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Reye Syndrome

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Reye syndrome is an uncommon neurologic disorder with an annual incidence ranging from 0.3 to 6.0 cases per 100,000 children.[18,24,60] These statistics are influenced by the periodic coincidence of influenzal epidemics. When first described in 1963, it was considered to be a rare and often devastating illness of childhood.[51,85] There is little doubt that the illness antedated these two reports;[8,16] but the earlier literature is sketchy and anecdotal. Pathologists overlooked (or dismissed as unrelated) the fatty degeneration of the liver and other viscera, and liver function tests were not readily available for clinical use. Consequently, these earlier cases were classified as acute encephalopathies[64] or encephalitides.[1,63]

This clinical entity is now recognized throughout the world.[20,26,85] It is a major cause of noninfectious neurologic death following a viral illness in the pediatric age group; and despite the fact that it is an uncommon disease, it still represents one of the primary causes of death for young children in the United States. The dramatic nature of the presentation, the possibility for complete recovery, and the relative frequency of the illness have encouraged physicians and scientists to investigate this illness in some detail. This increasing level of awareness and interest has been paralleled by an apparent reduction in the annual morbidity and mortality.

CLINICAL MANIFESTATIONS

Children of all ages may be at risk for developing Reye syndrome. Occasional cases have been described in early infancy[49] and in adults.[105,115] There is no sex preference. The epidemic forms of the syndrome usually parallel the annual incidence of influenza B or A; the sporadic cases typically follow varicella. Other viral agents also have been implicated,[18,26] and occasionally the illness may develop after bacterial pharyngitis.

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There is no clear correlation between the intensity of the antecedent viral illness and the encephalopathy that follows. Often, the child is recovering from the viral illness when pernicious vomiting begins. Occasionally, the antecedent viral illness is appreciated only in retrospect after the encephalopathy has passed. The encephalopathic phase of the illness is heralded by irritability, lethargy, and vomiting; occasionally fever may be present.

Vomiting is the cardinal clinical manifestation introducing the second phase of the illness. The mechanism underlying the vomiting remains unexplained. Campbell has suggested that elevated polyamines, and specifically spermine, may be the mechanism causing the vomiting.[13] He cites the experiments of Risetti and Mancini who noted pernicious vomiting in human volunteers after the intramuscular administration of spermine.[86] The child often will recall the early phase of vomiting after recovering from the encephalopathy, suggesting that cerebral function and specifically memory remains preserved at this point in the illness. Some patients experience no demonstrable neurologic disturbance and they are suspected of having Reye syndrome only because of chemical evidence of hepatic dysfunction. Other less fortunate children are plunged into coma after a few hours of pernicious vomiting. The diagnosis may be unclear in selected cases because of the marked variability of the encephalopathic phase. Typically, however, the patient enters a hyperexcitable state (toxic delirium) after the initial period of vomiting. Such a patient is extremely restless and vigorously resists restraints. The hyperexcitable state is associated with sympathetic nervous sytem overactivity manifested by fever, sweating, tachycardia, pupillary dilation, and tachypnea. Catecholamine (norepinephrine, epinephrine, and dopamine) concentrations may be elevated in the blood and cerebrospinal fluid (CSF), and the degree of elevation may correlate with the patient's stage at the time of admission.[32]

The encephalopathy characteristically lasts for 24 to 96 hours, and complete recovery of organ function is expected in patients who survive. The quality of survival is determined by many factors including hypoglycemia, cerebral hypoxia, hyperpyrexia, hyperammonemia, free fatty acidemia, systemic hypotension, and intracranial hypertension. Other devastating complications include gastrointestinal hemorrhage, pancreatitis, focal or generalized convulsions, and intractable brain swelling. The intensity of these complications determines the quality of survival. A full recovery can be anticipated in almost every case, despite severe neurologic dysfunction during the height of the acute encephalopathy.

The stage of the illness upon admission correlates with the likelihood of recovery.[48,60,94] Several staging criteria have been promulgated over the past decade including the original staging method outlined by Huttenlocher.[48] We continue to use this four-stage method. Others subscribe to the five-stage criteria outlined by Lovejoy and colleagues[62] or the five-stage criteria resulting from the National Institutes of Health Consensus Conference.[16] The

Glasgow coma scale also has been used for the evaluation of level of consciousness in children with Reye syndrome.[30] Duncan and colleagues concluded that the Glasgow coma scale provided better earlier indication of progressive central nervous system (CNS) disease than the Lovejoy scale, and therefore may be of greater value to physicians caring for such patients. Whether one chooses the Huttenlocher, the Lovejoy, or the Glasgow coma scale, it appears that the common denominator is a well-defined set of criteria that enables the examining physician to assess the severity of the illness at the time of admission and to reassess the patient's condition serially as treatment is being administered. Any of these scales is satisfactory, particularly if the examining physician is familiar with the criteria.

Children admitted in the milder encephalopathic stages almost always do not progress before making a full recovery. Conversely, patients admitted in a comatose state frequently deteriorate further while in hospital before recovering completely or dying. The patients at greatest risk of dying are those admitted in deep coma with decerebrate posturing. These observations suggest that early diagnosis and treatment of the child with Reye syndrome aborts the progressive aspect and facilitates recovery. This conclusion, however, remains unproven, particularly as an increasing number of children with mild disease are being diagnosed. This has also contributed to the lower morbidity and mortality that has been noted in recent years.

LABORATORY ABNORMALITIES

The most significant abnormalities are elevated serum transaminases, hypoprothrombinemia, and hyperammonemia. Other serum enzyme abnormalities include elevated activities of creatine phosphokinase, lactic dehydrogenase, amylase, lipase, and glutamate dehydrogenase. The elevated glutamate dehydrogenase activity is masked by a dialyzable inhibitor.[46] This inhibitor may be GTP.[45] Experiments have shown the glutamate dehydrogenase activity in Reye syndrome sera to be inhibited about 1000-fold more potently by GTP than is the case with normal human enzyme; and that ADP, which normally reverses the GTP inhibition, has no effect on the aberrant enzyme present in the sera of patients with Reye syndrome.[45]

The serum glucose and phosphorus concentrations may be decreased, the uric acid level increased, and the carbon dioxide level decreased. The arterial pH, however, frequently is in the normal range despite the hyperpnea and the organic acidemia.[27] These abnormalites are consistent with a mixed acid-base disturbance, each component seemingly independent of the other. Elevated amino acids include alanine, glutamine, glutamate, lysine, and alpha-amino-N-butyrate. Amino acids that are normal or slightly increased include ornithine, aspartate, arginine, tyrosine, phenylalanine, methionine, leucine, isoleucine, valine, taurine, threonine, serine, proline, glycine, and histidine. Citrulline and argininosuccinic acid are not de-

tectable. Amino acids usually not found in the serum also may be detected including cystathionine, homocystine, beta-aminoisobutyric acid, and saccharopine.[42,44,54,89] Elevated organic acid concentrations include lactic, pyruvic, beta-hydroxybutyric, acetoacetic, butyric, isobutyric, propionic, isovalaric, and caprylic.[42,111,113] The fatty acid patterns of serum free fatty acids, triglycerides, and phospholipids are distinctly different in patients with Reye syndrome. The polyunsaturated fatty acid content of phospholipids is decreased and the polyunsaturated fatty acid content of the free fatty acid fraction is increased.[75] Ogburn and coworkers have postulated that the antecedent viral infection releases phospholipase A_2, which releases polyunsaturated fatty acids from tissue phospholipids into the free fatty acid pool, thereby stimulating prostaglandin synthesis. This metabolic cascade, in turn, leads to dysfunction of the liver and brain. The serum cholesterol concentration is decreased. Also, several serum proteins are decreased in amount or activity including lipoproteins (VLDL), clotting factors,[80,95] and components of the complement system.[66,81]

The concentrations of several circulating hormones also have been measured in Reye syndrome.[42,73] Plasma insulin concentrations are appropriate for the blood glucose concentrations. Plasma cortisol concentrations are markedly elevated; plasma glucagon, growth hormone, and prolactin concentrations are less strikingly elevated. Also, the plasma concentrations of cyclic adenosine monophosphate (AMP) have been found to be elevated,[53] and aberrant activity of hepatic cyclic nucleotide phosphodiesterase has been reported.[52]

The decrease in the serum VLDL concentration and the absence of lipoprotein particles in the Golgi membranes observed by electron microscopy in liver biopsies suggests that a transient impairment in the extrahepatic transport of intracellular lipid exists in this disease process.[77] Pollack and coworkers have speculated that the antecedent viral illness facilitates fatty acid mobilization from peripheral adipose tissues, resulting in excessive lipolysis and free fatty acidemia.[83] This speculation is consistent with the more recent observations by Ogburn and coworkers.[75]

The histopathology of Reye syndrome has been studied in considerable detail. Changes in the liver include microvescicular steatosis, glycogen depletion, depleted Golgi membranes, proliferation of peroxisomes, and distorted mitochondria.[7,77] Mitochondrial abnormalities similar to those described in the hepatocyte have been noted in neurons, together with a peculiar unraveling and bleb formation of myelin, reminiscent of the myelin disturbances produced by the toxins hexachlorophene and triethyltin. Qualitatively similar abnormalities of mitochondria together with lipid droplet accumulation and glycogen depletion have been noted in muscle biopsies.[41,96] Type I muscle fibers are particularly vulnerable to these histologic changes.

The biochemical studies are consistent with the histopathologic observations; namely, that there is a universal decrease in the activity of all mitochondrial enzymes measured to date, with the sole excep-

tion of carnitine palmitoyltransferase.[116] The mitochondrial enzymes that are decreased in activity include ornithine transcarbamylase, carbamoyl-phosphate synthetase, the pyruvate dehydrogenase complex, pyruvate carboxylase, succinate dehydrogenase, cytochrome oxidase, glutamate dehydrogenase, isocitrate dehydrogenase, and monoamine oxidase.[25,69] Whether other mitochondrial enzyme systems are involved in this disease process is unclear, as a complete analysis of these enzymes has not been undertaken. By contrast, the cytosolic enzymes that have been measured have normal activities.[38,69] Resolution of the malate dehydrogenase isoenzymes by electrophoresis demonstrated that the cytosolic-to-mitochondrial isozyme ratio was significantly increased in patients with Reye syndrome.[69] Decreased activity of the mitochondrial isozyme accounted for the elevated ratio.

The histopathologic and biochemical observations have permitted investigators to speculate that Reye syndrome represents a metabolic response to a universal mitochondrial insult.[25] Most, if not all, of the laboratory abnormalities may be explained on the basis of a primary mitochondrial injury.[11]

EPIDEMIOLOGY

Certain facts are well established as they relate to the epidemiology of this illness. There is a specific relationship between two viruses, varicella and influenza, and Reye syndrome. Approximately 25 per cent of patients with Reye syndrome have varicella as the antecedent illness, and most of the remaining patients have influenza B or A as the antecedent infection. Other viral illnesses have been implicated, but less well documented, and occasional reports describe serologic evidence of simultaneous viral infections. The attack rate for Reye syndrome approximates 30 to 60 cases per 100,000 influenza B infections, 2.5 to 4.3 cases per 100,000 influenza A infections, and 0.3 to 0.4 cases per 100,000 varicella infections.[2] The temporal relationship between the seasonal occurrence of influenza B and epidemics of Reye syndrome has been documented on several occasions.[18,70,107] The sporadic cases are distributed more evenly throughout the year and usually follow varicella. Various epidemiologic surveys have shown that Reye syndrome is predominantly a rural-suburban entity rather than an urban entity. The urban-rural distribution of Reye syndrome in Ohio reported by Sullivan-Bolyai and coworkers[107] differed from the previous reports because the demographic classifications were redefined according to the 1970 U.S. Bureau of Census Definitions. The urban-noncentral city standard metropolitan statistical area demonstrated the highest rate (1.62 cases per year per 100,000 persons age 0 to 17 years). This study also suggested that rates of attack were lower in the low socioeconomic groups. These collective observations suggested that Reye syndrome may be influenced by individual susceptibility or the micro environ-

ment, rather than the global environment; that is, within and around the household as opposed to industrial or farming considerations. Lichtenstein and coworkers,[60] using only biopsy-proven cases, determined an even higher incidence of 3.5 cases per 100,000 children under the age of 17 years in metropolitan Cincinnati during a 1-year prospective study. This incidence figure was 11-fold higher than the incidence calculated by the Centers for Disease Control for the same time period. Lichtenstein and associates excluded some patients as examples of Reye syndrome because the histochemical stain for succinic dehydrogenase was equivocal or normal in the liver biopsy specimens. Inclusion of these patients gives a higher incidence figure approaching 6.06 cases per 100,000 children less than 1 to 17 years of age.[24]

These epidemiologic surveys have suggested the possibility that environmental factors may be contributory in Reye syndrome acting synergistically with an antecedent viral infection. A number of hypotheses have been advanced regarding insecticides, insecticide carriers, and emulsifiers as possible environmental toxins, but no confirmatory data have been forthcoming.[20] In addition, aflatoxins and salicylates have been implicated. For the moment, however, there is no compelling evidence linking any of these environmental toxins causally with Reye syndrome.

ETIOPATHOGENESIS

The abundance of histologic and metabolic abnormalities documented in Reye syndrome have tantalized students of this malady for years. Despite these clues, the etiopathogenesis remains obscure. The clinical phenotype has been mimicked by environmental intoxicants and various inborn errors of metabolism. Intoxication with salicylates, tetracyclines, valproic acid, disulfiram, phenformin, margosa oil, chlordane, pyrrolizidine, camphor, methylbromides, and lead produce a similar clinical syndrome.[33,50,76,90,97,101,103,106]

Several attempts have been made to identify a genetic predisposition in Reye syndrome, without success. The syndrome rarely recurs in patients.[36,93,114] Sibling involvement in Reye syndrome has been documented on several occasions.[18,24,80] Siblings of either sex and twins have been reported to be affected, and the antecedent infection often was varicella or influenza B. One sibling also had a diagnosis of ketotic hypoglycemia. Hilty[43] reported three families with sibling involvement. Varicella was the antecedent infection in two families and an upper respiratory tract infection in the third. Wilson[117] reported the simultaneous occurrence of Reye syndrome in three siblings with serologic data indicating that each had an H1 N1 influenza virus infection. There was no evidence of haplo-type segregation by HLA typing in either report. Similarly, neither Hilty nor Wilson was able to identify any environmental factor contributing to the simultaneous occurrence of disease in the siblings.

Initially, it was thought that the high mortality precluded recurrences. However, this explanation has become less tenable in recent years as the apparent mortality rate has declined. Also, more patients with "recurrent Reye syndrome" have been shown now to have inborn errors of metabolism. Ornithine transcarbamoylase deficiency, systemic carnitine deficiency, medium-chain and long-chain acyl-CoA dehydrogenase deficiencies, beta-hydroxy-beta-methylglutaric acidemia, isovaleric acidemia, and the various ketotic hyperglycinemic syndromes may demonstrate the Reye syndrome phenotype.[14,35,39,55,59,87,100,104] The recurrent nature of these inherited disorders is an important distinction. Recurrent attacks of "Reye syndrome" strongly imply an inborn error of metabolism unless proved otherwise. The laboratory abnormalities differ among these various disorders although varying degrees of hepatic dysfunction may be shared by all these entities. The absence of ketonuria is characteristic of systemic carnitine deficiency, medium-chain acyl-CoA dehydrogenase deficiency, and beta-hydroxy-beta-methylglutaric acidemia. Elevated ketone body concentrations occur in isovaleric acidemia, propionic acidemia, and methylmalonic aciduria. Increased urinary excretion of orotic acid, particularly between acute episodes, is characteristic of ornithine transcarbamoylase deficiency.

The pathophysiology of the clinical state may be similar in Reye syndrome and the other conditions that present with a similar phenotype. Several observations suggest that a child suffering from Reye syndrome is subjected to intense metabolic stress. There is tissue glycogen depletion, excessive peripheral lipolysis, and impaired biosynthetic processes. Disturbed protein synthesis is suggested by decreased pre-beta-lipoproteins, several clotting factors, and components of the complement system.[66] However, it remains unclear which of these metabolic abnormalities is primary and which is secondary. The relationship between the etiologic event, namely the viral infection and the subsequent mitochondrial injury, remains elusive; but there is circumstantial evidence to suggest an intracellular impairment in various biosynthetic and storage processes. Mitchell and coworkers[69] extended this speculation by suggesting that Reye syndrome may reflect a generalized decrease in the steady state level of mitochondrial enzymes because of selective impairment of mitochondrial biogenesis.

The mechanism of the encephalopathy also remains controversial.[22] Some consider it to be the consequence of hepatic failure, whereas others believe it is a manifestation of the primary mitochondrial injury suffered by many organs including liver and brain. Elevated blood ammonia concentrations were implicated initially as the possible cause of the encephalopathy.[84] More recently, investigators have focused on the free fatty acidemia as the pathogenetic mechanism.[3,10,111–113] Animal models have been developed to explore this mechanism further by infusing sodium octanoate.[112] These experiments also represent a model for the inherited deficiency of medium-chain acyl-CoA dehydrogenase, which simulates Reye syndrome.

A previous interest in salicylates as a pathogenetic factor has been rekindled by epidemiologic studies that document a statistical association between salicylate intake and the development of Reye syndrome.[40,79,80] These studies have been criticized because of methodologic flaws. Nevertheless, the current prevailing bias is that salicylates represent an added metabolic insult to an organism already burdened by a primary mitochondrial injury.

The apparent similarities between salicylate intoxication and Reye syndrome have intrigued investigators for the past decade. Hepatic dysfunction and encephalopathy occur in both settings, although hyperammonemia is never striking in salicylate intoxication.[9,29,71,90] Other similarities include a mixed acid-base disturbance and a coagulopathy.[4] However, important differences exist including the hepatic histopathology and the nature of the amino acidemia.[8,69] The reported serum salicylate concentrations in patients with Reye syndrome often fall within the therapeutic range.[79] However, these salicylate concentrations may be inappropriately high given the interval of time between the last dose of aspirin and the measurement of the serum concentration. One brief study documented a prolonged biologic half-life for aspirin during Reye syndrome;[88] another has reported decreased aspirin esterase activity.[109] These abnormalities disappeared after recovery. Salicylate also can produce gross swelling of isolated mitochondria suspended in isotonic salt solutions.[119] Given our current understanding of the problem, it seems prudent to conclude that a statistical association exists between salicylate intake and Reye syndrome. It is likely that this observation represents a compounding of the pathophysiology of Reye syndrome rather than a causal relationship. Other reports have indicated that Reye syndrome has developed in children who have taken acetaminophen rather than aspirin. Poisoning by acetaminophen causes centrilobular hepatic necrosis, and the toxic effects of this substance can be potentiated in mice by concurrent infection with influenza B virus.[65] Hepatic necrosis occurs infrequently in Reye syndrome; when present, it is usually periportal in distribution.[5] This pattern of distribution has suggested a toxic insult to the liver as may be seen with high concentrations of fatty acids or aflatoxin B.[11] The periportal distribution in Reye syndrome differs from the centrilobular pattern associated with acetaminophen intoxication.

Aflatoxin is a metabolite of the fungus *Aspergillus flavus*. This toxin has been suggested as an etiologic agent in Reye syndrome and was first identified in children with Udorn encephalopathy, an illness that resembles Reye syndrome.[6] Recent studies have shown that aflatoxin selectively depresses the mitochondrial enzymes carbamylphosphate synthetase and ornithine transcarbamoylase without affecting the cytosolic urea cycle enzyme arginase.[108] One study has demonstrated aflatoxin B_1 in 11 of 14 liver samples, 4 of 6 blood samples, and 4 of 5 urine samples obtained from patients with Reye syndrome.[102] A second study, however, has failed to demonstrate any significant difference in aflatoxin levels in serum and urine obtained

from patients with Reye syndrome when compared with control subjects.[72] Twenty-three per cent of all patients in this second study had measurable aflatoxin concentrations indicative of recent exposure. This observation suggests that people in the United States are constantly exposed to low levels of aflatoxin, a finding that may have public health significance.

Other xenobiotic initiating factors have been looked for in patients with Reye syndrome because of the epidemiologic data and the known association of enhanced viral virulence with certain chemicals in animals, insects, and cell cultures.[82] Environmental toxins such as aflatoxins, herbicides, insecticides, and surfactants have been studied in various animal models.[47] The ferret model also has been exploited, because this animal is susceptible to the human influenza virus.[23,61] Many of the histopathologic and biochemical abnormalities found in Reye syndrome have been replicated in these diverse animal models. The primary flaw, unfortunately, of these model systems is the lack of confirmatory evidence of a xenobiotic initiating factor in the tissues or biologic fluids of children with Reye syndrome. Davis and colleagues recently reported on their studies of experimental influenza B virus toxicity in mice.[21] Juvenile BALB/c mice were injected intravenously with a nonmouse-adapted strain of influenza B/Lee/40 virus. Lethargy, seizures, coma, and death developed 1 to 3 days later. The clinical, biochemical, and pathologic features of the mouse illness were remarkably similar to the human illness. The serum transaminases and plasma ammonia were elevated, the brain was swollen without any inflammatory changes, and the liver demonstrated microvesicular fatty metamorphosis. Viral propagation did not occur in brain or liver. Ultrastructural examination of the liver revealed microvesicular steatosis, mild glycogen depletion, and slight matrix expansion of occasional mitochondria. No viral particles were seen. Previous studies by these investigators also documented biochemical abnormalities in the livers of these animals. A particularly interesting observation is the abnormal compartmental redistribution of ornithine transcarbamoylase to the cytoplasm.[117] This enzyme is encoded by the nuclear genome, and the gene product then enters the mitochondrial matrix to assume its catalytic function in the urea cycle. Brownstein and colleagues observed a spontaneous viral illness occurring in BALB/cByJ mice that included the cardinal clinical and laboratory features of the human counterpart.[12] The mice developed histopathologic and chemical evidence of liver disease and clinical and histopathologic evidence of an encephalopathy, with convincing ultrastructural evidence of prominent mitochondrial injury. Unlike the occasional findings in the Davis model, the mitochondrial findings were striking both in liver and brain and very similar to the findings in Reye syndrome. Absence of very low density lipoprotein from the Golgi complexes was also noted. The prominence of cerebral astrocytosis was unusual and more reminiscent of a chronic hepatic encephalopathy. The mouse syndrome appears to have followed a coronavirus intestinal infection in 66 per cent of the cases. This report

by Brownstein represents the first documentation of a spontaneous illness resembling Reye syndrome developing in an animal. This model and the Davis model may prove to be important in studying the early phase of Reye syndrome, which currently seems unapproachable in the human setting.

TREATMENT

Early diagnosis is crucial to satisfactory outcome. Most patients present a stereotyped clinical and laboratory profile. The diagnosis is obvious in most situations, particularly if the physician has had previous experience with the syndrome. The diagnostic criteria include the following clinical and laboratory elements.

1. The presence of an antecedent viral illness
2. A latent interval of several days before the onset of pernicious vomiting
3. The development of a diffuse encephalopathy
4. No other obvious explanation for the encephalopathy
5. A three-fold or greater elevation of the serum transaminase activities
6. Prolongation of the prothrombin time
7. Hyperammonemia
8. Normal CSF examination.

Occasionally, the opening pressure at the time of lumbar puncture may be elevated and hypoglycorrhachia may be present in association with hypoglycemia. The advisability of a lumbar puncture has been challenged.[68] It has been our practice to perform a lumbar puncture as part of the initial evaluation, particularly if the diagnosis is in doubt. The presence in the CSF of white or red blood cells or the elevation of the protein concentration should cast doubt on the diagnosis and other possibilities should be considered. It is our belief that a lumbar puncture performed later in the course of treatment may be hazardous, with an increased likelihood of central herniation. Therefore, the lumbar puncture should not be performed later unless there is a compelling reason; for example, increasing concern about the possibility of intracranial infection.

Over the past 15 years we have developed a standardized form of intensive medical support for patients with Reye syndrome.[26,42] The management of the individual patient is determined by the neurologic "stage" of the child at the time of admission to hospital. We define stage I as a mildly affected patient with subtle behavioral disturbances such as inattention, inappropriateness, lethargy, somnolence, confusion, or mild irritability. Stage II describes the sicker child who is disoriented or demonstrates agitated delirium, stupor, or coma associated with decorticate posturing of the limbs and trunk. Overactivity of the sympathetic nervous system is manifested in stage II by tachycardia, systemic hypertension, hyperthermia, hyperpnea, diaphoresis, and dilated pupils. Stage III describes the gravely ill and comatose child with decerebrate posturing of limbs and trunk. The

eyes are intermittently or continuously forced into down gaze, indicative of midbrain dysfunction. Stage IV describes the moribund state with loss of brain-stem function. Pupils are nonreactive, spontaneous breathing has ceased, pulse is rapid and weak, blood pressure is low, and pulmonary congestion is present.

All patients with Reye syndrome should be hospitalized immediately. It is now generally accepted that early vigorous treatment will limit the progression of the syndrome.[94] Children in stage I are managed by intravenous hydration with a 10 per cent hypertonic glucose-multielectrolyte solution. Intravenous fluids are administered at a rate of 1600 to 1800 ml per m^2 per day. Vitamin K (Aquamephyton) is administered every 24 hours at a dose of 1 mg intravenously or 5 mg intramuscularly. Approximately 90 per cent of children admitted to the hospital in stage I will remain stable and make an uneventful recovery. The remaining 10 per cent of patients will deteriorate neurologically and require more intensive medical support.

Children in stages II through IV and those children who have progressed to stage II after being admitted in stage I should be transferred to the intensive care unit. A servocontrolled cooling blanket should be placed on the bed, and a number of procedures should be carried out while the patient is anesthetized and paralyzed with 4 mg per kg of sodium thiopental (Pentothal) intravenously and 1 mg per kg of succinylcholine (Anectine) intravenously. These medications should be repeated as necessary to permit completion of the procedures. During this time, the patient should be hyperventilated, maintaining an arterial carbon dioxide tension of approximately 25 mm Hg. The procedures include placement of a nasotracheal tube, radial artery catheter, central venous catheter, nasogastric tube, and urinary catheter. These procedures should be carried out as expeditiously as possible by experienced personnel. We prefer to thread the central venous catheter through the superficial saphenous vein into the inferior vena cava for delivery of hypertonic solutions of glucose and mannitol. Occasionally, access to the subclavian vein necessitates placing the child in the Trendelenburg position; this position may aggravate the coexisting intracranial hypertension. The head is turned to one side to carry out this procedure; this position may compromise venous drainage of the head. Also, there is a tendency to drape the patient's head and neck when access to the subclavian vein is being attempted, thereby precluding minute-to-minute observation of the patient during this critical time. A femoral approach obviates these concerns. The central venous catheter permits continuous infusion of the hypertonic glucose solution and intermittent administration of hypertonic mannitol. The gastric contents should be emptied through the nasogastric tube, and the tube should then be placed to intermittent low suction to prevent subsequent regurgitation. The lumbar puncture, if it is to be performed, should be carried out at this time, preferably while the patient remains sedated and paralyzed with thiopental and succinylcholine.

The liver biopsy is reserved for the more puzzling atypical cases, for "recurrent" cases, and for infants. The coagulopathy must be corrected before this procedure is performed.

The Reye syndrome solution, which is administered to patients in stages II through IV, contains 200 gm of glucose, 40 mEq of sodium chloride, 15 mEq of potassium acetate, and 15 mEq of potassium phosphate per liter. One ampule (10 cc) of multiple vitamins (MVI) is added per liter of solution, and this solution is infused at a daily rate of 1600 to 1800 ml per m^2. This daily rate of infusion provides approximately 500 mg glucose per kg body weight per hour and an adequate fluid volume to permit gradual rehydration of the dehydrated patient. The blood glucose concentration usually reaches 250 to 350 mg per dl. Lower blood glucose concentrations are seen in patients who are less compromised metabolically; no further effort need be made to achieve higher circulating glucose concentrations. Blood glucose concentrations in excess of 400 mg per dl may occur in the more desperately ill patients who are severely compromised metabolically. The glucose concentration of the Reye syndrome solution may be decreased to 15 per cent or 10 per cent as necessary under such circumstances, while still maintaining a constant fluid rate of 1600 to 1800 ml per m^2 per day. Maintaining glucose concentrations in the range of 300 mg per dl lessens the requirement for administration of mannitol and provides more optimal circulating concentrations of glucose to meet increased apparent rates of cerebral glycolysis. We have assumed, but it has not been proved, that the brain glucose requirements are relatively increased in Reye syndrome during the time that mitochondrial mechanisms are compromised. We also believe that it is important to maintain a constant rate of glucose infusion once the patient has adapted metabolically and has stabilized after the initial diagnostic and therapeutic procedures have been completed. Continual readjustments of the fluid rate should be discouraged. Continual fluctuations of the glucose concentration appear to be associated with continuing clinical and metabolic instability of the patient. The constant infusion of glucose should never be interrupted; otherwise, the blood glucose concentration and the associated serum osmolality will decrease rapidly.

Intracranial hypertension is managed primarily by the administration of 20 per cent hypertonic mannitol. We are now inclined toward earlier placement of a Ladd epidural monitor to determine the need for mannitol. All patients in stage III, and more patients in stage II, have an epidural monitor placed through a burr hole overlying the right frontal cortex. The procedure is carried out by a neurosurgeon in the intensive care unit using local anesthesia. Thiopental and succinylcholine may be administered as necessary to facilitate this procedure. Intravenous boluses of hypertonic mannitol (0.25 gm per kg) often are sufficient to control the intracranial hypertension. The dose of mannitol is administered ("piggy-backed") through the central venous catheter over 3 to 5 minutes. This dosage of mannitol may be repeated as frequently as necessary. Alternatively, larger

doses of mannitol ranging from 0.5 to 2.0 gm per kg may be administered. Larger doses should be infused over longer periods of time (10 to 30 minutes) to minimize the transient elevations of systemic blood pressure associated with expansion of the vascular compartment. In our experience, daily mannitol doses of 4 to 6 gm per kg usually are sufficient to control cerebral edema. Smaller daily doses often are adequate. We believe that the induced hyperglycemia resulting from the infusion of a 20 per cent glucose-containing solution decreases the daily requirement of mannitol in these patients. As a result, malignant hyperosmolality is seldom encountered with this regimen. Rarely do we encounter osmolalities in excess of 320 mOsm per L, and most patients maintain a serum osmolality of 290 to 310 mOsm per L. Elevation of the head of the bed by 20 to 30 degrees and maintenance of the head and neck in a neutral midline position also are important considerations to facilitate cerebral venous drainage.

We prefer to allow the patient to breathe independently, if possible, maintaining a state of mild hyperoxia and hypocapnia with Pao_2 values of 100 to 150 mm Hg and $Paco_2$ values of 20 to 27 mm Hg.[27] Most patients in stage II and early stage III maintain these arterial values spontaneously while breathing humidified oxygen through a T-tube adapted to the nasotracheal tube. Alternatively, ventilatory assistance in the IMV mode is necessary, particularly if a patient has an altered respiratory pattern, hypoventilation or periodic breathing. Elective nasotracheal intubation immediately upon admission to the intensive care unit ensures control of the patient's airway and permits intervention when necessary. Suctioning of the airway should be carried out carefully and coordinated with administration of mannitol or after the administration of thiopental and succinylcholine, when these medications are indicated for other procedures. Excessive suctioning of the patient under other circumstances often is associated with dramatic elevations of the intracranial pressure.

Fever is managed by the use of a cooling blanket and acetaminophen suppositories. No effort is made to lower the body temperature below normal. The gastric contents commonly contain small amounts of blood, but no specific treatment is necessary. Less than 10 per cent of patients with Reye syndrome develop clinically significant hemorrhaging requiring the infusion of freshly frozen plasma or fresh whole blood.

Pentobarbital may be administered to patients with intracranial hypertension that persists despite frequent doses of mannitol.[67] Pentobarbital doses of 1 to 5 mg per kg intravenously may be repeated every 4 to 8 hours as necessary to achieve a serum concentration of approximately 30 to 50 mg per L. These doses often are adequate to provide control of the intracranial hypertension. Increasing use of mechanical ventilation becomes necessary as the patient is further sedated by the administration of pentobarbital. Complications deriving from pentobarbital include impaired cardiac output and falling systemic blood pressure.[34] Systemic hypotension may be more de-

vastating than intracranial hypertension, particularly as it relates to cerebral metabolic activity. Accordingly, we recommend the judicious use of pentobarbital in the lowest dose possible to achieve adequate control of the intracranial hypertension. In most cases mannitol is adequate for control of intracranial hypertension, and pentobarbital is not necessary. Seizures, when they occur in gravely ill patients, also may be managed with pentobarbital. Phenobarbital may be used instead of pentobarbital, but the longer-acting barbiturate has no particular therapeutic advantage.

The therapeutic goal in the management of patients with Reye syndrome is to achieve a metabolic steady state as soon as possible after the initial diagnostic and therapeutic procedures have been carried out. Relatively few adjustments are necessary once the patient has adapted metabolically to the intravenous fluids and to the respiratory settings. It is important to minimize stimuli that arouse the patient, as dramatic increases of intracranial pressure may occur. Repeated neurologic examinations by multiple observers is particularly inappropriate under these circumstances. Careful serial observations of the patient's posturing, size and reactivity of the pupils, and positioning of the eyes provide sufficient information to gauge the clinical course. This information, together with the serial laboratory observations, is sufficient to monitor the patient's progress.

A battery of blood studies are obtained routinely at the time of the patient's admission to the hospital. These studies include a total hematologic and chemical profile, coagulation studies, ammonia, osmolality, and lactate concentrations. These studies are repeated every 24 hours. In addition, the blood concentrations of glucose, lactate, osmolality, pH, Pao_2, and $Paco_2$ are obtained every 4 hours. These studies are sufficient to monitor the metabolic progress of the patient. Hypophosphatemia commonly is present, and the serum phosphorus concentration would decline further after administration of hypertonic glucose.[17,56] It is important, therefore, to maintain adequate amounts of phosphate in the Reye syndrome solution to buffer this tendency. A falling serum calcium concentration may be an indication of pancreatic involvement.[37] This complication may be devastating; fortunately, it is rare and usually associated with the administration of corticosteroids.[15,31] There is little or no indication for the use of corticosteroids in the management of patients with Reye syndrome.

Most patients, treated in this manner demonstrate clinical and laboratory improvement within 24 to 72 hours. Once consciousness has been regained, the glucose concentration and the Reye syndrome solution is decreased by 25 per cent decrements every 8 hours and the patient is extubated. Usually within 24 hours of regaining consciousness, patients are able to take liquids by mouth, and the remaining catheters may be removed.

Our experience with this current regimen or one of its earlier versions involves 61 patients from 1971 to 1983. Fifty-four patients have survived, three have had residual neurologic deficits, but in each case they have returned to school. The patients are summarized in Table 1.

Table 1. *Reye Syndrome Treatment Protocol: Results (1971–1983)*

ADMISSION STAGE	NO. OF PATIENTS	OUTCOME	
		Alive	*Dead*
I	13	13	0
II	33	33	0
III	15	8	7
IV	0	0	0
Total	61	54 (89%)	7 (11%)

ALTERNATIVE THERAPEUTIC CONSIDERATIONS

The medical management of patients with Reye syndrome has become increasingly standardized over the past decade, thereby minimizing alternative considerations. Generally accepted as standard treatment is the use of hypertonic glucose and hypertonic mannitol, early elective intubation, placement of the patient in an intensive care unit setting if they deteriorate beyond grade I, parenteral administration of vitamin K and monitoring of the intracranial pressure.[74,92,110] Various techniques have been used to monitor the intracranial pressure including placement of the sensor either in the epidural space, subarachnoid space, or the lateral ventricle.[98] Each technique has its advantages and disadvantages. On balance, we have been quite satisfied with the use of a Ladd epidural monitor and a similar experience has been reported from Cincinnati.[33] Controversies still remain about the advisability of exchange transfusions,[18,70] deep hypothermia, barbiturate-induced coma,[34,67] and bilateral craniectomies for the relief of intractable cerebral edema.[78] Other alternatives have been discarded including peritoneal dialysis and total body asanguinous perfusion.[58] Available statistics, uncontrolled as they are, clearly suggest that intensive medical support of the patient with Reye syndrome produces satisfactory results as often as, or more frequently than, any other approach.[18,70,92]

Current evidence suggests that corticosteroid therapy may be associated with a higher mortality and may contribute to pancreatic complications. It continues to be our impression that the frequency of complications in Reye syndrome is determined, in part, by the choice of management. Restriction of fluid, together with administration of hyperosmolar agents clearly contributes to prerenal azotemia and renal failure. Pulmonary complications appear to be more common in patients subjected to deep hypothermia and perhaps also to barbiturate-induced coma. Barbiturates also increase the possibility of cardiovascular collapse with attendant hypoperfusion of the brain.

Fortunately, considerable progress has been made in the care of patients with Reye syndrome. Today, most patients make a full and complete recovery without any neurologic or psychological sequelae.[99] The sequelae associated with Reye syndrome probably derive in large part from attendant complications that occur during the

acute encephalopathy including hypoglycemia, systemic hypotension with resulting cerebral ischemia, hypoxia, and uncontrolled intracranial hypertension. The therapeutic approaches now available minimize the likelihood of these complications and maximize the quality of recovery.

SUMMARY

Reye syndrome has emerged as the quintessential example of an acute metabolic encephalopathy. The clinical presentation is quite stereotyped in most instances permitting rapid, accurate diagnosis and early therapeutic intervention. Intoxications and certain inborn metabolic errors may mimic Reye syndrome. All patients with a recurrent episode should be investigated thoroughly for evidence of a metabolic disorder associated with an enzyme deficiency. Notable in this regard are inborn errors affecting organic acid, ammonia, and carbohydrate metabolism. The mitochondrial disturbance in Reye syndrome is well documented but the pathophysiologic sequence linking the antecedent viral illness to the mitochondrial injury remains obscure. Recent identification of a spontaneous Reye-like illness in mice that is associated with a coronavirus infection may provide an opportunity to investigate this initial phase of the pathophysiologic sequence.

The primary cerebral insult presumably derives from insufficient substrate availability and results in massive cytotoxic cerebral edema. Treatment revolves around the continuous infusion of hypertonic glucose and intermittent infusion of hypertonic mannitol. Management is designed to attenuate or avoid the various compounding metabolic insults during this critical period when the child is metabolically crippled. In 1963, the disorder was considered to be rare and almost irreversibly fatal. Today, the disorder is recognized to be more common, and the outcome is very satisfactory in 85 to 90 per cent of the cases. The role of aspirin remains very controversial. A number of studies suggest an association between this potential mitochondrial toxin and Reye syndrome, but a causal relationship has not been established. Until better understood, it seems advisable to avoid use of aspirin in children exhibiting symptoms suggestive of Reye syndrome.

REFERENCES

1. Anderson, R., McD.: Encephalitis in childhood: Pathological aspects. Med. J. Aust. *1*:573, 1963.
2. Anonymous: Reye's syndrome: Epidemiological considerations. Lancet, *1*:941, 1982.
3. Ansevin, C. F.: Reye syndrome: Serum-induced alterations in brain mitochondrial function are blocked by fatty-acid-free albumin. Neurology, *30*:160, 1980.
4. Atwood, S. J.: The laboratory in the diagnosis and management of acetaminophen and salicylate intoxications. Pediatr. Clin. North Am. *27*:871, 1980.
5. Bentz, M. S., and Cohen, C.: Periportal hepatic necrosis in Reye's syndrome. One case in a review of eight patients. Am. J. Gastroenterol., *73*:49, 1980.

6. Bourgeois, C., Olson L., and Comer, D.: Encephalopathy and fatty degeneration of the viscera: A clinicopathologic analysis of 40 cases. Am. J. Clin. Pathol., *56*:558, 1971.
7. Bove, K. E., McAdams, A. J., Partin, J. C., et al.: The hepatic lesion in Reye's syndrome. Gastroenterology, *69*:685, 1975.
8. Brain, W. R., Hunter, D., and Turnbull, H. M.: Acute meningoencephalomyelitis of childhood: Report of six cases. Lancet, *2*:221, 1929.
9. Bray, P. E., and Gardiner, A. Y.: Salicylism and severe brain edema. N. Engl. J. Med., *297*:1235, 1977.
10. Brown, R. E., and Forman, D. T.: The biochemistry of Reye's syndrome. CRC Crit. Rev. Clin. Lab. Sci., *17*:247–297, 1982.
11. Brown, R. E., and Ishak, K. G.: Hepatic zonal degeneration and necrosis in Reye's syndrome. Arch Pathol. Lab. Med. *100*:123, 1976.
12. Brownstein, D. G., Johnson, E. A., and Smith, A. L.: Spontaneous Reye's-like syndrome in BALB/cByJ mice. Lab. Invest., *51*:386, 1984.
13. Campbell, R. A.: Polyamines, uremia, and anemia. Semin. Nephrol. *3*:273–285, 1983.
14. Chapoy, P. R., Angelini, C., Brown, W. J., et al.: Systemic carnitine deficiency: A treatable inherited lipid-storage disease presenting as Reye's syndrome. N. Engl. J. Med. *303*:1389, 1980.
15. Chaves-Carballo, E., Menezes, A. H., Bell, W. E., et al.: Acute pancreatitis in Reye's syndrome: A fatal complication during intensive supportive care. South. Med. J., *73*:152–154, 1980.
16. Consensus Conference: Diagnosis and treatment of Reye's syndrome. J.A.M.A., *246*:2114–2444, 1981.
17. Cooperstock, M. S., Tucker, R. P., and Baublis, J. V.: Possible pathogenic role of endotoxin in Reye's syndrome. Lancet, *1*:1272–1274, 1975.
18. Corey, L., Rubin, R. J., Hattwick, M. A. W., et al.: A nationwide outbreak of Reye's syndrome: Its epidemiologic relationship to influenza B. Am. J. Med. *61*:615, 1976.
19. Corey, L., Rubin, R. J., and Hattwick, M. A. W.: Reye's syndrome: Clinical progression and evaluation of therapy. Pediatrics, *60*:708–714, 1977.
20. Crocker, J. F. S., and Bagnell, P. C.: Reye's syndrome: A clinical review. Can. Med. Assoc. J., *124*:375, 1981.
21. Davis, L. E., Cole, L. L., Lockwood, S. J., et al.: Experimental influenza B virus toxicity in mice: A possible model for Reye's syndrome. Lab. Invest., *48*:140–146, 1983.
22. Delong, G. R., and Glick, T. H.: Encephalopathy of Reye syndrome: A review of pathogenetic hypotheses. Pediatrics, *69*:53, 1982.
23. Deshmukh, D. R., Deshmukh, G. D., Shope, T. C., et al.: Free fatty acids in an animal model of Reye's syndrome. Biochim. Biophys. Acta, *753*:153, 1983.
24. De Vivo, D. C.: How common is Reye's syndrome? (Editorial) N. Engl. J. Med., *309*:179–181, 1983.
25. De Vivo, D. C.: Reye syndrome: A metabolic response to an acute mitochondrial insult? (Editorial) Neurology, *28*:105, 1978.
26. De Vivo, D. C., and Keating, J. P.: Reye's syndrome. Adv. Pediatr., *22*:175, 1976.
27. De Vivo, D. C., Keating, J. P., and Haymond, M. W.: Acute encephalopathy with fatty infiltration of the viscera. Pediatr. Clin. North Am. *23*:527, 1976.
28. De Vivo, D. C., Keating, J. P., and Haymond, M. W.: Reye syndrome: Results of intensive supportive care. J. Pediatr. *87*:875–880, 1975.
29. Dove, D. J., and Jones, T.: Delayed coma associated with salicylate intoxication. J. Pediatr., *100*:493, 1982.
30. Duncan, C. C., Ment, L. R., and Shaywitz, B. A.: Evaluation of level of consciousness by the Glasgow coma scale in children with Reye's syndrome. Neurosurgery, *13*:650–653, 1983.
31. Eichelberger, M. R. , Chatten, J., Bruce, D. A., et al.: Acute pancreatitis and increased intracranial pressure. J. Pediatr. Surg., *16*:562–570, 1981.
32. Faraj, B. A., Caplan, D. B., Newman, S. L., et al.: Hypercatecholaminemia in Reye's syndrome. Pediatrics, *73*:481–488, 1984.
33. Fox, D. W., Hart, M. C., Bergeson, P. S., et al.: Pyrrolizidine (Senecio) intoxication mimicking Reye syndrome. J. Pediatr., *93*:980, 1978.

34. Frewen, T. C., Swedlow, D. B., Watcha, M., et al.: Outcome in severe Reye syndrome with early pentobarbital coma and hypothermia. J. Pediatr., *100*:663–665, 1982.
35. Glasgow, A. M., Eng, G., and Engel, A. G.: Systemic carnitine deficiency simulating recurrent Reye syndrome. J. Pediatr., *96*:889, 1980.
36. Glasgow, J. F. T., and Halliday, H. L.: Recurrence of Reye's syndrome. Lancet, *1*:974, 1976.
37. Glassman, M., Tahan, S., Hillemeier, C., Rothstein, P., et al.: Pancreatitis in patients with Reye's syndrome. J. Clin. Gastroenterol., *3*:165–169, 1981.
38. Green, H. L., Wilson, F. A., Glick, A. D., et al.: Hepatic ATP concentrations and glycolytic enzyme activities in Reye syndrome. J. Pediatr., *89*:777, 1976.
39. Hale, D. E., Coates, P. M., Stanley, C. A., et al.: Long-chain Acyl CoA Dehydrogenase Deficiency. Pediatr. Res., *17*:290A, 1983.
40. Hall, W.: Michigan studies of Reye's syndrome, aspirin, suggest preventive measures available. Mich. Med., *486*, 1981.
41. Hanson, P. A., and Urizar, R. E.: Ultrastructural lesions of muscle and immunofluorescent deposits in vessels in Reye's syndrome: A preliminary report of muscle biopsies. Ann. Neurol. *1*:431, 1977.
42. Haymond, M. W., Karl, I., Keating, J. P., et al.: Metabolic response to hypertonic glucose administration in Reye syndrome. Ann. Neurol., *3*:207, 1978.
43. Hilty, M. D., McClung, H. J., Haynes, R. E., et al.: Reye syndrome in siblings. J. Pediatr., *94*:576, 1979.
44. Hilty, M. D., Romshe, C. A., and Delamater, P. V.: Reye's syndrome and hyperaminoacidemia. J. Pediatr., *84*:362, 1974.
45. Holt, J. T., Arvan, D. A., Mayer, T., et al.: Glutamate dehydrogenase in Reye's syndrome. Evidence for the presence of an altered enzyme in serum with increased susceptibility to inhibition by GTP. Biochim. Biophys. Acta, *749*(1):42–46, 1983.
46. Holt, J. T., Arvan, D. A. and Mayer, T.: Masking by enzyme inhibitor of raised serum glutamate dehydrogenase activity in Reye's syndrome. Lancet, 2:4–7, 1983.
47. Hug, G., Bosken, J., Bove, K., et al.: Reye's syndrome simulacra in liver of mice after treatment with chemical agents and encephalomyocarditis virus. Lab. Invest., *45*:89–109, 1981.
48. Huttenlocher, P. R.: Reye's syndrome: Relation of outcome to therapy. J. Pediatr., *80*:845, 1972.
49. Huttenlocher, P. R., and Trauner, D. A.: Reye's syndrome in infancy. Pediatrics, *62*:84, 1978.
50. Jimenez, J. F., Brown, A. L., Arnold, W. C., et al.: Chronic camphor ingestion mimicking Reye's syndrome. Gastroenterology, *84*:394–398, 1983.
51. Johnson, G. M., Scurletis, T. D., and Carroll, N. B.: A study of sixteen fatal cases of encephalitis-like disease in North Carolina children. N. C. Med. J., *24*:464, 1963.
52. Kang, E. S.: Cyclic nucleotidephosphodiesterase activities of the human liver: Comparison between control and Reye's syndrome samples. Pediatr. Res., *12*:761, 1978.
53. Kang, E. S., Chiang, M. H., Kang, A. H., et al.: Evidence of a transient disturbance of cyclic 3′,5′-adenosine monophosphate metabolism in adipose tissue in Reye's syndrome. *In* Pollack, J. D. (ed.): Reye Syndrome. New York, Grune & Stratton, 1975, page 261.
54. Kang, E. S., and Gerald, P. S.: Hyperammonemia and Reye's syndrome. N. Engl. J. Med., *286*:1216, 1972.
55. Karpati, G., Carpenter, S., Engel, A. G., et al.: The syndrome of systemic carnitine deficiency. Neurology (Minneap.), *25*:16–24, 1975.
56. Keating, J. P., Karl, I. E., De Vivo, D. C., et al.: Hypophosphataemia in Reye's syndrome. Lancet, 2:39–40, 1975.
57. LaBrecque, D. R., Latham, P. S., Riely, C. A., et al.: Heritable urea cycle enzyme deficiency: Liver disease in 16 patients. J. Pediatr., *94*:580, 1979.
58. Lansky, L. L., Fixley, M., Romig, D. A., et al.: Hypothermic total body-washout with survival in Reye's syndrome. Lancet, 7–33, 1019, 1974.

59. Leonard, J. V., Seakins, J. W. T., and Griffin, N. K.: Beta-hydroxy-beta-methylglutaricaciduria presenting as Reye's syndrome. Lancet, *1*:680, 1979.
60. Lichtenstein, P. K., Heubi, J. E., Daughterty, C. C., et al.: Grade I Reye's syndrome. A frequent cause of vomiting and liver dysfunction after varicella and upper-respiratory-tract infection. N. Engl. J. Med., *309*:133, 1983.
61. Linnemann, C. C., Jr, Ueda, K., Hug, G., et al.: Salicylate intoxication and influenza in ferrets. Pediat. Res., *13*:44, 1979.
62. Lovejoy, F. H., Smith, A. L., Bresnan, M. J., et al.: Clinical staging in Reye syndrome. Am. J. Dis. Child., *128*:36–41, 1974.
63. Low, A. A.: Acute, toxic (nonsuppurative) encephalitis in children. Arch. Neurol. Psychiatry, *23*:696, 1930.
64. Lyon, G., Dodge, P. R., and Adams, R. D.: The acute encephalopathies of obscure origin in infants and children. Brain, *84*:680, 1961.
65. MacDonald, M. G., McGrath, P. P., McMartin, D. N., et al.: Potentiation of the toxic effects of acetaminophen in mice by concurrent infection with influenza B virus: A possible mechanism for human Reye's syndrome? Pediatr. Res. *18*(2):181–187, 1984.
66. Marder, H. K., Strife, C. F., Forristal, J., et al.: Hypocomplementemia in Reye syndrome: Relationship to disease stage, circulating immune complexes, and C3b amplification loop protein synthesis. Pediatr. Res., *15*:362, 1981.
67. Marshall, L. F., Shapiro, H. M., Rauscher, A., et al.: Pentobarbital therapy for intracranial hypertension in metabolic coma. Crit. Care Med., *6*:1–5, 1978.
68. Menkes, J. H.: To tap or not to tap. Pediatrics, *51*:560–561, 1973.
69. Mitchell, R. A., Ram, M. L., Arcinue, E. L., et al.: Comparison of cytosolic and mitochondrial hepatic enzyme alterations in Reye's syndrome. Pediatr. Res., *14*:1216, 1980.
70. Morens, D. M., Sullivan-Bolyai, J. Z., Slater, J. E., et al.: Surveillance of Reye syndrome in the United States. Am. J. Epidemiol., *114*:406, 1981.
71. Mortimer, E. A., and Lepow, M. L.: Varicella with hypoglycemia possibly due to salicylates. Am. J. Dis. Child., *103*:91, 1962.
72. Nelson, D. B., Kimbrough, R., Landrigan, P. S., et al.: Aflatoxin and Reye's syndrome: A case control study. Pediatrics, *66*:865, 1980.
73. Newman, S. L., Caplan, D. B., Camp, V. M., et al.: Prolactin and the encephalopathy of Reye's syndrome. Lancet, *2*:1097, 1979.
74. Newman, S. L., Caplan, D. B., and Ahmann, P. A.: Reye's syndrome: Success of supportive care. N. Engl. J. Med., *229*:1079, 1978.
75. Ogburn, P. L., Sharp, H., Lloyd-Still, J. D., et al.: Abnormal polyunsaturated fatty acid patterns of serum lipids in Reye's syndrome. Proc. Natl. Acad. Sci. USA, *79*:908, 1982.
76. Partin, J. C., Partin, J. S., and Schubert, W. K.: Fatty liver in Reye's syndrome: Is it a distinct morphologic entity? Gastroenterology, *65*:563, 1973.
77. Partin, J. C., Schubert, W. K., and Partin, J. S.: Mitochondrial ultrastructure in Reye's syndrome (encephalopathy and fatty degeneration of the viscera). N. Engl. J. Med., *285*:1339, 1971.
78. Partin, J. S., McAdams, A. J., Partin, J. C., et al.: Brain ultrastructure in Reye's disease. II. Acute injury and recovery process in three children. J. Neuropathol. Exp. Neurol., *37*:796–819, 1978.
79. Partin, J. S., Schubert, W. K., Partin, J. C., et al.: Serum salicylate concentrations in Reye's syndrome: A study of 130 biopsy-proven cases. Lancet, *1*:191, 1982.
80. Pegelow, C., Goldberg, R., Turkel, S., et al.: Severe coagulation abnormalities in Reye syndrome. J. Pediatr., *91*:413, 1977.
81. Pickering, R. J., Urizar, R. E., Hanson, P. A., et al.: Abnormalities of the complement system in Reye syndrome. J. Pediatr., *94*:218, 1979.
82. Pollack, J. D.: Models of chemical and virus interaction and their relation to a multiple etiology of Reye's syndrome. *In* Crocker, J. F. S. (ed.): Reye Syndrome II. New York, Grune & Stratton, 1979, page 341.
83. Pollack, J. D., Cramblett, H. G., and Flynn, D.: Serum and Tissue Lipids in Reye's syndrome. *In* Pollack, J. D. (ed.): Reye Syndrome. New York, Grune & Stratton, 1975, page 227.

84. Randolph, M., and Gelfman, N. A.: Acute encephalopathy in children associated with acute hepatocellular dysfunction. Am. J. Dis. Child., *116*:303, 1968.
85. Reye, B. D. K., Morgan, G., and Baral, J.: Encephalopathy and fatty degeneration of the viscera: A disease entity in childhood. Lancet, *2*:749, 1963.
86. Risetti, U., and Mancini, G.: The Tokuoka reaction for spermine. Acta Neurol. (Napoli), *9*:391–395, 1954.
87. Robinson, B. H., Oei, J., Sherwood, W. G., et al.: Hydroxymethylglutaryl CoA lyase deficiency: Features resembling Reye syndrome. Neurology, *30*:714, 1980.
88. Rodgers, G. C., Jr., Weiner, L. B., and McMillan, J. A.: Salicylate and Reye syndrome. Lancet, *1*:616, 1982.
89. Romshe, C. A., Hilty, M. D., McClung, H. J., et al.: Amino acid pattern in Reye syndrome: Comparison with clinically similar entities. J. Pediatr., *98*:788, 1981.
90. Rosenfeld, R. G., and Liebhaber, M. I.: Acute encephalopathy in siblings: Reye syndrome vs. salicylate intoxication. Am. J. Dis. Child., *130*:295, 1976.
91. Samaha, F. J., Blau, E., and Berardinelli, J. L.: Reye's syndrome: Clinical diagnosis and treatment with peritoneal dialysis. Pediatrics, *53*:335–340, 1974.
92. Schubert, W. K.: Treatment controversies in Reye's syndrome. J. Natl. Reye's Syndrome Found., *4*:48–54, 1983.
93. Schubert, W. K., Bove, K., Partin, J., et al.: Recurrent Reye's syndrome: Case report. Gastroenterology, *58*:292, 1970.
94. Schubert, W. K., Partin, J. C., and Partin, J. S.: Management of Reye's Syndrome: Cincinnati Experience. New York, Grune & Stratton, 1979, page 155.
95. Schwartz, D. A.: The coagulation defect in Reye's syndrome. J. Pediatr., *78*:326, 1971.
96. Shapira, Y., Deckelbaum, R., Statter, M., et al.: Reye's syndrome: Diagnosis by muscle biopsy? Arch. Dis. Child. *56*:287–291, 1981.
97. Shield, L. K., Coleman, T. I., and Markes-Bery, W. R.: Methyl bromide intoxication: Neurologic features, including simulation of Reye syndrome. Neurology (Minneap.), *27*:959, 1977.
98. Shaywitz, B. A., Rothstein, P., and Venex, J. L.: Monitoring and management of increased intracranial pressure in Reye syndrome: Results in 29 children. Pediatrics, *66*:198–204, 1980.
99. Shaywitz, S. E., Cohen, P. M., Cohen, D. J., et al.: Long-term consequences of Reye syndrome: A sibling-matched, controlled study of neurologic, cognitive, academic, and psychiatric function. J. Pediatr. *100*:41–46, 1982.
100. Shutgens, R. B. H., Haymans, H., and Ketel, A.: Lethal hypoglycemia in a child with a deficiency of 3-hydroxy-3-methylglutaryl coenzyme A lyase. J. Pediatr., *94*:89, 1979.
101. Sinniah, D., and Baskaran, G.: Margosa oil poisoning as a cause of Reye's syndrome. Lancet, *1*:487, 1981.
102. Siraj, M. Y., Hayes, A. W., Unger, P. D., et al.: Analysis of aflatoxin B_1 in human tissues with high-pressure liquid chromatography. Toxicol. Appl. Pharmacol., *58*:422, 1981.
103. Smith, A. L., and Lovejoy, F. H.: Reye's syndrome: Management. New York, Stratton Intercon, 1979, page 202.
104. Stanley, C. A., Hale, D. E., Coates, M. P., et al.: Medium-chain Acyl-CoA dehydrogenase deficiency in children with non-ketotic hypoglycemia and low carnitine levels. Pediatr. Res., *17*:877–884, 1983.
105. Stillman, A., Gitter, H., Shillington, D., et al.: Reye's syndrome in the adult: Case report and review of the literature. Am. J. Gastroenterol., 78(6):365–368, 1983.
106. Suchy, F. J., Balistreri, M. F., Buchino, J. J., et al.: Acute hepatic failure associated with the use of sodium valproate. N. Engl. J. Med., *300*:962, 1979.
107. Sullivan-Bolyai, J. Z., Marks, J. S., Johnson, D., et al.: Reye syndrome in Ohio, 1973–1977. Am. J. Epidemiol., *112*:629, 1980.
108. Thurlow, P. M., Desai, R. K., Newberne, P. M., et al.: Aflatoxin B_1 acute effects on three hepatic urea cycle enzymes using semiautomated methods: A model for Reye's syndrome. Toxicol. Appl. Pharmacol. 53:293, 1980.
109. Tomasova, H., Nevoral, J., Pachi, J., et al.: Aspirin esterase activity and Reye's syndrome. Lancet, *2*:43, 1984.

110. Trauner, D. A.: Treatment of Reye syndrome. Ann. Neurol., 7:204, 1980.
111. Trauner, D. A., Nyhan, W. L., and Sweetman, L.: Short-chain organic acidemia and Reye's syndrome. Neurology, 25:296, 1975.
112. Trauner, D. A., Stockard, J. J., and Sweetman, L.: EEG correlations with biochemical abnormalities in Reye syndrome. Arch. Neurol., 34:116, 1977.
113. Trauner, D., Sweetman, L., Holm, J., et al.: Biochemical correlates of illness and recovery in Reye's syndrome. Ann. Neurol., 2:238, 1977.
114. Van Caillie, M., Morin, C. L., Roy, C. C., et al.: Reye's syndrome: Relapses and neurological sequelae. Pediatrics, 59:244, 1977.
115. Varma, R. R., Riedel, D. R., Komorowski, R. A., et al.: Reye's syndrome in non-pediatric age groups. J.A.M.A., 242:1373, 1979.
116. Willner, J. H., Chutorian, A. M., and DiMauro, S.: Tissue carnitine in Reye syndrome. Ann. Neurol., 4:468, 1978.
117. Wilson, R., Miller, J., Greene, H., et al.: Reye's syndrome in three siblings. Association with type A influenza infection. Am. J. Dis. Child., 134:1032, 1980.
118. Woodfin, B. M., and Davis, L. E.: Altered OCTase location in the influenza B-Lee virus model for Reye's syndrome. Biochem. Med., 28:109, 1982.
119. You, K.: Salicylate and mitochondrial injury in Reye's syndrome. Science, 221(4696):163–165, 1983.

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