Reye's Syndrome in the Adult Patient

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Reye's syndrome has been thought to represent a childhood illness. Our thesis is that it is a postviral systemic disease which may affect adults as well. A 51 year old woman is presented whose case meets all of the major criteria for Reye's syndrome. The diagnostic criteria for Reye's syndrome are summarized, and two other reported cases of Reye's syndrome in adults are reviewed. The diagnosis of Reye's syndrome in adults requires familiarity with the diagnostic criteria and a "high index of suspicion."

The purpose of this paper is to review the diagnostic criteria as well as the reported cases of Reye's syndrome in adults. Also described is an adult who had an illness consistent with Reye's syndrome. Our thesis is that Reye's syndrome is a postviral systemic disease which may affect adults and that it can be diagnosed only by maintaining a high index of suspicion.

The neurologic sequelae of influenza infection have included encephalitis, meningitis, Guillain-Barré syndrome and Reye's syndrome. The latter has been extensively reviewed recently [1] and is usually considered to be a childhood disorder. Reye's syndrome was described by Sir W. Russell Brain in 1929 [2], and 1963 [3], and by Johnson et al. [4] in 1963, but it received world-wide attention in 1963 through Reye and his associates [5]. The syndrome described by these observers occurred in children following apparent upper respiratory tract infection and was associated with a high mortality.

CASE REPORT

The patient was a 51 year old white woman referred from her local hospital for further evaluation of unexplained obtundation and left-sided seizure activity. She had previously been in good health, actively employed as a sewing machine operator, with no recognized drug or toxin exposure. One week prior to transfer, she had cough, rhinorrhea, headache, weakness, and anorexia; three days previously, her husband had similar complaints. Three days after the onset of her viral symptoms, the patient had a single episode of nonprojectile vomiting. She continued to be active around the home. On the morning after the vomiting episode, the patient was found unresponsive, with no evidence of trauma. She was admitted to her local hospital where evaluation included skull roentgenograms, technetium brain scintiscans, lumbar puncture, chest roentgenograms and cerebral arteriograms, none of which disclosed any abnormality. The laboratory data are presented in **Tables I and II.**

On admission to our hospital, the patient was a well-developed, well-nourished white woman who was responsive only to deep pain. A nasotracheal tube was in place. Her respirations were 14/min, regular and unlabored. The

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TABLE I Cerebral Spinal Fluid Analysis

	Referring Hospital	N.C.B.H
White blood cell count	0	0
Red blood cell count	0	0
Protein (mg/100 cc)	16.5	13
Glucose (mg/100 cc)	ND	91
Countercurrent immunoelectrophoresis*	ND	Negative
Venereal disease research laboratory	ND	Negative
Acid-fast bacteria culture	ND	No growth
Fungal culture	ND	No growth
Routine culture	No growth	No growth
Viral culture	ND	No growth
Initial pressure (mm H_2O)	120	150

NOTE: N.C.B.H. = North Carolina Baptist Hospital; ND = not done.

* Antigens for Streptococcus pneumoniae, Hemophilus influenzae, Neisseria meningitidis.

blood pressure was 130/70 mm Hg, pulse 110/min and regular, and temperature was 38.3°C orally. There was no evidence of head trauma. The pupils were 5 mm in diameter and were reactive to direct and consensual light. The funduscopic examination was within normal limits. The tongue and uvula were midline, with an intact gag reflex. The neck was supple without masses or neck vein distention and the neurovascular examination was within normal limits. The cardiovascular system showed no abnormality. Auscultation of the chest demonstrated rhonchi and crackles in both lung fields. The abdomen was soft without masses, peritoneal signs, or organomegaly. The extremities showed no clubbing, cyanosis or edema, and peripheral pulses were intact. The patient had no lymphadenopathy, and examination of the skin was within normal limits. Neurologic evaluation disclosed a comatose patient with no focal defects and with minimal appropriate movement of all extremities to deep pain. The seventh, ninth and tenth cranial nerves were intact, the third, fourth and sixth nerves showed activity to the dolls eye test, and the second and third cranial nerves reacted with direct and consensual light stimulation. The remaining cranial nerves showed no activity to testing.

Over the next 48 hours, the patient remained comatose and began to exhibit decorticate and decerebrate posturing with painful stimulation. She also experienced tonic-clonic movements of her left side. An electroencephalogram obtained during one of these episodes demonstrated no electrical seizure activity. There was no concomitant electrolyte abnormality, although a mild respiratory alkalosis was present. Computerized axial tomography of the brain, with and without contrast, disclosed no abnormalities. The drug screen for amphetamines, cocaine, morphine, methadone, chlordiazepoxide, diazepam, barbiturates, codeine and phenothiazines was negative. The heavy metal screen for lead, mercury and arsenic was also negative. Supportive laboratory data included an elevated serum glutamic oxaloacetic transaminase (SGOT) level, an elevated serum glutamic pyruvate transaminase (SGPT) level, prolonged prothrombin time and an elevated serum ammonia level. The patient also had a mildly elevated bilirubin level. The viral titers during the acute and convalescent phases were 1/80 and 1/320, respectively; they were determined by hemagglutination inhibition and demonstrated a fourfold increase to the influenza A Texas virus. Cultures from the cerebral spinal fluid, nasopharynx, rectum and liver were negative for pathogens. The cerebral spinal fluid disclosed no pleocytosis or evidence of infection.

On the third hospital day, the patient began to move her extremities spontaneously and was no longer posturing on painful stimulation. By the fourth hospital day, she was arousable and could give her name. On the fifth hospital day, a liver biopsy was performed. At that time, results of coagulation studies were normal, the patient was cooperative, two biopsy specimens were obtained, and the procedure was technically easy; nevertheless, it was complicated by hemorrhage with

TABLE II Laboratory Data During Illness

	Patient's Values	Normal Values
White blood cell count (per mm^3)	14.4–8.6	7.0–12.0 × 10^3
Hematoglobin (g/100 ml)	15.1–11.3	12–16
Platelets (per mm^3)	300,000	150,000–250,000
Blood urea nitrogen (mg/100 ml)	55–32	5–25
Inorganic phosphorus (mg/100 ml)	1.7–4.0	2–5
Cholesterol (mg/100 ml)	78–184	120–300
Total bilirubin (mg/100 ml)	2.9–0.7	0.3–1.5
Alkaline phosphatase (mU/ml)	127–77	30–120
Lactic dehydrogenase (mU/ml)	468–280	80–250
Serum glutamic oxaloacetic transaminase (mU/ml)	750–17	8–50
Prothrombin time (sec)	13.7–11.0	10–12
Activated partial thromboplastin time (sec)	36.1	25–35
Ammonia (μmol/liter)	92–10	11–35
Serum glutamic pyruvate transaminase (IU/liter)	87.7	3–36

NOTE: These data represent the ranges seen in our patient during her hospitalization. Data listed to the left represent values from the early portion of her hospitalization and values to the right are those after clinical improvement.

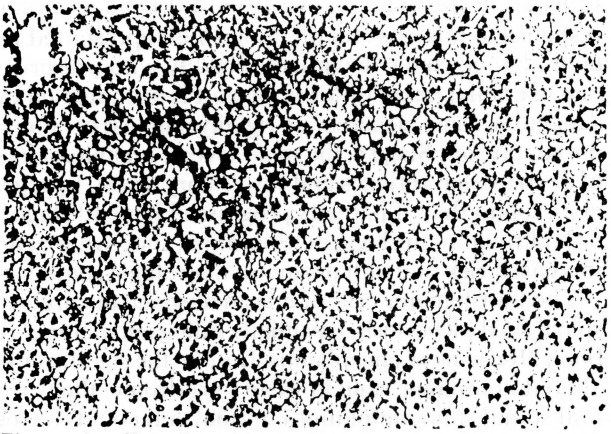

Figure 1. This liver biopsy specimen reveals a uniform steatosis. The hepatocyte nucleus usually maintains a central position despite the presence of fat and a few lipid droplets. There is minimal inflammation and regeneration. Hematoxylin and eosin stain; original magnification equals × 160, reduced by 50 per cent.

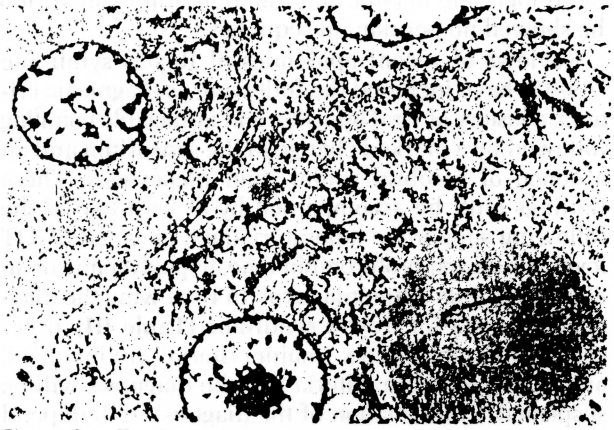

Figure 2. The liver biopsy specimen illustrates an increased amount of rough endoplasmic reticulum and flocculation of the mitochondrial matrix. Also shown are one large and three small lipid droplets. Lead citiate and urananel acetate stain; original magnification equals × 8,600, reduced by 50 per cent.

associated hypotension which required replacement of 5 U of blood. The liver biopsy specimen (**Figures 1, 2 and 3**) showed a uniform fatty infiltration. The electron microscopy demonstrated flocculation of the mitochondrial matrix and an increased amount of rough endoplasmic reticulum. Over the remainder of her 11 day hospitalization, the patient showed dramatic improvement. By the time of her discharge, her only neurologic deficit was an absence of recent past memory.

The results of laboratory studies and other investigations performed during hospitalization are recorded in Tables I and II. During the patient's hospitalization, other problems included an aspiration pneumonitis with Staphylococcus aureus predominating and an enterococcal urinary tract infection. Both organisms were sensitive to and treated with penicillin. The patient was afebrile for five days prior to discharge.

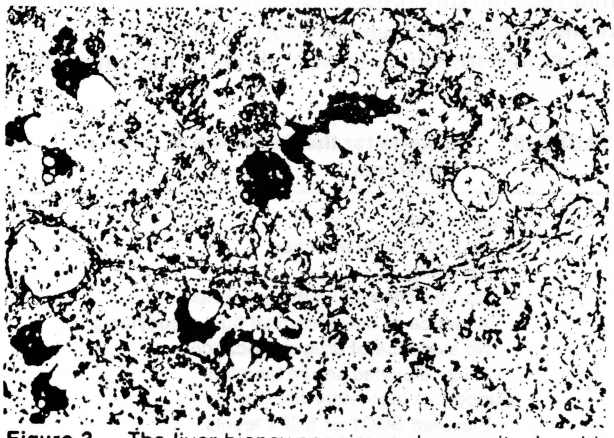

Figure 3. The liver biopsy specimen shows mitochondria with flocculated matrix. A few discernible cisterna are present but not in close approximation. The dense material is associated with small lipid aggregates. Lead citiate and urananel acetate stain, original magnification equals × 14,000, reduced by 50 per cent.

She was seen in follow-up three weeks after discharge at which time there was no evidence of hepatic or neurologic dysfunction. Her memory had returned to its normal baseline state.

COMMENTS

Brain 1929 [2], 1963 [3], Johnson 1963 [4] and Reye 1963 [5] and their associates describe a highly fatal illness characterized by an upper respiratory tract infection, followed by abrupt neurologic deterioration. The latter included a profound disturbance in consciousness, altered muscle tone and reflexes, convulsions, protracted vomiting, fever and a disturbed respiratory rhythm. Initial reports stressed that the patient frequently had hypoglycemia, hypoglycorrhachia, elevated transaminase levels, and an absence of cerebral spinal fluid pleocytosis. More recently, it has been recognized that hypoglycemia and hypoglycorrhachia are found primarily in children under five years of age [6]. Reye's syndrome, often thought to be exclusively a disorder of childhood and adolescence, has previously been described in two adults [7,8]. In the first, a 28 year old woman, the diagnosis of acute noninflammatory encephalopathy accompanied by a microvascular fatty metamorphosis of the liver was made at postmortem examination. The second case involved a 25 year old man who experienced a viral syndrome. He then had protracted vomiting, and three days later became progressively confused and combative. His bilirubin level was found to be mildly elevated, and there was no cerebral spinal fluid pleocytosis. Supportive laboratory data included an elevated SGOT and SGPT level, prolonged prothrombin time and an elevated serum ammonia level. His influenza viral titer was initially elevated 1:128 and did not change with convalescence. Lastly, the patient had a confirmatory liver biopsy. His

neurologic and hepatic abnormalities diminished, and he showed no permanent sequelae.

Reviews of recent epidemics of Reye's syndrome [7,9-13] have included the following as diagnostic criteria: a history of viral infection and intractable vomiting followed by a marked change in the sensorium and an absence of cerebral spinal fluid pleocytosis. These findings must be accompanied by at least two of the following supportive laboratory data: elevated SGOT level, prolonged prothrombin time, hypoglycemia or an elevated serum ammonia level. In reviewing the diagnostic criteria for Reye's syndrome (**Table III**), it becomes apparent that six "major criteria" are involved, and it is upon these criteria that the diagnosis will be suspected. Confirmation of the diagnosis will depend on the presence of at least two of the four possible "supportive" laboratory findings consistent with the diagnosis. The "associated" findings (**Table IV**) are abnormalities that have been documented to occur in Reye's syndrome and, if present, lend further support to the diagnosis.

A history of viral infection in the diagnosis of Reye's syndrome is significant. Reye's syndrome has occurred frequently after influenza B epidemics, sporadically following influenza A, varicella, adenovirus and parainfluenza [10-12]. Proof of viral infection can be shown only through positive cultures or a fourfold increase in the viral serology during the acute and convalescence phases. Indirect evidence for a viral infection is presumed when the patient or a family member has a history of viral symptoms. The historic account can be very helpful in determining the appropriate diagnosis, but some variability should be recognized. The viral symptoms may precede Reye's syndrome by days or weeks, and a small percentage do not give a history of viral symptoms nor do they have serologic evidence of a recent infection.

Vomiting is another major criterion for the diagnosis of Reye's syndrome. Historically, this was described as protracted emesis which usually commenced after the child had shown marked diminution in the symptoms of viral infection [5]. Emesis also was the herald of rapid neurologic deterioration. Although most often protracted, the emesis of Reye's syndrome is occasionally described as minimal [12].

The third major criterion of Reye's syndrome is a marked change in sensorium. Although, it was originally thought that all patients became comatose, now it is accepted that combativeness and confusion simply represent a milder alteration in the sensorium. The milder degree of altered neurologic state is usually encountered early in the illness or in mild cases. Lovejoy et al. [14] have divided the neurologic manifestations into five stages, which offer some help in prognosis and therapy. Stage 1 is the mildest alteration in neurologic function with vomiting, lethargy and sleepiness. Stage 2 demonstrates further neurologic deterioration with delirium, combativeness, hyperventilation and hyperreflexia. In this stage the patients still have a normal response to noxious stimuli. Stage 3 is represented by obtundation, coma, decorticate rigidity with preservation of cranial nerve reflexes. Stage 4 is documented by deepening coma, decerebrate rigidity and loss of cranial nerve reflexes. Stage 5, the most severe, includes a loss of deep tendon reflexes and respiratory arrest. Lovejoy et al. found that, if patients progressed beyond stage 3 or had rapid neurologic deterioration, they were at an increased risk of death or severe neurologic sequelae.

The fourth major criterion is an absence of cerebral spinal fluid pleocytosis, essentially ruling out meningitis, brain abscesses or encephalitis. Despite the significantly altered neurologic state in Reye's syndrome, the cerebral spinal fluid maintains a normal cell count (fewer than 8 white blood cells, mm^3) [7].

The fifth major criterion is an absence of drug intoxication. It is, therefore, recommended that drug screening be performed in all suspected cases. In the early course of the illness, when only mild neurologic abnormalities exist, it may be impossible on clinical grounds to differentiate Reye's syndrome from a drug overdose. Methyl bromide ingestion has been reported to produce a clinical picture that is very similar to Reye's syndrome but without any changes in the liver on biopsy [15].

The final major criterion is a mild increase in the bilirubin. Hyperbilirubinemia is usually not clinically apparent, and it is unusual for the total bilirubin to be greater than 4 mg/100 ml in children. Of the two cases in which the bilirubin levels were recorded in adults, the level in one reached a maximum of 7.5 mg/100 ml and in our patient it reached 2.9 mg/100 ml. In the patients with clinical jaundice, care must be taken to insure that other liver problems are not overlooked.

Supportive laboratory data are used to aid in the confirmation of the diagnosis of Reye's syndrome. In past epidemics of Reye's syndrome, at least two of the four possible supportive laboratory findings have been required for the diagnosis [7,9,12]. In adults, one can expect abnormalities in only three of the supportive

TABLE III Criteria for the Diagnosis of Reye's Syndrome

Major criteria
History of viral infection
Vomiting
Marked changes in the sensorium
Absence of cerebrospinal fluid pleocytosis
No evidence of drug intoxication
Mildly elevated serum bilirubin
Supportive laboratory findings
Elevated SGOT or SGPT levels
Prolonged prothrombin time
Elevated serum ammonia levels
Hypoglycemia (under the age of five years)

NOTE: SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

tests. Elevation of the serum transaminase levels is variable, with some authorities requiring a threefold elevation [7]. The use of SGPT is primarily for confirmation of the origin of the SGOT.

Prolongation of the prothrombin time is also a supportive laboratory finding. The prothrombin time may be moderately to extremely prolonged. Patients who have a prothrombin time greater than 13 seconds from control have had a poorer prognosis [14].

The third laboratory finding which supports the diagnosis is an elevated serum ammonia level. The elevated levels are seen early in the illness and may return to normal paralleling clinical improvement or, on occasion, returning to normal without clinical improvement, in which case the patient usually has died. Ammonia levels greater than 300 mg/100 ml carry a poor prognosis [14].

The last of the supportive laboratory data is hypoglycemia which, in Reye's syndrome, is ordinarily seen in children under five years of age and correlates with hepatic glycogen depletion [6,16]. This laboratory finding in all likelihood will not be found in adults.

The associated findings (Table IV) represent abnormalities which have been reported to occur in Reye's syndrome. Their significance is that knowing about them allows the physician some mobility in treatment and a reassurance of the diagnosis.

Cerebral edema has been well documented in Reye's syndrome; it is thought to aggravate, if not cause, the neurologic manifestations of the disease. Intracranial pressure monitoring is an effective method of measuring this edema (17) and may disclose pressure waves that are not recognizable by checking the initial pressure of cerebral spinal and lumbar fluid. The pressure of the cerebrospinal fluid may be normal or increased in Reye's syndrome. In Lovejoy's stages 4 and 5, it tends to be increased [14,18]. The differential diagnosis of cerebral edema of unknown cause should include Reye's syndrome. In one retrospective study, eight of 31 cases of suspected Reye's syndrome had been diagnosed as cerebral edema or encephalitis [19].

Seizure activity is associated with a comatose state (stage 3, 4 or 5 of neurologic aberration as described by Lovejoy), but is not a common finding until the patient is in stage 5. The seizure activity may be focal or generalized, and an interesting and unexplained finding is that occasionally the seizure activity is *not* associated with electroencephalographic spike activity. Seizure activity may indicate a poor prognosis [5,14,18].

Serum amino acid analyses in children with Reye's syndrome have shown increases in many amino acids but the glutamic acid, alanine, lysine and alpha-amino-N-butyrate have especially shown significant increases [20,21]. The serum for amino acid analysis should be drawn within 24 hours of onset of the clinical syndrome in order to allow comparison to published normal values. Amino acid analysis of the cerebral spinal fluid tends to reflect the general pattern seen in the serum [21,22].

Most authorities have described the liver biopsy as diagnostic for Reye's syndrome, although some do not advocate liver biopsy when the clinical picture is otherwise definitive because of the potential risk involved [23]. Many patients have abnormal clotting studies. Liver biopsies have frequently been performed despite prolongation of the prothrombin time [16]. The liver biopsy in Reye's syndrome typically discloses a steatosis that is microvesicular in type and not associated with lipid lakes or large lipid deposits. There is minimal necrosis, hepatic regeneration and inflammation. The electron microscopic picture is one of mitochondrial swelling with an amorphous matrix. The mitochondria take on ameboid forms, the membrane is intact, and the cisternae are preserved although not in close proximity. The mitochondrial abnormalities rapidly return to normal as the clinical situation improves. It is also reported that the smooth endoplasmic reticulum proliferates to occupy large areas of the cytoplasm [24]. At present, it may be advantageous to obtain a liver biopsy specimen in those patients in whom the diagnosis is suspected. As the clinical picture of Reye's syndrome in adults becomes clearer, the liver biopsy may become less important as a diagnostic tool.

Hypophosphatemia has been reported to occur in Reye's syndrome, but no absolute values were reported [25]. Lipid abnormalities such as a low cholesterol level and an increased free fatty acid level have also been observed [21].

The arterial blood gas usually shows a metabolic acidosis early in the illness, which is then complicated by a respiratory alkalosis. The respiratory alkalosis may become the major acid-base disturbance [16,22].

Normal findings in Reye's syndrome include cerebral spinal fluid protein level, hemoglobin, white cell count and differential, and electrolytes. These values may be abnormal when Reye's syndrome is complicated by other conditions.

The pathogenesis of Reye's syndrome is unknown. It is postulated that an enzyme block exists in the urea cycle affecting the levels of ornithine transcarbamylase and carbamylphosphate synthetase [26]. Elevations of tissue ornithine and depression of hepatic citruline levels support this hypothesis. Furthermore, these re-

TABLE IV Findings Asssociated with Reye's Syndrome

Cerebral edema
Seizure activity
Serum and cerebrospinal fluid amino acid abnormalities
Liver biopsy abnormalities
Hypophosphatemia
Hypocholesterolemia
Elevated free fatty acid levels
Acid-base disturbances

actions occur in hepatic mitochondria, which have been demonstrated to be physically abnormal by electron microscopy.

The treatment of patients with Reye's syndrome is controversial and it is, for the most part, supportive in nature [27]. Small numbers of patients have been treated with peritoneal dialysis [23], total body "washout" and exchange transfusions [28-30]. The therapeutic efficiency of these treatment modalities has not been adequately substantiated. Hypoglycemia and hypophosphatemia may be corrected by varying infusion solutions. Patients with hyperammonemia may be treated with lactulose (although its efficiency in Reye's syndrome is not known). Abnormal clotting factors frequently do not respond to the administration of vitamin K alone [21,31], and the patient may require infusion of fresh frozen plasma if bleeding becomes a problem. The respiratory alkalosis may be beneficial provided the patient is not having serious arrhythmias. By decreasing the carbon dioxide tension and the cerebral blood flow, one decreases cerebral edema. Thus, respiratory alkalosis should be evaluated in relation to cardiac and cerebral function. Intracranial pressure probably should be monitored [32] and can be manipulated with mannitol, dexamethasone, hyperventilation or combinations of mannitol and phenobarbitol [17,33]. The insertion of an intracranial pressure monitor is advocated primarily in the presence of rapid neurologic deterioration and in patients in whom neurologic aberration is at least in stage 3.

Intensive medical support for those whose neurologic status is in stage 3 or beyond may require elective intubation, insertion of an arterial line with measurement of electrolytes, blood gases, glucose, phosphate, blood urea nitrogen and ammonia levels on a regular basis. The use of a bladder catheter and a nasogastric tube may also be indicated.

Our patient fulfills the criteria as set forth in our paper. She had the major criteria of a history of a viral infection which was proved to be influenza A by viral titers. She had emesis that was followed by a marked change in the sensorium. There was no cerebral spinal fluid pleocytosis, no evidence of drug intoxication and only a mild elevation of her bilirubin level. She also had all of the supportive laboratory data that can be expected in adults: a significantly elevated SGOT level, prolonged prothrombin time and an elevated serum ammonia level. Finally, our patient had the following associated findings. She demonstrated seizure, activity without electroencephalographic spike activity, a liver biopsy that disclosed findings consistent with Reye's syndrome, mild hypophosphatemia, hypocholesterolemia and a mild respiratory alkalosis.

Our patient apparently represents the *oldest* patient with Reye's syndrome described to date and should serve to alert physicians to the fact that this syndrome may occur in adults as well as in children and adolescents. It is important to recognize that adults are at risk from this sequelae of influenza infection. Diagnosis requires a high index of suspicion and the exclusion of other treatable disorders. Appropriate preparation for aggressive supportive measures is mandatory once the diagnosis of Reye's syndrome is made.

ACKNOWLEDGMENT

We would like to thank Sandra Glasgow for her help in the manuscript preparation. We would also like to thank Joseph E. Johnson, III, M.D. and James F. Toole, M.D. for their constructive review of the manuscript, and Richard B. Marshall, M.D. for his performance and interpretation of the electron microscopy.

REFERENCES

1. Pollack JD: Reye's Syndrome, Proceedings. New York, Grune & Stratton, 1975.
2. Brain WR, Hunter D, Turnbull HM: Acute meningo-encephalomyelitis of childhood: report of six cases. Lancet 1: 221, 1929.
3. Brain WR, Hunter D: Encephalopathy and fatty degeneration of the viscera. Lancet 2: 881, 1963.
4. Johnson GM, Scurletis TD, Carroll NB: A study of sixteen fatal cases of encephalitis-like disease in North Carolina children. North Carolina Med J 24: 464, 1963.
5. Reye RDK, Morgan G, Baral J: Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. Lancet 2: 749, 1963.
6. Bove KE, McAdams J, Partin JC, et al.: The hepatic lesion in Reye's syndrome. Gastroenterology 69: 685, 1975.
7. Corey L, Rubin RJ, Hattwick MAW, et al.: A nationwide outbreak of Reye's syndrome: its epidemiologic relationship to Influenza B. Am J Med 61: 615, 1976.
8. Morse RS, Holmes AW, Levin S: Reye's syndrome in an adult. Am J Dig Dis 20: 1184, 1975.
9. Ruben FL, Streiff EJ, Neal M, et al.: Epidemiologic studies of Reye's syndrome: cases seen in Pittsburgh, October 1973-April 1975. Am J Pub Health 66: 1096, 1976.
10. Linnemann CC Jr, Shea L, Partin JC, et al.: Reye's syndrome: epidemiologic and viral studies, 1963-1974. Am J Epidemiol 101: 517, 1975.
11. Linnemann CC Jr, Shea L, Kauffman CA, et al.: Association of Reye's syndrome with viral infection. Lancet 2: 179, 1974.
12. Ruben FL, Michaels RH: Reye syndrome with associated Influenza A and B infection. JAMA 234: 410, 1975.
13. Hochberg FN, Nelson K, Janzen W: Influenze type B-related encephalopathy: the 1971 outbreak of Reye syndrome in Chicago. JAMA 231: 817, 1975.
14. Loyejoy FH, Smith AL, Bresnan MJ, et al.: Clinical staging in Reye syndrome. Am J Dis Child 128: 36, 1974.
15. Shield LK, Coleman TL, Markesbery WR: Methyl bromide intoxication: neurologic features, including simulation of Reye syndrome. Neurology 27: 959, 1977.
16. Partin JC: Reye's syndrome (encephalopathy and fatty liver): diagnosis and treatment. Gastroenterology 69: 511, 1975.
17. Chandler WF, Kindt GW: Monitoring and control of intracranial pressure in non-traumatic encephalopathies. Surg Neurol 5: 311, 1976.
18. Aoki Y, Lombrosco CT: Prognostic value of electroencephalography in Reye's syndrome. Neurology 23: 333, 1973

19. Reiner CB: Reye's syndrome, a retrospective study. Reye's Syndrome, Proceedings, (Pollack JD, ed), New York, Grune & Stratton, 1975, p 75.
20. Hilty MD, Romshe CA, Delameter PV: Reye's syndrome and hyperaminoacidemia. J Pediatr 84: 362, 1974.
21. Romshe CA: Laboratory diagnosis of Reye's syndrome. Reye's Syndrome, Proceedings, (Pollack JD, ed), New York, Grune & Stratton, 1975, p 15.
22. Shannon DC, Delong R, Bercu B, et al.: Studies on the pathophysiology of encephalopathy in Reye's Syndrome: hyperammonemia in Reye's Syndrome. Pediatrics 56: 999, 1975.
23. Samaha FJ, Blau E, Berardinelli JL: Reye's syndrome: clinical diagnosis and treatment with peritoneal dialysis. Pediatrics 53: 336, 1974.
24. 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, 1971.
25. Cooperstock MS, Tucker RP, Baublis JV: Possible pathogenic role of endotoxin in Reye's syndrome. Lancet 1: 1272, 1975.
26. Thaler MM: Pathogenesis of Reye's syndrome: a working hypothesis. Pediatrics 56: 1081, 1975.
27. Devivo DC, Keating JP, Haymond MW: Reye syndrome: results of intensive supportive care. J Pediatr 87: 875, 1975.
28. Cooper GN, Karlson KE, Clowes GHA, et al.: Total body washout and exchange: a valuable tool in acute hepatic coma and Reye syndrome. Am J Surg 133: 522, 1977.
29. Berman W, Pizzi F, Schut L, et al.: The effects of exchange transfusion on intracranial pressure in patients with Reye syndrome. J Pediatr 87: 887, 1975.
30. Bobo RC, Schubert WK, Partin JC, et al.: Reye syndrome: treatment by exchange transfusion with special reference to the 1974 epidemic in Cincinnati, Ohio. J Pediatr 87: 881, 1975.
31. Schwartz AD: The coagulation defect in Reye's syndrome. J Pediatr 78: 326, 1971.
32. Kindt GW, Waldman J, Kohl S, et al.: Intracranial pressure in Reye's Syndrome: monitoring and control. JAMA 231: 882, 1975.
33. Marshall LF, Shapiro HM, Rauscher A, et al.: Pentobarbital therapy for intracranial hypertension in metabolic coma Reye's syndrome. Crit Care Med 6: 1, 1978.