ERYTHROBLASTOSIS FOETALIS

Part II

BY

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Erythroblastosis foetalis type I (hydrops foetalis) has been described in part I, p. 1.

Type II. Icterus gravis (26 cases)

Maternal and obstetric history, age and sex. The sixteen mothers about whom information was available had had a total of sixty-eight previous pregnancies, an average of 4.3. Thirty-one infants of these pregnancies were stillborn or died in infancy and the cause of death was not stated. Another four infants died with jaundice, apparently icterus gravis. One sibling of the subject in one case, and probably another, had icterus gravis while a third was a stillborn achondroplasiac. In the latter there was excessive haemopoiesis in the liver, but not greater than was found in other achondroplasiac infants. However, there was haemosiderosis of the liver, ferrous and ferric iron impregnation of the capsule and trabeculae of the spleen, and the secretory epithelium of the kidney often gave a diffuse prussian-blue reaction. These changes probably signified erythroblastosis which might have manifested itself as icterus gravis, had the foetus not died in consequence of its deformity. The subjects in two cases were siblings. There was evidence that in seven of the sixteen mothers icterus gravis occurred in more than one of their offspring. There was no evidence of a hereditary influence except that the father in one case developed jaundice following influenza fifteen days before the birth of the child.

The labours were apparently normal. There was no unusual frequency of albuminuria, oedema or hydramnios in the mothers as in hydrops foetalis.

In the twenty-six cases there were sixteen males and ten females. The age varied from two to thirty-five days. The body length varied from 43 to 58 cm. crown-heel. The duration of pregnancy, determined from the length or body weight after allowing for the duration of post-foetal life appeared to be from thirty-two weeks to full term, with an average of 35.6 weeks; six infants were full term.

Examination of cases in the literature showed, as in hydrops foetalis, that the number of those who were stillborn or died in infancy without definite erythroblastosis was much greater when infants with icterus gravis occurred in the families than when they did not, and that the average number of

pregnancies before those that produced infants with icterus gravis was high. In one hundred and fifteen reported families there were fifty-seven with more than one instance of icterus gravis in siblings and fifty-eight with only one. These figures, and mine, show that icterus gravis is more commonly familial than hydrops foetalis. Five instances of icterus gravis affecting twins have been reported. Reports of erythroblastosis of types I or III in siblings or twins of infants with type II will be mentioned in part 3.

Seulen (1835) described icterus gravis and hydrops foetalis in siblings, whose father became jaundiced about a year before the birth of the jaundiced child. In a case of Bernheim-Karrer (1936-37) the father had been jaundiced. Palm (1919) described the appearance of jaundice in the mother two months before the birth of the child and its continuance into the puerperium. Ritchie (1912-13), Smith (1902) and Dam, Tage-Hansen and Plum (1939) described cases in which the mothers were jaundiced during one pregnancy. Tylecote (1913-14) described jaundice during the mother's eight pregnancies which persisted after her last. Seven of her infants developed jaundice from which only one recovered. Nason (1910) and Rolleston (1910) each described repeated jaundice in the numerous pregnancies of mothers of whose infants many had icterus gravis. Bernheim-Karrer (1936-37) recorded a case in which the mother was always jaundiced and another in which she was jaundiced from time to time and throughout one pregnancy. Hilgenberg (1925), Altitzoglou (1933), Boehncke (1938-39) described infants with icterus gravis born during the mothers' second marriage and none with icterus gravis during the first. Fordyce and McAfee (1924) recorded two or three instances of icterus gravis in one family; one sister of the mother of this family was jaundiced shortly after birth and the second child of another sister was severely jaundiced at birth. Hoffmann and Hausmann (1926) mentioned four infants with icterus gravis born of one mother and another of her sister. Hawksley and Lightwood (1934) described icterus gravis in two sisters and a brother of the father of an infant with icterus gravis; the marriage of the parents was consanguineous. These reports give slight evidence of hereditary tendency.

In seventy-four reported cases there were forty-two males and thirty-two females. These figures and mine show a slight predominance in males. The proportion of full-term pregnancies in reported cases was higher than in hydrops foetalis, although many infants were premature. This is in keeping with a higher average duration of pregnancy in

icterus gravis than in hydrops foetalis among my cases. About 75 per cent. of reported cases were fatal, but this figure is probably too high, especially for recent times. In one hundred and twenty reported fatal cases the commonest day of death was the third and in all but sixteen it was in the first three weeks. Smith (1902), M'Gibbon (1912-13), Capon (case 8, 1922) and Schminke (1923) described icterus gravis in stillborn.

Clinical history

No clinical data were available in several cases. Jaundice was present at birth in three or appeared in the first three days, except in one case in which it was never present. Pallor was noticed in a few and in one preceded jaundice. Haemorrhages into the skin or from the umbilicus or mucous membranes were noted in some cases. Loss of weight occurred in many, while in a few it was marked. Twitchings or convulsions occurred in three. The immediate cause of death was haemorrhage in five, bronchopneumonia in two, while in the remainder it was apparently due to toxæmia associated with jaundice, probably aided by anaemia in some. The infant without jaundice was cyanosed at birth, and on the fourth day developed slight diarrhoea and vomiting, and twitchings of the face and limbs. The abdomen was distended from enlargement of the liver and the abdominal wall was slightly oedematous. On the next day, the day of death, more vomiting and convulsions occurred. The cause of death was probably toxæmia associated with changes in the liver.

In one hundred and sixty-one reported cases jaundice was present at birth in fifty-four or appeared in the first three days in ninety-seven. There was no record of absence of jaundice as in one of my cases. The jaundice became rapidly severe at the onset or was mild at first and in a few days rapidly deepened; in a few it remained mild throughout. It persisted a few weeks and subsided, but Ellis (1938) described persistence for twelve weeks, Braid and Ebbs (1937) for eight months and Hart (1925) for one year. Smith (1902), de Lange (1926), de Lange and Arntzenius (1929), Diamond, Blackfan, and Baty (1932), Altitzoglou (1933), Hawksley and Lightwood (1934), Peck (1935), Weinberg and Rockaway (1939), and Wolfe and Neigus (1940) described jaundice, usually yellow, either of the vernix caseosa or liquor amnii. Pallor was present in many cases and usually appeared when the jaundice was subsiding; in some it became so marked that the disease changed from type II to III.

Blood counts in the literature showed a considerable variation. In most cases there was a moderate anaemia, but in a few erythrocytes fell below one million per c.mm. Erythroblasts were usually present in excess in the circulation; a few in the first week is not abnormal. Åkerrén (1932-33), de Lange (1934) and Boehncke (1938-39) found basophil erythroblasts (primary erythroblasts). Ylppö (1918), Plaut (1927), Rosenbaum (1928), Altitzoglou (1933), Bernheim-Karrer (1936-37), Tow (1938), Boehncke (1938-39), and Wolfe and Neigus (1940) have reported cases in which in the

first week there was no anaemia or the erythrocytes were not lower than 4.5 million per c.mm., yet there was an excess of erythroblasts, usually considerable. A moderate anaemia developed later in some of these cases. Greenwald and Messer (1927), Bernheim-Karrer (1936-37), Zuelzer and Bigler (1940), and Wolfe and Neigus (1940) have described similar cases without anaemia, but erythroblasts were apparently absent or not in excess in the blood. Hart (1925), St. Kramstyk (1931), Parsons, Hawksley and Gittins (1933), Montlaur and Lévy (1937), and Boehncke (1938-39) reported cases with moderate anaemia but no erythroblastæmia. Thorling (1922-23) and Weinberg and Rockaway (1939) described cases with no erythroblasts in the blood on the tenth day although there was anaemia and excessive haemopoiesis in the liver. Poikilocytosis, anisocytosis, polychromatophilia, reticulocytosis and punctate basophilia were mentioned by several authors, Cabot's rings and Jolly bodies by a few. Erythrocytes were seen in the blood by Buchan and Comrie (1909) and Bernheim-Karrer (1936-37). The leucocyte count varied greatly; usually it was within normal limits; it was raised moderately in many and greatly in a few, reaching 136,000 per c.mm. in the case of Peck (1935). When greatly raised anaemia was usually severe. Myelocytes and haemocytoblasts were commonly present, especially in cases with severe anaemia.

The plasma van den Bergh test when reported gave usually an immediate direct reaction, but in many cases a biphasic reaction. Rarely was it indirectly positive alone, as in a case of Hawksley and Lightwood (1934). Kleinschmidt (1930) recorded an increased blood haematin and von Gierke (1930) found xantorubin in the serum.

Slight subcutaneous oedema limited to sites such as the feet, external genitalia or eyelids were observed by a few authors. Haemorrhages were commonly mentioned; they varied from petechiae in the skin to larger haemorrhages in the subcutis and conjunctiva or from the nose, mouth, anus, umbilicus or less commonly the urethra.

In a minority of cases the stools were clay coloured and bile salts appeared in the urine, but this occurred during part of the illness only.

Convulsions were commonly mentioned and varied from twitchings to marked general rigidity, in some with opisthotonus.

The spleen was palpable at some time in most recorded cases; this was rare before the onset of jaundice and commonly persisted after the jaundice had cleared.

Death in most recorded fatal cases appeared to be due to toxæmia with jaundice, but haemorrhage, anaemia or bronchopneumonia was the cause in many.

In children who recovered certain sequelae have occurred. The commonest was mental backwardness or imbecility usually associated with spasticity and frequently with choreiform or athetoid movements. Rarely the teeth were jaundiced as described by Ellis (1938), or the liver became cirrhotic as will be mentioned later. Braid (1932, 1939), McCune and Bruch (1937) and Albright, Scoville, and Sulko-witch (1938) described cases in which, following icterus gravis, children developed a syndrome of a bone disease resembling radiologically generalized osteitis fibrosa, areas of cutaneous pigmentation and, in females, sexual and somatic precocity.

Macroscopic appearances at necropsy

Jaundice was present in all cases. It was limited to the liver in one and to the kidneys, liver, endocardium, aortic intima and conjunctiva in another. It was slight in five and marked in the remainder. In five cases numerous areas of grey matter in the brain were jaundiced (nuclear jaundice). The regions most commonly affected were the nucleus of Luys, hippocampus, caudate and lenticular nuclei, optic thalamus, dentate nucleus and nuclei in the mid-brain and medulla. In another case there was less extensive nuclear jaundice. In another the nucleus of Luys and ependyma of the ventricles alone were yellow, and in another jaundice was limited to the cerebral cortex for a distance of 1 mm. beneath the whole of its surface. In three of these cases jaundice was also present in the white matter, in one in the central semiovalia, in another in the fronto-parietal regions beneath the convolutions, and in the other diffusely through the whole brain. In eight cases the medullary pyramids of the kidneys, especially their apices, were coloured yellow. This was usually regarded as uratic infarction, but was probably for the most part due to jaundice. The bile pigment in the brain and medullary pyramids remained yellow in formaldehyde solution instead of turning green.

Anaemia of the tissues, especially of the skin and muscles, was observed in eleven cases.

In one case there was some oedema of the abdominal wall and in two others there were effusions, the largest 3 drachms, in the coelomic cavities. Haemorrhages were present in all but three cases. They were more numerous and of wider distribution than one would expect in infants dying of other causes. Most were petechial; larger haemorrhages were common in the lungs. Petechiae in the brain were very numerous and probably caused death in one case. Death was due to multiple intestinal haemorrhages in one, haemorrhage from the umbilicus in one, subdural haemorrhage associated with a ruptured tentorium cerebelli in one, and haemoperitoneum due to rupture of a haematoma of the liver in another.

In three cases there were yellowish-white or white flecks of necrosis in the cerebral white matter; in one a fleck (2×1 mm.) lay in the right parietal lobe 3 mm. from the ventricle and another behind it close to the ependyma; in one a fleck (1.5 mm. diam.) was present in the right frontal lobe anterior to the lateral ventricle; in the other a streak (7×1.5 mm.) lay in the left pre-Rolandic gyrus 1.8 mm. below the surface. Cerebral jaundice was present in all but the last of these cases.

In two cases the umbilicus was inflamed. Haemorrhagic gastric erosions were present in one.

In sixty-nine cases of icterus gravis reported with necropsies in the literature thirty-three or about half showed cerebral jaundice. In case 8 of Capon (1922) it was described as green; in the remainder it was yellow. Usually it was nuclear alone, less commonly it was diffuse throughout the brain,

but with more intense staining of certain areas of grey matter, rarely, as described by Capon (case 8, 1922) and Hawksley and Lightwood (case 11, 1934), there was an apparently even, diffuse coloration. Schmorl (1904) showed that the bile pigment in nuclear jaundice remained yellow in formaldehyde solution and believed this signified a difference in chemical composition of the pigment from that in other forms of jaundice. The xanthorubin reported in the serum by von Gierke (1930) in a case of nuclear jaundice is possibly the pigment which stains the brain tissue.

In about three-fifths of the cases there were haemorrhages in various tissues or from the umbilicus or mucous membranes. This tendency to haemorrhage is probably due to reduced prothrombin in the blood. This was found in icterus gravis by Dam, Tage-Hansen and Plum (1939). The low prothrombin content probably depends chiefly upon deficient formation in the liver.

Orth (1875), Schmorl (1904), Möbius (quoted by Schmorl) and von Gierke (1921) described yellowish-white flecks in the white matter of the brain in infants with a jaundice either definitely or probably icterus gravis.

Umbilical sepsis has been recorded in a few cases of icterus gravis. De Lange (1924-25), Biemond and van Creveld (1937), and Lightwood (1938) described infants or children with nervous symptoms, and jaundice and umbilical sepsis had been present in early infancy. They ascribed the nervous symptoms to sequelae of nuclear jaundice and believed the jaundice was secondary to the sepsis. There is no reason for not regarding these cases as example of icterus gravis with accidental umbilical sepsis.

Beneke (1907), Pfälzter (1915), and Hilgenberg (1925) described gastric erosions in cases of nuclear jaundice. In my case with erosions there was no cerebral jaundice.

Capon (case 8, 1922), von Gierke (1930), and Rhamy (1938) described rupture of greatly enlarged spleens, with retroperitoneal haemorrhage in Rhamy's case and haemoperitoneum in the others.

Weights of body and organs

The figures of Cruickshank and Miller (1924) and Browne (1924) for body and organ weights and ratios in normal foetuses and infants up to one day old give approximate values for comparison with those in cases of icterus gravis in the absence of satisfactory figures for older normal infants.

In one case the body weight and body-weight to length ratio was high and no case in a similar age group of Browne had as high a ratio. There was no oedema and the high weight was probably due to solid tissues, especially fat. In another case the weight was low and no case in a similar age group of Browne had as low or a lower body-weight to length ratio. This was probably due to wasting. These findings were probably not significant.

The mean liver weight was 146 gm. and this is probably slightly above the normal. In four cases the weights were abnormally high. The mean spleen weight was 17.7 gm., and this is definitely above the normal. Abnormally high weights were found in eleven cases, the highest 43 gm.; in nine cases the weights were about the normal. The mean

heart weight was 19 gm., and this is probably about the normal. In none was the weight abnormally high. The mean thymus weight was 5.8 gm. This is probably slightly below the normal. In three cases the weight was abnormally low.

Enlargement of the liver has been reported by many authors and enlargement of the spleen by many; the largest spleen was 125 gm. (Rhamy, 1938). The spleen weight in some cases was normal or quite small, for example, 3.5 gm. in a case of Ylppö (1918). A few authors reported hypertrophy of the heart, but gave no statistical proof of it. Capon (case 8, 1922), von Gierke (1930), and Diamond, Blackfan and Baty (1932) described enlargement of the placenta, but this is probably only an occasional finding. There were no data concerning the placenta in my cases. There is apparently no record of abnormally low thymus weight in the literature.

Microscopical appearances

HAEMOPOIESIS. One case is excluded because the brain alone was examined histologically. In four of the remaining cases no abnormality of haemopoiesis was found in the liver and other tissues examined. In twenty-one cases the liver and often other tissues showed excessive haemopoiesis, either by its excess in amount or by its presence at a time when it is normally absent.

In the liver in all these twenty-one cases excessive haemopoietic tissue was present in the lobules in the distribution normal for foetal life. In five there was also focal erythropoiesis in portal systems; this is probably abnormal for post-foetal life. In two of the twenty-one cases there was no leucopoiesis in the portal systems; in the remainder it was present and not greater in amount in any one system than might be found normally, but implicating a greater number of systems than is normal. Megakaryocytes were present in the lobules in six of the twenty-one cases, being in normal scanty numbers. The relative amounts of leucopoiesis and erythropoiesis were similar to those in foetal life except in two in which the relative amounts of leucopoiesis were abnormally high. The character of the erythropoiesis was normal for the age in most cases, the secondary erythroblasts being normoblasts with, in some, a few late megaloblasts. In nine cases it was probably more megaloblastic than normally, intermediate megaloblasts being present at ages when they should have been absent. In two cases there appeared to be a hold up in the development of the erythron in that haemocyto blasts and early primary erythroblasts were in moderate numbers while intermediate and late primary erythroblasts and secondary eosinophilic erythroblasts were scanty.

The spleen was examined in eighteen cases, all among the twenty-one with excessive haemopoiesis in the liver, and in all an excess was present proportional to that in the liver. The amount was never as great as that found in some cases of hydrops foetalis and the Malpighian bodies were well developed and not obscured. In some cases it would

have been difficult to establish an increase of haemopoiesis without control. Leucopoiesis and erythropoiesis were in relative amounts similar to those in late foetal life except in five cases in which leucopoiesis greatly predominated. Erythropoiesis was more megaloblastic than normally, as shown by the presence of intermediate megaloblasts, in the same nine cases in which they were found in the liver. There were a few megakaryocytes in three.

In the kidneys a few foci of erythropoiesis in one case, and foci of leucopoiesis in two cases, were abnormal. In one case a small focus of erythropoiesis resembled those often found normally. No haemopoiesis was present in the kidneys examined in another eleven cases.

In the thymus, in one of the four cases in which it was examined, leucopoiesis was slightly excessive in both the parenchyma and interlobular septa, and there were numerous foci of haemocyto blasts and primary erythroblasts and a few foci of normoblasts in the cortex beneath the capsule.

In the lungs, in one of the six cases in which they were examined, there were foci of haemocyto blasts and primary erythroblasts in greatly distended capillaries of several scattered alveolar walls, and in another there were a few extravascular foci of leucopoiesis in the peribronchial tissue and alveolar walls.

In the suprarenals, in three of the eleven cases in which they were examined, focal erythropoiesis was present in the cortex similar to that in many cases of hydrops foetalis.

The marrow in various bones examined in eight cases showed no definite abnormality, but because of the effect of decalcification it could not be fully studied.

Lymph glands, in two of five cases in which they were examined, showed slightly excessive leucopoiesis.

Excessive haemopoiesis in the liver, spleen and occasionally other organs has been frequently reported. Hoffmann and Hausmann (1926), Altitoglou (1933), Hawksley and Lightwood (1934) described cases in which there appeared to be no excess of haemopoietic tissue. Hawksley and Lightwood also described a case in which leucopoiesis was much greater than erythropoiesis in the spleen.

LIVER. In twenty of the twenty-five cases in which the liver was examined jaundice was seen. In eight it was slight and shown by bile thrombi in a few intercellular canaliculi usually in the centres of the lobules; in the remaining twelve, including that of the infant which had had no jaundice of the skin, it was marked and shown by thrombi in numerous intercellular canaliculi, by bile droplets or globules in variable numbers of hepatic cells within the columns, by bile globules or streaks in variable numbers of free round or oval hepatic cells and in some cases by extracellular bile pigment in the lobules or portal systems (fig. 13). The free hepatic cells were often large and usually had a pale-staining rather dropsical cytoplasm. There

was no apparent obstruction to the bile capillaries. In two of these cases no abnormality of haemopoiesis was detected.

Haemosiderosis was marked in two cases, most hepatic cells containing granules of haemosiderin, and in thirteen cases less marked. Haemosiderin

cells seen in paraffin sections. It was present in the four cases in which there was no apparent abnormality of haemopoiesis. Among the twenty cases with jaundice one showed numerous submiliary foci where the hepatic cells had disappeared leaving an uncollapsed reticulum, the meshes of which en-

FIG. 13.—Icterus gravis. Liver. A, bile thrombi in intercellular canaliculi; B, granules of bile in hepatic cells in columns; C, bile in free rounded hepatic cells. Haem. and eosin. $\times 570$.

was normal in amount in six cases and absent in four. In three cases with haemosiderosis no abnormality of haemopoiesis was detected, but haemosiderin was in normal amount in four and absent in four with abnormal haemopoiesis. Kupffer cells were large and clearly demarcated by

closed erythrocytes and nucleated blood cells (fig. 14), and two others had similar foci in association with foci in which the hepatic cells appeared necrosed. In another there was a slight increase of reticulin around the sinusoids with fibres running into the liver columns between individual cells more

FIG. 14.—Icterus gravis. Liver. Focus with loss of hepatic cells. Haem. and eosin. $\times 420$.

giving a diffuse prussian-blue reaction in eleven cases, but this was present in most control infants. Erythrophages were found in sinusoids in all cases within normal numbers.

Frozen sections, made in fourteen cases, showed fatty degeneration marked in three, slight in five and absent in six. In two others fatty degeneration was shown by marked vacuolation of the hepatic

frequently than normally. Evidence of slight regeneration was shown by small rounded areas of wide hepatic columns in tissue composed of atrophied-looking columns. In another there was a similar increase of reticulin most marked in the periphery of the lobules where the fibrils sometimes stained with van Gieson's mixture. The portal systems were enlarged in this case and their peri-

phery showed an increase of fibroblasts, collagen formation and a slight proliferation of pseudobile canaliculi. Among the five cases without jaundice four had fatty degeneration, with a slight increase of reticulin in one, and the other showed albuminous degeneration and foci of necrosis of hepatic cells.

Most authors have recorded the presence of haemosiderosis and jaundice of the liver, but a few found them absent. Haemosiderosis has been reported in the absence of an abnormality in haemopoiesis by Hoffmann and Hausmann (1926) and Hawksley and Lightwood (1934), but the absence of haemosiderosis in the presence of abnormal haemopoiesis was observed by Buchan and Comrie (1909) and Hawksley and Lightwood (1934). Fatty degeneration has been reported by many authors and Miller (1938-39) described focal necroses. Portal fibrosis was apparently present in cases of Buchan and Comrie (1909), Pfannenstiel (1908), Hoffmann and Hausmann (1926), and Hawksley and Lightwood (1934). Klemperer (1924), Diamond, Blackfan and Baty (1932), Hawksley and Lightwood (1934), and Bernheim-Karrer (1936-37) described cases with a diffuse intercellular type of fibrosis. De Lange (1916-18) reported a child who died of diffuse cirrhosis of the liver which appeared to be a sequela of icterus gravis. Bossert (1916-18), Hannau (1924-25), Braid and Ebbs (1937), Curtiss (1934), Webster (1938), and Zuelzer and Bigler (1940) described reticular fibrosis of the liver with nodular regeneration in infants or children who had had icterus gravis.

SPLEEN. Haemosiderosis of the spleen was present in seven cases, the iron being diffuse or in granules or globules in fixed or free reticulum cells or in fewer sinus cells and some was free in the pulp. Much iron, but not an abnormal amount, was found in five cases, a moderate amount in three, an abnormally scanty amount in one and none in one. In the remaining cases the spleen was not examined. Impregnation of the capsule and trabeculae with ferric and ferrous iron, which was stained deeply with Ehrlich's haematoxylin, occurred in three cases, and in another a similar impregnation occurred in small trabeculae, while in two of these four cases and a fifth some reticulin fibres of the pulp were impregnated.

Iron impregnation of the trabeculae was observed by Hewer (1928-29) and MacClure (1931) and of the capsule by de Lange (1934). Many authors described haemosiderosis.

KIDNEYS. In two of the eight cases in which the medullary pyramids were macroscopically yellow, this coloration was seen in sections to be due to bright lemon-yellow amorphous bile pigment in the interstitial tissue, and in one no urates were found in alcohol-fixed tissue. The colour at necropsy was regarded as uric acid infarction, but jaundice was the more probable cause in all the cases. The pigment in the remaining six cases had probably been dissolved out by the chloroform used in clearing the blocks. Uric acid infarction might have been

present in addition in some cases. In three cases there were some brownish-yellow casts in secretory tubules, and in another lumpy eosinophil casts lay in discharging tubules; these were suggestive of haemoglobin casts. In three cases a few haemosiderin granules were seen in the cells of some secretory tubules. These cells, and cells without granules in two other cases, gave a diffuse prussian-blue reaction. Haemosiderin in interstitial cells in four cases was not abnormal. In one case diffuse brownish iron-free pigment in the cells of some secretory tubules was not removed by 10 per cent. liquor ammoniae fortis in 70 per cent. alcohol, while in another some finely granular brown pigment in similar cells was dissolved by ammoniacal alcohol and was probably haematin. Slight fatty degeneration was present in two of the seven kidneys examined for fat.

Several authors have reported coloration of the medullary pyramids. It was yellow in most cases, but described as brick-red by Beneke (1907), yellowed by Palm (1919) and yellowish-red, -green, or -brown in three cases of Hilgenberg (1925). In all these cases there was nuclear jaundice whereas only half my instances of this coloration were associated with nuclear jaundice. Orth (1875) demonstrated bilirubin in the intertubular tissue, but most authors regarded the condition as uratic infarction. In the case of Boehncke (1938-39) the pigmented medullary pyramids were necrosed. I have seen a similar case, not included among those in this paper. Eosinophil or brown tubular casts, and iron or iron-free pigments in the tubular epithelium, as occurred in some of my cases, have been observed by a few authors.

CENTRAL NERVOUS SYSTEM. The brain was examined in nine of the ten cases with cerebral jaundice and in two a few cells were faintly jaundiced. In the other cases the pigment had probably been extracted completely in the embedding process, probably by the chloroform. In seven cases there appeared to be no abnormal degree of degeneration of ganglion cells. In an infant of twelve days the ganglion-cell layer of the hippocampi, the hippocampal gyri and the strata granulosa of the dentate gyri showed marked degeneration or necrosis of many cells which were chiefly ganglionic, but some may have been glial. In the hippocampi and dentate gyri the cytoplasm of the cells was usually eosinophil, homogeneous and opaque and necrosis of many was shown by severe karyorrhexis. Many cells had probably disappeared. Numerous fat granule cells were present in the zones of degeneration and necrosis, and rendered them conspicuous in frozen sections stained with Scharlach R. Gliosis was absent. The nerve cell part of the dentate gyri, superficial to the strata granulosa was oedematous and showed fewer fat granule cells and degenerated ganglion cells. In the hippocampal gyri many of the ganglion cells showed karyolysis and chromatolysis in greater degree than could occur from post-mortem changes alone. These cells had a homogeneous cytoplasm which stained deeply with haematoxylin. In another infant of twelve days

the nuclei of Luys were the only ganglia jaundiced, and the one nucleus examined was occupied by a cellular area (10×2 mm.) in which only a few ganglion cells were recognizable (fig. 15). Most of the

FIG. 15.—Icterus gravis. Nucleus of Luys. Haem. and eosin. $\times 200$.

cells were fat granule cells and the remainder appeared to be astrocytes. There had probably been degeneration, necrosis and loss of ganglion cells associated with accumulation of fat granule cells and early gliosis.

In the fleck of necrosis in the parietal white matter in an infant of twelve days there was a miliary structureless area of necrosis surrounded by a zone of closely packed fat granule cells (fig. 16) and a focus of fat granule cells alone. The area of necrosis in the frontal white matter of an infant of five days was not examined, but in sections of the

outer side of the posterior horn of the left lateral ventricle there was a miliary area of structureless necrosis without accumulation of fat granule cells. The yellow streaks in the pre-Rolandic white matter seen in an infant of fourteen days resembled the nucleus of Luys described above. They were composed of fat granule cells and astrocytes and showed a few granular plaques (up to $33 \times 12\mu$) of material deeply stained by haematoxylin, some of which lay in processes of glial cells. The cells had probably replaced an area of necrosis. An additional case of cerebral jaundice may be mentioned here. It was excluded from the series because of the presence of umbilical sepsis and because the diagnosis of icterus gravis could not be confirmed as the brain only was examined microscopically. The subject was a jaundiced infant of seven days and the unfixed brain showed diffuse jaundice of the whole brain with more intense staining of the right caudate nucleus. Microscopically the white matter on the outer side of the posterior horn of the right lateral ventricle showed miliary foci of structureless necrosis with numerous fat granule cells around them. In the white matter in the region of the left basal ganglia there were several foci of numerous fat granule cells without necrosis. The cause of these necroses in white matter, and that of the degeneration or necrosis of ganglion cells, was not apparent. It was probably toxic. Cerebral jaundice was present in all the cases except that in which fat granule and glial cells had replaced an area of necrotic white matter, but cerebral jaundice might have been present in this case when the necrosis occurred. It is possible that the toxin was the same that causes changes in the brain in rare cases of liver disease and, as shown by Crandall and Weil (1933), in experimentally produced liver disease.

Several authors, notably Schmorl (1904), Beneke (1907), Esch (1908), Hart (1917), Zimmerman and Yannet (1933), and Zuelzer and Bigler (1940) described degeneration or necrosis of ganglion cells in jaundiced parts of the brain. This has been

FIG. 16.—Icterus gravis. Area of necrosis in white matter of brain. Haem. and eosin. $\times 98$.

regarded as the cause of the nervous symptoms which frequently occur during the illness or later. Burghard and Schleussing (1933), de Lange (1934, 1936), Zimmerman and Yannet (1933), Biemond and van Creveld (1937), Fitz Gerald, Greenfield, and Kounine (1939) and Sobel and Zucker (1940) have described, in infants or children with marked nervous sequelae of icterus gravis, histological changes following degeneration or necrosis of ganglion cells. The chief changes were diminution or absence of ganglion cells, paucity of myelin and, in some cases, gliosis or infiltration with fat granule cells.

OTHER TISSUES. Fatty degeneration was present in the myocardium in one case. No abnormality was seen in various bones in eight cases, nor in the suprarenals in ten, the myocardium in four, the pancreas in five, the thymus in four and voluntary muscles in two.

Diamond, Blackfan, and Baty (1932) in two cases found iron pigment in epithelial cells in the pancreas and, like Beneke (1912) also in the thyroid. Ferguson (case 1, 1931) stated that the cartilaginous trabeculae near the zone of provisional calcification of cartilage in a bone were incompletely covered with bone. There was no description of the bone change in case 8 of Capon (1922) in which radiographs showed increased density at the ends of the long bones. These observations may have been significant of bone changes in erythroblastosis of type II resembling those in type I. Esch (1908), Bencke (1912), Pfältzer (1915), and Zimmerman and Yannet (1933), in cases of nuclear jaundice, found Zenker's waxy degeneration of certain voluntary muscles. It might have been the result of convulsions; they were mentioned in the cases of Esch and Bencke. The placenta was not examined in any of my cases, but Hellman and Hertig (1938) found in cases of icterus gravis changes like those in hydrops foetalis, but of milder degree. In two cases of icterus gravis Potter, Seckel and Stryker (1941) found increase in size and number of islets of Langerhans, such as I found in hydrops foetalis. Lipoid infiltration of the suprarenal cortex has not been described.

Differential diagnosis

Congenital syphilis. Diamond, Blackfan, and Baty (1932), Hawksley and Lightwood (1934), and Monfort and Brancato (1935) described cases of congenital syphilis, with jaundice and anaemia, which resembled cases of icterus gravis. I have seen three similar cases in slightly premature syphilitic infants who lived three days, two weeks, and three weeks. In all there was general jaundice, marked tendency to haemorrhage, and jaundice resembling that in cases of icterus gravis in livers within the normal limits of weight. General anaemia was present in two, splenomegaly in one, and haemopoiesis was excessive in the liver and spleen in all three, in the kidneys in two and suprarenals in two. Haemosiderosis of the liver was absent. Points of histological difference from icterus gravis were lymphopoiesis and plasma cells in the portal systems in one, plasma cells in the splenic pulp in two, lymphopoiesis and plasma cells in the kidneys

in two, plasma cells, megakaryocytes and marked leucopoiesis in the suprarenal cortex in one, excess of megakaryocytes in the liver and bone marrow in one, proliferation and necrosis of cells in centres of Malpighian bodies in the spleen in two, interstitial pneumonia in one, and syphilitic osteochondritis in all three.

Other forms of jaundice in newly born. Rarely acholuric jaundice is present at birth; the erythrocyte fragility test should separate the condition from icterus gravis. The jaundice that occurs with congenital obliteration of the bile ducts and in Winckel's disease should never be confused with icterus gravis because of other special features in these diseases. Septic jaundice is caused by infections, especially of the umbilicus, in the first days of life. Umbilical sepsis may, however, be incidental in icterus gravis, and in such cases there could be difficulty in diagnosis, especially if there was no anaemia or familial incidence. The jaundice would probably precede the infection in onset, whereas in septic jaundice the infection would occur first. Icterus neonatorum should not be confused with icterus gravis since in the former the jaundice is always mild and never prolonged or present in the first two days, the general condition is good, anaemia is absent, there is no tendency to haemorrhage, and the van den Bergh reaction is indirectly positive only.

Definition of type II

Type II (icterus gravis) is seen in infants at birth or in the first weeks of life. They are rarely still-born and many recover. There is no constant pathological or clinical change, except jaundice. The jaundice is associated with one or more other characteristic but inconstant features, and the other causes of jaundice given above under 'differential diagnosis,' can be excluded. Among these features nuclear jaundice, areas of necrosis in the cerebral white matter and jaundice of the renal medullary pyramids appear to be peculiar to this type and to erythroblastosis as a whole. Other features are: a familial incidence; a tendency to haemorrhages and convulsions; enlargement of the liver and spleen; an abnormality of haemopoiesis; microscopic jaundice, haemosiderosis, increase of reticulin and fatty or other degenerations in the liver; haemosiderosis and iron impregnation of collagen and in the spleen.

The abnormality of haemopoiesis was present in twenty-one of twenty-five cases, and in three of the other four haemosiderosis of the liver indicated that it might have been present earlier; in the remaining cases the disease was shown by nuclear jaundice, jaundice of renal medullary pyramids and bile thrombi in intercellular canaliculi.

In one case jaundice had disappeared from the skin by the time of death on the second day and was limited macroscopically to the conjunctivae, endocardium, intima of aorta and liver, but was not seen in the liver microscopically. Other features in this case were abnormal haemopoiesis, pallor, haemo-

siderosis of the liver and of renal tubular epithelium, and fatty degeneration of the liver. In another case jaundice was absent from the skin at and after birth and was limited to the liver at death on the fifth day; there was marked abnormality of haemopoiesis, and marked microscopic jaundice, increase of reticulin within the lobules, fibrosis of the portal systems and fatty degeneration in the liver.

Type II differs from I chiefly in that oedema is absent at birth and, if it occurs later, is slight and localized, while lipoid infiltration of the suprarenal cortex does not occur. It differs from type III in that pallor, if present, is relatively slight compared with the intensity of the jaundice, and in that in type III marked microscopic jaundice of the liver, nuclear jaundice and necrosis in the cerebral white matter do not occur.

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