Neonatal jaundice is a common finding in general paediatrics. Many babies, as many as 30–50% of normal term newborns, have transient jaundice 3–5 days after birth. This unconjugated hyperbilirubinaemia is due to immaturity of the hepatic enzyme glucuronosyl transferase, which is responsible for glucuronidation of bilirubin. Unconjugated hyperbilirubinaemia occurring later in the perinatal period may be associated with breast feeding, so-called ‘breast-milk jaundice’. Elevated blood levels of unconjugated bilirubin can be due to haemolysis, sepsis, hypothyroidism or pyloric stenosis. In contrast, conjugated hyperbilirubinaemia nearly always reflects hepatic dysfunction, which may be due to many different disorders, such as the neonatal hepatitis syndrome, biliary atresia or duct paucity syndromes, all of which have different long-term outcomes. The nature of the liver disease must be determined as early as possible in order to start appropriate treatment or provide supportive therapies. The best current practice is to investigate jaundice in any infant who is 14 days old, to determine whether unconjugated or conjugated hyperbilirubinaemia is present.

Unconjugated hyperbilirubinaemia

Bilirubin, a breakdown product of haem, is extremely toxic. When it binds to cellular macromolecules, as in neural tissue, it causes damage, disrupts metabolic processes and leads to cell death. As bilirubin is normally tightly bound to albumin in the vascular compartment, concentrations of free bilirubin, which is capable of diffusing into brain tissue, are extremely low. Several parameters influence the level of free bilirubin: production of unconjugated bilirubin can be due to haemolysis, levels of unconjugated bilirubin can be due to haemolysis, sepsis, hypothyroidism or pyloric stenosis. In contrast, conjugated hyperbilirubinaemia nearly always reflects hepatic dysfunction, which may be due to many different disorders, such as the neonatal hepatitis syndrome, biliary atresia or duct paucity syndromes, all of which have different long-term outcomes. The nature of the liver disease must be determined as early as possible in order to start appropriate treatment or provide supportive therapies. The best current practice is to investigate jaundice in any infant who is 14 days old, to determine whether unconjugated or conjugated hyperbilirubinaemia is present.
or cause severe movement disorders (choreoathetosis), mental retardation and deafness.

Physiological jaundice

As hepatic bilirubin glucuronosyl transferase activity is low at the time of birth, nearly all newborn babies have hyperbilirubinaemia in the first week of life. Unconjugated bilirubin predominates whereas serum conjugated bilirubin is low or undetectable (Keffler et al. 1998). Approximately half of term babies are jaundiced; more severe jaundice (serum bilirubin ≥200μmol/l) occurs in 8–20% in the first week of life (Maisels et al. 1988). Factors associated with severe jaundice include breast feeding, exaggerated perinatal weight loss (>7% of birth weight), maternal diabetes mellitus, bruising, and induction of labour with oxytocin. The severity and duration of jaundice may be increased in infants born premature. Infants of Oriental, Inuit, or North American Indian extraction tend to have more severe jaundice, with as many as 24–54% developing serum bilirubin >200μmol/l. In general, physiological jaundice peaks on day 3 of life, although hyperbilirubinaemia may persist as long as 2 weeks.

The mechanism(s) of such severe physiological jaundice remain uncertain, and while environmental factors cannot be entirely excluded, genetic control of bilirubin production and clearance appears to be most important (Kaplan et al. 2002). There may be increased bilirubin load due to shortened red blood cell lifespan (Kaplan et al. 2002a), increased activity of the enterohepatic circulation, and inefficient uptake of bilirubin by hepatocytes due to relatively immature expression of ligandin, which mediates uptake of organic anions, in addition to immaturity of hepatic bilirubin glucuronosyl transferase. Infants who have abnormalities in the bilirubin glucuronosyl transferase which cause Gilbert’s syndrome (Burchell & Hume 1999) alone or in addition to glucose-6-phosphatase dehydrogenase deficiency (Kaplan et al. 1997; Kaplan & Hammerman 1998) are at greater risk for severe physiological jaundice and breast-milk jaundice.

Treatment

Treatment may not be necessary in most cases. Phototherapy should be initiated for normal term infants only when serum total bilirubin is >300μmol/l. The decision is complex and depends not only on the bilirubin concentration and its rate of increase, but also on the weight and gestational age of the infant, postnatal age, the rate at which bilirubin is generated and the adequacy of bilirubin–albumin binding. Numerous clinical trials have demonstrated the effectiveness of phototherapy for decreasing unconjugated hyperbilirubinaemia (bilirubin >300μmol/l) in term infants (Tan 1975; Brown et al. 1985) and in premature babies with serum bilirubin >200μmol/l. Body temperature and fluid status must be monitored closely; fluid loss may be excessive, mainly because of increased insensible loss and additionally due to frequent watery stools. Eye patches are required. The baby may be more irritable, especially as normal parental interaction is often interrupted. For babies of ethnic extraction in whom severe unconjugated hyperbilirubinaemia may commonly occur even in the absence of haemolysis, exchange transfusion remains a viable therapy to prevent kernicterus (Yeung 1985), although tin-protoporphyrin treatment has also been used (Rubaltelli et al. 1989; Galbraith et al. 1992). Exchange transfusion may be required to prevent possible kernicterus in any baby with severe unconjugated hyperbilirubinaemia.

Breast-milk jaundice

Moderately severe unconjugated hyperbilirubinaemia associated with breast feeding is common, occurring in 0.5–2% of healthy newborn babies. Jaundice may develop after the fourth day of life (early pattern) or towards the end of the first week of life (late pattern) and usually peaks around the end of the second week of life. Jaundice may overlap with physiological jaundice or be protracted and last 1–2 months.

The aetiology remains uncertain. Contamination of breast milk with steroids such as pregnanediols appears unlikely. Breast milk may contain endogenous substances, such as free fatty acids, which displace bilirubin in the intestinal contents and enhance the enterohepatic circulation of bilirubin, although increased free fatty acids were not found in freshly expressed breast milk from mothers of infants with breast-milk jaundice (Jalili et al. 1985). An alternative hypothesis is that breast milk contains β-glucuronidase, leading to deconjugation of glucuronide moieties from conjugated bilirubin and subsequent reabsorption of bilirubin (Gourley & Arend 1986). Breast-fed babies have less frequent stools and eliminate less bile in faeces than bottle-fed babies (De Carvalho et al. 1985), which may increase bilirubin reabsorption and contribute to hyperbilirubinaemia. More frequent breast feeding may enhance gut motility and stool output.

The diagnosis is clinical: an exclusively breast-fed infant with unconjugated hyperbilirubinaemia, normal conjugated bilirubin, haemoglobin and reticulocyte counts, no maternal blood group incompatibility, and a normal physical examination except for jaundice. The diagnosis is supported by a drop in serum bilirubin (≥50% in 1–3 days) if breast feeding is interrupted for 48 h (Lascari 1986). Breast-milk jaundice lasting 1–2 months requires surveillance by the physician to exclude liver disease, although pale stools, if noted, are highly suggestive of important liver disease.
Systemic disease

Unconjugated hyperbilirubinaemia is frequently associated with systemic disease. Haemolysis of any aetiology increases the bilirubin load and includes: rhesus and ABO incompatibility with Coombs’ positivity; glucose-6-phosphate dehydrogenase deficiency; erythrocyte membrane defects; and spherocytosis. Severe haemolytic disease of any aetiology can result in severe jaundice associated with kernicterus and requires aggressive treatment with phototherapy and/or exchange transfusion. Bruising, haemorrhage into brain or lung tissue, and neonatal polycythaemia also increase the bilirubin load.

The association of unconjugated hyperbilirubinaemia with congenital hypothyroidism is based on early observations (Weldon & Danks 1972). The mechanism of jaundice is not known, but thyroid function should be evaluated in any neonate with jaundice.

Unconjugated hyperbilirubinaemia is also found with pyloric stenosis and other forms of upper intestinal obstruction, which resolves rapidly after pyloric myotomy (Bleicher et al. 1979). The mechanism remains uncertain. A likely explanation is that these infants have Gilbert syndrome and develop unconjugated hyperbilirubinaemia due to reduced oral intake (Labrune et al. 1989; Trioche et al. 1999).

Other pathological conditions associated with unconjugated hyperbilirubinaemia include sepsis, hypoxia, hypoglycaemia, galactosaemia and fructose intolerance.

Inherited disorders

Crigler–Najjar syndromes

Crigler–Najjar syndromes type 1 and 2 are autosomal recessive conditions which lead to unconjugated hyperbilirubinaemia due to a deficiency of the enzyme bilirubin uridine diphosphate glucuronosyl transferase (UDPGT). In Crigler–Najjar type 1 there is effectively no UDPGT present; in type 2 the defect is partial.

The genetic basis for these diseases has been elucidated since the structure of the human bilirubin glucuronosyl transferase gene has been established (Owens & Ritter 1992; Ritter et al. 1992, 1993). Humans have two such genes (B-UGT1 and B-UGT2); B-UGT2 appears to play little if any role in bilirubin glucuronidation and is not responsible for induction of enzyme activity in Crigler–Najjar type 2 due to phenobarbital. B-UGT1 and 2 are members of a glucuronosyl transferase superfamily. In these genes exon 1 relates to substrate specificity, for example, for bilirubin, exons 2–5 code for the carboxy-terminal domains common to all glucuronosyl transferases. The clinical phenotype of Crigler–Najjar type 1 can result from mutations in exons 2–5, resulting in a truncated non-functional enzyme, or in exon 1, resulting in complete loss of substrate recognition for bilirubin. Genetic heterogeneity in this condition has been striking (Aono et al. 1993; Labrune et al. 1994). The genetic defect in Crigler–Najjar type 2 is somewhat subtler. Mutations leading to Crigler–Najjar type 2 appear to change the affinity of the enzyme for its substrate (Seppen et al. 1994; Guldutuna et al. 1995).

Clinical features and diagnosis Both conditions present early in the perinatal period with a rapid rise in bilirubin despite phototherapy. Kernicterus may develop in the perinatal period, particularly if treatment is delayed or if associated with dehydration or sepsis. Type 1 is much more severe than type 2, with peak serum bilirubin levels at 250–850μmol/l. In Crigler–Najjar type 2 serum bilirubin is lower (200–300μmol/l) and may reduce by ~40% when phenobarbitone is administered.

Liver function tests, including conjugated bilirubin, are normal. Liver histology is normal except for occasional bile plugs. Confirmation of the diagnosis may be obtained by detection of the enzyme deficiency in liver or estimation of bilirubin mono- and diglucuronides in bile aspirates. Bilirubin diglucuronides are not present in bile in type 1 but can be found in type 2 (Sinaasappel & Jansen 1991).

Management Treatment for Crigler–Najjar type 1 consists of aggressive use of measures to remove bilirubin with either phototherapy or exchange transfusion. Effective phototherapy depends on delivering radiant energy from light of wavelength 400–500nm to the skin. Irradiance is not related to the brightness of the lights; the quantity of irradiation is inversely related to the distance between the lights and the infant. Skin pigmentation does not influence effectiveness of treatment. The development of lighted mattresses (Hughes-Benzie et al. 1993) has facilitated treatment and permitted early discharge from hospital. The use of tin-protoporphyrin has been advocated as an alternative treatment, which works by interfering with the generation of bilirubin from haem (Kappas et al. 1988; McDonagh 1988).

The aim of therapy is to maintain bilirubin levels low enough (<300μmol/l) to prevent kernicterus, which may require up to 15h of phototherapy a day. Intercurrent infections with rapid increases in bilirubin should be managed with plasmapheresis or exchange transfusions.

Liver transplantation, including auxiliary transplantation, is a long-term option if damage to the nervous system has been avoided (Chapter 20) and may improve quality of life. It is the only effective method for preventing kernicterus. Hepatocyte transplantation has limited success (Fox et al. 1998).

In Crigler–Najjar type 2 prolonged treatment with phenobarbitone (5–10mg/kg/day) may provide cos-
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Metic improvement, but treatment is not usually required as kernicterus is rare.

Outcome Sudden late neurological deterioration in Crigler–Najjar type 1 may occur even if management of hyperbilirubinaemia has been meticulous. Late intrahepatic cholestasis has been reported. The outcome following liver transplantation is excellent.

Gilbert’s syndrome

This condition manifests with mild variable unconjugated hyperbilirubinaemia, with total serum bilirubin levels ranging from 30 to 90μmol/l. It is a heterogeneous condition in which the responsible gene defect has been identified: the presence of an extra TA tandem repeat in the promoter region of the bilirubin UDP glucuronosyl transferase 1 gene (Bosma et al. 1995). Instead of having the normal six repeats, seven are present. Although this promoter region abnormality is the prevailing abnormality in individuals of European extraction, a different genetic picture exists in Asians in whom mutations within the coding region of bilirubin UDP glucuronosyl transferase 1 gene have been found associated with Gilbert’s syndrome (Burchell & Hume 1999).

Clinical features There is mild jaundice which is exacerbated by dehydration, intercurrent illness or fatigue. Patients often complain of vague abdominal pain, lethargy and general malaise for which no good cause has been found. It is more common in males than females; most children present in adolescence. Serum aminotransferases are normal and biopsy is unnecessary. Infants homozygous for the genetic abnormality of Gilbert syndrome have a greater increase in jaundice in the first 2 days of life than heterozygotes or non-affected infants (Bancroft et al. 1998; Monaghan et al. 1999; Roy-Chowdhury et al. 2002). Asian infants with Gilbert’s syndrome associated with coding region mutations in the bilirubin glucuronosyl transferase gene are also more prone to physiological or breast-milk jaundice (Akaba et al. 1999; Maruo et al. 1999, 2000; Sutomo et al. 2002).

Treatment No treatment is required, but families often require reassurance.

Conjugated hyperbilirubinaemia

Conjugated hyperbilirubinaemia nearly always indicates liver disease, which may be due to the neonatal hepatitis syndrome, biliary atresia or duct paucity syndromes. The nomenclature for neonatal liver disease is problematic. The term ‘neonatal jaundice’ causes confusion with physiological jaundice, while ‘neonatal cholestasis’ is imprecise. In the first 3–4 months of life every infant has some degree of neonatal cholestasis on a physiological basis, which is multifactorial. Hepatocellular pathways of bile acid conjugation and biliary secretion are immature, and uptake of bile acids and other organic anions by hepatocytes is inefficient, leading to high concentrations of bile acids in blood; the circulating bile acid pool is contracted, and ileal uptake of bile acids is underdeveloped (Suchy et al. 1981; Balistreri et al. 1983). The term ‘neonatal hepatitis’ is inadequate because hepatic inflammation is not prominent in every condition. The term ‘neonatal hepatitis syndrome’ (NHS) is now used as it conveys the similarity of the clinical illness in infants and suggests a broad spectrum of causative disease processes.

Neonatal hepatitis syndrome (NHS)

The neonatal hepatitis syndrome is now the term given to non-specific hepatic inflammation, which develops secondary to many different aetiologies, including intrauterine infection, endocrine disorders and inborn errors of metabolism. Causes of the neonatal hepatitis syndrome and diagnostic approach are summarized in Fig. 4.1 and Table 4.1. Treatment is summarized in Table 4.5. (p. 61).

Clinical features

Conjugated hyperbilirubinaemia may present at any time after birth. If detected in the first 24h of life infection is usually the cause. Most causes of the neonatal hepatitis syndrome have a similar presentation:

- Jaundice, which may not be obvious at first.
- Dark urine and pale yellow stools. Abnormal stool colour, though suggestive of liver disease, is neither a specific nor a reliable feature.
- Infants may be small for gestational age, especially those with Alagille’s syndrome, metabolic liver disease and intrauterine infection (see Plate 1, Atlas: p. 440).
- Failure to thrive or poor feeding.
- Dysmorphic features in trisomy 18, trisomy 21, Alagille’s syndrome, Zellweger syndrome, and with certain congenital infections.
- Hypoglycaemia in metabolic liver disease, hypopituitarism or severe liver disease.
- Hepatomegaly.
- Splenomegaly (the spleen may also be palpated in healthy babies 1–2cm below left costal margin). An impalpable spleen in an infant with severe cholestatic jaundice may suggest extrahepatic biliary atresia with polysplenia.
- Ascites is rarely evident except in metabolic liver disease (Chapter 5).
- Cardiac murmurs or neurological abnormalities are associated with specific congenital syndromes.
- Bleeding from vitamin K deficiency or thrombocytopenia.
The cardinal feature is conjugated hyperbilirubinaemia of any degree. Even a mildly elevated conjugated bilirubin ($\geq 20\text{mol/l}$) in the absence of unconjugated hyperbilirubinaemia may indicate significant hepatic disease.

- Serum aminotransferases are frequently elevated 2–4 times normal, but they may be within normal limits for age. Higher elevations suggest an infectious process.
- Serum alkaline phosphatase may be normal or only mildly elevated. Higher levels may indicate biliary atresia or rickets.

**Investigations**

The following investigations and findings are used in determining a diagnosis of neonatal hepatitis syndrome:

- Ultrasound of bile ducts
- TORCH Serology for toxoplasma, other, rubella, cytomegalovirus and herpes simplex viruses; TIBC, total iron-binding capacity; GGT, gamma-glutamyl-transpeptidase; TEBIDA, Technetium trimethyl-1-bromo imino diacetic acid; ERCP, endoscopic retrograde, cholangiopancreatography.
- Abnormal: Cholangiography, Choledochal cyst, Surgery
- Normal/absent or concentrated gall bladder: Hepatobiliary (TEBIDA) scan
- Excretion within 4 hours: Liver biopsy, Neonatal hepatitis
- Delayed/no excretion within 24 hours: Liver biopsy, Biliary atresia, ERCP/operative cholangiogram
- Bile duct paucity: Alagille gene testing
- Laparotomy

**Fig. 4.1** Investigation of conjugated hyperbilirubinaemia in the neonate. TORCH, Serology for toxoplasma, other, rubella, cytomegalovirus and herpes simplex viruses; TIBC, total iron-binding capacity; GGT, gamma-glutamyl-transpeptidase; TEBIDA, Technetium trimethyl-1-bromo imino diacetic acid; ERCP, endoscopic retrograde, cholangiopancreatography.
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#### Table 4.1 Neonatal liver disease syndrome: differential diagnosis and diagnostic approach

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<tr>
<td>Rubella</td>
<td>IgM-specific antibodies</td>
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<td>Human herpesvirus-6, herpes zoster</td>
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<td>Human immunodeficiency virus</td>
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<td>Genetic</td>
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<td><strong>Endocrine</strong></td>
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<td>Hypothyroidism</td>
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<td>Extrahepatic biliary atresia</td>
<td>Delayed or absent excretion on hepatobiliary scan, biliary obstruction on histology</td>
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<td><strong>Duct paucity syndromes</strong></td>
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<td>Alagille syndrome</td>
<td>Echocardiogram, posterior embryotoxon, CXR for 'butterfly vertebrae'</td>
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<td>Non-syndromic duct paucity</td>
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<td><strong>Metabolic</strong></td>
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<td>Liver biopsy; EM, enzyme activities</td>
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<td>Niemann–Pick, type C</td>
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<td>Byler disease</td>
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<td><strong>Immune</strong></td>
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<td>Neonatal lupus erythematosus</td>
<td>Anti-Ro and anti-La antibodies (in infant and mother)</td>
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<tr>
<td>NH with autoimmune haemolytic anaemia</td>
<td>Coombs' test, giant cell hepatitis</td>
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</tbody>
</table>

AAT, α1-antitrypsin; Bx, biopsy; CBD, common bile duct; CXR, chest X-ray; EM, electron microscopy; FAB-M5, fast-atom bombardment-mass spectroscopy; FTA-ABS, fluorescent treponemal antibody, absorbed; GGT, gamma-glutamyl transpeptidase; HBV, hepatitis B virus; HCV, hepatitis C virus; PI, protease inhibitor; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase-polymerase chain reaction; STS, standard test for syphilis; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory.
particularly those with a neonatal hepatitis syndrome, is said to be prominent in bile duct obstruction, it also occurs in children with a neonatal hepatitis syndrome, particularly those with α1-antitrypsin deficiency, cystic fibrosis and endocrine deficiency. Paucity of bile ducts is a feature in Alagille’s syndrome (see Plates 4 and 6, Atlas: pp. 441 and 442, respectively).

**Infection**

**Toxoplasmosis, rubella, cytomegalovirus, herpes simplex** (‘TORCH’) infections

Congenital infections grouped under the acronym ‘TORCH’ often have very similar clinical features: hepatosplenomegaly, jaundice, pneumonitis, petechial or purpuric rash, and a tendency to prematurity or poor intrauterine growth. A presentation with fulminant hepatic failure in the newborn period is common with herpes simplex infection. Whenever possible, direct identification of viral infection or measurement of specific IgM antibodies should be sought for rapid diagnosis; relying on conventional TORCH titres is less preferable.

**Toxoplasmosis** Congenital toxoplasmosis is comparatively rare. Maternal infection in the third trimester is more likely to cause fetal infection than infection earlier in pregnancy. Neonatal hepatitis is an important feature but may be less obvious than central nervous system involvement with chorioretinitis (with large pigmented scars), hydrocephaly or microcephaly. Intracranial calcification is usually prominent, leading to convulsions, nystagmus and evidence of increased intracranial pressure. Liver biopsy may demonstrate a non-specific hepatitis or portal fibrosis with biliary ductule proliferation. Spiramycin therapy may prevent progression of central nervous system and liver disease. Prognosis depends on the extent of neurological or optic disease.

**Rubella** Congenital infection with rubella virus is now rare because of immunization. It may cause intrauterine growth retardation, anaemia/thrombocytopenia, congenital heart disease (patent ductus arteriosus or pulmonary artery stenosis), cataracts, chorioretinitis (‘salt and pepper’ appearance), mental retardation and sensorineural deafness. Hepatosplenomegaly is usual. Liver histology shows typical giant-cell hepatitis. The disease may be self-limited or progress to cirrhosis.

**Cytomegalovirus** Cytomegalovirus is the most commonest cause of congenital infection, affecting 1–2% of newborns, most of whom are asymptomatic. Those with evident disease may have intrauterine growth retardation or be pre-mature (Hart et al. 1991). Fetal ascites (Binder et al. 1988; Sun et al. 1990) may occur. Cytomegalovirus rarely causes acute liver failure in the newborn.

Clinical findings include: petechial rash, hepatosplenomegaly, and jaundice in 60–80%. Cytomegalovirus infection often affects the central nervous system, producing microcephaly, intracranial calcification, and chorioretinitis; progressive sensorineural deafness or cerebral palsy may develop later in childhood. Primary infection in the second and third trimesters ap-
pears to cause more severe fetal disease than recurrent infection.

Liver biopsy demonstrates a giant cell hepatitis; the classical inclusion bodies are rarely seen in neonatal infection. In a study of liver tissue in infants with neonatal hepatitis or extrahepatic biliary atresia, Chang et al. (Chang et al. 1992) found cytomegalovirus DNA in 23 of 50 infants with neonatal hepatitis by polymerase chain reaction, but in only two of 26 with extrahepatic biliary atresia, and in none of control specimens. Although differentiation from biliary atresia is usually easy, cytomegalovirus may be associated with extrahepatic biliary atresia. In one report of fraternal twins, both had congenital cytomegalovirus infection: one had hepatitis only and the other presented with ‘late’ pattern extrahepatic biliary atresia (Hart et al. 1991). In addition, 25% of infants with extrahepatic biliary atresia were found to have cytomegalovirus infection and were referred later than those without cytomegalovirus infection (Tarr et al. 1996). Cytomegalovirus is a candidate virus for causing ‘late’ presentation extrahepatic biliary atresia as it can infect bile duct epithelial cells directly and increase expression of MHC class II antigens (Arnold et al. 1992; Domiati-Saad et al. 2000). Infants with congenital cytomegalovirus infection and persisting conjugated hyperbilirubinaemia should have extrahepatic biliary atresia excluded.

Conclusive diagnosis requires cytomegalovirus to be cultured from the infant within the first 4 weeks of life. Serological studies and clinical features provide support for the presence of cytomegalovirus infection but do not distinguish congenital from early postnatal infection (Table 4.1).

In most children cytomegalovirus hepatitis is mild and resolves completely. A few children develop hepatic fibrosis (Zuppé et al. 1986; Le Luyer et al. 1990) or non-cirrhotic portal hypertension (Ghishan et al. 1984). Intrahepatic calcification has been reported (Alix et al. 1978). Cirrhosis with chronic cholestasis necessitated liver transplantation in one child. Persisting neurodevelopmental abnormalities become the main problem in the majority of patients (Conboy et al. 1987).

Herpes simplex. In the newborn this virus causes a severe multisystem disorder with encephalitis, severe hepatitis, or acute liver failure (Miller et al. 1970; Benador et al. 1990) due to either type 1 or type 2 virus, although type 2 virus shed from the infected cervix at birth is more common. Liver biopsy shows areas of necrosis with viral inclusions in intact hepatocytes; however, profound coagulopathy may preclude biopsy. Scrapings from vesicular skin lesions reveal herpes simplex virus, but these typical herpetic skin, mouth or eye lesions may not be present in neonates. Antiviral treatment with acyclovir should be administered to avert the otherwise high mortality.

Syphilis

Congenital syphilis is now rare in the developed world. It causes a multisystem illness, which may include intrauterine growth retardation and subsequent failure to thrive, severe anaemia and thrombocytopenia, nephrotic syndrome, periostitis, nasal discharge (‘snuffles’), skin rash, diffuse lymphadenopathy, and hepatomegaly. Jaundice may be present within 24 h of birth or develop after treatment (Long et al. 1984). Jaundice may be severe (Wolf et al. 1997). Some babies with congenital syphilis never develop jaundice but present with a typical rash on palms and soles or only with fever, as well as prominent hepatomegaly (Dorfman & Glaser 1990). Central nervous system involvement occurs in up to 30% of infants.

Liver histology in untreated congenital syphilis may reveal numerous treponemes in hepatic tissue, but after treatment with penicillin, giant-cell hepatitis without detectable treponemes is the usual finding. Diagnosis involves serological testing, including the Venereal Disease Research Laboratory (VDRL) test and confirmatory testing for specific antitreponemal antibodies. Radiographs of long bones may show typical bony abnormalities in the first 24 h of life and aid rapid diagnosis (Table 4.1).

Varicella

Varicella may occur in newborn infants if maternal infection occurs within 14 days of delivery. It tends to be more severe in premature infants and is mild in term infants after 10 days of age. Early presentation or protracted disease in an infant of any gestational age may lead to a fatal outcome. This severe disease is characterized by jaundice, and extensive skin and multisystem involvement, especially pneumonia. In fatal cases hepatic parenchymal involvement can be demonstrated (Brunell 1983; Feldman 1986).

Hepatotropic viruses: hepatitis A, B and C

In general, infection with hepatotropic viruses in neonates does not cause jaundice unless there is acute liver failure or severe hepatitis. Neither hepatitis A nor B have been associated with NHS or biliary atresia (Balisterri et al. 1980).

Hepatitis A Hepatitis A is rare in the neonate but congenital infection may occur if the mother is infected 1–2 weeks before delivery (Watson et al. 1993). The typical picture in the early neonatal period is a non-specific diarrhoeal illness, as shown by rare outbreaks of transfusion-related hepatitis in premature infants (Klein et al. 1984; Noble et al. 1984).
Hepatitis B Vertical hepatitis B infection is subclinical in the neonatal period; prompt administration of both hepatitis B immune globulin and hepatitis B immunization provides protection against chronic infection in 93% of infants at risk. Infants who fail this regimen may have been infected transplacentally. Without immunoprophylaxis, infants may become chronic carriers or develop acute hepatitis B or fulminant hepatic failure after a 3- to 4-month incubation period (Dupuy et al. 1975; Mollica et al. 1977; Shiraki et al. 1980; Delaplane et al. 1983) (Chapter 7).

Hepatitis C Hepatitis C is not a cause of neonatal hepatitis syndrome. A study of 33 infants with either idiopathic neonatal hepatitis or extrahepatic biliary atresia revealed only one (with extrahepatic biliary atresia) positive for anti-hepatitis C virus (anti-HCV) antibodies and for virus by reverse transcriptase-polymerase chain reaction (RT-PCR) (A-Kader et al. 1994). Similar studies in Taiwan, where hepatitis C is endemic, found no anti-HCV-positive infants among 42 with neonatal hepatitis and 11 with extrahepatic biliary atresia, by second-generation enzyme-linked immunoassay (Chang et al. 1993). Vertical transmission of hepatitis is less common than in hepatitis B viral infection. Jaundice does not occur.

Human immunodeficiency virus (HIV) infection

Although infants with congenital HIV infection may present with hepatosplenomegaly, conjugated hyperbilirubinaemia in the neonatal period is rare. A case of neonatal hepatitis was attributed to HIV infection despite concomitant congenital cytomegalovirus infection (Witzleben et al. 1988); an increased incidence of congenital cytomegalovirus infection has subsequently been found in HIV-infected infants. Congenital HIV infection may present clinically as hepatitis with jaundice although later than in the neonatal period, typically at ~6 months of age (Persaud et al. 1993).

Parvovirus B19 infection

Congenital parvovirus B19 infection may cause profound anaemia leading to hydrops (Essary et al. 1998) and fetal death. The spectrum includes conjugated hyperbilirubinaemia, hepatomegaly, severe coagulopathy, dermal erythroblastosis (‘blueberry muffin’ rash), anaemia and perinatal distress (Silver et al. 1996). Liver biopsy showed diffuse sinusoidal fibrosis, siderosis, little giant-cell transformation of hepatocytes but excessive extramedullary haemopoiesis (Metzman et al. 1989; Langnas et al. 1995; White et al. 1995). Despite features of early hepatic insufficiency, serum aminotransferases may be low or near normal. Diagnosis is made by PCR for presence of parvovirus 19, although placental histology may suggest prenatal parvovirus infection. Outcome depends on severity of infection.

Human herpesvirus-6 (HHV-6) infection

Human herpesvirus-6 causes exanthem subitum, a common but usually benign febrile illness in infants; other HHV-6 infections are common and self-limited without a rash. Acute liver failure has been reported (Asano et al. 1990; Aita et al. 2001).

Syncytial giant-cell hepatitis

‘Syncytial giant-cell hepatitis’ denotes severe liver disease attributed to paramyxovirus infection. The clinical liver disease varies with the age of the patient: in children, fulminant hepatic failure is common, while rapidly progressive chronic hepatitis occurs in adults. Infants may have features of a chronic active hepatitis or autoimmune haemolytic anaemia.

In neonates, syncytial giant-cell hepatitis is associated with a severe hepatitis, which does not meet the criteria for fulminant liver disease (Chapters 5 and 7). Hepatitis with moderately elevated serum aminotransferases progresses to chronic cholestasis and decompensated cirrhosis over 6–12 months.

Liver histology and electron microscopy show both the characteristic syncytial-type giant cells and viral inclusions consistent with the morphology of paramyxoviruses (Phillips et al. 1991; Sussman et al. 1994; Hicks et al. 2001). Formation of giant multinucleated hepatocytes is a characteristic response of infantile hepatocytes to injury, which is not often seen in hepatitis in adults. Syncytial giant cells differ from the giant cells of neonatal hepatitis because the outline of the liver cell plates remains evident, with indistinct, ‘smudged’ borders between the cells. They may form because of cell fusion secondary to parvovirus, in the same way as other viruses such as respiratory syncytial virus and measles virus.

Spontaneous recovery is uncommon. Treatment with the antiviral agent ribavirin appeared efficacious in one case (Roberts et al. 1993). Most babies require liver transplantation before the end of the first year of life.

Enteric viral sepsis (echovirus, Coxsackie viruses, adenoviruses)

The enteroviruses cause systemic viral infection in the newborn period, and severe hepatitis with acute liver failure may be a prominent feature. Incidence is greatest at the seasonal peak incidence of echovirus infections (late summer to early autumn). The infant’s mother may relate development of abdominal pain just prior to onset of labour. Vertical infection near the time of birth is associated with more severe disease in the infant. Most infants
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with enteric viral sepsis present between 1 and 5 weeks old. The infant is lethargic and jaundiced, with very high serum aminotransferases and severe coagulopathy; meningitis is usually present. Echovirus serotypes 3, 6, 7, 9, 11, 14, 19 and 21 have all been reported in severe infections with hepatitis (Modlin 1980; Gillam et al. 1986; Modlin & Kinney 1986). Echovirus serotype 11 appears to be most virulent for newborns.

Coxsackie A and B viruses are capable of causing an identical clinical picture, although myocarditis or heart failure suggests Coxsackie virus infection. Adenoviruses (Matsuoka et al. 1990) and herpes simplex infection (either type 1 or 2) also cause the same severe hepatitis (Benador et al. 1990). Mortality with acute liver failure is of the order of 85–90%. Meticulous supportive care is essential (Chapter 14). Infants who recover may develop severe cholestatic jaundice. Subsequent hepatic function in survivors appears entirely normal.

**Bacterial infection outside the liver**

Conjugated hyperbilirubinaemia may occur with sepsis or localized extrahepatic infection, such as a urinary infection, that is inapparent (Hamilton & Sass-Kortsak 1963; Franson et al. 1985; Garcia & Nager 2002). Serum aminotransferases may be slightly elevated; hepatosplenomegaly is uncommon. Jaundice may also occur with streptococcal and staphylococcal infections and Gram-negative bacterial septicaemia.

Infants with galactosaemia may present initially with jaundice and Gram-negative septicaemia, often due to *Escherichia coli* or *Klebsiella* species. Other typical features of galactosaemia may not be obvious. Galactosaemia should be investigated in any infant with conjugated hyperbilirubinaemia associated with sepsis by measuring erythrocyte galactose-1-phosphate uridyl transferase.

**Listeriosis**

Congenital infection with *Listeria monocytogenes* typically involves the liver. Although meningitis is the predominant clinical feature of the systemic disease, infants have hepatosplenomegaly and are sometimes jaundiced. Pneumonia is usually present. A history of maternal illness is common. Liver biopsy may reveal simply a diffuse hepatitis or, more commonly, diffuse areas of focal necrosis. Diagnosis is made by isolating the organism from blood, cerebrospinal fluid (CSF) or liver. Treatment is with penicillin.

**Tuberculosis**

Congenital tuberculosis is rare, but since the prevalence of tuberculosis in women of child-bearing age has risen in the past few years, tuberculosis in infants may become more common. Newborn infants may be infected by aspirating infected amniotic fluid or cervical secretions at the time of delivery.

Practical criteria for diagnosis are a proven tuberculous infection in a newborn baby with at least one of the following: lesions in the first week of life; primary hepatic complex or caseating granulomas in the liver; tuberculous infection of the placenta or maternal genital organs; and exclusion of postnatal infection by investigation of contacts (Cantwell et al. 1994).

Hepatomegaly is common in infants with tuberculosis, but jaundice is rare and indicates severe disease. Respiratory distress, poor feeding and fever are frequent. Mortality approaches 30%; a quadruple antitubercular antibiotic regimen excluding ethambutol is recommended. A high index of suspicion appears to be required for diagnosis, as tuberculosis in this age group often has atypical clinical features (Gogus et al. 1993).

**Endocrine disorders**

**Hypothyroidism**

Hypothyroidism is usually associated with an unconjugated hyperbilirubinaemia but may be associated with the neonatal hepatitis syndrome and should be excluded in every patient (Fig. 4.1).

**Hypopituitarism**

Pituitary–adrenal dysfunction is associated with neonatal hepatitis syndrome in 30–70% of patients (Hereman et al. 1975; Leblanc et al. 1981b; Kraehe et al. 1992; Sheehan et al. 1992; Ellaway et al. 1995). The cause of the hypopituitarism is variable. It is due to hypothalamic dysfunction in some; deficiency of anterior and/or posterior pituitary function may be present; a child with adrenal insensitivity to adrenocorticotropic was also described (Lacy et al. 1993). Clinical features include: conjugated hyperbilirubinaemia; hypoglycaemia in the perinatal period, which is usually symptomatic and persistent; and septo-optic dysplasia, which is a neuro-optical malformation that includes ventral midline developmental defect (absence of the septum pellucidum or corpus callosum) and hypoplasia of one or both optic nerves which is associated with hypopituitarism. There may also be midline facial abnormalities, nystagmus and microgenitalia in boys (see Plate 5, Atlas: p. 441).

The diagnosis is confirmed by detecting an extremely low random or 09.00h cortisol in association with a low thyroid-stimulating hormone (TSH) and thyroxine (T4). Liver biopsy usually reveals typical giant-cell hepatitis, but severe cholestasis may be present with dilated bile canaliculi and hepatocellular necrosis. There may be delayed excretion on radioisotope scanning (Kumura et al. 1993).
1987). Hormone replacement is essential and includes thyroxine, corticosteroids and occasionally growth hormone. Progression of the disease to cirrhosis and portal hypertension has been reported in those children who had delayed or no hormone replacement.

**Chromosomal disorders**

**Trisomy 18**

Trisomy 18 is associated with growth retardation, skeletal abnormalities and complex congenital heart disease. Both giant-cell hepatitis and extrahepatic biliary atresia have been reported (Alpert et al. 1969; Ikeda et al. 1999). In one infant with trisomy 18 serial liver biopsies suggested late evolution of neonatal hepatitis to extrahepatic biliary atresia.

Other cytogenetic abnormalities, including trisomy 13, deletion of the short arm of chromosome 18 and 49 XXXY (Silveira et al. 1991), have been reported in association with extrahepatic biliary atresia.

**Trisomy 21**

The association between trisomy 21 and neonatal cholestasis or extrahepatic biliary atresia (Henriksen et al. 1981) is not well substantiated. Recently, severe hepatic fibrosis associated with transient myeloproliferative disorder has been reported with Down’s syndrome (Ruchelli et al. 1991; Becroft 1993), raising the possibility that hepatic fibrogenesis might be due to high concentrations of growth factors derived from megakaryocytes.

**Cat-eye syndrome**

Cat-eye syndrome is a highly variable malformation syndrome associated with a supernumerary bistratified marker chromosome derived from duplicated regions of chromosome 22. Major features may include coloboma of the iris and other facial malformations involving the eyes, anal atresia with fistula, complex congenital heart disease and renal malformation. There is considerable phenotypical variability. Extrahepatic biliary atresia has been reported in association with this disorder. A candidate responsible gene in this condition has recently been identified as the human homologue of CECRI, which is an insect gene encoding growth factors. The expression pattern of hCECR1 in heart, cranial nerves and notochord and later in fetal liver, lung and kidney implicates it as leading to cat-eye syndrome when it is over-expressed (Riazi et al. 2000).

**Idiopathic neonatal hepatitis**

In up to 25% of infants presenting with conjugated hyperbilirubinaemia before 3 months of age, no aetiology is found, and these infants are considered to have idiopathic neonatal hepatitis. If cholestasis is severe, differentiation from extrahepatic biliary atresia and other cholestatic conditions is important. Infants with idiopathic neonatal hepatitis are more likely to be premature or small for gestational age than those with extrahepatic biliary atresia (Mowat et al. 1976), perhaps reflecting a genetic disorder or an intrauterine infection. An important subset of idiopathic neonatal hepatitis includes instances where more than one child in a single family is affected, accounting for 5–15% of cases in most series.

Liver biopsy shows an extensive giant-cell transformation of hepatocytes with inflammation, but bile ducts appear generally normal. A few infants with histologically severe inflammation also have small bile duct paucity. In general, it may not be easy to differentiate between severe idiopathic neonatal hepatitis and extrahepatic biliary atresia. An intraoperative cholangiogram may be required, and there is no evidence that diagnostic laparotomy for assessment of the extrahepatic biliary tree is adverse for infants with idiopathic neonatal hepatitis.

The prognosis is generally good. Mortality is 13–25% (Deutsch et al. 1985; Chang et al. 1987; Suita et al. 1992). Predictors of poor prognosis include: prolonged severe jaundice (beyond 6 months of age); acholic stools; familial occurrence; persistent hepatomegaly; and severe inflammation on biopsy. Peak bilirubin level is not necessarily predictive of outcome, and the prognostic importance of ductopenia has not been rigorously investigated. Septic complications may lead to decompensation. The long-term outlook for infants surviving the first year of life with little evidence of chronic liver disease is very good.

**Neonatal hepatitis in preterm infants**

Idiopathic neonatal hepatitis does occur in preterm babies, some of whom will have cholestasis due to immaturity of the biliary tree. They may be prone to hypoglycaemia and have a functionally immature gastrointestinal tract resulting in difficulties with feeding. It is important to differentiate this condition from other known causes of NHS and, in particular, extrahepatic biliary atresia. The prognosis is generally good.

**Structural abnormalities**

**Extrahepatic biliary atresia**

Extrahepatic biliary atresia (EHBA) is the cause of liver disease in ~25% of infants presenting with neonatal hepatitis syndrome and is the most important differential diagnosis. Early diagnosis is vital as the Kasai portoenterostomy is less likely to be successful the later it is performed (Mieli-Vergani et al. 1989; Chardot et al. 1999).
EHBA involves a progressive destruction of the extrahepatic bile ducts, with scarring, obliteration and concomitant damage to small and medium-sized intrahepatic bile ducts. The disease is classified according to the extent of damage at diagnosis. In type 1, damage is limited to the distal common bile duct (also known as ‘correctable’); in type 2 damage is limited to the common hepatic duct; in type 3, which is the most common, the entire extrahepatic biliary tree is involved. Type 1 accounts for ~10% of EHBA, and type 2 is extremely rare (Chapter 18).

EHBA is found worldwide in all racial groups, with an incidence of 1 in 8000–15000 live births. For discussion of aetiology and pathogenesis see Chapter 18.

Clinical features
The clinical presentation of EHBA is unremitting, progressive jaundice in an infant who usually looks well. The main features are:
- Normal birth weight and gestational age in the majority. Preterm infants can have EHBA.
- Jaundice, which is present from shortly after birth, continuous with physiological jaundice. There may be some variability in intensity; however, jaundice can be readily identified in affected infants by 4 weeks of age.
- Yellow or dark urine with increasingly pale stools, which eventually become acholic. Initially, there may be variation in stool colour, which may be confusing.
- Hepatomegaly is always present; the liver is usually firm.
- Splenomegaly is a late sign and implies some degree of hepatic fibrosis.
- Failure to thrive despite adequate feeding.
- Cardiovascular anomalies (ventricular or atrial septal defects) in 30%.
- Polysplenia syndrome; this includes preduodenal portal vein, situs inversus, absence of inferior vena cava and malrotation (Chapter 18).
- Bleeding from vitamin K-responsive coagulopathy, which is more common in breast-fed infants who did not receive vitamin K at birth.
- Ascites and pruritus are late complications indicating progression to cirrhosis.

Diagnosis
A diagnosis of EHBA involves the following investigations and findings:
- Serum conjugated bilirubin at presentation ranges from 40 to 200μmol/l.
- Serum aminotransferases are always abnormal: concentrations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are typically in the range of 80–200iU/l.
- Gamma-glutamyl tranpeptidase is usually elevated (×10 normal).
- Serum albumin is usually normal.
- Cholesterol may be elevated but triglycerides are normal.
- Prothrombin time is normal although 5–10% of cases present with vitamin K-responsive coagulopathy.
- Blood glucose is usually normal.
- Hepatic ultrasound, after a 4-h fast, may not demonstrate a gall bladder or only a contracted gall bladder (see Plate 2a, Atlas: p. 440); it rarely shows a dilated extrahepatic biliary tree, consistent with distal, ‘correctable’ atresia; dilated intrahepatic bile ducts are uncommonly found. Abnormal vascular anatomy consistent with the polysplenia syndrome may be seen.
- Hepatobiliary scanning, using TEBIDA, following phenobarbitone pretreatment (5mg/kg/day for 3–5 days) fails to demonstrate passage of the radiolabelled substance into the intestinal tract over a 24-h period (see Plate 3b, Atlas: p. 440). Although hepatobiliary scanning has high sensitivity, scanning may appear normal if performed very early in the disease process in late-pattern extrahepatic biliary atresia (Clarke et al. 1997; Gilmour et al. 1997). It may also fail to show bile drainage in severe idiopathic neonatal hepatitis or bile duct paucity syndromes.
- Percutaneous liver biopsy is essential and has high diagnostic specificity. Features of bile duct obstruction (bile ductular proliferation, bile plugs in small bile ducts, portal tract oedema) are usually obvious, along with variable fibrosis and some giant-cell transformation (see Plate 4b, Atlas: p. 441). The earlier the liver biopsy is performed, the more difficult it may be to interpret. When the hepatobiliary scan shows no drainage and the liver histology is ambiguous, close clinical surveillance is required to determine the evolution of disease.
- Uncertain cases require cholangiography, usually intraoperative, although endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and MR cholangiography are possible alternatives (Derks et al. 1994; Norton et al. 2002) (Chapter 18).

Management
Therapy consists of nutritional and family support. Palliative surgery, the Kasai portoenterostomy, should be carried out, if possible, to establish biliary drainage. See Chapter 18 for operative details and postoperative management.

Optimally, the diagnosis of EHBA must be established before the infant is 5–7 weeks old, so that the Kasai portoenterostomy can be performed by 6–8 weeks of age. The
operation should not be withheld from infants of 10–12 weeks of age because successful palliation can be achieved in one-third of patients. It is probably not indicated after 14 weeks of age, but every child should have a laparotomy to confirm the diagnosis and exclude unusual anatomy that might be amenable to surgical reconstruction. In one series there was no improvement in outcome associated with very early (before the infant is 40 days old) operation (Davenport et al. 1997). Contrary to initial impressions, the presence of the polysplenia syndrome does not in itself predict that the Kasai operation is likely to fail (Karrer et al. 1991; Vasquez et al. 1991).

**Complications and outcome**

The complications include recurrent cholangitis, malnutrition secondary to malabsorption, and progression to cirrhosis and portal hypertension. Patients with a well-functioning portoenterostomy appear to have some risk of recurrent cholangitis at any age despite prophylaxis. In one series, children with correctable atresia appeared unusually susceptible to septicaemia, presumably due to bacterial cholangitis.

Since damage to intrahepatic bile ducts is progressive irrespective of whether or not bile drainage is re-established, even children with a successful Kasai operation may be expected to develop biliary cirrhosis. Portal hypertension with variceal haemorrhage occurs in many long-term survivors, and endoscopic injection sclerotherapy or band ligation may be required.

In ~40% of children, a Kasai portoenterostomy fails to establish biliary drainage. These children remain cholestatic and develop the complications of fat malabsorption with subsequent protein-energy malnutrition, and should be referred immediately for liver transplantation (Chapter 20).

Five-year survival after Kasai portoenterostomy is 40–60% (Houwen et al. 1989). Patients in Japan (Nio et al. 1996) and elsewhere (Davenport et al. 1997) have survived 20 years or more after a portoenterostomy without liver transplantation: most are well and asymptomatic, with normal growth and psychosocial development, but have evidence of chronic liver disease. A few women have had babies after apparently uncomplicated pregnancies.

The majority of children will require liver transplantation at some stage, especially if the Kasai portoenterostomy has not been successful.

**Choledochal cyst**

Choledochal cyst refers to a group of congenital malformations of the biliary system. There are five major forms (Todani et al. 1977). Choledochal cysts may be identified in the fetus by prenatal sonography (Bancroft et al. 1994; Stringer et al. 1995; Burnweit et al. 1996) (see also Chapter 18).

**Clinical features and diagnosis**

The triad of symptoms associated with choledochal cyst consists of jaundice, abdominal mass and pain, but this is an unusual presentation in the neonatal period. There is female predominance (female: male is 5:1). Most affected infants have jaundice, abdominal mass or distension, and acholic stools (Stringer et al. 1995; Todani et al. 1995), and differentiation from biliary atresia or choledocholithiasis is important.

The diagnosis is made by identifying the choledochal cyst by ultrasound examination of the liver in a jaundiced infant (see Plate 2b, Atlas: p. 440). Cholangiography, either percutaneous or endoscopic, confirms the diagnosis (see Plate 3c, Atlas: p. 440). Hepatobiliary scanning has limited utility for diagnosis. Liver function tests are compatible with biliary obstruction.

**Treatment and outcome**

Treatment is aimed at removing the cyst as much as possible (Chapter 18). Excision of the cyst with hepaticoenterostomy offers the best outcome (Lispett et al. 1994; Miyano & Yamataka 1997; Yamataka et al. 1997). Complications are less with early surgical intervention. Surgery should be performed promptly in infants diagnosed prenatally who have conjugated hyperbilirubinaemia. If the infant remains free of jaundice, elective surgical resection of the choledochal cyst may be postponed until the infant is ~1 month old, but it should not be greatly delayed. Although ~50% of infants with prenatally identified bile duct dilatation have hepatic fibrosis, and a few have cirrhosis, most of these infants do well. A minority of infants may have correctable biliary atresia, and close follow-up is warranted.

**Caroli disease**

Caroli disease (also known as type 5 choledochal cyst) denotes congenital saccular dilatations of the intrahepatic bile ducts, without hepatic fibrosis or portal hypertension. It is often associated with autosomal recessive polycystic kidney disease. Caroli disease is rarely evident in infancy, but associated jaundice may be due to acute cholangitis. Some newborn infants with severe autosomal recessive polycystic kidney disease have extensive cystic bile duct changes, but renal insufficiency dominates the clinical picture. Ultrasound of the liver is often adequate for diagnosing Caroli disease; cholangiography is confirmatory. Outcome is related to the severity of renal disease (Chapter 9).
Congenital hepatic fibrosis, often associated with these same bile duct abnormalities (Caroli syndrome), may present in infancy with hepatomegaly and either autosomal recessive polycystic kidney disease or systemic hypertension. Jaundice and abnormal serum amino-transferases are uncommon (Alvarez et al. 1981). Outcome is variable and depends on the progression of hepatic and renal disease (Chapter 9).

**Cholelithiasis and choledocholithiasis**

Cholelithiasis was reported in four of 62 children with neonatal hepatitis syndrome (Lilly 1980). Two of these infants had structural abnormalities of the extrahepatic bile ducts (correctable biliary atresia in one and choledochal cyst in the other). Stones were of the bilirubinate type. The stones were removed without difficulty by standard methods once the diagnosis was secured. Subsequent reports indicate that cholelithiasis is not rare in infants (Debray et al. 1993; Bohle 1995; Rescorla 1997). Haemolysis, fasting and total parenteral nutrition may be contributing factors, in addition to anatomical abnormalities. The obstructing gallstone may not contain enough calcium to be seen on a plain abdominal X-ray, but ultrasound usually (though not consistently) identifies the gallstone or shows dilatation of the biliary tree due to obstruction.

Treatment may not be required if the stones are asymptomatic or pass into the duodenum without intervention (Monnerie & Soulard 1995). Prolonged obstruction or cholangitis require surgery (Ishitani et al. 1996; Wilcox et al. 1997). Alternatives to surgical treatment include ursodeoxycholic acid (20mg/kg/day); and percutaneous transhepatic cholangiogram with lavage of the bile ducts and ERCP combined with sphincterotomy in older infants (Wilkinson 1996). Adequate antibiotic treatment is required to avoid bacterial cholangitis (Chapter 18).

**Insipissated bile syndrome**

‘Insipissated bile syndrome’ is the term traditionally given to conjugated hyperbilirubinaemia complicating severe jaundice associated with haemolysis, usually due to rhesus factor or ABO incompatibility or erythrocyte membrane abnormalities. A multifactorial cause cannot be entirely excluded as these infants are often premature and present complex medical problems. Intrahepatic cholestasis is found on liver biopsy, and cholestasis may be due to direct hepatocellular toxicity of unconjugated bilirubin. The outlook is generally good, although early reports showed cirrhosis in some infants.

Obstruction of the intrahepatic biliary system with dried-out highly viscous bile has been reported in cystic fibrosis (Davies et al. 1986; Evans et al. 1991). Diagnosis is usually made by demonstrating dilated bile ducts on ultrasound or cholangiography. Treatment includes ursodeoxycholic acid (20mg/kg/day) or surgical or percutaneous lavage (Chapter 18).

**Spontaneous perforation of the common bile duct**

This condition usually presents as a severe acute illness resembling acute peritonitis with abdominal pain and distension, jaundice and fever, but may present as neonatal hepatitis syndrome with abdominal distension in addition to jaundice and acholic stools (Stringel & Mercer 1983). Biliary ascites is pathognomonic. Bacterial superinfection greatly increases the morbidity of this condition. Hepatobiliary scan may indicate the site of leakage and typically shows no drainage into the intestinal tract. In some cases perforation is associated with distal cholelithiasis. Surgical repair is usually curative (Lloyd & Mickel 1980) (Chapter 18).

**Neonatal sclerosing cholangitis**

Neonatal sclerosing cholangitis (NSC) was first reported in 1987 with a few subsequent reports (Amedee-Manesme et al. 1987; Sisto et al. 1987; Maggiore et al. 1988; Mulberg et al. 1992; Baker et al. 1993). The aetiology of this condition is unknown but may have a genetic basis (Baker et al. 1993). Currently the true nature of neonatal sclerosing cholangitis remains uncertain, although scepticism as to whether the entity exists seems unwarranted. In one case non-specific autoantibodies were detected (Bar Meir et al. 2000).

NSC is distinguished from childhood primary sclerosing cholangitis by the presentation in early infancy with conjugated hyperbilirubinaemia which then resolves. The clinical picture includes:

- Jaundice, which subsides within 3–6 months (Amedee-Manesme et al. 1987). Although some children with childhood primary sclerosing cholangitis present as infants (Wilschanski et al. 1995), they have not had early cholestatic jaundice.
- Recurrent hyperbilirubinaemia develops 1–2 years later or in mid childhood (8–10 years old).
- Development of hepatosplenomegaly, biliary cirrhosis and portal hypertension.

Laboratory investigations indicate obstructive biliary disease with elevated serum alkaline phosphatase and gamma-glutamyl transpeptidase. Endoscopic or percutaneous cholangiography demonstrates beaded irregularity of medium to large intrahepatic bile ducts in all patients and in extrahepatic ducts in 80%. Liver histology shows portal fibrosis with ductal proliferation developing into biliary cirrhosis.

Surgical treatment with Kasai portoenterostomy is not indicated and nutritional and supportive management is
required. The majority of children require liver transplantation at some stage.

**Hair-like bile duct syndrome**

This very rare disorder is known as extrahepatic biliary hypoplasia (Krant & Swenson 1973; Lilly 1976) or 'hair-like bile duct syndrome'. Infants present with conjugated hyperbilirubinaemia and features suggesting extrahepatic biliary atresia, but are found at laparotomy to have an intact but disproportionately small extrahepatic biliary tree. In some reports the extrahepatic bile duct was described as thickened. The clinical course is similar to that of neonatal sclerosing cholangitis: resolution of jaundice, development of biliary cirrhosis, progressive cholestasis with recurring jaundice, portal hypertension, and hepatic insufficiency. A Kasai portoenterostomy is not indicated for these children.

**Bile duct paucity syndromes**

**Alagille’s syndrome**

Alagille’s syndrome (syndromic duct paucity, Watson–Miller syndrome, arteriohepatic dysplasia) is a genetic disorder with autosomal dominant transmission but highly variable expression. Alagille’s syndrome was identified in the early 1970s (Watson & Miller 1973; but highly variable expression. Alagille’s syndrome (syndromic duct paucity, arteriohepatic dysplasia) is a genetic disorder with autosomal dominant transmission but highly variable expression. Alagille’s syndrome was identified in the early 1970s (Watson & Miller 1973; Alagille et al. 1975) because of the unusual association of congenital heart disease, usually peripheral pulmonary artery stenosis, with neonatal cholestasis. Alagille’s syndrome is thought to be rare, occurring in 1 in 100,000 live births. This is probably a gross underestimate, reflecting only those with disease severe enough to be recognized clinically.

**Genetic basis** The genetic basis for Alagille’s syndrome has been determined. Analysis of multiple kindreds indicates autosomal dominant inheritance, with essentially complete penetrance but highly variable expression. There is no evidence for anticipation or imprinting in the pattern of expression. The proportion of new mutations is uncertain, estimated at 15% to 50% (Dhorne-Pollet et al. 1994; Elmslie et al. 1995). The gene defect has been localized to the human JAG1 gene which is on the short arm of chromosome 20 (20p12) (Li et al. 1997; Oda et al. 1997). JAG1 is the human homologue of the rat gene Jagged 1. It codes for a ligand of Notch 1, which is one of four members in a family of transmembrane proteins with epidermal growth factor (EGF)-like motifs. Alagille’s syndrome is the first childhood disorder identified with a mutation in a ligand for a Notch protein. The expression of Notch 1 and its ligand includes many of the organs potentially abnormal in Alagille’s syndrome. JAG1 is expressed in adult heart and kidney; it is not expressed in adult liver, but it is in fetal liver (Li et al. 1997; Pollet et al. 1997). Haploinsufficiency of JAG1 causes Alagille’s syndrome. Dosage of Notch ligands is critical in development, and this may contribute to the clinical diversity of Alagille’s syndrome. Mutations result in truncated and thus inactive proteins; residual gene expression cannot compensate, leading to the phenomenon of haploinsufficiency (Spinner et al. 2001). Many mutations are sporadic. No clear relationship between genotype and phenotype has been found, although the Delta/Serrate/Lag-2 (DSL) domain in the JAG1 protein may influence the severity of liver disease (Crosnier et al. 1999; Colliton et al. 2001; Crosnier et al. 2001; Yuan et al. 2001).

**Clinical features** Alagille’s syndrome is fairly benign in the majority of children. The majority of patients with clinically important Alagille’s syndrome have conjugated hyperbilirubinaemia in the neonatal period (Deleuze et al. 1995; Emerick et al. 1999). The main clinical features are as follows (see Plate 6, Atlas: p. 442):

- Cholestasis, which may be sufficiently severe to produce acholic stools and dark urine.
- Characteristic facies, which consists of a broad forehead, deep-set eyes, mild hypertelorism, straight nose and small pointed chin. The facies may not be evident in the first months of life and the classic childhood appearance differs from the adult form.
- Skeletal abnormalities, which include ‘butterfly’ vertebrae due to failure of fusion on the anterior arch of the vertebral body, are commonly found in the thoracic spine (Sanderson et al. 2002). There may also be a decrease in the interpedicular distance in the lumbar spine, spina bifida occulta, short distal phalanges and fifth finger clinodactyly, and short ulna.
- Eye findings may be very diverse (Hingorani et al. 1999). Posterior embryotoxon, an abnormal prominence of Schwalbe’s line (junction of Descemet’s membrane with the uvea at the angle of the anterior chamber), is most common and requires slit-light examination for detection. It is not pathognomonic since it occurs in 8–15% of normal persons. Optic disc drusen, which are calcific deposits in the extracellular space of the optic nerve head, are common in Alagille’s syndrome and are not found in other cholestatic conditions. They are detected by ocular ultrasound examination (Nischal et al. 1997). Abnormal retinal pigmentation without evidence of functional retinal degeneration may occur. Strabismus, ectopic pupil and hypotrophic optic discs with or without abnormal retinal vessels have also been reported.
- Cardiac disease includes peripheral pulmonary artery stenosis, severe hypoplasia of the pulmonary artery branches (Silberbach et al. 1991; McElhinney et al. 2002), Fallot’s tetralogy, pulmonary valve stenosis, aortic stenosis, ventricular septal defect, atrial septal defect and anomalous pulmonary venous return. The severity of
Section 3: Neonatal Liver Disease

Cardiac disease varies between patients and careful assessment is required, particularly if liver transplantation is contemplated.

- Chronic cholestasis with pruritus, fat malabsorption, occasionally exacerbated by exocrine pancreatic insufficiency.
- Failure to thrive in association with intrauterine retardation.
- Severe malnutrition present in ~50% of patients may be part of the syndrome or secondary to fat malabsorption or gastroesophageal reflux.

**Minor features** Apart from the main aspects of Alagille’s syndrome outlined above, a number of other features may be present. These are:

- Renal disease, which includes defects in urinary concentrating function, nephrolithiasis, or structural abnormalities such as small kidneys or congenital single kidney, or renal cystic disease. Histological examination may reveal a membranous nephropathy or lipid accumulation in the kidney (mesangiolipidosis).
- Delayed puberty or hypogonadism.
- Abnormal cry or voice.
- Mental retardation, learning difficulties or antisocial behaviour.
- Vascular anomalies, including decreased intrahepatic portal vein radicals, coarctation of the aorta and other arterial abnormalities, and Moya Moya disease (Connor et al. 2002).
- Neurological abnormalities, such as peripheral neuropathy, may be related to vitamin E deficiency from severe chronic cholestasis.
- Hypothyroidism and pancreatic insufficiency.
- Recurrent otitis media (Quiros-Tejeira et al. 1999).
- Recurrent chest infections, perhaps secondary to gastrointestinal reflux and aspiration pneumonia.
- Xanthomata secondary to hypercholesterolaemia.

**Diagnosis** The diagnosis of Alagille’s syndrome is based on the characteristic clinical features, but laboratory investigations may indicate:

- Conjugated hyperbilirubinaemia in neonates, which may improve with age.
- Aspartate aminotransferase and alkaline phosphatase concentrations are usually elevated ($\times 10$ normal).
- Gamma-glutamyl transpeptidase concentration elevated 3–20 times normal.
- Serum cholesterol and triglyceride may be raised to values three times the upper limit of normal.
- Serum albumin and prothrombin time are normal except in decompensated disease.
- Abdominal ultrasound may be normal or show a small contracted gall bladder.
- Radiosotope scanning may show delayed or no excretion if intrahepatic cholestasis is severe.

- Liver biopsy classically shows reduced numbers of small (i.e. portal) bile ducts and in neonates there may be giant-cell transformation and cholestasis. In some infants (up to 20%) ongoing damage to small bile ducts may be found, or bile ductular proliferation suggestive of extrahepatic bile duct obstruction. The diagnostic histological findings may become obvious only with age (Deutsch et al. 2001). Alternatively, the number of portal tracts may be reduced. Periportal or centrilobular fibrosis is usually absent in infancy but progressive disease with biliary cirrhosis develops in 15–20% of patients. Differentiation from extrahepatic biliary atresia may be difficult on histological grounds alone, particularly if there is significant bile ductular proliferation (see Plate 6, Atlas: p. 442).

**Management** It is essential to exclude extrahepatic biliary atresia, which may be difficult in infants with severe cholestasis, acholic stools and non-excreting hepatobiliary scanning. Endoscopic or operative cholangiography may identify a patent extrahepatic biliary tree. Portoenterostomy is not indicated as this rarely improves bile flow and may increase portal fibrosis because of recurrent cholangitis.

Specific management of Alagille’s syndrome is dependent on the distribution and severity of associated disease. Severe cholestasis requires supportive management (see p. 60–3). Nutritional support with feeding via a gastric tube may be highly effective (Duche et al. 1999). Hypercholesterolaemia usually responds to a modified fat diet; gastroesophageal reflux requires standard medical or surgical management. Cardiac anomalies may require corrective surgery, with balloon dilatation or surgical correction of pulmonary valve or pulmonary artery stenosis. Children with Alagille’s syndrome are prone to bleeding episodes without necessarily having definite abnormalities of coagulation (Berard & Triolo 2000; Lykavieris et al. 2003). Special caution must be exercised with respect to head trauma. Renal disease requires specific management as indicated.

**Outcome** The outcome of Alagille’s syndrome depends on the hepatic and extrahepatic disease. The majority of children have a benign course. Most estimates put overall mortality at 20–30%, due to cardiac disease, intercurrent infection or progressive liver disease (Hoffenberg et al. 1995; Emerick et al. 1999; Lykavieris et al. 2001). Early reports of outcome minimize the role for liver transplantation. Liver transplantation should be reserved for patients with hepatic failure, intolerable pruritus unresponsive to medical treatment, and severe growth failure. Liver transplantation can be complicated by associated heart disease, renal impairment or vascular anomalies. Catch-up growth after transplantation often occurs (Cardona et al. 1995; Holt et al. 1997; Quiros-Tejeira et al. 2000) (Chapter 20).
Non-syndromic duct paucity

In a full-term neonate with small bile duct paucity in whom Alagille’s syndrome has been excluded, various disorders may cause portal ductopenia (small duct paucity), known as ‘non-syndromic duct paucity’. These disorders (Table 4.2) fall into the broad categories of infection, genetic (with chromosomal abnormalities), and metabolic diseases (Kahn et al. 1986). When idiopathic neonatal hepatitis is clinically severe, bile duct paucity may also be present.

Among congenital infections cytomegalovirus is the most important cause (Finegold & Carpenter 1982; Dimmick 1993) and cytomegaloviral inclusions may be found in bile duct epithelial cells. Chromosomal abnormalities associated with duct paucity include trisomy 18 and 21. Metabolic disorders associated with duct paucity in the infant are diverse and include α₁-antitrypsin deficiency (usually indicates more severe liver disease and a poor prognosis), Byler syndrome, and rarely cystic fibrosis or Zellweger syndrome. Duct paucity may also develop in late stages of extrahepatic biliary atresia following a Kasai portoenterostomy or in primary sclerosing cholangitis.

Small bile duct paucity may develop in infants as a result of graft vs. host disease (Shulman et al. 1988) or other immunological injury complicating allogeneic bone marrow transplant or a stem-cell transplant in the perinatal period. Occasionally this develops without features of graft vs. host disease (Wulffraat et al. 1997).

Where no specific associated condition can be found, then isolated non-syndromic bile duct paucity can be diagnosed. These children are supposed to have a less favourable outlook than children with Alagille’s syndrome, with persistent severe cholestasis and progressive liver damage. The relationship of childhood non-syndromic duct paucity to idiopathic adult ductopenia, which has recently been described and may be familial, remains uncertain (Ludwig et al. 1988; Bruguera et al. 1992).

Metabolic liver disease

α₁-Antitrypsin deficiency

This autosomal recessive condition is the most common inherited cause of neonatal hepatitis syndrome. Deficiency occurs in 1 in 1600–2000 live births in North American and European populations, but it is less common in people of other ethnic backgrounds. The protease inhibitor, α₁-antitrypsin, is a glycoprotein that is mainly produced in the liver. Only a small proportion of individuals with α₁-antitrypsin deficiency ever develop liver disease, but it is the main cause of emphysema in early adulthood.

Aetiology and genetics

A member of the serpin superfamily, α₁-antitrypsin binds and inactivates leucocyte elastase. More than 75 variants have been reported. The deficiency status is caused by a mutation in the gene at the PI locus on chromosome 14. There is impaired secretion of the mutant gene product, which can be demonstrated in the hepatocyte (periodic acid–Schiff (PAS)-positive diastase-resistant granules). The most common deficiency variant is ‘Z’, a slow-moving protein on electrophoresis, with a point mutation resulting in a single amino acid substitution (lysine replacing glutamic acid at position 342). Some variants such as M_Malton and M_Duarte show only subtle differences from the normal ‘M’ electrophoretically and may be difficult to recognize.

Structural variants of α₁-antitrypsin are classified according to the protease inhibitor (PI phenotype) system. More than 75 variants have been reported, most of which are not associated with clinical disease. Liver disease is associated with PI ZZ in the majority of cases. It may occur with PISZ at a relatively young age and with PI FZ and PI MZ later in adulthood (Gourley et al. 1989; Primhak & Tanner 2001).

The pathogenesis of liver disease is unknown, although studies in transgenic mice indicate that liver injury is caused by the intracellular accumulation of the abnormal α₁-antitrypsin gene product (Carlson et al. 1989). The Z mutation causes abnormal folding of the α₁-antitrypsin molecule so that it is caught in the endoplasmic reticulum (Lomas et al. 1992; Perlmutter 1996). Since
not everyone with PI ZZ α1-antitrypsin develops liver disease, additional factors such as increased production and decreased removal of abnormal α1-antitrypsin within hepatocytes might accelerate liver damage. One possible mechanism involves the serpin–enzyme complex (SEC), which is activated by α1-antitrypsin–elastase complexes and by inflammatory mediators such as substance P (Perlmutter 1994). When activated, it increases α1-antitrypsin synthesis. Since α1-antitrypsin is an acute-phase reactant, any inflammatory process might increase its production. Defects in hepatocellular proteasome action or other mechanisms for removing abnormal proteins from the endoplasmic reticulum might account for excessive accumulation of abnormal α1-antitrypsin in hepatocytes. New treatments are envisioned based on these mechanisms, including administration of chemical chaperones (Burrows et al. 2000; Perlmutter 2002).

Clinical features
Neonates with α1-antitrypsin deficiency who develop liver disease present with
• Conjugated hyperbilirubinaemia (see Plate1, Atlas: p. 440).
• Intrauterine growth retardation.
• Severe cholestasis with totally acholic stools; differentiation from extrahepatic biliary atresia may be difficult.
• Hepatomegaly is usual at presentation, but splenomegaly is unusual unless significant hepatic fibrosis develops.

Approximately 2% of infants present with a vitamin K-responsive coagulopathy, which is more likely in those infants not given prophylactic vitamin K at birth or who are breast fed. The coagulopathy may be obvious, with bruising and bleeding from the umbilicus, or the initial presentation may be an intraventricular haemorrhage. There is a rapid response to intravenous vitamin K (Hope et al. 1982).

Diagnosis
Biochemical evaluation demonstrates a mixed hepatocellular/obstructive pattern with raised aminotransferases, alkaline phosphatase and gamma-glutamyl transpeptidase.

Radiological investigation may demonstrate severe intrahepatic cholestasis with a contracted gall bladder on abdominal ultrasound and delayed or absent excretion of radioisotope on hepatobiliary scanning.

In homozygotes the diagnosis is confirmed by demonstrating low serum α1-antitrypsin levels (normal >1.0 g/l) and determining the phenotype (PI) by isoelectric focusing. Confusion may occasionally arise if α1-antitrypsin levels are increased secondary to hepatic inflammation because it is an acute-phase reactant, but in practice this is rarely a problem with homozygotes.

Liver biopsy typically demonstrates a giant-cell hepatitis in which the characteristic PAS-positive diastase-resistant (PASD) granules are detected in the hepatocytes, often noted as early as 6–8 weeks (see Plate6, Atlas: p. 441). Occasionally PASD-positive inclusions are found in individuals without the Z allele because of an M variant associated with hepatocellular α1-antitrypsin retention (Roberts et al. 1984).

Management
Management consists of nutritional support, fat-soluble vitamin supplementation, treatment of pruritus and cholestasis as required (see p. 60–3). Patients and parents should not be permitted to smoke, and phenotype inhibitor zz (PIZZ) individuals should be protected from secondary smoke. It is usual to offer family screening for families wishing to have further children. Parents are obliged heterozygotes, thus there is a 25% chance of each subsequent fetus being affected. Antenatal diagnosis by chorionic villus sampling is now available using synthetic oligonucleotide probes specific for the M and Z gene or by restriction fragment length polymorphism (Povey 1990).

Prognosis
The prognosis is varied. The long-term outlook for many infants with α1-antitrypsin deficiency is good, although a certain proportion of infants with early jaundice develop chronic liver disease (Moroz et al. 1976; Odievre et al. 1976; Ghishan & Greene 1988; Volpert et al. 2000). The outcome falls into four general categories (Psacharopoulos et al. 1983). Approximately half do well: of these infants, half are entirely normal and the other half have mildly abnormal serum aminotransferases but no progression of liver disease. The other half do poorly. Of the infants with poor prognosis, half develop persisting cholestasis with progressive hepatic decompensation and may die or require live transplantation in the first year of life. In the other half, jaundice resolves but serum aminotransferases are abnormal; the liver and spleen remain enlarged. These infants develop cirrhosis with eventual hepatic insufficiency. The small group of children with α1-antitrypsin deficiency who present later in infancy or in childhood with hepatomegaly, without neonatal jaundice, usually have early cirrhosis and a poor prognosis.

Early prognostication of individual infants with α1-antitrypsin deficiency is difficult. Standard indicators of hepatic decompensation, such as persistent or recurring jaundice, hepatosplenomegaly, prolonged prothrombin
time (PT), and elevated serum aminotransferases, are only helpful later in the course of disease (Nebbia et al. 1983). A retrospective analysis of 85 children with neonatal hepatitis and α1-antitrypsin deficiency showed that very elevated serum alanine aminotransferase, prolonged PT, and very low serum α1-antitrypsin concentration at presentation were associated with poor outcome; girls generally had a worse outcome than boys (Ibarguen et al. 1990). In another study of children with neonatal hepatitis, persisting elevation of serum aminotransferases and serum GGT through 6–12 months of age, or presence of bile ductular proliferation, bridging fibrosis or cirrhosis on the initial liver biopsy presaged rapidly progressive liver disease (Francavilla et al. 2000). Infants in whom jaundice or hepatomegaly resolves before the age of 6 months are likely to have a good outcome, but those with prolonged jaundice, cirrhosis or bile duct paucity pursue a downhill course. Infants whose liver disease appears to resolve should still be monitored for development of splenomegaly, as this may herald advancing hepatic fibrosis. Children with α1-antitrypsin-associated cirrhosis may remain stable for some time but may decompensate precipitously. Evaluation for liver transplantation should be considered early for these children. They tolerate liver transplantation well, although attention to potential kidney disease associated with α1-antitrypsin deficiency is required through the early postoperative period (Prachalias et al. 2000).

Cystic fibrosis

Abnormalities of liver function tests or hepatic pathology are found in one-third of infants with cystic fibrosis (Chapter 11). The spectrum of hepatic pathology includes: giant-cell hepatitis; extrahepatic bile duct obstruction by inspissated bile; massive hepatic steatosis usually without conjugated hyperbilirubinaemia, and paucity of small (portal tract) bile ducts. The clinical presentation is with jaundice, hepatomegaly, failure to thrive and extrahepatic biliary tract obstruction similar to extrahepatic biliary atresia due to plugging of the common bile duct by abnormal bile (Davies et al. 1986). Early studies suggested that infants with severe liver disease had meconium ileus, which is supported by more recent data obtained at autopsy in patients similar with respect to pulmonary function, nutritional status and Schwachman score (Maurage et al. 1989). Children with cirrhosis had a statistically significant relationship between incidence of mucous plugs in liver tissue histologically and meconium ileus in infancy or distal intestinal obstruction syndrome later in life. Occurrence of neonatal hepatitis syndrome in itself does not necessarily predict early development of cirrhosis.

Another rare lesion in cystic fibrosis in infancy is paucity of intrahepatic bile ducts (‘non-syndromic duct paucity’) (Furuya et al. 1991), raising the possibility that there is an inherent abnormality in the small bile ducts in cystic fibrosis.

Severe hepatic steatosis has been reported in infants with cystic fibrosis who are typically not jaundiced. In one case, carnitine deficiency was found, and the steatosis improved with carnitine supplementation (Treem & Stanley 1989).

Primary disorders of bile acid synthesis

Inherited defects in the enzymes involved in bile acid synthesis lead to neonatal hepatitis syndrome or to chronic cholestasis later in childhood. A number of new entities have been identified (Table 4.3), largely facilitated by fast atom bombardment-mass spectroscopy (FAB-MS) of urine to identify unusual intermediates arising from

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Cellular location</th>
<th>Features</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>3β-Hydroxy-5α-C27-steroid dehydrogenase/isomerase</td>
<td>Endoplasmic reticulum (‘microsomal’)</td>
<td>Severe neonatal hepatitis; normal serum GGT; low serum total bile acid concentrations; no pruritus</td>
<td>Cholic acid ± UDCA initially</td>
</tr>
<tr>
<td>Δ4-3-Oxosteroid 5β-reductase</td>
<td>Cytoplasm (‘cytosolic’)</td>
<td>Severe cholestasis, coagulopathy; elevated serum total bile acid concentrations</td>
<td>Cholic acid</td>
</tr>
<tr>
<td>24,25-Dihydroxy-cholanoic cleavage enzyme</td>
<td>Endoplasmic reticulum</td>
<td>Severe giant-cell hepatitis; normal serum GGT; elevated serum cholesterol; low serum total bile acid concentrations</td>
<td>Cholic acid</td>
</tr>
<tr>
<td>C27-Hydroxylase</td>
<td>Mitochondria</td>
<td>Cerebrotendinous xanthomatosis; No liver disease</td>
<td>–</td>
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GGT, Gamma-glutamyl transpeptidase; UDCA, ursodeoxycholic acid.
deranged bile acid synthesis. Although rare, these diseases can be treated by supplementation of critical bile acids if the diagnosis is made early in the course of disease.

**Aetiology**

Bile acid synthesis involves the conversion of cholesterol to the primary bile acids, cholic and chenodeoxycholic acid. This takes place in hepatocytes, and enzymes in the process are variously located in the endoplasmic reticulum (‘microsomal’), the cytoplasm (‘cytosolic’), mitochondria or peroxisomes. The initial, and rate-limiting, step is a change in the steroid nucleus: hydroxylation of cholesterol at the C7 position by the microsomal enzyme \( \Delta^7 \)-hydroxylase. Further modifications can then be categorized as involving the steroid nucleus or the side chain. Side-chain abnormalities are found mainly with mitochondrial or peroxisomal disorders. Cerebrotendinous xanthomatosis is due to deficiency of the mitochondrial enzyme \( \Delta^7 \)-hydroxylase, leading to abnormal side-chain modifications; neonatal cholestasis and jaundice do not occur in this disease. Autosomal recessive mutations in two enzymes associated with steroid nucleus modifications at early stages of bile acid synthesis have been associated with severe neonatal liver disease. Two other inborn errors of bile acid metabolism have been described in single patients presenting with neonatal liver disease. An infant with NHS progressing rapidly to biliary cirrhosis with a low-normal serum GGT was found to have \( \Delta^7 \)-hydroxylase deficiency; the liver disease did not improve with cholic acid treatment and required liver transplantation (Setchell et al. 1998). Rather mild NHS with profound fat-soluble vitamin deficiencies was found with deficiency of peroxisomal 2-methylacyl-CoA racemase (Setchell et al. 2003). The bile acid profile was similar to that found with Zellweger syndrome (alligator bile), and treatment with cholic acid was effective. NHS with a defect in bile acid conjugation (ligase deficiency) has also been observed (Bove 2000).

**3β-Hydroxy-\( \Delta^7 \)-C27-steroid dehydrogenase/isomerase deficiency** This microsomal enzyme is the second in the bile acid synthetic pathway. Infants lacking it present with jaundice and acholic stools in the first few days of life (Buchmann et al. 1990); neonatal hepatitis may be histologically severe (Clayton et al. 1987) or the cholestatic disease may be somewhat more indolent, resembling progressive intrahepatic cholestasis and therefore presenting later in childhood (Horslen et al. 1992; Jacquemin et al. 1994b). One patient was reported with rickets and fat-soluble vitamin deficiencies in the absence of jaundice (Akobeng et al. 1999). Typically affecting infants and children, this deficiency produces excessive amounts of \( \Delta^7 \)-bile acids with a 3β-hydroxy-\( \Delta^7 \) structure. Biochemically they have normal serum GGT and low serum total bile acid concentrations, and clinically have no pruritus. Treatment with chenodeoxycholic acid (Ichimiya et al. 1990; Horslen et al. 1992) or ursodeoxycholic acid (Jacquemin et al. 1994b) has been reported, but the preferred treatment strategy is cholic acid with or without ursodeoxycholic acid. This may improve bile flow and prevent cirrhosis and hepatic decompensation.

**\( \Delta^4 \)-3-Oxosteroid 5β-reductase deficiency** \( \Delta^4 \)-3-Oxosteroid 5β-reductase is an important cytosolic enzyme in the bile acid synthetic pathway. The original description of this disorder included two infants with early severe cholestasis and coagulopathy (Setchell et al. 1988); subsequent reports have included infants with a clinical presentation resembling perinatal haemochromatosis (Shneider et al. 1994; Siafakas et al. 1997). In this disorder \( \Delta^4 \)-3-oxo bile acids are overproduced and may be hepatotoxic. Serum GGT is usually, but not invariably, normal. Liver biopsy may reveal abnormal bile canaliculi in a focal, ‘mosaic’ pattern. Treatment with cholic acid (with or without ursodeoxycholic acid) appears beneficial in patients without iron overload (Daugherty et al. 1993).

There is a diagnostic subtlety in identifying patients with this genetic disorder because hepatocellular levels of \( \Delta^4 \)-3-oxosteroid 5β-reductase drop with progressive severe liver disease (Clayton 1994). Thus for diagnostic reasons, as well as therapeutic ones, diagnostic testing should be performed as early as possible.

**24,25-Dihydroxycholecalciferol cleavage enzyme deficiency** Infants have been described with a defect in the 25-hydroxylation pathway (Clayton et al. 1995) and excess production of a bile alcohol with an abnormal, eight-carbon side chain. Jaundice and hepatomegaly were noted in the first week of life; serum GGT was normal but alkaline phosphatase and cholesterol were elevated; biliary and serum bile acid concentrations were low; hepatobiliary scanning showed no drainage; pruritus later developed. Liver biopsy revealed severe giant-cell hepatitis with cholestasis. Treatment with chenodeoxycholic acid and ursodeoxycholic acid appeared beneficial.

**Treatment**

Treatment consists of nutritional support, therapy for cholestasis and with specific bile salts aimed at compensating for a defective synthetic pathway.

**Byler disease (progressive familial intrahepatic cholestasis)**

Byler disease was originally described as a disorder of intrahepatic cholestasis in an American Amish kindred named ‘Byler’: clinical features included pruritus, steatorrhoea, poor growth and inexorable progression to
cirrhosis in early childhood (Clayton et al. 1969). Non-Amish children were later reported with similar clinical characteristics (Tazawa et al. 1985; Maggiore et al. 1987; Winkhofer-Roob et al. 1992; Whittington et al. 1994; Bourke et al. 1996). A prominent finding was a low or normal serum GGT, which was discordant with the severe cholestasis. Low or normal serum cholesterol is also characteristic and may identify patients reported prior to 1969 (Gray & Saunders 1966). Nomenclature is problematic, especially as Byler disease is itself clinically somewhat variable and is probably only one of several diseases with progressive intrahepatic cholestasis that are clinically similar but mechanistically different. The term ‘progressive familial intrahepatic cholestasis’ (PFIC) has the advantage of being more general, but it is not strictly applicable until there are at least two affected children in a family.

Genetics
Recent genetic studies, mainly using a shared segment strategy for identifying a common mutation, have identified a group of diseases with progressive intrahepatic cholestasis in childhood with low GGT (PFIC-1 and PFIC-2) and one variant with high GGT (PFIC-3). Other high-GGT disorders exist and require further definition genetically (Chen et al. 2001). Most patients with Byler disease have a mutation on chromosome 18q21-22 in the FIC1 gene (Bull et al. 1998). FIC1 encodes a P-type ATPase (ATP8B1) involved in aminophospholipid transport between membrane leaflets. FIC1 is expressed in numerous tissues including the gastrointestinal tract, pancreas and lung. Mutations in FIC1 are also responsible for Greenland Eskimo cholestasis (Ornvold et al. 1989; Klomp et al. 2000). Mutations in FIC1 are often the cause of benign recurrent intrahepatic cholestasis, a disease mainly of adults but sometimes symptomatic in childhood (Carleton et al. 1995; Bull et al. 1997; van Ooteghem et al. 2002).

Clinical features
Byler disease (PFIC-1) presents with conjugated hyperbilirubinaemia in the first 3–6 months of life. The degree of jaundice may vary. Hepatomegaly persists, although progression to cirrhosis is variable. Fat-soluble vitamin deficiencies, including rickets, may be severe. Pruritus is problematic and refractory to most treatment. Growth retardation may not be evident initially. Children with Byler disease have persistent diarrhoea with fat malabsorption and protein loss, bouts of pancreatitis, and poor growth leading to short stature. Sensorineural hearing loss may occur. Cirrhosis usually develops in early childhood and liver transplantation is required. After liver transplant, pancreatitis may still occur, and the diarrhoea may get worse.

Chapter 4: The Jaundiced Baby

Diagnosis
The serum GGT is repeatedly normal, as is serum cholesterol. The total serum bile acid concentration is elevated. However, the concentration of chenodeoxycholic acid in bile from these patients is extremely low (Tazawa et al. 1985; Jacquemin et al. 1994a). Sweat chloride may be elevated (Lloyd-Still 1981). Liver biopsy shows little inflammation but has canalicular bile plugs of distinctive colour on routine histochemical staining, with a characteristic granular appearance on electron microscopy. Small duct paucity may be found. The main differential diagnosis is from an inborn error of bile salt metabolism (see above).

PFIC-2 Some children with intrahepatic cholestasis and normal serum GGT do not have this 18q mutation. Instead, they have a mutation in a gene found on chromosome 2q24 (Strautnieks et al. 1997). These children differ from those with Byler disease in some respects: they do not have pancreatitis or diarrhoea. There is evidence of inflammation with giant-cell hepatitis, fibrosis and ductular proliferation on liver biopsy. The PFIC-2 gene has now been identified as encoding a bile canalicular transporter, the human bile salt export pump (BSEP, ABCB11), an ATP-binding cassette transporter formerly known as sister of P-glycoprotein (SPGP) (Strautnieks et al. 1998; Jansen et al. 1999). A variety of functional disturbances in bile salt excretion due to different mutations leads to clinical disease (Wang et al. 2002).

PFIC-3 A further group of children has been identified with progressive intrahepatic cholestasis but elevated serum GGT (Jacquemin et al. 1997). Onset may occur later in childhood, but presentation in infancy is common. In children with PFIC-3 jaundice may be less prominent than pruritus; despite the clinical appearance of biliary tract obstruction, imaging reveals a normal biliary tree. Portal fibrosis with or without bile ductular proliferation is prominent on liver biopsy. Mutations in the P-glycoprotein MDR-3 gene (ABCB4) have been identified, and mutations resulting in a truncated protein appear to be associated with more severe disease than missense mutations (Jacquemin et al. 2001). The affected protein is the bile canalicular membrane translocator of phospholipids, and PFIC-3 patients have bile phospholipid concentrations which are <15% of normal. Most children with severe disease require liver transplantation.

Treatment and outcome
Treatment is as for other cholestatic disorders (see below). Treatment with ursodeoxycholic acid appears to be beneficial in many, if not most, patients with any PFIC disorder. Some children may have relief of pruritus following biliary diversion (Melter et al. 2000) provided it is per-
formed prior to development of significant hepatic fibrosis. Liver transplantation is indicated for those children with decompensated disease.

**Aagenaes syndrome**

Aagenaes syndrome is a very rare disorder with cholestasis and lower limb oedema. It was initially reported in a Norwegian kindred but has also been reported in children of Norwegian descent and in other ethnic groups (Aagenaes et al. 1968; Sharp & Krivit 1971; Vajro et al. 1984; Morris et al. 1997; Aagenaes 1998). The principal features are neonatal hepatitis syndrome evolving to a chronic cholestatic condition and a lymphatic disorder perhaps due to abnormal development of hepatic lymphatics. The lymphatic abnormalities may present clinically later than the jaundice and include localized lower limb lymphoedema like Milroy disease, a more subtle disorder with generalized oedema despite normal serum albumin, or haemangioma(s) and/or lymphangioma(s).

The neonatal hepatitis evolves into a cholestatic problem with pruritus and fat-soluble vitamin deficiencies which require treatment. While the initial cholestatic resolves in early childhood, recurrent bouts of cholestasis, similar to benign recurrent cholestasis, and lymphoedema become a prominent problem in adulthood. Chronic liver disease with portal hypertension has not been reported. Abnormal development of hepatic lymphatics has been postulated as part of the pathogenesis of this condition. The genetic basis of this familial cholestatic disorder remains unknown, but the genetic locus has been mapped to chromosome 15q (Bull et al. 2000).

**North American Indian familial cirrhosis**

Chronic cholestatic liver disease was described in 14 North American Indians living in north-western Quebec, Canada. Familial clustering of disease incidence was prominent and consanguinity a possible factor. Nine of the 14 presented with neonatal conjugated hyperbilirubinaemia, and in these infants jaundice disappeared during the first year of life. Chronic cholestatic disease was similar in all 14: hepatosplenomegaly, pruritus, facial telangiectasia, and eventually portal hypertension. Serum aminotransferases, alkaline phosphatase and bile acids were elevated, but serum cholesterol was normal in most patients. Serum gamma-glutamyl transpeptidase data were not reported. Electron microscopy revealed widening of the pericanalicular microfilament cuff, not unlike changes due to phalloidin intoxication (Weber et al. 1981). A subsequent report indicated most had moderate elevation of serum cholesterol and elevated GGT (Drouin et al. 2000). Liver disease typically progresses to biliary cirrhosis in this disorder, although liver transplantation is often not required in the first decade of life. The gene mutated in this disorder has recently been identified: it is FLJ14728, conventionally called cirhin, on chromosome 16q22, and it encodes a protein of unknown function which localizes to mitochondria (Chagnon et al. 2002). It may be appropriate to classify this disorder as one of the PFIC disorders (e.g. PFIC-4).

A second apparently different cholestatic disease has been described in North American Indians from various regions of Ontario, Canada (Phillips et al. 1996). Most belong to a single extended kindred and presented as infants with conjugated hyperbilirubinaemia and hepatomegaly; in some jaundice was transient and chronic cholestatic disease developed later in childhood. Two unrelated North American Indian children appeared to have extrahepatic biliary atresia clinically and at laparotomy. Increased concentrations of zinc were found in hepatic parenchyma obtained at the time of liver transplantation in all patients. The pathogenesis of this zinc-overload cholestatic liver disease remains to be determined.

**Zellweger syndrome**

Zellweger syndrome is the prototype of the peroxisomal biogenesis disorders, characterized by multiple abnormalities of peroxisome function. The molecular and cell biology of these disorders is complex, involving multiple PEX genes which encode peroxins, proteins required for peroxisome assembly. Zellweger syndrome is most often associated with mutations in PEX1 and PEX6 (Moser et al. 2002). Bile acid synthesis is abnormal because of selective or generalized deficiency of the peroxisomal enzymes involved in side-chain modification. In Zellweger syndrome, bile acids accumulate: principally, trihydroxycoprostanic acid (THCA) and dihydroxycoprostanic acid (DHCA). These would ordinarily undergo side-chain modification in the peroxisome to chenodeoxycholic acid and cholic acid. It is a rare disorder with an incidence of 1 in 100000. Sexes are affected equally.

**Clinical features and diagnosis**

Multiple systems besides the liver are affected: features include profound hypotonia, facial dysmorphism with a high forehead and large fontanelles, developmental delay, seizures, bony abnormalities such as epiphysial calcifications, and cystic malformations in the brain and kidneys (see Plate 7, Atlas: p. 442). Failure to thrive and feeding difficulties are common. In the first 3 months of life, hepatic involvement may not be prominent, although some babies have persistent conjugated hyperbilirubinaemia (Naidu et al. 1988). Fifty percent of infants are not jaundiced but have hepatosplenomegaly with evidence of poor hepatic synthetic function.
The diagnosis is confirmed by demonstrating abnor-
mal bile salt metabolites using FAB-MS or the detection of
very long-chain fatty acids in serum. Hepatic histology
may be normal, although there may be excess iron deposi-
tion. Hepatic fibrosis is typical. Paucity of the small
(portal) bile ducts may be found. Electron microscopic
studies of liver reveal the absence of peroxisomes in hepa-
tocytes. Mitochondria may appear abnormal. These
infants may develop cirrhosis, although extrahepatic
features of the syndrome typically overshadow the
hepatic disease.

Treatment and outcome
Treatment is supportive, as death is inevitable. Liver
transplantation is contraindicated because of the multi-
system disease. Attempts to produce peroxisomes with
hypolipaemic drugs were not successful (Lazarow et al.
1985). Primary bolus therapy with cholic and chen-
odeoxycholic acid may produce some initial improve-
ment but does not prolong life (Setchell et al. 1992).

Niemann–Pick disease, type A or type C
There are two types of Niemann–Pick disease (A and C)
associated with neonatal liver disease. Type B is defined
as a juvenile-adult form of sphingomyelinase deficiency
without neurological features (see also Chapter 12).

Niemann–Pick type A
This is due to lysosomal sphingomyelinase deficiency.
Clinical features include hepatosplenomegaly, failure to
thrive and progressive neurological deterioration. Jaun-
dice is unusual. Fetal ascites has been reported (Meizner
et al. 1990).

Niemann–Pick type C
Niemann–Pick type C is secondary to a disorder of cho-
sterol esterification (Pentchev et al. 1985). There are
two subtypes characterized by different mutations
(Millat et al. 1999; Naureckiene et al. 2000). Correlation of
genotype with phenotype is complex (Millat et al.
2001a,b). The gene product of NPC1 appears to mediate
trafficking of sterols and various other substrates out of
lysosomes to other subcellular compartments (Neufeld
et al. 1999). Numerous animal models exist for type C Nie-
mann–Pick disease. Recent studies in a mutant mouse
strain suggest that in addition to abnormal cholesterol
homeostasis, peroxisomal function is impaired. This ap-
pears to develop at an early stage of the disease and may
influence disease progression (Schedin et al. 1997). Some
infants may have a similar pattern of disease (Sequeira
et al. 1998).

Clinical features and diagnosis Two-thirds of infants present
with prolonged cholestasis, hepatomegaly and a particu-
larly prominent splenomegaly; some may have fetal
ascites (Maconochie et al. 1989; Kelly et al. 1993). They
appear neurologically normal at birth, although subse-
quent motor and speech development may lag (Semeraro
et al. 1986; Kelly et al. 1993). In one Indo-Pakistani kindred,
type C Niemann–Pick disease was associated with extra-
hepatic biliary atresia and meconium ileus in two of three
affected infants (Adam et al. 1988). The remainder of af-
fered children present with isolated splenomegaly with
or without neurological symptoms.

Liver biopsy shows a histologically severe neonatal hepati-
is, pericellular fibrosis and pseudocinar forma-
tion (Rutledge 1989). The diagnosis is confirmed by
identifying the characteristic PASD-resistant material in
Kupffer cells and hepatocytes, which may be difficult to
identify in neonates. It may be easier to detect the foamy
storage cells in bone marrow aspirate. Neuronal storage
is usually present at birth and may be demonstrated in the
ganglion cells of a suction rectal biopsy, which demon-
strate typically pleomorphic lamella cytoplasmic inclu-
sions (Kelly et al. 1993) (see Plate 8, Atlas: p. 442).

Studies of cholesterol esterification in the patient’s
cultured fibroblasts are definitive.

Management and prognosis In most infants liver disease
resolves and jaundice disappears in the first year of life.
Neurological symptoms become obvious by 5 years of age.
Most children develop loss of upward gaze due to verti-
cal supranuclear ophthalmoplegia, which is re-
garded as a pathognomonic sign. Other neurological com-
lications include ataxia, convulsions, developmental
delay and dementia. Most children die in early adoles-
cence from bronchial pneumonia rather than liver failure.
There is no specific treatment, although a low-cholesterol
diet has been suggested. Liver and bone marrow trans-
plantation are ineffective. Genetic counselling is essential
and antenatal diagnosis is available by chorionic villus
biopsy (Vanier et al. 1989) or by gene analysis (Vanier 2002).

Wolman disease
Wolman disease, and the associated milder disease, cho-
sterol ester storage disease, are both due to deficiency
of lysosomal acid lipase (also known as acid esterase,
cholesterol esterase, or sterol esterase). Inheritance is
autosomal recessive; some mutations in the lysosomal
acid esterase gene capable of causing severe functional
deficiency have been identified (Anderson et al. 1994).
Babies with Wolman disease are not usually jaundiced
but have deranged liver function, hepatosplenomegaly,
persistent diarrhoea and poor growth; calcified adrenal
glands are found radiologically. The majority die in early
infancy.
Citrullinaemia, type II

Citrullinaemia is due to deficiency of argininosuccinate synthetase. The classic form of citrullinaemia (type I) presents in infancy or childhood as a urea cycle disorder with hyperammonaemia. Jaundice is rare. The disorder is due to mutations in the argininosuccinate synthetase gene on chromosome 9q34. A second form of citrullinaemia has been described, which occurs mainly in adults, who present with fatty liver, hepatitis and iron accumulation. Type II citrullinaemia is due to a deficiency in citrin, a carrier protein of unknown function associated with the urea cycle, encoded by the gene SLC25A13. Several mutations in this gene have been identified in adults with type II citrullinaemia. Recently infants with NHS were found to have type II citrullinaemia, confirmed by genetic analysis (Tazawa et al. 2001; Ben-Shalom et al. 2002; Säheki & Kobayashi 2002; Tamamori et al. 2002). A distinguishing feature was the presence of steatosis and iron deposition histologically. Liver disease was severe enough in one infant to require liver transplantation.

Toxic injury

Total parenteral nutrition-associated cholestasis

Progressive cholestasis in infants receiving total parenteral nutrition without any enteral nutrition occurs mainly in critically ill, often premature infants.

Aetiology

Total parenteral nutrition-associated cholestasis is more likely to develop with increasing degree of prematurity and longer duration of exclusive dependence on total parenteral nutrition to meet nutritional needs. The setting of severe gastrointestinal disease (such as recurrent necrotizing gastroenteritis, gastrochisis or intestinal atresias), which may lead to recurrent bouts of sepsis or require surgical resection(s), or a short gut syndrome signals an especially difficult situation as these infants often cannot avoid protracted use of total parenteral nutrition. The more premature the infant is, the more underdeveloped are hepatocellular mechanisms of bile formation, leading to the development of total parenteral nutrition-associated cholestasis. Factors which amplify this physiological inefficiency by interfering with enterohepatic circulation of bile acids may contribute to the pathogenesis of total parenteral nutrition-associated cholestasis. Depending on gestational age, fetal patterns of bile acid biosynthesis may persist: synthesis of the toxic bile acid, lithocholic acid, may be higher than in older infants.

Fasting interrupts the enterohepatic circulation, diminishes the output of gut hormones needed for normal hepatobiliary function, and may promote small bowel overgrowth by bacteria that are capable of producing endotoxin or modifying endogenous bile acids to more toxic chemicals. Bacterial translocation may occur. All these mechanisms are compounded by systemic factors such as hypoxia or hypoperfusion, localized infection or septicaemia, and medications used to treat these sick infants. Specific nutritional deficiencies may also play a role: lack of taurine, essential fatty acids, carnitine, and antioxidants such as vitamin E, selenium and glutathione (Sokol et al. 1996).

It is not clear whether specific components in the total parenteral nutrition solution are toxic. High concentrations of amino acids do not necessarily promote more rapid protein synthesis and may be toxic to hepatocytes. Lipid preparations are probably not toxic as such, although some sources of lipid may be tolerated better than others; however, accumulation of lipofuscin in Kupffer cells appears to be due mainly to the lipid component.

Clinical features and diagnosis

Most infants present with conjugated hyperbilirubinaemia and hepatomegaly in the context of prolonged parenteral nutrition. Cholestasis may be so severe that extrahepatic biliary tract obstruction is mimicked with acholic stools. Serum aminotransferases, alkaline phosphatase and GGT are usually elevated, whereas albumin and coagulation times are usually normal unless affected by extrahepatic disease.

The diagnosis is relatively straightforward. A careful history mapping out feeding history, all other medications and intercurrent illnesses is essential. Other causes of neonatal hepatitis syndrome should be considered and excluded. Abdominal ultrasound may be normal or demonstrate a contracted gall bladder. If cholestasis is severe, there may be delayed excretion on a hepatobiliary scan. Liver biopsy shows cholestasis with hepatocellular necrosis, abundant lipofuscin, some fatty infiltration, mild giant-cell transformation, portal inflammatory infiltrate, and some bile ductular proliferation with or without portal fibrosis. Electron microscopy may reveal cholesterol crystals in hepatocytes.

Treatment

Treatment continues to be empirical. If possible, some oral nutrition should be introduced: even dextrose in water given in very small boluses (2–5ml) every few hours is beneficial. Oral or nasogastric feeding with a highly digested formula may be commenced concurrent with continued total parenteral nutrition. The components of the total parenteral nutrition solution should be reviewed carefully to be sure that amino acid requirements are being met but not exceeded and that essential

...
fatty acids and trace metals are supplied. Taurine and carnitine can be supplemented. Protecting the total parenteral nutrition solution from light, and cycling total parenteral nutrition administration are other simple strategies. Extreme care to avoid central venous catheter sepsis is critically important. There may be benefit from treating small bowel overgrowth with metronidazole, although no controlled trials are available; metronidazole is preferable to gentamicin. Once some oral intake is established, ursodeoxycholic acid (20 mg/kg/day) may promote bile flow and improve cholestasis, but there are few reports in children (Cocjin et al. 1993).

In general, recovery is slow, unless parenteral nutrition can be discontinued. Infants totally dependent on total parenteral nutrition because of massive bowel dysfunction due to severe inherited disorders of motility or short gut syndrome will develop progressive liver disease, cirrhosis and portal hypertension, which may be exacerbated by intercurrent portal vein thrombosis. Cirrhosis may be averted by either innovative bowel surgery or successful intestinal transplantation, and this should be considered at an early stage before a combined liver–intestinal transplant may be needed (Chapter 21).

Other complications of total parenteral nutrition

Other complications of total parenteral nutrition include: generation of ‘biliary sludge’ (material appreciated by sonography as echogenic, resembling a stone but without typical acoustic shadowing) (Matos et al. 1987); cholelithiasis (Whittington & Black 1980; Roslyn et al. 1983); or acalculous cholecystitis (Thurston 1986) (Chapter 18). Extensive abdominal surgery leading to short gut syndrome or resection of the ileocaecal valve as well as longer duration of parenteral nutrition may predispose to biliary tract disease. Regular ultrasound examination of the biliary tree at 4- to 6-week intervals during prolonged use of total parenteral nutrition may be of value in such patients. Spontaneous resolution of gallstones sometimes occurs in infancy, and thus surveillance of the asymptomatic infant is often appropriate, instead of immediate surgery (Debray et al. 1993).

Drug-induced hepatotoxicity

Drug hepatotoxicity as a cause of neonatal hepatitis syndrome is poorly documented. Prolonged chloral hydrate administration is associated with conjugated hyperbilirubinaemia in newborns, without other signs of liver toxicity (Lambert et al. 1990). Drug exposure might occur via breast milk, which has been reported for carbamazepine (Merlob et al. 1992; Frey et al. 2002). Cholelithiasis in infants has been attributed to certain drug therapies including prolonged use of frusenide (Whittington & Black 1980; Callahan et al. 1982) or various antibiotics such as ceftriaxone (Schaad et al. 1988). Without choledocholithiasis, jaundice is unusual.

Immune causes

Neonatal lupus erythematosus

Neonatal lupus erythematosus is due to passage of maternal anti-Ro and anti-La antibodies across the placenta leading to damage to fetal tissues, which express Ro and La antigenic determinants. The heart, skin and liver are most likely to be involved, rarely with thrombocytopenia and leukopenia (Silverman & Laxer 1997). Congenital heart block is the most dramatic cardiac manifestation. A rash resembling discoid lupus erythematosus may be present in the newborn period or develop some weeks later. Hepatic involvement, evident in ~10%, is often limited to elevated serum aminotransferases, but neonatal hepatitis syndrome is found (Laxer et al. 1990; Evans & Gaskin 1993). Occasionally this is severe enough to mimic extrahepatic biliary tract obstruction, with acholic stools and non-draining hepatobiliary scan (Rosh et al. 1993). In severe cases a clinical phenotype of neonatal haemochromatosis may be found (Schoenlebe et al. 1993). Deposits of associated antibodies (anti-Ro and/or anti-La) may be found in affected liver tissue by immunofluorescence (Selander et al. 1998). Transient unexplained isolated conjugated hyperbilirubinaemia in the perinatal period and later presentation at 2–3 months old with transient elevations of serum aminotransferases are other possible clinical presentations (Lee et al. 2002). In most infants the liver disease resolves completely between 6 and 12 months of age, as the maternal antibodies are degraded. Mild fibrosis was found in one child on repeat liver biopsy.

The diagnosis of neonatal lupus erythematosus is difficult in the child who does not have congenital heart block, a typical skin rash or a history of maternal systemic lupus erythematosus or Sjögren’s syndrome. The risk of neonatal lupus erythematosus in subsequent pregnancies appears variable, estimated at 10–50%.

Autoimmune haemolytic anaemia with giant-cell hepatitis

This condition is rare and poorly defined as only about 10 children with this complaint have been reported in the English language literature. Most are infants aged 6–24 months or more. Pallor, jaundice and hepatosplenomegaly are the important clinical findings. The autoimmune haemolytic anaemia is Coombs’ positive, but autoantibodies typical of autoimmune hepatitis are not present (Bernard et al. 1981). Viral studies are generally negative, although it is possible that the disease is related to syncytial giant-cell hepatitis attributed to paramyxoviral infection (Phillips et al. 1991). Liver biopsy
reveals extensive giant-cell transformation with fibrosis. Some patients have responded to treatment with prednisolone and azathioprine (Brichard et al. 1991), but the disease has frequently been refractory to immunosuppressive treatment and may recur following liver transplantation.

Miscellaneous causes

Vascular disorders

Budd–Chiari syndrome

Budd–Chiari syndrome is rarely diagnosed in infants (Jaffe & Yunis 1983; McClead et al. 1986; Gentil-Kocher et al. 1988) but may be due to endophlebitis from a venous catheter or associated with neoplasia, sepsicaemia or fungal infection (Brocart et al. 1974); membranous obstruction of the inferior vena cava probably represents previous thrombosis of the vessel. A prothrombotic disorder may be present (Dahms et al. 2002). Hepatic vein thrombosis may rarely occur due to other intra-abdominal congenital abnormalities (Yonekura et al. 1998). Affected children usually have hepatomegaly, splenomegaly or ascites; jaundice is more common in infants.

Budd–Chiari syndrome must be differentiated from veno-occlusive disease, where the vascular blockage is at the level of terminal hepatic venules, as opposed to larger hepatic veins. Veno-occlusive disease is rarely reported in infants, although an infant with congenital leukaemia developed veno-occlusive disease after treatment with antineoplastic drugs.

Severe congestive heart failure

The role of chronic passive congestion, or functional hepatic venous obstruction, in neonatal hepatitis syndrome is difficult to assess. Babies with severe chronic congestive heart failure may develop moderate hepatomegaly or hepatosplenomegaly, as well as ascites. Jaundice is uncommon (Chapter 15). Infants with acute circulatory failure associated with severe congenital heart disease or shock may develop elevated serum aminotransferases, coagulopathy and jaundice with mild to moderate conjugated hyperbilirubinaemia (Jacquemin et al. 1992), which resolves rapidly once hepatic perfusion is restored.

Neonatal asphyxia

Neonatal conjugated hyperbilirubinaemia with mild elevations of aminotransferases is associated with severe neonatal asphyxia (Vajro et al. 1997; Jacquemin et al. 1998). Conjugated hyperbilirubinaemia jaundice developed within 6 days of birth, and was protracted. Hepatobiliary scanning showed bile drainage. Spontaneous resolution typically occurs.

Neoplasia

Primary hepatic neoplasms rarely present with the neonatal hepatitis syndrome, although mesenchymal hamartoma may present with hyperbilirubinaemia in the neonatal period (Chapter 19). Rhabdomyosarcoma of the biliary tree rarely presents in infancy, but jaundice and acholic stools are the major clinical features. Any neoplasm which obstructs bile flow may cause jaundice (Finegold 1994). Langerhans cell histiocytosis is associated with sclerosing cholangitis in children and may present in early infancy with jaundice (Leblanc et al. 1981a). Jaundice rarely occurs with neuroblastoma, erythrophagocytic lymphohistiocytosis, or neonatal leukaemia.

Consequences of cholestasis

Many infants with neonatal liver disease will have a mild self-limiting disease, but those children with progressive disease, or following unsuccessful Kasai portoenterostomy, will develop significant fat malabsorption with consequent protein malnutrition. It is important to establish baseline anthropometric examinations in order to detect and prevent early malnutrition. This is best evaluated by using a combination of weight (may be imprecise because of fluid retention), height (may be useful for assessing chronic malnutrition), triceps skin fold (to evaluate fat stores), and mid-arm muscle area (to evaluate protein stores). Mid-arm circumference is a reliable marker of malnutrition in children under 5 years old.

The effects of chronic cholestasis are extensive: failure of biliary excretion of bilirubin, bile salts and cholesterol leads to jaundice, pruritus and xanthomata; decreased bile salts in the intestine leads to malabsorption of long-chain triglycerides and consequent fat malnutrition. Malabsorption of fat-soluble vitamins is inevitable (Table 4.4). If cirrhosis develops, then protein malnutrition and muscle wasting are likely.

Management of neonatal liver disease

Management should be supportive and, whenever possible, definitive. Disorders for which specific medical or surgical therapies are available are summarized in Table 4.5.

Nutritional support

The main aim of nutritional support is to provide sufficient calorie intake to reverse or prevent fat malabsorption and protein malnutrition. In extrahepatic biliary
atresia resting energy expenditure runs ~30% higher than in normal infants of the same age and sex (Pierro et al. 1989). Thus an aggressive approach to feeding is required, including nasogastric supplementation if oral feeding cannot meet caloric needs (Kaufman et al. 1987).

Infants with severe cholestatic jaundice require special formulas to ensure that calorie intake is 120–150% EAR (estimated average requirement) using either a standard infant formula with appropriate supplements or a modular feed in which individual constituents can be added according to requirement. A nearly elemental formula containing medium-chain triglycerides, which can be absorbed regardless of luminal concentrations of bile acids, is preferable. Caloric density can be increased further by concentrating the formula or adding starch powder (glucose polymer). If the infant is satisfactorily breast-feeding this should be encouraged with supplementation using a highly digestible high-caloric-density formula.

Fat-soluble vitamin supplementation

All infants with chronic cholestasis, whether jaundiced or not, require supplementation with fat-soluble vitamins. These can be provided as water-soluble preparations of vitamins A, D, E and K given orally (Kaufman et al. 1987), or less commonly, as parenteral supplementation (Alagille 1985) (Table 4.6). Vitamin levels should be monitored to ensure adequate absorption and prevent toxicity.

Vitamin A This is provided in a water-soluble preparation. Toxic levels may lead to hepatic fibrosis or pseudotumour cerebri.

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**Table 4.4** Consequences of chronic cholestasis and cirrhosis

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced excretion of bilirubin, bile acids</td>
<td>Pruritus, jaundice</td>
</tr>
<tr>
<td>Fat malabsorption</td>
<td>Steatorrhoea, loss of fat stores</td>
</tr>
<tr>
<td>Essential fatty acid deficiency</td>
<td>Peeling skin rash</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>Conjunctival and corneal drying, abnormal retinal function,</td>
</tr>
<tr>
<td>Vitamin E deficiency</td>
<td>Night blindness</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>Peripheral neuropathy, ophthalmoplegia, ataxia, haemolysis</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>Osteopenia, rickets, fractures</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>Bruising, epistaxis, coagulopathy</td>
</tr>
<tr>
<td>Increased protein catabolism</td>
<td>Xanthomata</td>
</tr>
<tr>
<td></td>
<td>Muscle wasting, motor development delay, growth failure</td>
</tr>
</tbody>
</table>

**Table 4.5** Neonatal liver disease syndrome: specific treatments

<table>
<thead>
<tr>
<th>Disease</th>
<th>Major diagnostic strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Infection</em></td>
<td></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Spiramycin</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Gancyclovir, if severe</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Bacterial infection elsewhere (sepsis)</td>
<td>Appropriate antibiotic(s)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Quadruple antitubercular therapy (not ethambutol)</td>
</tr>
<tr>
<td>Syncytial giant-cell hepatitis</td>
<td>Ribavirin (unproven benefit)</td>
</tr>
<tr>
<td><em>Endocrine</em></td>
<td></td>
</tr>
<tr>
<td>Panhypopituitarism (septo-optic dysplasia)</td>
<td>Corticosterone, thyroxine, growth hormone</td>
</tr>
<tr>
<td><em>Structural</em></td>
<td></td>
</tr>
<tr>
<td>Extrahepatic biliary atresia</td>
<td>Kasai portoenterostomy before 8–12 weeks old</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>Surgical resection</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Surgical removal</td>
</tr>
<tr>
<td>Spontaneous perforation of CBD</td>
<td>Surgical repair</td>
</tr>
<tr>
<td><em>Metabolic</em></td>
<td></td>
</tr>
<tr>
<td>Primary disorders of bile acid synthesis</td>
<td>Bile acid supplementation</td>
</tr>
<tr>
<td><em>Toxic</em></td>
<td></td>
</tr>
<tr>
<td>TPN-associated cholestasis</td>
<td>Enteral feeding; metronidazole; ursodeoxycholic acid</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Stop causative drug</td>
</tr>
<tr>
<td><em>Immune</em></td>
<td></td>
</tr>
<tr>
<td>Neonatal hepatitis with autoimmune haemolytic anaemia</td>
<td>Prednisolone + azathioprine</td>
</tr>
</tbody>
</table>

CBD, Common bile duct; TPN, total parenteral nutrition.
tosaemia and hereditary tyrosinaemia type I are available.

Special diets are used life-long for children with inborn errors of carbohydrate and amino acid metabolism. Supplementation with specific bile acids may arrest liver damage in inborn errors of bile acid metabolism (Suchy 1993).

Pruritus

Pruritus due to severe cholestasis interferes with the infant’s sleep and compromises quality of life. It is often difficult to treat; local measures such as non-perfumed skin cream may help. For infants with some duct patency and bile flow medical therapy includes:

- Cholestyramine (1–4g daily) is effective but is unpalatable. The mechanism of action is to bind bile salts in the intestinal lumen, thus interrupting the enterohepatic circulation and reducing bile salt concentration. Side-effects include malabsorption of fat-soluble vitamins and drugs, folic acid deficiency, constipation and acidosis. Cholestyramine can cause intestinal obstruction or hypernatraemia in small infants; adequate fluids must be given with it.
- Ursodeoxycholic acid (UDCA) may be effective when given in a dose of 15–30mg/kg/24h. It is thought to have a choleric action but is not universally effective. UDCA may transiently increase pruritus.
- Phenobarbitone (5–10mg/kg/day) may stimulate bile salt-independent bile flow and decrease jaundice and control pruritus. However, it is relatively ineffective, causes sedation and may exacerbate rickets.
- Biliary diversion may be effective in some conditions, including PFIC and Alagille’s syndrome (Emerick & Whitington 2002).
- Rifampicin (5–10mg/kg/day) relieves pruritus in at least 50%, producing a significant improvement in the remainder (Yerushalmi et al. 1999). Results are variable and experience in young infants limited (Banks et al. 1989;

Vitamin D

This is usually provided as alfalcaldol (1,25-dihydroxy-vitamin D), although the administration of 25-hydroxy-vitamin D may be more effective (Heubi et al. 1989). Vitamin D production in the skin can be enhanced through sunlight or sunlamp exposure, even for babies who are jaundiced (Kooh et al. 1989). Absorption of water-soluble vitamin D may be enhanced by simultaneous administration of alpha tocopheryl polyethylene glycol succinate formulation of vitamin E (Argao et al. 1992).

Vitamin E

Vitamin E transferred via the placenta to the fetus may keep the infant replete until the age of 3 months, but the sufficiency of maternal stores varies from baby to baby. Most babies require supplementation after 2 months of age or earlier if the baby was born preterm. Vitamin E linked to polyethylene glycol 1000 through a succinate linkage, alpha tocopheryl polyethylene glycol succinate (TPGS), has the best bioavailability in severe cholestasis (Sokol et al. 1987a,b) as its absorption depends on simple passive absorption of polyethylene glycol independent of bile acids in the intestinal lumen. This formulation is not universally available and the more traditional oral supplement vitamin E acetate may not be as quickly absorbed. Coagulation should be monitored closely in all infants with cholestasis, who should receive oral vitamin K prophylactically. Infants receiving rifampicin for pruritus should receive extra vitamin K.

Other dietary measures

It is reasonable to place an infant with conjugated hyperbilirubinaemia on lactose-free formula until the results of testing for galactosaemia are known; however, interrupting breast feeding is problematic. Brief use of a more restrictive diet is sometimes justifiable: an infant with severe neonatal hepatitis syndrome might be placed on a lactose-free/low-protein formula (to minimize aromatic amino acid intake) until the results of tests for both galactosaemia and hereditary tyrosinaemia type I are available.

Special diets are used life-long for children with inborn errors of carbohydrate and amino acid metabolism. Supplementation with specific bile acids may arrest liver damage in inborn errors of bile acid metabolism (Suchy 1993).

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- Phototherapy with infrared or ultraviolet radiation may improve pruritus if given for 3–10 min daily.
- Antihistamines are largely ineffective but as they cause drowsiness may be useful at night. Toxic side-effects include cardiac dysrhythmias.

**Family and psychological support**

Specific attention to the infant’s developmental needs is often beneficial. Physiotherapy may improve gross motor development while infant stimulation programmes enhance the mental development for infants who require frequent hospitalization. Family education and support are essential, particularly for children with progressive illness requiring liver transplantation.

**Indications for liver transplantation**

The indications for liver transplantation are severe cholestasis, decompensated liver disease and intractable pruritus (Chapter 20). Orthotopic liver transplant is often the only definitive treatment for severe infantile liver disease and can be performed safely in the first year of life (Casavilla et al. 1994; Colombani et al. 1996; Bonatti et al. 1997), especially if nutrition has been maintained well. In those who are malnourished, catch-up growth occurs after liver transplantation, including patients with Alagille’s syndrome (Holt et al. 1997; D’Antiga et al. 2002). The role of gene transfer therapies for genetic disorders causing the neonatal hepatitis syndrome requires further clarification.

**Inherited disorders of bilirubin conjugation**

These rare disorders are characterized by benign conjugated hyperbilirubinaemia and an unexplained abnormality of coproporphyrin metabolism. Clinical features include jaundice, which may be exacerbated by stress, intercurrent illness, pregnancy and oral contraceptives. There are no other clinical or laboratory features of liver disease. The diagnosis is made as described below.

**Dubin–Johnson syndrome**

Dubin–Johnson syndrome is due to mutations in the human gene MRP2, which encodes the bile canicular membrane transporter for anion conjugates (Kartenbeck et al. 1996; Paulusma et al. 1997). (Some initial reports used the terminology ‘canicular multispecific organic anion transporter’, or cMOAT, for this transporter.) Numerous mutations have been described, most of which cause functional deficits though defects in protein maturation and localization (Hashimoto et al. 2002; Keitel et al. 2003). Neonatal hepatitis syndrome has been reported rarely in Dubin–Johnson syndrome (Shieh et al. 1990; Regev et al. 2002). Treatment of severely affected neonates with ursodeoxycholic acid may be beneficial. Diagnosis is hampered by the difficulty in recognizing the typical melanin-containing pigment in the liver during infancy as little accumulates until later in childhood. Bromosulphophthalein sodium retention in the serum at 45 min is generally between 10 and 20%. Coproporphyrin excretion in urine is normal, but the ratio of coproporphyrin III to coproporphyrin I is reversed, with coproporphyrin I accounting for >75% of the total urinary coproporphyrins (Haimi-Cohen et al. 1998). Abdominal computed tomography scan showing high attenuation in the liver may provide important supporting evidence for the diagnosis in an infant (Shimizu et al. 1997). Liver histology in older children demonstrates a typical melanin-containing pigment, which is found predominantly in the centrolobular region.

**Rotor syndrome**

Rotor syndrome is also characterized by conjugated hyperbilirubinaemia without cholestasis but does not have pigment accumulation in the liver. The pathogenesis of Rotor syndrome remains unclear but is related to a defect in bilirubin secretion. Neonatal hepatitis syndrome has not been reported in infants with Rotor syndrome. The diagnosis is made by estimating the bromosulphophthalein sodium retention in serum, which is 30–50% at 45 min after injection, or by measuring urinary coproporphyrin excretion, which is generally increased, with a particular increase in coproporphyrin I. No treatment is required for either disorder apart from reassurance.

**References**


Section 3: Neonatal Liver Disease


Chapter 4: The Jaundiced Baby


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