Pediatric Gastroenterology 1/1/69–12/31/75: A Review

Part II. The Liver and Biliary Tract

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This is the second part of a two-part series. The first part was published in the January issue.

During the years covered by this review (January 1, 1969–December 31, 1975) a number of the important advances in pediatric gastroenterology were concerned with the liver and with bile acid metabolism. Reviews on *bile acids*, detailing alternative biochemical pathways peculiar to infants, have appeared (206, 207). Meconium is sterile and should presumably contain no secondary bile acids due to bacterial degradation. Sharp et al have found significant amounts of cholic and chenodeoxycholic acids (primary), as well as deoxycholic and lithocholic acids (secondary), in sterile meconium (208). Secondary bile acids disappeared following the first meconium passage and reappeared in stools of 5-day-old infants, simultaneously with colonic bacteroides colonization. The nonpersistence of the secondary bile acids in newborn stools suggests transplacental passage from the mother. Jackson and Lester have demonstrated bidirectional placental transfer of [^{14}C]24-cholate infused *in utero* in fetal dogs (209, 210).

Using deuterium-labeled cholesterol as a precursor, bile acids were quantitated in 5 normal neonates (211). Pool size for cholic acid is 290 mg/m^2 compared to 605 mg/m^2 for adults. The *de novo* synthesis rate of 110 mg/m^2/day is appreciably smaller than is the adult value of 194 mg/m^2/day. Similar reductions in pool size and synthesis rate occur with chenodeoxycholic acid. These findings may explain why intraduodenal bile salt concentrations in neonates are often below critical micellar levels (211). This is especially true for prematures in whom bile salt pool size and synthesis rate for cholic acid is ½ to ⅓ that of term infants, and in whom coefficients of fat absorption below 80% are the rule (212). The authors note that while *de novo* synthesis rates are increased relative to pool size when compared to adults, they are still insufficient to maintain an expanded pool (213). A new intermediate monohydroxy bile acid, 3-beta-hydroxy-5-cholenoic acid, has been found in meconium and may suggest an alternate fetal pathway to chenodeoxycholate (214). Its concentration is greater in meconium from prematures than from term infants. It is not detected in the pregnant mother, in cord blood, nor in stools shortly after birth.

Much of the bile acid literature in children is concerned with abnormal metabolism in prolonged neonatal icterus and in malabsorptive conditions. Javitt suggests a link between *biliary atresia* (BA) and *neonatal hepatitis* (NH) (215). His infants with NH and BA have similar ratios of serum cholic to chenodeoxycholic acid early in their courses and only as BA progresses do the ratios diverge. The author suggests that the similar ratios of NH and BA in-

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dicates NH to be the primary event and BA a sequela. Norman and Strandvik demonstrated that ^{14}C-labeled cholic and chenodeoxycholic acids administered to infants with extrahepatic BA are excreted unchanged in urine as 3-sulfated esters (216, 217). Endogenous urinary excretion of these two acids occurs in virtually identical amounts in BA and in intrahepatic cholestasis (217). This similarity in urinary levels, presumably reflecting serum levels, is in contrast with Javitt's finding of divergent levels of the two bile acids at various stages of both conditions. The large concentrations of 3-beta-hydroxy-5-cholenoic acid found in some patients with BA may represent an underlying metabolic derangement (213, 217, 218). Lithocholic acid, a known hepatotoxin which causes biliary ductular proliferation in animals (219), has been sought but not found in abnormal amounts in BA (215).

A number of *tests* have appeared, each in turn proposed as a clear differential of BA from NH. Alpha-feto protein (AFP) was found in 10 of 11 infants with NH and was absent in 7 of 8 infants with BA (220). However, AFP is not specific and has since been found to be increased in other conditions (221, 222). Yeung reported that the enzyme 5'-nucleotidase, which originates in the biliary canaliculus, is raised in the serum in BA but not in NH (223). Melhourn and Baehner report separately that red blood cell peroxide hemolysis was abnormal in 16 infants with BA and normal in 6 of 7 infants with NH (224, 225). Vitamin E prevents peroxide hemolysis and is malabsorbed in BA. Poley reports that lipoprotein-X (LPX), an abnormal low-density lipoprotein, is always found in BA (226, 227). Presence of LPX after feeding cholestyramine indicates BA. Three percent or less of an intramuscular dose of ^{14}C-labeled cholate was excreted in stools of patients with BA, while in NH excretion was usually greater than 3% (217). The percent excretion is clinically useful when above 3%. Unfortunately some patients with NH also excrete in the BA range. Suruga believes that ultrasound can detect patient intrahepatic bile ducts of 5 mm diameter (228). At present none of these tests conclusively distinguishes BA from the obstructive cholestatic phase of NH, nor are they superior to the quantitative Rose Bengal excretion test (229).

Medical management of BA still appears dismal. Cohen reports that MCT therapy increased growth and decreased steatorrhea in 3 of 11 patients with BA, but did not improve liver function tests (230). Presumably, such patients all progress to cirrhosis. Weber and Roy showed similar effects on growth and steatorrhea in 2 of 4 patients with cirrhosis (231). In addition, the use of MCT resulted in improvement in liver function tests. However, these effects were temporary, with ultimate decompensation. Hadorn described protein malabsorption in 3 children with BA (232). He postulates that bile acids activate enterokinase. Their deficiency inhibits enterokinase activation of trypsinogen. Maounis, in a large series, found high serum alkaline phosphatase and biochemical evidence of rickets frequently in both BA and NH on the usual doses of vitamin D. Treatment with 2400 IU/24 hr appeared to eliminate the problem (233).

Conventional surgical attempts at improving drainage in extrahepatic BA succeed in fewer than 15–20% of cases with a patent common bile duct and normal gall bladder (234). Berenson reports a 25-year survival in such a patient in whom the head of the gall bladder was anastomosed to the duodenum, but she suffered recurrent cholelithiasis, biliary cirrhosis, and cholangitis throughout her stormy course (235). The most interesting new treatment of BA is the hepatoportoenterostomy employed in the "inoperable" majority of cases. Microdissection to uncover patent ducts with a minimum diameter of 0.2 mm is critical to operative success (236). Originally described in the English literature by Kasai in 1968 (237), several versions are now done (234, 238). A summary of 212 cases from Japan cites 38 "cures" and 80 patients with improved bile excretion, each with at least a 6 month follow-up (234). These results are especially impressive since they include 43 cases operated on after 3 months of age when cirrhosis may already have been present. Campbell reports improvement in 43% of infants operated on under 3 months of age with a decrease to 7% after that time (239). Results with the Kasai procedure in the U.S. have been mixed (238, 239, 240). One series of 9 patients, almost all below 3 months of age at surgery, showed no improvement, either in survival or in bile excretion (239). Among 51 operated patients in another series, 15 showed initial improvement (241). Seven of these ultimately developed portal hypertension. A question exists whether the Kasai procedure and its variants may only improve biliary drainage but not affect ultimate liver deterioration because of continuing extrahepatic sclerosing cholangitis (236, 238, 241). Even if an additional 20% of infants are salvageable by this operation (240, 242), in addition to the 15–20% by conventional surgery,

and perhaps 2% who undergo spontaneous remission, the remaining majority still have a dim outlook (234). Untreated, their average life span is 19 months (242).

Cadaveric liver transplantation has been attempted in 29 patients with BA (243). The longest survivor is 4 years; a third lived at least 1 year. Starzl notes a peculiar triad of vascular anomalies often precludes transplantation, ie, missing inferior vena cava, anomalous origin of the hepatic artery, and preduodenal portal vein, seen in 8 of the patients; 5 others had only one of the above anomalies (243).

Additional causes of prolonged obstructive icterus in the young infant include specific syndromes of *familial cholestasis*, of bile duct "paucity," and choledochal cysts. Hanson et al report 2 siblings with the syndrome of intrahepatic ductular hypoplasia with a normal extrahepatic tract (244). Cholestasis led to progressive cirrhosis, fatal at 8 months in one and at 23 months in the other. Bile acid metabolism was traced via a normal cholate precursor, $3\alpha,7\alpha,12\alpha$-trihydroxy-5β-cholestan-26-oic acid (THCA), detected in abnormally high amounts in their urines by gas–liquid chromatography and mass spectroscopy. Despite the accumulation of THCA, pool size and synthesis rate of cholic acid were decreased. However, no abnormal metabolite of THCA nor of alternate pathways from its precursor was detected. This suggests that a block exists in conversion of THCA to cholate. Both parents and one normal sibling had normal quantities of THCA in their bile. To determine if THCA increased when cholic acid production increased, cholestyramine was fed to the parents and to 2 normal subjects. No increase was found. THCA was undetectable in 5 other children who also had paucity of bile ducts, and in 3 adults with alcoholic cirrhosis, indicating that the abnormal bile acid metabolite is unique.

Williams et al reported a family in which 3 children were affected by a fatal progressive cholestatic cirrhosis starting in the first 6 months of life (245). Serum lithocholate was found in an abnormally high amount of 51.6 nmole/ml, accounting for 15.8% of total bile acids. These infants all had liver biopsies interpreted as cholestasis with normal cell architecture and bile duct morphology. In each case pruritus preceded all other symptoms, including jaundice.

Byler's disease, a familial cholestatic syndrome, named after the inbred Amish kindred originally reported in 1965 (246), was the subject of an expanded report on 7 members of 4 related kinships (247). The entity fits a lethal autosomal recessive mode. Neonatal onset, failure to thrive, hepatosplenomegaly, steatorrhea, rickets, and cirrhosis lead to death, usually by 7 or 8 years of age. Elevations of bilirubin (2/3 direct reacting) and of alkaline phosphatase, prolonged prothrombin time, and normal or low serum cholesterol are characteristic. The clinical and laboratory pictures include intermittent exacerbations triggered by upper respiratory infections. Abnormal BSP retention is detected during pregnancy in heterozygous mothers. Abnormally low storage and excretory capacities for BSP are found in affected individuals. Heterozygotes display intermediately depressed values. A decreased concentration of trihydroxy bile salts was obtained on duodenal drainage of one patient. Liver biopsy showed minimal perivascular fibrosis around the central veins, cholestasis, but no ductular proliferation or giant cells. A later study of one patient from this kindred demonstrated increased plasma bile acids with an abnormal increase in concentration of lithocholic acid (248). This finding, together with bile acid losses in the urine, suggests that the disease is associated with a defective excretion of conjugated bile acids across the canalicular membrane (213).

Sharp gave *phenobarbital* (5 mg/kg/day) to 3 children with chronic cholestatic syndrome (249). In one patient with paucity of intrahepatic bile ducts, bile flow increased, duodenal aspirate showed an increase in conjugated bile acids and in bilirubin commensurate with a decline in serum values, decreased pruritus, and jaundice. Rose Bengal clearance doubled. All effects ceased with drug discontinuance. Thaler reports similar dramatic effects on a 10/mg/kg/day dosage of phenobarbital in 3 patients with the same entity of paucity of bile ducts (250). After 4 days of therapy serum bile acids decreased from 100–400 μg/ml to 1–10 μg/ml. Urinary bile acid excretion decreased and Rose Bengal clearance increased. Other patients with extrahepatic BA received no benefit from phenobarbital. Linarelli also reports phenobarbital to be useful in 4 children with paucity of bile ducts (251). Hyperlipemia and xanthomata were reduced by treatment. However, unlike the previous reports, serum bilirubin and transaminases were not significantly changed.

Arias points out in two studies that Dubin–Johnson syndrome is a benign noncholestatic organic anion excretory defect in liver heme metabolism which best fits an autosomal recessive mode of in-

heritance (252, 253). A specific urinary coproporphyrin pattern is described in which total values are normal but levels of coproporphyrin 1 are increased and those of corproporphyrin 3 are decreased (252). A deficiency of coproporphyrin 3 uroporphyrinogen cosynthetase is proposed as the etiology. In a second paper, pregnancy and oral contraceptives induced jaundice in a 27-year-old woman. Her serum bile acid levels were normal, but a characteristic defect in her storage and transport of BSP was detected (253). These studies indicate that the heterozygous carrier state may now be detected, obviating invasive investigations in this benign entity.

Choledochal cysts are reported commonly in Orientals (254), mostly Japanese (255–257). A female preponderance of 2:1 to 4:1 is noted (255–257). Fifty percent of cases are recognized before age 6 months but may present in adults (257, 259). The cysts are highly variable in size, configuration, and presentation (255, 260). They may contain up to 3 liters of bile (255). The classic triad of pain, abdominal mass, and jaundice is present in only a minority of patients (255, 261). Jaundice alone is by far the most common finding, especially in infants (255, 257, 258). A painless abdominal mass is next in frequency (257). Perforation, while rare, may follow abdominal trauma or present spontaneously in the neonate (255, 258). Confusion of NH with BA may explain why accurate diagnosis is made in less than half of the cases preoperatively (255, 258, 259). Attempts at improved diagnosis include use of total body opacification, intravenous and oral cholangiograms, Rose Bengal liver scan, and upper gastrointestinal studies (257, 259). The cholangiogram, while accurate, appears to be useful only in the unusual patient who is anicteric (256). Ultrasound tomography may be useful in distinguishing NH from cysts (256). Surgical mortality has been reduced to 5% (254). Classifications include intra and extrahepatic cysts with or without obstruction (254, 258). Several reports note that the extrahepatic cyst is the predominant form (255–257). However, associated atresia, both distal and proximal to the cystic dilatation, was found in 15 of 146 cases of one series (258). Choledochal cysts lined with duodenal mucosa are called "diverticula" by some.

A *choledochocele* refers to an intraduodenal cystic dilation of the common bile duct (260). This entity may manifest itself only in adult life with intermittent obstructive symptoms presumably due to meal-induced peristalsis (260). Multiple intrahepatic cysts and other anomalies may have been missed before the advent of newer radiographic techniques. Recent surgical reports stress the avoidance of external decompression except in emergent ruptured cysts in neonates. Roux-en-Y jejunostomies are advised to avoid the reflux and ascending cholangitis associated with the choledochocystoduodenostomies formerly advocated (257, 259, 261–263). Kottmeir, on limited experience, suggests cyst excision and direct duct enterostomy (258). However, other authors do not recommend direct excision (261). Cholecystectomy is controversial. One author suggests preservation of the gall bladder because it may provide a "life-saving means for rapid drainage in later acute duct obstruction" (255). Others prefer its removal to prevent the commonly encountered postoperative acute cholecystitis (258, 261) or to maintain anastomotic flow (257). It appears that no single operation is the procedure of choice in a condition with so varied an anatomic array (259). However, in view of a possible concurrent hepatitis-like picture and the danger of progressive biliary cirrhosis in misdiagnosed cases, and more recently, the finding of carcinoma in extrahepatic biliary cysts (including 10 patients under 35 years of age) (257), clinicians must be aware of this unusual entity.

Considerable literature deals with better differentiation of causes of *neonatal hepatitis (NH)*. New knowledge of viruses and antibodies derived from studies of infectious hepatitis sheds additional light on NH and requires a brief review.

A variety of viral particles and antigens associated with either hepatitis A (HA) or B (HB) is used in new differential tests. An enterovirus-like 27-nm particle has been described in HA. Specific complement fixation and immune adherence tests clearly detect antibody to HA (anti-HA) (264, 265). Krugman reports that all of 20 patients with clinical HA had negative titers before infection, a significant rise to greater than 1:1024 within 4 weeks of onset, and peak titers of greater than 1:81,920 up to 23 months later. Substantial anti-HA was detected as late as 10 years after onset. Although complement fixation titer is said to rise earlier than the immune adherence titer, the latter is more specific and sensitive to the HA antigen. Several HB antigens and particles are interrelated. Three basic lipoprotein moieties are thought to represent the virion and subvirion particles: (1) the Dane particle, 42-nm in diameter, is probably the complete HB virion (266); (2) a 100-nm filamentous particle (267); and (3) a 20-nm

sphere (268). Two immunologically distinct antigens are recognized: surface (designated HB_sAg) and core designated HB_cAg (269). HB_sAg, Australia antigen (AuAg), and hepatitis-associated antigen (HAA) are all identical. It is found on all subvirions and on the Dane particle. HB_cAg is found within the core of the Dane particle, in the nucleii of hepatocytes, and it results in the production of antibody to HB_cAg (anti-HB_c). It is associated with DNA polymerase activity (270). To date, free HB_cAg has not been detected but anti-HB_c is found in acute HB by immune electron microscopy, immunofluorescence, and complement fixation and radioimmunoassay: It appears that anti-HB_c is distinct in time course (271), appearing earlier than, and immunologically distinct from, anti-HB_s. With these considerations in mind the following observations may be made relative to NH.

Viral hepatitis is rare in pregnant women, estimated at one in 10,000 in the U.S. (272). Risk of infection approaches 50% for the infants whose mothers develop hepatitis late in pregnancy but the biochemical abnormalities are usually mild (272–274). Acute maternal hepatitis correlates with premature delivery (272, 275–277), possibly with spontaneous abortions (277), but with no apparent increase in congenital anomalies (278). Schweitzer reports 26 mothers with acute phase HB who gave birth to 10 infants positive for antigen (275). Eight of 17 additional infants developed antigenemia within 2 months of delivery. Their mothers had recovered from acute hepatitis in the second and third trimester but remained antigen-positive. In another study 15% of all mothers were HB-antigen-positive asymptomatic carriers. They appeared to transmit the antigen to 40% of their babies (279). Recent studies suggest that antigen transmission does not occur *in utero* but rather in the puerpurium if the mother is a chronic carrier or has overt hepatitis early in the pregnancy (273, 278, 280–283). Those infants that acquire antigen may be severely affected (273, 280). The maternal circulating titer of HB_sAg may be critical for transmission (279). The neonate appears to be "antigen tolerant" because, once acquired, his antigenemia persists for years and possibly indefinitely (272, 276). Maternal–infant transmission may thus be an important source of long-term carriage and dissemination of the virus (276, 279, 281, 284). Anti-HB_c has been found in the sera of carrier mothers, in cord blood, and in the neonate (274, 282). It disappears from the infant shortly after birth, and its significance is uncertain. Breast milk is not an important transmission vehicle since artificially fed infants commonly acquire antigen (281, 283). Colostrum may not carry either HB antigen or antibody (276, 281, 283). Nevertheless, Krugman recommends that infected mothers not breast feed (271).

A small prospective study demonstrated that standard immune globulin with a minimal anti-HB_s titer of 1:16 appeared as effective in preventing acquisition of antigen as did HB hyperimmune globulin (285). Although acute attack rates for anicteric hepatitis were 11% in each group, active antibody seroconversion occurred in 49% of children treated with standard immune globulin vs 18% with the HB immune globulin. Nine months following injection, when passively acquired antibody should not have been present, 55% of the patients who received standard immune globulin demonstrated anti-HB_s vs 23% in the hyperimmune globulin group. Thus, standard immune globulin appears to favor presumed subclinical infection with attendant active immunization. Another study showed that anti-HB_s can acutely clear HB_sAg but may not improve outcome in fulminant cases (274). It may be more beneficial to give prophylactically either 0.2 ml of HB hyperimmune serum globulin or 0.5 ml of standard immune globulin to all infants exposed to HB *in utero* or at birth (271, 274, 286).

Additional specific causes of NH have been elucidated. The *TORCH syndrome*, (toxoplasmosis, rubella, cytomegalic inclusion disease, herpes) is routinely examined for. Lues and other intrauterine septicemias are included in the differential. A new entity, *alpha-1-antitrypsin (AAT) deficiency*, has also been described, initially in adults (287), and more recently in children with liver, lung, and renal disease (288–290). AAT deficiency was found to cause NH once in 14,000 live births in a prospective study (291), and may ultimately emerge as a major forerunner of cirrhosis in childhood (292).

AAT is a serum antiprotease which inhibits the activities of trypsin, chymotrypsin, collagenase, elastase, plasmin, thrombin, and leukocytic protease (293, 294). It accounts for 90% of the serum tryptic inhibitory capacity (295). Hereditary deficiency of this protease inhibitor is easily detected by a virtually absent alpha-1-globulin peak with serum protein electrophoresis on cellulose acetate (294). The clinical picture in deficient infants is one of neonatal cholestatic hepatitis (289, 292, 294, 296, 297), followed by a variable asymptomatic period with ultimate onset of cir-

rhosis (289, 296, 297). If the onset of jaundice is in the first few days of life or if the duration of initial hepatitis is 2–4 months, cirrhosis usually develops before 2 years of age. In rare instances onset of cirrhosis is as late as 16 years. Serum transaminases, alkaline phosphatase, bile acids, bilirubin, and stool fat output are elevated (296). Rose Bengal excretion is between 10 and 20% of the administered dose. The severity of periportal infiltration and fibrosis, and the degree of giant-cell formation in the liver biopsy does not correlate directly with the clinical state (291, 298). Focal hypoplasia of the extrahepatic tree may occasionally be seen. A PAS-positive stain after diastase digestion of liver biopsy specimens consistently shows accumulation of an abnormal granular pigment in the cytoplasm of perilobular hepatocytes (296, 299). The pigment is contained in the rough endoplasmic reticulum on electron microscopy (297, 300). These granules are glycoproteins that specifically bind fluorescent antibody (296, 300, 301). This finding may indicate that instead of a deficient synthesis, a congenital variation in the structure of the AAT molecule (absence of the terminal sialic acid moiety), may impair its release from the liver, resulting in a deficient serum level (300).

The single most important advance in this field has been the recognition of an extensive electrophoretic polymorphism of AAT, named the protease inhibitor (Pi) type (302). At least 13 autosomal codominant alleles with 20 phenotypes have been identified (303, 304). The most prevalent allele is the normal Pi^M, whereas childhood liver disease is highly associated with the Pi^Z allele (phenotype ZZ) (296). The *MZ* parents of these children may also have abnormal liver accumulations, although in lesser amounts than in the deficiency state, *ZZ* (296, 301). This finding correlates well with the observation of an intermediate serum concentration of AAT in heterozygous MZ carriers (296). The SZ, FZ, and ZZ phenotypes have each been identified in AAT-deficient adults with cirrhosis and pulmonary disease and, more recently, in children. Several authors (290, 299, 305, 306) suggest that additional factors superimposed on the defective genetic matrix of *ZZ* individuals account for the observation that only some AAT-deficient infants suffer from progressive liver disease. The suggested role of HB virus as such a trigger is controversial (297, 307, 308). Either pregnancy or hormonal contraceptives has been shown to raise serum AAT transiently in both the heterozygote and homozygote (288). Under these circumstances, a random single serum electrophoresis may be misleading. Attempts at hormonal therapy have been unsuccessful. Portacaval (307) shunts have been recommended as treatment (294). One ambitious report of a "cure" was achieved with a cadaveric liver transplant which normalized serum AAT levels (293).

A major advance in the management of persistent *unconjugated hyperbilirubinemia* has been introduction of two new treatment modalities. Both techniques were initially applied to physiologic jaundice but were later expanded to disease states (309). Phenobarbital, a potent inducer of liver enzymes (310, 311), is useful as an antenatal preventive measure. Early uncontrolled retrospective analysis failed to show a difference attributable to phenobarbital ingestion in the mother (312). However, Williams et al (245) subsequently showed in a series of controlled trials that if mothers took 60 mg of phenobarbital daily from the 32nd week of gestation onward, they gave birth to infants with a significantly lowered bilirubin. In two other groups of infants given 2.5 mg of phenobarbital daily during the first 3 days of life no statistically significant effect was demonstrated. Cunningham et al also found that once established, neonatal hyperbilirubinemia is unresponsive to phenobarbital therapy (313). Others, however, claim efficacy for phenobarbital treatment in infants in whom jaundice has already developed (314, 315). Stern and Yaffe found that 8 mg/kg daily of phenobarbital given to 20 term infants during the first 4 days of life lowered their bilirubin level (316). The drug had the same effect on a group of 4-day-old infants with bilirubin levels of 8 mg/100 ml or more at onset of therapy vs similar controls. Another controlled study from Hong Kong showed that phenobarbital given prophylactically in a dose of 15 mg daily for 5 days to normal term infants and to a group with ABO incompatible hemolysis prevented hyperbilirubinemia (314). Whether phenobarbital exerts its effect on enzyme induction, increases bile flow (250), or acts via another mechanism is unclear (317). One study showed that when phenobarbital is given to moderately jaundiced term infants, increased BSP clearances occur, with enhancement of both uptake and excretory phases within 24 hr of administration (318). However, the interpretation of the BSP test in such jaundiced infants is itself controversial (314). Phenobarbital has been correlated with an increase in excretion of salicylamide as the glucuronide, presumably due to glucuronyltransferase induction (319). There is no evi-

dence in therapeutic concentrations that phenobarbital affects bilirubin binding to albumin or has any other significant toxicity (316, 317). Phenobarbital given to mothers throughout pregnancy also increases bile salt synthesis and pool size in their babies.

Phototherapy is a second new treatment modality for hyperbilirubinemia. Exposure to light of wavelengths greater than 390 nm (not UV) has been shown to degrade bilirubin pigment into water-soluble, more polar compounds that, unlike the parent compound, appear to be less toxic and are readily excreted in bile and urine (320, 321). Tabb et al performed a prospective controlled study of 289 infants weighing less than 2500 g at birth, 78 of whom had serum unconjugated bilirubin levels of 10 mg/100 ml or higher (322). They were divided randomly into two treatment groups in which phototherapy was administered for 12 or 24 hr, respectively, and a third control group which did not receive phototherapy unless their bilirubin levels exceeded 13 mg/100 ml. Results clearly demonstrated the beneficial effect of phototherapy in direct proportion to total exposure time; 42% of controls ultimately required phototherapy (bilirubin above 13 mg/100 ml) whereas only 24% of babies given 12 hr and 17% percent of those given 24 hr of light exposure reached these levels. A major limitation of the technique relates to the rate rise of bilirubin. In those infants whose bilirubin levels rose to 10 mg/100 ml by 72 hr, ie, a relatively rapid rise, phototherapy did not slow the subsequent rise enough to prevent exchange transfusion. Additional risk factors, especially in prematures in whom kernicterus may develop at indirect bilirubin levels as low as 10 mg/100 ml, ininclude hypoalbuminemia, hypoglycemia, hypothermia, hypoxia, acidemia, and infection. Rebound hyperbilirubinemia was observed in some infants during the 2–3 days following discontinuance of phototherapy, thus requiring further monitoring. Although hazards of light exposure (the eyes are routinely shielded) are not fully elucidated (323, 324), increasing experience suggests that it is a relatively safe modality. Addition of phenobarbital to phototherapy appears to confer no advantage over the use of light alone (325). Phototherapy has also been used to good effect in the *Crigler–Najjar syndrome*. Large amounts of an administered dose of ^{14}C-labeled bilirubin are detected in the bile and urine of such patients during phototherapy and correlate with the fall of serum bilirubin from a level of 35 mg/100 ml to 9 mg/100 ml upon 12 hr of illumination per day. A single case of a new iatrogenic entity of the *bronze baby syndrome* has been described as a result of phototherapy to an infant with underlying liver disease (326).

In 1963 Reye et al described from Australia a syndrome with sudden onset and fulminant neurologic deterioration associated with liver dysfunction and visceral fat deposition (327). A prodromal upper respiratory infection or mild gastroenteritis, usually of 2–4 days duration, typically precedes the onset of encephalopathy (328–330). Many authors have since confirmed, extended, or reviewed *Reye's syndrome* (328, 330–337). The disease occurs in children from 2½ months to 16 years, but 85% of patients are below 6 years of age (328, 330, 338, 339). It has occurred in twins, and in siblings, concurrently or up to 9 months apart at onset (336, 340, 341). Reye's syndrome is endemic in New Zealand and has also been found in Thailand (337, 338, 342), Puerto Rico (343), Canada (331), and Chile (344). In the U.S., it is seasonally prevalent from December through March. Up to 50% of cases are reported from the Midwest (329, 345). There is neither sex predilection nor known socioeconomic determinant (332, 337, 338, 343). Various inborn enzymatic defects, exogenous toxins, common medications, and viral agents have been proposed as causative or contributory to its cause (330, 333–335, 337, 338, 343, 346, 347). Varicella has been identified sporadically (330, 336, 343), but cases have been documented in association with influenza epidemics (348). Influenza B (329), A_1, A_2 (330, 332), EB virus (349, 350), coxsackie A (351), B_4 (346), reovirus 2 (341), ECHO 11 (352), 8 (331), adenovirus (353), herpes simplex (332, 362), vaccinia (332), and rubeola (332) have all been associated or isolated from patients with the syndrome. Despite serologic evidence of influenza A_1 and A_2 and of varicella in some, and isolation of varicella virus from the liver in another patient, a failure consistently to isolate one specific viral strain and the absence of viral particles in ultrastructural studies of liver is noted (330, 332, 338). The presence of 3–4-μm diameter intracytoplasmic fat droplets (332), composed of di- and triglycerides and fatty acids with concomitant absence of inflammatory changes is characteristic of the diseased liver (330, 332, 334, 338, 342). Transitory mitochondrial pleomorphism is described and suggests that mitochondrial injury may uncouple energy production and, in turn, prevent normal fatty acid metabolism (332). Glycogen is usually minimal or absent (328, 332, 334, 335). This finding is con-

sistent with a report of failure of administered glucagon to elevate serum glucose (354). Liver disease is often deceptively inapparent. Clinical jaundice is rarely seen and mild elevations of serum bilirubin, SGOT, and SGPT, with modest prolongations of clotting function tests, are the rule (327, 330, 334, 343). Fresh plasma is recommended for the coagulopathy since it is characterized as secondary to a decreased hepatic synthesis of factors 1, 2, 5, 7, 9, 10; vitamin K therapy is usually ineffective because factors 1 and 5 are not K-dependent. Despite the apparently mild liver disease, the neurologic disturbances, ie, delirium, coma, seizure, hyperreflexia, decerebrate posturing, and central hyperventilation have been attributed to acute hepatic failure (355). These symptoms usually correlate with an increase in the serum ammonia level (330). There are few survivors if the initial ammonia is greater than 300 μmole/100 ml, but clinical deterioration may be experienced in the face of an apparently normal serum value (328, 349, 356). While not universal, hypoglycemia and reduced levels of CSF glucose are consistently noted. In a review of the literature they were found in 50% of patients under 4 years of age (343). Hypoglycemia is frequently found in fatal cases (330) and may be associated with cerebral edema and neuronal degeneration. Another detected serum abnormality is an elevated LDH isoenzyme level associated with heart muscle (356). This finding is not surprising, since fatty infiltration of the atria and conduction system was reported in 28 of 29 patients at postmortem (338). Liver biopsy confirmation of the fatty metamorphosis is essential for diagnosis (341).

Prognosis has improved from the 80% mortality originally reported by Reye to more recent values ranging from 20 to 50% (337, 339, 344). Improved survival rates are attributed to earlier diagnosis with better clinical staging of neurologic status and to more vigorous therapeutic techniques. Neurological staging has been, with slight variations, after Plum and Posner (328, 332, 357). Stages 1 through 3 involve progressive lethargy and appearances of decorticate posturing. Stages 4 and 5 include decerebrate posturing and dysconjugate eye movements leading to deep coma, fixed pupils, areflexia, and respiratory arrest. The few survivors who are reported from stage 4 or 5 coma often have severe brain damage (330, 349). Extracorporeal liver perfusion, plasmaphoresis, human-to-primate cross-circulation, human-to-human cross-circulation, peritoneal dialysis, exchange transfusions, or orthoptic liver transplantation have been utilized in management (328, 330, 339, 358–360). Despite his earlier discouraging experience with exchange transfusions, Huttenlocher recently reported that 8 of 9 patients recovered completely when therapy with fresh heparinized blood was instituted before onset of stage 3 coma (330). Exchanges were repeated every 12 hr until improvement or irreversible brain damage occurred. Lovejoy reported 14 patients who underwent exchange transfusions (328). Patients who survived had some transitory improvement but complications were high. All 7 children in stage 4 and 5 coma who were exchanged died, while all 3 in stage 3 survived. Samaha compared results of peritoneal dialysis with more conservative therapy in 24 patients (339). Of 11 treated with dialysis in addition to other medical measures, 9 survived, whereas only 2 of 13 lived who were treated with conservative therapy alone. A fault in most of these studies is that they are retrospective and do not compare patients in the same time period. The most promising modality appears to be exchange transfusion prior to the onset of deep coma.

The terminology of chronic hepatitis is as confused as it is in adults. The distinction between *chronic active hepatitis* (CAH), which often progresses to cirrhosis, and the more benign forms is difficult. Although the course of CAH is highly variable, 40% of patients or more will progress to liver failure, ascites, and coma (361–364). Mortality is 50% within 5 years of diagnosis in untreated cases (362, 363). There are no certain etiologic factors. Hepatotoxic drugs (oxyphenacetin, alpha-methyl-DOPA, INH) may present a similar picture (362, 364–366). CAH has a peak incidence between 10 and 20 years of age, although it may occur earlier (362, 367). It has a high predilection for females (30/38 in one series) (365). Its mode of onset in children is more abrupt than in adults, often indistinguishable from acute viral hepatitis (362, 363, 365, 368). In one series 9 patients with CAH had arthritis, 3 had acute colitis or erythema nodosum, 7 others had evidence of concurrent endocrine or renal disease (365). Serum alpha-fetoprotein, associated with regenerating liver, is a measure of parenchymal damage (370). All of 36 patients in one series had a markedly elevated IgG level (mean 3.78 g/100 ml) (365). Antibody to mitochondria and to nuclear antigen, both associated with biliary cirrhosis, may be found in 25–30% of patients with CAH (364, 373, 374). A positive LE prep, antibody to double-stranded DNA, to cytoplasmic elements,

and disturbances in delayed hypersensitivity are frequently found in CAH (364, 365, 371). Despite these immune derangements, their exact relationship to the progressive liver pathology is unclear (372).

Persistence of piecemeal necrosis and bridging upon liver biopsy, transiently seen in acute viral hepatitis, is indicative of CAH. A periportal inflammation with plasma cells and lymphocytes, loss of the limiting plate, and ductular proliferation favor CAH (373). Several authors believe that acute viral hepatitis resolves within 3 months, but prolonged cholestasis may continue for one year with eventual recovery (362, 373–375). Therefore they delay biopsy until that time. Others prefer 6 months; one believes that 6 weeks of continuous disease signals chronicity (364, 376, 377).

In all three forms of childhood hepatitis, NH, IH, and CAH, few controlled therapeutic trials have appeared, none exclusively in children (377, 378). Steroids are of no benefit and may increase relapse rate in uncomplicated IH (366, 379, 380). However, in hepatic failure the use of steroids is controversial. Its use in childhood CAH, singly or in combination with azathioprine, is advocated prior to onset of cirrhosis (365, 379, 381). DuBois had good results overall with prednisone (2 mg/kg/day) used for a median of 5.8 months (1–36 months) in 38 children with CAH (371). Reduction of dosage to below 10 mg/day was subsequently made possible with the addition of azathioprine (1 mg/kg/day) in 22 of these patients. Major risks of prolonged steroid therapy are infection, diabetes, osteoporosis, and stunting of growth. Hypoalbuminemic hepatitis adds special hazards. The percent of unbound steroid, the active metabolite, may be higher. In a survey of these patients, steroid-related side effects were doubled (382). Prednisone may be ineffective because the diseased liver may not convert it to the active form, prenisolone (383).

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