found glucose absorption rate in the proximal intestine to be 12 mmol/hr/10 mg dry weight and in the distal intestine to be 4 mmol/hr/10 mg dry weight. From a similar solution (56 mM), the rate of absorption in the present study was approximately 18 mmol/hr/10 mg dry weight of the jejunum + ileum. Rider *et al.* (11), in perfusion studies of the proximal intestine, found rate of absorption of glucose to be about 10 mg/hr/10 cm. In the present study, rate of absorption from a solution with a similar mean glucose concentration was 8 mg/hr/10 cm of the perfused jejunum + ileum.

SUMMARY

In vivo study of D-glucose absorption in small intestine of rats between 7 and 73 days of age suggested that rate of absorption normalized for intestinal weight increased twofold at the time of weaning (21–23 days of age) with no further increase thereafter.

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Hypoglycin pentenoic acid
Jamaican vomiting sickness Reye's syndrome

Production of the Features of Reye's Syndrome in Rats with 4-Pentenoic Acid

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Extract

4-Pentenoic acid, an analog of hypoglycin which is believed to cause Jamaican vomiting sickness, was administered intraperitoneally to rats in an attempt to produce the features of Reye's syndrome in rats. Mean ammonia levels in plasma were found to be elevated approximately four-fold after injection of 200 mg/kg pentenoic acid in fed rats. Pentenoic acid caused hypoglycemia in fasted rats and hyperglycemia in fed rats. In chronic experiments rats were injected intraperitoneally every 4 hr with 50 mg/kg body weight of pentenoic acid for 10 doses, followed by a single dose of 200 mg/kg. The livers of the treated group were enlarged and yellow and showed extensive fatty degeneration. The blood-urea-nitrogen (BUN) was significantly higher and the free fatty acids (FFA's) significantly lower in these rats. This study shows that pentenoic acid administered to rats produces findings similar to those of Reye's syndrome and Jamaican vomiting sickness.

Speculation

The similarity of the features of Reye's syndrome, Jamaican vomiting sickness, and pentenoic acid and hypoglycin toxicity

suggests that they may be related, perhaps sharing a common pathophysiology.

Reye's syndrome was first defined as a clinicopathologic entity in 1963 (16), and usually presents as encephalopathy with evidence of hepatic dysfunction in children. The most consistent pathologic findings are fatty degeneration of the viscera, especially the liver, and cerebral edema. Common laboratory findings include hypoglycemia, elevated ammonia, and serum transaminases and a prolonged prothrombin time (8). It is relatively common, with 10–20 cases seen/year in Denver. The cause is unknown. One of the factors limiting the study of the pathophysiology and treatment of Reye's syndrome is the lack of a well defined experimental model. A preliminary account of a model, involving the toxicity of octanic acid in rabbits, has appeared (28).

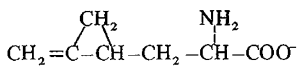
Jamaican vomiting sickness is characterized by vomiting, encephalopathy, hypoglycemia and fatty degeneration of the viscera (10, 13, 18). It is thought to be caused by ingestion of the ackee fruit which contains a toxic compound, hypoglycin (3). Most of the evidence for a causal relation rests on the fact that hypoglycin and related chemicals produce a similar syndrome in laboratory animals (3, 9).

We were impressed with the similarity of Jamaican vomiting sickness and Reye's syndrome. Because of the unavailability of hypoglycin, a related compound, 4-pentenoic acid (Scheme 1), hereafter referred to as pentenoic acid, was used in the present experiments in an attempt to produce the features of Reye's syndrome in rats. This study shows that pentenoic acid administered to rats produces findings quite similar to those of Reye's syndrome.

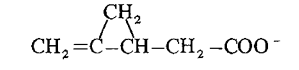
METHODS AND MATERIALS

Male Sprague-Dawley rats weighing 200–330 g were maintained on commercial rat chow (30). At the time of the experiment, rats were transferred to individual wire-bottom cages and food, but not water, was removed for the duration of the experiment. At the start, control and test rats were paired to within 10 g body weight and similar treatment was maintained throughout in that injections, sample collections, and biochemical determinations were always done on the pair at the same time.

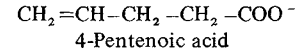
Initial experiments were performed with pentenoic acid (31) that had been neutralized without prior purification with 5 M NaOH to pH 7.4 ± 0.1. It was later found by gas liquid chromatography and mass spectrometry that there was a substantial (roughly 10%) contamination. Subsequently, pentenoic acid was purified by dissolving it in ether, making the sodium salt by the slow addition of an equimolar amount of NaH, and twice recrystallizing the product from methanol with the slow addition of ether. The product was essentially free from contamination in the same chromatography system. Inasmuch as purified and unpurified pentenoic acid gave similar results, the data were combined. In all cases, pentenoic acid was made up to a concentration of 50 mg/cc (based on the weight of the free acid) and passed through a 0.45-μm Millipore filter. Controls received an equal volume of 0.5 M NaCl.



Hypoglycin



Methylene-cyclopropyl acetic acid
(active metabolite of hypoglycin)



4-Pentenoic acid

Scheme 1

Preliminary experiments showed pentenoic acid has a relatively short duration of action. Because some of the abnormalities might be expected to be present only in acutely ill rats (*e.g.*, elevated ammonia, hypoglycemia), whereas other alterations might occur only over a longer time period (*e.g.*, fatty liver, elevated BUN), models for acute and chronic toxicity were developed.

In the acute experiments rats were given one dose of 200 mg/kg pentenoic acid intraperitoneally and a short time later (specified in figures) samples were collected. In chronic experiments rats were injected intraperitoneally every 4 hr with 50 mg/kg body weight of pentenoic acid for 10 doses. One to 2 hr after the last 50 mg/kg dose, 200 mg/kg were given intraperitoneally and samples collected 20–45 min later.

For sample collection, rats were anesthetized with ether, their abdomens opened, and blood collected from the abdominal aorta. In chronic experiments, the total body weight and the liver weight were measured and tissue placed in 10% formalin for histologic examination. Appropriate sections were stained with hematoxylin and eosin (H & E) and osmic acid stains.

Serum glucose, glutamic oxaloacetic transaminase (SGOT), Na^+, BUN, and bilirubin were determined as described previously (15). Blood gases were measured using a blood gas analyzer (32). Ammonia in plasma was measured using a commercial ammonia kit (33). Free fatty acids were estimated by the method of Novak (14).

Differences were tested for significance by the paired *t* test (17).

RESULTS

Formal testing of the LD_{50} was not done. However, some rats given 100 mg/kg pentenoic acid died within 2 hr. Other animals given this dose progressed to the stage of prostration and recovered after 2 hr, and thereafter appeared normal. At a dose of 200 mg/kg all rats died, fed rats in 20–30 min and fasted rats in 45–60 min. The first noticeable sign of toxicity was increased depth of respirations, followed by prostration and then seizures, coma, and death.

ACUTE STUDIES

Acute studies were done in both fed and fasted rats. Mean plasma ammonia levels were found to be elevated approximately fourfold after the injection of 200 mg/kg pentenoic acid in fed rats (Fig. 1). Two fasted rats treated acutely with purified pentenoic acid had levels of ammonia in plasma of 249 and 281 μg/100 ml and the respective controls had levels of 42 and 45 μg/100 ml. Pentenoic acid caused hypoglycemia in fasted rats (Fig. 3) and hyperglycemia in fed rats (Fig. 1). There was a suggestion that FFA's were elevated in the fasted animals given pentenoic acid, but the differences were not statistically significant (Fig. 2). Blood gases were measured in eight rats (Table 1). Three treated rats had a mild acidosis, with CO_2 retention in two of these. In agreement with our observation of hyperventilation, four test rats had a pH higher than all control rats and relatively low P_{CO_2} values.

CHRONIC STUDIES

Rats treated chronically with pentenoic acid showed no obvious signs of illness until after the last dose of 200 mg/kg. Treated rats lost significantly more weight ($P < 0.001$) than

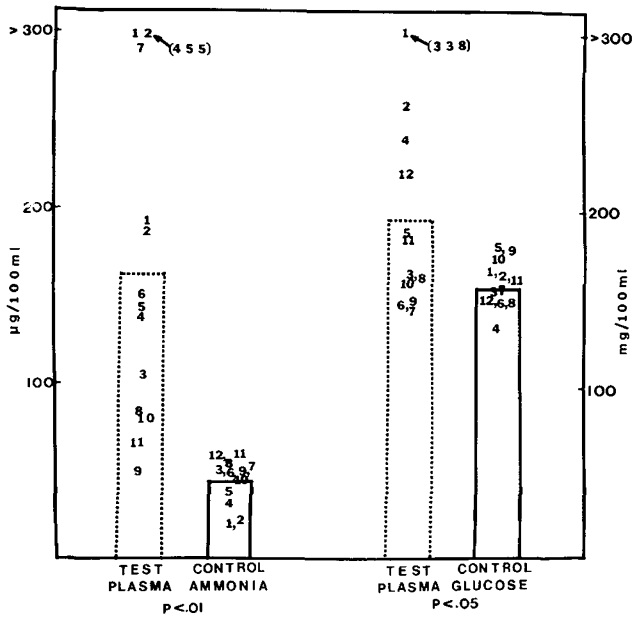


Fig. 1. Acute treatment in fed rats. Rats that had been allowed free access to food were given 200 mg/kg pentenoic acid and 20–25 min later samples were collected. The numbers refer to the pair number. Rats 7–12 were given purified pentenoic acid. Twelve pairs of rats were studied.

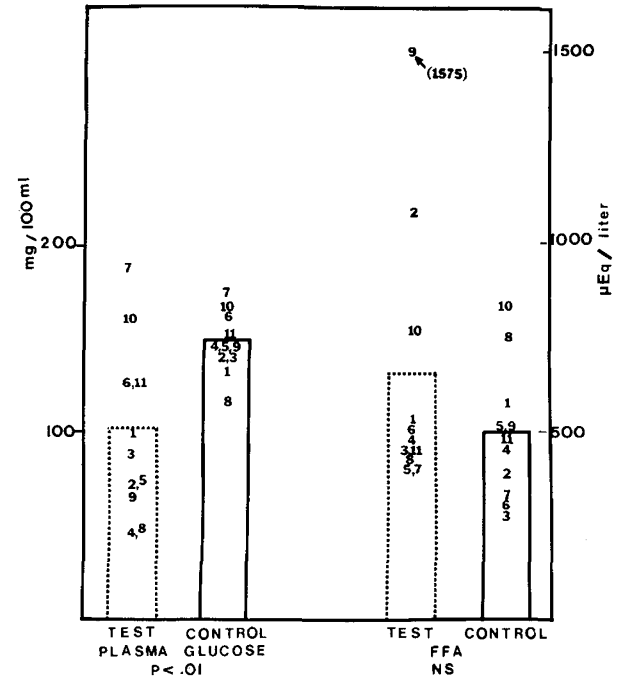


Fig. 2. Acute treatment in fasted rats. Rats that had been fasted for 20 hr were given 200 mg/kg pentenoic acid and 45–60 min later, as soon as the rats began having seizures, samples were collected. The numbers refer to the pair number. Rats 7–11 were given purified pentenoic acid. Eleven pairs of rats were studied.

control rats. The treated group lost 18.2 ± 1.8% (1 SD) initial body weight (mean weight loss 43 ± 5.7 g) and the control group 15.3 ± 2.1% initial body weight (mean weight loss 36 ± 8.2 g) from an initial mean weight of 236 g in both groups.

The livers of the treated group were enlarged on gross inspection and weighed more than the livers of the controls ($P < 0.001$). The mean (±1 SD) percentage of initial body weight was 3.17 ± 0.41% for test livers (actual mean weight = 7.49 g) compared with 2.48 ± 0.15% for control livers (actual mean weight 5.87 g).

Figure 3 shows an H & E-stained section of liver from typical control and test rats and a similarly prepared section from a patient with Reye's syndrome for comparison. The livers from the pentenoic acid-treated rats showed extensive fatty degeneration. The fat was distributed in small droplets throughout the cellular cytoplasm, with no displacement of the nucleus. Individual hepatocytes were enlarged and nucleoli were prominent. There was no evidence of necrosis, inflammation, or bile stasis.

In the chronic experiments there was no significant difference between the glucose in plasma in the control and experimental groups, although the glucose in two treated rats was clearly low (91 and 106 mg/100 ml). Chronic treated rats were killed before they had seizures, in contrast to the acutely treated fasted rats. The SGOT activity was statistically elevated when both the rats given the unpurified and purified pentenoic acid were compared with controls. The SGOT was higher, but not significantly so, in the five rats given purified pentenoic acid compared with their paired controls. The BUN was signficantly higher in the treated rats and the FFA's lower than in control rats (Fig. 4).

The mean serum sodium in both the test and control groups was 142 mEq/liter. The total bilirubin was measured (to the nearest 0.1 mg/100 ml) in 10 pairs and was 0.1 mg/100 ml in nine treated and nine control rats and 0.3 mg/100 ml in one test and one control rat.

DISCUSSION

The present study shows that pentenoic acid produces in rats most of the essential features of Reye's syndrome. Table 2 combines the data from the present paper and previous reports and shows a striking similarity between Reye's syndrome, Jamaican vomiting sickness, and findings produced in animals by hypoglycin or pentenoic acid.

The elevated ammonia in the pentenoic acid-treated rats presumably reflects inhibition of hepatic ureagenesis. The fact that the serum ammonia rises fourfold only 20–25 min after the injection of pentenoic acid illustrates the rapid turnover of ammonia in relation to the plasma level. Since there is no clear relation between plasma ammonia levels and the resultant encephalopathy, the role of the elevated ammonia in the toxicity of pentenoic acid is not established, but should receive consideration as a possible factor.

Hypoglycemia from pentenoic acid occurred only in fasted rats, and could be consistently demonstrated only shortly before death. Pentenoic acid probably causes hypoglycemia by inhibiting gluconeogenesis (see below), and thus the lack of

Table 1. *Acute treatment in fed rats*[1]

	pH		P_{O_2}		P_{CO_2}		Base excess	
	P	C	P	C	P	C	P	C
1	7.39[2]	7.48	26[2]	81	41[2]	30	0[2]	0
2	7.52	7.51	85	85	26	27	0	0
3	7.50	7.48	84	76	29	30	0	0
4	7.52	7.49	81	76	20	29	−4	0
5	7.42	7.50	86	67	21	26	−10	−1
6	7.53	7.47	70	64	25	30	0	0
7[3]	7.54	7.45	80	54	28	34	+2	0
8[3]	7.44	7.45	50	74	40	30	+3	−2

[1] Rats that had been allowed free access to food were given 200 mg/kg pentenoic acid and 20–25 min later samples were collected; P: pentenoic acid; C: control.

[2] Values obtained from animals that were barely gasping. The other animals manifest only hyperventilation.

[3] Purified pentenoic acid.

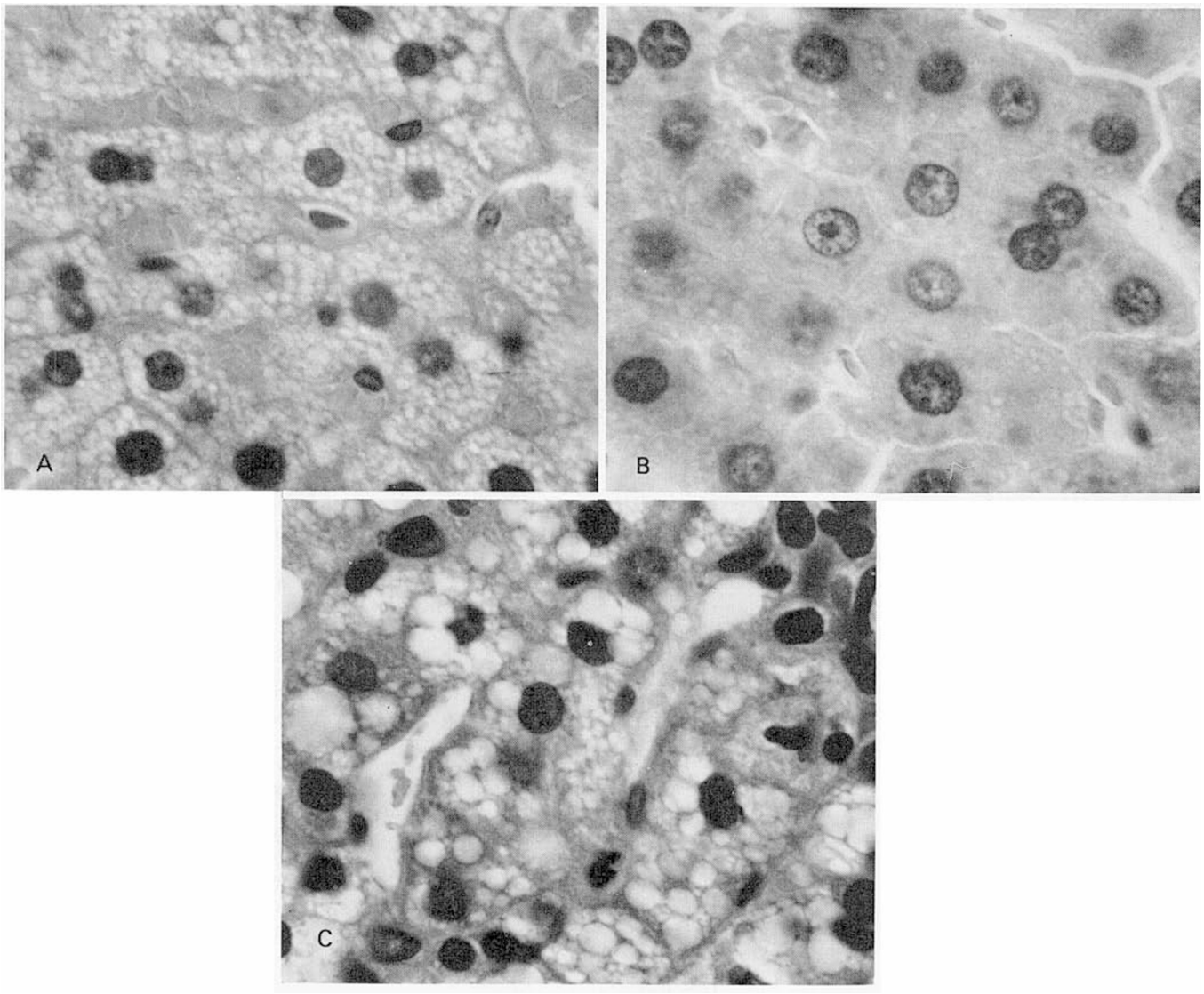


Fig. 3. Hematoxylin and eosin-stained sections of liver from test (*A*) and control rats (*B*) and a patient with Reye's syndrome (*C*). Original magnification × 650.

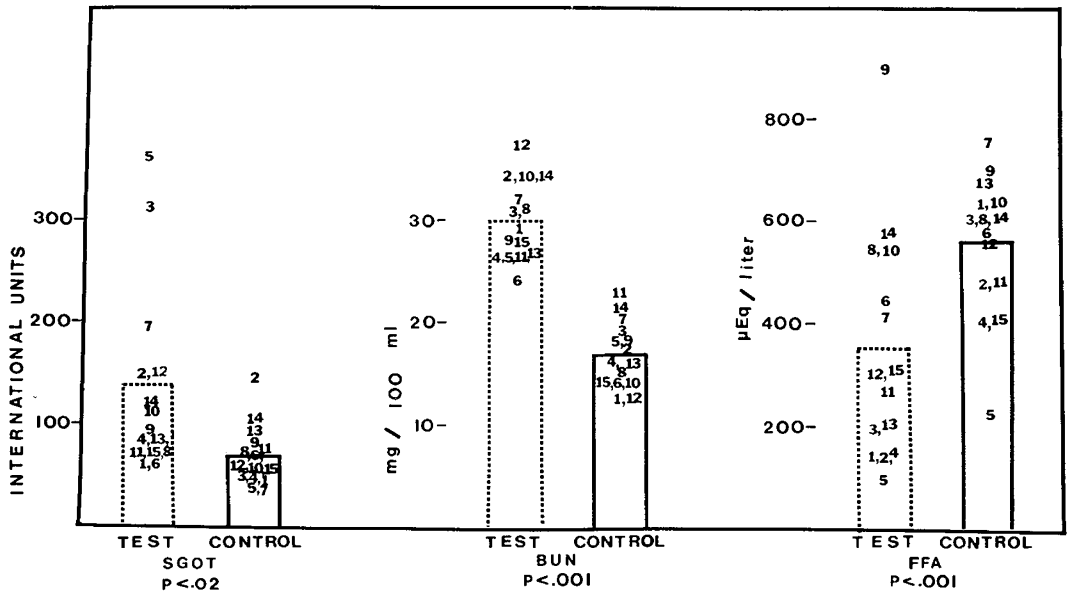


Fig. 4. Chronic treatment. See *Methods* for dosage schedule. The numbers refer to the pair number. Rats 11–15 were given purified pentenoic acid. Rats 6–10 were killed 45 min after the 200 mg/kg dose. All others were killed 20 min after this dose. Fifteen pairs of rats were studied.

Table 2. *Comparison of Reye's syndrome, Jamaican vomiting sickness, hypoglycin, and pentenoic acid poisoning*

Finding	Reye's syndrome	Jamaican vomiting sickness	Hypoglycin given to animals	Pentenoic acid given to animals
Vomiting common	Yes	Yes (18)	Yes (3)	
Acute encephalopathy	Yes	Yes (18)	Yes (3)	Yes[1] (22)
Children primarily affected	Yes	Yes (18)		
Hypoglycemia common	Yes	Yes (10,13)	Yes (3)	Yes[1] (22)
Rapid Response to glucose uncommon	Yes	Yes (13)	Yes (3)	
Decreased liver glycogen	Yes	Yes (13)	Yes (3)	
Decreased gluconeogenesis	Yes		Yes (3)	Yes (21)
Elevated ammonia	Yes			Yes[1]
Elevated BUN[2]	Yes		Yes (3)	Yes[1]
Bilirubin usually normal	Yes	Yes (10, 13)		Yes[1]
Fatty infiltration of liver	Yes	Yes (10, 18)	Yes (9)	Yes[1]
Hepatic mitochondrial swelling	Yes		Yes (4)	
Cerebral edema	Yes	Yes (10)		
Survivors usually normal	Yes	Yes (13)		Yes[1] (22)

[1] Present paper.

[2] Blood-urea-nitrogen.

hypoglycemia in fed rats is not unexpected. The fact that the fed rats were hyperglycemic indicates that factors other than hypoglycemia are important in the toxicity of pentenoic acid.

The elevated urea in the pentenoic acid-treated rats may be caused by dehydration, impaired renal function, or increased utilization of amino acids for energy. The former seems least likely since the weight difference between test and control rats would indicate at most about 3% dehydration in the test rats.

Some workers have suggested that elevated FFA's may be important in the pathophysiology of Reye's syndrome (5, 6). Thus the low free fatty acids in the rats given the chronic pentenoic acid treatment might be interpreted as an important difference between pentenoic acid toxicity and Reye's syndrome. We suspect that the level of FFA's is probably often a reflection of stress and hypoglycemia. The mean levels of FFA's of 2.41 mEq/liter in a group of patients with Reye's syndrome (1) are not markedly different from the mean level of 1.95 mEq/liter in a group of normal children fed a ketogenic diet and fasted (23). The FFA's were higher (although not significantly so) in the acutely treated 20-hr fasted rats that were severely ill and hypoglycemic. In another study, a single dose of pentenoic acid did result in an apparent elevation of FFA's in rats fasted only 4 hr (22). Elevated FFA's have been reported in hypoglycin-treated hypoglycemic rats (7). In the chronically treated rats in this study there was a suggestion that FFA's rise in response to stress. The five rats killed at 45 min after the 200 mg/kg dose (prostrate and hyperventilating) had mean FFA levels of 565 mEq/liter compared with a mean level of 240 mEq/liter in rats killed at 20 min (not obviously ill). Thus chronic treatment of rats with pentenoic acid results in low FFA's but the level of FFA's probably rises in response to stress.

The SGOT in the pentenoic acid-treated rats was higher than in controls but was not statistically different for the group given purified pentenoic acid and was not of the magnitude often seen in Reye's syndrome. The meaning of this apparent difference between pentenoic acid toxicity and Reye's syndrome is not clear, since there is little basis for interpreting SGOT values in rats. In addition, even the apparent elevation that did occur could be caused by factors such as an irritative effect of pentenoic acid in the peritoneal cavity.

The similarity between this model and Reye's syndrome suggests that they may share a common pathophysiology. It is possible that Reye's syndrome is caused by exposure to pentenoic acid or a related compound. Although this possibility should not be completely discarded, it seems unlikely. More likely is the possibility that pentenoic acid-treated animals and patients with Reye's syndrome share the same or a similar biochemical defect or defects. Thus, it seems appropriate to review briefly what is known about the pathophysiology of the toxic effects of pentenoic acid.

Pentenoic acid is a potent inhibitor of fatty acid oxidation (2, 19). Bressler *et al.* (3) has proposed that this inhibition is caused by depletion of intracellular free CoA and carnitine; however, Sherrat and coworkers (12), using isolated mitochondria, have shown that there is no relation between the ability of related compounds to reduce mitochondria-free CoA and their ability to inhibit fatty acid oxidation. They have shown that a metabolite of pentenoic acid, 2,4-pentadienoyl-CoA, is a potent inhibitor of 3-oxoacyl-CoA-thiolase, an enzyme of fatty acid oxidation, and proposed this as the cause of the impaired fatty acid oxidation (11). In any case, one direct effect of pentenoic acid is interruption of fatty acid oxidation. At higher concentrations it also impairs other mitochondrial functions (20). Pentenoic acid results in decreased tissue ATP and NADH (2, 29).

The reduced availability of energy probably accounts for the decreased gluconeogenesis (24). Because fatty acids cannot be metabolized, there is increased use of glucose for energy. The impaired gluconeogenesis and, to some extent, increased glucose utilization results in hypoglycemia. The hypoglycemia thus is probably secondary to the direct effect of pentenoic acid on fatty acid oxidation (24). Presumably, since fatty acids cannot be oxidized they are esterified to triglycerides accounting for the fatty degeneration of the liver. It is not known whether the impairment of fatty acid oxidation accounts for all of the effects of pentenoic acid.

Tanaka *et al.* (25–27) have shown that hypoglycin inhibits the enzyme isovaleryl-CoA dehydrogenase and probably also glutaryl-CoA dehydrogenase and in rats results in the excretion of isovaleric, glutaric, and several other unusual carboxylic acids. In this respect hypoglycin toxicity and probably Jamaican vomiting sickness differ from pentenoic acid toxicity and Reye's syndrome. For more details on pentenoic acid and related compounds the reader is referred to reviews by Bressler (3) and Sherratt (24).

SUMMARY

4-Pentenoic acid, an analog of hypoglycin which is believed to cause Jamaican vomiting sickness was administered to rats in an attempt to produce the features of Reye's syndrome. Pentenoic acid produced most of the essential features of this disorder, including fatty degeneration of the liver, hyperammoniaemia, hypoglycemia, and elevated SGOT and BUN levels.

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