Commentary

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The decision to severely restrict the use of aspirin in children in the United Kingdom was probably influenced by components of the carefully analysed study by Hall and her colleagues. Please note that 40% of the cases in the study were not thought to have taken aspirin before or during their illness. Note that four out of five of the cases who had taken aspirin had taken it in the past without ill effects. Note too that the authors conclude that 'If aspirin has an aetiological role there must be an exceptional unpredictable combination of circumstances that act as a trigger.' Reye's syndrome 25 years after it was first defined still presents many challenges.

For the clinician the first is early consideration of the diagnosis in any child with encephalopathy and vomiting so that steps can be taken to prevent a further increase in intracranial pressure and so that glucose may be given intravenously in sufficient concentration to provide energy for cells deprived because of disordered mitochondrial function. The second challenge is to arrange appropriate investigations to identify genetically determined metabolic disorders which may present as Reye's syndrome. At least 23 have been reported to date. Defects of fatty acid oxidation and urea synthesis can cause particular difficulties in diagnosis. While most of these disorders present before 3 years of age, presentation in the second and third decade has been reported.

Accurate diagnosis may only be possible if samples of serum or urine have been collected in the acute stage and stored at −70°C for subsequent analysis. It is not clear how many of these disorders have been rigorously excluded in any of the epidemiological studies. We should be very cautious about diagnosing cryptogenic Reye's syndrome in the first three years of life. Accurate diagnosis of alternative genetic disorders is essential for genetic counselling and to prevent relapse with the risk of brain damage or death in the proband. Siblings may be at risk, not only of Reye's syndrome but of 'cot death'.

In cryptogenic Reye's syndrome there are two characteristic but unexplained pathogenic phenomena.

(1) An unusual disturbance of mitochondrial structure associated with a decreased activity of all mitochondrial enzymes, best documented in liver tissue. These abnormalities are most severe in the first 48 hours after onset, progressively returning to normal within five to nine days. Other subcellular organelles show only minor changes.

(2) An intense catabolic state, the duration of which seems to be similar to the mitochondrial abnormality.

At least 19 different viruses, including examples from major groups of RNA and DNA containing viruses, have been implicated in the viral prodromal. Viruses are rarely recovered from the liver or brain. Just why such viral infection could cause a specific mitochondrial lesion in between 1:20 000 to 1:500 000 of children infected is quite unknown. In laboratory studies it has been shown that hepatic
changes, and sometimes encephalopathy, mimicking Reye's syndrome, can be produced by viral infections in animals who have been exposed to a variety of exogenous agents. These include dicophane (DDT), fenitrothion (an organophosphate), butylated hydroxytoluene, pentenoic acid, and pesticide emulsifiers such as polyoxyethylene and Toximul. Some of these effects are limited to particular genetic strains. A common theme in the animal work is the increased susceptibility of the young or fasted to mitochondrial dysfunction. It is not clear whether these agents act on peripheral tissue metabolism causing a catabolic state, influence the immune system, cause metabolic abnormalities which interfere with intermitochondrial protein synthesis and thus lead to a secondary disturbance of mitochondrial function or whether these environmental agents interfere with the interaction of the virus with mitochondria. These agents could interfere with metabolic processes leading to increased accumulation of toxic products in a fashion similar to that which is believed to occur in patients with isovaleric acidemia who are given aspirin. Aspirin inhibits glycine conjugation and may precipitate more severe encephalopathy.

With the present swing away from aspirin towards paracetamol in children, we should remember that in mice exposed to an emulsifier and mouse adapted influenza B virus, mortality was increased if the animals were given paracetamol or aspirin. Furthermore, encephalopathy with liver failure has been reported in a 15 month old infant who received four 500 mg tablets per day over a four day period before the onset of the liver failure. He had received intermittent paracetamol for fever in the previous month.

As you assiduously complete your orange British Paediatric Surveillance forms, anxious lest the next analysis of returns will show that your unit has been responsible for the relatively low rate of return in your region, pause at Reye's syndrome. It is still with us and with many unresolved problems. We have much to learn about the influence of environmental factors and genetic make up on our response to viral infection.

References