ERYTHROBLASTOSIS FOETALIS

Part I

BY

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The literature on erythroblastosis is unsatisfactory in regard to its morbid anatomy, particularly in its failure to show the great variation of pathological changes and the inconstancy of any one change. The study is upon 52 fatal cases, twelve of the necropsies having been performed by myself. To save paper, clinical data, descriptions of individual cases and references to the literature have been reduced to a minimum. One case was among those of Hawksley and Lightwood (1934) and I reported two cases previously (O'Sullivan and Gilmour, 1940; Bonney and Morton, 1938). Syphilis was excluded in all cases by Wassermann reactions upon the blood of the mother or infant or by examination of the tissues for treponemata. Not all cases fit into one or other of the recognized types of the disease, hydrops foetalis, icterus gravis and congenital anaemia. To avoid creating subtypes or new names the disease has been divided into types I, II and III to include all cases, and the reasons for typing the case have been given at the end of its description.

Type I. Hydrops foetalis (24 cases)

Maternal and obstetric history, age and sex. Albuminuria, usually associated with variable degrees of oedema, occurred in ten mothers during the pregnancy, and hydramnios in two. Breech delivery occurred in four cases, and face presentation in one. Evisceration because of foetal ascites obstructing labour was performed in one. A macerated foetus papyraceus, 6.15 cm. long, without evidence of the disease, accompanied the subject in one case and had a separate placenta. Three mothers each gave birth to two subjects with hydrops foetalis, all in this series. The twenty mothers about whom there was information had an average age of 32.8 years at the time of the pregnancy in question, and had had one hundred and seven previous pregnancies, an average of 5.3. The infants from forty-two of these pregnancies died in utero or in the first thirty-two days of life; three had evidence of hydrops foetalis and three of icterus gravis. In about one-third of mothers hydrops foetalis was proved or probable in more than one of their offspring.

In the twenty-four necropsies there were seven

males and seventeen females. Eleven were still-born and macerated, seven stillborn and well preserved and six survived birth, the oldest for thirty-six hours. The crown-heel body length varied from 35 to 51 cm., averaging 43 cm. and corresponding according to Mall's figures (1910) to a duration of foetal life of from twenty-six weeks to full-term, with an average of thirty-three weeks. Only two pregnancies were full-term. The average length of the non-macerated stillborn was 41 cm., and that of the macerated 45 cm., corresponding to pregnancies lasting thirty to thirty-one and thirty-four to thirty-five weeks respectively.

Ballantyne (1902) showed, and Capon (1922) confirmed that the mothers were usually well advanced in the child-bearing age and that previous pregnancies had been numerous and many of the infants had been stillborn or died soon. These features were present in the present series. In reported cases the incidence in the mothers of albuminuria, oedema and hydramnios was abnormally high. Enlargement of the placenta and foetus was in some diagnosed erroneously as hydramnios. Perforation of the abdomen or evisceration of the foetus had to be performed in some cases because of obstructed labour. Breech presentation was erroneously diagnosed in a few cases at vaginal examination because of oedema of the foetus's face. Eight twin pregnancies are recorded; in four only one foetus, and in the others both showed evidence of the disease. A familial incidence has been frequently reported; Oberndorfer (1927) described as many as five affected foetuses born of the same mother. Instances of erythroblastosis of types II or III in siblings or twins of infants with type I will be mentioned in part 3.

In sixty-seven cases in the literature there were twenty-seven males and forty females. These figures and mine suggest a predominance in females. No instances of recovery have been recorded. The longest survival appears to be thirty-six hours—in one of my cases. Botrret and Lathoud (1912) described an infant with congenital hydrops which lived 8 days, but because of cystic disease in the liver and kidneys the case cannot be regarded definitely as one of erythroblastosis. In the majority of reported cases the infants were premature; in forty-seven the average length was 44 cm., corresponding to pregnancy of 33–34 weeks.

Macroscopic appearances at necropsy. In eighteen cases there was generalized oedema, most conspicuous in the subcutaneous tissue. In one the omentum was transformed into a cyst-like structure. Oedema was absent in three macerated cases and limited to the abdominal wall in two others, and in one non-macerated case it was limited to the retro-peritoneal tissue. Ascites was present in all non-macerated cases and varied from $1\frac{1}{2}$ to 20 oz. Hydrothorax and hydropericardium were usually present but in small amount. In macerated cases haemoglobin-stained effusions were usually found in less amount, but were observed in two without oedema. In three cases the ascitic fluid contained flakes of fibrin. Jaundice of the liver was seen in seven cases, and in two it was slight in the skin, conjunctivae, kidneys and other tissues. Pallor of the skin, voluntary and cardiac muscle, and brain was noted in many. Petechiae occurred in nine of the thirteen non-macerated cases in one or more sites, such as the pleura, pericardium, bladder, lungs and thymus, but there was no apparent excessive tendency to haemorrhage. The spleen often appeared to be enlarged. In eleven cases an increase of lipid in the suprarenals was seen as a profuse yellow radial streaking of the inner part of the foetal cortex. Normally at birth lipid in the foetal cortex is invisible or seen as a horizontal line in the innermost part. This lipid infiltration must not be confused with fatty degeneration which gives the foetal cortex a diffuse yellow colour. It is occasionally found in association with fatty degeneration of the liver, kidneys and myocardium in otherwise apparently healthy newly-born infants or stillborn. In twelve cases the normally shallow yellowish-white or white zone of provisional calcification of cartilage at the osteo-chondral junctions appeared to be abnormally deep in most bones examined. The normal zone is less than 0.5 mm. deep. The deepening was slight and only once reached as much as 2 mm. It was not noticed in all bones nor was it equal at the two ends of any bone affected. The zone was straight and of even depth in any affected bone and continuous except for interruptions normally produced by vertical vessels passing from diaphysis to chondral canals. The placenta was examined in fourteen cases; those I saw were bulky and thick, while the tissue was spongy, friable and of a greyish-pink colour, paler than the normal. Infarcts were less commonly present than normally; they were seen in two cases and were few and small. The umbilical cords were thick and oedematous.

Ferguson (1931), Salomonsen (1931), de Lange (1932) and Macklin (1939) described cases without oedema and Schminke (1923) one in which it was slight and not general. A few authors have described fibrin flakes in ascitic fluid and Hueper and Mullen (1930) found a cyst-like omentum as in one of my cases. The cause of the oedema is not known. Figures of the serum protein and blood chloride are very few and conflicting. Kratzeisen and Ballhorn (1925) and Schminke (1923) described cases with

general jaundice. The average length in these and my case with general jaundice was 47.8 cm. and is higher than that of my cases as a whole. All the subjects were born alive. These features suggest that cases with general jaundice are transitional between types I and II. O'Sullivan and Gilmour (1940) described deepening of the zone at the osteo-chondral junction due to calcified cartilage. Sanger (1888), Fischer (1912a) and Capon (1922) described changes which can be interpreted as a similar deepening. Caffey (1937), in skiagraphs of a subject apparently with hydrops foetalis, saw transverse lines of increased density near the epiphyses probably due to a similar deepening of the zone of calcified cartilage. Yasukawa (1934), Liebegott (1938) and O'Sullivan and Gilmour (1940) described the increase of lipid in the suprarenal cortex and in several earlier papers there are poor or incorrect descriptions of it.

Weights of body and organs. The mean body weight was 2448 gm.,—2457 in the non-macerated and 2436 in the macerated. The mean weight was probably considerably above the normal since the mean normal weight in an age group corresponding to the mean age in my cases is 1860.5 gm. according to Cruickshank and Miller (1924). In two cases the weight was above normal for age and sex. The lower mean weight in the macerated, in whom the mean age was about four weeks more than that in the non-macerated, was probably due to loss of fluid during maceration. The mean body-weight to length ratio was 57,—60 in the non-macerated and 54 in the macerated. These means were probably unusually high and in ten cases the ratio was higher than in any cases in corresponding normal age groups of Browne (1924). The fact that the ratio was higher in the younger non-macerated group than in the macerated again suggests loss of fluid from the latter since the ratio normally increases with age.

The mean liver weight was 111 gm.,—128 in the non-macerated and 91 in the macerated. The mean in the non-macerated group was probably very high since the normal mean of Cruickshank and Miller for males and females in a corresponding age group was 91.58 gm. The lower mean in the older macerated fetuses probably depended upon diffusion out of the liver of fluid products of digested tissue. In only one case was the liver weight above the maximum normal for age and sex. The mean liver to body-weight ratio in the non-macerated was 22 and approximately the same as in any normal age group of Cruickshank and Miller, showing that the increase in mean liver weight was in proportion to that of the body. The ratio in the macerated was 32 and therefore high, pointing to decrease in liver weight from maceration greater than the decrease in body weight.

The mean spleen weight was 19 gm.,—24 in the non-macerated and 15 in the macerated. These figures are probably abnormally high as they are above the mean for full-term foetuses and considerably above the normal mean (5.98 gm.) for males and females in a corresponding age group.

In six cases the weights were above the maximum normal for age and sex, but in eight they were approximately normal. The mean spleen to body-weight ratio was 220,—203 in the non-macerated and 238 in the macerated. These figures are considerably lower than the mean normal ratios in any age group in late foetal life and shows that splenic enlargement was greater than that of the liver and out of proportion to that of the whole body.

The mean heart weight was 15 gm. In two cases the weights were above the maximum normal for age and sex; the sex in each was male, the body length 40 and 44 cm. and the heart weight 21 and 32 gm.

The mean thymus weight in twenty cases was 3.08 gm. This was considerably below the mean normal for males and females in a corresponding age group and below the mean for seventh-month foetuses. In three cases the weights were below the minimum normal, but in two were about normal. The mean thymus to body-weight ratio was 1325 and considerably higher than in any normal age group in late foetal life.

The mean placenta weight in fifteen cases was 1041 gm. and considerably higher than that for normal males and females in a corresponding age group and much higher than the normal for full-term foetuses. In four cases the weight was above the maximum normal. Reduction in weight from loss of fluid was noted in two cases from 1814 and 1928 gm. shortly after delivery to 1162 and 1361 gm. respectively at necropsy. The mean placenta to body-weight ratio was 2.97 in the non-macerated cases. This was considerably lower than the normal in any age group in late foetal life and showed that enlargement of the placenta was greater than that of the whole body.

Many authors have reported enlargement of the spleen, liver and placenta. The largest spleens recorded were those of Harbitz (1923) and Ferguson (1931), 90 gm. each. Several authors have recorded cardiac enlargement, but gave no weights. Others have given high weights, but none was above the maximum normal for age and sex found by Cruickshank and Miller. The statement that cardiac hypertrophy occurs in hydrops foetalis needs statistical confirmation, but my two instances with abnormally high weights suggest that it occurs occasionally. Nyhoff (1911), Capon (1922), Holland (1922) and Browne (1924) have reported very low thymus weights or high thymus to body-weight ratios.

Microscopical appearances

HAEMOPOIESIS. A disturbance of haemopoiesis in the liver or other tissues was apparent in all but one of the thirteen non-macerated subjects; the macerated were unsuitable for study. A description of normal haemopoiesis (Gilmour, 1941) formed a control. In nine cases the tissues were anaemic and the blood abnormally rich in nucleated cells, chiefly erythroblasts. Most of these were intermediate and late megaloblasts and normoblasts, but there were

also primary erythroblasts of all stages, chiefly intermediate. Haemocytoblasts, myelocytes, leucocytes and lymphocytes were also present. In one case there was no anaemia but the blood had a slight excess of nucleated cells. In three cases the tissues were not anaemic and the blood showed no excess of nucleated cells.

In the liver in eight cases haemopoiesis was greatly excessive (fig. 1), in two it was moderately

FIG. 1.—Hydrops foetalis. Liver. Excessive amount of haemopoiesis. Haem. and eosin. $\times 155$.

excessive, in two slightly excessive and in one there was no excess. In only a few cases did it appear to exceed the maximum normally found in early intra-uterine life (26 to 190 mm.). Its distribution and character was normal except that in a few cases megakaryocytes were absent.

In the spleen haemopoiesis was greatly excessive in nine cases (fig. 2), exceeding that which may occur at any intra-uterine stage normally, and Mafpighian bodies were absent in six of these. It was normal in character and distribution except that in a few cases megakaryocytes were absent. In two cases there was no excess, in one a slight excess, and in the remaining case the spleen was not examined.

The kidneys showed abnormally numerous foci of haemopoiesis in four cases, while in one the foci were within normal limits of size and number, in two haemopoiesis was absent, and in the others the organs were not examined.

In the suprarenals focal haemopoiesis was present in the cortex in eight cases. It was almost entirely erythropoietic and extravascular. Such haemopoiesis is abnormal. None was seen in three cases and in the remainder the glands were not examined.

In the bone marrow haemopoietic cells did not appear to be packed abnormally closely and in a few cases adipose cells lay among them in the lower

end of the femur. In four cases haemopoiesis was present in a few chondral canals; haemopoiesis is normally absent here. As far as could be seen in decalcified tissue the haemopoiesis did not appear abnormal. Sections of decalcified bone are, however, useless for the study of the character of erythropoiesis since the haemoglobin in primary erythroblasts may become stainable by eosin as the result of acid treatment.

In the placenta focal haemopoiesis was present in capillaries in terminal villi in four of six cases. It was chiefly erythropoietic; such haemopoiesis is abnormal in this site.

In the thymus in two cases there were a few foci of normoblasts and megaloblasts in the capsule and

FIG. 2.—Hydrops foetalis. Spleen. Excessive amount of haemopoiesis. Haem. and eosin. $\times 250$.

intralobular septa and, in one, in many places in the superficial cortex, there were haemocytoblasts, primary erythroblasts and intermediate and late megaloblasts. Erythropoiesis is abnormal in the tissue about the thymus in late foetal life and in the thymus at all times.

A lymph gland in one case showed slightly excessive leucopoiesis and a few small groups of primary erythroblasts or of late megaloblasts or of normoblasts. In another case two glands showed a few groups of late megaloblasts. Erythropoiesis is abnormal in glands after the 170-mm. stage. Lymph glands in four other cases were normal.

In the majority of cases the erythropoiesis in the various tissues did not appear to be more megaloblastic than was normal for the age, that is to say, these did not appear to be an abnormally high proportion of megaloblasts to normoblasts or an abnormally high proportion of earlier forms of megaloblasts to later forms. In two cases the erythropoiesis was slightly more megaloblastic than

normally. In the blood, however, intermediate megaloblasts were present in most cases, whereas I believe they are normally absent in late foetal life. In one case a film of the heart's blood showed definite megalocytosis, the mean diameter of the erythrocytes as measured by an ocular micrometer being about 10μ .

Most authors since Schridde (1910) have found increased haemopoiesis in the liver and other tissues and Rautmann (1912) called the condition erythroblastosis because of the increased erythroblasts in the tissues. Salomonsen (1931), Weinberg and Rockaway (1939) and Fleischmann and Wolff (1914) recorded blood counts made during life; erythrocytes varied from 2.6 to 3.765 million per c.mm., and erythroblasts and myelocytes were present in excess.

LIVER. In ten of the thirteen non-macerated cases there was an increase of reticulin in the liver. Normally within the lobules it is limited to a meshwork around the sinusoids with only a very few fibres passing from this meshwork into the liver columns between individual cells (fig. 3). The

FIG. 3.—Infant of eight days without erythroblastosis. Liver. Normal amount of reticulin. Laidlaw's silver method. $\times 390$.

increase was shown by an increase in the number of fibres passing into the liver columns (fig. 4). In two of them the reticulin fibres were thickened and stained in van Gieson's mixture, thus constituting a fibrosis. It was slight but of a degree and appearance such as commonly occurs in congenital syphilis. It was diffuse throughout the lobule and the liver and the columns appeared interrupted and broken into small groups of cells. In three cases a somewhat similar disorganization of the columns occurred

but the fibres were very seldom stained with van Gieson's mixture. In these five cases there was a slight proliferation of pseudobile canaliculi in the portal systems. Bile thrombi in intercellular canaliculi indicated retention of bile in seven cases, but they were few and limited to the centre of the lobules. In four cases several free round or oval hepatic cells, full of bile globules and streaks, were present in the centre of lobules. In ten cases marked haemosiderosis was shown by numerous granules in hepatic cells in all parts of the lobules, but especially near the portal systems and in the epithelium lining

did not resemble bile. In one case there was haemosiderosis. In nine cases haemosiderin was very scanty in the pulp, usually abnormally scanty, and in two cases it was absent. In four cases the collagen of the capsule or trabeculae was impregnated with ferric iron chiefly, but partly with ferrous which stained deeply with Ehrlich's haemotoxylin.

Several authors have recorded absence of iron or a very scanty amount in the spleen, for instance, Rautmann (1912), Lutz (1914), Salomonsen (1931) and de Lange (1932). Schmidt and Mönch (1918), de Lange and Arntzenius (1929) and de Lange (1932) described iron-free pigment in the spleen.

BONES. Endochondral ossification was abnormal in fourteen of the nineteen cases in which bones were examined, including the twelve in which the zone of provisional calcification of cartilage appeared macroscopically to be deepened. Microscopically this zone of calcified hypertrophic cartilage was found to be deepened in none. In seven cases, however, beneath the whole or parts of it there was a slightly deepened zone of trabeculae of calcified cartilage. The trabeculae were more numerous than normally, and in consequence the primary medullary spaces bounded by the trabeculae were narrow. A few hypertrophic cells persisted in the zone, either singly, in small groups or rarely as narrow short tongues continuous with the hypertrophic zone above. Occasionally focal shallow deposits of osteoid tissue had been deposited

FIG. 4.—Hydrops foetalis. Liver. Increased amount of reticulum. Laidlaw's silver method. $\times 390$.

the beginnings of bile ductules or pseudobile canaliculi. Haemosiderosis was slight in two cases and absent in the remaining non-macerated case, that in which there was no evidence of abnormal haemopoiesis. Kupffer cells frequently contained iron pigment and erythrocytes, but not in abnormal amount. Fatty degeneration of hepatic cells was marked in one case, slight in two and absent in four other cases in which frozen sections were made. The case in which it was marked was that in which no abnormality in haemopoiesis could be detected.

Fibrosis of the liver was described by Fischer (1912a), Sauvage (1913) and a few others. Haemosiderosis was reported by all authors who examined the liver for iron. Bile thrombi were seen by Fischer (1912a and b), Lutz (1914), de Lange and Arntzenius (1929), Hueper and Mullen (1930) and Salomonsen (1931).

SPLEEN. In the twelve spleens examined in the non-macerated cases variable numbers of reticulum cells contained diffuse or globular, yellowish-brown pigment which did not give an iron reaction and

FIG. 5.—Hydrops foetalis. Metaphysis of upper end of a femur. Abnormally numerous, delicate trabeculae of calcified cartilage (darkly stained) with narrow seams of bone or no bone at all laid down upon them. Jenner stain. $\times 115$.

on some trabeculae. Below this zone abnormally numerous trabeculae of calcified cartilage were continued into the diaphysis for abnormal distances and were covered with seams of bone or osteoid tissue; focally near the zone of trabeculae of calcified cartilage the seams were usually abnormally shallow. In the other seven cases this condition was present without the deepened zone of trabeculae of calcified cartilage. The changes were probably due to deficient osteoblastic activity in the presence of normal provisional changes in the cartilage. This is shown by the shallowness or focal absence of

FIG. 6.—Hydrops foetalis. Upper end of femur. Abnormally numerous trabeculae of calcified cartilage in metaphysis with very little bone or no bone laid down upon them. Jenner. $\times 42$.

deposits of bone or osteoid on the calcified cartilaginous trabeculae and the failure in the first seven cases of the deposits to reach the normal height on the trabeculae. The increase in number of trabeculae of calcified cartilage is probably due to a decrease in osteoclastic absorption so that many more trabeculae persist than normally in order to strengthen the bone weakened by deficient osteoblastic activity. The macroscopic resemblance to a deepened zone of provisionally calcified cartilage was probably due partly to the increased number of trabeculae of cartilage in the metaphysis and partly to anaemia of the capillaries in the narrow primary medullary spaces. Changes in the bones similar to those described above may occur in congenital syphilis either with or without syphilitic osteochondritis. The latter is shown by fibrosis of the metaphysis, fibrosis enlarging chondral canals, periostitis causing periosteal buttressing with newly formed bone, submiliary gummata in the meta-

physis, and in some cases necrosis of cartilage or defective capillary invasion of hypertrophic cartilage leading to deepening of the hypertrophic zone.

In four cases a few sinuses in the marrow were dilated and partly or completely filled with amorphous granular material containing ghosts of cells and a few minute haematoidin crystals. The amorphous material gave a prussian-blue reaction. The change appeared to be the result of disintegration of blood, possibly preceded by thrombosis. In two it was associated with a few miliary necroses of the marrow. It was probably unrelated to

FIG. 7.—Normal infant, 44 cm. long, lived five hours. Upper end of a femur. Control for fig. 6. Fewer trabeculae of calcified cartilage in metaphysis and greater bone formation upon them. Dilated sinuses containing amorphous granular material. Jenner. $\times 42$.

erythroblastosis as it was seen in four normal foetuses of 343, 395, 444 (fig. 7) and 508 mm.

SUPRARENALS. In sixteen of eighteen cases in which the glands were examined the cells of about the inner half of the foetal cortex were excessively vacuolated (fig. 8) and in ten frozen sections stained with Scharlach R. showed that the vacuolation was due to infiltration with fatty material. In the normal suprarenal at birth the outer zone of the cortex, the adult cortex, contains in its inner two-thirds a moderate amount of fat which is anisotropic, pink or purple when stained with Nile blue sulphate and which gives a positive Schultz reaction for cholesterol. The outer third of the zone has less abundant fat which is in finer granules, isotropic, deep blue when stained with Nile blue sulphate and does not give a Schultz reaction. The inner zone of the cortex, the foetal cortex, contains less fat,

most of which resembles that in the outer third of the adult cortex, but towards the inner part of the zone the granules increase in size and may give a Schultz reaction, usually weakly. The innermost part of the zone contains some large anisotropic globules which give a Schultz reaction and are stained pink or purple by Nile blue sulphate, but in about twenty-four hours after staining they become blue. In the cases of hydrops foetalis the inner part of the foetal cortex showed a great increase of the large globules of anisotropic fat giving a Schultz reaction. In one case the fat was pink when stained with Nile blue sulphate, but later turned blue.

In four cases a few foetal cortical cells had giant nuclei. This is not abnormal. In one case cells with giant nuclei were much more numerous than I

FIG. 8.—Hydrops foetalis. Suprenal. Excessive vacuolation of cells in inner half of foetal cortex. Granules and plaques of material, containing iron and staining deeply with haematoxylin, in the inner part of the cortex. Iron and calcium impregnation of thrombus in a central vein. Haem. and eosin. $\times 35$.

have ever encountered normally and one or two nuclei had giant nucleoli. Whether or not this change had any relation to the erythroblastosis is very doubtful.

In five cases there were in the foetal cortex scattered minute granules or plaques of material stained very deeply by Ehrlich's haematoxylin (fig. 8). The material was at first granular and within very vacuolated cells. The granules then fused to form plaques, the largest of which was 28 by 12μ . Nuclei were sometimes present in cells with granules, but never in those with plaques. The plaques were often extracellular, but had probably been liberated from necrosed cells. Both ferric and ferrous iron was present in the material, the former more abundantly. In two cases Kossa's reaction was positive, but in two the reaction could not be obtained by repeated tests. No gypsum

crystals could be produced, but the deposits were too small for this test for calcium. In the normal foetal cortex a very few cells may be found containing similar granules and plaques, but they were never anything like as numerous as in these five cases.

In one case the one gland examined showed thrombosis of several central veins (fig. 8). The thrombus was impregnated with numerous granules which stained deeply with Ehrlich's haematoxylin, gave reactions for ferric and ferrous iron, gave Kossa's reaction, and contained calcium as numerous gypsum crystals could be produced from them. I believe the intensity of staining with Ehrlich's haematoxylin of the granules, as of the granules and plaques in the foetal cortex, is due to the presence of ferrous salts. Similar staining is present in the splenic trabeculae and placenta in some cases of hydrops foetalis, in Gandy-Gamma nodules in the spleen, in the lung in some cases of chronic passive congestion and in other iron impregnations. I have always found this intense staining associated with ferrous salts whether calcium can be demonstrated or not. Only traces of ferrous salts need be present to cause the staining, as is shown by the frequent dark-brown staining by Ehrlich's haematoxylin of naturally yellowish-brown haemosiderin in which ferrous salts can be demonstrated by potassium ferricyanide and hydrochloric acid.

KIDNEYS. In two of the eight cases in which the kidneys were examined the cytoplasm of some of the cells of the so-called secretory tubules gave a slight diffuse prussian-blue reaction and in another a few granules of haemosiderin were also present. In one some spindle interstitial cells contained haemosiderin, but this may occasionally be found normally. In five cases yellowish-brown granular pigment was present in epithelial cells of secretory tubules and did not give a prussian-blue reaction. It was dissolved by 10 per cent. liquor ammoniae fortis in 10 per cent. alcohol and was probably haematin. In three cases there were a few yellowish-brown pigmented casts possibly of altered haemoglobin. In one case a few eosinophil lumpy casts, like haemoglobin casts, in discharging tubules did not give a positive reaction in a benzidine test, but had a pale yellow colour.

Schridde (1910), Lutz (1914), Schmidt and Mönch (1918), Capon (1922), Schminke (1923), Bullard and Plaut (1926), de Lange and Arntzenius (1929) and de Lange (1932) have described iron-free or iron pigments, or both, in epithelium of the secretory tubules. De Lange and Arntzenius (1929), Hueper and Mullen (1930) and de Lange (1932) described brown casts.

PANCREAS. In one of the four cases in which the pancreas was examined many acinar cells contained iron granules. In one the islets of Langerhans were normal. In the other three there was an apparent increase in number and a definite increase in average size of islets (fig. 9). The average diameter of islets measured in single sections was about 195μ .

whilst that in ten control pancreases (fig. 10) was about 160μ . In paraffin sections of formaldehyde-fixed tissue Mann's methyl-blue eosin stain showed that the majority of the islet cells, at least five-sixths, were granular. The minority of the granular cells, not more than one-third, had abundant brightly

PLACENTA. The placenta was examined in seven non-macerated cases. Most of the terminal branches of the villi were enlarged with consequent diminution of the intervillous spaces. The stroma was oedematous and rich in cells, most of which were large, oval, vacuolated Hofbauer cells. The

FIG. 9.—Hydrops foetalis. Pancreas. Increase in size of islets of Langerhans. Haem. and eosin. $\times 90$.

eosinophil alpha granules. The remainder had smaller, less numerous and less eosinophil granules which were probably beta. The latter usually had enlarged cell bodies and frequently enlarged nuclei. No mitoses were seen. This change in the islets I found identical with that in the pancreas of an infant born of a diabetic mother and that of a normal

capillaries in some villi appeared to be increased in number. The epithelium of the villi was often unusually well developed, resembling that in early placentas. A few phagocytes containing yellowish-brown pigment lay in capillaries in a few terminal villi in two cases. While the enlargement of the villi and increase of their cells is probably chiefly

FIG. 10.—Normal stillborn foetus, 48 cm. long. Pancreas. Control for fig. 9. Haem. and eosin. $\times 90$.

post-mature stillborn foetus of 546 mm. and 5365 gm., whose mother had had no glycosuria on several examinations.

Liebegott (1938) described two cases of hydrops foetalis and Potter, Seckel and Stryker (1941) one case with similar increase in size and number of islets. Helwig (1940) described one case and Potter, Seckel and Stryker (1941) eight cases with a similar change in normal infants.

due to oedema, it may in part be due to hypertrophy, as suggested by the young appearance of the epithelium and frequent apparent increase of capillaries. The purpose of this hypertrophy would be to facilitate oxygen exchange from the mother to the foetus.

In four of the seven placentas examined in macerated cases and in that of the small macerated twin accompanying a non-macerated foetus, the

stroma of numerous terminal branches of the villi showed granules and small plaques of material which stained deeply with Ehrlich's haematoxylin, gave reactions for ferric and ferrous iron and Kossa's reaction, and showed the presence of calcium by producing with sulphuric acid gypsum crystals. The iron and calcium salts were probably derived from the foetal tissues by autolysis and

pulmonary alveoli; there were a few granules in foetal cortical cells in the suprarenal and in a few pancreatic acinar cells and none in the pituitary. In some control foetuses glycogen was present in epithelial cells of the renal pelvis, renal discharging tubules and pulmonary alveoli, and, in one, in some pancreatic acinar cells and cells of bronchial cartilages. In a previous paper (1941) I remarked on

FIG. 11.—Hydrops foetalis. Placenta. Enlargement of villi with reduction of intervillous spaces. Haem. and eosin. $\times 98$.

therefore the impregnation was probably post mortem. I have not found a similar impregnation in placentas of macerated foetuses without erythroblastosis except in that of the foetus papyraceous accompanying a non-macerated foetus in this series. This foetus may have had erythroblastosis and died early.

OTHER TISSUES. In the myocardium in one case in which the heart weight was above the maximum normal there was a mitotic figure in two muscle fibres. The mitoses probably signified a hyperplasia, but there was no hypertrophy of fibres. The thymus, examined in five cases, showed no abnormality, even when the weight was below the minimum normal. The small weight of most glands was probably due, therefore, to hypoplasia rather than to atrophy. Capillaries in alveolar walls in the lungs in four cases showed a few macrophages containing yellowish-brown pigment that did not give a prussian-blue reaction. Similar pigment formed casts in the lumen of a few gastric glands in one case and in the stroma of intestinal villi in two cases.

In one case the glycogen distribution was examined. A little was present in many liver cells; it was abundant in myocardial muscle fibres; there were a few granules in the renal secretory epithelium and many in the epithelium of the renal pelvis and discharging tubules; much was present in the cells of the bronchial cartilage and epithelial cells lining

the frequent dropsical appearance of the liver cells at full term and have since found this due to glycogenous infiltration. It was not present in premature foetuses or in infants shortly after birth. The amount of glycogen in the liver in the case of hydrops foetalis was much less than that found in full-term foetuses, but may have been normal as the infant was premature. In the hearts of six normal foetuses glycogen was present in two only, and then in scanty amount. However, the dropsical appearance of the muscle cells suggested that glycogen had been abundant. It is doubtful whether the glycogen in the heart was increased in the case of hydrops foetalis, but its abundance at the time of necropsy may signify less post-mortem digestion. This and the presence of glycogen in a few cells of the secretory renal tubules and suprarenal cortex is very scant evidence of an abnormality in the glycogen metabolism.

Liebegott (1938) in two cases of hydrops foetalis found much glycogen in liver cells, although the infants were premature, and in other cells. He claimed an abnormal distribution of glycogen.

Differential diagnosis

Congenital syphilis. Lahm (1914) and Kogel (1922) described foetuses with congenital syphilis, general oedema and excessive haemopoiesis in the

liver and other tissues. I report three similar cases. The infants were premature. One was stillborn, the others lived a few hours. They showed general oedema, ascites, enlargement of liver and spleen, excessive haemopoiesis in the liver, kidneys and, in the two cases in which the organ was examined, in the spleen. Unlike erythroblastosis, much of the haemopoiesis in the portal systems and kidneys was lymphopoietic and plasma cells were present in these sites and in the two spleens. In one case there was slight chronic laryngitis; bronchitis and bronchial lymphadenitis; germ centres in bronchial lymph glands; leucocytes, necrosis and fibrinous exudate around arterioles in splenic Malpighian bodies; and several calcareous casts in discharging renal tubules. In another case there were bullae on the hands, wrists and feet. The changes in the

FIG. 12.—Full-term foetus with achondroplasia and without erythroblastosis. Liver. Excessive amount of haemopoiesis. Haem. and eosin. $\times 155$.

bones were similar to those in hydrops foetalis in that the metaphyses contained abnormally numerous trabeculae of calcified cartilage upon which only very shallow seams of bone or no bone had been laid down. One case showed in addition fibrosis of the marrow and two minute foci of leucocytic infiltration in the metaphyses, another showed fibrosis of the metaphyses, periosteal buttressing with new bone, deepening of the zone of provisional calcification and fractures across the metaphyses, and the third showed, in some bones, fibrosis of the metaphyses and deepening of the zones of provisional calcification of cartilage. The marrow contained an excess of megakaryocytes in one.

Achondroplasia. In five achondroplastic subjects, stillborn or dying during the first day, I found excessive haemopoiesis of normal character and distribution in the liver (fig. 12). In two the spleen weight was high and in another it was above the

maximum normal, and in these the organ showed slightly excessive haemopoiesis. This excessive haemopoiesis was probably a simple displacement from the bones whose shortness must have greatly reduced the space available for haemopoietic marrow. In a sixth achondroplastic infant which lived six weeks there was no haemopoiesis in the liver. This was probably because the amount of haemopoietic tissue required is relatively less after birth than in foetal life. A seventh achondroplastic infant was stillborn and a sibling of an infant which died with icterus gravis; owing to the above findings an excessive haemopoiesis in the liver could not be accepted as evidence of erythroblastosis, but haemosiderosis of the liver suggested its presence.

Other causes of congenital oedema. Congenital oedema and ascites were described in association with atresia of the larynx in stillborn by Frankenberg (1905) and Schweitzer (1931), with atresia of the right bronchus in a stillborn infant and an infant of three days by Meyer (1924) and Werbter (1925), with hyperplasia of the lungs in a stillborn infant by Sternberg (1923), with solitary adenomas of the lung in stillborn by Stoerk (1897), Lahm (1919) and Esch (1928) and with a large left accessory lung in a stillborn infant by Nordmann (1926). The enlargement of the lung or lungs associated with these conditions produced mechanical interference with the circulation. Congenital oedema and effusions were described in three foetuses with cystic hygroma of the neck by Simmonds (1922–3), in a foetus with an umbilical hernia pressing on the vessels of a very short umbilical cord by Fischer (1911), in foetuses with absence of the thoracic duct by Smith and Birmingham (1888–9) and Tew (1925), in acardiac monsters by Ballantyne (1902), Capon (1922) and others, in foetuses or infants with congenital morbus cordis by Dick (1925), Weiner (1928), Wanstrom (1933) and others. Of the cases above those of Dick, Esch, Lahm (according to Seyffert, 1920), Nordmann, Schweitzer, Simmonds, Wanstrom and Weiner showed excessive blood formation in the liver. Seyffert and Schweitzer regarded this as erythroblastosis secondary to the circulatory disturbance produced by the congenital abnormality.

Definition of type I

Type I (hydrops foetalis) is found in foetuses or in infants living for not more than thirty-six hours. There is no change which is constant; consequently the definition is based upon the presence of some or all of certain clinical and pathological features and the exclusion of other diseases which may also produce them. Chief among these features is lipoid infiltration of the suprarenal cortex which was found in sixteen of eighteen cases. It is peculiar to this type and is not known to occur in any disease other than erythroblastosis foetalis. It can be recognized in macerated foetuses when many other changes cannot. Other important features and their incidence in my cases are as follows: a familial incidence, in about one-third of the families; general oedema and serous effusions, in eighteen of twenty-four cases; bone changes resulting from

diminished osteoblastic activity, in fourteen of nineteen cases; haemosiderosis and abnormal haemopoiesis in the liver, in twelve of thirteen cases; increase of reticulin in the liver, in ten of thirteen cases; increase in size and number of islets of Langerhans, in three of four cases; enlargement of the liver, spleen and placenta and hypoplasia of the thymus, in many cases.

Cases without general oedema are included in the type because of abnormal haemopoiesis and other features. The non-macerated foetus with slight and focal oedema showed the typical changes in the haemopoietic tissue, pancreas, suprarenals and bones, an increase of reticulin and haemosiderosis in the liver. One of the two macerated foetuses with no oedema or effusions had haemosiderosis of the liver and an enlarged spleen and was a sibling of the infant with slight oedema mentioned above; the other had an enlarged spleen and lipid infiltration of the suprarenals and a sibling died with jaundice, apparently icterus gravis. In the case without histological evidence of abnormal haemopoiesis there were suprarenal and bone changes, increase of reticulin in the liver, and general oedema.

Types I and II differ in that in type I, jaundice, if present, is seldom general and is slight, associated with oedema and never cerebral, while in type II lipid infiltration of the suprarenals does not occur. In type III death, if it occurs, is always later than in type I, and lipid infiltration of the suprarenals does not occur. The cases of type I with localized or absent oedema differ from type III in these respects only.

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