voices at our meetings. Right from its beginning we have had a slot in which we place brave parents who stand up and talk for ten minutes about their experiences of caring for their child with a metabolic disease. When we have our evaluation sheets returned, both from the professionals and for many parents as well, they always say the parent voice is the most powerful and relevant section of the conference.

Because of that we are also further developing our training. As Founder of the organisation I have always wanted to have a training and educational arm of CLIMB. We are hoping to extend the training week that we have for befrienders, to parents who are willing to train to be effective parent voices. This would be in conferences and workshops and seminars giving them more confidence to do presentations and also training them in more assertiveness skills because the government is now asking that patients' voices, patients' groups, parent representatives should be on all these bodies. That is a very daunting prospect and what we are planning to do is train assertiveness skills so that parents can make a positive contribution. We are not here to "gripe and snipe" we want to make a positive contribution that will be helpful. Then parents and patients can be used as voices to give that extra dimension to the training and to policy issues - whatever they may be.

As far as information in the parent held record is concerned, or the Birth to Five book, the families who responded to our questionnaire did say yes. CLIMB is mentioned in the Birth to Five Book, but MCADD or the other inborn errors are not mentioned. I think we need to be careful that information remains relevant to families, and perhaps given in the context of information about screening. Certainly with the parent held record it would be good to name the relevant voluntary groups there as well.

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## **FINAL DISCUSSION**

**Professor Hall.** I attended one of your conferences a while ago and heard some parent stories and I think they are a tremendously good mechanism, both for changing people's attitudes and specifically on teaching points as well. They bring out sometimes some specific clinical

issues which are very useful. So in any teaching package we would be very keen to get parent voices.

**Professor Stephenson.** The reason I made those comments about text books, journals etc is that there is published evidence that guidelines can alter practice whereas it is very hard to show that text books, visiting lecturers, annotations in Archives or indeed almost any other tactic, alter practice.

**Professor Hall.** I am sure that's right - I think it alters the practice of the few who read these things and digest them but they are a minority and it's disseminating it across the country that is the difficulty.

**Dr Tasker.** Have you at Nottingham undertaken Cochrane type reviews for all of acute paediatrics?

**Professor Stephenson.** No, because Cochrane reviews only reveal randomised controlled trials. I was at a meeting at the Department of Health recently where lots of things were knocked on the head because the Cochrane review said there were no data. But in fact there are lots of other, less good, data that we shouldn't just dismiss. What we *have* done is to research the database for vomiting, seizures and breathing difficulties. We have not done a literature search for encephalopathy. It would be big and would not be confined to RCTs, because that would miss a great deal of important information. Cochrane reviews always conclude that we need more studies, but they're very much focused on high class randomised trials of which there are few in paediatrics.

**Dr Bonham.** The message is well taken about the non-specialist SHOs being the frontline troops who have initially got to assess the patient and take the right samples, but there are also second line troops in the laboratories that we ought not to forget because very often the laboratories will sort out what needs to be done, almost irrespective of what is requested. Laboratories in the UK are good at that, provided we are given some fairly basic information and also given some samples that can be re-routed for further investigation. So we need to target any educational package at that group as well.

I am just a bit concerned about losing the terminology of "Reye's syndrome". I think it's almost a double edged sword: I think it's bad if it becomes a classification that ends up being a dead end with relatively little meaning; on the other hand as a kind of grouping term for a constellation of things that might take us down a pathway of investigation then it can be helpful. We do about 1500-2000 organic acids a year at Sheffield, but a very small proportion

would come from the cohort of encephalopathic patients that we are talking about. Some of them would be failure to thrive, some would be developmental delay.

So we need to have in whatever educational literature there is, something that allows first of all the troops on the ground in A & E to send us a basic minimum sample set and supply us with basic minimum information so that even if they forget to request specific things then nevertheless we can act appropriately in the laboratory and either save samples or re-route them or do additional investigations. But we do need that basic information. Then of course the DGH laboratories need to know, given these particular stimuli recorded on the request form, that they need to perhaps re-route or save those samples. So somehow we've got to include that information and target it properly.

**Dr Masters.** I agree totally with that. I was going to make exactly the same point - that laboratories can be often be very proactive in sorting out things, and it's important to include them as a stakeholder in whatever protocol you come up with.

**Dr Hall.** Where are we with regard to local availability of blood ammonia measurement? It's all very well getting the troops educated and getting them taking specimens but if they can't actually get ammonias done, then they are going to get discouraged!

**Professor Hall.** Yes, from the discussion about ammonia it is clear that its availability does seem to differ in different part of the country. One of the points I've noted is why there is so little demand from the adult medical sector, and as we've got no adult physicians here we haven't got an answer to that question. But it is something I think we need to check out because knowing an answer to that question would certainly be important in knowing what action is needed to make sure it's provided. If it's only going to be provided for paediatrics and the adult physicians say they are not interested, it's going to be that much more difficult. I think there's going to be a bit of work to do on that and it's on my action list.

**Dr Glasgow.** I think what we've had put to us from this afternoon's presenters makes a lot of sense. The question I want us to reflect on is this - are there measures such as upgrading the level at which DGHs do ammonia, upgrading the level at which casualty officers function, upgrading the level of the relationship between DGHs and the central PICU that at this stage we should be going away and setting in train in our own regions? Should we not be going away and trying to identify - what are the things in *my* region that really need attention *now*? Do we not need a two track approach, one for the regional level and one for the national level?

**Professor Hall.** I am sure the answer is - yes we do, and it's a very different set of initiatives that's required for unravelling the minutiae of the metabolic disease in the individual patient.

**I would like now to pull together action points that I have listed.**

Then I would like some feedback from the group because there will be several other things that you will have as priorities. Then from that we will have at least an idea of what we might focus on first, because so many things have come up in this discussion.

The first comment I would like to make, is on Dr Baumer's list of the people to be targeted. I think there has to be some sense of the order and the payback for these things, because there is potentially a significant payback from this investment - in paediatricians, in A & E doctors and in A & E nurses. It seems to me that these are probably the three professional groups where the payback from investment in whatever sort of education we want, is going to be most relevant as far as clinical care is concerned.

And then there are the pathologists and coroners who are also two important target groups. I would not want to underestimate the importance of all the other groups that Dr Baumer listed, but we can't do everything at once and I think we should start by focusing on those groups. I am assuming that parents are absolutely central to a lot of the discussion we are having, but I am not sure that we need to target parents in quite the same way. We need to work *with* parents to decide what the messages are and how to get them across.

**Dr Bonham.** Are you bracketing clinical biochemists and chemical pathologists in with histopathologists in that context? Because let's say that every child is going to have a true laboratory glucose measured if they are possibly hypoglycaemic, then that means in the hands of every chemical pathologist or consultant clinical biochemist there would be a potential diagnostic sample on which to subsequently perform perhaps an acyl carnitine analysis or free fatty acids or 3 hydroxybutyrate. They are either going to keep that sample for a week and then discard it, or they are going to send it off - depending on the information that is supplied to them and also on what advice *we* give to them about further analysis. So they need to be told, in a succinct way, about what to do with that sample.

**Professor Hall.** I agree, I will add clinical chemists to this list.

Moving on, although not in any rational order, *there are two very specific fast track methods of influencing practice among paediatricians and A & E physicians.*

**First**, we need to get this into the exams. I know that's already begun, so the metabolic diseases group hopefully will be feeding good questions to the RCPCH exams board. We

need to maintain the pressure, aiming to make sure that the candidates never know what is going to come up so they've got to study everything! You only need to insert a few questions now and then to keep them on their toes. If this happens in MRCPPath as well that would be very good and, following Dr Bonham's line, I imagine there are separate exams for the chemical pathologists into which it can be incorporated.

**Second**, the Advanced Paediatric Life Support is an action point for conveying to Dr Barbara Phillips once we're clear exactly what it is we want to see in there. One of the points that we might come back to is this question of the ammonia because as Professor Stephenson was indicating, if we put ammonia in the list of "must do's" in the first hour, the laboratories may not thank us, so we need more thought as to how we handle that.

Going on to *pathology* - it seems as if a guideline, an article, an annotation, a handout, an insert via the College journal or whatever you think is the most appropriate mechanism and then a slightly longer term exercise, a more evidenced based approach to today's best buy practice, would reach the relevant pathologists. Regarding the *coroners* I think we have to pick up the points and use the opportunities that are available at the moment to influence them. I know lots of groups will be pressing the coroners to modernise their attitude to this.

Then going on to what Mrs Greene and Mr Denney have said about the question of news breaking; information for parents; *what parents want and expect when they have a major life event like a diagnosis of this kind* : that I think is totally accepted and is the same message from virtually all parent groups. But it's been the same message for thirty years and it seems very slow to penetrate, so I think *that is another thing we might put in the exam from time to time*. We might even put it in as a clinical task as a role play exercise: "tell this parent that their child has got citrullinaemia" for example.

I was particularly interested in Mrs Greene's last round of comments. You may have seen the Chief Medical Officer's (CMO) document called *Expert Patients*. It's about involving people who've got a long term condition, in which they themselves are the expert, and "allowing" them to be the expert in how to manage their own disease. It's also about how you can take that further and use that expertise for other people, both in teaching and supporting other patients. I wrote to the CMO and said that I had been doing this in paediatrics for a long time with the voluntary sector, but it would be helpful if Mrs Greene could also write to tell the CMO of CLIMB's example of good practice regarding what you are now doing with your expert parents. It seems to me that, in whatever teaching package we come up with, the role of the expert parent is something we really should investigate I think a thirty second clip of a parent just telling their story is enormously powerful, even for the most disinterested SHO!



There is also the CLIMB magazine which has twenty years' worth of wonderful stories in it, which really ought to be captured and used for trainees.

*Regarding guidelines* – it seems to me that we were working towards a proposal for going through a proper literature review process with the focus on encephalopathy\*, defined as this group understands it, for shorthand. Where a literature review would be helpful would be to focus it around that first hour, where you are looking at the presenting symptoms and signs, rather than focusing it specifically on IMDs, which is perhaps a totally different exercise.

**Dr Baumer.** I think from the earlier discussion I wouldn't restrict it to the first hour but would say it's the emergency management, which is a little longer than that.

**Dr Glasgow.** Yes I absolutely agree - I was a bit uneasy about the short time.

**Professor Hall.** The main point is - it's the "front door", it's how the child comes *into* those algorithms. It's the first two or three blocks of the algorithm that we are focusing on.

**Dr Tasker.** That is why I prefer the word coma as opposed to encephalopathy. How are children actually going to come into the health care system if the neurological features consist of just behavioural disturbance? They are probably not going to come in via A & E, they might be seen by their GP then they might go to the ward.

The processes involved in this sort of clerking and managing of the child that comes to the ward with a behavioural disorder, might induce a very different approach which we have not tackled at all.

**Professor Hall.** Yes but it's the acute bizarre behaviour or the sudden strange unexplained behavioural change isn't it. I am not sure that we can or should try and resolve this today, but what I meant was that if we were going to focus on *something*, it will be about the presenting complaints that the child comes with, rather than focus specifically on inherited metabolic disorders. Because if this is going to have any credibility to the trainees they've got to feel they are working through real life problems and clearly although one of the conditions that they might find is an IMD, there are several others they might find as well. This really won't have any impact on practice unless they can think in terms of what they actually see.

There were a few specific questions where either the literature or a Delphi consensus or other

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\* Professor Stephenson and his team subsequently successfully applied to the National Reye's Syndrome Foundation for a grant to develop a formal guideline on the diagnosis and management of acute childhood encephalopathy including Reye's syndrome and Reye-like IMDs. The project began in November 2003 (Ed.).

methods might give us information. *There was an unresolved question about what is really best practice for measuring blood glucose in the emergency situation*, because it does sound as though there is variation in practice. Is there enough evidence that the current situation is unsatisfactory to do more work on that and if so what ought to be done and how would we go about it? I expect there is a literature on that which might be fairly circumscribed which might be looked at and there will be people who can advise us perhaps from a very detailed knowledge.

*I think there is a similar question about ammonia* and there is also a much narrower bit of guideline work to be done on the issue as to exactly how the doctor on duty should take that sample. It does sound as though nothing much has changed in the thirty years that I've been in medicine and there are still concerns about the quality of the specimen and how it is transported to the laboratory. There is also the question as to whether a less than perfect specimen should be analysed or a repeat sample taken. There are some very practical questions there that it would be helpful to focus on.

We have discussed the fascinating thought that next time we have an epidemic of classic Reye's syndrome it might be treated in a different way. I don't know what to do with that but certainly one day it might suddenly become very important.

*Regarding the shelf life of the specific drugs for acute management of these IMDs - it would help to know what the policy is there.* How often would the pharmacy have to replace it, that struck me as a very answerable short question.

Then lastly there was this question of *service development*. Dr Glasgow's point that what we ought to be doing is to develop a network of linkages, is vitally important. Also, since there is a gross shortage of new potential consultant specialists in metabolic medicine, and even if there wasn't, we should now certainly be looking to develop the expert specialist nurse role. We should be making that part of the care provision which parents ought to expect and call on and I would like to see that become one of the standards that we push for.

**Mr Denney.** Are all these jobs going to be allocated?

**Professor Hall.** Yes I think they are, I would certainly hope things will happen, although none of these things will come free of charge I am afraid, because they all cost people's time and in most cases these days time translates into money, even if it's to find someone as an assistant to do some of the leg work. But some of them are issues of principle which will cost very little money, while others clearly need a significant investment.

Finally I should remind you that Dr Hall has the unenviable job of pulling all this together and doing some sort of editorial tidying up of all the wealth of material we have got and that will then be passed back to you. You can then make sure you have not been misquoted, misheard, mistyped or misunderstood. There can then be an accuracy check and a chance to update anything. Clearly a lot of the work that has been presented has involved people doing some literature reviewing, or in acquiring data by asking colleagues, doing surveys etc., that they might not have done otherwise. We just want to be sure that you are happy for it to be published in whatever form we eventually decide on - whether it is on a web site or hard copy or an annotation or whatever. If there are data that you want to publish separately, let Dr Hall know so that we do not embarrass your subsequent chance of publication. I would have thought, however, that most of the work that people have done is exactly the sort of information that should be published in a symposium proceedings.

**Dr Baumer.** I just wanted to thank Dr Hall for arranging the meeting.

**Professor Hall.** That's a very good moment to wrap up and let me also thank Dr Hall, I think the meeting has been very useful indeed. Can I also thank Dr Baumer and Dr Champion who also worked hard on it and the vital people in the voluntary sector, Mrs Greene and CLIMB and Mr Denney and the National Reye's Syndrome Foundation.

**END OF MEETING**

## WORKSHOP PROCEEDINGS PART 8: GLOSSARY OF TERMS

<b>ALP</b>	Alkaline phosphatase
<b>ALT</b>	Alanine transaminase
<b>APLS</b>	Advanced Paediatric Life Support
<b>ARDS</b>	Adult Respiratory Distress Syndrome
<b>ASA</b>	Argininosuccinic aciduria
<b>AST</b>	Aspartate transaminase
<b>AVPU</b>	Alert, Voice, Pain, Unresponsive
<b>BIMDG</b>	British Inherited Metabolic Disease Group
<b>BPSU</b>	British Paediatric Surveillance Unit
<b>BRSSS</b>	British Reye's Syndrome Surveillance Scheme
<b>CACT</b>	Carnitine acyl-carnitine translocase (deficiency)
<b>CAT</b>	« « «
<b>CATR</b>	« « «
<b>CBF</b>	Cerebral blood flow
<b>CDC</b>	Centers for Disease Control
<b>CESDI</b>	Confidential Enquiry into Stillbirths and Deaths in Infancy
<b>CK</b>	Creatine kinase
<b>CLIMB</b>	Children Living with Inherited Metabolic Diseases
<b>CNS</b>	Central nervous system
<b>CPS</b>	Carbamoylphosphate synthetase 1 (deficiency)
<b>CPT I &amp; II</b>	Carnitine palmitoyl transferase (deficiency) (Types 1&2)
<b>CSF</b>	Cerebrospinal fluid
<b>CT</b>	Computerised tomography
<b>CVVH</b>	Continuous veno-venous haemofiltration
<b>DGH</b>	District General Hospital
<b>DKA</b>	Diabetic ketoacidosis
<b>DOH</b>	Department of Health
<b>EDTA</b>	Ethylenediamine tetraacetic acid
<b>EEG</b>	Electroencephalography
<b>EFCNS</b>	European Federation of Child Neurology Societies
<b>EM</b>	Electron microscopy

<b>F1,6 BP</b>	Fructose -1,6 bisphosphatase (deficiency)
<b>FLP</b>	Fatty liver of pregnancy
<b>GA I &amp; II</b>	Glutaric aciduria types 1&2
<b>GABA</b>	Gamma amino butyric acid
<b>GCS</b>	Glasgow coma scale
<b>GGT</b>	Gamma glutamyl transferase
<b>GOS</b>	Great Ormond Street (Childrens Hospital)
<b>GSD</b>	Glycogen storage disease
<b>H&amp;E</b>	Haematoxylin and eosin
<b>HD</b>	High dependency
<b>HELLP</b>	Haemolysis, elevated liver enzymes, low platelet count (in pregnancy)
<b>HFI</b>	Hereditary fructose intolerance
<b>HHH</b>	Hyperammonaemia, hyperornithinaemia, homocitrullinuria
<b>HIMP</b>	Health Improvement Programme
<b>HMG CoA lyase</b>	Hydroxymethyl glutaryl-CoA lyase (deficiency)
<b>HSP60</b>	Heat shock protein 60
<b>HTA</b>	Health Technology Assessment
<b>IBEM</b>	Inborn errors of metabolism
<b>IC</b>	Intracranial
<b>ICP</b>	Intracranial pressure
<b>IMD</b>	Inherited metabolic disorder
<b>IMV</b>	Intermittent mechanical ventilation
<b>INR</b>	International normalised ratio
<b>IPPV</b>	Intermittent positive pressure ventilation
<b>ITU</b>	Intensive therapy unit
<b>IV</b>	Intravenous
<b>IVA</b>	Isovaleric acidaemia
<b>LCHAD</b>	Long chain 3-hydroxy acyl CoA dehydrogenase (deficiency)
<b>LP</b>	Lumbar puncture
<b>LPI</b>	Lysinuric protein intolerance
<b>MCAD (D)</b>	Medium chain acyl CoA dehydrogenase (deficiency)
<b>MELAS</b>	Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke
<b>MMA</b>	Methyl malonic acidaemia

<b>MRI</b>	Magnetic resonance imaging
<b>MSUD</b>	Maple syrup urine disease
<b>NKH</b>	Non-ketotic hyperglycinaemia
<b>NRSF UK</b>	National Reye's Syndrome Foundation of the UK
<b>NSC</b>	National Screening Committee
<b>NSF</b>	National Service Framework
<b>OA</b>	Organic acidaemia
<b>OTC</b>	Ornithine transcarbamylase (deficiency)
<b>P5CSdef<sup>n</sup></b>	Pyrroline-5-carboxylate synthase deficiency
<b>PA</b>	Propionic acidaemia
<b>PCR</b>	Polymerase chain reaction
<b>PCT</b>	Primary Care Trust
<b>PDH</b>	Pyruvate dehydrogenase (deficiency)
<b>PICU</b>	Paediatric intensive care unit
<b>PKU</b>	Phenylketonuria
<b>PM</b>	Post Mortem
<b>PT</b>	Prothrombin time
<b>RCGP</b>	Royal College of General Practitioners
<b>RCP</b>	Royal College of Physicians
<b>RCPCH</b>	Royal College of Paediatrics and Child Health
<b>RCT</b>	Randomised controlled trial
<b>R-L</b>	Reye-like
<b>RLS</b>	Reye-like syndrome
<b>RS</b>	Reye's syndrome
<b>RSM</b>	Royal Society of Medicine
<b>RTA type1</b>	Renal tubular acidosis type 1
<b>SHO</b>	Senior House Officer
<b>SIDS</b>	Sudden infant death syndrome
<b>SUD (I)</b>	Sudden unexpected death (in infancy)
<b>TMS</b>	Tandem mass spectrometry
<b>TPN</b>	Total parenteral nutrition
<b>U&amp;E</b>	Urea and electrolytes
<b>UCD</b>	Urea cycle disorder

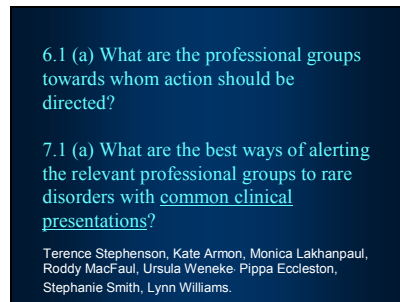
<b>URTI</b>	Upper respiratory tract infection
<b>UTI</b>	Urinary tract infection
<b>VCZ</b>	Varicella zoster
<b>VLCAD</b>	Very long chain acyl-CoA dehydrogenase (deficiency)
<b>WBC</b>	White blood cell count
<b>ZETOC</b>	Z39.50-compliant access to the British Library's Electronic Table of Contents

## WORKSHOP PROCEEDINGS PART 9

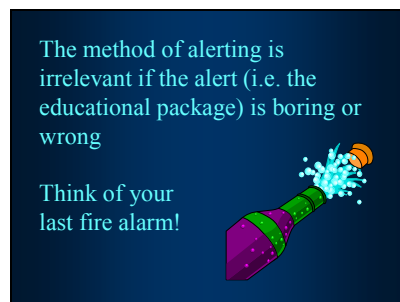
### Powerpoint presentation by Professor Stephenson and Dr Lakhanpaul (14 slides)

1. There is very little in the UK literature describing paediatric attendance patterns to A&E departments. We wanted these data primarily to determine the commonest presenting problems so that we could develop guidelines to manage them. Such Data are very useful for planning staffing levels, developing training, auditing change.
2. We wanted to produce presenting problem based guidelines such that the junior clinician when faced with a particular problem is guided in the initial diagnosis and then guided through management. We recognised that the literature was likely to be of poor quality and sparse. We therefore used a Delphi development technique to determine consensus. - described further later.
3. Having produced a comprehensive guideline we wanted to implement it in the A&E department in a way that encouraged its use. Saw Care pathways as a way to encourage this

Slide 1



Slide 2





### Slide 3

The guns jam in the trenches -  
who to consult?

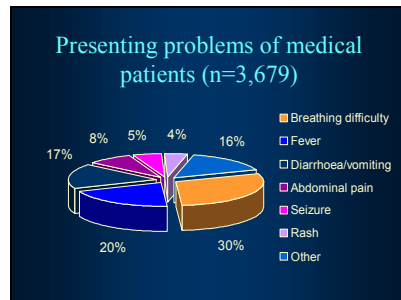
- \* The troops - the problem
- \* The NCO's - the experience
- \* Front line officers - overview
- \* Staff officers - too remote
- \* The manufacturers
- \* The history books

### Slide 4

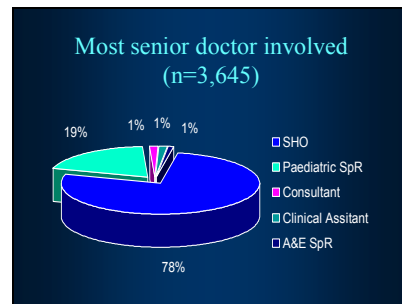
The guns jam in the trenches -  
who to target?

- \* The troops
- \* The troops
- \* The troops
- \* The troops
- \* The troops
- \* The troops

### Slide 5



## Slide 6



## Slide 7

Who are the relevant professional groups? In order of target importance:

- \* SHO's.
- \* SpR's.
- \* DGH Consultants.
- \* General Teaching Hospital Consultants.
- \* Intensivists (incl. Paed anaesthetists)
- \* Other specialists. Other specialities?
- \* Pathologists.
- \* Not IMD specialists!

## Slide 8

Who are the relevant professional groups?

- \* Nurses
- \* Pharmacists
- \* GP's

Non-professionals

- \* Teenagers (who self prescribe aspirin)
- \* Parents

## Slide 9

### Alerting the relevant professional groups

- \* Journal - **small senior readership**
- \* Textbooks - **no impact**
- \* RCPCH enclosure - **bin**
  - separate mailshot
- \* Guideline - **disseminate to every Dr.**
- \* Press campaign - **capricious**
- \* All of the above

## Slide 10

### Aim

- \* To develop evidence based guidelines for the child with acute medical problems - 'the concrete path'
- \* Where evidence is lacking to use a Delphi consensus development technique to determine intervening management - 'the rope bridges'

## Slide 11

### Method

- \* Systematic review of literature
- \* Grading of literature
- \* Development of statements
- \* Involvement of Delphi panel to identify consensus, especially where lack of evidence

Slide 12

### Delphi consensus method

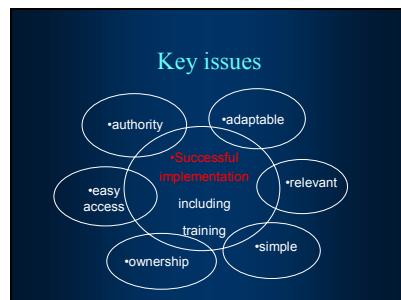
- \* Panellists' composition is key
- \* Larger numbers
- \* Anonymous
- \* Several rounds of iteration
- \* Relatively cheap

Slide 13

### Strategy

- \* Problem based guideline - evidence & consensus
- \* For doctors - guidelines help the decision making process
- \* For parents - info leaflets
- \* For child services - awareness

Slide 14



## WORKSHOP PROCEEDINGS PART 9

### Powerpoint Presentation by Dr Baumer ( 4 slides)

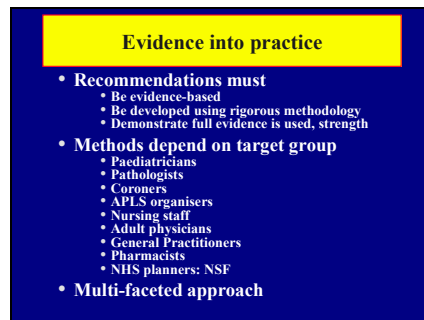
Slide 1



What do DGH's need?

- Access to 24hr emergency advice
- Rapid, easily available blood ammonias
- Access to specialist diagnostic laboratories
- Combined clinics
- Education & championing from specialists
- Paediatric expertise in "breaking bad news"
- Lead paediatrician
- Dietetic input
- Access to specialist nursing service

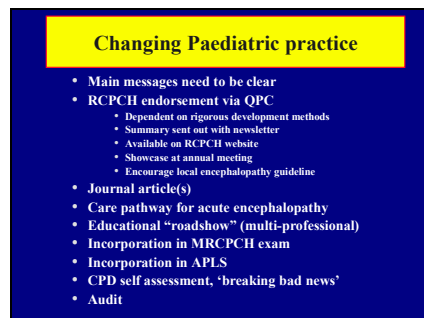
Slide 2



Evidence into practice

- Recommendations must
  - Be evidence-based
  - Be developed using rigorous methodology
  - Demonstrate full evidence is used, strength
- Methods depend on target group
  - Paediatricians
  - Pathologists
  - Coroners
  - APLS organisers
  - Nursing staff
  - Adult physicians
  - General Practitioners
  - Pharmacists
  - NHS planners: NSF
- Multi-faceted approach

Slide 3



Changing Paediatric practice

- Main messages need to be clear
- RCPCH endorsement via QPC
  - Dependent on rigorous development methods
  - Summary sent out with newsletter
  - Available on RCPCH website
  - Showcase at annual meeting
  - Encourage local encephalopathy guideline
- Journal article(s)
- Care pathway for acute encephalopathy
- Educational "roadshow" (multi-professional)
- Incorporation in MRCPC exam
- Incorporation in APLS
- CPD self assessment, 'breaking bad news'
- Audit

## Slide 4

### Measuring the impact

- MRCPCCH exam questions
  - How they are answered
- CPD responses
- Audit returns from paediatricians
  - Reporting all acute encephalopathies
  - What Ix's performed acutely
- Adverse event reviews
  - Involving IMD specialists
- Audit by Coroners of their PM's?
  - Investigations performed
- Surveys of parents
  - Experiences of being told diagnosis
- Guideline existence at accreditation visits?