Reprinted from PEDIATRICS 62:84-90, 1978

Reye's Syndrome in Infancy

Peter R. Huttenlocher, M.D., *and* Doris A. Trauner, M.D.

From the Departments of Pediatrics and Neurology, University of Chicago

ABSTRACT. Reye's syndrome in infancy is not a well-defined entity and is infrequently diagnosed. Eight infants 6 months of age or younger had a prodromal viral illness followed by the rapid onset of lethargy, seizures, and coma, resulting in the diagnosis of Reye's syndrome. All had abnormal results of liver function tests including elevations of blood ammonia level. Three patients had pathological studies that confirmed fatty visceral infiltration.

The data on these patients, as well as a review of the literature, indicate that the most prominent clinical findings in Reye's syndrome in infancy include marked respiratory abnormalities with tachypnea and apneic episodes; frequent occurrence of seizures in the early stages of the illness; and hypoglycemia in most cases.

A strong socioeconomic bias was noted in these patients, with the infants coming primarily from lower socioeconomic, urban environments, while older children with Reye's syndrome have been observed to be predominantly middle-class and from suburban or rural areas. *Pediatrics* 62:84-90, 1978, *Reye's syndrome, coma, hypoglycemia, apnea, socioeconomic class.*

The clinical presentation of Reye's syndrome, or encephalopathy with hepatic dysfunction and fatty infiltration of viscera,[1] in childhood and adolescence is well described, and early diagnosis has become widespread. Much less is known regarding this disease in the young infant. Differentiation from respiratory disorders, anoxic encephalopathy, and inborn errors of metabolism presents a considerable diagnostic problem in this age group. While instances of Reye's syndrome have been reported in the newborn period and in the first few months of life, there has been no study encompassing a series of such cases. The purpose of this report is to summarize findings in eight infants under age 6 months, to review previous cases reported in the literature, and to delineate some of the diagnostic problems encountered in this age group. Review of these cases suggests a difference in social class distribution between the infants and the older children, the former being mostly of urban or lower socioeconomic groups and the latter being suburban or rural and middle-class.

METHODS

The diagnosis of Reye's syndrome was made using a modification of the criteria of Glasgow et al.[2]: acute onset of stupor or coma after an antecedent viral illness; abnormal results of liver function tests, including hyperammonemia and elevated SGOT level, but without associated jaundice; and no other explanation for the encephalopathy. Other disorders that could produce similar findings, especially salicylism and sepsis, were ruled out by appropriate tests. Recognizable inborn metabolic errors such as ornithine transcarbamylase or carbamylphosphate synthetase deficiency were excluded by the clinical history and by follow-up examinations of the survivors. None of the infants had a history of recurrent vomiting, drowsiness, or previous episodes of coma or convulsions. None of the survivors had persistent long-term or recurrent biochemical abnormalities, nor did they develop repeated episodes of vomiting, lethargy, or coma during at least 12 months of observation. One patient received a liver biopsy which tended to confirm the diagnosis histologically; two infants who died had typical pathological changes at autopsy. Case reports on patients 1 and 8 have been previously published.[3,4]

CASE REPORTS

Case 5

A 7-week old black girl was well until five days before admission when a fever of 38.9°C (102°F) developed without other clinical abnormalities. She was given sodium salicylate, 75 mg, and oral electrolyte solution, resulting in rapid improvement. On the morning of admission she was afebrile

Received September 14; revision accepted for publication November 28, 1977.

Supported by U.S. Public Health Service grant PHS 5 T01 NS-05033-22 and by the Reye's Syndrome Research Fund, University of Chicago.

Dr. Trauner is now with the University of California Medical Center, San Diego.

ADDRESS FOR REPRINTS: (P.R.H.) University of Chicago, Department of Pediatrics, 950 East 59th Street, Chicago, IL 60637

but vomited twice and refused her feedings. She soon developed rapid, noisy breathing and was brought to the emergency room, where she was noted to be tachypneic (respirations, 65/min) with audible wheezes. She was comatose, responded only to deep pain, and had intermittent decorticate posturing. Cranial nerves were normal. She was hypotonic, but with hyperactive tendon reflexes.

Initial laboratory values were as follows: sodium, 153 mEq/liter; potassium, 6.0 mEq/liter; pH, 7.21; PCO_2, 19 mm Hg; PO_2, 110 mm Hg; blood glucose, 18 mg/dl; calcium, 7.6 mg/dl; salicylate, 14 mg/dl; BUN, 20 mg/dl; and creatinine, 0.9 mg/dl. CSF culture was negative.

She was admitted to the hospital with the diagnosis of dehydration and hypoglycemia, and was treated with intravenous glucose, calcium, and fluid replacement. She failed to respond to an elevation of the blood glucose level into the normal range, and her neurologic status showed further deterioration. Sixteen hours after admission she developed intermittent apnea, each episode lasting 30 to 45 seconds and requiring assisted ventilation. The anterior fontanel was full. Pupils were in midposition and unreactive to light. She was flaccid and responded only feebly to deep pain. Bilateral subdural taps were negative. A clinical diagnosis of Reye's syndrome was suggested, and subsequent laboratory values showed a blood ammonia level of 549 μg/dl; SGOT, 760 IU; SGPT, 785 IU; lactic dehydrogenase (LDH), 380 IU; and bilirubin, 1.8 mg/dl. A single intravenous infusion of mannitol, 1 gm/kg, was given over a 30-minute period. Twenty percent dextrose in 0.2N saline was infused at a rate of 15 ml/hr, and small doses of insulin were given to keep the blood glucose level between 100 and 180 mg/dl. The child received an exchange blood transfusion with about double her estimated blood volume. Subsequently, she was breathing normally, the anterior fontanel was soft, and the pupils were reactive to light. Muscle tone was increased, and there now were brisk tendon reflexes and ankle clonus. Blood ammonia level after exchange transfusion was 293 μg/dl. On the third hospital day frequent, brief, multifocal motor seizures developed and continued intermittently over the next five days. However, the patient gradually became more responsive. At the time of discharge on the ninth hospital day the patient was alert and had a strong suck and normal muscle tone and reflexes. She smiled and had good visual fixation and following. Results of liver function tests had returned to normal. Reexamination at age 8 months showed normal developmental progress.

Case 6

A 4½-month-old black girl was well until two weeks before admission when an upper respiratory tract infection developed and quickly resolved. One week before admission she received a DPT injection. Two days later she again became febrile, and on the next day generalized and multifocal motor seizures developed. She was admitted to another hospital where she was given diazepam intravenously. Shortly afterward she had a respiratory arrest and was resuscitated. She was subsequently unresponsive to all stimuli and her breathing was irregular. She had repeated episodes of hypoglycemia (blood glucose level, about 30 mg/dl) despite intravenous glucose administration. The patient was noted to have an enlarged liver, and subsequently abnormal results of liver function tests were reported. The question of Reye's syndrome was raised and the patient was transferred to Wyler Children's Hospital after three days.

On arrival the infant was comatose but responded to deep pain. She had no spontaneous respirations. The liver edge was palpable 5 cm below the right costal margin. Blood pressure was 60/40 mm Hg. The anterior fontanel was soft. Pupils were small but reactive to light. Oculocephalic reflexes were present. Deep tendon reflexes were hyperactive and bilateral ankle clonus was present.

Results of laboratory studies on admission to the hospital included a WBC count of 28,700/cu mm; glucose, 36 mg/dl; SGOT, 476 IU; SGPT, 280 IU; LDH, 920 IU; bilirubin, 1.0 mg/dl; creatine phosphokinase, 4,860 IU; and prothrombin time, 20.0 seconds (control, 12.2 seconds). Blood ammonia level was 160 μg/dl (normal, up to 125 μg/dl). BUN level was 81 mg/dl and creatinine level was 1.7 mg/dl. CSF protein level was 38 mg/dl, there were no cells, and culture was negative.

Treatment was initiated with intravenous 20% glucose in 0.2N saline, and when the blood glucose level rose above 130 mg/dl intravenous insulin therapy was also begun. Transfusions with fresh-frozen plasma were given to correct clotting abnormalities. A needle biopsy specimen of the liver showed diffuse small-droplet fatty accumulation in liver parenchyma. On electron microscopic study of the tissue there was dilatation of the cisternae of the endoplasmic reticulum in hepatocytes. Mitochondrial swelling was present in some cells, often interspersed with mitochondria that showed a dense matrix but otherwise normal morphology.

Generalized clonic seizure activity continued intermittently. Spontaneous breathing resumed gradually during the next week and neurologic status improved. Biochemical abnormalities, including results of liver and renal function tests, returned to normal. Three weeks after her initial hospitalization she was awake, appeared to look at a light, had a hoarse cry, and moved all four extremities spontaneously. However, she had poor head control, hyperreflexia, intermittent ankle clonus, and a poor suck, necessitating nasogastric tube feedings. At age 1 year she had persistent marked neurologic deficits, including spasticity, poor head control, and myoclonic seizures. There has been no recurrence of encephalopathy or hepatic disease.

RESULTS

Data on the eight infants are summarized in Tables I and II. Five of the infants were female. The ethnic distribution included four blacks and four of Mexican descent. This is strikingly different from the ethnic distribution of the older children with Reye's syndrome whom we saw in the same time period (Table III). Furthermore, all eight of the infants resided in urban environments, while most of the older children were from suburban or rural areas.

Six of the infants survived, but four of them had evidence of residual neurologic deficit, which was profound in three. The clinical course differed somewhat from that commonly seen in older children with Reye's syndrome. Vomiting was not a prominent finding, but some vomiting occurred in six infants. There was a rather sudden onset of respiratory distress, usually tachypnea, which was noted in every case, followed rapidly by seizures and coma. Apneic episodes were present in all but one of the infants during the acute phase of the illness.

All of the infants had hypoglycemia on admission, which in some cases responded slowly to intravenous glucose replacement. The CSF

TABLE I

CLINICAL FEATURES IN EIGHT INFANTS WITH REYE'S SYNDROME*

	Patient							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Age	3 mo	4 mo	2 mo	2½ mo	7 wk	4 mo	4 mo	4 mo
Ethnic origin	Mexican-American	Mexican-American	Mexican	Mexican	Black	Black	Black	Black
Sex	F	F	M	F	F	F	M	M
Presenting complaint	Vomiting, cyanosis	Vomiting	Diarrhea, lethargy	Diarrhea, lethargy	Respiratory distress	Seizures	Lethargy, seizures	Lethargy, seizures
Vomiting	+ + +	+ + +	+	+	+	0	0	+
Seizures								
Early	+ +	+	+	+	0	+ +	+	+
Late	+ + +	0	0	0	+ +	+ +	+	+
Tachypnea	+ + +	+ + +	+ +	+ +	+ + +	+ +	+ +	+
Apnea	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Hepatomegaly	+ +	+ +	0	+	+	+ + +	+ +	+ +
Outcome	Lived; severe neurologic deficit	Lived; mild neurologic deficit	Lived; normal on discharge	Died	Lived; normal on discharge	Lived; severe neurologic deficit	Lived; severe neurologic deficit	Died
Liver pathology	ND	ND	ND	Fatty accumulation	ND	Fatty accumulation	ND	Fatty accumulation

*Key: 0 = negative; + = minimal, + + = moderate, + + + = marked, ND = not done.

glucose level was strikingly low in five patients, reflecting the presence of hypoglycemia. Prothrombin time was prolonged in all patients; in contrast, bilirubin values were normal. Histological examination of liver specimens in three patients showed diffuse small-droplet fatty accumulation in liver parenchyma. Ultrastructural changes in liver in one case were similar to those previously reported in Reye's syndrome (case 6).

DISCUSSION

The incidence of Reye's syndrome in infancy is unknown. It is likely that many cases remain undiagnosed. This may in part explain the marked variation in the proportion of infants in different reported series. For example, eight of 14 patients with Reye's syndrome reported by Simpson[5] in 1966 were under 6 months of age, and a retrospective study by Norman[6] found eight of 21 children with this disease to be under 12 months of age. In their original description of the disease Reye et al.[1] described 21 patients, the youngest of whom was 5 months old. However, infant cases have been rare or absent in several more recent series.[7,8]

A literature review revealed 51 infants under age 10 months whose cases fulfilled our clinical and/or pathologic criteria for Reye's syndrome. These include the cases reported by Golden and Duffell,[9] Utian et al.,[10] Simpson,[5] Becroft,[11] Dvorackova et al.,[12] Cullity and Kakulas,[13] Glasgow and Halliday,[14] Barr et al.,[15] Corlett,[16] Samaha et al.,[17] Bobo et al.,[18] and van Caillie et al.[19] Several other case reports containing insufficient information or considered doubtful were omitted from the analysis. For example, a neonatal case reported by Papageorgiou et al.[20] was considered questionable since inborn metabolic errors which may present with identical findings in the newborn period, such as the inherited defects in enzymes of the Krebs urea cycle, were not excluded by proper laboratory tests or by the clinical course.

Findings in the 51 cases, together with those of the eight patients in the present report, are summarized in Table IV. Twenty-eight, or about 50%, of the cases occurred at ages 4 and 5 months. Ethnic or social class affiliations were not included in most previous studies with the exception of the report by Golden and Duffell,[9] which was concerned with an American Indian child, and that of Becroft,[11] which included several Polynesian children. As in the older children, there is almost always a mild prodromal illness,

TABLE II

LABORATORY STUDIES IN EIGHT INFANTS WITH REYE'S SYNDROME

	Patient							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Blood glucose (mg/dl)	30	11	22	9	18	30	23	40
CSF glucose (mg/dl)	10	8	34	...	...	20	19	44
Serum ammonia (μg/dl)	2,070	1,200	320	617	549	160*	400	762
SGOT (IU)	455	622	375	3,738	760	476	800	450
SGPT (IU)	...	422	183	1,860	785	280	282	...
Prothrombin time, patient/control (seconds)	...	20/11	76/...	76/...	...	20.0/12.2	16.5/11.6	23/...
Total bilirubin (mg/dl)	1.0	...	...	...	1.8	1.0	0.4	0.6
Serum calcium (mg/dl)	9.4	8.3	8.6	...	7.6	7.3	7.9	...
Creatine phosphokinase (IU)	...	...	...	...	...	4,860	573	...
BUN (mg/dl)	19	11	28	4	23	81	35	32
WBC count	33,100	12,200	24,800	...	7,800	28,700	21,000	9,300

*Three days after onset of encephalopathy.

which in the infants is often accompanied by diarrhea. Vomiting is a somewhat less constant finding than in older children. Coma, seizures, and disturbances in respiration are the most frequent clinical manifestations. The seizures may be grand mal, multifocal, or myoclonic. Respiratory disturbances include hyperventilation as well as repeated episodes of apnea. Increased intracranial pressure, as judged by fullness of the anterior fontanel, is often present, but there rarely is marked tenseness of the fontanel to the point where increased intracranial pressure per se would be likely to be life-threatening. This is in contrast to the older child with Reye's syndrome, in whom severe and fatal cerebral edema may occur.[21,22] The difference may well be secondary to a decreased susceptibility of the infant brain to edema formation.[23,24] However, the infant appears to be more susceptible to direct damage from the metabolic disturbances that occur in Reye's syndrome. The mortality in the infants appears to be higher than in the older children, and there is a definite increase in risk of survival with severe neurologic impairment. The group with severe residual brain damage accounts for 40% of the survivors in the cases reviewed in this report. The outcome in the eight infants reported here resembles that in the infants collected in the literature review: only two of the eight made a good recovery, and four were left with neurologic

TABLE III

ETHNIC DISTRIBUTION OF CHILDREN WITH REYE'S SYNDROME

	Age < 6 mo			*Age > 6 mo*		
	Black	*Mexican-American*	*White*	*Black*	*Mexican-American*	*White*
New Haven, Conn. (1966-1974)	1	0	0	1	0	24
San Diego (1972-1975)	0	4	0	0	1	8
Chicago	3	0	0	0	0	10
Total	4	4	0	1	1	42

TABLE IV

SELECTED CLINICAL, LABORATORY, AND PATHOLOGIC FINDINGS IN 59 INFANTS UNDER AGE 10 MONTHS WITH DIAGNOSIS OF REYE'S SYNDROME

	% *of Infants**	
Clinical data		
Sex	53% female	(47)
Vomiting	86%	(50)
Seizures	98%	(44)
Disturbances in respiration	91%	(22)
Fatal outcome	61%	(59)
Recovery	24%	(59)
Severe neurologic sequelae	15%	(59)
Recurrent attacks	7%	(59)
Laboratory data		
SGOT > twice normal	100%	(59)
Prothrombin time < 75%	91%	(34)
Blood glucose < 50 mg/dl	79%	(33)
Pathologic findings		
Hepatic steatosis	100%	(52)

*Numbers in parentheses indicate number of cases for which information was available and on which the percentages are based.

deficits. This may be compared to the experience in 44 older children whom we saw in the same period of time. These patients, ranging in age from 1 to 17 years, had 83% survival without major residual neurologic disabilities (Huttenlocher and Trauner[25] and unpublished recent cases). The cause of the poor outcome in infants is unknown. It is possible that irreversible brain damage is related to profound hypoglycemia, which occurs in most of the infants but which is uncommon in older children with Reye's syndrome.

Laboratory data in the infants generally seem to parallel those in older children except for the more frequent occurrence of hypoglycemia.[25] The possibility of Reye's syndrome should be considered in all infants who have unexplained hypoglycemia and seizures or an altered state of consciousness. Liver function tests, including determination of blood ammonia level, should be performed in these infants.

Pathologic findings in the liver in the infants appear to be similar to those in older children. Diffuse, microvesicular accumulation of fat in hepatocytes is almost invariably described. In addition, a variety of mitochondrial alterations in hepatocytes has been stressed, primarily by Partin and co-workers, who consider liver biopsy a necessary adjunct to the diagnosis of Reye's syndrome.[18,26] However, the specificity of these pathologic changes is doubtful. Similar hepatic abnormalities have been reported in other conditions which may resemble Reye's syndrome clinically, especially in the inborn errors of Krebs urea cycle enzymes.[27-31] Fatty infiltration of the liver of sufficient degree to lead to hepatomegaly has been found in carbamyl phosphate synthetase deficiency,[27,28] in ornithine transcarbamylase deficiency,[29] in citrullinemia,[30] and in argininosuccinicaciduria.[31] All of these conditions have in common the occurrence of hyperammonemia, which has led to the suggestion that ammonia intoxication may be the cause of the fatty change in the liver.[30] Both the specificity and the occurrence of mitochondrial abnormalities in electron-microscopic sections from liver biopsies in Reye's syndrome have also been challenged.[32,33] We therefore would agree with a recent discussion by Haller[34] that stresses clinical and biochemical criteria for the diagnosis of Reye's syndrome and that criticizes a too-heavy reliance on the histologic changes, which may be nonspecific. At present the only definite method for exclusion of the inborn errors of the urea cycle enzymes appears to be liver biospy after the child has recovered from the acute illness, with measurement of the activity of these enzymes in the biopsy tissue. Biochemical study of the liver during the illness is of limited value, since activity of at least two of the urea cycle enzymes, i.e., carbamyl phosphate synthetase and ornithine transcarbamylase, is transiently decreased in patients with Reye's syndrome.[35,36] Ethical considerations usually prevent the performance of a liver biopsy in a well child. On clinical grounds alone, an inborn metabolic error is not likely in a child who has a single episode of encephalopathy and hepatic dysfunction, without either a history of similar attacks or recurrence on prolonged observation after recovery. Biochemical study of the liver clearly is indicated for proper diagnosis in patients with recurrent episodes.

A striking and unexpected finding in the infants in this report is a difference in their living pattern and in ethnic origin from most older children with Reye's syndrome. This difference appears to have persisted in three locations where we have studied Reye's syndrome (New Haven, Connecticut; San Diego; and Chicago). Recent demographic data indicate that in the United States Reye's syndrome occurs predominantly in white children, with only 4% of 349 cases having occurred in blacks.[7] The median age in this large series was 11 years. Our own experience in older children has been similar: only 4% of 44 children over age 6 months who were studied from 1968-1977 were nonwhite. It appears likely that environmental and socioeconomic rather than genetic factors underlie this difference. This is suggested by the

fact that the white children we saw in New Haven and Chicago were exclusively from middle-class and suburban backgrounds while the black children were from poor families in inner-city environments. Supporting this conclusion is the observation that four young infants with Reye's syndrome seen by one of us (D.A.T.) in San Diego were Mexican-American and from an urban, lower-socioeconomic background.

The age and socioeconomic distributions show an interesting resemblance to those well known for poliomyelitis. This disease also affected infants primarily in lower-socioeconomic groups and older children and young adults in the middle class.[37] In the case of poliomyelitis, the explanation for this difference was the fact that children living under less sanitary conditions acquire enterovirus infections earlier in life. As a matter of fact, the emergence of polio as a disease of the older child, adolescent, and young adult during the first half of the 20th century appears to have been the direct result of improved sanitation, leading to later exposure. This simple explanation does not appear to be directly applicable to cases of Reye's syndrome, which is known to follow infection with a large variety of viral agents. However, it has been postulated that Reye's syndrome may be a reaction to a toxin elaborated by several viruses.[3,38,39] Age at first exposure to a virus capable of inducing this reaction might be expected to vary with life-style.

The preliminary findings in this small series of patients indicate the need for a larger epidemiologic study of Reye's syndrome which takes into account age, social class, and urban versus suburban or rural residence.

REFERENCES

1. Reye RDC, Morgan G, Baral J: Encephalopathy and fatty degeneration of the viscera. *Lancet* 2:749, 1963.
2. Glasgow AM, Cotton RB, Dhiensiri K: Reye's syndrome: I. Blood ammonia and consideration of the nonhistologic diagnosis. *Am J Dis Child* 124:827, 1972.
3. Huttenlocher PR, Schwartz AD, Klatskin G: Reye's syndrome: Ammonia intoxication as a possible factor in the encephalopathy. *Pediatrics* 43:443, 1969.
4. Trauner DA, Stockard JG, Sweetman L: EEG correlation with biochemical abnormalities in Reye's syndrome. *Arch Neurol* 34:116, 1977.
5. Simpson H: Encephalopathy and fatty degeneration of the viscera: Acid-base observations. *Lancet* 2:1274, 1966.
6. Norman MG: Encephalopathy and fatty degeneration of the viscera in childhood. *Can Med Assoc J* 99:522, 1968.
7. Corey L, Rubin RJ: Reye's syndrome 1974: An epidemiological assessment, in Pollack JD (ed): *Reye's Syndrome.* New York, Grune & Stratton, 1974, pp 179-187.
8. Hilty MD, Romshe CA, Delamater PV: Reye's syndrome and hyperaminoacidemia. *J Pediatr* 84:362, 1974.
9. Golden GS, Duffell D: Encephalopathy and fatty change in the liver and kidney. *Pediatrics* 36:67, 1965.
10. Utian HL, Wagner JM, Sichel RJS: White liver disease. *Lancet* 2:1043, 1964.
11. Becroft DMO: Syndrome of encephalopathy and fatty degeneration of viscera in New Zealand children. *Br Med J* 5506:135, 1966.
12. Dvorackova I, Vortel V, Hroch M: Encephalitic syndrome with fatty degeneration of viscera. *Arch Pathol* 81:240, 1966.
13. Cullity GJ, Kakulas BA: Encephalopathy and fatty degeneration of the viscera: An evaluation. *Brain* 93:77, 1970.
14. Glasgow JFT, Halliday HL: Recurrence of Reye's syndrome. *Lancet* 1:974, 1976.
15. Barr R, Glass HJ, Chawla G: Reye's syndrome: Massive fatty metamorphosis of the liver with acute encephalopathy. *Can Med Assoc J* 98:1038, 1968.
16. Corlett K: Encephalopathy and fatty degeneration of the viscera. *Lancet* 2:937, 1963.
17. Samaha FJ, Blau E, Berardinelli JL: Reye's syndrome: Clinical diagnosis and treatment with peritoneal dialysis. *Pediatrics* 53:336, 1974.
18. Bobo RL, Schubert WK, Partin JC, Partin JS: Reye's syndrome: Treatment by exchange transfusion with special reference to the 1974 epidemic in Cincinnati, Ohio. *J Pediatr* 87:881, 1975.
19. van Caillie M, Morin CL, Roy CC, et al: Reye's syndrome: Relapses and neurological sequelae. *Pediatrics* 59:244, 1977.
20. Papageorgiou A, Wiglesworth FW, Schiff D, Stern L: Reye's syndrome in a newborn infant. *Can Med Assoc J* 109:717, 1973.
21. Berman W, Pizzi F, Schut L, et al: The effects of exchange transfusion on intracranial pressure in patients with Reye's syndrome. *J Pediatr* 87:887, 1975.
22. Kindt GW, Waldman J, Kohl S, et al: Intracranial pressure in Reye's syndrome: Monitoring and control. *JAMA* 231:822, 1975.
23. Spector RG: Water content of the immature rat brain following cerebral anoxia and ischemia. *Br J Exp Pathol* 43:472, 1962.
24. Streicher E, Wisniewski H, Klatzo I: Resistance of immature brain to experimental cerebral edema. *Neurology* 15:833, 1965.
25. Huttenlocher PR, Trauner DA: Reye's syndrome, in Vinken PJ, Bruyn GW (eds): *Handbook of Clinical Neurology.* Amsterdam, North Holland Publishing Co, 1977, vol 29, part 3, pp 331-344.
26. Partin JC, Schubert WK, Partin JS: Mitochondrial ultrastructure in Reye's syndrome. *N Engl J Med* 285:1139, 1971.
27. Freeman JM, Nicholson JF, Schimke RT, et al: Congenital hyperammonemia. *Arch Neurol* 23:430, 1970.
28. Ebels EJ: Neuropathological changes in a patient with carbamylphosphate-synthetase deficiency and in two sibs. *Arch Dis Child* 47:47, 1972.
29. Hopkins JJ, Connelly JF, Dawson AG, et al: Hyperammonemia due to ornithine transcarbamylase deficiency. *Arch Dis Child* 44:143, 1969.
30. Wick H, Bachmann R, Baumgartner T, et al: Variants of

citrullinaemia. *Arch Dis Child* 48:636, 1973.
31. Lewis PD, Miller AL: Arginino succinic aciduria. *Brain* 93:413, 1970.
32. Thaler MM, Bruhn FW, Applebaum MN, Goodman J: Reye's syndrome in twins. *J Pediatr* 77:638, 1970.
33. Svoboda DJ, Reddy JK: Pathology of the liver in Reye's syndrome. *Lab Invest* 32:571, 1975.
34. Haller JS: Commentary, in Gellis S (ed): *Year Book of Pediatrics*. Chicago, Year Book Medical Publishers, 1977, p 195.
35. Brown T, Hug G, Lansky L, et al: Transiently reduced activity of carbamyl phosphate synthetase and ornithine transcarbamylase in liver of children with Reye's syndrome. *N Engl J Med* 294:861, 1976.
36. Snodgrass PJ, De Long GR: Urea-cycle enzyme deficiencies and and increased nitrogen load producing hyperammonemia in Reye's syndrome. *N Engl J Med* 294:855, 1976.
37. Paul JR: *A History of Poliomyelitis*. New Haven, Conn, Yale University Press, 1971.
38. Linnemann CC, Kauffman CA, Shea L, et al: Association of Reye's syndrome with viral infection. *Lancet* 2:179, 1974.
39. Colon AR, Ledesma F, Pardo V, Sandberg DH: Viral potentiation of chemical toxins in the experimental syndrome of hypoglycemia, encephalopathy, and visceral fatty degeneration. *Am J Dig Dis* 19:1091, 1974.