HEPATIC CIRRHOSIS IN CHILDREN,
with special reference to the Biliary Forms.

BY

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The occurrence in hospital within a comparatively short space of time of four unusual examples of cirrhosis of the liver in young children has led us to make this communication.

Disorders of the liver in childhood have in recent years not attracted much attention in this country, and we feel that the mere ventilation of the subject, though we may have little new to add, may serve a useful purpose.

It is possible that others besides ourselves have been inclined to be guided in their views upon cirrhosis of the liver by a recollection of cases of alcoholic cirrhosis in the adult, and to recall such symptoms as chronic gastritis and vomiting, haematemesis, ascites, jaundice, pruritus, dilated capillaries on the cheeks, the caput medusae, and concomitant results of the particular cause such as sleeplessness, wasting, loss of memory, and tremor. Again it is possible that admitting the rarity of alcohol as a causal factor in the child we incline over much to a syphilitic origin. It is, we believe, a more illuminating, though certainly a difficult undertaking, to discard entirely our views upon cirrhosis of the liver in adults and to approach the problem in the child from the clinical and pathological features at that age.

Among the symptoms that we associate with cirrhosis of the liver in childhood there are many of those which we have already mentioned in referring to alcoholic cirrhosis. Epistaxis may be frequent, and telangiectases are often present, so that the face may present at a glance an aspect similar to that of chronic alcoholism. Ascites, however, and dilatation of the superficial abdominal veins, are often absent, and more remarkable still there may be no digestive disturbance. Special features related to childhood are infantilism, and a familial occurrence of the disease, which in its frequency is very striking.

In adults suffering from chronic cirrhosis there may occur a sudden intensification of the jaundice with fever, nervous symptoms and death in coma, and microscopy shows an acute destruction of liver cells. In childhood, also, such a development may supervene and be a cause of death from acute red atrophy. In these instances we seem to be able to trace a correlation between the urgent symptoms and the destruction of the liver cells. Here in child and adult the picture is identical. In children, however, more than in adults, this exacerbation of damage to the hepatic cells may assume a subacute form, possibly owing to the greater reparative powers possessed by the liver in the young.

The pathogenesis of hepatic cirrhosis in children is more often obscure than it is in adults. As to its frequency in childhood, some idea of the rate of incidence may be gained from the figures given by Graham Forbes. He collected forty cases out of a total of five thousand, five hundred autopsies at the Children’s Hospital, Great Ormond Street, which covered a period of forty-five years.
ARCHIVES OF DISEASE IN CHILDHOOD

Case I.

Katherine H., aged eight years, had a history, covering a period of nine months, of loss of appetite, listlessness, chilliness, sleepless nights, pains across the stomach, and of becoming yellow. There was no diarrhoea, vomiting, or epistaxis. The only previous illness had been whooping cough, but she was stated not to have been in really good health for the last three years. Both parents were healthy, but several of the mother’s relatives had suffered from tuberculosis. There were four other children living besides the patient, these being younger than herself, but none of these had ever been jaundiced. In two young sisters, however, the liver was easily palpable.

On admission to hospital the patient was considerably jaundiced, had dilated veins on the chest and abdomen and a few telangiectases on both cheeks. The abdomen was rather large and doughy, the lower edge of the liver extending two finger-breadths below the costal margin. The liver was hard in consistency and the spleen was just palpable. There was no ascites. Bile pigments were not found in the urine and the faces were quite well coloured.

Slight enlargement of the cervical glands was present. The tonsils had been enucleated previously. No evidence of disease of the heart, lungs or nervous system was obtained. Examination of sputum for tubercle bacilli was negative.

Investigations:

Van den Bergh’s test gave both positive biphasic and indirect reactions (suggestive of an incomplete obstruction of the bile passages, with a fair degree of liver damage). The blood fragility test gave a normal result. Erythrocytes amounted to 4,320,000; leucocytes 5,920 per cubic millimetre, of which 46% were polymorphs and 49% lymphocytes. In both the patient and her mother the Wassermann reaction of the blood was negative. The patient gave a positive von Pirquet reaction to human tuberculin. A subcutaneous injection of Koch’s O.T. 0·001 cc. produced both a general and a local reaction, and both the liver and spleen subsequently became larger.

Progress:

On discharge from hospital the jaundice had entirely disappeared, but both the liver and the spleen were still easily palpable. Within the next twelve months she had two attacks of erysipelas, and several attacks of jaundice with haematemesis and epistaxis. When last seen, at a recent date, there was no jaundice, the liver was palpable, but the spleen could not be felt. She appeared to be in fairly good health.

Cases II. and III.

These patients, a brother and sister, were of an even more unusual type. That the disorder was of congenital origin was indicated by the fact that the abdomen in each case was enlarged at birth. One of the most puzzling features, however, was the absence of jaundice except as a transient complication of an intercurrent infection.

Both children, A. B., seven years and four months, and O. B., three years and two months, were born at full term and in normal labour. In both it was noticed at birth that the abdomen was abnormally large. The parents were both healthy and had never been jaundiced. There was a third child, an infant of five months, which was...
ARCHIVES OF DISEASE IN CHILDHOOD

examine also, in whom neither the liver nor the spleen was increased in size.
A history of alcoholism in the parents could be excluded. The Wassermann
reactions of the blood of the parents and of the two affected children were negative.

A. B. was first admitted to hospital in May, 1920, when three years and two months
old. At this time a history was obtained that he had suffered from epistaxis, but had
never been jaundiced. He had an attack of pneumonia a few months previously. The
liver was found to extend below the umbilical level, its upper limit being at the fifth rib in
the mammary line. In circumference the abdomen at its widest girth measured 28 inches.
The spleen and kidneys were not palpable. Numerous dilated superficial veins were present on
both cheeks. Icterus and ascites were absent. No rise of temperature occurred and the
stools were of a normal colour. The urine presented no peculiarities. A blood count
showed R.B.C. 4,900,000, and W.B.C. 10,600; polymorpho-nuclears 80%.

In March, 1921, the child was re-admitted with a history of having been suddenly
overcome, four weeks previously, with sickness, which lasted for five hours. Three days
from the onset of the sickness he became feverish, drowsy, constipated, and had headache
and abdominal pains. Four days later he vomited blood, his nose bled, and jaundice
appeared for the first time. The jaundice deepened, and there were two further attacks of
epistaxis, one being brought on by a fit of coughing. On examination he was found to be
deeply jaundiced and the lower edge of the liver reached down to the right iliac fossa and
the spleen was definitely enlarged. In circumference the abdomen measured 26½ inches.
In little more than a month from its onset the jaundice had entirely disappeared. The
child then developed scarlet fever and was transferred to the fever hospital.

When next re-admitted to hospital in June, 1924, when seven years and four months
old, the liver was found to extend downwards only as far as the umbilicus; the spleen and
kidneys were not palpable. The abdominal girth was 25½ inches. On palpation the liver
was hard but no irregularity of its surface could be detected. Jaundice and ascites were
absent, and the stools and urine were those of a normal healthy child. Epistaxis did not
occur. No prominence of the superficial abdominal veins was observed. Telangiectases
were present on the face as mentioned already. There was no clubbing of the fingers. A
blood count showed the erythrocytes to number 4,240,000, leucocytes 22,540, of which 51%
were polymorpho-nuclear cells. The child's height was 38 inches, the normal average for
his age being 47 inches. His mother declared that he had developed normally up to the
time he became sick, but when seven months old, she had noted no bony deformities,
but showed a delay in the ossification of the carpus. It was also thought that the splenic and renal shadows were larger than normal.

O. B., the sister of the last patient, was first examined at the age of three years and
two months. She had previously had measles, whooping cough, and an attack of
tonsilitis, which was complicated by jaundice, lasting only a few days. The mother stated
that the child's stools had always been of a natural colour, and there was no history of
epistaxis.

In appearance the child was small and fat, and the abdomen was strikingly prominent.
In circumference it measured 22½ inches. She was roughly 4½ inches beneath the average
height for her age. Numerous telangiectases were present upon the cheeks, but there was
no jaundice or ascites. The superficial abdominal veins were not visible. The lower edge
of the liver reached the level of the umbilicus, its upper limits being normal. In consist-
ency this organ was firm and hard, but no nodules could be detected. The spleen was
thought to be just palpable; the kidneys could not be felt. No trace of bile was discovered
in the urine, and the stools and temperature were normal. Examination of the blood
showed the R.B.C. 4,500,000 per c.mm. and W.B.C. 19,688, of which the percentages of
polymorpho-nuclears and lymphocytes were equal. Skiagrams showed variations from the
normal very similar to those found in the brother, namely, a delay in ossification of the
carpus and an increase in the size of the splenic and renal shadows. There was no
clubbing of the fingers.

Various tests of the state of the blood and the efficiency of the liver were

The blood fragility, blood diastase and cholesterol were all within normal
limits in both cases. The blood sugar, however, was slightly below the
average, being 0·053 and 0·056 respectively. There was a very definite
lipemia of the blood of each patient, as seen in the separated serum. Van
den Bergh's and the laevulose tests both gave normal results. There were,
therefore, no definite signs of inefficiency of the hepatic functions. It must
be observed, however, that an absence of abnormality in the results of the
various hepatic efficiency tests is in no way conclusive that the liver is sound.
To obtain results indicative of an impaired efficiency, as is known from
experiments upon animals, a very large proportion of the whole hepatic
substance must be in a state of disorder. It is probable, therefore, that the
two children were examined during a quiescent stage of the disease, and
that they might give positive results of impaired efficiency to the tests on
other occasions. In this connection it is of interest that icterus had appeared
temporarily in each child as a complication of some intercurrent febrile dis-

Reviewing these three cases, it is to be noted that in one the condition
was first noticed at the age of eight years, attention being drawn to it by the
presence of jaundice. The jaundice was intermittent, disappearing entirely
from time to time. Such symptoms as telangiectases on the face, dilatation of
the superficial abdominal veins, epistaxis and haematemia were all present.
Ascites, however, did not occur. The child appeared to be the only affected
member of a numerous family.

In the other two cases the condition was both familial and congenital.
The familial occurrence of hepatic cirrhosis and even a history of jaundice in
one or other parent has often been recorded. In the present instance, how-
ever, although both parents were apparently exempt, it was stated that an
uncle of the father, and two children of one of the father's cousins, had had
enlarged abdomens and were stunted in growth, though otherwise healthy.
It has not been possible to verify these statements.

Both these children showed distinct signs of infantilism, particularly in
their stature; both had telangiectases on the face, and both had a history of
epistaxis. Other symptoms common to hepatic cirrhosis were absent, such
as ascites, dilatation of the superficial abdominal veins, and the degree and
duration of jaundice in either case were remarkably slight.

The amount of splenic enlargement in all three cases was a minor
feature in the clinical picture, and moreover was not of a permanent
character.

The possibility of an infection invading the system and proving a factor
in the development of cirrhosis is suggested by the following case.

Case IV.

A female, aged five years, was admitted on March 6th, 1925, with
a history of jaundice of eight weeks' duration, with headache and grey motions.
The three children of this family had developed jaundice after "colds"
within a week of one another. In each case the urine became high coloured
and the motions pale, and all complained of headache.

The eldest, a boy aged nine years, recovered in three days; the
youngest, a girl aged four, in a week; the middle one, the patient, appeared
to have recovered after three weeks but then relapsed.

Their mother gave no history of previous attacks in the family, but a
maternal uncle and aunt had suffered from jaundice when young. The three
children were examined. The two that had recovered showed a slight icteric
tinge of the sclerotics, and in both the liver, but not the spleen, was felt
below the costal arch. The fragility of the blood cells was normal. Both
showed some pallor but otherwise were healthy.

The child in hospital was well nourished but considerably jaundiced. There was no
headache, pain or vomiting; the temperature was raised (100 F.). The liver extended three
fingers breadth below the costal arch and was firm and smooth. The tip of the spleen
could be just felt. The stools were light in colour, and the tests for bile in the urine were
positive. Van den Bergh's test was positive, highgrade and indirect. The fragility of the
red cells was diminished and the R.B.C. numbered 4,900,000 per c.mm., W.B.C. 9,000,
the differential count giving polymorpho-nucleares 37%, small mononucleares 51%, large
3.5%, eosinophils 2%. After a few days the jaundice lessened, and though the stools were
pale, bile was not again demonstrated in the urine.
ARCHIVES OF DISEASE IN CHILDHOOD

Three weeks after admission the temperature, which had never been normal, began to rise, and on the twenty-eighth day reached 104 F., but the child, though listless, had no pain and did not seem ill. Both liver and spleen now commenced to enlarge, particularly the spleen, which, at the end of the month, reached nearly to the umbilicus. Neither organ was tender and there was no enlargement of the lymphatic glands. The urine, though darker, did not contain bile; the motions were, as before, pale in colour.

The enlargement of the spleen continued until it reached four inches below the costal margin, and the liver then extended below the level of the umbilicus. The wave of fever then slowly declined, and with this the liver and spleen, the latter particularly, began to diminish in size. The child herself looked better and gained in weight. By May the liver had shrunk to midway between the right costal margin and the umbilicus, and the spleen could only just be felt projecting below the left flank. The child still showed a yellow tinge in the conjunctiva and skin, and developed a peculiar rash, lichenoid in type, during this stage of recovery.

Prior to advancing any views as to the causation, congenital or acquired, or to the type of cirrhosis presented by these cases, the moment appears opportune to give a brief description of the various forms of hepatic cirrhosis, which may be met with in childhood.

Types of Hepatic Cirrhosis.

1. Multilobular (portal, "hobnail" or "alcoholic").
2. Syphilitic (pericellular).
3. Type associated with Wilson's disease (progressive lenticular degeneration).
4. Type associated with Icterus Gravis Neonatorum.
5. Hepatic cirrhosis in Banti's disease.
6. Type sometimes found in combination with "red atrophy" of the liver.
7. The Biliary Cirrhoses, including hypertrophic biliary cirrhosis (Hanot), congenital cirrhosis, with or without obliteration of the bile ducts, and obstructive biliary cirrhosis.

Relative Incidence.

It must be stated at the outset that the various forms are not given in order of the frequency of their occurrence. Some idea of their rate of incidence can be gained from the following figures which are taken from the postmortem records of the Children's Hospital, Great Ormond Street, covering the period from January, 1910, up to June, 1925. There were twenty-two cases of congenital biliary cirrhosis. Obliteration of the larger bile ducts was present in fifteen of these, while in the other seven the ducts were patent. The duration of life in both types did not exceed six months, the majority succumbing in the first few weeks, except in two cases without obliteration of the bile ducts, which lived just over a year. It is worth mentioning in connection with the group of congenital biliary cirrhoses that other congenital abnormalities were discovered in three instances. A congenital cardiac lesion, together with Mongolism on the one hand and deformity of the feet on the other, was present in two cases with obliteration of the bile ducts, and a patent ductus arteriosus was found in one case in which the bile ducts were not obliterated. Nineteen cases of syphilitic cirrhosis came to autopsy, and in one only were gummata of the liver found. All died below the age of eight months. A Wassermann test was performed in all except four and found to be positive. In the four cases just mentioned the family history and other signs of syphilis, besides the condition of the liver, confirmed the diagnosis. Of the portal or hobnail variety there were only three examples, two being nine, and the third three, years old. The types found in combination with splenic anaemia (Banti's disease), and "red atrophy" of the liver numbered one each. Obstructive biliary cirrhosis was present in two cases. There were no examples of icterus gravis neonatorum, nor of the cirrhosis associated with Wilson's disease.
True cases of portal or multilobular cirrhosis are much less common in children than those of the biliary type. Clinically the jaundice is intermittent and seldom deep, ascites usually makes its appearance and there is dilatation of the superficial abdominal veins. The tendency of the liver to become small by contraction of the fibrous tissues is much less noticeable in children than it is in adults with the same type of cirrhosis. Facial telangiectases, epistaxis and haematemesis occur. These latter symptoms, however, are common to nearly all the different forms of cirrhosis. It is seldom that any definite factor can be unquestionably accepted as the cause of the disease, but it is generally held that the exciting agents are conveyed to the liver by way of the portal tributaries and possibly by the splenic vein.

As examples, the cases recorded by Jolly(2) of a brother and sister, eleven and ten years of age, conform most closely to the "alcoholic" type. These children had been in the habit of drinking frequently small quantities of vinegar. Neither child was jaundiced, and the liver and spleen were not palpable. At the autopsy, permitted on one of the children, the liver was found to be granular and yellowish. Histologically the cirrhosis was definitely multilobular in distribution.

Out of the cases collected from the hospital records the following (one of Sir Archibald Garrod's) is a good example of multilobular cirrhosis where no predisposing cause can be traced in the previous history of the patient.

It is that of a girl of nine years, who developed jaundice, ascites and hydrothorax. At autopsy the liver was found to be much reduced in size, very rough and nodular, and with adhesions to the parietal peritoneum. During life there was no evidence of enlarged abdominal veins, but at the section large vessels were seen communicating between the right kidney, suprarenal and diaphragm, also between the diaphragm and the right pleura. The pancreas was very firm, the spleen large and congested. Old caseating glands were present in the mesenteric glands.

Pathologically, in a typical case the liver is usually enlarged, rather than reduced in size, coarsely nodular, pale and mottled, and shows on

Fig. 2.
Photograph of liver of Sir Archibald Garrod's case showing "hobnail" type of cirrhosis.

Fig. 3.
Liver from the same case as in Fig. 2, the cut-surface showing multilobular distribution of fibrosis.
section a multilobular distribution of the fibrosis. It is inaccurate, however, to suppose that all cases of the portal type show a multilobular cirrhosis, as not infrequently the fibrosis may be chiefly monolobular or mixed. In his Lumleian lecture of 1900, Cheadle, in discussing adult alcoholic cirrhosis, stated that there was no question that a fine fibrosis, monolobular or intralobular in arrangement might occur in conjunction with hypertrophy of the liver. This variability in the distribution of the fibrous overgrowth occurs also in cirrhosis of the biliary type. Of greater importance, in distinguishing the two forms, is the presence of bile casts in the intrahepatic ducts and between the columns of liver cells, and of stippling of the liver cells with bile granules, which is a feature of the biliary form of cirrhosis. In portal cirrhosis the presence of pigment in the cells and bile casts is not seen unless jaundice has been definitely present at the close of the illness. Compression of the intrahepatic branches of the portal vein is more evident in the portal type of cirrhosis than in any other, which may be accounted for by the entry of the exciting poisons via the portal system.

2. Syphilitic Cirrhosis.

Syphilitic cirrhosis, in most cases, is readily distinguishable histologically by its pericellular distribution. The virus is conveyed to the liver from the placental blood by the umbilical vein. Jaundice is almost always present in this form, but in degree may be no more than a slight pigmentation of the skin. Ascites and dilatation of the superficial abdominal veins are frequently present.

As a typical case the following instance will serve:—

A female infant of four weeks was admitted to hospital with vomiting and progressive enlargement of the abdomen. A slight icteric tint of the skin had been noticed from birth. Ascites was present and the superficial veins of the abdomen were dilated. The liver was firm and easily palpable, and the spleen could also be felt. Other symptoms included snuffles, excoriations about the mouth, a papular eruption on the forehead, and one or two blisters on the palms of the hands and soles of the feet. The Wassermann reaction of the blood was strongly positive. She was the third child; the first, aged four and a-half, was alive and well; the second, born prematurely, died jaundiced a few weeks after birth.

Pathologically, in congenital syphilitic cirrhosis the liver is usually found to be enlarged, firm and smooth or finely granular, and of a dark colour, sometimes slate blue. The cirrhosis is brought about by a small celled infiltration, which spreads indiscriminately throughout the organ. The cells are considered to arise from a proliferation of the connective tissue cells and of the endothelium of the intralobular capillaries and lymphatics (Allbutt and Rolleston). The fibrous tissue which is formed is both intralobular and pericellular. Obliterative changes of the hepatic artery are very rarely found. An apparent increase of the small bile ducts is sometimes present. Spirochaetes in large numbers may be demonstrated by suitable methods of staining.


In these cases there is rarely any indication during life of hepatic disorder, but in three described by Wilson, attacks of jaundice, oedema of the legs and ascites occurred before the onset of the nervous symptoms. Tests of hepatic function, in suspected cases, have failed to reveal a morbid state of the liver.

Clinically, the essential features of the disease are related to the nervous system. Wilson described the disease as being "characterised predominantly
ARCHIVES OF DISEASE IN CHILDHOOD

by bilateral degeneration of the lenticular substance," and considered that there was evidence of a toxic origin, the toxins possibly being elaborated in the liver.

A feature of great importance, from the point of view especially of the hepatic changes, is that the disease may be familial. In his original paper in *Brain*, 1912, Wilson found the average age of onset to be fifteen years. The youngest of the cases he recorded was ten. In a case of one of us, published in full in *Brain*, the onset was in the fourteenth year. The liver was small, tough and nodular, and presented the usual appearance of a multilobular cirrhosis. During life, however, no symptoms of hepatic disorder were present, and the liver was not palpable.

![Image](https://example.com/image.png)

**Fig. 5.**

(x60) Section of liver from case of Progressive Lenticular Degeneration, showing coarse multilobular cirrhosis with very little damage to hepatic cells.

Here the type of cirrhosis is mainly multilobular. The liver is usually coarsely nodular and of a pale colour. There is considerable thickening of the portal tracts, but the portal vessels show little alteration. The bile canaliculi appear increased in number, but without any evidence of obliteration. In some nodules the hepatic cells appear fairly normal, in others necrotic.

4. *Icterus Gravis Neonatorum.*

A rare variety of disease of the liver, which in some ways closely resembles Progressive Lenticular Degeneration, is known as *Icterus Gravis Neonatorum*. Pfannenstiel(6) was the first to separate this condition from the other more common forms of icterus of the new born. The disease is often
Fig. 4.—(X 225) Example of pericellular cirrhosis of syphilitic origin.

Fig. 9.—(X 60) Shows early cirrhosis of a monolobular type and pigmentation with bile granules of the cells towards the centre of the lobule. A higher magnification revealed the presence of numerous bile-casts lying like cement between the apposed hepatic cells.
Fig. 10.—(X 135) From a case of Congenital Obliteration of the bile ducts. Bile pigmentation of the cells and bile-casts are conspicuous. The cirrhosis tends to be monolobular.

Fig. 11.—(X 300) From a case of Congenital Biliary Cirrhosis without Obliteration of the Bile ducts. The appearances are similar to those seen in Fig. 10.
familial, and a disposition towards hepatic disorders may be present in the family history. In Esch’s case the mother’s father had suffered from severe jaundice, one of her sisters had been jaundiced, and another had suffered from gall stones. Beneke recorded two cases in twins which died within the first three days of life.

In icterus gravis neonatorum the jaundice is usually intense, is commonly observed at birth, and death occurs in a few days, sometimes within twenty-four hours.

The nervous symptoms, in icterus gravis neonatorum, are not present at first, but develop later. They consist chiefly of head retraction, rigidity of the limbs, and tonic contractions of the upper extremities. These symptoms cannot be said to form a special syndrome of the disease, as they are sometimes seen in the terminal stages in patients dying from any form of hepatic cirrhosis.

The essential feature of the disease is the selective staining of certain parts of the central nervous system, the lenticular nucleus in particular, the corpus Luysii, nucleus dentatus, the olives and other gray matter at the base of the brain. These areas would appear to have a special affinity for the circulating pigment, and are stained a bright yellow, bile pigment being found in the bodies of the nerve cells. In no other type of hepatic disease, except that found in progressive lenticular degeneration, does the brain show any morbid changes.

Pathologically, there may seem to be very little evidence in favour of grouping such cases among the cirrhoses of the liver. In affected infants, dying in the first few days after birth, the liver is usually enlarged, of a normal colour and consistency, or it may be soft. The gall bladder contains viscid bile. Beneke, reporting on the pathology of Esch’s case, which died on the day of birth, found no indication of increased connective tissue. The liver cells commonly contain bile pigments, and bile concretions are sometimes present in the intrahepatic ducts. In the more chronic cases, however, as for example in the fourth child in Pfannenstiel’s family, which died on the twenty-first day, the liver was enlarged, coarse, and dark green; the spleen very rough and of a dark reddish-brown colour. Microscopically the interstitial tissue of the liver was irregularly broadened and had an edematous appearance, with here and there small collections of cells. The liver cells contained bile and the cell-columns were very narrow; the bile ducts were widened at several points. These details are strongly suggestive of an early biliary cirrhosis, the fibrosis not commencing until after birth. We have met with no example of this type.

5. Hepatic Cirrhosis in Splenic Anæmia (Banti).

In splenic anæmia there may occur, in the later stages of the disease, a multifolobular cirrhosis, thus constituting what is known as Banti’s disease. This affection is stated to occur at any age outside infancy, the incidence being greatest between the age of twenty and forty. The spleen enlarges long before the liver, and may attain considerable dimensions. Other characteristics of the disease are anæmia, absence of leucocytosis, low haemoglobin percentage, and the tendency to hæmorrhages, especially gastrointestinal.

Although very few authentic cases have been recorded in children, cases do occur, which conform to this type more closely than to any other.

For example, in a case seen by one of us, a boy of four and a-half years, the spleen was noticed to be large at the age of two. In the same year he had a severe hæmatemesis. The child was extremely pale, had a cardiac murmur of the hæmio type, his spleen was
large, liver small. R.B.C. amounted to 2,750,000 per c.mm., W.B.C. 2,400, and haemoglobin 30%. He died suddenly after a profuse haematemesis. At autopsy large varices were found at the lower end of the oesophagus. The spleen was large and cicatrised, and there was considerable peri-splenitis. The liver was small, pale and firm. Histologically it showed early cirrhosis of the portal type.

Here we appear to have an example of a cirrhosis very different from the biliary type, in which the toxins presumably were carried to the liver by the splenic vein.

A second case observed by one of us illustrates in addition the interesting fact that whether the spleen or the liver appears to be the predominant organ, the clinical symptoms may in some cases be latent.

A boy, H. C., aged twelve years, had been attending school until the evening of his illness, and though of late his mother had thought him pale, and he had occasionally complained of abdominal pain, he was supposed to be in his usual health. This boy was brought to hospital late in the evening of December 30th, 1924, moribund, from repeated haematemeses, which had commenced on his return from school on December 29th, and had continued at intervals through the following day and night. On admission he was almost pulseless and died that night. His spleen extended to the umbilicus, and the edge of the liver could be felt, firm and well defined, below the costal arch. The liver was cirrhotic with numerous large "regeneration" nodules. The spleen was deep red. The remaining organs were avascular. The Wassermann reaction was negative. The necropsy showed an ulcer through an oesophageal varix.

6. Cirrhosis associated with "Red Atrophy" or subacute Yellow Atrophy.

Occasionally, in the course of a case of cirrhosis of the liver, an abrupt exacerbation of the symptoms, sometimes febrile, occurs, culminating in death; or without a previous history of hepatic disorder, a patient may
suddenly and unaccountably develop jaundice, pyrexia, enlargement of the liver, ascites, and die in a few weeks' time. In such cases sections of the liver microscopically show areas of necrosis of the parenchyma, other areas of degeneration of the hepatic cells, some extravasation of red corpuscles and varying degrees of fibrosis. The appearances correspond closely to what is known as subacute yellow atrophy in adults. Marchand states that anatomically there may be typical red atrophy of the liver, while clinically the course of the disease may be that of a chronic, possibly recurrent, type of the disease.

Recently R. Hutchison and D. Paterson recorded the case of a child of fourteen months, who died after an illness lasting seven weeks.

The symptoms consisted of jaundice, enlargement of the liver and spleen, ascites, general oedema, and slight irregularity of the temperature. A blood count showed W.B.C. 80,000 per c.mm., which was suggestive of an infective cause. The Wassermann reaction was negative. Histologically there was a well marked cirrhosis of the liver of a mixed type, multi- and unilobular and intercellular. Extensive destruction of the cells was present besides areas of regeneration, and the newly-formed fibrous tissue was very cellular.

A similar case of our own is that of a girl of six years, who became jaundiced and died at the end of nine weeks.

There was nothing in her past history which would have led one to suspect disease of the liver. Following upon the jaundice other symptoms were enlargement of the liver, epistaxis, ascites, haematuria, putty-coloured stools, and vomiting. The blood count was not abnormal, and the Wassermann reaction was negative. The liver in this case was small, shrunken and "hobnail"; spleen considerably enlarged; pancreas fibrotic. A mixed cirrhosis, both multi- and monolobular was present, with extensive necrosis of liver cells and round-celled infiltration. Incidentally the thyroid gland was in an advanced stage of disintegration. There was no colloid, and no secreting cells were visible.

![Fig. 7.](attachment:image.png)

(x52) Represents the appearance seen on section of the liver in the case just described. The cell atrophy, however, unequal staining of the hepatic cells, and disappearance of many of the nuclei is not so obvious as in the original section.
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Whether this rapid destruction of the liver cells marks some particular type of hepatic disease, or whether it is a possibility in all forms of cirrhosis is difficult to decide on account of the rarity of its occurrence. There is considerable evidence to show in many cases that there has existed a chronic but latent cirrhosis of the liver. This suggests sudden intensification of the poisons affecting the organ.

7. The Biliary Cirrhoses (a) Hypertrophic Biliary, (b) Congenital Cirrhosis with or without Obliteration of the Bile Ducts, and (c) Obstructive Biliary Cirrhosis.

In contrast to what is found in adults, cirrhosis of the liver in children is more often of the biliary or unilobular than of the portal type. These biliary cirrhoses, with the exception of the obstructive forms, are remarkable for the frequency with which they are familial.

(a) The form known as hypertrophic biliary cirrhosis, or Hanot’s cirrhosis, occurs in the first half of life, probably commencing as a cholangitis and pericholangitis of the smaller bile ducts. Most of the cases described by Hanot were in adults, but later Gilbert and Fournier(10) published their observations on seven cases in children, the youngest of their series being a child of five years.

We have no record of a case of Hanot’s form of cirrhosis, and it would appear to be a rare occurrence in this country if we may judge by the writings of others. It is possible that this type depends upon certain climatic or racial factors and that, in this country, we have cases akin, rather than identical. Hanot (11) defines this condition clinically as a chronic affection, characterised by permanent jaundice, febrile disturbances with exacerbations of the icterus, recurrent abdominal pain, considerable enlargement of the liver and spleen, and by an absence of ascites and dilatation of the superficial abdominal veins.

(b) The chief symptoms of the form of cirrhosis associated with obliteration of the extrahepatic bile ducts (congenital biliary cirrhosis) are jaundice, usually intense, present at birth or appearing shortly afterwards, and considerable enlargement of the liver, and to some extent of the spleen. Edema of the extremities and ascites are sometimes present. Pallor of the stools is always observed, although a small quantity of normal coloured meconium may be passed at first. Death may occur after a period of a few days or weeks, usually before the fourth month, and always, according to Dr. John Thomson, under the year. Cases of congenital biliary cirrhosis without obliteration of the bile ducts, or in which there is only a partial interference with the passage of bile into the duodenum, are clinically indistinguishable from those which present obliteration of the ducts. Jaundice may be present at birth, or appears a few days or weeks afterwards, and the stools become pale. With few exceptions death occurs within the year, and usually before the sixth month.

Two examples are of interest in so far as the onset of jaundice was later in the case with obliteration of the bile ducts than in the one in which the ducts were patent. In the former jaundice was first noticed at the age of seven weeks, and the liver was found to be considerably enlarged. Jaundice in the second case appeared at the end of the third week. The stools became pale, the urine green, and the liver was slightly enlarged. Death occurred in the tenth and eighth weeks respectively. The Wassermann reaction of the blood in both cases was negative.

(c) Obstructive biliary cirrhosis in children is a rare event. The common causes in adults, such as cancer of the head of the pancreas and impacted stone in one of the large bile ducts, are not met with below the age

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of puberty. It has, however, been stated to occur as the result of pressure on the common bile duct by tuberculous glands in the hilum of the liver. Considering the large number of cases of general tuberculosis in which large caseating glands are found between the head of the pancreas and hilum of the liver, and in which no evidence of biliary obstruction is present, either during life or at autopsy, this method of production appears to us doubtful.

Two cases of obstructive biliary cirrhosis were observed recently at Great Ormond Street, one of which, Dr. Still's case, was recorded in the Lancet, May 9th, 1925, and the other in the same journal, June 27th of this year. Dr. Still's case was that of a girl of six years, in whom an intermittent over-distension of a congenital cystic abnormality of the common bile duct had brought about a secondary cirrhosis of the liver.

FIG. 8.

(x67) Section of the liver from Dr. Still's case showing cirrhosis and an apparent increase of bile ducts. The cirrhosis was of a mixed type.

The liver was found to be slightly enlarged, firm and finely granular superficially. Microscopy showed some thickening of the portal tracts, and the fibrosis was specially distinct around the smaller bile ducts, spreading also into the lobules and compressing the peripheral ends of the columns of liver cells, thus giving the appearance of pseudo-bile ducts. The bile ducts themselves were not dilated. In the other case secondary sarcoma of the pancreas was the cause of obstruction in a girl of ten years. The liver, which was considerably enlarged and of a dark green colour, showed no evidence of metastatic invasion. An early definitely unilobular cirrhosis was present, with thickening of the portal tracts, bile casts in the small bile ducts, and granules of bile pigment in the liver cells.

COMPARISON OF THE TYPES OF BILIARY CIRRHOSIS.

When we consider biliary cirrhosis we are at once met by the numerous writings devoted to the proof that there is a distinct pathology for the various
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types. Yet we are left doubtful as to whether there is evidence of sufficient weight to allow us to go further than to consider the distinctions to be rather those of degree than of nature.

(A) Hanot\(^\text{(14)}\) certainly considered that the so-called hypertrophic biliary cirrhosis possessed peculiarities sufficient to isolate it from all other forms. His definition was that of an interstitial hepatitis, both extra and intra-lobular, with catarrhal changes and a great increase in the number of the small intrahepatic bile ducts. The liver was described as being usually of a dark green colour, enlarged, and having a smooth, or finely granular surface, the fibrosis being chiefly unilobular in type. In the portal spaces the connective tissue was less dense than in multilobular cirrhosis, and signs of fibrosis and cellular reaction were more evident in relation to the sheaths of the biliary than of the vascular channels. Catarrhal changes, with desquamation and renewal of the epithelial cells lining the inter-lobular bile ducts were observed, and many of the smaller ducts were found to be in a state of oblitative cholangitis.

Constriction of the hepatic vessels and of the branches of the portal vein was absent. In fact some dilatation of the latter was frequently present in the portal spaces. The hepatic cells were for the most part little altered, except where the intra-lobular cirrhosis was well marked, and then the columns of the liver cells were often seen to be flattened and squeezed together, or separate cells at the periphery of the lobule were surrounded by connective tissue as in a pericellular cirrhosis. Pigmentation of many of the hepatic and endothelial cells lining the smaller bile ducts was noticed, and also the presence of bile casts between the columns of compressed liver cells and in the smaller extra-lobular bile ducts. Attention was particularly drawn to the absence of contraction of the fibrous tissue, which might be accounted for by the unobstructed state of the blood supply. Hanot stated that the liver, in a small number of his cases, did actually lose some of its increased bulk in the later stages of the disease. The cirrhosis in these latter cases was found to be of a mixed type, both unilobular and multilobular, but chiefly the former. In explanation it was suggested that a portal or atrophic cirrhosis had arisen as a late complication, the result of a general toxæmia, consequent upon the absorption of poisons from the infected biliary reservoir.

The apparent increase of bile canaliculi at the periphery of the lobules in Hanot’s hypertrophic biliary cirrhosis is a feature which has aroused much interest. The question is whether many of them are really permeable, and for this reason they are usually referred to as pseudo-bile ducts. Undoubtedly some appear to be developed in a genuine effort to maintain a connection between the larger ducts of the portal spaces and the peripheral ends of the column of liver cells. Others are probably only columns of newly-formed endothelial cells of the biliary type, which it is supposed play a small part in the formation of hepatic cells in the regeneration of the lobule (MacCallum). Or again, the appearance of bile ducts may be simulated, as has been pointed out by Ford,\(^\text{(15)}\) by the compression and squeezing together of columns of liver cells at the periphery of those lobules which show much intra-lobular fibrosis.

Lefas\(^\text{(16)}\) examined the pancreas in several cases of hypertrophic biliary cirrhosis and found a slight amount of interacinar fibrosis. Moreover, in the vicinity of the islets of Langerhans he stated it was not unusual to observe small fibrous foci, many of which enclosed a number of cells having an exactly similar appearance to that of the pseudo-bile ducts in the liver.

The explanation of the cirrhosis has given rise to much speculation. Gilbert and Fournier\(^\text{(11)}\) considered that organisms normally present in the
bowl invaded the bile ducts and were the cause of cholangitis. Boinet, who suggested chronic intestinal disturbances as the cause, recorded a family in which the father and four children were all affected at one time or another by a febrile disturbance resembling typhoid fever. The fever was followed by jaundice and enlargement of the liver and spleen in the father and two elder children. The two younger children and another, in whose case fever was not mentioned, had big spleens, but their livers were not enlarged. Boix, who held that the enlargement of the spleen preceded that of the liver in hypertrophic biliary cirrhosis, stated that the children of a parent with this disease were sometimes found to have large spleens without any other signs. He considered there was a hepato-splenic infection of a specific type.

Against the theory of an ascending infection from the bowel, there is the absence of any evidence at autopsy of inflammation of the duodenal mucosa. Also, with the prevalence of disorders of the alimentary tract in childhood, this form of cirrhosis would be expected to be a much more common occurrence. It is more likely to be, as Sir H. Rolleston suggests, a local result of a chronic general toxæmia, with the conveyance of the toxin to the smaller bile ducts by means of the hepatic artery.

When compared with the histological features of the other forms of biliary cirrhosis there is very little that is peculiar to Hanot’s form. In his type the course of the disease is certainly more chronic, and for this reason the microscopical appearances are the more outstanding, but the liver is usually dark, bile-stained and often green, in the congenital and obstructive forms of biliary cirrhosis. Pseudo-bile canaliculi are common to all forms of hepatic cirrhosis, though less often seen in the syphilitic variety. Bile casts in the smaller ducts and masses of bile in their lining cells and in the hepatic cells are constantly found in cases of congenital obliteration of the bile ducts. Some fibrosis of the pancreas occurs also in all long standing cases of hepatic cirrhosis. The spleen tends to be enlarged to a less extent in the portal than in the biliary type with the exception of the obstructive form, which is usually of short duration.

A type of cirrhosis with very little jaundice, which resembles hypertrophic biliary cirrhosis in the majority of its histological features, must also be mentioned. Examples of this kind were described by Hayem in 1874, and referred to later by Hanot as cases of "sclerose sans ictere." Here the liver is greatly enlarged, smooth, not dark green but usually of a mottled yellow colour, and microscopy shows little or no alteration of the bile canaliculi. In all probability this is the same type of hypertrophic portal cirrhosis described by Cheadle, to which reference has already been made. Hayem’s examples of this condition were in adults.

(a) In congenital obliteration of the bile ducts the cirrhosis is often of a mixed character, but speaking generally is chiefly monolobular. Externally the liver may be smooth or finely granular, but both extra- and intra-lobular cirrhosis may occur. Degenerative changes of the hepatic cells on the other hand are more common than in the hypertrophic biliary form, and many of the cells in the more affected lobules are swollen, vacuolated, and their nuclei invisible. The bile ducts are not dilated.

Here once more opinions differ as to whether the cirrhosis is primary or secondary to the occlusion of the larger bile ducts. Dr. John Thomson on the one hand, considered that a malformation of the ducts was the essential lesion, and that subsequent catarrhal changes, occurring usually in intra-uterine life, led to the occlusion and obliteration of the ducts. At the same time biliary cirrhosis was produced, as a result of obstruction of the bile and the spread of the catarrhal changes to the small intra-hepatic ducts. The
theory of a primary congenital abnormality is strengthened by the frequency
with which cases of the kind occur in more than one child of the same family.
Holmes,(22) after reviewing all the recorded cases of congenital obliteration
of the bile ducts up to 1916, came to the same conclusion.

In regard to the possibility of inflammatory changes occurring in foetal
life, it is well known that peritonitis can occur. Adhesions between the liver
and peritoneum have been described in this and other morbid conditions of
the newly-born. A localised peritonitis in the region of the common and
hepatic ducts has been suggested as a possible cause of their occlusion.
Thomson, however, considered that the peritonitis, when present, was
secondary to the malformation of the ducts.

Sir H. Rolleston,(23) on the other hand, regarded the cirrhosis as the
initial lesion, and the fibrosis and obliteration of the larger ducts as secondary
to a descending cholangitis. A primary cirrhosis would certainly help to
explain those cases, which, though clinically indistinguishable from those
with obliteration of the ducts, anatomically show no occlusion of the latter.
Moreover, examples of this type in which no obliteration of the ducts exists,
are by no means uncommon. In the case recorded by Keith Gordon,(24)
jaundice was present at birth. At autopsy, however, the bile ducts were
found to be patent. In Dunn’s(25) case also the ducts were not occluded.
The infant did not begin to be jaundiced until the twelfth day after birth.

Those in favour of the view of a primary cirrhosis suggest that toxic
substances, from the maternal blood, enter the foetal circulation by the
umbilical vein. The irritant bodies would then pass partly to the liver
directly, and partly into the general circulation, whence they would also
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reach the liver by the hepatic artery. West(26) considered this method of distribution would account for the frequency with which the fibrosis, in this form of cirrhosis, is both unilobular and multilobular.

(c) In regard to the obstructive type complete and sudden obstruction of the common bile duct is known to give rise to dilatation of the bile ducts and widespread degeneration of the liver cells. The occurrence of cirrhosis, according to Rolleston,(27) is in such cases the result of an added inflammatory process. When obstruction and inflammation are present, there result an extra- and intra-lobular cirrhosis. The bile ducts remain dilated but show signs of catarrhal inflammation and fibrosis spreading to the surrounding tissues. The inflammation spreads from the larger to the smaller ducts. In time a mixed form of cirrhosis is produced both unilobular and multilobular. The latter is possibly due to the absorption of poisons into the portal system from the alimentary tract, in which putrefactive changes are in excess owing to the absence of bile. Degenerative changes of the hepatic cells are often more evident in this type than in the other forms of biliary cirrhosis.

There would appear then to be many common features in the hypertrophic biliary, the congenital infantile, and the chronic obstructive forms of biliary cirrhosis. The macroscopic changes are fairly similar, and their microscopy essentially alike, for in all the fibrosis is related primarily to the bile ducts and becomes both extra and intra-lobular in distribution. Jaundice, once it has appeared, is usually a permanent symptom of each type, and the degree of biliary stasis, as indicated by bile casts in the ducts and between the columns of liver cells and bile granules in the cells themselves, is proportionately far greater than is found in the case of a portal cirrhosis. In the biliary cirrhoses infection or toxic irritation of the biliary reservoir appears to be essential to their production, and whether this inflammation is primary, or consecutive to a congenital or mechanical obstruction is of secondary importance. In obstructive biliary cirrhosis the dilatation of the intra-hepatic ducts is best explained by the onset of the obstruction preceding the inflammatory reaction.

The interesting speculation arises whether the congenital form, if slight in degree, may not later develop into a hypertrophic biliary cirrhosis, and there are suggestive cases bearing upon this theory.

In a case recorded by Smith,(28) an infant recovered from an attack of icterus neonatorum after fourteen days and subsequently developed hypertrophic biliary cirrhosis of the liver with a large spleen, dying at the age of fourteen and a-half years. The initial jaundice was slight, but recurred with added severity during the terminal illness. Whipham(29) described the case of a girl who was born with icterus, which lasted six weeks. Jaundice reappeared at the sixth year, and the liver and spleen were discovered to be much enlarged.

Special Features.

Finally, we come to certain remarkable features associated with cirrhosis of the liver in the young. The first is the familial tendency, the second infantilism, and the third, a feature also of adult life, the liability to haemorrhage.

The familial tendency has attracted the attention of many writers, and there are numerous examples in the literature (Hasenclever,(90) Parkes Weber,(31) Dreschfeld,(32) Finlayson(33). For example, Byrom Bramwell(33) described the case of a boy, nine years of age, who died of cirrhosis of the "hobnail" type, three of whose sisters had apparently died of the same disease. Schusck(34) recorded the case of a girl, aged two years,
hypertrophic biliary cirrhosis. Of the other children in the family two boys were apparently healthy, but two girls had died jaundiced at the ages of two and a-half and two and a-quarter years respectively. The parents were healthy, but the paternal grandfather had been jaundiced for many years.

The majority of these cases with a familial history belong to the group of biliary cirrhoses, and to such Parkes Weber has given the name "family biliary cirrhosis."

The question naturally arises as to the explanation of this familial tendency. Is there some toxic cause peculiar to the mother which develops in pregnancy and affects the foetus through the placenta, or is there a repetition of a developmental malformation? Considering the scant knowledge at our disposal on the subject of disease in utero it is impossible to make any dogmatic statement, but we are inclined to support the view of a primary developmental defect in these cases. That obvious congenital defects of development may occur in the liver as well as in any other organ is well exemplified by the following three cases. Two are cases of cystic liver, associated with cystic disease of the kidneys; one an unrecorded case of Sir Archibald Garrod's, the other published by Dr. Still. Both are from the case reports of the Great Ormond Street Hospital, a boy, aged nine months, and a girl, aged eight weeks. The kidneys, in either case, were greatly enlarged and of the "honeycomb" variety. The livers were of a normal size, hard and slightly roughened externally. Microscopical examination showed a great increase of fibrous tissue about the portal canals and a large number of irregular branching cavities, situated mostly in the fibrous tissue. These cavities were lined by flattened columnar epithelium. In all probability

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they were remains of the spaces between the cell cylinders or groups of cells of entodermal origin, which are derived from the duodenal diverticulum to form the liver. If development proceeds normally, these spaces become narrowed and surrounded by fever cells, and are supposed to become finally bile ducts.

The third case, recorded by Forbes,(36) was a girl of two years and eight months. She presented cirrhosis of the liver, "honeycomb" lung, and tuberculosis of the tonsils, mediastinal and mesenteric glands. No trace of tubercle was discovered in the liver, lungs or pancreas. The liver was greatly enlarged, slightly roughened, pale and hard, and in section showed scattered islets of fibrous tissue, which were mainly white, but at some points bile stained. There was no evidence, other than the glands, to point to tuberculosis as the cause. Although not being familial, attention is particularly drawn to these three cases as showing the occurrence of errors of development of the liver, in addition to obvious abnormalities in other organs.

Infantilism.

Infantilism as a result of chronic disease of a vital organ is well recognised, and illustrated in the young by the occurrence of this feature in "caeliac disease" in addition to the hepatic form.

Arrest of growth is particularly striking in these hepatic cases, possibly because the large abdomen emphasises the short stature.

Arthritic changes of the fingers and clubbing of the finger tips have also been noticed in chronic hepatic cirrhosis.

Hæmorrhage.

Hæmorrhage occurs in two ways; there may be varices of the lower end of the œsophagus or rectum, and fatal bleeding as exemplified in two of our cases of the Banti type; or there may be general bleeding from the gums and under the skin and elsewhere associated with a widespread toxic condition.

The first type is the result of a portal cirrhosis and local venous high tension. The second probably the result of some toxic agent affecting the blood or capillary walls.

The toxic agent may be actually produced by the disordered hepatic metabolism; or result from inability of the damaged organ to maintain the supply of protective substances normally produced by healthy liver tissue. Bouchard(37) is of the opinion that bleeding of this type is arterial and not venous, as in a case recorded by him of alcoholic cirrhosis, accidental scratching of a nævus on the face and of one on a finger had caused jet-like bleeding in both instances.

Conclusion.

Lastly, as to the nature of the four cases recorded in this paper, the first, that of a girl of nine with intermittent jaundice, epistaxis and hæmatemesis, is most likely to be a case of portal cirrhosis, associated with tuberculosis, possibly mesenteric, and without congenital predisposition.

In the cases of the brother and sister, who had enlargement of the abdomen from birth and very little jaundice, we are probably dealing with a form of hypertrophic cirrhosis, similar to the sclerose sans ictere described by Hayem. Here we think the cirrhosis is of portal rather than of

19
biliary origin, both because of the transitory nature of the jaundice, and because a hypertrophic form of portal cirrhosis is known to exist, as pointed out by Cheadle. Presuming our supposition to be correct these two cases are specially interesting owing to the rarity of a familial occurrence of the portal type, as compared with the biliary form of hepatic cirrhosis.

The history of the fourth case is too short to justify any dogmatic statement, but the fact that the children in a family almost simultaneously developed jaundice suggests an infective cause and a catarrhal jaundice. In the child the liver undoubtedly enlarges more than in the adult in catarrhal jaundice, and this enlargement may remain for weeks. In this case, however, the size and hardness of the liver, and the duration of the jaundice were unusual. Also the outbreak of fever with the rapid and great enlargement of the spleen as a late event were features we have never observed in the catarrhal jaundice of childhood. On the other hand the remarkable subsidence of the liver and spleen before the child left hospital favoured some degree of biliary obstruction rather than cirrhotic changes in the liver.

In conclusion, then, it is obvious that many difficulties beset the clinical interpretation of cases of hepatic cirrhosis in children. It is often impossible to be certain either of the nature of the cirrhosis or of its origin. The latency of the condition before symptoms manifest themselves is a striking feature of many cases. The pathogenesis of the congenital and familial forms of cirrhosis rests obscure.

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