WORKSHOP ON REYE'S SYNDROME AND REYE-LIKE INHERITED METABOLIC DISORDERS:

EXECUTIVE SUMMARY

PART A:
SUMMARY OF PAPERS AND DISCUSSION (PAGES 1-14)

PART B:
SUMMARY OF RECOMMENDATIONS AND ACTION POINTS SUGGESTED BY SPEAKERS AND DISCUSSANTS (PAGES 15 -17)

PLEASE NOTE THAT THIS SUMMARY DOCUMENT HAS BEEN POSTED SOME 3 YEARS AFTER THE WORKSHOP WAS HELD AND THAT SOME OF THE RECOMMENDATIONS HAVE BEEN ADDRESSED (ALTHOUGH NOT NECESSARILY ACTIONED) IN THE INTERIM – RELEVANT REFERENCES ARE INCLUDED IN THE TEXT AND/OR PART B. MOREOVER OTHERS ARE CURRENTLY BEING ADDRESSED IN COLLABORATION WITH PARTICIPANTS AND WITH OTHER RELEVANT BODIES.

COMMENTS ARE WELCOME - PLEASE SEND TO DR HALL: s.hall@sheffield.ac.uk

(FOR EXPLANATION OF ABBREVIATIONS SEE GLOSSARY OF TERMS – MAIN DOCUMENT PART 8)

S.Hall March 2005

SUMMARY PART A

INTRODUCTION AND BACKGROUND (MAIN DOCUMENT INTRODUCTORY SECTION, pages 1-15)

This Workshop was held in Doncaster, England, in March 2002. It was fully funded by the National Reye's Syndrome Foundation of the UK. There were 28 participants ***(Pages 1-2)*** from a range of paediatric disciplines: metabolic medicine; intensive care; accident and emergency medicine; neurology; hepatology; general paediatrics; clinical chemistry; pathology. There were nurse specialists in metabolic medicine, an epidemiologist, a guideline methodologist and representatives of parent organisations.

Purpose of the Workshop (pages 3-6)
The Workshop had been convened because of concerns about the diagnosis and management of classic Reye's syndrome and the inherited metabolic disorders which can mimic it, generated by the findings of the British Reye's Syndrome Surveillance Scheme.
The hypotheses to be addressed were:
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 inherited metabolic disorders (IMDs) and of classic Reye's syndrome (RS) itself.
Second, that there is imprecise diagnosis of these cases at autopsy, which may result in avoidable morbidity and mortality in subsequent children.
Third, that the morbidity and mortality associated with RS and Reye –like IMDs can be reduced by optimising their early diagnosis and management.

The **purposes** of the Workshop were: 1) to examine the evidence which might or might not support these hypotheses, including "best practice" methods of diagnosis and treatment; and 2) to review methods of resolving problems and actually changing practice. The overall aim was to produce practical proposals to put existing knowledge and evidence into practice.

Methods (pages 6-7): The Workshop was an expert, multi-disciplinary, 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.
A framework of detailed questions ***(pages 8 -15)*** which broke down the basic tenets of the working hypotheses into a series of small steps was devised by a small Steering Group. 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.
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. The Workshop programme reflected the questions framework and the importance of time for discussion.

PART ONE ***pages 1-75*****: (WORKSHOP QUESTIONS 1.1 TO 1.3.2.)**

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

Professor Stuart Tanner reviewed the clinical and pathological case definitions of classic RS and the evidence that it is a specific entity and not another as yet unidentified IMD *(Pages 1-10).* He concluded that the definitions are unsatisfactory because they are non-specific: temporary mitochondrial dysfunction may be part of the hepatic disturbance in many childhood viraemic illnesses and they also describe the manifestations of the RS-like IMDs. However, it is hard to think of better ones.

Classic RS is probably a distinct entity because of its clinical homogeneity, its clustering in association with outbreaks of flu and chickenpox and its disappearance after the warnings on aspirin. It is unlikely to be an IMD because comprehensive investigation of survivors has not revealed any such disorders; there are epidemiological differences (in particular RS presents at an older age) and survivors do not have repeat episodes.

Dr Michael Champion reviewed the IMDs known to be capable (however rarely) of presenting as a RS-like illness and the evidence that they are underdiagnosed or diagnosed too late *(Pages 10-17)*. He identified a total 29 disorders of which the commonest are fat oxidation defects, organic acidaemias and urea cycle defects. He presented published evidence on MCAD and OTC deficiency to support his conclusion that there is substantial under-diagnosis and delayed diagnosis of these disorders.

Dr Sue Hall reviewed the evidence from the UK and overseas literature that these IMDs may be misdiagnosed as RS and that classic RS is underdiagnosed *(Pages 18-27*).There is substantial published evidence that misclassification of IMDs as RS can occur resulting in missed opportunities for appropriate management, genetic counselling and prenatal diagnosis. Young age (under 5 years) was the most important predictor of a RS-like illness being caused by an IMD. By contrast there was little published on underdiagnosis of classic RS, although the potential was there particularly for Grade 1 illness. However underdiagnosis, especially of cases in teenagers over 16 years and adults, is likely in the event of any future 'flu pandemic because paediatricians in training are now not clinically exposed to the condition and adult physicians may not be aware of it.

Professor Jem Berry reviewed the evidence that both IMDs and classic RS are underdiagnosed at autopsy in cases of sudden unexpected death and that IMDs may be misclassified as RS in this setting *(Pages 27 -34).* The literature was sparse but he concluded that IMDs are both being missed and RS overdiagnosed and that this is a problem caused both by the non-specificity of the diagnostic criteria and failure to take the appropriate samples at the optimum time.

Professor James Leonard summarised the literature on "the size of the problem" of the RS-like IMDs –their birth prevalence, the proportions that die in the neonatal period or present later as a RS-like illness or SUD *(Pages 34-40).* He emphasised that the published data are both poor and sparse and mostly guesswork with the exceptions of MCADD and OTC deficiency.

Dr Anupam Chakrapani presented data on mortality and morbidity rates and the nature of the morbidity for each IMD if it is untreated or treated late *(Pages 40-46).* Again the data were sparse and mainly on MCADD (20% mortality, & 70% morbidity) with much higher rates in the others. Morbidity centred mainly on brain injury and severe cardiac problems.

Dr Chakrapani, Mrs Greene (representing the support group Climb) and Mr Denney (National Reye's Syndrome Foundation of the UK) presented the evidence for parental psychological and other morbidity caused by delayed diagnosis of an IMD or RS *(Pages 46-51).* No literature specific to these disorders was found but that on the impact of SIDS indicated that severe prolonged grief reactions are associated with the unknown cause of death and the unexpected occurrence.
This was also the anecdotal experience of the parent organisations, especially for classic RS where the precise cause of the illness is not well understood. Climb had surveyed its (then) 65 MCADD families in just under half of whom the diagnosis was delayed. A range of stress symptoms requiring medication and/or counselling was reported.

Dr Chakrapani also reviewed the evidence that that the morbidity and mortality caused by the RS-like IMDs can be avoided by prompt diagnosis and treatment *(Pages 52-55).* The literature was sparse except for MCADD where there was evidence that early diagnosis improved outcome. The severe forms of some conditions like urea cycle defects and organic acidaemias have a poor outcome regardless of early treatment.

Dr Anne Green addressed the issue of whether there would still be a clinical problem with the RS-like IMDs if comprehensive neonatal TMS screening is introduced nationally *(Pages 56-65).* She assessed the probability of each disorder being detected and demonstrated that the FAODs and carnitine disorders would be detected but not, at present (March 2002), all of the UCDs. For many conditions the position was uncertain. Conclusion: the answer is "yes".

Dr Sue Hall presented data from the BRSSS on trends in the occurrence of classic RS in the British Isles to 2001 *(Pages 65-69).* Numbers had declined dramatically since the 1986 aspirin warning with fewer than 5 reported in the last 5 years of surveillance. However, numbers could increase again in the setting of a 'flu pandemic or epidemic. It is important not to dismiss RS as "eradicated" because the experience with diseases like TB or diphtheria, where delayed diagnosis associated with low clinical awareness has occurred, may be repeated. In the USA long term aspirin therapy is an indication for annual flu vaccination in children. One discussant reported doing this with her patients even though it is not officially recommended in the UK.

Dr John Glasgow reviewed data on the morbidity and mortality of classic RS if it is untreated or treated late *(Pages 69-74)*.Mortality rates from national surveillance data were 50-60% in the British Isles and 30% in the USA, but only 18% in his Belfast series. Residual CNS morbidity was about 10% (3%severe). Little is published on long term minor sequelae but cognitive disorders appear to occur. Early diagnosis improves outcome but less so in patients already in coma at presentation.

In summing up this session the moderator concluded that it had been convincingly demonstrated that there is potentially a substantial clinical problem caused by classic RS and the RS-like IMDs possibly preventable by early diagnosis and treatment although the literature on most of the IMDs is sparse.

PART TWO pages 1-60 **(WORKSHOP QUESTIONS 2.1- 2.3)**

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?

CLINICAL DIAGNOSIS: POINTERS IN THE HISTORY: this section deals with infants and children who present during life and addresses the problem of detecting the Reye/IMD "needle" in the "haystack" of ill infants and children attending Accident and Emergency.

Dr John Walter reviewed data on useful diagnostic pointers for IMDs from the history and presentation, such as age, family and past medical history, seasonality, peri-admission features *(Pages 1-7)*. Most RS-like IMDs present in the newborn period, especially the severe end of the spectrum. However, milder variants can present in later childhood and even adulthood and the commonest, MCADD, has a median age of 18 months at first presentation. There is no clear seasonality other than that of the viral illnesses which can lead to decompensation. A history of developmental delay or previous episodes is suggestive but family history may be unhelpful though it must be taken very carefully. Hypoketotic hypoglycaemia and encephalopathy are common peri-admission features. The difficulty of recognising encephalopathy in the apparently conscious child was highlighted in discussion.

Professor Tanner reviewed similar data on classic RS *(Pages 7-10)*. The median age at presentation is 8-9 years in the USA and just under 4 years in UK. There is marked seasonality in association with 'flu epidemics and history of a flu-like or varicella prodrome is an important pointer as is aspirin exposure, although absence of this should not rule it out. A family or past history of similar illness makes an IMD more likely, but doesn't rule RS out in the presence of the other features. The characteristic effortlessness of the vomiting was highlighted in discussion.

Dr Fenella Kirkham presented a paper on recognition of encephalopathy *(Pages 10-31)*. As encephalopathy describes a change in the patient's interaction with his environment –evident by alteration in consciousness/abnormal behaviour, she reviewed the pros and cons of the various scales and scores which have been devised to detect, measure and monitor this. The presentation and subsequent discussion highlighted some important issues eg: encephalopathic children may not, at presentation, have obvious "eyes closed" reduction in conscious level *which has implications for clinical training*; vomiting without diarrhoea is potentially an indication of raised ICP and should always be taken seriously; how to distinguish encephalopathy from simple sleep/drowsiness or the post-ictal state; the importance of monitoring "state variation"; best methods of training; when and when not to lumbar puncture; the importance of listening to parents, who know best if their child's state is deviated from normal.

Dr Chakrapani addressed the question of the proportion of cases of acute encephalopathy in which an IMD is found *(Pages 32-39)*. The literature was sparse but one population-based study suggested 2.5%. There were no reliable data on the proportion of encephalopathic cases where a RS-like IMD was suspected but not found after detailed investigation. Participants gave anecdotal descriptions of such cases in discussion. The inadequacy of full IMD investigations at post mortem in patients with unexplained fatty livers (with the possible exception of those for MCADD) in the UK was highlighted. More use could be made of stored dried blood spots. It was considered that there are more IMDs as yet undiscovered.

Dr Barbara Phillips addressed the issue of the incidence of non-traumatic encephalopathy among children attending A&E departments in the UK, the proportion of these in which an obvious cause is quickly found and whether the presenting clinical features of those who turn

out to have RS or an IMD related illness differ from the rest *(Pages 40-47)*. There are no national routinely collected data and only one relevant study had been published. Meningitis/sepsis was the commonest cause and there was no information on distinguishing clinical characteristics of the few IMD cases. Other data and points emerged in discussion: 1 in 300 critically ill children or 1 in 60 cases of all non-traumatic coma would have an IMD/RS related encephalopathy (this could alter in a flu epidemic); 30 per 100,000 children attending A&E will have acute manifestations of an IMD, approximating to one a year out of every three hospitals. This rarity poses a major challenge for training. The importance of asking about previous similar episodes and of assessing blood sugar with investigation and follow up of unexplained hypoglycaemia, even if the patient recovers with IV glucose, was emphasised. Although vomiting without diarrhoea is a common A&E problem it was suggested that it would still be feasible to measure acylcarnitines on all such cases. A parallel with management of head injury was suggested, in which patients who are sent home are given a return card with symptoms and signs to look out for. This proposal was enthusiastically supported by the parent group participants.

Dr Glasgow reviewed other acute presenting clinical features in classic RS *(Pages 47-52)*. He highlighted the difference between the biphasic pre-admission illness typical of North American cases and the monophasic illness more commonly seen in the UK where cases are also younger. Nevertheless such cases were otherwise typical RS and exhaustive investigations had revealed no IMDs. Hepatomegaly may be present but is not typical. He reviewed the differential diagnosis, distinguishing between the conscious and the unconscious patient.

Dr Champion reviewed other acute presenting features of the RS-like IMDs *(Page 53)*. These varied according to the IMD and included hepatomegaly, cardiomyopathy, tachypnoea and various dysmorphic features.

Points made in discussion and summing up by the Moderator (Pages 54-60) included: acyl carnitine assessment is insufficient in IMD investigation as UCDs will not be detected; RS should not be ruled out if there is no history of aspirin exposure; there is evidence that RS patients have some innate susceptibility to aspirin; developmental problems in association with acute encephalopathy suggest an IMD rather than RS especially (but not exclusively) in children under three; state variation must be monitored in patients with suspected encephalopathy; unexplained hypoglycaemia must always be investigated for an IMD; importance of agreed, standardised investigation protocols in A&E and at autopsy; value of parent return cards.

PART THREE pages 1-33 WORKSHOP QUESTIONS 3.1-3.5

Laboratory and pathological diagnosis of RS and RS-like IMDs: investigations
"Best practice" –ideal world, no resource constraints

Dr Neil Dalton reviewed, giving practical details, the optimal *initial* investigations to be undertaken locally in all cases of non-traumatic unexplained encephalopathy *(Pages 1-7)*. The clinical and laboratory objectives are to ensure rapid and accurate diagnosis of hyperammonaemia and hypoglycaemia. The lab must be warned in advance if an ammonia is required and the sample must be separated and transferred quickly. Liver function tests and urine ketones should also be assessed. Practical details of the acute specimens necessary for *subsequent non-routine* investigation were also reviewed. These should be taken in all such patients ideally and it is essential that they are taken before, or immediately after, preliminary treatment (especially IV glucose) has been started even if there is a rapid clinical response. For these specimens it is essential to request measurement of urinary orotic acid (to detect OTC deficiency) *as well as* a plasma acyl carnitine scan to detect fat oxidation defects.

Dr Jim Bonham addressed the question of how the initial lab results should be interpreted – what findings might suggest what diagnoses and what other causes there are of raised plasma ammonia *(Pages 8-20)*. He reviewed ammonia measurement experience at Sheffield: only just under 20% patients had a level > 200μmol/L and of these just over half had confirmed IMDs. Apart from liver disease he identified 11 other non-IMD causes of hyperammonaemia. The height of the ammonia level can suggest certain diagnoses (eg UCDs are more likely when it is > 600 μmol/L especially in neonates) but this is not a reliable indicator.

Points made in discussion of both papers: PT or INR is a useful initial investigation –likely to be raised in both classic RS and UCDs; blood gas analysis another important initial investigation; problems with the validity of the ammonia result can be associated with errors in specimen collection, delay in reaching the laboratory, use of certain "kits in DGHs, inadequacy of external quality assessment of local labs; how to identify patients among the very large numbers attending A&E in whom blood glucose - with or without ammonia, LFTs, urine analysis - should be measured: not resolved but agreement that at least it should be all those in coma; the need for a "kit" in A&E with instructions and pre-labelled bottles to help juniors take a manageable minimum sample set (this can be done with < 1 ml of blood); how best to assess blood sugar: stix are practical for large numbers but have been abandoned in some places because they are unreliable; others use them as a screen, following up low sugars and getting a lab measurement on all cases of seizures/encephalopathy; the excess of opinion over evidence in this area was evident and the lack of quality assurance of near patient test in the acutely sick child highlighted.

Dr Eileen Naughten addressed the questions of whether all suspected "classic" RS patients should be fully investigated for all known RS-like IMDs and the diagnosis only made once they are excluded *(Pages 20-22)*. She concluded the answer to both is yes, but highlighted the difficulty of knowing when to *stop* investigating, especially as new disorders continue to be recognised. Laboratories should be informed if a change in clinical condition makes the diagnosis of RS/IMD less likely –they often are not and valuable resources wasted on ever more complex tests.

Professor Bernard Portmann addressed the question of the value of liver histology and ultrastructure (in tissue obtained either in life or at post-mortem) in the investigation of "classic" RS and IMDs *(Pages 23-33)*. Providing it is deemed clinically safe, ideally liver tissue is examined for all these disorders. The ultrastructural and histochemical changes in RS are virtually diagnostic. It is also important to obtain, with appropriate consent, a perimortem liver biopsy to avoid problems caused by post mortem autolysis; some disorders, notably some UCDs can only be confirmed by enzymology of liver tissue.

PART 4 Pages 1-53 WORKSHOP QUESTIONS 4.1 -4.5

Management of suspected Reye's syndrome and RS-like encephalopathy: best practice (ideal world, no resource constraints)

Dr Champion reviewed practical details of optimal *initial* management: first, while awaiting the results of initial investigations, and second, if hyperammonaemia is found (Pages 1-7). In addition to following APLS Guidelines, measures specific to a possible IMD should be instituted: stop feeds; promote anabolism; correct metabolic disturbance, but do not overcorrect acidosis because of possible hyperammonaemia. If ammonia raised: consider "alternate pathway" treatment; refer/transfer to specialist unit if NH3 > 150 μmol/L; urgent dialysis required if > 300μmol/L. Rapid acute TMS screen can provide rapid diagnosis of a fat oxidation defect, urea cycle defect, MSUD and some organic acidaemias.

Professor Leonard reviewed the published evidence for the effectiveness of treatment of each IMD *(Pages 7-12)*. There are no randomised controlled trials and treatment is simply aimed at correcting the abnormal biochemistry; early diagnosis and intervention is the key to optimising outcome.

***Points raised in discussion of both papers*:** some smaller DGHs have a problem with intubation in children other than neonates –this should be addressed in collaboration with *local* anaesthetists; questionable availability of alternate pathway treatments like arginine, benzoate, phenylbutyrate at DGHs, especially as some may have a short shelf life –an option is to courier or taxi them out from the specialist unit but this may take too long in some places; need for more information on the shelf life of these compounds so that they can be kept locally; value of carnitine in initial management too controversial to make it a recommendation for local management; patchy availability of plasma ammonia measurement around the country –not only at DGHs but also some tertiary centres; relatively few ammonia assays requested by adult physicians observed by labs which cover both adult and paediatric services (why?) – supportive pressure from physicians would help requests for improvement of the service; concern about low awareness of IMDs among adult physicians in this country, largely considered to be a paediatric issue only; need for a local *advance plan* for management of children with hyperammonaemia.

Dr Rob Tasker addressed the optimum management, from the intensivist's viewpoint, both of classic RS and RS-like disorders at the DGH, indications for transfer to a specialist centre and stabilisation of the patient before transport *(Pages 12-27)*. He found no class I evidence so used current (nb March 2002) national standards to provide detailed answers. Combining data from several studies he concluded that only approximately 1 in 90 children *with critical illness* have metabolic disease-related encephalopathy (needle/haystack problem again). First line doctors, - casualty officers and junior paediatricians, should have received some form of acute life support training, ideally APLS which includes guidelines on criteria for referral to Regional centres for paediatric intensive care. However, there is no mention in APLS of checking plasma ammonia in children with disordered consciousness; also, although classic RS is mentioned as a metabolic cause of coma, IMDs are not included.
Following the Troop report, Each NHS region is required by the Department of Health to produce a protocol for the acute management of seriously ill children with head injury, meningococcal disease and acute respiratory failure; *non-traumatic coma needs to be added*.
Points raised in discussion: should measurement of ammonia and of coagulation be included in the APLS secondary assessment of children with depressed consciousness? Need for a review of the evidence for the effectiveness of this as there could be resource implications; rarity of IMD related encephalopathy presentation at A&E - ? only 60 per annum for the whole UK.

Dr Glasgow addressed the same questions but focussed specifically on details of the management of classic RS *(Pages 27-47)*. Here too there are no RCTs. Management guidelines depend largely on experience in the USA and Belfast in the early 1980s when the incidence of RS was at its height. After the initial APLS approach, the 3 principle elements of management of classic RS are: continuous use of hypertonic glucose infusion, intermittent use of hypertonic mannitol and early elective endotracheal intubation – all within a full intensive care setting. Management specifics, described in detail, depend on continual assessment of conscious level using the Lovejoy staging or its GCS equivalent and on clinical and laboratory monitoring. Intracranial pressure monitoring may be undertaken but is controversial. All children in whom the diagnosis is considered, even those in Lovejoy Stage 1, should be transferred to a regional PICU after discussion. The important message is to have a written multidisciplinary agreed strategy led by 2 senior consultants (IMD, PICU).

Points raised in discussion: modern technologies, such as in vivo microdialysis and new knowledge since the 1980s such as the risks of hyperglycaemia, could mean that management of RS, were it to re-emerge, would be different in the 21st century. However, the huge amount of past experience should not be ignored.

Mrs Greene (Climb) and Mr Denney (Reye's syndrome Foundation) addressed the issues of how, when and by whom, information about their child's condition, including that about relevant support groups, is best conveyed to parents *(Pages 47-53)*. The findings of a Climb survey of MCADD parents suggested that: the information must first be given as soon as possible, face to face by a familiar health professional –preferably either the specialist or the DGH paediatrician; there should be plenty of opportunity for questions, written information in lay friendly language (copied to the GP) and the opportunity to return for further discussion. Support groups play an important role in providing information material; information about them including how to contact them should be offered at the time of diagnosis; however doctors should not ask groups to *initiate* contact with parents.
Points raised in discussion: resources limited even for specialist clinical departments to produce good written information specific to the disorder for *all* IMDs; Climb is addressing this problem on their website; sometimes parents complain they are given too much information at first; if the information is to be given by the DGH paediatrician s/he will need specialist support; "news-breaking" (how to) courses are very helpful; some parents contact support groups because they want help in making a formal complaint; difficulty of conveying seriousness of the condition in those cases at the "mild" end of the severity spectrum of an IMD; the value of specialist outreach nurses/ clinical liaison nurse specialists in enhancing the quality of after-care –more are needed!

PART 5 Pages 1-44 WORKSHOP QUESTIONS 5.1-5.7

Diagnosis at autopsy

Professor Berry addressed the question – in what proportion of cases of sudden unexpected death and death from unexplained encephalopathy, both in infancy and in childhood, are IMDs discovered and in what proportion of such deaths is an IMD suspected, fully investigated, but not found (Pages 1-12). Data from CESDI suggest that a) about 1% of SUDI are caused by an IMD, most commonly MCADD, then other FAODs; OTC reported in the literature; b) in about a third of suspected cases, fully investigated, no IMD is found. Sudden unexpected death is very rare in older children and there are no data on IMDs in these cases and none on IMDs in deaths from unexplained encephalopathy. Some IMDs are probably being missed at autopsy and better recognition could be achieved by: raising awareness among pathologists (eg via the Bulletin of the Royal College of Pathologists or direct mailings); clinicians always providing pathologists with a detailed history and provisional differential diagnosis; sampling of fluids and tissues perimortem by the clinician where appropriate.
Points raised in discussion: in contrast to CESDI, one ongoing study was finding a rate of about 4-5% IMDs in SUDI cases, none of which so far had been MCADD; finding a possible cause of death doesn't necessarily rule out concomitant presence of an IMD, especially true of infections, which can precipitate the decompensation; all sudden unexpected deaths and deaths from unexplained: cardiomyopathy, encephalitis, or seizures - *irrespective of age of the child* - should have a metabolic workup; there should be a protocol in A&E with appropriate instructions and sample tubes, for clinicians to take perimortem samples for later examination; ideally this should include skin biopsy but difficult in practice and can be deferred until the post mortem.

Professor Portmann described and contrasted the pathognomic features of classic RS and the RS-like IMDs and addressed the feasibility of using electron microscopic investigation to

distinguish between them (Pages 12-26). The light microscopic features of classic RS are considered pathognomic but it is the EM mitochondrial changes which are diagnostic and it cannot reliably be diagnosed without liver morphology. Microvesicular steatosis occurs both in RS and the IMDs and also incidentally in other causes of death without any specific connotation. He reviewed the morphological data in a range of RS-like IMDs: argininosuccinicaciduria; OTC and CPS deficiency; mitochondrial cytopathies and oxidative phosphorylation disorders; valproate and ecstasy toxicity. EM examination is not widely available in UK outside tertiary centres, it requires special expertise and extra funding. If to be undertaken it is essential to obtain the liver material perimortem or as soon as possible after death because the findings are rapidly obscured by autolysis.

Points raised in discussion: the absence of succinic dehydrogenase in liver cells is also said to be specific to classic RS and histochemical examination is more widely undertaken than EM - the time after death of the assay is not so critical, so if classic RS were to recur this could be a useful diagnostic tool which requires further evaluation; pathologists must be discouraged from recording Reye's syndrome as the cause of sudden unexpected death purely on the basis of a fatty liver; reluctance to pursue IMD investigations of such cases in some parts of the country may reflect cost constraints because the cost (nb 2002) had to be met by the coroner's budget.

Dr Marian Malone reviewed the "best practice" autopsy investigations, both local and specialist, for suspected IMDs and classic RS and the indications for undertaking them (Pages 26-37). They are most likely to be undertaken in the setting of all the other investigations for sudden unexpected death.

<u>At the time of post mortem</u>:

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?

<u>After the post mortem</u>

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).

Since most of these post mortems are performed under the Coroners' 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.

Although ideally the brain should be retained in all cases, since Alder Hey this has become problematic. GOS practice (at the time -2002) was to retain the brain for 1 week for fixation for thin sectioning and then return it to the body for release.

Points raised in discussion: investigations listed above should be undertaken on every case of sudden unexpected death irrespective of age of the child; importance of perimortem urine sample

(include in protocol for casualty officers); value of bile in post mortem IMD diagnosis – not often used by clinical chemistry labs but commonplace for pathologists; problem of lack of investigations because coroners will not pay and confusion about responsibility of heath authorities in such cases; problem of delays between death and post mortem –ideally 4 hours maximum for valid sampling otherwise risk of false positives; need to provide pathologists with a sampling protocol including instructions on where to send samples; vitreous humour *not* helpful; cerebral oedema often recorded in autopsy reports and used to support diagnosis of RS, but only reliable if gross; CESDI showed only 40% cases of SUDI were autopsied by paediatric pathologists.

Dr Graham Shortland (in absentia) addressed the collection of *antemortem* pathological specimens from moribund patients – is it important and if so what specimens (Pages 37-44). It *is* important as such specimens are more likely to yield accurate results than equivalent post mortem ones –but they complement them. The appropriate specimens (tests listed) are blood, urine and, if possible, ideally skin and liver biopsies.
Points raised in discussion: once the child dies the body is the property of the coroner in cases of sudden unexpected death and samples should not be taken by clinicians without permission; urine carnitine is not helpful; urine orotic acid, muscle biopsy, and blood and urine for microbiological investigations to be added to Dr Shortland's list; problem of collating all results –all unexpected childhood deaths should be the subject of a formal multidisciplinary case review which would include parent counselling – coordination especially important when the patient has been admitted to a DGH then transferred to a PICU *(update: this has been addressed in the National Service Framework for Children published in Sept 2004, Ed)*; DGH labs are getting less keen to store specimens because of increased demand and limited space; post mortem samples still need to be taken, as the pathologist is responsible for the cause of death diagnosis made; the recommendations made at this meeting amplify but do not duplicate those made by CESDI.

PART 6 Pages 1-31 (WORKSHOP QUESTIONS 6.1- 6.2.4)

Obstacles to achieving "best" practice: why have we got a problem?

The first three questions were taken together: *Dr Andrew Boon* reviewed the professional educational bodies towards whom action directed at removing barriers to changing paediatric practice should be aimed; *Dr Mike Champion* reviewed the reasons why IMDs are under/mis-diagnosed or diagnosed late and the obstacles to best practice and *Professor Stuart Tanner* addressed the same issues with regard to classic RS (Pages 1-11).

♦The relevant professional bodies are the Royal Colleges (Paediatrics and Child Health, Physicians, General Practitioners, Pathologists); Royal Pharmaceutical Society; Coroners. Within the RCPCH –the general paediatric advisory committee because there is a need to include education on RS and RS-like IMDs as causes of encephalopathy in the paediatric core training – most juniors will never see cases during clinical training. The RCP because older patients with these disorders may present to adult physicians and A&E departments and most physicians will be unaware that these conditions can present in teenagers and young adults. GPs and pharmacists may need reminding for time to time about the risks of aspirin especially in teenagers in a flu epidemic. Coroners need to be aware that these cases can present as SUD and that such cases need a specially detailed autopsy (as described in part 5) if the disorder is to be diagnosed and the cause of death correctly ascertained.
♦The main reason for failure to diagnose IMDs is lack of exposure of trainees to what are rare disorders presenting with common symptoms and signs which often resolve with non-specific supportive treatment. There are also the problems of obtaining a suitable sample for measuring plasma ammonia; in some places limited availability of laboratory resources to undertake the assay; and a perception that the conditions are not only very rare but largely untreatable so take a low

priority among other health issues. The obstacles to improving this situation included lack of attention to IMDs both in membership teaching and in the exam (although this was beginning to improve) and in the APLS course. There are insufficient teachers, teaching centres and training for teachers.

♦Reasons for under or late diagnosis of classic RS, should it recur, would also include lack of exposure to cases, and probably beliefs that it is a condition of the past and that it doesn't occur in teenagers or young adults. Cases in young adults in a flu epidemic may in fact be more prevalent than in the past as this cohort may be taking aspirin for the first time; this has implications for education of adult physicians.

Points raised in discussion: action points and key messages – include IMDs/RS in APLS and membership courses and exams; unified *national*, not regional, organisation of training of consultants in mall specialties is needed; need for a joint initiative with the RCP –one was already being planned but this needs be further pushed, perhaps drawn to the attention of the RCPCH academic vice-president and/or the RCPCH Clinical Effectiveness Unit.

The next three questions were also taken together: *Dr Paul Masters* addressed the issue of biochemical investigations at DGH level: what is routinely available, are there geographic variations, how can we ensure reliable 24 hour availability of plasma ammonia measurement everywhere, what are the obstacles to improving local services? *Dr Anne Green* reviewed specialist laboratory provision in the UK, whether stored Guthrie cards have a role in retrospective diagnosis of these patients and the obstacles to improving the service. *Dr Jane Collins* reviewed specialist clinical support and the obstacles to improving that service (Pages 11-27).

♦Because most local laboratories now use main analysers on a 24/7 basis there should be no difficulty in providing plasma glucose and liver function tests at any time. Availability of ammonia nationwide is unknown but a 2002 survey of DGH labs in the Trent region showed that all were also offering plasma ammonia on the same basis, treating it as an emergency investigation without having to consult senior staff. Problems centre on the low frequency with which the test is done with attendant risks of reduced quality; pre-analytical factors such as delay in reaching the lab or inadequate skin cleansing; lack of an external quality assessment scheme, low threshold of rejecting suboptimal samples. There is a need for a national standard operating procedure to address the pre-analytical and interpretative aspects of ammonia tests.

♦An informal survey of the 20 specialist laboratories (*nb 2002 ed*) in the UK showed that all provided amino acid analyses, most provided organic acid and mono/disaccharide assays but only about half provided acyl carnitines and orotic acid; there was a wide and unexplained variation in (population based) workload; very few had a protocol for investigation of encephalopathy and just under ¾ had one for SUDI. A quarter did not have a 24 hour advice service and among those that did this was informal and unpaid. A survey in 2000 by the UK National Screening Laboratory Network had revealed deficiencies and variability in Guthrie card storage and retrieval. This had implications for the diagnosis of MCADD; their role in other disorders was still unclear. Reported problems impeding a good service included the European Working Time directive and manpower shortage, especially clinical scientists.

♦As at 2002 there were only 2 major paediatric metabolic centres capable of providing a 24/7 comprehensive range of services and seven others with a smaller service. The major obstacle to a better service is the unknown size of the unmet need which means that IMDs are at risk of being perceived as unimportant. A 4 country strategic plan to develop all aspects –lab diagnosis, treatment, specialist nurses, consultants, is needed in order to recruit people into metabolic medicine. The new UK National Newborn Screening Programme centre at GOS would be promoting development of a performance management framework for blood spot screening. This would include addressing some of the problems described above.

***Points raised in discussion**:* metabolic clinicians and scientists should work more closely with parent groups associated with rare diseases (eg Climb, UK Rare Disorders Alliance, Eurordis) to highlight inequitable service provision as this can open "political doors"; there is a need for outreach services, including nurse specialists, from the metabolic centres to DGHs so that patients do not have to travel long distances; the National Service Framework *(nb published September 2004, ed.)* will state that any child who has a disorder recognised as "specialised" should have access to an appropriate specialty care service;

Dr Marian Malone addressed the issue of the quality of autopsies of sudden unexpected death or death after unexplained encephalopathy, geographical variations and obstacles to best practice (Pages 27-31). The proportion of such autopsies in which a satisfactory examination (i.e. as described in Part 5) is undertaken, is unknown. Most are investigated under the coroners' system. Coroners meet the cost of these autopsies and vary in how much they are prepared to pay for detailed investigations beyond those necessary to determine if death was from natural causes. Other obstacles to best practice are 1) organ retention issues following Alder Hey – pathologists feel that retention of *specimens* (as against *organs*) should be an inherent part of the pathology examination; 2) the fact that some cases are not examined by a paediatric pathologist but only by a forensic pathologist; 3) there is no quality control or audit of the system.
***Points raised in discussion**:* the extent to which coroners vary in use of their budgets for these autopsies should be the subject of further enquiry.

PART 7 PAGES 1-45 Workshop questions 7.1 – 7.2

DISSEMINATION AND IMPLEMENTATION OF THE EDUCATIONAL PACKAGE

The best methods of alerting relevant professional groups to rare disorders with common non-specific clinical presentations were reviewed by Jane Gick, specialist nurse, and by Professor Terence Stephenson (Pages 1-30 and powerpoint presentation in Part 9).

- *Miss Gick*'s experience was that the best method of education is outreach from the specialist centre in the form of shared care: patients admitted to and diagnosed at, the specialist unit at first presentation are returned to the care of their DGH, GP and community paediatric nurse team who then take responsibility for long term management including any decompensation illnesses. The specialist nurse visits the district to advise on putting a care package in place and educates all relevant health professionals who will be involved with the patient. Parents also hold information about their child's condition and are given some means of urgent access to maximise speed of readmission if necessary. This process often stimulates requests for further education on IMDs locally.

Study days are often unsuccessful as nurses may not be allowed the time if there are staff shortages but are better attended if held locally rather than at the tertiary centre. Receptiveness to offers of further education is highly variable between districts –exemplified by the recent response to such an offer by her unit regarding the proposed expansion of neonatal screening. Knowledge, even about the existing PKU programme, is also in Miss Gick's experience highly variable even among health professionals directly involved.

- *Professor Stephenson,* drawing also on work by *Dr Monica Lakhanpaul,* presented in detail the case for formal, evidence-based guidelines as the best method to alert health professionals to the diagnosis and management of these rare disorders and to influence practice. The starting point for the guideline should not be the disorder but the presenting problem –eg in the cases under discussion, disordered consciousness. He outlined the methodology - starting with audit of current practice and selecting areas for improvement; deriving an evidence base; consensus methods – including the Delphi approach, nominal group technique and consensus development conference; dissemination; implementation; evaluation. The guideline development group should be

representative of all the relevant disciplines and grades and include patient/parent representatives. The finished product should be visually arresting and easy to use.
The most important target group at whom a guideline on RS/IMDs should be directed, is A&E junior doctors (both paediatric and general) as it is to them that these cases will first present. In order for guidelines to work they have to be widely disseminated eg to RCPCH members, clinical directors of all UK A&E departments and chief executives of every acute hospital trust, alerting them to the clinical governance issues.
Although a guideline is rolled out nationally it is essential that it is amended locally to suit local circumstances. The roll out needs to be preceded or accompanied by publicity and training eg workshops, roadshows, journal, conference, and website alerts. It will be important in the longer term to incorporate guidelines into electronic patient record systems.

Professor Jem Berry reviewed best methods of educating pathologists –both coroners' and hospital (Pages 30-31). He felt that update reviews in the journal of the Royal College of Pathologists *would* be read and would be helpful. But most useful would be to develop a new practice guideline for investigating all SUD in infancy and childhood which would include *routine* metabolic investigations; this would have to be under College auspices. The worksheet for pathologists should include not only indications for metabolic workup but clear instructions in kit form about sampling and where to send them. There also need to be recommendations about terminology –i.e. *not* to give a diagnosis of RS in the absence of a typical clinical history of classic RS and of typical findings in antemortem investigations. This guideline should be aimed at paediatric and forensic pathologists and at general histopathologists undertaking autopsies for coroners. RS and IMDs should be included in the MRCPath courses and exam.

Dr Harry Baumer addressed the issue of how to disseminate knowledge widely and sustainedly (Pages 32-35 and PowerPoint presentation in Part 9). The RCPCH sends out summaries of guidelines with their Newsletters –those appraised and endorsed by the College are more likely to be adopted; the College's Annual Scientific Meeting is also planning to showcase guidelines in the process of appraisal; journal articles can be useful to highlight the existence of a guideline; care pathways can be structured around guidelines; educational roadshows have been effective in spreading the message; incorporation of RS and RS-like IMDs and non-traumatic encephalopathy into the membership exam and the APLS course could help; CPD is important not only for these rare disorders but associated aspects like breaking bad news; audit may encourage change of practice.

Mrs Lesley Greene and Mr Gordon Denney outlined how parents and support groups can participate in disseminating knowledge about RS and IMDs (Pages 36-38). By speaking as parent voices with "patient as expert" experience at professional meetings; by providing lay friendly written literature and website information; by being available to families in times of crisis. A survey of Climb's MCADD families showed that parents want information about support groups to be given as soon as possible after diagnosis and that, if a screening programme is introduced, information about it should be available in the parent held record and the Birth to Five Book. A reminder about the dangers of aspirin would also be useful in these documents alongside general information about management of minor illnesses. Climb was planning to hold training days for health visitors and social workers and was hoping to attract non-metabolic health professionals to their conferences. Training for parents to be befrienders and speakers was also planned.

Final discussion –points raised: **(Pages 38-41).** Endorsement of importance of parent voices in training health professionals cf excellent presentations at Climb conferences and articles in their magazine; in contrast to articles published in journals there is *evidence* that guidelines alter practice; educational packages should also be targeted at front line district level laboratory scientists; the package for front line clinical staff should include instructions on basic minimum information to

accompany laboratory samples to facilitate appropriate investigations; the availability of ammonia measurement nationwide and whether adult physicians perceive a problem (nb could be useful allies in steps to improve the service); need for someone in each region to take responsibility to review the network of: availability of ammonia, training of casualty officers, relationship between DGHs and the PICU.

Convenor's summing up and action list (Pages 41—45)
In the context of this meeting the most important target groups for educational/training packages are A&E doctors and nurses, paediatricians, coroners and pathologists (bracketing histopathologists and chemical pathologists and clinical scientists). These are the groups on which to *start* focussing.

The two fast track methods of influencing practice among paediatricians and A&E doctors are: 1) getting the subject of IMDs/encephalopathy into the relevant membership exams; and 2) getting the message about emergency ammonia measurement and RS-like IMDs as a cause of disordered consciousness into the APLS –with the caveat that there will be service implications for laboratories.

For pathologists a guideline or annotation via their college journal was suggested. The points raised are also likely to be addressed in the Kennedy Report *(nb published 2004, Ed. See Part B)*

For coroners the points that have been raised are likely also to be addressed in the forthcoming reviews (by the DoH and by the Shipman enquiry) of coroners' and death certification practice in the UK *(nb both published in 2003, Ed. See Part B).*

News-breaking and giving information to parents about rare serious disorders should also feature in the MRCPCH exam, possibly as a role play clinical exercise.

The material in the Climb Magazine should be used as a teaching resource for juniors.

A proposal is needed to develop formal evidence-based guidelines on the diagnosis and management of disordered consciousness *(nb a project to undertake this subsequently began at Nottingham in November 2003 under the direction of Professor Stephenson and funded by the National Reye's syndrome Foundation, Ed. See Part B)*

There was an unresolved question about what is best practice for measuring blood glucose in an emergency situation. There is variability in practice; does it need a literature review? The same applies to blood ammonia –best sampling technique, transport, lab criteria for acceptance/rejection.

If classic RS does re-emerge there will be a need for systematic study of the best methods of modern management with new technologies not available when it was a problem in the past.

Regarding the shelf life of the specific therapeutic interventions (alternate pathway treatments) for acute management of crises in these IMDs –what is known, what needs to be known, what should be policy on storage and replacement, can they be available in every DGH?

Development of standards of service provision for IMDs, especially appropriate consultant staffing levels and nurse specialists needs to be pushed.
The Proceedings of this meeting will be published on the website of the National Reye's Syndrome Foundation (www. reyessyndrome.co.uk).

SUMMARY PART B: ACTION POINTS AND RECOMMENDATIONS

POINT NUMBER	PAGE OF SUMMARY	ACTION POINTS
		CLINICAL TRAINING
1.	11&14	Include RS and IMDs in APLS and membership courses
2.	7	APLS Course/Manual: need for addition of plasma ammonia measurement and mention of IMDs in the differential in the section on management of altered consciousness
3.	4	Juniors need to be trained how to recognise encephalopathy in the apparently conscious child
4.	5	Clinical trainees in A&E and paediatrics should be taught that unexplained hypoglycaemia must always be followed up and an IMD considered; they must always ask about previous similar episodes
5.	6	Clinical trainees should be taught to always inform the lab of any changes in the patient's clinical condition which makes an IMD/RS less likely - to save resources
6.	8	Clinical trainees should be taught to always provide pathologists with a detailed premortem history and provisional differential diagnosis, to get the best out of a post mortem[1]
7.	10	Need to include RS and RS-like IMDs as causes of encephalopathy in paediatric core training
8.	13 & 14	Organisers of professional meetings should consider inviting "expert parents and patients" to speak; lay material such as articles in the Climb magazine should be included in training packages
9.	7,10 &`11	Need to educate adult physicians: i)about RS as may resurge in teenagers and adults in a 'flu epidemic
10.	7,10&11	Need to educate adult physicians ii) about IMDs, both because they may present late and because they will have to manage childhood cases who survive
11.	10	Need for reminder publicity about aspirin risks in the event of a flu epidemic - aimed at GPs and pharmacists
12.	13	Need for CPD credited courses on IMDs and on news-breaking
13.	14	News-breaking should be part of membership exam (? Role play)
		PATHOLOGIST TRAINING[1] [2]
14.	8	Need for increased awareness among pathologists of RS-like IMDs in investigation of fatty livers and SUD – via direct mailing and/or updates in the RCPath Bulletin
15.	8	Need for post mortem metabolic work-up in ***all*** cases of SUD, and unexplained :- cardiomyopathy, encephalitis, and seizures, irrespective of age
16.	9	Pathologists need to be educated about *not* diagnosing RS purely on basis of a fatty liver at autopsy
17.	4-5	Pathologists need to be educated about use of stored neonatal blood spots in investigation of unexplained fatty liver and/or SUD
18.	13	RS/IMDs should be included in MRCPath courses and exam

POINT NO.	PAGE	LAB INVESTIGATIONS FOR FURTHER RESEARCH
19.	5	Need for feasibility study of measuring acylcarnitines on all patients presenting with vomiting *without* diarrhoea – even though a common problem
20.	7	Information needed on availability of ammonia measurement nationwide and on value of it to, and use by, *adult* clinicians (potential support in any demands for expansion of the service)
21.	9	Need for further evaluation of role of hepatic histochemistry (eg succinic dehydrogenase) in p.m. diagnosis of classic RS if it recurs
22.	10	Use of post mortem bile in investigation of IMDs needs further investigation
23.	14 & 6	Need for literature review on optimal methods of measuring blood glucose and ammonia in A&E and other emergency situations
24.	7	Value of ammonia in the emergency investigation of depressed consciousness needs an evidence review because of the resource implications
		THERAPEUTIC RESEARCH
25.	14	Need for a review of potential for, and actual, availability of alternate pathway treatments for IMDs, at DGH level – to include storage and replacement policy
26.	7	Information needed on shelf life of "alternate pathway" treatments to facilitate decisions on whether to stock and on storage
27.	14	If there is a resurgence of classic RS –need for systematic study of modern management techniques not available when it was at its peak incidence before
		STANDARDISED PROTOCOLS: A&E
28.	5	Need for standardised protocols in A&E for investigation of disordered consciousness, unexplained hypoglycaemia
29.	6	As part of this -need for "kits" in A&E with instructions on sampling and prelabelled containers and where to send
30.	14	A&E packs should include instructions on what information accompanying specimens should be provided for the lab
31.	8-9	Need for A&E protocol (instructions, sample tubes) for ***peri***-mortem samples in moribund children with uncertain diagnosis, urine especially important, skin biopsy ideal but can be deferred to autopsy
		STANDARDISED PROTOCOLS: AUTOPSY
32.	5	Need for standardised protocols for investigation at autopsy of cases of SUD or death from unexplained encephalopathy, for IMDs
33.	10	Pathologists need detailed sampling protocol including information on where to send specimens
		TRAINING AND PROTOCOLS: CLINICAL CHEMISTRY
34.	11	Need for all specialist clinical chemistry labs to have protocols for investigation of both SUD *and* encephalopathy
35.	14	Educational packages on IMDs should also be targeted at front line clinical scientists
		NON-CLINICAL MANAGEMENT
36.	5	Evaluate use of *return cards* for parents in cases of possible non-traumatic encephalopathy but who recover and NAD so sent home (modelled on those used for head injuries, include symptoms and signs to look out for)
37.	13	Information about any neonatal IMD screening programme should

		be included in the parent held record and in the Birth to Five Book
		STRATEGIC PLANNING AND POLICY
38.	7, 8 &14	Need for regional protocols for acute management of non-traumatic coma like that required by the Troop report for head injury, acute respiratory failure and meningococcal disease
39.	8 &12	Need for more specialist outreach/ clinical liaison IMD nurse specialists
40.	10	All unexpected childhood deaths should be subject of formal multidisciplinary case review including parent counselling
41.	11	Need for unified *national* organisation of training of consultants in small specialties, in conjunction with RCP
42.	11-12	Need for UK-wide strategic plan to develop *all* aspects of metabolic medicine
43.	14	Need to push development of standards of service provision for IMDs especially consultant and nurse specialist staffing levels
44.	12	Metabolic clinicians and scientists should work more closely with parent groups involved with rare diseases to highlight inequitable service provision –can open "political doors"
45.	7	Need for local advance plans for management of hyperammonaemia
46.	11	Need for national standard lab operating procedures to address pre-analytic, analytic and interpretative aspects of ammonia assays
47.	12	All paediatric autopsies, whether coroners' cases or not, should be undertaken by a paediatric pathologist or pathologist with a special interest [1]
		CORONERS/THEIR BUDGETS[3]
48.	9-10 & 12	Inequity of extent of p.m. investigations permitted to pathologists according to different coroners' use of their budgets is deplorable and should be the subject of further enquiry
49.	9&10	Need to educate coroners that IMDs can be cause of SUD but need detailed autopsy to diagnose with appropriate funding for the extra investigations
50.	12	Need for audit of conduct of coroners' cases of SUD
		GUIDELINES
51.	12	Need for formal evidence-based guideline to alert clinical health professionals to diagnosis and management of these disorders and to influence practice; should be aimed at A&E staff and focus on disordered consciousness[4]
52.	13	Need for new practice guidelines for pathologists under auspices of RCPath for investigation of all SUD, irrespective of age, to include routine metabolic investigations and advice not to diagnose classic RS in the absence of a typical premortem history[1]

[1] Also addressed in: Sudden Unexpected Death in Infancy, a Joint Report of the RCPath and RCPCH, 2004, www.rcpch.ac.uk/publications/recent publications (chaired by Baroness Kennedy)
[2] Also addressed in: The Future of Paediatric Pathology Services, March 2002 ibid plus /pathol.pdf
[3] Also addressed in: Shipman Inquiry the third report July 2003, www.the-shipman-inquiry.org.uk/reports.asp and in The Report of the Fundamental Review of Death Certification and Coroner services, June 2003, www.official-documents.co.uk/document/cm58/5831/5831.htm
[4] See Paediatric Altered Consciousness Guideline www.nottingham.ac.uk/paediatric-guideline/home.htm