Extrahepatic biliary atresia versus neonatal hepatitis

Review of 137 prospectively investigated infants

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Mowat, A. P., Psacharopoulos, H. D., and Williams, R. (1976). Archives of Disease in Childhood, 51, 763. Extrahepatic biliary atresia versus neonatal hepatitis: review of 137 prospectively investigated infants. In a prospective regional survey of neonatal hepatitis syndrome 32 infants had extrahepatic biliary atresia (EHBA) and 103 had hepatitis. No cause for the lesion was found in infants with extrahepatic biliary atresia, but in 32 with hepatitis a specific cause was identified, 24 having genetic deficiency of the serum protein $\alpha_1$-antitrypsin. No differences were observed in parental age, mother’s health in pregnancy, month of birth, birth order, or sex of the infants. Familial idiopathic hepatitis occurred in 3 of 67 sibs of patients with idiopathic hepatitis, but the 33 sibs of EHBA patients had no liver disease. Of the infants with hepatitis, 36 were of low birthweight, $<2.5$ kg, and 23 were born prematurely. Infants with biliary atresia were all of normal birthweight and only one was born prematurely.

Consideration of clinical and biochemical abnormalities in the first 2 months of life showed no differences between the two groups except that infants with EHBA were more commonly jaundiced from birth (80%) and had more frequently acholic stools (83%). The frequency of these features in patients with hepatitis being 68% and 52%. Standard tests of liver function were not discriminatory. Percutaneous liver biopsies were diagnostic in 75% of those with EHBA and in 92% of those with hepatitis. The $^{131}$I Rose Bengal faecal excretion was less than 10% in 26 of 28 infants with EHBA and in only 5 of 18 with hepatitis. These latter two investigations together allowed a correct preoperative diagnosis of EHBA in all instances. Bile drainage was achieved surgically in only 3 cases. A major reason for these poor results may have been the late referral of cases for diagnosis and laparotomy, which should be performed as soon as the diagnosis is suspected and always by 70 days of age.

Extrahepatic biliary atresia (EHBA) carries a poor prognosis. Only 5% of cases have distal obstructions with patent bile-containing proximal bile ducts which allow bile drainage by standard surgical techniques (Arima, Fonkalsrud, and Neerhout, 1974). Many of these will have developed cirrhosis by early childhood, though occasional cases survive to adulthood (Berenson, Garde, and Moody, 1974). The remaining 95% usually die by the age of 2 years (Campbell et al., 1974a), though the operation of hepatic portoenterostomy introduced in Japan 15 years ago by Kasai and co-workers has given encouraging results in such patients with symptom-free survival to the age of 17 years (Kasai, Watanabe, and Ohi, 1975). Confirmation of these Japanese results (Lilly and Altman, 1975) and the observation that portoenterostomy is most likely to be successful if carried out before 70 days of age necessitates careful assessment of investigations necessary to make the diagnosis at a sufficiently early stage.

Relevant to such considerations are new ideas about the pathogenesis of biliary atresia. Although the lesion is commonly regarded as congenital, it is now thought that the hepatic parenchymal cells develop as outgrowths from the primitive bile duct system (Koga, 1971), and as there is no evidence
that the former are abnormal a primary failure of development of the bile ducts seems unlikely. Further, the degree of duct involvement is very variable (Alagille, 1972; Strauss, Valderrama, and Alpert, 1972; Landing, 1974), which is difficult to explain on the basis of a single antenatal insult or abnormality in organogenesis. Also, in some infants with classical extrahepatic biliary atresia there is evidence that the bile ducts were previously intact (Holden, 1964; Poley et al., 1972; Danks, 1974). The more likely pathogenesis, therefore, is that the condition results from a sclerosing inflammatory lesion initiated in the bile duct epithelium and involving part or all of the biliary tract, starting late in fetal life, or early in postnatal life. The aetiology is unknown. It has been suggested that both neonatal hepatitis and EHBA may be due to the same basic disease process with the major damage occurring in some instances in the bile ducts (Alagille, 1972; Strauss et al., 1972; Landing, 1974). We report an analysis of data collected during a prospective study of the neonatal hepatitis syndrome, in which findings in 32 infants with extrahepatic biliary atresia are compared with 105 with other forms of the syndrome. Clinical and biochemical features of possible diagnostic importance during the first 2 months of life when surgery has the best chance of success, and the particular value of percutaneous liver biopsy and the 131I Rose Bengal faecal excretion test, are also considered.

**Materials and methods**

Infants in this report are those born before June 1974 who are included in a prospective regional survey (Porter et al., 1972) of the neonatal hepatitis syndrome. This was defined for the purpose of the study as a conjugated hyperbilirubinaemia starting within the first 4 months of life and accompanied by biochemical and pathological evidence of hepatocellular necrosis. This, therefore, includes both patients with EHBA and those with intrahepatic disease or hepatitis, but with patent biliary passages. Final proof of EHBA was obtained in all instances at laparotomy. In all cases known genetic, metabolic, infectious, or environmental causes of the neonatal hepatitis syndrome were fully investigated. Those patients with hepatitis in whom no causative agent was identified or in whom the association with the putative cause was tenuous, for example, sepsis or a rise in cytomegalovirus antibody titre in the serum without recovery of the cytomegalovirus from liver tissue, were classified as idiopathic hepatitis.

Standard laboratory methods were used to determine serum bilirubin, aspartate aminotransferase, alkaline phosphatase, and prothrombin time. Percutaneous liver biopsies were performed using the Menghini technique.

In the Rose Bengal excretion test, Lugol's iodine, 3 drops daily for 3 days was administered to block possible thyroid uptake of free radioactive iodine, followed by intravenous 131I Rose Bengal in a dose of 1 μCi/kg. Stools uncontaminated with urine were collected for 72 hours and the amount of isotope recovered in the stools expressed as a percentage of the administered dose. Excretion of <10% of the injected dose was taken to indicate extrahepatic bile duct obstruction or severe cholestasis. In cases in whom the initial excretion was <10% but in whom other findings, particularly the liver biopsy, were not diagnostic of EHBA, the test was repeated 18–21 days after starting cholestyramine orally in a dose of 1g four times a day, a measure associated with increased excretion in hepatitis but not in EHBA (Campbell et al., 1974b).

**Results**

Of the 137 cases investigated, 32 infants were found to have EHBA. 2 infants had large choledochal cysts with narrow, totally obstructed bile ducts shown by cholangiography. The remaining 103 cases were classified as having hepatitis, a specific cause being identified in 32. Genetic deficiency of α1-antitrypsin was by far the most frequent, accounting for 24 of these 32 infants (Table I). None of these causes could be identified

### TABLE I
Aetiological and structural classification of neonatal hepatitis syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrahepatic biliary atresia</td>
<td></td>
</tr>
<tr>
<td>Hepatitis group</td>
<td>32</td>
</tr>
<tr>
<td>α1-antitrypsin deficiency</td>
<td>103</td>
</tr>
<tr>
<td>Galactosaemia</td>
<td>24</td>
</tr>
<tr>
<td>Tyrosinosis</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2</td>
</tr>
<tr>
<td>Rubella</td>
<td>2</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic hepatitis</td>
<td>71</td>
</tr>
<tr>
<td>Choleodochal cyst</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
</tr>
</tbody>
</table>

in patients with EHBA. The remaining 71 patients with hepatitis are considered idiopathic, though 9 of these had conditions which may be associated with hepatitis but which were not definitely causative in these patients (chromosomal trisomy, 4; sepsis, 3; cystic fibrosis, 2; halothane, 1). One other infant in this idiopathic hepatitis group was shown to have hypoplasia of intrahepatic bile ducts and normal extrahepatic ducts at laparotomy.
There may have been other infants in the series with similar pathologies in whom jaundice cleared and therefore did not come to surgery and wedge biopsy of the liver.

**Comparison of factors of possible aetiological importance.** When findings in patients with EHBA are compared with those of the hepatitis cases, no seasonal variation in the month of birth was found (Fig.) or in the distribution of birth order. Of the EHBA infants, 46% were first-born, 18% second-born, 18% third, 12% fourth, 3% fifth and sixth in family position. Parental ages were not significantly different; the mean (±SD) age of the fathers being 31·4±7·4, 29·3±6·4, 30·7±6·7 years, and of the mothers, 27·8±6·1, 26·3±6·2, 27·1±6·2 years in the EHBA group, total hepatitis group, and idiopathic cases respectively. In the same groups of patients the percentage of males was 59%, 62%, and 60·5% respectively. No liver disease could be detected in the 33 sibs of patients with EHBA, but 3 of 67 sibs of those with idiopathic hepatitis had chronic liver disease which started as neonatal hepatitis.

There was no difference in the incidence of minor intercurrent infections or exposure to drugs during pregnancy and labour in the EHBA cases compared with those with hepatitis. As shown in Table II, one child with EHBA had a gestation of <37 weeks, and only one mature child was light-for-gestational age; whereas in the hepatitis group a significantly greater number of infants had short gestations (P<0.005). None of these infants with EHBA weighed less than 2·5 g at birth, in contrast to the 35% of infants in the complete hepatitis group and 39% of those with idiopathic hepatitis who had a birthweight of less than 2·5 g (P<0·005).

Chromosomal abnormalities were present only in the hepatitis patients, 4 of whom had trisomy. Identifiable congenital abnormalities such as congenital heart disease, meningomyeloceles, and cleft palate, and significant clinical disorders outside the gastrointestinal system occurred more commonly in hepatitis than in EHBA.

**Clinical features.** Jaundice had started in the first 2 weeks of life in 80% of those with EHBA as opposed to only 68% of those with hepatitis. In 6 patients with EHBA, however, jaundice was first noted at varying times between the third and

**TABLE II**

*Incidence of factors of possible aetiological significance*

<table>
<thead>
<tr>
<th></th>
<th>EHBA</th>
<th>Hepatitis group</th>
<th>Idiopathic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td><strong>Gestation (w)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;32</td>
<td>0</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>33–37</td>
<td>1</td>
<td>3·1</td>
<td>18</td>
</tr>
<tr>
<td>38–40</td>
<td>28</td>
<td>87·5</td>
<td>63</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>9·4</td>
<td>17</td>
</tr>
<tr>
<td><strong>Birthweight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2·0</td>
<td>0</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>2·25</td>
<td>0</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>2·5–3·0</td>
<td>13</td>
<td>40·6</td>
<td>27</td>
</tr>
<tr>
<td>&gt;3·0</td>
<td>19</td>
<td>59·3</td>
<td>40</td>
</tr>
<tr>
<td><strong>Light-for-dates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3·2</td>
<td>19</td>
</tr>
<tr>
<td><strong>Congenital abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>9·3</td>
<td>11</td>
</tr>
<tr>
<td><strong>Disorders outside gastrointestinal system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>18·7</td>
<td>35</td>
</tr>
</tbody>
</table>

EHBA, extrahepatic biliary atresia.
sixth week of age (Table III). 83% of those with EHBA were recorded as having acholic stools in the first 2 months of life as opposed to 52% of those with hepatitis and 41% of those with idiopathic hepatitis (P < 0.005).

There were no significant differences in the frequency of abnormal physical features in the three groups except hepatomegaly (a liver edge palpable more than 5 cm below the costal margin), which occurred more commonly in EHBA than in the hepatitis group (P < 0.05). Splenomegaly, or at least palpable splenic enlargement, was also more common in this group.

Comparison of liver function tests in the first 2 months of life showed considerable overlap between the three groups, but serial determinations of serum bilirubin concentrations showed that a steady fall occurred only in hepatitis and that a stable bilirubin was significantly more common in EHBA (P < 0.005). In both EHBA and hepatitis, however, a progressive rise in bilirubin or fluctuations of serum bilirubin concentration of more than 51 \( \mu \)mol/l (3 mg/100 ml) occurred with equal frequency. A direct reacting bilirubin of 68 \( \mu \)mol/l (4 mg/100 ml) was found significantly more frequently in EHBA (P < 0.001) but the frequency of serum bilirubin levels of > 235 \( \mu \)mol/l (15 mg/100 ml) was similar in the two groups (Table IV). Raised

TABLE III

<table>
<thead>
<tr>
<th>Clinical features in first 2 months of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHBA</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Age at onset of jaundice (w)</td>
</tr>
<tr>
<td>0-2</td>
</tr>
<tr>
<td>3-4</td>
</tr>
<tr>
<td>5-6</td>
</tr>
<tr>
<td>7-12</td>
</tr>
<tr>
<td>&gt;12</td>
</tr>
<tr>
<td>Acholic stools</td>
</tr>
<tr>
<td>Oedema</td>
</tr>
<tr>
<td>Haematic lesions</td>
</tr>
<tr>
<td>Palpable spleen</td>
</tr>
<tr>
<td>Hepatomegaly &gt;5 cm below costal margin</td>
</tr>
</tbody>
</table>

TABLE IV

<table>
<thead>
<tr>
<th>Biochemical abnormalities in first 2 months of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHBA</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>(a) Pattern of serial serum bilirubin concentrations</td>
</tr>
<tr>
<td>Progressive increase</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>Fluctuations of &gt;51 IU/l</td>
</tr>
<tr>
<td>Steady fall</td>
</tr>
<tr>
<td>(b) Maximum abnormality</td>
</tr>
<tr>
<td>Total bilirubin &gt;235 ( \mu )mol/l</td>
</tr>
<tr>
<td>Direct bilirubin &gt;68 ( \mu )mol/l</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/l)</td>
</tr>
<tr>
<td>&lt;200</td>
</tr>
<tr>
<td>200-400</td>
</tr>
<tr>
<td>&gt;400</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
</tr>
<tr>
<td>&lt;150</td>
</tr>
<tr>
<td>150-300</td>
</tr>
<tr>
<td>&gt;300</td>
</tr>
<tr>
<td>Prothrombin time</td>
</tr>
<tr>
<td>Prolonged &gt;4 s</td>
</tr>
</tbody>
</table>

Conversion: SI to traditional units—Bilirubin: 1 \( \mu \)mol/l ⇆ 0.06 mg/100 ml.
aspartate transaminase levels more than twice normal occurred in all instances, but levels > 400 IU/l were more frequent in hepatitis than in EHBA (P < 0.05). Serum alkaline phosphatase levels were raised in all patients with levels > 300 IU/l (43 KA units/100 ml), occurring as frequently in hepatitis as in EHBA. A prothrombin time prolonged by more than 4 s was equally common in both groups (EHBA 19%, hepatitis 16%).

Liver biopsy interpretation. In 15 of the 20 infants with EHBA who had percutaneous liver biopsies the histological abnormalities were suggestive or diagnostic of EHBA (Table V). EHBA was considered to be the most likely diagnosis if the biopsy showed widened portal tracts with prominent, distorted, elongated, angulated bile ducts, increased fibrosis, and inflammatory cell infiltrate with preservation of normal hepatic architecture and cholestasis with bile lakes. The diagnosis of hepatitis made in 5 of the EHBA patients was on the basis of prominent hepatocellular necrosis, disorganization of liver cords, giant cell transformation, and inflammatory cell infiltrate in the parenchyma and portal tracts. Cholestasis, prominent particularly within the hepatocytes, also favoured a diagnosis of hepatitis. While portal bile duct proliferation was often noted, the severity of the bile duct lesion was much less than that of the hepatocellular lesion. Mistakes in pathological diagnosis occurred as frequently if the biopsy was done early, i.e. between 9 and 12 weeks, as after this time (Table V). The 2 infants with choledochal cysts showed features of extrahepatic biliary atresia. 76 of the 82 patients with hepatitis who had percutaneous liver biopsies were correctly diagnosed but in 6 histological features were either diagnostic or more suggestive of EHBA than of hepatitis. No complications of percutaneous biopsy occurred.

131I Rose Bengal faecal excretion. 26 of 28 patients with EHBA excreted <10% of the injected dose in 72 hours on initial investigation. Both those with high excretion were females and in one of these the test was repeated during cholestyramine administration with excretion falling from 11.2 to 7%. 13 patients in whom excretion was <10% on first testing but in whom the biopsy appearances were those of hepatitis, or were only suggestive of extrahepatic biliary atresia, also had repeat excretion determined during cholestyramine administration and in all of these the excretion remained <10%.

These findings are to be contrasted with the excretion in hepatitis which was >10% in 13 of 18 infants. Of the 5 who excreted <10% 2 excreted 17 and 31% on repeat testing during cholestyramine administration, jaundice subsequently cleared completely, and they were not subjected to laparotomy. Excretion remained persistently low (5%) during cholestyramine administration in 2 patients who at laparotomy had patent extrahepatic ducts; one had severe hepatitis and cirrhosis, the other intrahepatic biliary hypoplasia. The remaining child proceeded to laparotomy without repeat testing and was found to have intact extrahepatic bile ducts.

Results of operative management. In only 3 of the 32 patients with EHBA was bile drainage established. One patient had distal atresia with patent proximal extrahepatic bile ducts which contained bile and allowed cholecystenterostomy to be carried out. Subsequently, jaundice remitted and liver function returned to normal, and at follow-up at 8 months of age this child is clinically and biochemically normal. The other 2 had a hepatic portoenterostomy. In this procedure the portahepatis is explored, residual bile ducts are removed, together with any fibrous tissue in the portahepatis, and an anastomosis fashioned between the portahepatis and a Roux-en-Y loop from the jejunum. In both of these children effective biliary drainage was established in operations at 5 months of age. Both however had subsequent intermittent attacks of jaundice and fever due to cholangitis, with persistently abnormal liver function tests and icterus at 33 months in one and clinical features of cirrhosis already at the age of 26 months in the other. The same operation carried out in 13 others produced no clinical or biochemical improvement, but in only 4 was portoenterostomy carried out before 70 days of age. In 2 patients hepatic bile ducts were anastomosed to bowel, one had a cholecystenterostomy, and one a hepatic lymphaticojejunostomy, all without apparent benefit to the patient.

Eight who had attempted anastomosis of liver

<table>
<thead>
<tr>
<th>Duration of jaundice at biopsy (w)</th>
<th>Pathological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>EHBA (n = 15)</td>
</tr>
<tr>
<td>4-7</td>
<td>1</td>
</tr>
<tr>
<td>8-11</td>
<td>2</td>
</tr>
<tr>
<td>&gt;12</td>
<td>7</td>
</tr>
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</table>
Mowat, Pscharopoulos, and Williams

or bile duct to bowel are dead, the mean age of
death being 11·6 months (range 2–27 months).
The 7 survivors of portoenterostomy who did not
have biliary drainage range in age from 20–38
months (mean 26 months). In 13 patients advanced
cirrhosis was found at laparotomy and no surgical
therapy was considered worthwhile. 9 of these
died at a mean age of 19 months (range 8–26
months, while the 4 survivors have a mean age of
32 months (range 30–34 months).

Discussion

Early and positive differentiation of biliary atresia
from the various forms of neonatal hepatitis is
clearly essential if hepatic portoenterostomy is to be
carried out by 10 weeks of age and unnecessary
laparotomy avoided in hepatitis. Unfortunately,
analysis of prospectively collected data, including
a wide range of clinical and biochemical findings in
the first 2 months of life in 32 patients with EHBA
and 103 with hepatitis, shows that only a progressive
fall in serum bilirubin concentration is of discrimi-

natory value in the individual patient. The
observation that prematurity and low birthweights
are unusual in atresia may be of negative diagnostic
value. In contrast to the findings in older children
or adults presenting with features suggestive of
hepatitis or biliary obstruction, in whom spleno-

megaly would suggest hepatitis, in this series spleno-

megaly was more commonly observed in
atresia. While certain biochemical features oc-
curred significantly more frequently in one or other
group of patients, for example high aspartate
transaminase levels in hepatitis, such levels did
occur in atresia patients. Thus clinical findings
and standard laboratory tests of liver function are as
likely to be misleading as helpful in the individual
patient.

None of the patients with EHBA were shown to
have any of the recognized specific infectious or
metabolic causes of hepatitis. Thus, systematic
screening for such causes which is essential since
specific treatment may be required, is also of value
in limiting patients in whom EHBA must be
considered. It is particularly important to ex-

amine for $\alpha_1$-antitrypsin deficiency, which is found
in 25% of the hepatitis patients in this series,
particularly since histological features may mimic
atresia (Porter et al., 1972). Unless this condition
and biliary atresia are mutually exclusive both could
occur in the same patient, but this has not yet been
recorded. The extrahepatic biliary hypoplasia
recorded in some infants with $\alpha_1$-antitrypsin
deficiency is thought to be due to diminished bile
secretion rather than a primary disease process

affecting extrahepatic bile ducts. (Porter et al.,
1972; Christen, Bau, and Halsband, 1975). Un-
fortunately, indirect methods of diagnosing EHBA,
such as the ratio of serum bile salts (Javitt et al.,
1973), red cell haemolysis test (Lubin et al., 1971),
and serum $\alpha$-fetoprotein concentration (Zeltzef
et al., 1974), which have been claimed to be or
discriminatory value, have not been confirmed in
practice (Manthorpe and Mowat 1975; Mowat,
1973; Johnston et al., 1976). The safety and
value of percutaneous liver biopsy in distinguishing
patients with EHBA from those with hepatitis is
well illustrated in this study. By the early use of
this technique a diagnosis of hepatitis is confirmed
in a large percentage of cases. In the majority of
patients with EHBA the correct diagnosis was made.
Nevertheless, in a number of instances the biopsy
was not considered suggestive of EHBA though this
proved to be the correct diagnosis, a difficulty
reported by other authors (Alagille, 1972; Thaler
and Gellis, 1968). In this series the timing of
percutaneous liver biopsy in relation to the duration
of jaundice did not seem to influence significantly
the correct histological diagnosis of EHBA.

We have used the Rose Bengal faecal excretion
test primarily to confirm liver biopsy findings where
they have been diagnostic or suggestive of EHBA,
or in instances in which persistent jaundice and
acholic stools have made this diagnosis a possibility
even though the biopsy appearances were not
typical. We have repeated the test during chole-

styramine administration when the biopsy was not
diagnostic and confirmed that a persistently low
excretion is of value in distinguishing patients with
extrahepatic biliary obstruction from those with
patent ducts. In this study the distinction, how-
ever, was not complete as had been previously
reported (Campbell et al., 1974b). 2 patients with
intact extrahepatic ducts, one having severe liver
disease and the other intrahepatic biliary hypoplas-
ia, had persistently low excretion. Whether the
improvement in excretion with hepatitis is attribu-
table to the beneficial effect of cholestyramine on
liver function, or to a reduction in the enteric
reabsorption of Rose Bengal, is not clear. Urinary
contamination of stools is particularly difficult to
prevent in female infants and this may account for
the false high excretion found in 2 infants. In
this series both tests indicated that laparotomy was
necessary in the 2 patients with choledochal cysts.
The combination of percutaneous liver biopsy and
$^{131}$I Rose Bengal faecal excretion test thus distin-

guishes satisfactorily between patients with extra-
hepatic biliary obstruction who require laparotomy
in case they have a surgically correctable lesion, and
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Effective in arresting the process. These observations and the low success rate in the series of patients we report lead us to advocate at the present time a policy of surgical intervention as soon as the diagnosis of extrahepatic biliary atresia is suspected on the basis of biopsy findings and the Rose Bengal excretion studies. Conjugated hyperbilirubinaemia in infants is never a benign condition, biliary atresia should be suspected if it persists for more than 2 weeks, and patients should be submitted to surgery in all instances by 70 days of age rather than wait until 4 to 5 months of age, as is still common practice. Such early surgical intervention might cause an increased number of infants with intrahepatic lesions and intact extrahepatic ducts to be subjected to laparotomy with its attendant risks, including possible destruction of normal patent but collapsed hypoplastic ducts by discrete surgery (Mason, Northway, and Kohn, 1966). It is essential therefore that such cases be operated on in centres where there is the necessary expertise available, both in making a presumptive diagnosis and in assessing the condition of the bile ducts at laparotomy.

From the present study no clues emerge as to what initiates extrahepatic biliary atresia. Males predominated in this series, but as in other reports (Alagille, 1972) the sex incidence was not significant. Neither seasonal factors, adverse factors in the pregnancy or perinatal period, nor birth order have been implicated in this study. Nor could the condition be related to the age of the parents, as reported from Hawaii and Japan (Shim, Kasai, and Spence, 1974) in a study which also suggested that familial cases occurred and that the birthweights in biliary atresia were low. This was not confirmed in the present series in which prematurity and low birthweight was a feature of the hepatitis group only. The exact reason for the poor intrauterine growth in the hepatitis cases was rarely identified, but such reduction in intrauterine growth is commonly found in fetuses subjected to a massive prenatal insult, such as rubella embryopathy. There is thus no evidence that the patients with extrahepatic biliary atresia were subjected to such a cause, and it seems that the adverse factor or factors which affect only the bile ducts must be very selective whether it operates antenatally or only postnatally. Our observation that in 6 of 32 infants jaundice was not observed until the third week of life supports the contention that the lesion is acquired rather than congenital in some patients at least. These observations provide a basis for hoping that in some cases removing the diseased extrahepatic bile ducts may allow the
Liver to function normally, and cause us to be cautiously optimistic about the place of hepatic portoenterostomy in the management of biliary atresia.

The study would not have been possible without the co-operation of many paediatricians and paediatric surgeons in the South of England. Many data were collected by Dr. Andrew Porter, Canterbury Hospital, and Dr. K. Cottrall, The Hospital for Sick Children, London, while Research Assistants in the Department of Child Health, King's College Hospital.

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