MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

May 8, 1975

REYE'S SYNDROME

BURTON COMBES, M. D.

Reye's Syndrome

Case 1 [redacted]

[redacted], a 54/12 year old [redacted] girl, developed an upper respiratory tract infection with fever on [redacted]/74. This was treated with Dimetane expectorant and with four baby aspirins (75 mg each) every four hours with good results. On [redacted] the patient began vomiting and was given 25 mg phenergan suppositories at 1:30 and 7:30 PM. Temperature was 104.5°F later that evening. At about 5 AM on [redacted] the patient awakened her family with cries. She was found unresponsive, having grand mal seizures. At 5:30 AM the patient was seen in an Emergency Room still convulsing T 102.4, BP 90/70 P 138. Phenobarbital 60 mg was given IV at 5:45. An LP was performed, blood tests obtained, then an IV of 5% D/W started. Ampicillin 500 mg, and Solu Cortef 100 mg were administered IV. When seizures recurred at 6:35 AM, the patient received valium 1.5 mg IV and was transferred to [redacted]

Laboratory tests in the Emergency Room revealed a WBC of 20,200 with 72 polys, 6 bands, 20 lymphs, 2 monos, Hgb 13.7, Hematocrit 41.8. Cerebrospinal fluid clear, 1 lymph, glucose 8 mg%, protein 13 mg%, culture negative. Na 141, K 5.1, Cl 102, CO_2 18, amylase in normal range.

At 0700, the patient was comatose, responsive only to deep pain. Doll's eyes were present. Pupils were not described. The neck was supple. Reflexes were equal and active. Bilateral Babinski's were present. The liver was palpable 2 cm below the right costal margin.

The patient had recurrent seizures and received IV valium 1.25 mg at 0735, 0745, 0825, 0828, 0910 and 0915. At 0850 she received 250 mg calcium gluconate and 25 cc of D25W IV. Seizures subsided, the patient remained comatose. At 1100, respirations slowed, then stopped. After intubation, it was noted that the patient was flaccid, areflexic and pupils were dilated and fixed. Disc margins were blurred. Subsequently the patient was maintained on a respirator. Neurologic function remained unchanged. Isoelectric EEGs were recorded on [redacted] and [redacted] The patient died on [redacted]/74.

	[redacted]	[redacted]	[redacted]	[redacted]
WBC	20,200	18,700		11,100
Urinalysis				
glucose		+	3+	2+
ketones		moderate	negative	negative
sp.gravity		1.023	1.002-1.005	1.002-1.009
Arterial blood gasses		After intubation only		
Na/K	141/5.1	134/4.0	151/4.7	153/4.8
CO_2/Cl	18/102	16/92	/111	/118
BUN/Creat.	24/1.1		26/0.2	
Glucose	(CSF 8)	*$\bar{p}$ I.V. 178	227	355
Bilirubin		0.8		
SGOT		420		
Alkaline Ptase		44		
Prothrombin time- seconds pt/control		25/10.2	>120/10.1	
NH_3 µg%		441	238 145	

The pathological examination revealed cerebral edema with herniation of the cerebellar tonsils; marked anoxic encephalopathy; fatty metamorphosis of the liver; and slight fatty metamorphosis of the heart. The combination of encephalopathy with fatty degeneration of the viscera led to a diagnosis of Reye's syndrome.

Case 2 [redacted].

[redacted], a 15 yr old [redacted] boy, on [redacted]/75 experienced the onset of a "flu-like" illness characterized by cough, rhinorrhea, sore throat and myalgias. Several other family members had the same illness concurrently. The patient took Ornade and Anacin 10 grains every few hours. On [redacted], although his respiratory symptoms improved, and fever subsided, he became lethargic, vomited and decreased his intake of food. On [redacted] he did not recognize his parents. On [redacted], he was seen at a local hospital with these symptoms and was said to be "out of his head." Therapy there included aspirin and terramycin. The patient continued to act inappropriately, had difficulty ambulating and later on [redacted] became unresponsive to commands and was brought to [redacted].

On physical examination the patient was stuporous, combative and occasionally cried out. T 99, P132, R 18, PB 150/70. The neck was supple. Pupils were slightly dilated but reacted briskly. Doll's eyes were intact. Fundi were normal. The patient moved his extremities spontaneously and in response to pain; reflexes were active; bilateral ankle clonus and Babinskis were elicited.

When a blood salicylate level of 80 mg% was recorded, the patient was treated for salicylate intoxication with gastric lavage, charcoal and a cathartic. Urine flow was increased with IV fluids, diuretics, and the urine was alkalinized. The blood salicylate concentration fell rapidly. On [redacted] the patient remained lethargic, periodically would thrash about, and maintained his ankle clonus and bilateral Babinskis. An EEG revealed diffuse slowing consistent with a metabolic encephalopathy. By [redacted] the patient was alert and oriented although still somewhat somnolent. Clonus and Babinskis were no longer elicited.

The combination of a "flu-like" illness, followed by an encephalopathy, and documentation of abnormal liver tests suggested a diagnosis of Reye's syndrome. A liver biopsy on [redacted]/75 revealed normal liver histology with a few fine droplets of fat. The patient continued to improve and was discharged on [redacted]/75. He has since returned to school and is reportedly back to his pre-illness state. Serological studies performed by Dr. James Luby suggest the patient's original illness was Influenza A.

	[redacted] 1700 hrs	[redacted] 2230 hrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WBC	12.1	7.8	10.5			6.0	
Urinalysis							
glucose	0		0			0	
ketones	0		0			0	
specific gravity	1.031		1.007			1.005	
Arterial blood gasses while on IV fluids	pH 7.37 pCO_2 22.7 pO_2 116 CO_2 13.3		7.49 22.7 112 18.0				
Na/K	142/4.2	145/33	140/3.5	143/3.3	141/3.7		
CO_2/Cl	22/104	15/104	14/102	21/108	20/110		
BUN/Creat.	-/0.5	-/0.9	10/0.7			-/0.9	
Glucose-blood	117	150	285	110			
Glucose-CSF			105				
Amylase			<F320				
Bilirubin			0.6			0.4	0.2
SGOT			2330	1725		498	60
CPK						568	
Aldolase						10.0	
Alk.Ptase			25.1 KA			38.0 KA	27.5 KA
Protime	14.5/12.		16/12		12.5/11.5	10.5/12.0	
Blood Salicylate mg%	80		21 5	2.5			

In 1963, three Australian physicians, Reye, Morgan and Baral (1), described the clinical and pathological features of a severe illness occurring in 21 children characterized by encephalopathy, fatty degeneration of the viscera and a high mortality rate (17 of 21 died). Numerous additional reports (211) of similar cases have appeared from various parts of the world in the ensuing 12 years, further establishing the existence of this clinicopathological entity which is now generally referred to as Reye's (rhymes with "eye") syndrome.

1. Reye RDK, Morgan G, Baral L: Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. Lancet 2:749-752, 1963.
2. Johnson GM, Scurletis TD, Carroll NB: A study of sixteen fatal cases of encephalitis-like disease in North Carolina children. NC Med J 24:464-473, 1963.
3. Anderson RM: Encephalitis in childhood: pathological aspects. M J Aust 1:573-575, 1963.
4. Stejskal J, Kluska V: Encephalopathy and fatty degeneration of the viscera. Lancet 1:615, 1964.
5. Joske RA, Keall DD, Leak PJ, et al: Hepatitis-encephalitis in humans with reovirus infection. Arch Intern Med 113:811-816, 1964.
6. Utian HL, Wagner JM, Sichel RJS: "White liver" disease. Lancet 2: 1043-1045, 1964.
7. Becroft DMO: Syndrome of encephalopathy and fatty degeneration of viscera in New Zealand Children. Br Med J 2:135-140, 1966.
8. Dvorackova I, Vortel V, Hroch M: Encephalitic syndrome with fatty degeneration of viscera. Arch Pathol 81:240-246, 1966.
9. Barr R, Glass IHJ, Chawla GS: Reye's syndrome: massive fatty metamorphosis of the liver with acute encephalopathy. Can Med Assoc J 98:1038-1044, 1968.
10. Norman MG: Encephalopathy and fatty degeneration of the viscera in childhood. 1. Review of cases at the Hospital for Sick Children Toronto (1954-1966). Can Med Assoc J 99:522-526, 1968.
11. Bourgeois C, Olson L, Comer D, et al: Encephalopathy and fatty degeneration of the viscera: a clinicopathologic analysis of 40 cases. Am J Clin Pathol 56:558-571, 1971.

Cases were clearly described in a number of reports published prior to 1963 (12-15). The entity is not new, therefore. However, focus on the clinical syndrome largely stems from the report of Reye and associates.

12 Brain WR, Hunter D, Turnbull HM: Acute meningoencephalomyelitis of childhood: report of six cases. Lancet 1:221-227, 1929.
13. Lyon, G, Dodge PR Adams RD: The acute encephalopathies of obscure origin in infants and children. Brain 84:680-705, 1961. (contains numerous references to cases described in the early 1900s)

14. Mortimer EA Jr, Lepow ML: Varicella with hypoglycemia possibly due to salicylates. Am J Dis Child 103:583-590, 1962.
15. Bourne WA: Liver disease in infancy. Postgrad Med J 38:642-652, 1962.

Clinical Events in Reye's Syndrome

1. The illness typically begins in the setting of an acute infectious disease in children. The initial event or underlying illness has consisted of:

   a. An upper respiratory tract infection or pneumonia
   b. An influenzal syndrome
   c. Acute exanthematous diseases
   d. Gastroenteritis
   e. Pertussis
   f. Otitis media
   g. Vaccination in infants

2. The initial event is usually considered to be of average severity, is frequently improving, when after 1 to 3 days, but as long as 2 to 3 weeks, the patient begins to vomit. Within 1 to 2 days, the child becomes irritable, restless, screams, becomes lethargic, then lapses into coma, frequently complicated by seizures.

3. The neurological events may rapidly move through progressive rostralcaudal central nervous system involvement to decorticate, then decerebrate stages and finally terminates with respiratory arrest. Staging of the patient's neurological involvement is useful, since outcome relates to the extent to which the neurological deficit progresses.

Clinical Staging of Reye's Syndrome*

Stage I- Vomiting, lethargy and sleepiness.

Stage II- Delirium, combativeness, hyperventilation, hyperactive reflexes, appropriate response to noxious stimuli.

Stage III- Obtunded, coma, hyperventilation, decorticate rigidity, preservation of pupillary light reaction and oculovestibular reflexes.

Stage IV- Decerebrate rigidity, loss of oculocephalic reflexes, large fixed pupils (with hippus on occasion), dysconjugate eye movements in response to caloric stimulation of the oculovestibular reflex.

State V- Seizures, loss of deep tendon reflexes, respiratory arrest, flaccidity.

(*Modified by Lovejoy et al. (16) from classification of progressive cerebral dysfunction of Plum and Posner (17).

Rapid progression through the first three clinical stages, and the onset of seizure activity in Stage III, suggest a poor outcome. Death or severe neurological impairment occurred in the vast majority of patients who progressed to Stages IV and V (16).

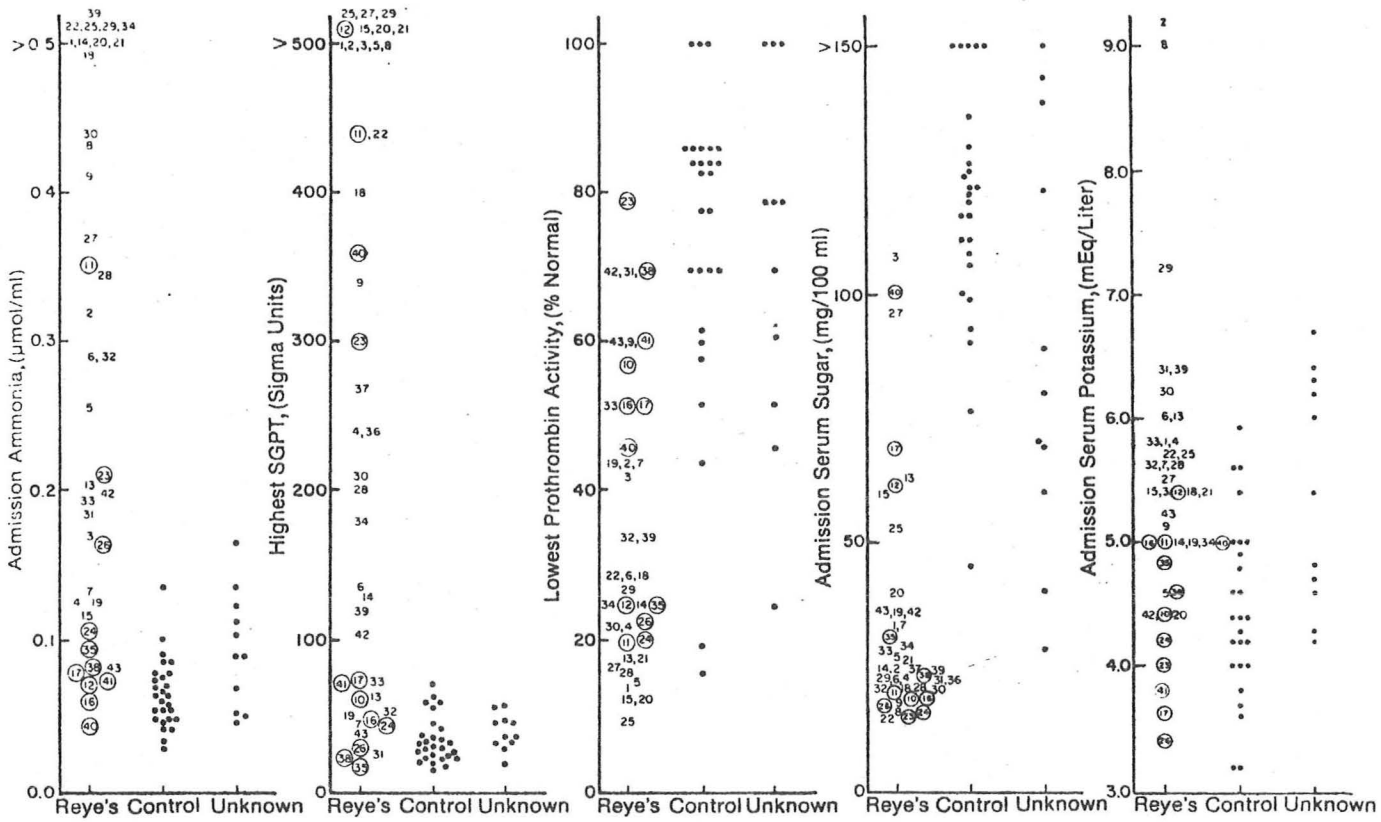
16. Lovejoy, FH, Smith AL, Bresnan MJ et al.: Clinical staging in Reye Syndrome. Am J Dis Child 128:36-41, 1974.
17. Plum F, Posner JB: Diagnosis of Stupor and Coma. FA Davis Co. Philadelphia. 1966.

Laboratory Findings in Reye's Syndrome

Low blood sugar
Low CSF sugar
High SGOT and SGPT
Prolonged prothrombin time
Elevated blood NH_3
Metabolic acidosis - respiratory alkalosis
Neutrophilic leukocytosis

See references 1 - 11, 16

18. Simpson H: Encephalopathy and fatty degeneration of the viscera acid-base observations. Lancet 2:1274-1278, 1966.
19. Huttenlocher PR, Schwartz AD, Klatskin G: Reye's syndrome: ammonia intoxication as a possible factor in the encephalopathy. Pediatrics 43:443-454, 1969.
20. Glasgow AM, Cotton RB, Dhiensiri K: Reye's syndrome. Amer J Dis Child 124:827-833, 1972.
21. Glasgow AM, Cotton RB, Dhiensiri K: Reye Syndrome III. The Hypoglycemia. Am J Dis Child 125:809-811, 1973.



—Biochemical findings from cases in the Reye's syndrome, control, and unknown encephalopathy groups. Case numbers are given for members of the Reye's syndrome group, circled numbers are survivors.

From Glasgow AM, Cotton RB, Dhiensiri K: Reye's syndrome. Amer J Dis Child 124:827-833, 1972 (20).

Pathologic Findings in Reye's Syndrome

Brain edema
Fatty metamorphosis of liver
Fatty changes of kidney, heart, skeletal muscle
Pancreatitis

See references 1 - 11

22. Stover SL, Wanglee P, Kennedy C: Acute hemorrhagic pancreatitis and other visceral changes associated with acute encephalopathy. J Ped 73:235-241, 1968.
23. Morens DM, Hammar SL, Heicher DA: Idiopathic acute pancreatitis in children. Am J Dis Child 128:401-404, 1974.
24. Glasgow AM, Cotton RB, Bourgeois DH, et al.: Reye's Syndrome II. Occurrence in the absence of severe fatty infiltration of the liver. Amer J Dis Child 124:834-836, 1972.

Etiology of Reye's Syndrome

Viral Infection

The frequency with which a prodromal illness, either upper respiratory tract infection, "flu-like" disease, exanthematous disease or gastroenteritis precedes the more severe manifestations of Reye's syndrome, has led to repeated search for an infectious agent. No bacterial pathogen has been identified. Numerous attempts have been made to isolate viruses from blood, secretions and tissue. Various viruses have been found in isolated cases.

Viruses Isolated from Cases of Reye's Syndrome

(* Virus isolated from brain or spinal fluid)

Adenovirus 3
Coxsackie A, A_9, B_1, B_4, B_5
Echo 2, 8*, 11, untyped*
Ebstein-Barr virus
Herpes simplex*
Influenza B*
Parainfluenza 2, 3
Polio virus
Reovirus 1*, 2

See references 6, 9

25. Norman MG, Lowden JA, Hill DE et al.: Encephalopathy and fatty degeneration of the viscera in childhood: II. Report of a case with isolation of influenza B virus. Can Med Assn J 99:549-554, 1968.
26. Thaler MM, Bruhn FW, Applebaum MN et al.: Reye's syndrome in twins. J Ped 77:638-646, 1970.
27. Powell HC, Rosenberg RN, McKellar B: Reye's syndrome: Isolation of parainfluenza virus. Arch Neurol 29:135-139, 1973.
28. Brunberg JA, Bell WE: Reye Syndrome. An association with type 1 vaccine-like poliovirus. Arch Neurol 30:304-306, 1974.
29. Linnemann CC, Shea L, Kauffman CA et al.: Association of Reye's syndrome with viral infection. Lancet 2:179-182, 1974.
30. Rabal JJ, Heule G: Infectious mononucleosis and Reye's syndrome. A fatal case with studies for Ebstein-Barr virus. Pediatrics 46:776-779, 1970.

In a number of instances, although viruses have not been isolated, serological or epidemiological data have indicated association of Reye's syndrome with additional viruses. There exists particularly strong association with epidemics of Influenza B.

Viruses Associated with Reye's Syndrome
(These were usually not cultured from the infected host)

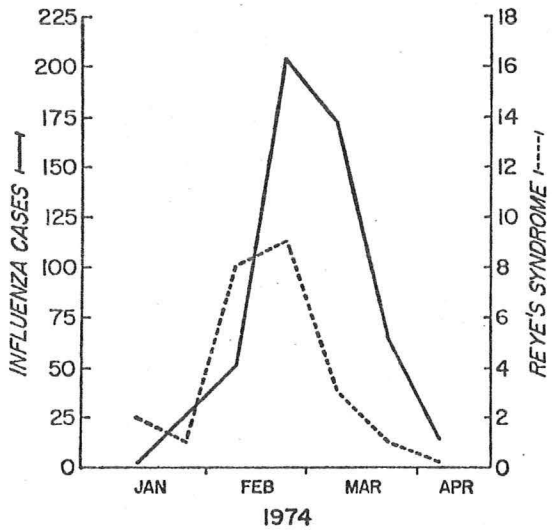
Herpes zoster
Influenza A_2
Influenza B^2
Rhinovirus
Rubeola
Vaccinia
Varicella

Clustered Cases of Reye Syndrome Related to Influenza Type B Prior to January 1971*

Location	Date	No. of Cases
Tampa, Fla	1967	6
Oklahoma	February 1969	6
Atlanta, Ga	February 1969	6
Massachusetts, Vermont	January 1970	24
Guam (Ebeye)	August 1971	6

* Reported to the Center for Disease Control, Atlanta.

From Hochbert FH, Nelson K, Janzen W: Influenza type B-related encephalopathy. JAMA 231:817-821, 1975 (35).



Cases of Reye's syndrome by date of hospital admission and reported cases of influenza in Cincinnati, Ohio, January to April, 1974.

From Linnemann CC, Shea L, Kauffman CA et al: Association of Reye's syndrome with viral infection. Lancet 2:179-182, 1974 (29).

30. Carpenter, RL: Reye's Syndrome - Oklahoma. Morbidity and Mortality Weekly Report, April 19, 1969, p. 134.
31. Glick TH, Ditchek NJ et al.: Acute encephalopathy and hepatic dysfunction associated with chickenpox in siblings. Amer J Dis Child 119:68-71, 1970.
32. Glick TH, Likosky WH, Levitt LP et al: Reye's syndrome: An epidemiologic approach. Pediatrics 46:371-377, 1970.
33. Hart JC, Fiumara NJ, Smith V: et al: Reye's Syndrome - New England and New York State. Morbidity and Mortality Weekly Report, March 27, 1971, p.101.

34. Schubert WK, Partin JC and Partin JS: Encephalopathy and fatty liver (Reye's syndrome). Chapter 28 In Progress in Liver Disease, Vol IV. Ed. Popper H and Schaffner F. Grune & Stratten 1972.
35. Hochbert FH, Nelson K, Janzen W: Influenza type B-related encephalopathy. JAMA 231:817-821, 1975.

The multiplicity of viral agents isolated from or associated with cases of Reye's syndrome, and the infrequency with which patients with identical viral illness develop encephalopathy argue against a common biological property of the viruses as being responsible for pathogenesis of the clinicopathological syndrome. Nonlethal viral infection has sensitized young mice to otherwise nontoxic doses of insecticides and resulted in encephalopathy and fatty visceral changes (36). Whether infection may act in a similar manner in the human is not clear.

36. Crocker JFS, Rozee KR, Ozere RL et al: Insecticide and viral interaction as a cause of fatty visceral changes and encephalopathy in the mouse. Lancet 2:22-24, 1974.

Toxins

Extensive searches for exogenous toxins have largely been unrewarding. Randolph et al (37) identified isopropyl alcohol in the gastric contents and viscera of one of their four patients. Glasgow and Ferris (38) obtained evidence suggesting that their patient's illness and death were caused by poisoning with a commercial paint-thinner. Bougeois, Olsen and their associates (39,40) have provided evidence that an illness with all of the features of Reye's syndrome occurring in Northern Thailand is the consequence of poisoning with aflatoxin.

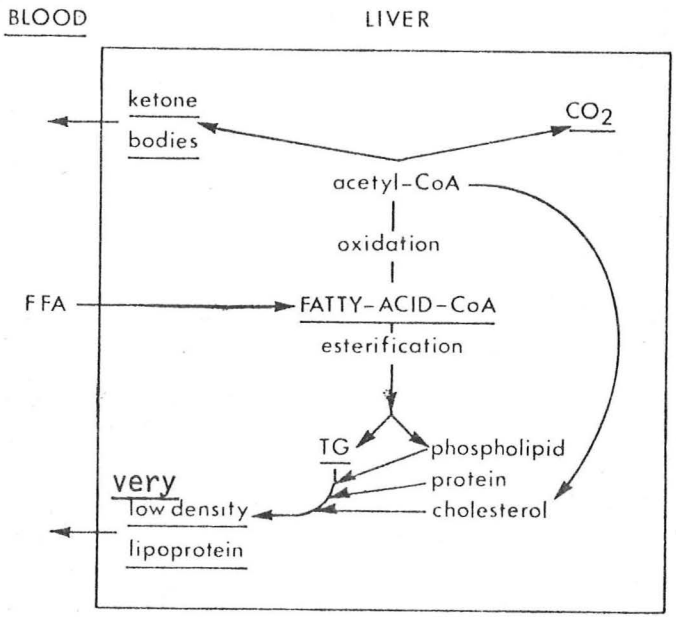
37. Randolph M, Kranwinkel M et al: Encephalopathy, hepatitis and fat accumulation in viscera. Amer J Dis Child 110:95-99, 1965.
38. Glasgow JFT, Ferris JAJ: Encephalopathy and visceral fatty infiltration of probable toxic aetiology. Lancet 1:451-453, 1968.
39. Olson LC, Bourgeois CH, Cotton RB et al: Encephalopathy and fatty degeneration of the viscera in northeastern Thailand. Clinical syndrome and epidemiology. Pediatrics 47:707-716, 1971.
40. Bourgeois C, Olson L, Comer D et al: Encephalopathy and fatty degeneration of the viscera: A clinicopathologic analysis of 40 cases. Amer J Clin Pathol 56:558-571, 1971.

Pathogenesis of the Biochemical and Pathological Findings

Fatty Liver

In virtually all forms of fatty liver, triglyceride is the major lipid that accumulates in the liver.

Regulation of Hepatic Triglyceride Content



Sustained elevations of FFA in plasma lead to increased hepatic uptake of FFA, enhanced esterification and increased triglyceride release from liver. Plasma VLDL rises. The rate of triglyceride formation exceeds that of release, and hepatic triglyceride content rises.

41. Feigelson EB, Pfoff WW, Karmen A et al: The role of plasma free fatty acids in development of fatty liver. J Clin Invest 40:2171-2179, 1961.

Impairment of VLDL synthesis or release, as induced by tetracycline, ethionine, puromycin and orotic acid will also result in increased hepatic triglyceride content. Under these circumstances plasma VLDL concentration falls.

42. Lombardi, B: Pathogenesis of fatty liver. Fed Proc 24:1200-1205, 1965.

Surprisingly, even though fatty liver is a major pathological finding in Reye's syndrome, very few studies have been carried out to examine the mechanism of its development.

The increased lipid in the liver in Reye's syndrome is largely accounted for by triglyceride (25,40), although free fatty acids are also increased (40). These chemical findings are supported by histochemical observations (43).

43. Brown RE, Johnson FB, Mullick FG: Hepatic lipid in Reye's syndrome: histochemical and ultrastructural characteristics. Penna. Med 77:39-41, 1974.

Plasma FFA are elevated (40,44). The extent of elevation is comparable to that found in a child fasted or given a low CHO high fat diet for 24-48 hours (45).

44. Brown RE, Madge GE, Trauner DA et al: Lipid and lipoprotein studies in Reye's syndrome. Virginia Med Monthly 99:622-626, 1972.
45. Senior B, Loridan L: Gluconeogenesis and insulin in the ketotic variety of childhood hypoglycemia and in control children. J Ped 74:529-539, 1969.

A paucity of data suggests that plasma VLDL is decreased (44,46).

46. Partin JC, Schubert WK, Partin JS: Mitochondrial ultrastructure in Reye's syndrome (encephalopathy and fatty degeneration of the viscera). N Engl J Med 285:1339-1343, 1971.

The composite observations indicate that the fatty liver of Reye's syndrome is at least accounted for by increased delivery of FFA to the liver. Whether a) impaired fatty acid oxidation, thus diverting intrahepatic fatty acids to esterification, and b) impaired triglyceride release from liver also contribute is at present unresolved.

Hypoglycemia

Effect of Fasting on Children (45)

	Blood			
	Glucose mg%	FFA μmEq/liter	Glycerol mmole	Insulin μmU/ml
Overnight fast	78.6	1110	0.195	7.4
48 hours restricted diet + 15-20 hour fast	34.2	1936	0.440	6.1

Children, when starved, are prone to develop hypoglycemia, ketosis and ketonuria, increased FFA and increased glycerol. The response to starvation is comparable to that observed in adults save that children develop a greater fall in blood sugar.

Admission serum insulin levels were low in patients with Reye's syndrome. Growth hormone levels were appropriately high (21).

—Serum Insulin and Growth Hormone Levels

Diagnosis	Plasma Sugar (mg/100 ml)	Serum Insulin (μu/ml)	Serum Growth Hormone (mμg/ml)
Reye	28	<1	21
Reye	29	<1	40
Reye	22	<1	22
Reye	22	<1	>40
Reye	21	<1	7.0
Reye	22	<1	>40
Reye	24	<1	11
Pneumonitis febrile convulsion	137	16.4	2.0
Encephalitis	116	<1	25
Hypertensive encephalopathy	194	7.4	20

From Glasgow AM, Cotton RB: Am J Dis Child 125:809-811, 1973 (21).

These findings argue against hyperinsulinism and hypopituitarism as causes of the hypoglycemia of Reye's syndrome. No data are available concerning rates of glucose infusion required to maintain a normal blood sugar in Reye's patients. Furthermore, no comparable data are available in normal children who are starved to serve as controls. Definitive statements cannot be made therefore about whether overutilization of glucose or underproduction of glucose is the major factor accounting for the hypoglycemia of Reye's syndrome. No author indicates that hypoglycemia is difficult to reverse with IV glucose. Therapy of the finding is not difficult therefore.

Starvation per se, associated with a viral illness could contribute significantly to the development of hypoglycemia. To what extent coexistent hepatic disease, insufficient hormonal response to starvation (glucagon, catecholomines, adrenocortical steroids), drug intake, and impaired fatty acid oxidation further contribute to the pathogenesis of the low blood sugar remains to be assessed.

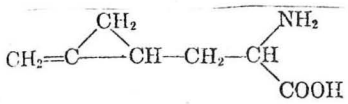
Jamaican Vomiting Sickness (47,48)

An illness resembling Reye's syndrome occurs in persons who eat the unripe fruit of the Ackee tree. The illness is more common in children and is characterized

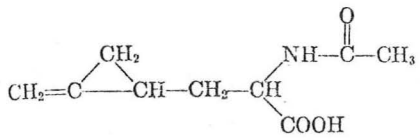
by vomiting, profound hypoglycemia, metabolic acidosis, a lack of ketosis, and fatty metamorphosis of liver, kidney and other organs.

Toxicity is accounted for by a water soluble material isolated from the seeds and pods of the Ackee fruit, and called hypoglycin. Hypoglycin, or methylene cyclopropyl alanine, is metabolized to a series of compounds which also can induce hypoglycemia and other biochemical defects. These compounds become activated to acyl CoA compounds whose further oxidation is impaired. The activated compounds serve as substrates for carnitine acetyltransferase. As a result of their impaired metabolism, tissue levels of both coenzyme A and free carnitine are depressed.

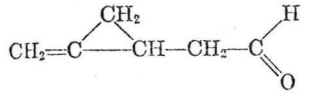
Hypoglycin and Related Biochemically Active Compounds



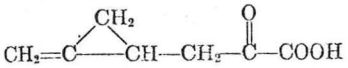
Methylenecyclopropyl alanine
hypoglycin



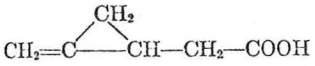
Acetyl and isoacetyl hypoglycin



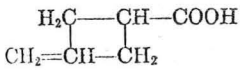
Methylenecyclopropyl acetaldehyde



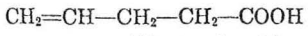
Methylenecyclopropyl pyruvic acid



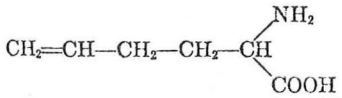
Methylenecyclopropyl acetic acid



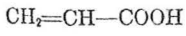
3-Methylenecyclobutanecarboxylic acid



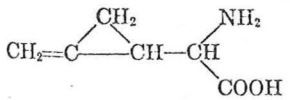
4-Pentenoic acid



2-Amino-5-hexenoic acid



Acrylic acid



Methylenecyclopropyl glycine

Biochemical Effects of Hypoglycin and Related Compounds

1. Inhibit fatty acid oxidation

   Coenzyme A, Carnitine } trapping
   Inhibition of 3-oxoacyl-CoA-thiolase

2. Inhibit gluconeogenesis

   Probably secondary to 1.

   ↓ acetyl CoA
   ↓ NADH
   ↓ ATP

3. Inhibited fatty acid oxidation increases need for glucose utilization in peripheral tissue and is met initially by increased glycolysis. When hepatic glycogen stores are exhausted, hypoglycemia ensues.

The biochemical effects can be corrected to a large extent by replacement of coenzyme A and carnitine, but not completely. The hypoglycin compounds may in addition have effects on oxidative phosphorylation and the electron transport system.

Clinical data also indicate that ketogenesis is impaired. This is to be expected when fatty acid oxidation is inhibited (49). Ketone bodies can serve as fuel for the brain (50). Impaired ketogenesis in a hypoglycemic patient removes the important compensatory fuel the brain can utilize to sustain its function.

47. Hill KR: The vomiting sickness of Jamaica, a review. West Indian Med J 1:243, 1952.
48. Bressler R, Corredor C, Brendel K: Hypoglycin and hypoglycin-like compounds. Pharmacol Rev 21:105-130, 1969.
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50. McGarry JD, Foster DW: Regulation of ketogenesis and clinical aspects of the ketotic state. Metabolism 21:471-489, 1972.
51. Owen OE, Morgan AP, Kemp HG et al: Brain metabolism during fasting. J Clin Invest 46:1589-1595, 1967.

Salicylates

Aspirin is taken by most children during the prodromal illness. Salicylate intoxication can produce many of the findings encountered in Reye's syndrome. High doses stimulate, then depress the central nervous system. Hyperventilation, confusion, delirium, psychosis, stupor and coma are well recognized components of severe intoxication.

Biochemical Effects of Salicylates

1. Uncouple oxidative phosporylation
2. Increase oxygen consumption, metabolic rate and CO_2 production
3. Increase glucose utilization in muscle
4. Inhibit gluconeogenesis
5. Inhibit ketogenesis
6. Additional effects include:
   Inhibition of dehydrogenases, decarboxylases, aminotransferases
   Inhibition of protein synthesis

These effects can clearly account for the biochemical abnormalities documented in Reye's syndrome including hypoglycemia, increased blood ammonia, increased FFA, and metabolic acidosis. In many instances, the blood levels of salicylate are in a "nontoxic" range. One wonders about individual differences in sensitivity to salicylate.

52. Woodbury DM: Chapter 17 in The Pharmacological Basis of Therapeutics, 4th edition. ed: Goodman LS, Gilman A. The MacMillan Company, 1970.
53. Smith, MJH, Smith, PK (eds) The Salicylates: A Critical Bibliographic Review. John Wiley & Sons, Inc. 1966.
54. Reid J, MacDougall AI and Andrews MM. Aspirin and diabetes mellitus. Brit. Med J 2:1071, 1957.

Normalization of blood glucose in maturity onset diabetes at blood salicylate levels of 40 mg%.

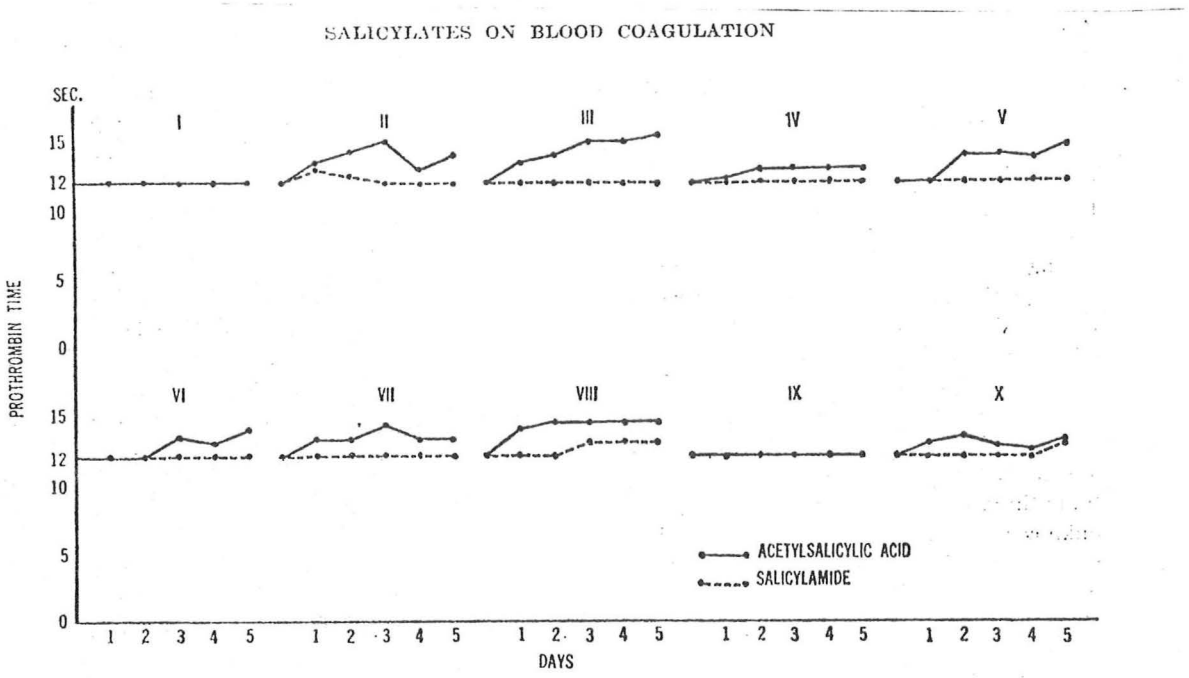
55. Manchester KL, Randle PJ, Smith GH: Some effects of sodium salicylate on muscle metabolism. Brit Med J 1:1028, 1958.
56. Seltzer HS: Quantitative effects of glucose, sulfonylureas, salicylate and indole-3-acetic acid on the secretion of insulin activity into pancreatic venous blood. J Clin Invest 41:289-300, 1962.
57. Thurston JH, Pollock PG, Warren SK et al: Reduced brain glucose with normal plasma glucose in salicylate poisoning. J Clin Invest 49:2139-2145, 1970.

58. Smith MJH and Dawkins PD: Salicylates and enzymes. J Pharm Pharmacol 23:729-744, 1971.
59. Burleigh M, Smith MJH: The site of the inhibitory action of salicylate in protein biosynthesis in vitro. J Pharm Pharmacol 23:519-527, 1971.
60. Poser W and Rust A: Inhibition of hepatic gluconeogenesis by salicylate (abstract) Naunyn Schmiedeberg's Arch Pharm 282:Supp. R 76, 1974.

In addition, salicylates can produce other effects encountered in Reye's syndrome.

Prolongation of Prothrombin Time

These observations were stimulated by the finding that dicumarol as it is metabolized yields salicylic acid.



The effect of acetylsalicylic acid and salicylamide on the prothrombin activity in ten normal subjects.
The dosage was 0.0857 g/kg of body weight; subject IX took only one-half the dosage.

From Quick AJ, Clesceri L: J Pharm Exp Ther 128:95, 1960

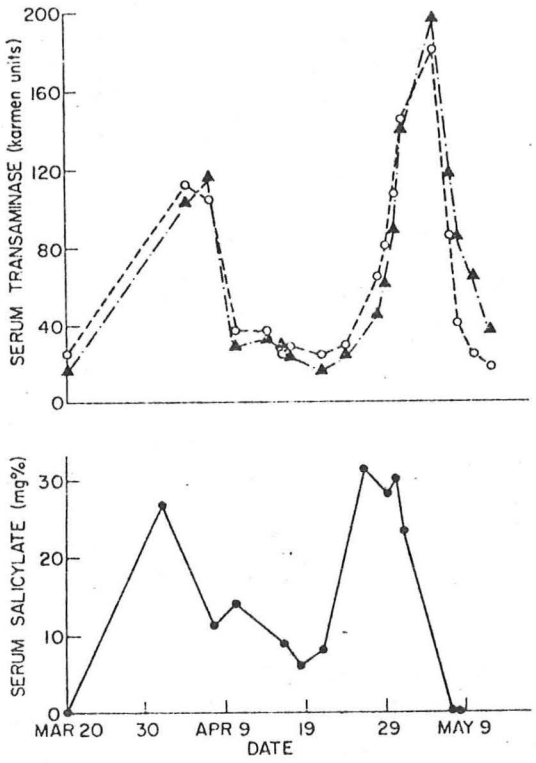
61. Link KP, Overman RS, Sullivan WR, et al: Studies on the hemorrhagic sweet clover disease: XI. Hypoprothrombinemia in the rat induced by salicylic acid. J Biol Chem 147:463-474, 1943.

62. Meyer OO, Howard B: Production of hypoprothrombinemia and hypocoaguability of the blood with salicylates. Proc Soc Exp Biol Med 53:234-237, 1943.
63. Shapiro S, Redish MH, Campbell HA: Studies on prothrombin: IV The prothrombinopenic effect of salicylate in man. Proc Soc Exp Biol Med 53: 251-254, 1943.
64. Butt HR, Leake WH, Solley RF, et al: Studies in rheumatic fever 1. The physiologic effect of sodium salicylate on the human being with particular reference to the prothrombin level of the blood and the effect on hepatic parenchyma. JAMA 128:1195-1200, 1945.
65. Clausen FW, Jager BV: The relation of the plasma salicylate level to the degree of hypoprothrombinemia. J Lab Clin Med 31:428-436, 1946.
66. Quick AJ, Clesceri L: Influence of acetylsalicylic acid and salicylamide on the coagulation of blood. J Pharm Exp Ther 128:95-98, 1960.

Increase in SGOT and SGPT

A high incidence of increased serum transaminase activity is encountered when serum salicylate concentration is greater than 30 mg%. The degree of transaminase rise is usually modest, to less than 200 Karmen units. However, values in the 500-1500 range have been recorded. Most reports obviously concern patient groups that take significant doses of salicylates (rheumatoid arthritis, lupus erythematosus, rheumatic fever). Abnormal transaminases can be produced in normal control subjects.

67. Manso C, Taranta A, Nydick I: Effect of aspirin administration on serum glutamic oxaloacetic and glutamic pyruvic transaminases in children. Proc Soc Exp Biol Med 93:84-88, 1956.
68. Russell AS, Sturge RA, Smith MA: Serum transaminases during salicylate therapy. Brit Med J 2:428-429, 1971.
69. Iancu, T: Serum transaminases and salicylate therapy. Brit Med J 2:167, 1972.



Elevations of SGOT (o---o) and SGPT (▲— · —▲) with aspirin therapy in Case 2 (Patient CA).

From Rich RR, Johnson JS: Arthritis Rheum. 16:1-9, 1973.

70. Rich RR, Johnson JS: Salicylate hepatotoxicity in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 16:1-9, 1973.
71. Seaman WE, Ishak KG, Plotz PH: Aspirin-induced hepatotoxicity in patients with systemic lupus erythematosus. Ann Int Med 80:1-8, 1974.
72. Wolfe JD, Metzger AL, Goldstein RC: Aspirin Hepatitis. Ann Int Med 80: 74-76, 1974.
73. Lyon LJ, Nevins MA, et al: Viral hepatitis and salicylism simulating Reye's syndrome. J Med Soc NJ 71:657-660, 1974.

Elevated Blood NH_3 in Reye's Syndrome

Huttenlocher, Schwartz and Klatskin (19) brought attention to the presence of hyperammonemia in patients with Reye's syndrome, and indicated that a high blood ammonia might be a factor accounting for the encephalopathy. The finding has been repeatedly confirmed (16,20,74).

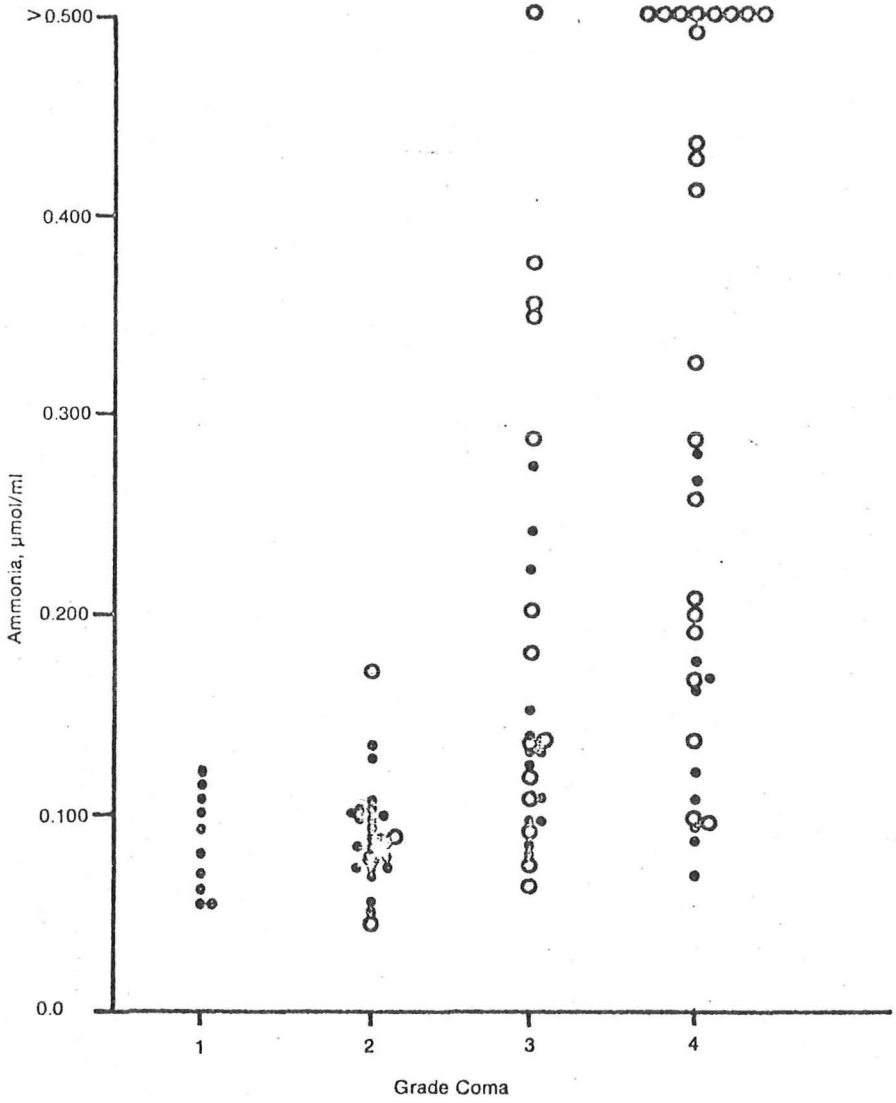
74. Huttenlocher PR: Reye's syndrome: Relation of outcome to therapy. Ped Pharmacol Ther 80:845-850, 1972.

Summary of clinical and laboratory data, use of exchange transfusions,* and outcome in 11 patients with Reye's syndrome

Case	*Age (yr.)*	*Sex*	*Date of illness*	*Prodromal illness*	*Initial blood NH_3 (μg/100 ml.)*	*Initial SGOT (units)*	*Maximum depth of coma*	*No. of exchange transfusions*	*Outcome*
1	12	M	[redacted]/67	Varicella	1,027	1,660	4	4	Died
2	1/12	M	[redacted]/68	Cough, coryza, fever	762	148	4	4	Died
3	3 9/12	M	[redacted]/68	Influenza A_2	542	490	3	2	Recovered
4	5	M	[redacted]/68	Cough, coryza, fever	280	1,300	2	0	Recovered
5	6	F	[redacted]/69	Cough, sore throat	306	340	3	1	Recovered
6	5	F	[redacted]/70	Cough, coryza	241	930	2	0	Recovered
7	11	F	[redacted]/71	Influenza B	502	160	4	0	Died
8	9	F	[redacted]/71	Influenza B	243	1,840	1	0	Recovered
9	7	F	[redacted]/71	Varicella	484	2,000	2	2	Recovered
10	1	F	[redacted]/71	Fever, anorexia, irritability	330	540	3	1	Recovered
11	3	F	[redacted]/71	Influenza B	604	1,250	3	3	Recovered

*In children treated with exchange transfusions the depth of coma at the initiation of transfusions coincided with the "maximum depth of coma" listed in the table. Cases 1, 2, and 3 have been previously reported as Cases 8, 9, and 10.[5]

The height of the blood ammonia correlates with the extent of encephalopathy and with the ultimate prognosis.

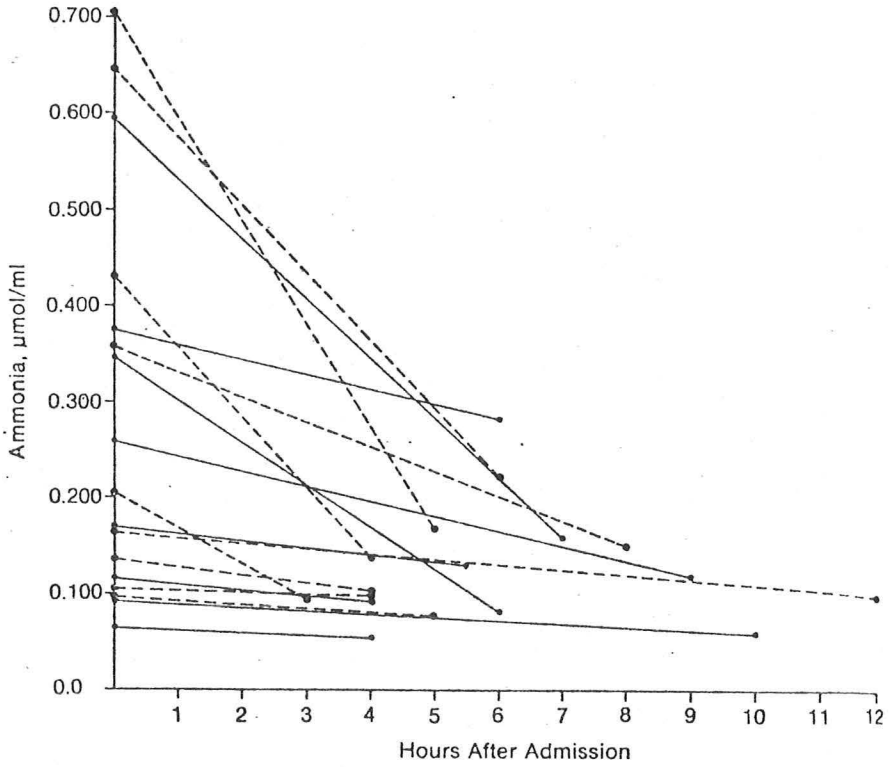


—Blood ammonia level and grade of coma in Reye's syndrome. Open circles are admission values; dots, subsequent values. See "Methods" for grading coma.

From Glasgow AM, Cotton RB: Amer J Dis Child 124:827-833, 1972.

Blood ammonia invariably falls, even without "specific" therapy (cleansing enemas, antibiotics, various exchange and dialysis procedures) suggesting that the biochemical defect is a functional one and not due to hepatic necrosis.

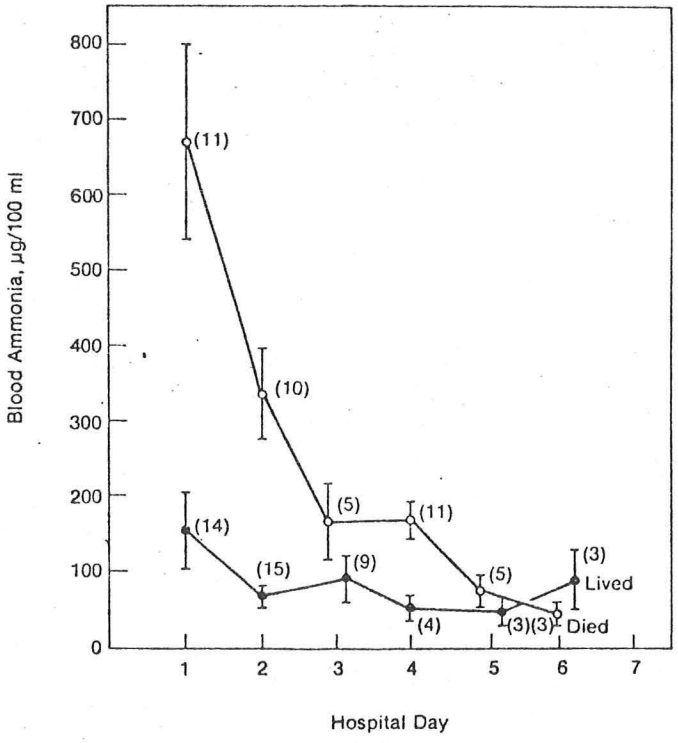
From Glasgow AM, Cotton RB:
Amer J Dis Child
124:827, 1972.(20)



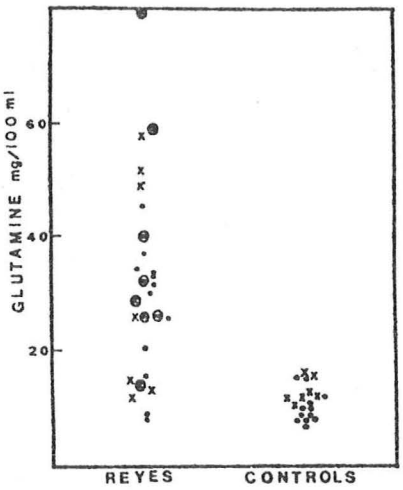
–Admission and second ammonia level determinations; solid lines indicate patients given no specific therapy; broken lines, patients treated with cleansing enemas.

From Lovejoy FH, Smith AL
Bresnan MJ, et al.
Amer JzDis Child
128:36, 1974 (16)

–Temporal course of blood ammonia concentration in survivors and nonsurvivors. Vertical lines indicate ±SE. Numbers in parentheses indicate number of patients.



Spinal fluid glutamine is elevated (75), just as it is in other hyperammonemic states associated with encephalopathy (76-79).



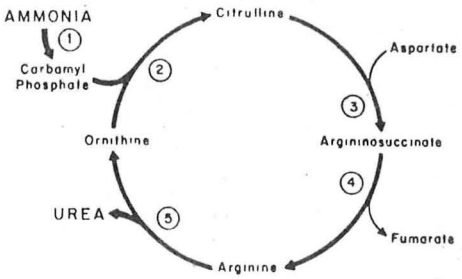
Spinal fluid glutamine in cases of Reye's syndrome and in controls

X = H_2SO_4 method; ●, glutaminase method; ⊗ or ⊙, survivor. All survivors in this study recovered completely

From Glasgow AM, Dhiensiri K: Clin Chem 20:642,1974 (75).

75. Glasgow AM, Dhiensir K: Improved assay for spinal fluid glutamine, and values for children with Reye's syndrome Clin Chem 20:642-644, 1974.
76. Gilon E, Szeenberg A, et al: Glutamine estimation in cerebrospinal fluid in cases of liver cirrhosis and hepatic come J Lab Clin Med 53:714, 1959.
77. Steigman F, Kazemi F, Duben A: Cerebrospinal fluid glutamine in the diagnosis of hepatic coma. Amer J Gastroenterol 40:378, 1963.
78. Zacarias, J, Harun A, Brinck P: Glutamine values in cerebrospinal fluid of children. Some observations on clinical application. J Pediat 78:318, 1971.
79. Hourani BT, Hamlin EM, Reynolds TB. Cerebrospinal fluid glutamine as a measure of hepatic encephalopathy. Arch Int Med 127:1033, 1971.

The clinical symptoms and neurologic manifestations in Reye's syndrome resemble those seen in persons with genetic defects of ammonia disposal (80). Amino acid patterns in serum in children resemble those seen in ornithine transcarbamylase deficiency (81,82). Carbamyl phosphate synthetase and ornithine transcarbamylase activities have been found to be decreased, either singly or together in livers of patients with Reye's syndrome (83-87). Citrulline has been administered to several children with Reye's syndrome with good effects (88,89).



The Krebs-Henseleit cycle for urea biosynthesis. Urea nitrogen is derived equally from ammonia and aspartate. Enzymes of this cycle are: (1) carbamyl phosphate synthetase I; (2) ornithine transcarbamylase; (3) argininosuccinic synthetase; (4) argininosuccinase; (5) arginase.

From Hsia YE: Gastroenterology 67:346,1974 (80).

80. Hsia YE: Inherited hyperammonemic syndromes. Gastroenterology 67:346-374, 1974.
81. Hilty MD, Romshe CA, Delamater PV: Reye's syndrome and hyperaminoacidemia. J Ped 84:362-365, 1974.
82. Kang ES, Gerald PS: Hyperammonemia and Reye's syndrome. N Engl J Med 286: 1216-1217, 1972.
83. Thaler MM, Hoogenraad NJ, Boswell M: Reye's syndrome due to a novel protein-tolerant variant of ornithine-transcarbamylase deficiency. Lancet 2: 438-440, 1974.
84. BrownT, Hug G, Brown H, et al: Reye's syndrome. Lancet 2:716-717, 1974.
85. Thaler MM: Role of ornithine transcarbamylase in Reye's syndrome. N Engl J Med 291:797, 1974.
86. Brown T, Brown H, Lansky L, et al:Carbamyl phosphate synthetase and ornithine transcarbamylase in liver of Reye's syndrome N Engl J Med 291:797-798, 1974.
87. Thaler MM, Hoogenraad NJ: Reye's syndrome. Lancet 2:1203, 1974.
88. DeLong GR, Glick TH, Shannon DC: Citrulline for Reye's syndrome. N Engl J Med 290:1488, 1974.
89. Oetgen WJ, Shira JE, Hyman LR, et al: Citrulline for Reye's syndrome. N Eng J Med 291:421, 1974.

Role of Short Chain Fatty Acids

The following types of observations have suggested that fatty acids per se may account for some of the major abnormalities of Reye's Syndrome.

1. Short chain fatty acids can induce coma in experimental animals (90,91)
2. Fatty acids can induce swelling of mitochondria and inhibit mitochondrial metabolism (92,93)
3. Mitochondrial swelling and pleomorphism is characteristically seen in liver of patients with Reye's syndrome (46)

90. Samson FE, Dahl N, Dahl DR: A study on the narcotic action of the short chain fatty acids. J Clin Invest 35:1291-1298, 1956.
91. Walker CO, McCandless DW, McGarry JD et al: Cerebral energy metabolism in short-chain fatty acid-induced coma. J Lab Clin Med 76:569-583,1970.
92. Zborowski J, Wojtczak L: Induction of swelling of liver mitochondria by fatty acids of various chain length. Biochim Biophys Acta 70:596-598, 1963.
93. Vazquez-Colon L, Ziegler FD, Elliott WB: On the mechanism of fatty acid inhibition of mitochondrial metabolism. Biochemistry 5:1134-1139, 1966.

Although FFA are elevated in patients with Reye's syndrome, they are no higher than that seen in many patients without encephalopathy. Some short chain fatty acids are elevated in serum in Reye's syndrome but only to micromolar levels(94), not to the millimolar levels required to induce coma.

Serum short-chain fatty acid levels (μmoles/L) in Reye's syndrome

	Propionate	Isobutyrate	Butyrate	Isovalerate
[redacted]	10.372	6.605	3.486	6.40
[redacted]	11.449	2.713	5.430	3.09
[redacted]	7.720	—	—	—
[redacted]	24.121	3.387	15.353	1.667
[redacted]	7.006	3.612	2.434	1.217
[redacted]	10.038	3.018	3.543	0.876
[redacted]	7.494	1.801	4.203	2.738
Mean ± S.E.M.	11.171 ± 2.249	3.530 ± 0.675	5.742 ± 1.964	2.665 ± 0.825
Controls Mean ± S.E.M.	1.29 ± 0.52	0.77 ± 0.39	0.68 ± 0.40	1.87 ± 1.53
	$p < 0.001$	$p < 0.01$	$p < 0.02$	Not significant

From Trauner DA, Nyhan WL, Sweetman L: Neurology 25:296, 1975 (94)

94. Trauner DA, Nyhan WL, Sweetman L: Short-chain organic acidemia and Reye's syndrome. Neurology 25:296-298, 1975.

Miscellaneous Observations

Serum creatine phosphokinase and lactic dehydrogenase levels are elevated in patients with Reye's syndrome. Isozyme analyses suggest that the increased serum enzyme is derived from muscle (95,96).

95. Alvira MM, Forman DT. Biochemical abnormalities in Reye's syndrome. Ann Clin Lab Sci 4:477-483, 1974.
96. Roe CR, Schonberger LB, Gelbach SH, et al: Enzymatic alterations in Reye's syndrome: Prognostic implications. Pediatrics 55:119-126, 1975.

Therapy of Reye's Syndrome

1. Provide fuel for the brain
   glucose
   oxygen

2. Lower blood ammonia

3. Enhance removal of salicylate

4. Treat cerebral edema
   Mannitol
   ?Steroids

Various additional therapeutic modalities are of unproven value and include

Insulin plus glucose
Hemodialysis
Peritoneal dialysis
Exchange transfusions

See reference 34

97. Samaha FJ, Glau E, Berardinelli JL: Reye's syndrome: Clinical diagnosis and treatment with peritoneal dialysis. Pediatrics 53:336-340, 1974.
98. Lansky LL, Fixley M, Romig DA, et al: Hypothermic total body-washout with survival in Reye's syndrome. Lancet 2:1019, 1974.
99. Haller JS: The enigmatic encephalopathy of Reye's syndrome. Hospital Practice Feb., 1975, pp 91-99.
100. Kindt GW, Waldman J, Kohl S, et al: Intracranial pressure in Reye syndrome Monitoring and control. JAMA 231:822-825, 1975.
101. Partial skull removal operation major factor in saving boy's life. Dallas Times Herald, April 30, 1975, p 16A.