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Severe Rhesus Haemolytic Disease of the Newborn, obstructive jaundice and hydrops fetalis*

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INTRODUCTION

I intend to discuss an early interest of mine, namely that hydrops fetalis and a number of other manifestations of severe Rhesus haemolytic disease of the newborn (Rh HDN) are due to liver damage or what I have termed '*Rh haemolytic hepatitis*'.

When I started to train as a perinatal paediatrician in the old Birmingham Maternity Hospital (BMH) in Loveday Street between 1958 and 1962, Rhesus haemolytic disease dominated neonatal paediatrics and young registrars such as myself spent much of our time doing exchange transfusions. In those days one in every twenty-three newborn babies at the BMH were affected by Rhesus disease. Now thanks to prophylaxis the condition is rare. Anyone training these days will have had limited exposure to this disease compared with previous experience. It is important therefore that lessons learnt many years ago are not overlooked.

My studies were based on observations made in Birmingham, Bristol and in San Francisco between 1958 and 1967. I presented my findings in a number of publications and in lectures in this country and in the USA over the following few years. But as a Lancet editorial in 1971 suggested, my conclusions did not seem to have made an impact:

' ... there are still many unexplained aspects of erythroblastosis, such as the aetiology of hydrops fetalis.' [1]

Nor in the years since has the significance of liver damage in these infants always been fully appreciated. This then is my justification for re-presenting the conclusions of those studies made many years ago.

*** Based on a talk to the Perinatal Club(UK), in Birmingham, March 12th, 1994**

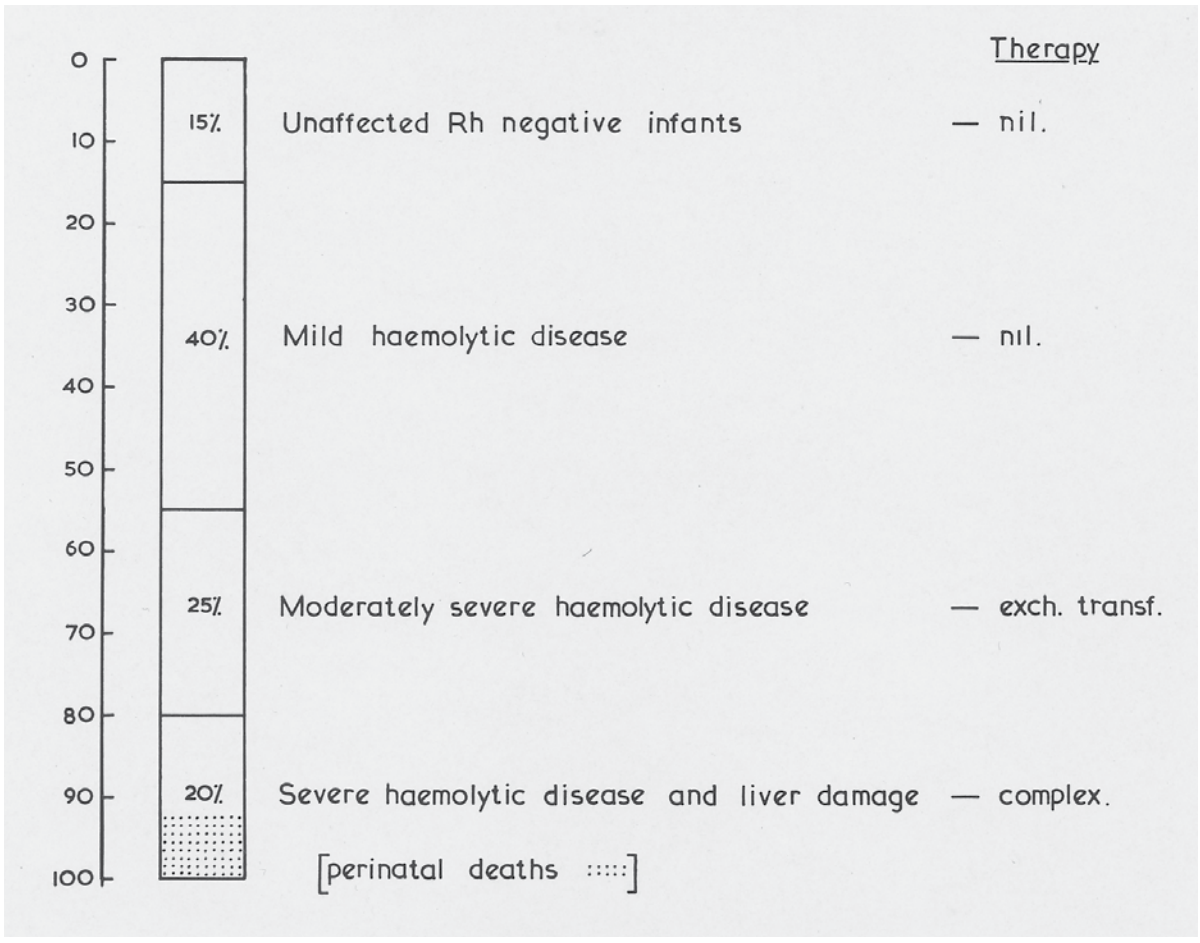

Fig 1: Outcome among infants born to women with Rh immunisation

CLINICAL OBSERVATIONS

In 1952 Hsia and colleagues in Boston [2] termed the complication of obstructive jaundice occurring among Rhesus babies *"the inspissated bile syndrome"*, suggesting incorrectly that viscid bile plugged the bile canaliculi leading to regurgitation of conjugated bilirubin into the blood stream. A decade later I was able to confirm [3,4] an observation previously made by Oppé and Valaes in 1959 [5] that approximately 10% of infants with Rh HDN showed evidence of obstructive jaundice at birth and that their clinical condition and cord blood findings revealed them to be at the severe end of the spectrum of this disease (Fig 1).

Cord blood haemoglobin and serum bilirubin levels of Rhesus babies born at the BMH in 1960-61 are shown in Fig 2. The big circles towards the top right hand corner, representing the most anaemic and jaundiced babies, are those that were born with obstructive jaundice.

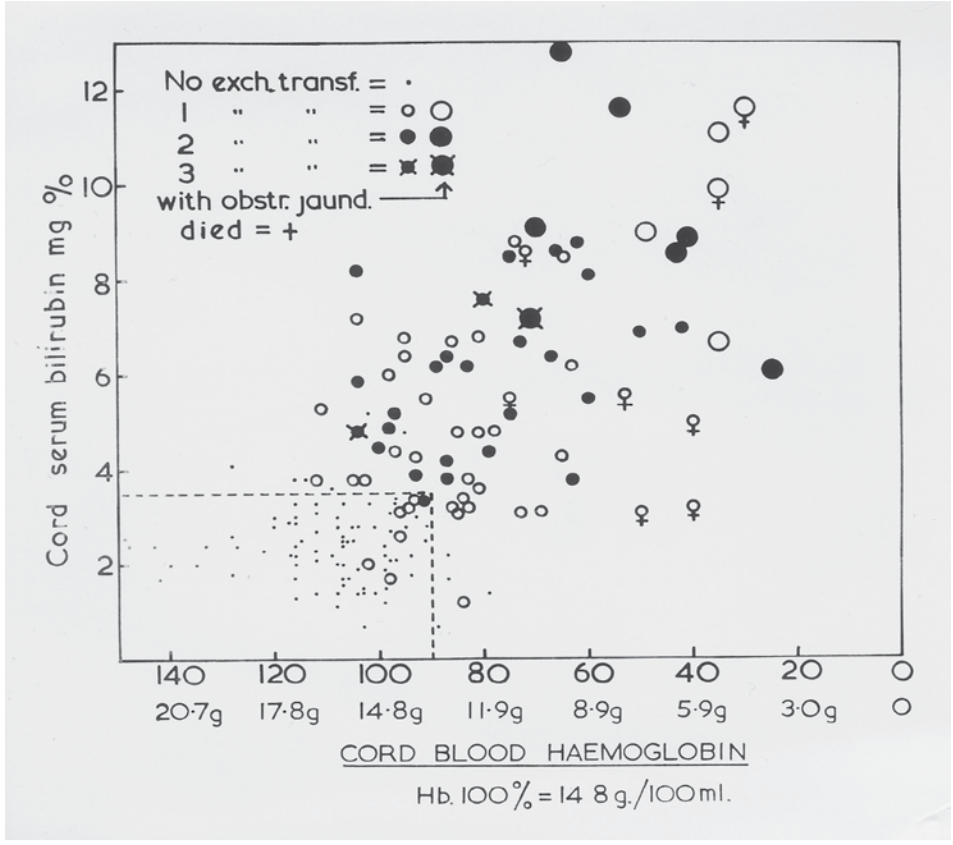

Fig 2: Cord blood haemoglobin and serum bilirubin values of 122 babies born with Rh HDM at the Birmingham Maternity Hospital (1960-61) in relation to exchange transfusion therapy, obstructive jaundice and mortality

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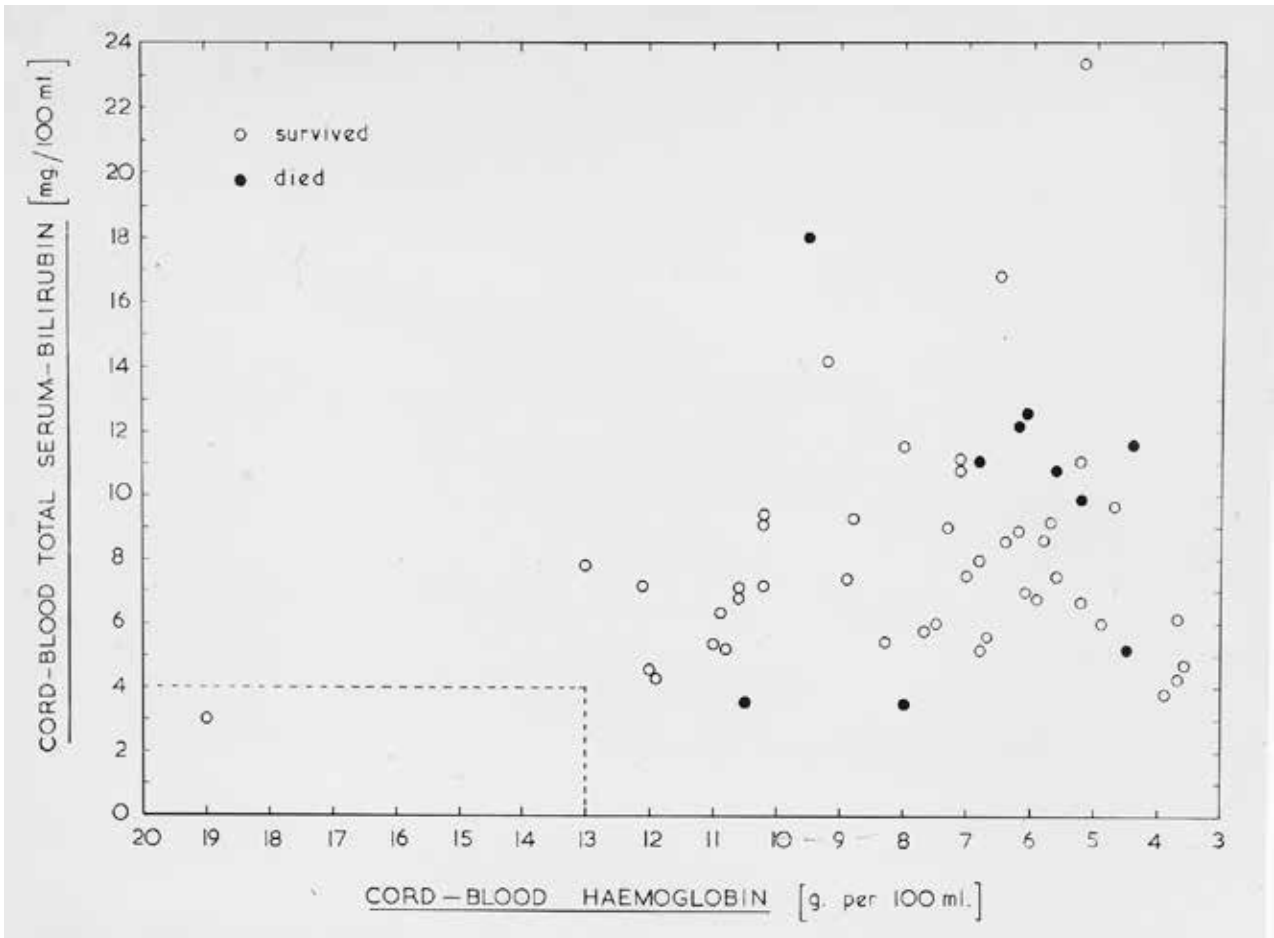

Fig 3: Cord blood findings and mortality among fifty-four infants with severe Rh HDN and obstructive jaundice. Note that two thirds of the Rh infants shown in Fig 2 without obstructive jaundice fall within the box in the bottom left hand corner of this diagram

Fig 3 makes the same point more clearly, in that it shows the cord-blood findings of my larger series of infants with obstructive jaundice due to Rhesus disease. The mean cord-blood serum bilirubin in this series was 8.4mg% and the mean cord haemoglobin 7.9g%. You will also note a significant neonatal mortality among these infants, an event most unusual among the great majority of the Rh infants born without obstructive jaundice, whose cord-blood findings usually fall within the box at the lower left hand corner.

Besides congenital anaemia and the signs of obstructive jaundice these infants all had marked hepato-splenomegaly.

Among the serious complications associated with Rh obstructive jaundice is haemorrhagic disease of the newborn secondary to deficiency of coagulation factors normally produced in the liver, such as prothrombin. Half the infants in my series with obstructive jaundice exhibited this complication.

In addition, over half the Rh infants with obstructive jaundice that I studied were oedematous at birth, many of them grossly hydropic. I was able to show a close relationship between the cord serum albumin level and hydrops fetalis. My studies showed that with Rh hydrops fetalis the total serum protein at birth was almost always below 4g% (average 3.1g%) and the serum albumin below 2.5g% (average 1.6g%). The level of the serum globulin was usually normal or only slightly reduced (2.1 – 1.5g%).

Yet another serious complication was the occurrence of kernicterus. During the period 1960-63 I saw three infants with this condition. All three had Rh HDN with obstructive jaundice. In no case had the serum indirect bilirubin level risen over the recognised danger level of 20mg%. All three survived but later had the stigmata of kernicterus such as high tone deafness and choreo-athetosis. However by 1965 we had come to appreciate the importance of serum albumin in retaining unconjugated bilirubin within the vascular system, and I have little doubt that these infants with obstructive jaundice had low protective serum albumin levels though unfortunately these levels had not been measured at the time. From 1963 on I was forewarned and saw no further such cases of kernicterus.

There are many potential causes of cerebral dysfunction with severe Rhesus disease such as kernicterus but I would particularly draw attention to hypoglycaemia which I found to be another common association with obstructive jaundice, again presumably due to liver damage.

In the presence of severe liver damage, intrauterine growth retardation might be anticipated and indeed, it was possible to show that the infants with obstructive jaundice were significantly small-for-dates, though this was often masked in respect to their birthweight when they were hydropic.

Late anaemia, defined as a haemoglobin below 7g% after the first month, was 12 times more common in the Rh infants with obstructive jaundice than in those Rhesus affected infants without it. There was evidence that erthropoiesis was depressed in these infants.

Other complications included deep prolonged jaundice sometimes lasting many weeks and hepato-splenomegaly lasting months, and, very occasionally, cases of portal hypertension and cirrhosis in later infancy and early childhood.

And for completeness, bile staining of the primary dentition was yet another late manifestation (Fig 4).

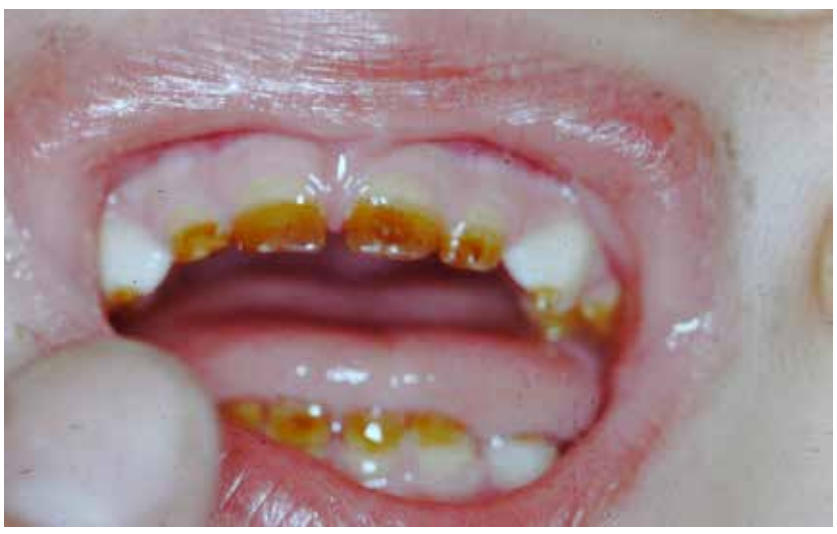

Fig 4: Enamel hypoplasia and bile stained primary dentition at the age of 2 years in an infant born with severe Rh HDN and obstructive jaundice.

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In summary, in Fig 5 are listed the clinical complications of severe Rhesus disease which led me in 1960-61 to suspect liver damage to be the cause of the obstructive jaundice and caused me to undertake histo-pathological study of the livers of those cases that came to necropsy.

Fig 5:
Complications of severe Rh HDN attributable to liver damage

- Obstructive jaundice
- Haemorrhagic disease
- Hydrops fetalis
- Kernicterus at 'safe' levels of indirect-acting serum bilirubin
- Hypoglycaemia
- Intrauterine growth retardation
- Late anaemia
- Portal hypertension and cirrhosis (rare)

LIVER HISTOLOGY

During the years 1961-1967 I studied the liver histology of twenty-one infants dying of Rh HDN in the neonatal period. Six of these infants had died without showing any evidence of obstructive jaundice. None of their livers showed evidence of damage at post-mortem (Figs 6 & 7).

In contrast the 15 infants with severe Rh HDN with obstructive jaundice all showed evidence of severe liver damage. There was widespread disorganisation of the hepatic lobules and cords; destruction of liver cells was accompanied by regeneration and the creation of islands of multinucleated syncytial masses of cytoplasm containing many large and pale staining nuclei and also many granules of haemosiderin and bilirubin. Erythropoiesis might be present or absent. The hepatic sinusoids appeared to be packed with sludged erythrocytes; the bile ducts in some cases showed proliferative activity within the portal tracts. There was sometimes a marked increase in reticulum, and collagen fibres were sometimes seen especially in the portal tracts even when death had occurred shortly after birth.
The first such infant studied was a baby born in May 1961 (Fig 8). Liver histology of the baby shown in Fig 8 revealed extensive disorganisation and damage. (Fig 9 & 10).
There follows the liver histology from other infants with severe Rh HDN and obstructive jaundice dying soon after birth (figures 11-15).

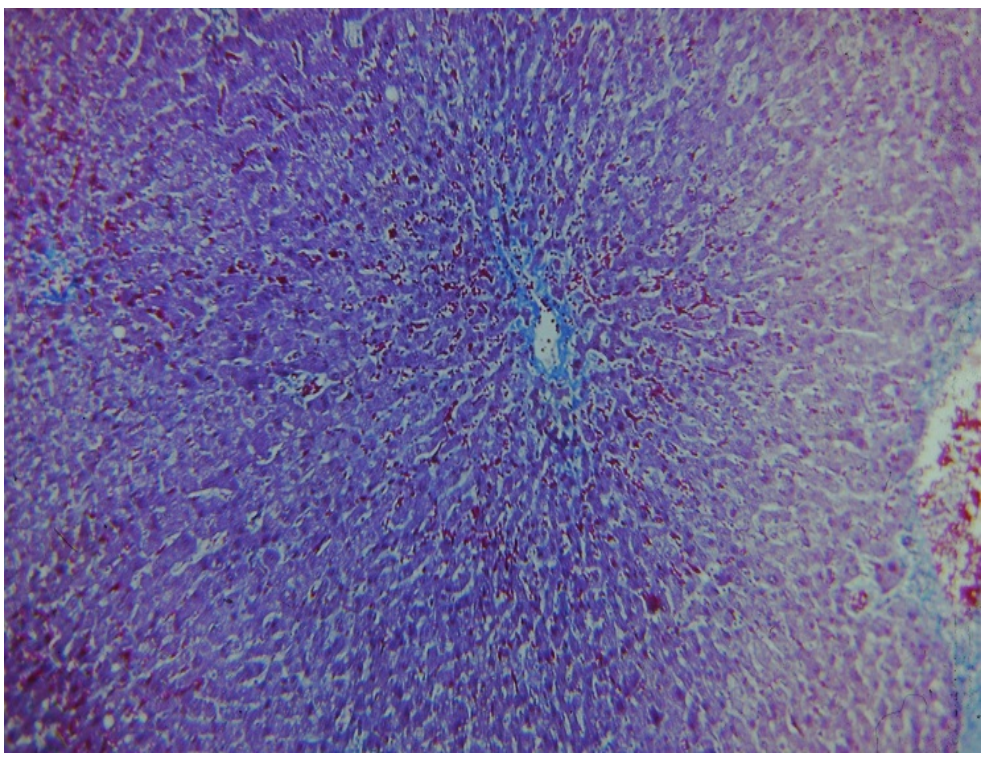

Fig 6: Liver histology from infant with moderate Rh HDN without obstructive jaundice dying from kernicterus on third day of life (reticulum stain; low power). Shows normal lobular pattern.

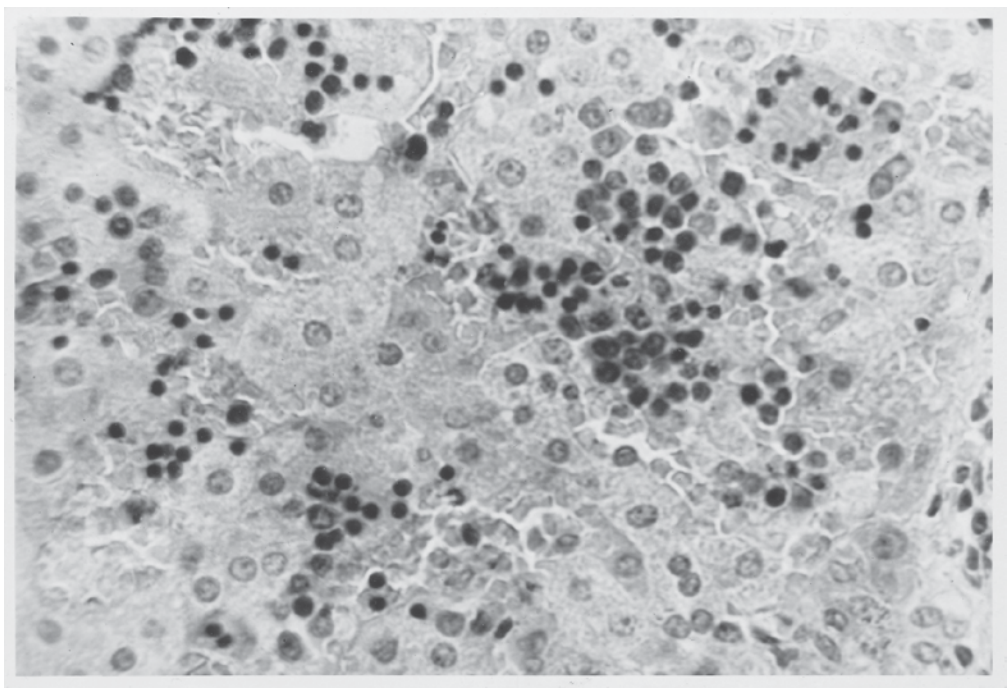

Fig 7: Liver histology from infant with moderate Rh HDN without obstructive jaundice dying from RDS on first day of life (high power). Shows normal hepatic architecture with abundant evidence of erythropoiesis

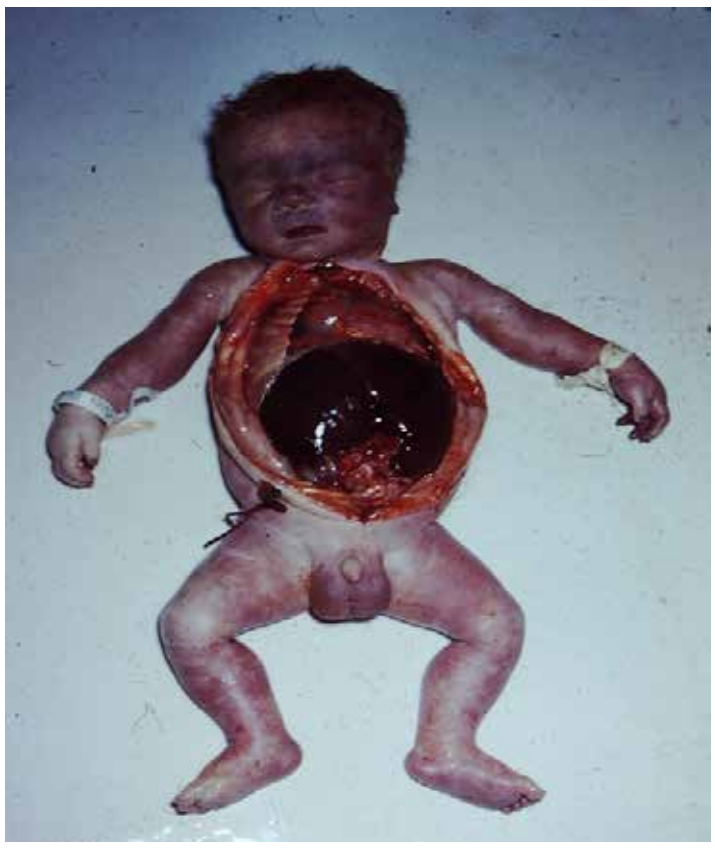

Fig 8: Severe Rh HDN with obstructive jaundice that died on the first day of life. Note the presence of hydrops fetalis with widespread bruising and gross hepatosplenomegaly.

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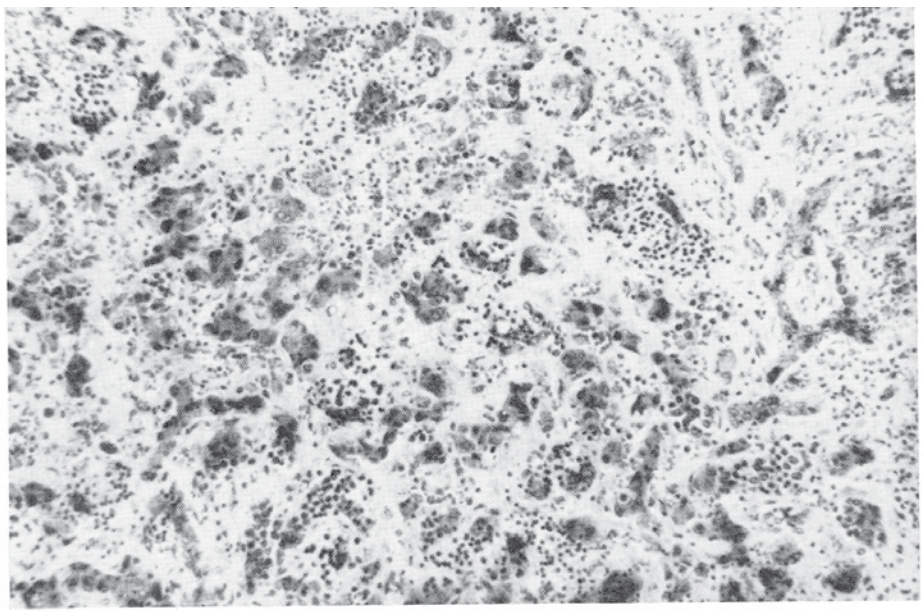


Fig 9: Liver histology (low power) of the infant seen in Fig 8 that died on the first day of life.

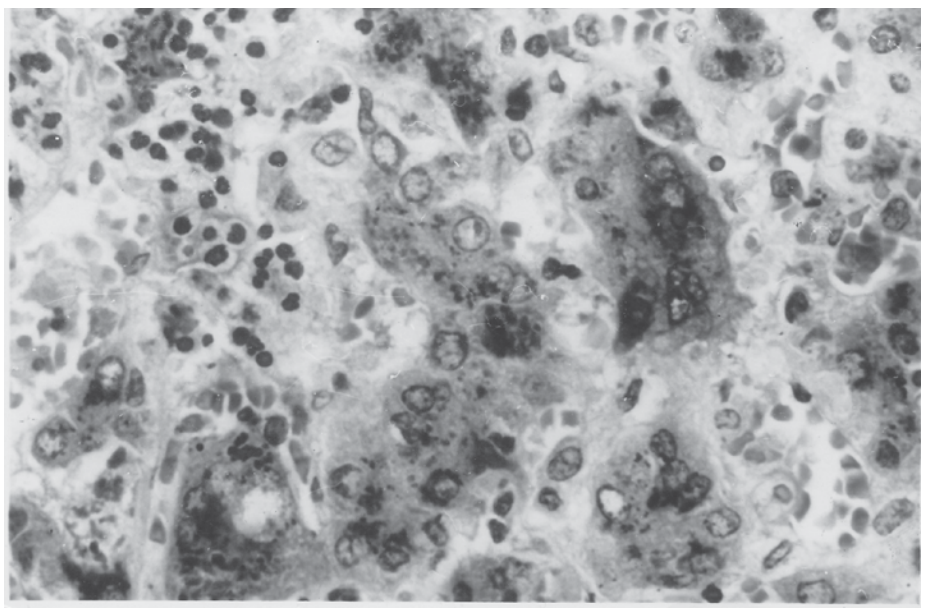


Fig 10: Liver histology (high power) of infant seen in Figures 8 & 9

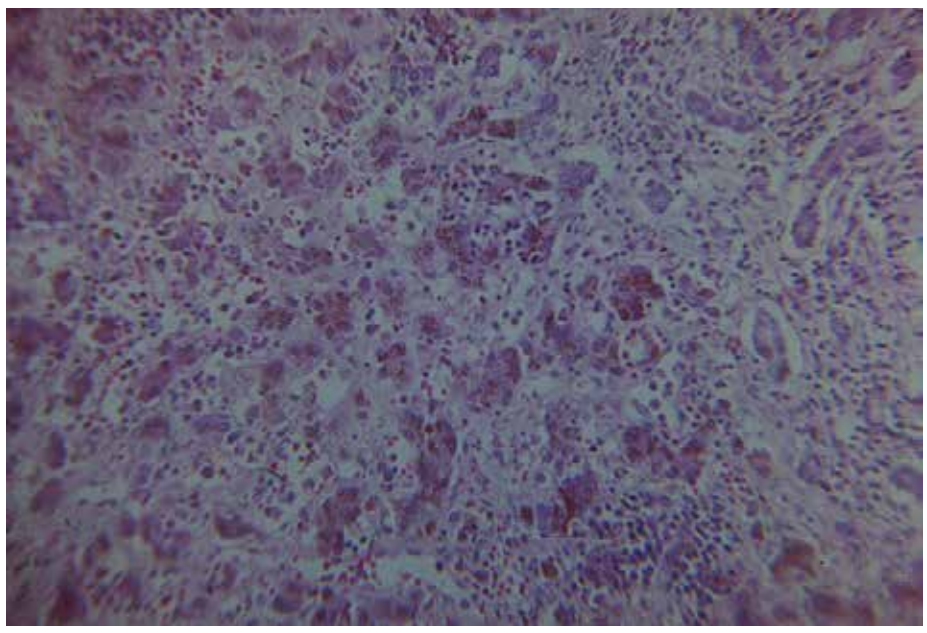


Fig 11: Severe Rh HND with obstructive jaundice dying on first day of life (H & E stain, low power).

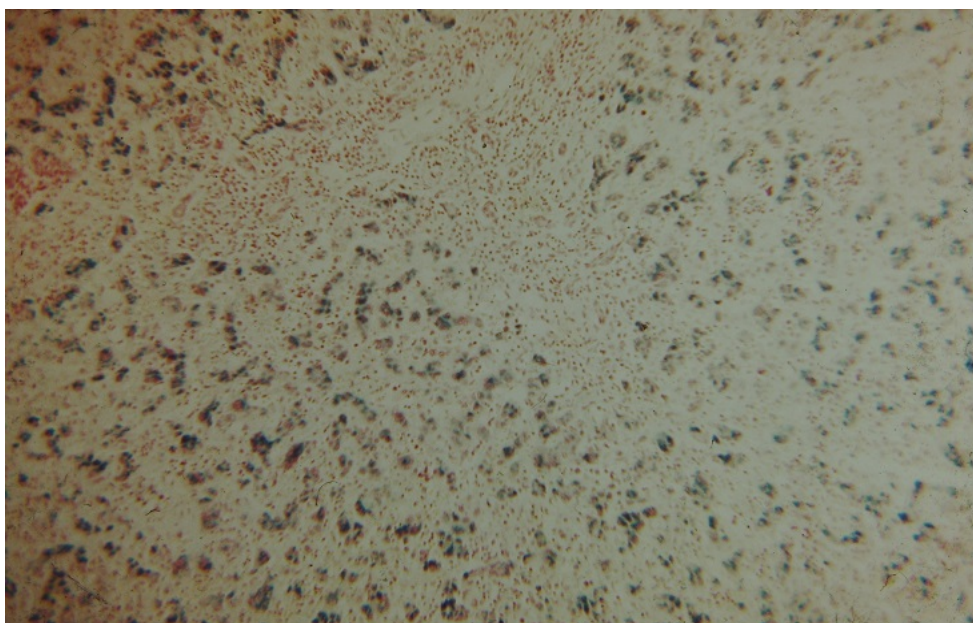


Fig 12: Severe Rh HDN with obstructive jaundice that died on the first day of life (low power) stained with Prussian blue to show heamosiderin.

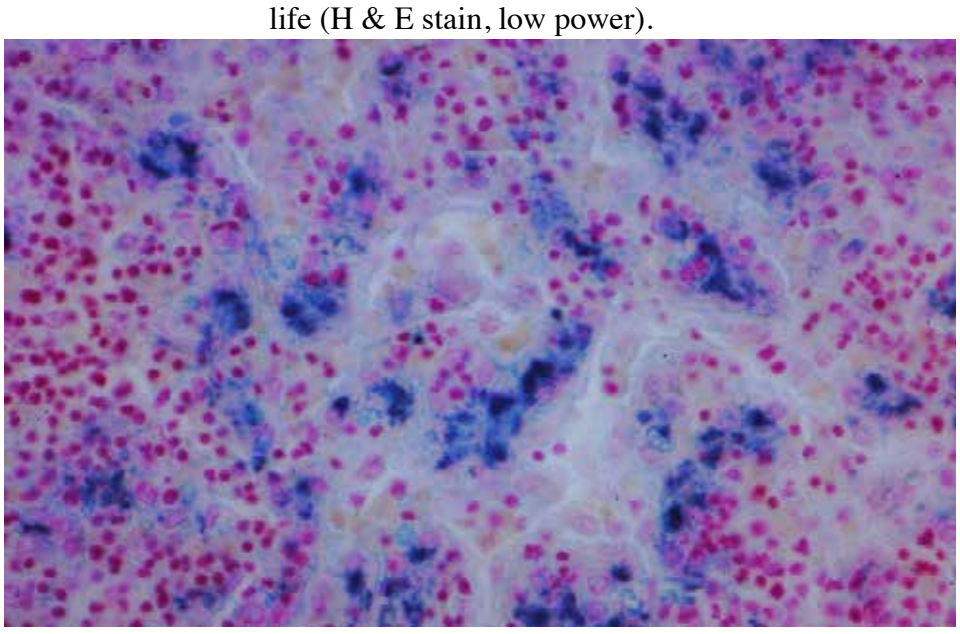


Fig 13: Severe Rh HDN with obstructive jaundice, dying on second day of life (high power), stained with Prussian blue to show haemosiderin within hepatic cells.

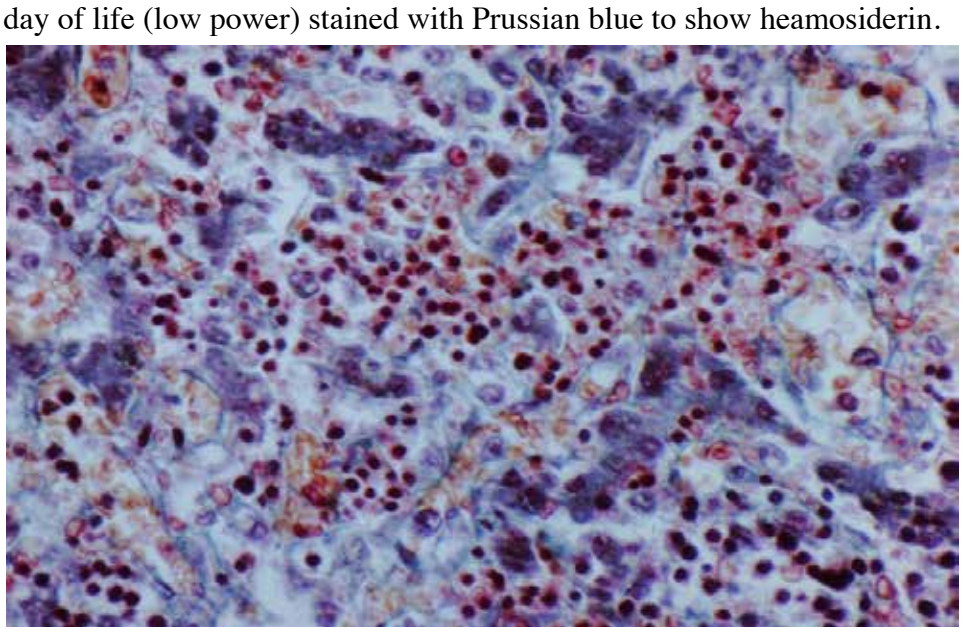
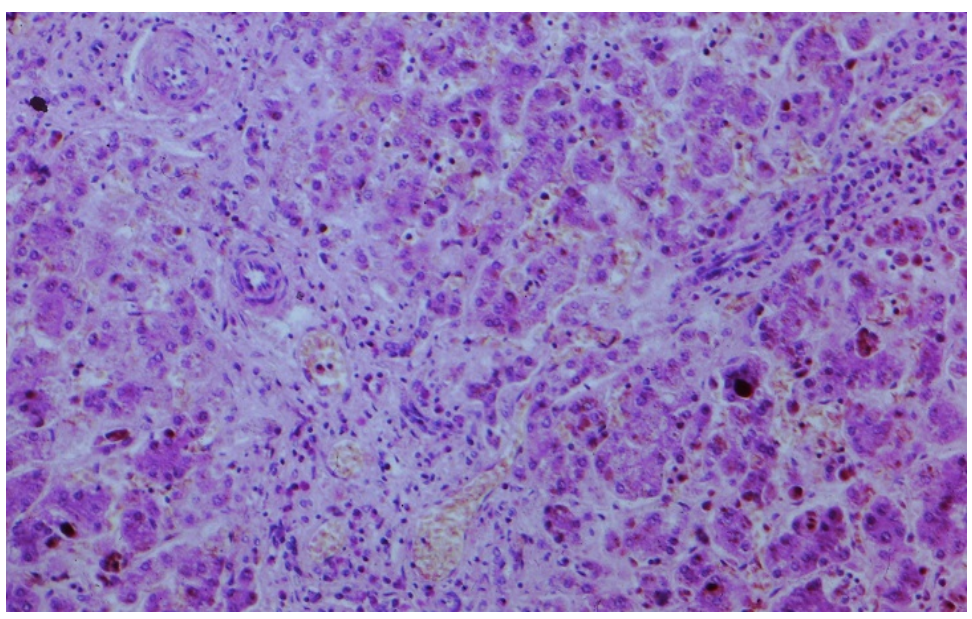


Fig 14: Severe Rh HDN with obstructive jaundice, dying on first day of life. Stained with Trichrome to show green fibrils of collegen.

Fig 15: ⇒
Severe Rh HDN with obstructive jaundice that died at the age of twenty-three days. Shows some regeneration of liver lobules and extensive fibrosis in the portal tracts.



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AETIOLOGY OF LIVER DAMAGE

Probably more than one factor contributes to liver damage in these infants with obstructive jaundice but I believe the main cause is the sludging of agglutinated and damaged red blood cells in the hepatic sinusoids leading to secondary hepatic hypoxia and haemosiderosis. I suggest that there is evidence that this only occurs to any extent once haemolytic *'overload'* had led to splenic *'failure'* to deal adequately with the damaged circulating red cells. Hence the large spleens found in those infants (Fig 16). The haemosiderosis due to hepatic haemolysis may be a further cause of damage, especially from oxygen-free radicles following birth. Other factors that may play a part include the anaemia, and in some cases congestive cardiac failure.

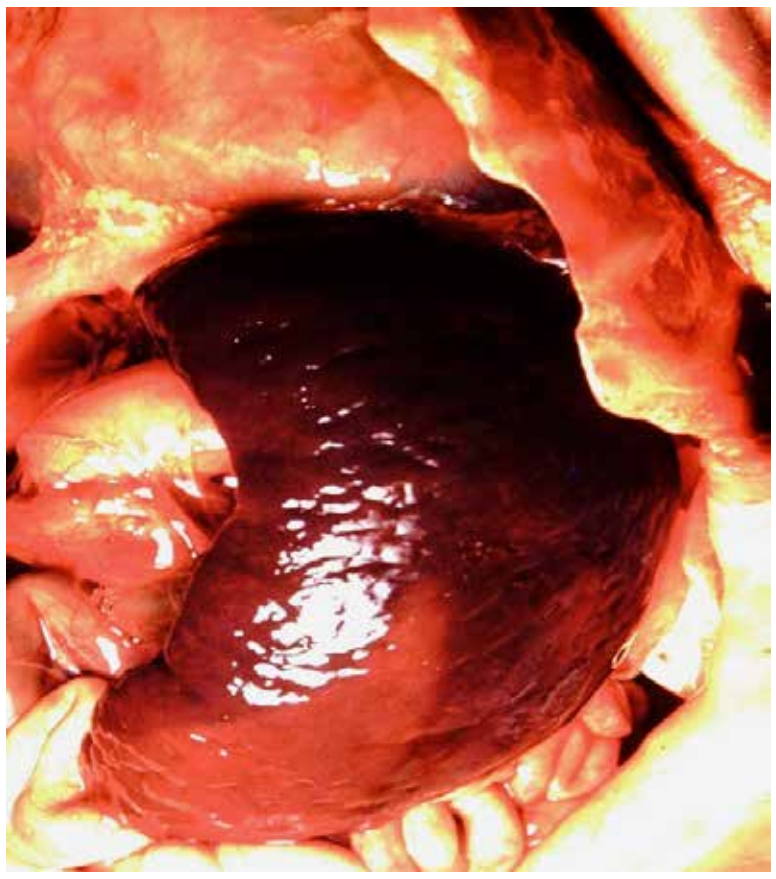

Fig 16: Gross splenomagaly of an infant with severe Rh HDN and obstructive jaundice dying on the first day of life.

In the 1960s in my experience some 10% of Rh infants born alive exhibited signs of haemolytic hepatitis. But it should also be appreciated that most of the 10% stillborn Rh infants, many hydropic, had also probably died with this condition. Haemolytic hepatis may also occur, though less commonly, in association with other severe congenital haemolytic conditions, such as thalassaemia, congenital spherocytosis, and ABO haemolytic disease.

Fig 17 indicates the mechanisms by which liver cell damage leads, I believe, to the complications of severe Rh disease which I have discussed – namely, cholestasis, growth retardation, hypoglycaemia, haemorrhagic disease, kernicterus and hydrops fetalis.

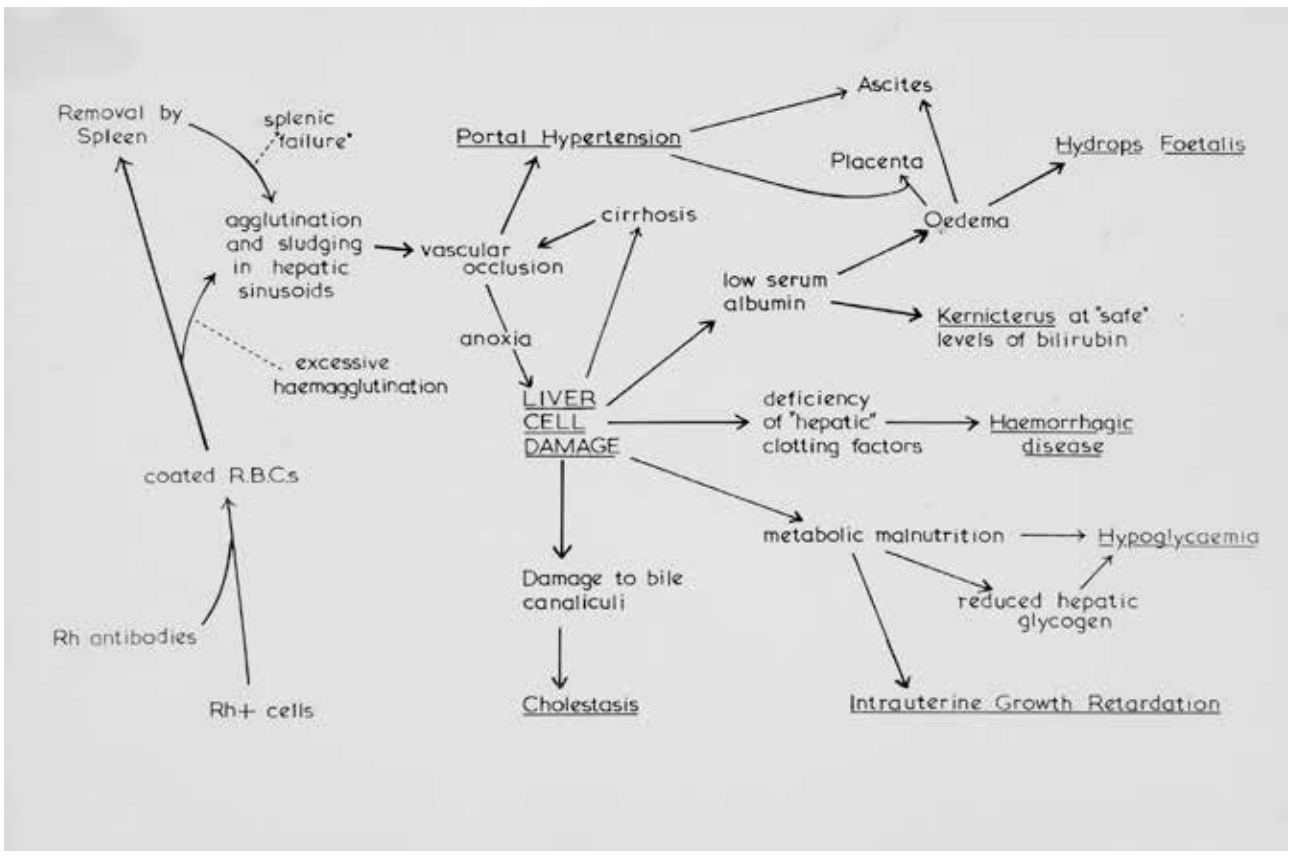

Fig 17: Diagramatic explanation of how severe Rh HDN may lead to liver damage, obstructive jaundice and various complications.

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