Pathology with reference to the bile retention syndrome

J. L. EMERY
M.D., F.R.C.Path., D.C.H.

Department of Pathology, Sheffield Children's Hospital

Summary
The pathological significance of giant cells, inspissated bile plugs and hepatic fibrosis in the liver of infants is critically reviewed. Evidence is presented suggesting that a wide variety of pathological change in the paediatric liver results from the interaction of the effects of growth, metabolic maturity, genetic metabolic variability and infection. Understanding of the bile retention syndromes might increase if the diagnosis of 'Neonatal Hepatitis' and 'biliary atresia' as finite conditions, were to cease and their pathogenesis considered in such a multifactorial way.

The study of hepatic pathology in young children has now reached a new stage. We are leaving the somewhat static concept of a series of isolated diseases of the liver and reaching one in which increased knowledge of the chemical activities of liver cells, an insight into the mechanisms of some virus affections of the liver, and more dynamic approach to the effect of disease processes on a developing, as distinct from a static, organ is forcing us now to think of liver disease in at least a type of four-dimensional way. The dimensions are: (1) growth; (2) metabolic maturity; (3) genetic metabolic variability; and (4) infection.

One of the present problems in discussing liver pathology in the infant is the difficulty in the use of terms as those in common use are usually related to unifactorial concepts of disease, and in particular, the use of the term 'hepatitis' in somewhat the same way as nephritis as applied to kidney disease, is ceasing to be meaningful. The well-established bacterial and allied infections affecting the liver such as syphilis, tuberculosis, Listeriosis (Hood, 1957), Entamoeba histolitica (Shute, 1947), and parasitic infections, and umbilical sepsis (Morrison, 1944), are well described and known not to require further discussion at this meeting but they can be correctly described as syphilitic hepatitis and amoebic hepatitis, and so on.

When we come to diseases of the liver related to virus invasion of the body, things are not so simple. The situation, again, varies in some degree with the particular virus (Pugh, Newns and Dudgeon, 1953; Stern and Williams, 1966; Strauss and Bernstein, 1968). The problem here appears to be that most of the viruses which affect the liver appear to be able to reside within the hepatocytes for varying periods of time in a state of apparent symbiosis and it is only when this symbiotic balance is disturbed that massive destruction of hepatocytes and the resultant calling into play of the usual inflammatory responses produces a situation which can legitimately be called hepatitis. Much current interest lies in the mechanisms that make a liver, existing in a state of virus symbiosis, go into a state of virus hepatitis. It is in this field that our immunological colleagues are, by the present time, having a field day.

Progressive liver destruction and failure also occurs in association with metabolic diseases. Here the diseases which are of greatest current interest are those associated with Wilson's disease, cystic fibrosis, and with alpha-1-antitrypsin deficiency. These conditions are important because we have some external guides by which we can measure them—the changes in the pancreas in cystic fibrosis, and the serological test in alpha-1-antitrypsin. Here we have diagnosable conditions that are sometimes associated with a progressive degenerative and inflammatory state within the liver, but more frequently are not. Others will discuss alpha-1-antitrypsin. Since cystic fibrosis and cytomegalovirus infections have long been amenable to the simple tools of my own craft, my observations on 'neonatal hepatitis' and 'congenital biliary atresia' have largely been derived from them.

The histopathology of the infant's liver is made up of a combination of factors—multinucleate giant cells, infiltration with leucocytes, bile infarcts, fibrosis, retention products in hepatic cells, proliferation of bile ducts, the presence of inspissated bile plugs, vascular changes and bile-laden cells in lymphatics. Some of these that have gained perhaps undue prominence in isolation need brief comment.

'Giant cell hepatitis'
'Giant cell hepatitis' is known to be a condition of the very young child and the discussion went on for years on the possibility that the giant cells are a specific reaction to a virus infection in the young
liver. I well remember taking part in a symposium in
the Ciba Foundation 15 years ago that was chaired
by the late Sir Roy Cameron in which we spent the
whole day on this subject; some maintained that the
presence of giant cells meant hepatitis of almost
certain virus aetiology and others that such lesions
could be produced as a result of congenital atresia of
the bile duct. The answer is still not certain but most
now consider that they are non-specific. I believe that
the numbers seen are the result of a balance between
the growth activity of the liver and the effect of living
or non-living mechanisms altering the metabolism
of the cell at the same time.

The giant cell state in the liver is progressively
more prominent as the neonate is approached and
even more so when one deals with intrauterine
disease. The facts concerning the multinucleate cells
were largely worked out by Popper and Schaffner
(1963) and Olefzka-Slotwinski and Desmet (1969)
who showed that there are no cell wall remnants in
giant cells and that the chief characteristics of the
cells are that the nuclei are smaller than normal
hepatocyte cells and that they often show budding
with rupture of the nuclear envelope.

The cytoplasmic activity of the giant cells varies
very considerably. Some appear to be able to handle
glycogen normally, others not. Cells also show varying
abilities to handle iron and bile and there rests a
nice problem as to why, in some of these livers,
multinucleate cells are filled with iron or glycogen or
fat and others, often cells adjacent, have a different
chemical storage pattern (Reubner and Miyai, 1963).
These giant cells can be produced by a number of
factors and not necessarily be of virus aetiology.
Campbell and Gilbert (1967) produced them using
an E. coli endotoxin. It must not be forgotten that
dividing cells are very common features of the normal
liver in the very young child.

It is usually believed and, I think, true that most
of these multinucleate cells will eventually degenerate
and are destroyed—they are the result of incomplete
cell division. Thus they are, at the same time,
regenerative and degenerative. The situation is that
of a boat tacking up an estuary in a good wind,
moving well over the water, but the movement of
the tide makes the true movements, that over the
bottom of the sea, something quite different from
the appearances on the surface. The younger the
child, the faster runs the tide!

*Insipissated bile plugs*

Small bile plugs can be found in the livers of a
very high proportion of children dying within a
month of birth if the child has been ill for more than
a few days with almost any condition. This particularly
applies to children who have surgical conditions
of the gut with peritonitis. The bile plugs appear to
be concentrated bile but they also contain protein
and sometimes a little iron-staining material.

These bile plugs are not necessarily due to the
complete blockage of the bile ducts because if one
injects the common bile duct with a thin fluid such
as Indian ink, it is possible to get the Indian ink up
through the bile ducts and into the intercellular
canalici beside the bile plug. This is by no means
an easy manoeuvre and if a simple injection of the
common bile duct is attempted, failure certainly
follows. It is only possible to get the ink to penetrate
if it is injected at a fairly low and constant pressure
and the liver is gently palpated, squeezed and
massaged for several minutes during this time. Fluid
appears to have to be coaxed rather than forced
along bile passages.

The bile plugs are associated with diminution and
absence of the micro-villi of the canalici of the liver
cells. It is easy to conceive of a situation in which
once a bile plug has formed, a diminished fluid
excretion could take place so that a vicious circle
can be set up with a persistence of the plug. This is a
situation that appears to occur in a number of
instances, quite independent of those associated with
general liver disease when an isolated plug occurs
surrounded by a small rosette of abnormal hepatocytes.

The aetiology of insipissated bile plugs will only be
certain when we understand the mechanism by which
bile moves through the canalici and through the
terminal bile passages. I have always been impressed
by the continual movement of the form and shape
of the liver consequent upon the movement of the
diaphragm and it is my belief that there is an increase
in the number of these insipissated plugs in conditions
in which there is a defect in mobility of the diaphragm,
whether it be due to an abnormal structure of the
diaphragm, to the presence of peritonitis or of
pleurisy. Thus it is my belief that a major factor in
the movement of bile along the canalici is due to
the continual movement of the liver. This lends sup-
port to the concept which was suggested by workers
in Boston (Hsia et al., 1958), that massage of the
liver may be of some assistance in bile excretion
although I feel that enforced active respiratory
movements may be the most effective chologogue.

Insipissated bile plugs also occur within the small
extra-canalicular bile ducts as, indeed, the cells of
these ducts often show the presence of bile granules
in their cytoplasm and appear to show similar
reactions to the formal hepatocytes. These occur
similarly in livers where rubella is involved as well
as those in which no known infective agent is
recognized.

*Fibrosis*

One of the characteristics of infant tissue is that
the amount of connective tissue is prominent. This is perhaps well seen in the pancreas and, since the pancreatic ducts and bile ducts are almost brothers, it is natural enough that the structure of the portal triads has a parallel development. The connective tissue in the young liver is more labile than in adults and care must be taken not to overemphasize the importance of ‘fibrosis’ of the liver as the amount of fibrous tissue in infant livers does not necessarily imply the same severity of disease and prognosis of that in adults.

In taking needle biopsies from livers in children it is wise deliberately to sample either the right or the left physiological lobe as, in the ill newborn, the left frequently shows a much increased amount of connective tissue and this is related probably more to the general perinatal state of the child than to any specific pathology (Ghosh and Emery, 1970).

**Bile retention syndrome**

Much of the most recent work on specific liver disease is being presented by others, in particular that of alpha-1-antitrypsin but when we have done the tests for this, for cytomegalovirus, for rubella, for syphilis and other known diseases, we have accounted for probably less than a third of children who present with prolonged jaundice (Hsia et al., 1958). Of these, we know that while perhaps a third will completely recover untreated, a third will also succumb with hepatic failure within the following 2 years. These children form the bulk of our present clinical problem. They often have somewhat fluctuant jaundice, their general body state can vary very considerably and their inconclusive liver function tests have been the worry of my clinical friends for years. Many come into hospital on the surgical side and the question always arises as to whether or not there is an element of significant large duct obstruction present that is amenable to surgery. These children present as an Infant Bile Retention Syndrome and the question that always arises is— are they a virus hepatitis, a congenital obstruction of the bile ducts, congenital absence of bile ducts, an inborn error of metabolism, or something else? (Harris and Anderson, 1960). My present belief is that most of these cases are probably a combination of several of the factors that were mentioned in the opening paragraph and the structural pathology is also a combination of several factors. The reasons are as follows.

1. The same virus seems to be able to ‘cause’ neonatal hepatitis, congenital absence of bile ducts, and bile duct atresia. This is well established in the case of rubella and cytomegalovirus. A perhaps over simple explanation of this is that the virus affects the liver at different stages of development.
2. Metabolic errors affecting liver cells occur with and without there being bile retention. This has long been known in cases of cystic fibrosis and, more recently, in alpha-1-antitrypsin states.
3. In most of the children with ‘bile duct atresia’, the meconium was normal. Meconium is a mixture of mucus, epithelial cells and bile and it derives itself bile from the bile duct and liver. In order to obtain normal meconium, bile excretion must have been functioning normally for a considerable time. This indicates that most bile duct atresias are secondary and acquired states coming on late in intrauterine life, or after birth.
4. Evidence from serial biopsy of the liver lends support to the idea that bile ducts can atrophy after birth. This was first brought home to me in Melbourne with Peter Campbell when, in a sequential series of four biopsies from the same child, the last biopsy showed a ‘congenital absence of bile ducts’ and the first, a ‘hepatitis’ picture. This type of finding is not invariable and must be interpreted carefully as changes can be different in different parts of the same liver.
5. The association of cytomegalovirus lesions with cystic fibrosis. In cytomegalovirus infection of the infant liver, the typical ‘owl’s eye’ lesions are more frequently found in the duct than in the parenchymal cells and in the cases that I have seen much more marked when the ‘hepatitis’ is associated with cystic fibrosis, which can affect these same ducts in isolation. It would appear that when the ducts are affected by one metabolic abnormality, then the cytomegalovirus becomes more damaging to the duct cells.
6. In biopsies from livers of children with the Bile Retention Syndrome, when the liver lobule shows a variety of lesions, so do the bile ducts and it is not uncommon to see areas of bile ducts in which the lining cells appear to be undergoing necrosis. This is usually in empty ducts rather than in those showing bile plugs.

My conclusions from these points are that we must look on the pathology of the Bile Retention Syndrome in a factorial sense and not in terms of finite aetiology. We see livers in different stages of combined disease processes and affecting some parts more than others. Thus, in any liver there is usually both cell damage and bile duct obstruction. Also, a balanced symbiotic virus is likely to become pathogenic in the presence of an inborn error of metabolism in the cells that are again affected by such non-specific features as E. coli infection of hypoxia (Reubner et al., 1969).

My plea is—cease to diagnose ‘Neonatal Hepatitis’ and ‘Congenital Bile Duct Atresia’ as finite conditions but look on infants with a Bile Retention Syndrome in a multifactorial way. We may obtain more success by so doing.
References
OLEDZKA-SLOTWINSKA, H. & DESMET, V. (1969) Morphologic and cytochemical studies on neonatal liver giant cell transformations. Experimental and Molecular Pathology, 10, 162.

Discussion
Dr Emery was asked if he had followed by a series of liver biopsies changes from classical neonatal hepatitis with bile ducts present to that of biliary atresia, either with absent bile ducts in the intrahepatic system or proliferation of the bile ducts in the liver and absence of the external biliary system. Dr Emery replied that he had seen progression from the picture of neonatal hepatitis to that of complete absence of bile ducts. Dr David Danks of Melbourne elaborated on this, reporting on six patients he had followed with clinical and histological neonatal hepatitis who initially had quite obviously bile-containing stools. These infants went on to develop typical clinical features, liver biopsy histology and surgical findings in the porta hepatitis of extrahepatic biliary atresia. In one of these infants an exploratory operation was made when the bile ducts were 'hot, red and oedematous'. Dr Emery reminded the audience that it was usual for infants with biliary atresia to have had bile stained meconium and thus must have had bile flow at some stage in development.