Twin Siblings with a Reye's-Like Syndrome Associated with an Abnormal Organic Aciduria, Hypoglycemia, Diarrhea, and Vomiting with Close Similarities to Jamaican Vomiting Sickness

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Summary

Seventeen-month-old identical Caucasian male twins developed vomiting and diarrhea, and both were admitted to hospital 30 hr after the onset of symptoms. One was dead on arrival. Hepatic histology showed fatty degeneration affecting all parts of the lobule. Death was due to aspiration of gastric contents. Electron microscopic examination of the intestine showed the presence of replicating adenovirus. The other infant was comatose with undetectable blood glucose. He was maintained on IV glucose for 48 hr and made a complete recovery with no further hypoglycemia even after an overnight fast. Eighteen months later, he was a normally developed child for his age. The clinical diagnosis made in both infants was Reye's syndrome.

Urinary organic acids were determined by gas chromatography and identified by gas chromatography-mass spectrometry. Greatly increased concentrations of adipic acid, 4-hydroxyphenylacetic acid, suberic acid, and of a previously unrecorded urinary organic acid which has been identified as 5-hydroxyhexanoic acid were observed. There were also increased concentrations of octanoic, sebacic, decenedioic, octenedioic, and 3-hydroxyisovaleric acids, and greatly reduced concentrations of the aldonic and deoxyaldonic acids and acids of the tricarboxylic acid cycle. Lactic acid excretion was not increased, and there was only a moderate increase in the concentrations of 3-hydroxybutyric and acetoacetic acids. No gross increase in concentrations or abnormal acids were observed in the urinary volatile short chain fatty acids.

The organic acids observed in the urine of the present patients have been compared to those observed in patients with Jamaican vomiting sickness and those with Reye's syndrome. The similar dicarboxylic C₆-C₁₀ aciduria and profound hypoglycemia observed in the present patients and in those with Jamaican vomiting sickness is of interest and probably occurs due to a similar mechanism, inhibition of β -oxidation of medium-chain fatty acids by a chemical toxin. Some differences between the organic aciduria observed in these cases and in patients with Jamaican vomiting sickness suggest that the nature of the possible toxin, although closely similar, is not identical. The occurrence in both of the present patients of high concentrations of 5-hydroxyhexanoic acid may indicate the nature of the causative xenobiotic agent, and it has been suggested that this could be hex-4-enoic acid.

Speculation

The occurrence of profound hypoglycemia and abnormal organic aciduria in twin English siblings with a Reye's-like syndrome and

close clinical and biochemical similarities to Jamaican vomiting sickness suggests that some cases of Reye's syndrome in infants are due to causes similar to that involved in Jamaican vomiting sickness, that is, organic acid chemical toxins related to metabolites of hypoglycin.

Encephalopathy and fatty degeneration of the viscera in infants and children (Reye's syndrome) has been widely reported since the original description by Reye *et al.* (27), and a consistent clinical, biochemical, and pathological picture has evolved from these reports (12, 22). There is a considerable variation, however, in the incidence, presentation, and severity of the disease, and the etiology, particularly in infants, is unclear (17, 22). It has been suggested that the syndrome may represent the effects of many different etiologic factors acting on the same or common metabolic pathways and thereby leading to similar results. The similarities of Reye's syndrome and the vomiting sickness of Jamaica (ackee poisoning or hypoglycin toxicity) have also been noted (21). Tanaka *et al.* (30) have reported the biochemical investigation of two siblings with Jamaican vomiting sickness and included detailed organic acid analyses that confirmed the cause of the disease and also the dissimilar findings in patients with Reye's syndrome. The recent presentation of identical twin siblings with an unusual Reye's-like syndrome (8, 36), enabled a detailed study to be made of the urinary organic acids in the disease that show close similarities to those reported in Jamaican vomiting sickness that provide information on the biochemical mechanisms of the disease and of the possible underlying etiology in these cases. This paper presents the detailed case reports and biochemical studies on the abnormal organic aciduria in these infants.

CASE REPORT

Seventeen-month-old identical Caucasian male twins, R. B. and T. B., developed vomiting and diarrhea on October 30, 1976. Their mother treated them both with plain water, one 75 mg aspirin tablet every 12 hr, and 5 ml of Kaolin mixture. They became drowsy, and 30 hr after the onset of symptoms, R. B. was found blue and cold in his bed. Both twins were brought to Northwick Park Hospital immediately by ambulance.

PAST MEDICAL HISTORY AND FAMILY HISTORY

There was an uneventful twin pregnancy with vaginal delivery at 38 wk. Birth weight for both was 2.2 kg. The twins spent two

wk in the Special Care Baby Unit because they were initially slow to feed. Urinary organic acids examined at this time were entirely normal. Subsequent growth and development were normal. The parents are nonconsanguineous and healthy. The sister, aged 4½ years, had diarrhea and vomiting 2 wk previously.

CLINICAL COURSE

R. B. was dead on arrival at the hospital. Blood culture was sterile, but a throat swab grew β -hemolytic streptococci. Autopsy revealed some hepatic enlargement. Histology showed fatty degeneration affecting all parts of the lobule. The lungs showed intense vasocongestion, but no pneumonia, the appearances being similar to those seen in aspiration of gastric contents. Brain histology was normal. Electron microscopic examination of the intestine (Heather A. Davies) showed adenovirus particles within the nucleus of a mucosal cell and in scrapings of the mucosa. The intranuclear virus particles were in crystalline array, indicating virus replication. There was no virus in the liver, lung, or brain. There was no intestinal lymphoid nodular hyperplasia.

T. B. was comatose on arrival, responding sluggishly to painful stimuli and with brisk tendon reflexes. He began to convulse and was given IM paraldehyde immediately. A Detrostix showed an unrecordable blood glucose [later confirmed at 0.2 mmol/liter (4 mg/100 ml)]. After IV injection of 5 g of glucose, his clonic movements stopped, and he sat up. Investigation at the time of admission showed: blood glucose, 0.2 mmol/liter (4 mg/100 ml); plasma urea, 13.5 mmol/liter (88 mg/100 ml); bicarbonate, 11 mmol/liter; serum insulin, 48 munits/liter (raised); plasma cortisol, 1460 nmol/liter (appropriate); growth hormone, 69 munits/liter (appropriate); aspartate transaminase, 208 IU/liter (raised). Plasma calcium, sodium, potassium, bilirubin, and alkaline phosphatase were normal. He was maintained on IV glucose for the next 24 hr, blood glucose levels being around 6 mmol/liter (120 mg/100 ml). When IV glucose was discontinued, he became drowsy and hyperreflexic again and the blood glucose fell to 1.9 mmol/liter (36 mg/100 ml). Glucagon, 1 mg IM, raised the blood glucose to 4.2 mmol/liter (76 mg/100 ml), and IV glucose was given for a further 24 hr. He made a complete recovery with no further hypoglycemia even after an overnight fast and had a normal fasting serum insulin level. Eighteen months later, he was a normally developed child for his age with a tendency to upper respiratory infections and a low serum IgA.

MATERIALS

Postmortem urine was obtained from R. B. on admission by suprapubic aspiration, and urine collections were made from T. B. on admission and on days 1 to 2, and 4, and follow-up on day 37 after admission. Normal control data were obtained on urine specimens collected from 20 infants in the same age groups, and comparison was also made to specimens from over 650 neonates and infants with acute illness of other causes. Other specimens were taken, and investigations were made as described in the case reports.

METHODS

Urinary organic acids were determined by gas chromatography using previously described methods (9, 16, 19) that involve quantitative extraction by anion-exchange chromatography onto DEAE-Sephadex, stabilization of oxo acids as *O*-ethylloximes, and freeze-drying under controlled conditions of -10°C and 0.5 torr. The dry residue was then either trimethylsilylated with minimum quantity of *N,O*-bis(trimethylsilyl)trifluoroacetamide or reconstituted in 2 ml water for further extraction with solvents. In the latter procedure, which is designed to examine in more detail the more hydrophobic acidic metabolites, the reconstituted extract is saturated with solid sodium chloride, acidified to below pH 2 with hydrochloric acid, and extracted successively three times with diethyl ether and three times with ethyl acetate. The solvent

extracts are combined without drying to avoid loss of acids in the water component, blown down to dryness at room temperature with a stream of dry nitrogen, and trimethylsilylated as above.

The individual organic acids were identified using gas chromatography-mass spectrometry including repetitive scanning and maximizing ion techniques as described elsewhere (7). Before gas chromatography-mass spectrometry, trimethylsilyl-sulphate was removed from the DEAE-Sephadex extracts by chromatography on Lipidex 5000 (34). Completely unknown acids were identified with the aid of high-resolution mass spectrometry and by comparison to synthesized standards as detailed elsewhere (6).

Amino acids were determined by quantitative ion-exchange chromatography with a Technicon TSM analyzer.

RESULTS

Urinary and blood amino acids were normal except for increased levels of urinary β -aminoisobutyric acid which did not persist as the patient recovered. This amino acid is associated with tissue catabolism.

Figure 1 illustrates the chromatogram of urinary organic acids in the specimen of urine from T. B. collected during the day after admission. The upper part of Figure 2 shows the computer plot of the summed ion intensity or total ionisation plot *versus* scan number for the sample (desulphated) illustrated in Figure 1. This plot closely resembles the gas chromatogram (Fig. 1) obtained with a conventional flame ionization detector. The lower part of Figure 2 is of the summed maximizing ion intensity plot *versus* scan number and illustrates the large increase in apparent resolution which can be achieved by applying the "maximizing ion" criteria (7), for example in the areas of peak numbers 18, 19, 20, and 21. Peak numbers in Figures 1 and 2 correspond, and identifications are given in the legend to Figure 1. The chromatograms illustrate the greatly increased concentration of adipic acid (peak 10), 4-hydroxyphenylacetic acid (peak 14), suberic acid (peak 16), and of a previously unrecorded urinary organic acid (peak 8) which has been identified as 5-hydroxyhexanoic acid (6). There were also increased concentrations of octanoic, sebacic, decenedioic, and octenedioic acids and greatly reduced concentrations of the aldonic and deoxyaldonic acids (19) and of acids of the tricarboxylic acid cycle. Lactic acid excretion was not increased, and there was only a moderate increase in the concentration of 3-hydroxybutyric and acetoacetic acids.

Figure 3 illustrates the conventional gas chromatogram of the more hydrophobic acids in the same urine specimen obtained by solvent reextraction of the reconstituted DEAE-Sephadex extract. Peak identifications are given in the legend to Figure 3. This extract enables a more detailed study of the minor acidic components in the urine, allowing, for example, the identification and semiquantitation of additional previously unrecorded hydroxyhexanoic acids, 3-methylglutaconic acid, 2-hydroxyglutaric acid, pimelic acid, and salicylic acid, which are otherwise obscured by other components or present at very low levels in the urine.

Table 1 records the quantitative urinary concentrations of the major organic acids observed in both R. B. and T. B. at the time of admission and in T. B. on subsequent days and compared to the normal levels of excretion observed in infants, together with 24-hr excretions of major acidic metabolites in T. B.

No gross increase in concentration or abnormal acids were observed in the urinary volatile short-chain fatty acids in T. B. No acylglycines were observed in any of the extracts.

DISCUSSION

Reye's syndrome has been associated with a number of viruses, for example, influenza B virus in older children (11) and in infants is almost always preceded by a mild illness, often accompanied by diarrhea (17). Vomiting is a less constant feature, and coma, seizures, and respiratory disturbances are the most frequent clinical manifestations. The incidence in infants is unknown, and

Fig. 1. Gas chromatogram of urinary organic acids from T. B. (day after admission) obtained by DEAE-Sephadex extraction. Separated as their trimethylsilyl and trimethylsilyl ethoximes by gas chromatography on 1.83 x 0.003 m glass columns packed with 10% OV 101 on High Performance Chromosorb W, 80 to 100 mesh, by temperature programming from 110 to 285°C at 4°C/min with a 5-min initial isothermal delay. Peak identifications are: 1, sulphate; 2, 3-hydroxybutyric acid; 3, acetoacetic acid; 4, 3-hydroxyisovaleric acid; 5, octanoic acid; 6, phosphate; 7, glyceric acid; 8, 5-hydroxyhexanoic acid; 9, 2-deoxytetroneic acid; 10, adipic acid; 11, methyladipic acid; 12, tetronic acids; 13, 3-hydroxy-3-methylglutaric acid; 14, 4-hydroxyphenylacetic acid; 15, octenedioic acid; 16, suberic acid; 17, homovanillic acid (+); 18, glycerophosphoric acid; 19, pentonic acids; 20, decenedioic acid; 21, sebacic acid; 22, glucuronic acid; 23, glucaric acid; 24, *n*-tetracosane (internal standard); 25, *n*-hexacosane (internal standard).

many cases probably remain undiagnosed (17). The outcome of Reye's syndrome in infants is generally poor, and residual neurologic deficits often occur (35). The syndrome is uncommon in siblings, although familial occurrences, including at least one in twin infants (33), have been reported (17). The absence of familial occurrences tends to negate the suggested genetic susceptibility towards Reye's syndrome in some infants with prodromal infections (2). Encephalopathy and fatty degeneration of the viscera also characterize specific diseases in which chemical toxins have been identified or implicated including Jamaican vomiting sickness, mycetismus, and aflatoxin ingestion (10, 24). It has been suggested that these agents act as mitochondrial toxins, and it has been demonstrated that viruses may potentiate the action of similar synthetic toxins (10), for example pent-4-enoic acid, an analogue of the active metabolite of hypoglycin, methylenecyclopropylacetic acid. A xenobiotic origin of Reye's syndrome has been suggested in line with these findings (23), with the toxin causing mitochondrial metabolic disruption of differing severity dependent on the toxin concerned, which is perhaps potentiated in many cases by viral infections (10). It is of note, however, that Mullen (23) has suggested that the exposure to the toxin occurs prior to the viral agent, causing subclinical damage, altered lipid metabolism, and impaired immune responsiveness, leading to susceptibility to viral infection. It is of interest in this context that the liver appearances in R. B. indicated a lesion of some time.

Similarities between Reye's syndrome and Jamaican vomiting sickness are frequently indicated (10, 21, 22), but discrete and

fundamental differences also occur. Table 2 compares the reported features of these two syndromes with the observations in the present cases that show closer similarities to Jamaican vomiting sickness than to Reye's syndrome. As indicated by Table 2, the present cases were associated with replicating adenovirus in the gut (36). Adenovirus has been implicated as a cause of gastroenteritis, and adenoviruses have been isolated from children with a wintertime diarrheal illness associated with respiratory symptoms (3). Reye's syndrome has been compared with viral ketoacidosis (1), but adenovirus occurs in the gut of normal children, and the organic aciduria observed in the present cases is inconsistent with a diagnosis of gastroenteritis. Children with gastroenteritis show a gross ketonuria with greatly elevated urinary concentrations of 3-hydroxybutyrate and acetoacetate without an increase in the concentration of 4-hydroxyphenylacetic acid (5). The present cases showed little evidence of ketosis and had high concentrations of 4-hydroxyphenylacetic acid in their urine, this being consistent with intestinal stasis, malabsorption, or intestinal mucosal damage, as could be expected with an ingested toxin. The other organic acids observed in the urine of the present cases provide vital information on the underlying biochemistry and suggest that the etiology of these cases is a chemical toxin producing a syndrome with close similarities to Jamaican vomiting sickness.

Table 3 compares the organic acids observed in the urine of the present infants to those observed in patients with Jamaican vomiting sickness (30) and those with Reye's syndrome (15, 30). The similar dicarboxylic C_{10} - C_{16} aciduria in both disorders is of interest

Fig. 2. Organic acids in the same urine specimen extracted illustrated in Figure 1 after desulphation on Lipidex 5000. The upper part of the figure shows the computer plot of the summed ion intensity or total ionization plot versus scan number and closely resembles the gas chromatogram obtained with conventional flame ionization detection shown in Figure 1. The lower part of the figure is of the summed maximizing ion intensity plot versus scan number and illustrates the large increase in apparent resolution obtained by this technique.

and probably occurs due to a similar mechanism. Urine from healthy infants and adults may contain low amounts of aliphatic dicarboxylic acids of chain length C_6 - C_{10} (4, 19) and very low amounts of dicarboxylic acids of similar chain length containing methyl branches, cyclopropane rings, and acetylenic bonds (19, 20). Increased excretion of C_4 - C_{10} dicarboxylic acids have been reported in a number of pathologic conditions including ketoacidosis, where increased concentrations of adipic and suberic acids occur (25). High concentrations of saturated and monounsaturated dicarboxylic C_6 - C_{10} acids have been observed in patients with carnitine deficiency (18) and those with possible inherited defects in the β -oxidative pathway of fatty acid metabolism (14, 20, 26, 31). In the present cases and in those with Jamaican vomiting sickness, there was little ketosis, and the dicarboxylic aciduria was different from that in ketotic patients. It is apparent that the mechanisms by which they are produced are probably different, with ω -oxidation of long-chain fatty acids followed by normal β -oxidation in ketosis compared to inhibited β -oxidation of medium-chain fatty acids in the present cases. Jamaican vomiting sickness, and similar disorders, followed by ω -oxidation to the dicarboxylic acids. Inhibition of β -oxidation occurs via inhibition of specific acyl CoA dehydrogenases and of the formation and transport of acyl carnitine esters through the mitochondrial membrane. Defective β -oxidation by inhibition of these acyl CoA dehydrogenases is also indicated in these cases by excretion of octanoic acid because this acid and the shorter chain fatty acids do not require carnitine for mitochondrial transport. There is no general increase in dicarboxylic acid excretion in Reye's syndrome (15, 30) indicating relatively normal β -oxidation. Further evidence of the specificity of acyl CoA dehydrogenase inhibition is given by the increased urinary concentrations of 3-hydroxyisovaleric acid, due

Fig. 3. Gas chromatogram of the urinary organic acids in T. B. (day after admission), obtained by solvent reextraction with ether and ethylacetate of the acidified and sodium chloride saturated reconstituted residue from the freeze-dried DEAE-Sephadex extract. Separation conditions are as described for Figure 1. Peak identifications are: 1, lactic acid + phenol; 2, cresol + 3-hydroxypropionic acid; 3, 3-hydroxybutyric acid; 4, 3-hydroxyisovaleric acid; 5, phosphate; 6, succinic acid; 7, 3-hydroxyhexanoic acid?; 8, 5-hydroxyhexanoic acid; 9, glutaric acid; 10, 2-methylglutaric acid?; 11, unidentified; 12, 3-methylglutaconic acid; 13, unidentified; 14, adipic acid; 15, 3-methyladipic acid; 16, trihydroxybenzene (artefact); 17, 2-hydroxyglutaric acid; 18, pimelic acid; 19, 3-hydroxy-3-methylglutaric acid; 20, 4-hydroxyphenylacetic acid; 21, octenedioic acid; 22, suberic acid; 23, aconitic acid?; 24, unidentified; 25, hippuric acid; 26, decenedioic acid; 27 and 28, unidentified; 29, sebacic acid + some 4-hydroxy-3-methoxymandelic acid; 31, salicyluric acid; 34, 4-hydroxyhippuric acid; 38, *n*-tetracosane (internal standard); 39, *n*-hexacosane (internal standard).

to inhibition of isovaleryl CoA dehydrogenase (28, 29), similar to the observations in Jamaican vomiting sickness. In contrast, however, is the absence of ethylmalonic acid, said to be characteristic of butyryl CoA dehydrogenase inhibition (31, 32), and only a minimal amount of glutaric acid that occurs due to inhibition of glutaryl CoA dehydrogenase (30). The lack of inhibition of butyryl CoA dehydrogenase would explain the reduced accumulation of short C_3 - C_6 fatty acids in these patients, and although the accumulation of these acids is similar in all disorders, there were no detectable urinary mono- or dicarboxylic acid acyl glycines in the present cases. This is in contrast to the observation of hexanoylglycine in the urine of patients with Jamaican vomiting sickness (30) and a patient with proposed butyryl CoA dehydrogenase deficiency (31), indicating little or no accumulation of hexanoic acid or hexanoyl CoA in the present children.

The difference in specificity of inhibition of acyl CoA dehydrogenases in these children compared to patients with Jamaican vomiting sickness indicates that the nature of the possible toxin, although closely similar, is not identical to methylenecyclopropylacetic acid, the active metabolite of hypoglycin. The occurrence in the urine of both of the present cases of high concentrations of a previously unrecorded urinary organic acid that has been identified as 5-hydroxyhexanoic acid (6) may indicate the nature of the causative xenobiotic agent. 5-Hydroxyhexanoic acid would conceivably occur due to ω -1 oxidation of accumulating hexanoic acid (6), but this seems unlikely, unless these infants represent a peculiar genetic entity compared to the several reported cases of dicarboxylic aciduria with accumulation of hexanoic acid (14, 18, 25, 30, 31), none of whom apparently excreted detectable 5-hydroxyhexanoic acid. The possible alternative origins of this acid are therefore of particular interest, and it has been suggested (6) that this acid could be derived from its immediate metabolic precursor hex-4-enoic acid, an analogue of methylenecyclopropylacetic acid and pent-4-enoic acid.

Table 1. Concentrations of urinary organic acids (extracted by DEAE-Sephadex) (mg/g creatinine)

Acid	T. B.					
	R. B. (postmortem urine)	Day 1-2 (IV glucose)	Day 4 (normal food)	Day 37 (fully recovered)	Normal ranges	T. B. (mg/24 hr; day after admission)
Lactic (+)	180	90	— ²	—	70 ¹	—
3-Hydroxybutyric	30	250	—	—	—	39
Acetoacetic	—	50	—	—	—	8
3-Hydroxyisovaleric	40	60	2	20	10	9
Octanoic	—	3	—	—	—	0.5
Glyceric	—	3	—	—	—	—
4-Deoxytetronic	—	—	2	80	5-70	—
5-Hydroxyhexanoic	340	330	—	—	—	51
2-Deoxytetronic	—	10	10	80	2-60	—
Adipic	1340	410	50	—	10 ¹	64
Methyladipic	—	10	—	—	45 ¹	—
Tetronics	—	70	95	210	2-210	—
2-Oxoglutaric	—	—	30	20	50	—
4-Hydroxyphenylacetic	500	320	10	20	90	50
Octenedioic	—	10	—	—	—	—
Suberic	1150	220	150 ¹	—	—	34
2-Deoxypentonic	—	—	—	140	5-75	—
Aconitic	—	—	70	70	2-80	—
Pentonic + decenedioic	—	50	—	—	—	8
Pentonic + Citric	—	10	70	1100	2-1000	—
Sebacic (+)	350	10	—	—	—	1.5
Glucuronic	200	180	20	10	80	—
Gluconic	80	50	40	10	60	—

¹ Multiple peak.² —, not observed.

Table 2. Relationship of Reye's syndrome, Jamaican vomiting sickness (hypoglycin toxicity), and the Harrow, England cases

	Reye's syndrome	Jamaican vomiting sickness	Harrow cases
Clinical features	Often epidemics Rarely familial Respiratory abnormalities Associated with viral infections	Isolated outbreaks Often familial Gut lymphoid hyperplasia Hypoglycin toxicity	? Identical twins Adenovirus in gut, low immunoglobulins ?
Biochemical features	Ketone bodies in urine Some hypoglycemia Metabolic acidosis Raised lactate and pyruvate	Little ketosis Severe hypoglycemia Severe acidosis with acid urine	Little ketosis Profound hypoglycemia Severe acidosis Normal lactate and pyruvate
Common features	Occur in winter months, vomiting, convulsions, coma death/high mortality, depletion of liver glycogen, small droplet fatty infiltration of liver (and kidney and myocardium in Reye's syndrome and Jamaican vomiting sickness)		

Methylenecyclopropylacetic acid, pent-4-enoic acid, and hex-4-enoic acid, which all contain the $\text{CH}=\text{C}-\text{C}-\text{COOH}$ group that appears to be necessary for their hypoglycemic effects (28), presumably act via their coenzyme A and carnitine esters to inhibit fatty acid β -oxidation, specific acyl CoA dehydrogenases, and reactions in which acetyl CoA normally participates to produce the symptoms and biochemical findings observed. The chemical nature of the toxins appears to be critical, and their effects would be expected to vary in detail, as has already been observed for methylenecyclopropylacetic acid and pent-4-enoic acid (28, 29), although closely similar in overall effects. Inhibition of fatty acid

β -oxidation and transport leads to depletion of acetyl CoA, decreased availability of NADH, and inhibition of the mitochondrial malate "shuttle" and of acetyl CoA activation of the key enzyme in gluconeogenesis, pyruvate carboxylase (Fig. 4). These effects lead to profound hypoglycaemia, inactivation of the tricarboxylic acid cycle, and depletion of glycogen stores. Fatty acids and lipids accumulate with ω -oxidation of the fatty acids to yield the dicarboxylic aciduria, without ketosis, that is observed. It is possible that some cases of Reye's syndrome are due to potentiation by viral agents of the apparently endogenous inhibitor of green acyl (butyryl) CoA dehydrogenase (13).

Table 3. *Urinary organic acids in Reye's syndrome, Jamaican vomiting sickness, and the Harrow, England cases*

Jamaican vomiting sickness [Tanaka <i>et al.</i> (30)] (2 siblings)	Reye's syndrome [Tanaka <i>et al.</i> (30)] (5 patients)	Reye's syndrome (Harrington <i>et al.</i> (15) (9 patients)	Harrow cases (Twin siblings)
Adipic Glutaric Suberic	Low levels of adipic and sebacic in one ketotic patient		Adipic Suberic
Ethylmalonic n-Hexanoylglycine 2-Methylsuccinic 4-Octenedioic 4-Decenedioic Sebacic 3-Hydroxyisovaleric Octanoic Methylenecyclopropylacetyl-glycine		Pyruvic Lactic	4-Hydroxyphenylacetic 5-Hydroxyhexanoic Methyladipic Octenedioic Decenedioic Sebacic 3-Hydroxyisovaleric Octanoic
		Normal levels of tricarboxylic acid cycle acids.	Low or absent levels tricarboxylic acid cycle acids, aldonic acids

Mechanism of hypoglycaemia and dicarboxylic aciduria

Fig. 4. Proposed mechanisms of action of the hypoglycemic analogues of methylenecyclopropylacetic acid.

The observations on the present cases have provided some insight into the biochemistry underlying two cases of apparent Reye's syndrome and have demonstrated the occurrence of a syndrome in England with close clinical and biochemical similarities to Jamaican vomiting sickness. It is apparent that some cases of Reye's syndrome at least are probably due to similar causes, that is organic acid chemical toxins related to hypoglycin and its metabolites and that it is essential to examine urinary organic acids at presentation in such cases to improve further the knowledge of the etiology of Reye's syndrome in infants.

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