Jaundice in Early Infancy*

THE MEDICAL ASPECTS

BY

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It is common knowledge that about half of all newborn infants show some degree of jaundice during the first two weeks of life. In the light of medical progress in the past two decades there have emerged a number of disease patterns unique to this age group which present with jaundice in the neonatal period. In the past many such cases undoubtedly masqueraded as "physiological jaundice," moderate, deep or prolonged jaundice often being regarded merely as an exaggeration of this. It is now known that kernicterus, a form of brain damage occurring in jaundiced infants, may result when the serum bilirubin rises above 20 mg. per 100 ml. and possibly at lower levels in premature infants. Such bilirubin levels, seemingly high by adult standards, may be reached with astonishing rapidity in infants. It is thus of the utmost importance in such instances to recognise deviations from normal as early as possible and thereupon to institute prompt measures to determine the diagnosis and severity of the disease.

In this paper I shall firstly attempt to define what may be regarded as "normal jaundice" in the newborn. The known pathological causes will then be classified. Time would not permit a detailed account of all these conditions; only the most important will be elaborated upon. Several will be illustrated by cases recently seen in private practice.

Icterus Neonatorum

Whereas only 50 per cent. of all mature infants show icterus neonatorum, it has been repeatedly demonstrated that almost all infants have some degree of hyperbilirubinaemia during the first four or five days. The bilirubin concentration in blood taken from the umbilical cord is raised to between 1 and 2 mg., and this rises to a maximum on the second day. Whether the jaundice appears clinically or not will depend on the cutaneous circulation, the degree of skin pigmentation and the height of the serum bilirubin. In any event, jaundice only appears on the second or third day, regresses by the seventh and disappears completely by the fourteenth. The level rarely rises above 10 mg. It is now accepted that this "normal" increase of serum bilirubin is at least in part the result of failure to dispose of the pigment owing to hepatic immaturity (Hsia *et al.*, 1953).

It is doubtful whether any symptoms or signs are attributable to this jaundice and the spleen and liver are not larger than normal for the age. Urobilin is present in the urine, which never contains more than traces of bile pigment. Bile is present in the stools. Mature infants who have icterus neonatorum do not require treatment.

Icterus of Prematurity

A somewhat different pattern is found in premature infants. Here the bilirubin level at birth is the same as in mature infants (between 1 and 2 mg. per 100 ml.), but this rises to higher levels, reaching a maximum later. The lower the birth weight and the less mature the infant, the higher are the bilirubin levels. For example, a group of infants weighing 2½ to 3½ pounds at birth were found to average a maximum of 14 mg. per 100 ml. on the sixth or seventh day, and much higher concentrations are frequently reached (Billing, Cole and Lath, 1954).

Such high bilirubin levels are now known to be dangerous to the premature infant, who is particularly susceptible to kernicterus. A replacement transfusion to remove bilirubin when this reaches critical levels may therefore be indicated as a life-saving measure in premature infants presenting with purely physiological jaundice.

Various factors have been incriminated in aggravating the jaundice and/or increasing the incidence of kernicterus in premature babies. This has been proved in the case of a vitamin K analogue when used in large doses (Bound and Telfer, 1956; Meyer and Angus, 1956), and the harmful effect of sulphisoxasole when used prophylactically against infection is almost certain (Silverman *et al.*, 1956; Harris *et al.*, 1958). Synthetic vitamin K should therefore never be used in a dosage exceeding 1 mg.

Case I.—Benjamin W., firstborn. Born eleven weeks prematurely on the 25th June, 1958. Birth weight was 2 lb. 10 oz. The infant was very oedematous, but active with normal respiratory function. Vitamin K 1 mg. was given intramuscularly on the first and third days. Mild jaundice was noted on the second day. On the third day the serum bilirubin was 15.8 mg. per 100 ml. in the morning, rising to 18.4 mg. in the evening. He was otherwise normal. The infant's and mother's blood groups were both O Rh positive, so that Rhesus and ABO incompatibility could be ruled out. By the fourth day the infant's condition had de-

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teriorated, with marked dehydration and limpness. The serum bilirubin was now 19.6 mg. As a further rise could be anticipated until the sixth day with the real danger of kernicterus, an exchange transfusion was performed; 115 ml. of fresh citrated sedimented O Rh positive red cells were exchanged.

Later he became apnoeic and moribund, but was resuscitated by intratracheal intubation, manual inflation of the lungs, intravenous fluids and nikethamide intravenously and intramuscularly. Serum bilirubin after the procedure was 12.5 ml. He remained extremely jaundiced for two days, but this then diminished rapidly. Further course is depicted in Fig. 1.

Table I

JAUNDICE IN EARLY INFANCY

Physiological Jaundice—
- Jaundice in full-term infants.
- Jaundice of prematurity.
- Prolonged "physiological" jaundice.

Haemolytic Disease of the Newborn—
- Rh incompatibility.
- ABO incompatibility.
- Rare groups.

Infective Jaundice—
- Septicaemia.
- Congenital syphilis.
- Cytomegalic inclusion body disease.
- Congenital toxoplasmosis.
- Virus hepatitis.
- Other rarities.

Miscellaneous—
- Galactosaemia.
- Familial haemolytic anaemia.
- Familial non-haemolytic jaundice.
- "Congenital familial non-haemolytic jaundice with kernicterus."
- Other rarities.

Obstructive Jaundice—
- Inspissated bile syndrome.
  - (1) Complicating haemolysis.
  - (2) Idiopathic ? neonatal hepatitis.
- Congenital obliteration of bile ducts.
- Other rarities.

Icterus Neonatorum Prolongatum

Icterus neonatorum occasionally persists in mature infants for long periods. The infants are otherwise well, the stools of normal colour and there is no evidence of haemolysis, anaemia or disturbed liver function. The interesting observation has recently been made that this persistent jaundice is often associated with congenital hypothyroidism (Christensen, 1956). Recognition that prolonged jaundice in a newborn can be the first sign of cretinism may help in making an early diagnosis.

Occasionally also physiological jaundice may be seen in a very severe form in mature infants, the bilirubin rising to dangerously high levels. This is presumed to be due to unusual immaturity of the enzyme system conjugating bilirubin with glucuronic acid.

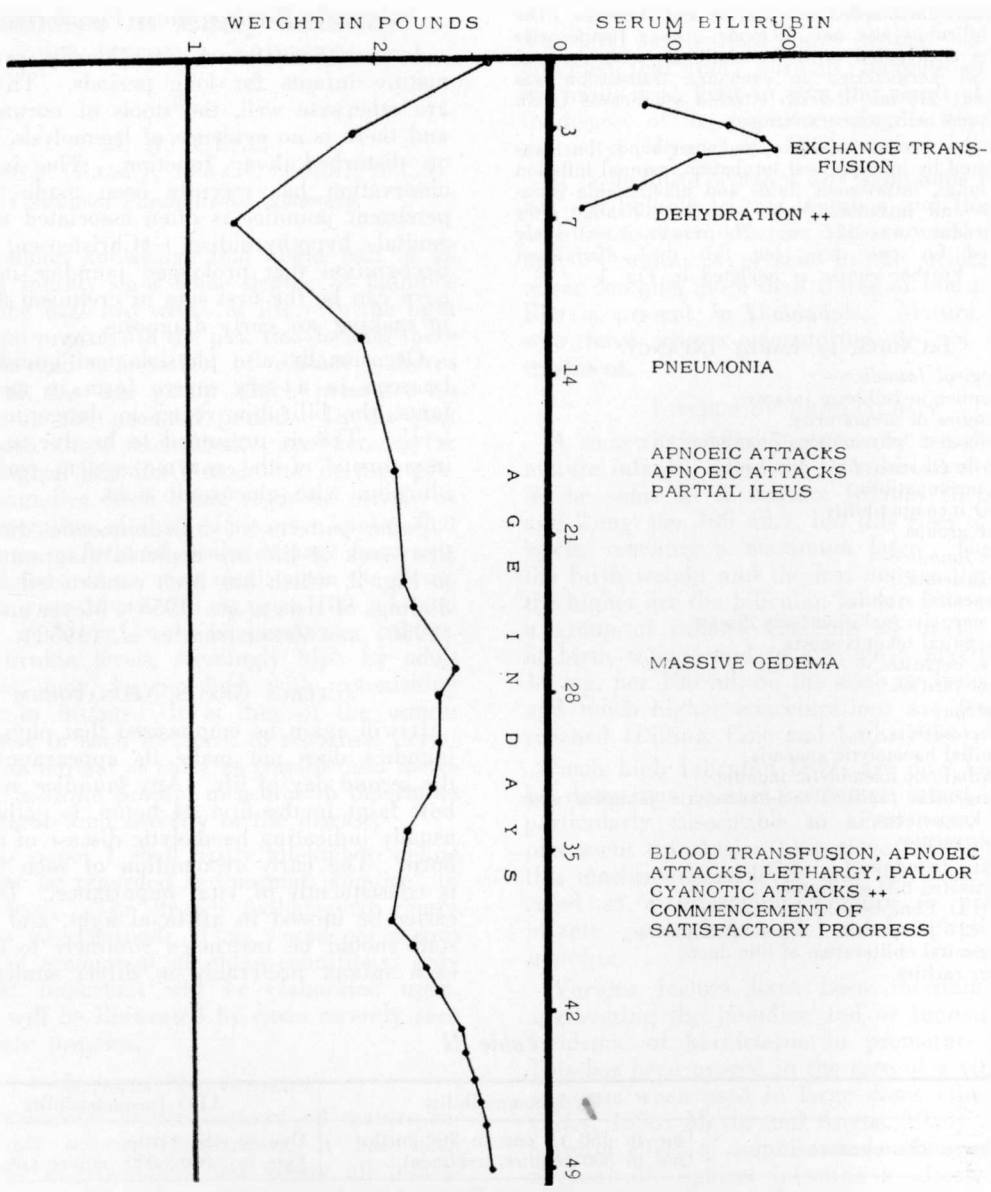
Some patterns of bilirubinaemia during the first week of life are depicted diagrammatically in Fig. 2, which has been constructed from the findings of Hsia *et al.* (1953), Meyer and Angus (1956) and Zetterstrom *et al.* (1958).

Icterus Gravis Neonatorum

It will again be emphasised that physiological jaundice does not make its appearance before the second day of life. Any jaundice, no matter how faint in the first 24 hours, is pathological, usually indicating haemolytic disease of the newborn. The early recognition of such jaundice is consequently of vital importance. This may easily be missed in artificial light, and nursing staff should be instructed routinely to examine each infant, preferably in direct sunlight, im-

Table II

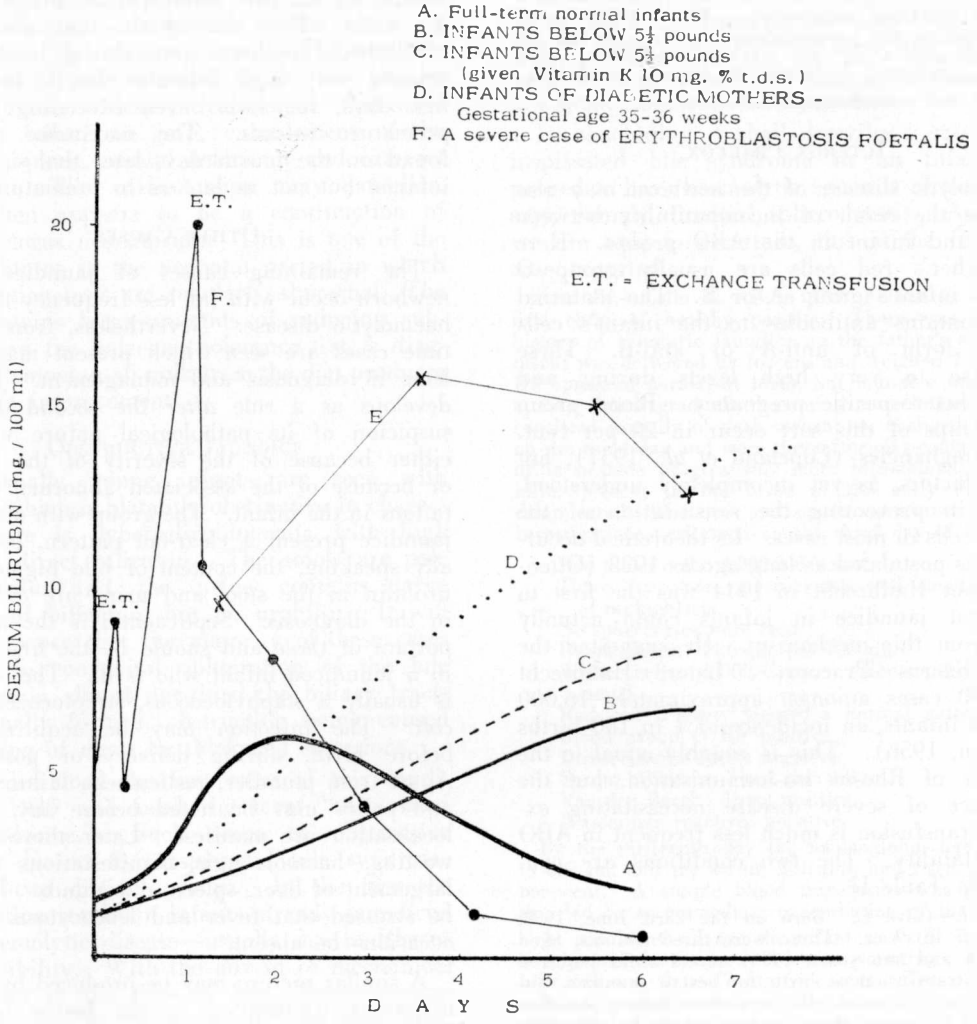
	Rh Incompatibility	ABO Incompatibility
Incidence (Europeans)	One in 150 to one in 200 births. One in 300 require treatment.	One in 150 births. One in 2,000-3,000 require treatment.
Familial incidence	Successive siblings affected, "never" firstborn.	Successive siblings affected, 50 per cent. of firstborn.
Clinical features	Hydrops, anaemia, jaundice, macrosomia, haemorrhage, heart failure.	Usually only jaundice.
Cord blood	Direct Coomb's test positive, anaemia, erythroblastosis, Rh positive.	Direct Coomb's test negative, anaemia slight, spherocytosis, increased osmotic fragility of red cells, group A or B.
Maternal blood	Indirect Coomb's test positive, antibodies (anti-D), mother Rh negative.	Immune anti-A or B; mother usually group O (Witebsky test).
Diagnosis	Easy. Predictable before birth.	More difficult. Not predictable before birth.



mediately reporting any icterus. In this regard the recent recommendations of Allen (1958) concerning the use of direct fluorescent white light for the detection of jaundice are of importance.

Haemolytic disease of the newborn results from the agglutination of the infant's red blood corpuscles by an antibody produced in the maternal circulation. The mother's red cells lack a factor which the infant's red cells possess, and antibody against this factor is formed by the mother, passing into the infant's circulation.

The Rhesus factor is responsible for most cases of haemolytic disease of the newborn. Since the classical experiments of Landsteiner and Wiener, reported in 1941, the problems of erythoblastosis foetalis have been largely unravelled and the dangers facing the Rhesus positive infant born of a Rhesus negative mother widely understood. Antenatal blood grouping



SEMI-DIAGRAMMATIC REPRESENTATION
of SOME PATTERNS OF HYPERBILIRUBINAEMIA
SEEN IN THE FIRST WEEK OF LIFE

is now performed routinely and it is often possible to anticipate an affected infant. The diagnosis of haemolytic disease of the newborn is usually easily established by testing blood obtained from the umbilical cord. The usual findings are summarised in Table II. Jaundice and anaemia, rapidly increasing in intensity, are noticed at or soon after birth. The clinical manifestations cannot be enlarged upon here, but the following example will illustrate the features of a moderately severe case.

Case II.—Baby S. A male infant born on the 23rd March, 1958. There were two siblings, both with normal birth histories. The mother was group A Rh negative and the father group O Rh positive. The mother's blood, taken two weeks before delivery, showed a positive indirect Coomb's test, but no antibodies. When membranes ruptured, liquor was noted to be khaki-coloured. The infant weighed 7 lb. 12 oz. and was oedematous, pale and slightly jaundiced. There were petechiae and an enlarged spleen. Cord blood revealed the group to be O Rh positive. The direct Coomb's test was strongly positive and the haemoglobin 10.3 gm. A slide showed 40 nucleated red cells per 100 white cells. The serum bilirubin was 5.6 mg. per 100 ml. There was rapid increase in jaundice, so that when the exchange transfusion was started two hours after delivery, the serum bilirubin had risen to 8.4 mg. per 100 ml. Approximately 700 ml. of fresh sedimented citrated red cells were exchanged (90 ml. per pound) via the umbilical vein. Throughout the procedure,

which lasted one hour and fifteen minutes, the infant's condition remained satisfactory. After completion of the transfusion the haemoglobin was 15.6 gm. and the serum bilirubin 4 mg. per 100 ml. There was rapid disappearance of jaundice and oedema during the next two days and no subsequent anaemia.

Icterus Praecox

Haemolytic disease of the newborn may also occur as the result of incompatibility between mother and infant in the ABO groups. Here the mother's red cells are usually group O and the infant's group A or B. The maternal blood contains antibodies to the infant's cells in the form of anti-A or anti-B. These may rise to very high levels during and after a heterospecific pregnancy. Blood group relationships of this sort occur in 20 per cent. of all pregnancies (Copeland *et al.*, 1957), but several factors, as yet incompletely understood, operate in preventing the sensitisation of the infant's cells in most cases. Its theoretical occurrence was postulated as long ago as 1923 (Ottenberg), but Hallbrecht in 1944 was the first to show that jaundice in infants could actually occur from this mechanism. He suggested the term "Icterus Praecox." Later, Hallbrecht found 90 cases amongst approximately 16,000 newborn infants, an incidence of 1 in 180 births (Mollison, 1956). This is roughly equal to the incidence of Rhesus iso-immunisation, but the occurrence of severe disease necessitating exchange transfusion is much less frequent in ABO incompatability. The two conditions are contrasted in Table II.

Case III.—Clive C. Born on the 23rd June, 1958, weighing 7 lb. 9 oz. There were three siblings, aged ten, seven and two years. The second child required exchange transfusion at birth for severe jaundice, but the others were normal. In the present infant, jaundice was noted at twelve hours, the infant being otherwise quite normal and the colour excellent. His blood group was A Rh positive and the mother's O Rh positive. The Rhesus sub-types were identical. The mother's serum when neutralised with A substance gave a strongly positive indirect Coomb's on A cells. On the fourth day the serum bilirubin had risen to 14.2 mg. per 100 ml. and on the fifth day to 20.8 mg. per 100 ml. The haemoglobin was 17 gm. and occasional spherocytes were seen in the blood. Because of the danger of kernicterus with a further rise in the serum bilirubin, an exchange transfusion was performed on the fifth day by cutting down on the umbilical vein; 450 ml. of packed three-day-old group O Rh positive cells were used. The post-transfusion bilirubin was 13.3 mg. per 100 ml. Jaundice disappeared rapidly and further progress was uneventful.

A remarkably high incidence of ABO haemolytic disease has recently been reported from Sweden in newborn of diabetic mothers (Zetterstrom *et al.*, 1958). These workers, describing 29 such infants, found definite evidence of ABO disease in all five heterospecific pregnances in the series. They showed also that infants born of diabetic mothers, even though mature, developed very high bilirubin levels during the first days, the levels even exceeding those in premature infants. The maximum rise was found on the fourth day, later than in normal infants, but not as late as in prematures.

Other Causes

The remaining causes of jaundice in the newborn occur with far less frequency than does haemolytic disease. Nevertheless, from time to time cases are seen which present many problems in diagnosis and management. Jaundice develops as a rule *after* the second day, and suspicion of its pathological nature will arise either because of the severity of the jaundice or because of the associated abnormal manifestations in the infant. The group with obstructive jaundice present a clear-cut pattern, but generally speaking, the content of bile pigments and urobilin in the stool and urine are of no help in the diagnosis. Septicaemia is the most important of these and should be the first thought in a jaundiced infant who is ill. The organism is usually a staphylococcus, streptococcus or *E. coli*. The infection may be acquired either before birth, during delivery or post-natally. Apart from jaundice, restlessness, failure to suck and pallor may be noted before any signs of localisation are manifest. Later there may be wasting, haemorrhagic manifestations and enlargement of liver, spleen and glands. It should be stressed that fever and leucocytosis may on occasions be absent.

A similar picture may be produced by various infections transmitted to the foetus *in utero*. These include congenital syphilis, congenital toxoplasmosis, cytomegalic inclusion disease and virus hepatitis. Of these, syphilis is easily diagnosed by infant's and mother's serology and often by accompanying manifestations. Cytomegalic inclusion disease has on occasions been diagnosed during life by the demonstration of typical cells in the urine or by biopsy. Toxoplasmosis is demonstrable by the presence of retinal lesions, cerebral calcification and dye and complement fixation tests. Virus hepatitis as distinct from the neonatal hepatitis to be mentioned later can be diagnosed only on liver biopsy.

Galactosaemia, though very rare, is of considerable importance to the clinician, since early recognition and prompt treatment may result in complete cure. Inherited as a Mendelian re-

cessive trait, this disorder of metabolism is due to lack of enzyme required in the chain of conversion of galactose to glucose. The resultant high levels of galactose and/or the low glucose levels produce widespread damage. There is vomiting, failure to gain, enlargement of the liver and spleen, mental deficiency and cataract formation. The earliest sign may jaundice, which often appears to be a continuation of normal icterus neonatorum. This is one of the few conditions in the neonatal period in which liver function tests are regularly abnormal. The urine contains large amounts of reducing substances and the galactose tolerance test is diagnostic. Removing all milk from the diet produces immediate improvement.

Obstructive Jaundice

Occasionally young infants are seen with jaundice which is blatantly obstructive in character. There is hyperbilirubinaemia with high levels of direct bilirubin. The stools are pale and acholic and the urine contains large amounts of bilirubin, but no urobilin. It will later be shown that the majority of these cases are due to congenital obliteration of the bile ducts, yet in almost one-third the biliary tracts are normally formed, obstruction being caused by clogging of ducts by thickened secretions.

Ladd described the first cases of this condition in 1935 and used the term "inspissated bile syndrome." Such cases of obstructive jaundice due to the inspissated bile syndrome fall into two distinct groups. In the first the complication results in infants already jaundiced from haemolytic disease—usually due to Rhesus incompatibility. With the advent of mechanical obstruction to the flow of bile, direct-reacting bilirubin rises in the serum for the first time, the stools become pale and the urine dark. Exchange transfusion does not produce the expected decrease in jaundice in these circumstances. Stempfel *et al.* (1956) have reviewed the syndrome and reported seven cases amongst 83 Rh-iso-immunised infants with erythroblastosis. Jaundice persists for a variable period up to four months, but the eventual prognosis is excellent. The inspissated bile syndrome may, however, also occur without any previous evidence of haemolysis or preceding disease. The work of Craig and Landing (1952) and Gellis *et al.* (1954) suggests that a form of hepatitis is responsible. The latter workers postulate a virus transmitted to the foetus *in utero*—perhaps the virus of serum hepatitis. The eventual prognosis is usually good, although some cases may progress to cirrhosis of the liver.

Laparotomy for suspected atresia of the bile ducts greatly increases the mortality (Gellis *et al.*, 1954; Gross, 1956). Cortisone and A.C.T.H. have been found to have a beneficial effect, producing diminution of jaundice.

In concluding, I shall describe a case of the inspissated bile syndrome in an infant who proved to have haemolytic anaemia of a different sort, namely, familial spherocytosis. As far as we are able to ascertain, this is the first such case reported.

Case IV.—Colin K. Born 12th February, 1957, the first child of healthy parents. There was a strong history of acholuric jaundice on the father's side. The infant was delivered by forceps and weighed 7 lb. 11 oz. He appeared normal at birth, but jaundice was noticed at four hours, gradually becoming more intense. Stools consisted initially of dark meconium, changed to brown on the third day and were thereafter clay-coloured. The urine became progressively more bile-stained, and urobilin, present in the urine in the early days, later disappeared. The liver and spleen were much enlarged. Investigations performed on the third day of life were:

Red blood cells: 4,000,000/c.mm.
There was some macrocytosis and small numbers of normoblasts.
No spherocytes were seen.
Haemoglobin: 14.6 gm. per 100 ml.
White cells: 8,000/c.mm. (Neutrophils, 51 per cent.)
Red cell fragility yielded a normal pattern.
Blood group O Rh positive.
Direct Coomb's test: negative.
Serum bilirubin: 7 mg. per 100 ml.
Van den Bergh: direct positive.
Wasserman reactive: negative.

By the thirteenth day the haemoglobin had dropped to 8.5 gm. and the serum bilirubin had risen to 8.1 mg. per cent. A simple blood transfusion was given, but this led to an immediate exacerbation of the jaundice.

At one month of age the infant was still at his birth weight and there was troublesome vomiting. The serum bilirubin was then 17 mg. per cent. The picture was that of complete biliary obstruction. Instillation of concentrated magnesium sulphate into the duodenum, however, produced transient green stools. This procedure was repeated three times a day for ten days without materially altering the jaundice. The diagnosis was thought to be the inspissated bile syndrome due to either neonatal hepatitis or to familial haemolytic anaemia (spherocytosis), but the persistent absence of spherocytes and the normal fragility of the red cells seemed against this diagnosis. Treatment with cortisone was commenced at six weeks. By three months of age jaundice had disappeared, but there were still varying amounts of bile in the urine and the liver and spleen were greatly enlarged.

When next seen at seven months he weighed 15 lb. 12 oz. and was regarded by his parents as quite normal. The liver was now soft and normal in size, the spleen still being palpable one finger's breadth below the costal margin. The haemoglobin was 8.6 gm. No spherocytes were seen and a battery of liver function tests showed no abnormality.

At eleven months the haemoglobin had fallen to 5.8 gm. and there was persistent reticulocytosis. Again no spherocytes were seen, but the red cell fragility

was now slightly increased. Splenomegaly was still present. Two blood transfusions were followed by rapid haemolysis and slight jaundice. It was now definite that the child had a chronic haemolytic anaemia and the family history pointed to acholuric jaundice. The spleen was accordingly removed at thirteen months. Since then his haemoglobin has been well maintained and the only residua of a harrowing illness are the splenectomy scar and green deciduous teeth.

SUMMARY

The various causes of jaundice in early infancy are enumerated and the more important of these discussed.

The importance of recognising jaundice in the first 24 hours of life is stressed.

Four case histories, illustrating the problems of diagnosis and management of "medical" jaundice, are presented.

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The Management of Epilepsy

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The management of epilepsy is the care of the epileptic patient, and it is of the first importance to realise that most patients with epilepsy are otherwise perfectly normal people. Of necessity, their lives may be disturbed or their viewpoint distorted, but it is the physician's job, as far as is possible, to prevent these effects. He should realise that if a patient who has epilepsy also has intellectual defect or disorder of personality, he must have some other condition as well as the epilepsy, as surely as if he had abnormal neurological signs to prove it. The disorder of intellect, temperament or behaviour may be due to the cause of the epilepsy or to its treatment. It is probable in this respect that bromides, the centenary of whose use occurred last year, on balance did more harm than good to epileptic patients. They may have reduced the number of fits, but in so doing they converted so many intelligent people into retarded dullards that the word epilepsy became linked in everyone's mind with mental disease.

Always consider the kind of person who has the fits and the impact of the fits on him, his family and his way of life. See his life problem through his eyes and try to put yourself in his place in arranging for education, in sorting out home difficulties, in advising on games, bike-riding or driving a car, and later on in advising upon training for a career and preparing for parenthood. If you do this successfully you may find that the problem of epilepsy was not such a big one in that case after all, and that you had used much less anticonvulsants than did your predecessor.

Epilepsy is often evidence of organic brain disorder, but it is not often that that disease is advancing. Fits in childhood rarely need more investigations than those of general medical survey, X-rays of skull and chest and an electro-encephalogram. Even in adults, if the electro-encephalogram does not show a local lesion and there are no neurological signs, more elaborate "neurosurgical" investigations can wait. The patients who are going to need craniotomy are few, those who will really benefit from it still fewer, whilst great suffering may be caused through the anxious over-investigation of the