FOUR CASES OF CONGENITAL ANÆMIA WITH JAUNDICE AND ENLARGEMENT OF THE SPLEEN.¹


(PLATES LI.—LIII.)

The following paper deals with a series of cases of congenital anaemia, associated with jaundice and splenic enlargement.² Four of the cases were members of one family, and a description of the clinical features and haematology of one of them has already appeared in the Scottish Medical and Surgical Journal for September 1906. A note of the leading points in that case has been embodied in this article to make the series complete. We shall refer to the two families as A and B respectively.

**Family A.—**Nothing of special interest noted as regards heredity. Parents apparently healthy. No history of syphilis could be discovered. No miscarriages. Mother, æt. 20 years at the birth of her first child; father, æt. 23.

**Child 1 (male).—**Born at full term on 9th September 1902. Appeared a normally developed child at birth, and showed no obvious morbid appearances. In the course of a series of observations on infants' blood which one of us was making it chanced that a blood film was taken from the umbilical cord of this child. It showed nothing abnormal.

Fifteen nucleated red cells were seen in making a differential count of 500 leucocytes. A photograph of this blood is given in Plate LI. Fig. 1.

**Child 2 (male).—**Born at full term on 7th October 1904. At birth the great pallor and lemon-yellow tint were obvious. The jaundice deepened for some weeks. The spleen was enlarged, its size increasing for three weeks and then gradually returning to normal. Some enlargement of lymphatic

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² For providing us with the clinical notes our thanks are due to Dr. John M'Gibbon of Edinburgh, and to Dr. William Stewart of Leith, in whose practices the cases occurred. We have also to thank Dr. Lovell Gulland, who examined the blood of some of the cases and performed the post-mortem examination in one, and who also has given us much kind help in this work. To Mr. Richard Muir, of the Pathological Department of the University of Edinburgh, we are indebted for the great trouble he has taken in connection with the microphotographs which accompany this article.
glands was perceptible. Blood examined on 21st October 1904. Haemoglobin difficult to estimate on account of jaundice,—say 25 per cent. Red corpuscles, 1,840,000 per c.mm. Films showed large numbers of nucleated reds. In making a differential count of 500 whites, 225 nucleated red cells were seen, 69 per cent. of these being megaloblasts and 23 per cent. normoblasts, 2 per cent. with mitotic figures, and 6 per cent. examples of karyorrhexis. Some irregular mitoses were found,—cells with three or four stars or resting nuclei. Polychromatophilia common, poikilocytosis slight. Granular basophilia present.

In making a differential count of 500 whites, 225 nucleated red cells were seen, 69 per cent. of these being megaloblasts and 23 per cent. normoblasts, 2 per cent. with mitotic figures, and 6 per cent. examples of karyorrhexis. Some irregular mitoses were found,—cells with three or four stars or resting nuclei. Polychromatophilia common, poikilocytosis slight. Granular basophilia present.

White cells, 23,696 per c.mm. Neutrophils—(a) Myelocytes, 2·2 per cent.; (b) Polymorpho-nuclears, 41 per cent. Eosinophils—(a) Myelocytes, 0·8 per cent.; (b) Polymorpho-nuclears, 2·5 per cent.; basophils, 0·6 per cent.; lymphocytes, 43·5 per cent.; large mononuclears and transitional, 9·4 per cent. Some cells with mixed granules seen.

October 28.—Haemoglobin, 28 per cent. Red cells, 1,376,000 per c.mm. White cells, 27,868 per c.mm.; 110 nucleated reds seen in counting 500 whites.

November 4.—Red cells, 1,960,000 per c.mm. White cells, 15,797 per c.mm.; 190 nucleated reds per 500 whites.

July 24, 1905.—Haemoglobin, 76 per cent. Red cells, 4,290,000 per c.mm. White cells, 10,400 per c.mm.

Film showed only a trace of poikilocytosis and granular basophilia. The child seemed now to be practically well, all splenic enlargement and jaundice having disappeared.

The child was again examined on 8th February 1909. Although he has a somewhat pallid complexion, the general health seems good. Haemoglobin, 80 per cent. Red cells, 5,450,000 per c.mm.; no abnormality seen in films. White cells, 15,000. Differential count: polymorpho-nuclear neutrophils, 43·8 per cent.; eosinophils, 4 per cent.; basophils, 0·4 per cent.; large mononuclears, 8 per cent.; lymphocytes, 43·8 per cent.

Child 3 (female).—Born at full term on 7th April 1906. Great pallor and jaundice at birth. Spleen enlarged. No glandular enlargement could be felt. Haemic murmurs present. Urine bile-stained. The child became gradually weaker, and died on 9th April. Blood films taken from the umbilical cord (Plate LI. Fig. 2) showed a very large number of nucleated reds, 990 being counted per 500 whites. Of the nucleated reds, 77·5 per cent. were megaloblasts, 16·3 per cent. normoblasts, 3·6 per cent. cells in mitosis, 2·6 per cent. cells with karyorrhexis. Polychromatophilia common; also cells with stippled protoplasm; poikilocytosis very slight. Some irregular mitoses. Examples of phagocytosis of red cells by large mononuclear leucocytes were seen; also similar phagocytes containing large black pigment masses. A differential count of 500 white cells showed:

Neutrophils—(a) Myelocytes, 2 per cent.; (b) polymorpho-nuclears, 52 per cent. Eosinophils—(a) Myelocytes, 0·2 per cent.; (b) polymorpho-nuclears, 3·4 per cent.; basophils, 1 per cent.; lymphocytes, 36·2 per cent.; large mononuclears, 5·2 per cent. Cells with coarse mixed granules seen.

April 8.—Haemoglobin about 40 per cent. Red cells, 2,056,000 per c.mm.; 322 nucleated reds per 500 whites. Of the nucleated reds, 50·2 per cent. were megaloblasts, 16·8 per cent. normoblasts, 30 per cent. cells in mitosis, and 30 per cent. in karyorrhexis. White cells, 50,000 per c.mm. Differential count gave the following percentages:

Neutrophils—(a) Myelocytes, 5·8 per cent.; (b) polymorpho-nuclears, 55·8 per cent. Eosinophils—(a) Myelocytes, 0·4 per cent.; (b) polymorpho-nuclears, 3·6 per cent. Basophils, 0·4 per cent. Lymphocytes, 29·6 per cent. Large mononuclears, 4·4 per cent.

Post-mortem examination was made on 9th April by Dr. Gulland, who subsequently kindly gave us the organs for examination. All the organs were much jaundiced. The heart was slightly fatty. Large vessels healthy.
Some haemorrhages beneath the serous membranes. The lungs showed minute areas of catarrhal pneumonia, with haemorrhages in the interalveolar septa.

The liver showed a considerable disintegration of the cells with poor staining of the nuclei, and there appeared to be in Glisson's capsule a distinct increase of fibrous tissue and of fibroblasts. The bile canaliculi stood out very markedly here and there in sections, being dilated and filled with thickened bile. From the stasis in the bile canaliculi within the lobules it may be confidently assumed that there was at the time of death, or had been previously, some obstruction to the outflow of bile (Plate LIII. Fig. 9). Around some of the smaller branches of the portal vein were areas in which numerous megaloblasts and normoblasts occurred, but these blood-forming islands were not quite so large as in Cases A 4 and B 9.

The spleen was enlarged and firm, and sections showed much dilatation of the pulp sinuses with blood. The most noticeable feature was the presence of a great number of phagocytes containing brown granules of various sizes. There was no evidence of greater haemopoietic activity in the splenic sinuses than in the circulating blood.

Stomach, intestines, and pancreas apparently healthy.

Kidneys showed a very slight degree of cloudy swelling in the secreting tubules.

Suprarenals large; sections showed, in some of the medullary sinuses, collections of nucleated red corpuscles, around which cloudy swelling of the parenchyma cells was very noticeable.

Thyroid moderate in size: acini collapsed, with no secretion, but the cells lining them showed slight degenerative changes resembling those of cloudy swelling. Thymus healthy, and contained many cells in a state of active proliferation. Lymph glands showed active proliferative changes.

Bone marrow showed active erythroblast formation, both megaloblasts and normoblasts being present in great numbers. Neutrophil and eosinophil myelocytes were numerous, and mast cells were present as well as many non-granular white cells.

**CHILD 4.**—Female. Born at full term on 20th July 1907. Great pallor and jaundice at birth. At birth a discharge occurred from the bowel of brown semi-fluid material resembling meconium (probably bile-stained mucus). Thereafter the stools seemed almost devoid of bile, containing, at most, a slight admixture with bile-stained mucus. On the third day there was some haemorrhage from the umbilical cord, and on the sixth day a severe haemorrhage from the edge of the umbilical ring. The child died suddenly on 27th July, after a haemorrhage from the umbilical ring. Films taken from the umbilical cord at birth showed per 800 white cells, 920 nucleated red cells, 54 per cent. of these being megaloblasts, 23.8 per cent. normoblasts, 1.1 per cent. cells in mitosis, and 21.1 per cent. cells with karyorrhexis. Examples of irregular mitosis were found. Cells with double nuclei of frequent occurrence. Polychromatophilia and stippling well marked in many cells. Poikilocytosis very slight. Red corpuscles on day of birth 2,700,000 per c.mm. White cells, 80,000. Differential count: Neutrophils—(a) Myelocytes, 1.4 per cent.; (b) polymorpho-nuclears, 24.6 per cent.; eosinophils—(a) Myelocytes, 0.6 per cent.; (b) polymorpho-nuclears, 4.8 per cent.; lymphocytes, 64.6 per cent.; large mononuclears, 4 per cent. Examples of large mononuclears phagocytizing red blood corpuscles were found; also a cell of similar type containing large black granular bodies in its cytoplasm (Plate LIII. Fig. 6 d).

*July 21.*—Red corpuscles, 2,120,000 per c.mm. White cells, 60,000 per c.mm.

*July 22.*—Red corpuscles, 2,890,000 per c.mm. White cells, 68,000 per c.mm. Haemoglobin, 50 per cent.
CONGENITAL ANÆMIA WITH JAUNDICE.

July 26.—Red corpuscles, 1,875,000 per c.mm. White cells, 5800 per c.mm. Haemoglobin, 55 per cent. This great fall in the number of red cells occurred after a haemorrhage from the umbilical ring. Films taken on the 26th showed eighty-five nucleated reds per 500 white cells; 30.5 per cent. of the nucleated reds were megaloblasts, 65.8 per cent. normoblasts, 1.3 per cent. cells in mitosis, 2.4 per cent. cells with karyorrhexis. Neutrophils—(a) Myelocytes, 8.3 per cent.; (b) polymorpho-nuclears, 36.8 per cent.; eosinophils—(a) Myelocytes, 0; (b) polymorpho-nuclears, 34 per cent. Basophils—(a) Myelocytes, 0.2 per cent.; (b) polymorpho-nuclears, 0.2 per cent. Lymphocytes, 48.8 per cent. Large mononuclears, 2.3 per cent.

Post-mortem examination on 27th July.—All the organs jaundiced. Heart healthy, but the foramen ovale still fully open, though ductus arteriosus narrowed. Haemorrhages beneath the epicardium and peritoneum numerous, but not large. The lungs showed a marked catarrhal condition of the bronchial tubes, with areas of collapse, catarrhal pneumonia, and (small) haemorrhages.

The liver was firm, and on section showed large well-marked areas of blood formation, in which megaloblasts were numerous, as well as normoblasts. In addition to these there were seen, round the interlobular veins, collections of young fibrous tissue, considerably greater in amount than that usually seen in this situation. No iron reaction. On tracing the bile ducts down to the duodenum one found Vater's papilla projecting to an abnormal distance into the lumen of the bowel and considerably enlarged. It was found impossible either to pass a probe through it or to express bile; on section it showed itself to be lined with a low epithelium, resembling endothelium, and to present, close to its inner surface, an infiltration with small round cells and fibrin. No actual obliteration was, however, found, although the sides were apparently swollen and closely apposed.

The spleen was enlarged, firm in consistence, and gave the iron reaction. Sections showed wide pulp sinuses, containing many phagocytes with brown pigment masses and similar material lying free. No evidence of special blood formation.

Stomach, intestines, and pancreas apparently quite healthy. The small intestine was covered on its inner surface with a layer of bile-stained mucus, but the large intestine contained only acholic faeces.

Kidneys showed very slight cloudy swelling in the secreting tubules, but were practically quite healthy.

Suprarenals large; showed collections of nucleated red corpuscles here and there in the medulla, and areas of marked cloudy swelling.

Thyroid not enlarged; acini contained no secretion, cells slightly granular. Thymus healthy. Lymph glands showed active proliferation.

Bone marrow erythroblastic; showed greater numbers of megaloblasts than of normoblasts. Polymorpho-nuclear and myelocyte cells with eosinophil, neutrophil, and basophil granules. In films stained by Leishman's method an exceptional proportion of lymphoid non-granular cells (presumably pre-myelocytes) were seen. By Ehrlich's triacid stain following heat fixation many of these showed fine granulation.

Family B.—Father 45, mother 44 at birth of ninth child. No history of syphilis, no miscarriages. Eight previous children apparently healthy, with the exception that one was defective in moral perception.

Child 9 (Male).—Born at full term on 26th September 1908. During pregnancy mother had suffered much from eczema of hands, and had a deal of mental worry. At birth great pallor and jaundice noticeable. During life enlargement of spleen not very evident, but distinct at sectio.

Urine bile-stained. Some echchymosis occurred about the knee. The
child gradually became weaker, and died on 29th September. Blood was counted on 27th September by Dr. W. Stewart, who found the red corpuscles to be 1,746,000 per c.mm., white cells 53,763 per c.mm. Films showed per 500 white cells, 523 nucleated reds, 55.2 per cent. being megaloblasts, 31 per cent. normoblasts, 24 per cent. cells in mitosis, and 11.4 per cent. cells with karyorrhexis. Irregular mitoses were present, also cells with double nuclei. Polychromatophilia common, poikilocytosis slight. Differential count of white cells showed: neutrophils—(a) Myelocytes, 2.8 per cent.; (b) polymorpho-nuclears, 50.8 per cent. Eosinophils—(a) Myelocytes, 1.2 per cent.; (b) polymorpho-nuclears, 2.4 per cent. Basophils, 0.6 per cent. Lymphocytes, 40 per cent. Large mononuclears, 2.2 per cent. On 28th October: Hæmoglobin, 30 per cent. (f). Red corpuscles, 1,680,000 per c.mm., white cells, 46,666 per c.mm.; 751 nucleated reds per 500 white cells, 55.9 per cent. of the nucleated reds being megaloblasts, 31.8 per cent. normoblasts, 2.1 per cent. mitoses, and 10.2 per cent. karyorrhexis. The differential count of white cells gave: Neutrophils—(a) Myelocytes, 9.2 per cent.; (b) polymorpho-nuclears, 53.6 per cent.; eosinophil polymorpho-nuclears, 2 per cent.; basophils, 1 per cent.; lymphocytes, 34.6 per cent.; large mononuclears, 1.4 per cent.

Post-mortem examination performed on September 29.—All the organs much jaundiced.

Heart healthy, save for a few very minute hemorrhages. Foramen ovale and ductus arteriosus still had small openings. Lungs showed a few small hemorrhages into the interstitial tissue.

Liver (Plate LIII. Fig. 7) showed well-marked islands of blood formation, three or four times the diameter of those seen in a section of the liver of a healthy full-term child placed alongside it in Plate LIII. Fig. 8 for comparison. These consisted in great part of megaloblasts. There appeared to be also a slight cirrhotic change, especially in the lobules near the surface of the organ. No iron reaction could be obtained. The bile ducts were pervers down to the duodenum, but the papilla was blocked, extremely prominent, and, together with the duodenal mucosa immediately surrounding it, was intensely congested (Plate L. Fig. 15).

(Note.—Although the papilla in the infant is always more prominent relatively than in later life, it was in this case several times the size seen usually.)

The spleen was very large and firm, and gave a marked iron reaction in patches. The number of phagocytes containing brown pigment seen in the pulp sinuses was very large, and many of them were completely choked with the granules (Plate LIII. Fig. 10).

Stomach, intestines, and pancreas healthy. Small intestine practically empty. Large intestine contained some acholic feces. Kidneys showed cloudy swelling of the secreting tubules, a little more marked than in either Case A 3 or Case A 4, but still no more noticeable than is often seen in cases of moderate jaundice in adults. Suprarenals showed marked cloudy swelling. Thyroid not enlarged; acini empty of secretion; granularity visible in the cells with disintegration at their free surfaces. Thymus healthy.

Bone marrow erythroblastic; megaloblasts very numerous; a special feature of this marrow was the great number of large red cells with nuclei showing karyorrhexis. Neutrophil and eosinophil cells of polymorpho-nuclear and myelocyte type and lymphoid cells numerous. Mast cells present.

General Characters observed in Blood Films.

The blood films of all the cases resembled each other very closely. The majority were stained by Leishman's or Jenner's method, but
other methods were also used, e.g. Ehrlich's haematoxylin followed by watery eosin after fixation in Merck's methyl-alcohol, and Ehrlich's triacid stain after heat fixation.

The following were the general characteristics of the films:

**Red Cells.**

Rouleaux formation was ill defined in all cases. The cells appeared generally larger than those of normal adult blood or than that of a normal infant at birth. Some microcytes were present. The haemoglobin content of many corpuscles seemed very considerable,—above the average of normal blood,—but some corpuscles were unduly pale, and "ghost cells" were noticed. Polychromatophilia was very common. Punctate basophilia was present in a few instances. Poikilocytes were not such a marked feature of the films as one would expect in cases of pernicious or secondary anæmia of similar blood count in the adult.

The larger proportion of nucleated red cells were undoubtedly megaloblasts. While in many cases the distinction between these and normoblasts was obvious, in others it was difficult or impossible to make out,—cells of an intermediate type being common. In differentiating between the two classes, chief stress was laid on the character of the nucleus, but the size of the cell was also considered where the nucleus was not clearly of megaloblastic type.

The megaloblasts varied considerably in form and character, many departing more or less from what one is most accustomed to meet with in pernicious anæmia. It was very common to find a large cell with a relatively small rim of cytoplasm, often polychromatophilic, and a large nucleus with open chromatin network tending towards a wheel-like arrangement and staining well. In other usually somewhat smaller cells the proportion of cytoplasm was greater; the nucleus was relatively smaller, its network closer and staining more deeply. But these various characters—the size of the cell, the relative proportions of cytoplasm and nucleus, the closeness and depth of staining of nuclear network, the degrees of polychromatophilia or pure hemoglobin staining—were combined in every possible manner in different cells. On the whole, however, it seemed that there was more tendency to basophilia where the nucleus filled a relatively large proportion of the cell than where the reverse relationship obtained, and that the largest cells were of this type. Many nuclei whose size corresponded to those of normoblasts approached the megaloblastic type and occurred in cells both of megaloblastic and normoblastic size (Plate LII. Fig. 6, e and f).

As regards the normoblasts, there is not much to note. Varying degrees of nuclear pyknosis were present. Polychromatophilia was not as a rule so marked a feature of these cells as it was of the megaloblasts.
Mitotic figures were of frequent occurrence, especially in films taken at or shortly after birth, but were less numerous in slides of the blood at a later date. One notes in Child A 4 how their number, along with that of the nucleated reds, had diminished before death; indicating, one may suppose, an exhaustion of haemopoietic tissue. Mitotic figures or double nuclei were generally found in cells of megaloblastic size. In all cases it was very common to see a large cell with two nuclei which had apparently returned to the resting state, while the cytoplasm showed no signs of division. These nuclei were generally megaloblastic, though sometimes they might be better described as intermediate. It was rare to find two definitely pyknotic normoblastic nuclei in one cell (Plate LII. Fig. 1, g). In the cells with mitotic figures the cytoplasm showed, very frequently, marked polychromatophilia, or a species of coarse blue stippling with little or no indication of the presence of haemoglobin (Plate LII. Fig. 6, h, i, and m). But mitoses were also common in cells where the haemoglobin was well defined (Plate LII. Fig. 6, k).

Irregular mitotic figures were present in all the cases. Plate LII. Fig. 1, m and n, show erythroblasts dividing into four and three respectively. There were also examples of mitosis in which the chromatin was unequally distributed in the daughter nuclei. Cells whose nuclei appeared to be undergoing direct division were in all probability instances of an early stage of karyorrhexis (Plate LII. Fig. 1, c). Karyorrhexis was a very noticeable feature in all cases; it seemed specially frequent in some films taken in the later days of life, but it was also very marked in films from the cord of Child A 4. Numerous examples are seen in Plate LII. Figs. 2, 3, and 4. The cells in which these fragmentation forms occurred appeared, judging from their size and from the character of the nucleus in many of them, to be for the most part megaloblasts. They generally showed, distinctly, the presence of hemoglobin and but little polychromatophilia (Plate LII. Fig. 6, p).

Blood platelets were of infrequent occurrence in all the cases, even in films from Child A 4 taken after a sharp haemorrhage.

White Cells.

Neutrophils.—(a) Myelocytes.—In size these corresponded to Ehrlich's rather than to Cornil's type. The number of granules in some was small, and chiefly located at one part of the cytoplasm,—such cells closely resembling other non-granular cells present in the films. Probably some of the cells entered as lymphocytes in the counts were really pre-myelocytes, but the distinction is very difficult and has not been attempted in our tables.

(b) Polymorpho-nuclears.—A few showed degenerative changes in the form of vacuolation in the cytoplasm, and a very few extreme
pyknosis of nucleus. Glycogenic reaction was tested for in three of the cases with doubtful results.

**Eosinophils.**—A few cells were found in Cases A 2 and 3, some of whose granules took up the acid and some the basic dye,—presumably unripe forms of eosinophil cell. The protoplasm of a few cells seen in Cases A 2 and B 9, especially when stained by Leishman's method, was very intensely basophil, and contained dark purple ill-defined patches, and had scattered through it pale granules nearly as large as those of ordinary eosinophil cells. These granules took up hardly any stain. The nucleus of such cells appeared oval, and of very fine network. It appears to us that these are related to a very curious type of cell some examples of which were found in Child A 2, and which we have never come across in any other case. Cells apparently resembling them very closely have been described and figured by Dr. M. W. Rowley, who says that "they resembled in general the large lymphocytes, but their protoplasm was intensely basophilic (bright blue with Wright's stain), and contained large unstained granules." Dr. Rowley adds that "they corresponded fairly well to one of the types described by some writers as plasma cells."

**Basophils.**—True mast cells with metachromasia of granules were found in all cases. (The statement sometimes made to the effect that mast cells do not occur in the circulating blood at birth was not borne out by the examination of a series of films taken by one of us from umbilical cords of normal infants and stained with alcoholic solutions.)

**Lymphocytes.**—These varied greatly in size. Large forms, larger than a megaloblast, and having a small rim of basophil cytoplasm which stained more deeply than the nucleus, were a characteristic feature of all the films (Plate LI. Figs. 2-4). "Budding of the basic zone" was not infrequent.

**Large Mononuclears and Phagocytes.**—Plate LII. Fig. 2, d, shows a cell from the blood of Child A 4. Phagocytosis seemed the most likely explanation of the granular bodies seen in its cytoplasm. It closely resembled cells found in the spleen post-mortem (v. infra). A similar cell was seen containing like substance, together with a megaloblast in the blood of Case A 3. In Plate LII. Fig. 6, c, a phagocytic cell is seen with what is obviously a digestive vacuole containing a dark body in its centre. In Plate LII. Fig. 6, a, a red corpuscle is seen in process of phagocytosis in a similar cell, while in Plate LII. Fig. 6, b, in addition to the two corpuscles in the upper part of the cell, there is in the lower part another body of purple tint.

Numerous nuclear remains were scattered over the field in many films. Their appearance suggested their having belonged for the most part to leucocytes. A few free nuclei of red cells were also seen.
GENERAL MORBID ANATOMY.

The general conditions of the internal organs common to all the cases may be summed up as follows:—

Liver.—The noteworthy features were the signs of biliary obstruction and the great increase in size of the islands where blood formation was in progress. All four cases, A 2, A 3, A 4, and B 9, showed jaundice; in A 4 and B 9 there was found a distinct blockage of the common bile duct at its entrance into the duodenum (Plate LI. Fig. 5), while in A 3 some such condition may be inferred from the dilatation of and bile retention in the canaliculi (Plate LIII. Fig. 9). A large number of cases of fatal jaundice in newly born children have been recorded at various times, before special methods of blood examination came into vogue (collected by Thomson, 1891). Some of these were probably of a character similar to the cases here described.

The increase in size of the blood-forming islands between the lobules may be gauged by a comparison of Plate LIII. Fig. 7, from the liver of Child B 9 with Plate LIII. Fig. 8 from the liver of a healthy child delivered at full term by craniotomy. In the former the areas in which megaloblasts and normoblasts are collected have a diameter about two or three times as great as that of similar collections in the liver of the healthy infant. Accordingly, one may assume that the haemopoietic activity of this pathological liver is approximately ten or thirty times greater than normal. Some authorities state that the blood-forming function of the liver has ceased at birth, e.g., Luzet (1891) as regards the human liver, and Goodall (1908) with reference to the liver of the foetal sheep. Ewing (1904) considers that the liver does not entirely abandon this rôle till some time after extra-uterine life has commenced. However, Plate LIII. Fig. 8 may fairly be taken to represent the average state of these blood-forming areas at the time of birth, so far as the human liver is concerned.

The liver from two of our cases, A 3 and A 4, showed evidence of increased connective-tissue formation, and this is probably a result of the irritation caused by the biliary obstruction acting in the manner described by Thomson (1908).

The bone marrow was of distinctly erythroblastic character, with the noticeable feature that cells possessing nuclei of the megaloblastic type were more numerous than those with pyknotic nuclei. Myelocytes were present as in normal marrow, but there appeared to be an unusually large number of early myelocytes.

The lymph glands showed active proliferative changes, with numerous mitotic figures, and large endothelioid cells were common, though none of these appeared to be actively phagocytic. The thymus gland was not specially increased in size, and sections presented characters similar to those of the lymph glands.

The thyroid gland in all the cases showed no special naked-eye
changes; on section all showed a strong stroma, complete absence of colloid secretion, and slight granularity, with breaking down at their free surface of the epithelial cells lining the acini. In a healthy control full-term child the stroma was found to be less in amount, the cells were clear and sharply defined, and many acini were distended with colloid material. In all these cases, therefore, distinct changes were observed in the thyroid, although we are unable to say whether these have any bearing upon the general pathological condition.

The kidneys showed in A 3 very slight cloudy swelling of the secreting tubules, in A 4 they were practically quite healthy, and in B 9 they showed rather more cloudy swelling than in A 3. This trivial change was not, even in B 9, more marked than one usually finds in an adult who has died in a jaundiced state, and it seems unlikely to co-exist with the presence in the circulation of any very deleterious toxic agent.

The suprarenal glands in all three cases showed cloudy swelling with poor staining capacity of the nuclei in the medullary cells. This was especially noticed in the cells for some distance round sinuses containing groups of erythroblasts tightly packed together. These groups were seen here and there, and may have been of the nature of thrombi, while the change in the suprarenal parenchyma cells was very marked upon comparison with suprarenal sections from a healthy child. One might perhaps throw out, as a suggestion, the possibility of a causal connection between these suprarenal changes and the haemorrhages which were commonly found in the cases, and which, in the case of Child A 4 at least, were directly responsible for the death.

**THEORIES AS TO CAUSATION.**

As regards the etiology of the conditions above described, while we recognise that the data furnished from the four cases are probably insufficient to justify a dogmatic statement of opinion, it appeared to us that several possible theories might be suggested.

The leading features of the cases were—(1) Profound anaemia. (2) The occurrence along with this anaemia of evidence of rapid blood formation, resulting in the appearance in the circulation of large numbers of premature or foetal types of blood cell. This active haemopoiesis was taking place in the bone marrow and also to an abnormally marked degree in the liver. (3) Destruction of red cells was going on. This was very evident in the spleen, which showed large numbers of phagocytic cells with blood pigment. The spleen also gave marked iron reaction in two cases where the test was made. It is of interest to note that in the case of the liver this reaction was almost absent. Phagocytic cells engulfing red blood corpuscles were also found in the circulating blood. (4) Obstructive jaundice was present, as evidenced by the distension of biliary canaliculi.
with this there were signs in Cases A 4 and B 9 of an inflammatory process round the large bile ducts.

Such are the main co-existing features for which one has to seek an explanation.

1. One might look on the haemolytic action of the bile as the important factor, and consider the anaemia as secondary to an obstructive jaundice. While organic closure of the common bile duct was clearly seen to be present in Cases A 4 and B 9 the recovery of Case A 2 would seem to exclude one from regarding this as the essential cause of the biliary obstruction. One would look rather to the swelling of the mucous membrane found in the large bile ducts, as seen in Cases A 4 and B 9 and to inflammation round the interlobular ducts, as in Case A 3.

The jaundice was a constant and prominent feature of all the cases. But a difficulty in the way of accepting this explanation lies in the fact that we have little evidence that bile absorbed into the circulation has such an intense hemolytic influence, although several observers have recorded severe anaemia in the course of biliary cirrhosis in adults (Cabot, 1904).

In even profound jaundice in the adult, anaemia is not a marked feature; while the blood in cases of icterus neonatorum does not show the changes we have described. One might, however, assume that on account of the obstruction developing during foetal life the blood and haemopoietic organs reacted in a special manner. One has also to bear in mind that before birth the liver has a very important part to play in blood production, and, if its bile-forming function were disturbed, its blood producing activity might be altered.

2. Haemolytic action of some abnormal secretion in the bile might also be thought of as an explanation. In Family A three children out of a family of four showed the symptoms. This might lead one to think of some special family metabolism resulting in the production of a deleterious substance, either developed in the mother and under special circumstances passing through the placental circulation to the child, or else being formed in the child itself. The placenta was examined microscopically in two cases (A 3 and A 4), and in neither did it show greater abnormality than a slight degree of fibrosis. Against the theory of a special family metabolism is the fact that in Family B only one child out of nine was affected.

3. The jaundice and anaemia might be referred to a common cause—say, a general toxæmia producing rapid haemolysis, inflammation of the bile ducts, and obstructive jaundice. Such a theory would cut the knot of several difficulties. In all the cases both jaundice and anaemia were equally well marked, and, as far as observation was possible, contemporaneous. Further, there is little evidence to show that jaundice causes such severe anaemia, or, on the other hand, that anaemia has as one of its results a profound jaundice. Other organs
of the body were not specially affected. In the presence of a toxæmia so powerful as to cause such results in the liver and blood, one would have expected to find greater changes in the kidneys. In neither family could any evidence of the presence of a syphilitic taint be found. There was nothing pointing to a bacterial infection. Further, no symptom in the maternal history, nor any appearance in the maternal blood examined three weeks after the birth of Child A 2, suggested in the least any inflammatory process.

4. The suggestion that the blood-forming organs in these cases were imperfect, and that the anaemia was a primary one, similar or analogous to pernicious anaemia in the adult, does not commend itself to us. The blood was, indeed, intensely megaloblastic, but all anaemias in infancy tend to this type. Against this theory is to be reckoned the fact that Child A 2, in whose blood the changes were fully developed, made a complete recovery. Further, this theory does not account for the presence of obstructive jaundice.

5. A theory, open perhaps to fewer objections, would be one which assumed the existence of some special fragility of the red cells in these cases. This fragility would result in their being broken up by slighter causes than would be required in the case of normal blood. The presence in the circulation of biliary constituents or of the substances which brought about the obstruction might be sufficient in some cases to produce an extreme and fatal haemolysis (A 3 and 4 and B 9), while in another case, the blood destruction being relatively slight, complete recovery might take place (A 2). When the circulation was free of deleterious substances the blood would appear, in all probability, normal (A 1?), even though the fragility were present.

Such a theory would explain the great collections of phagocytic cells containing remains of red blood corpuscles which were found in the spleen. While the number of phagocytes engulfing red cells seen in the blood was too small of itself to produce the anaemia, their presence was significant. Such cells are very rarely seen in the circulation, and may be taken as indicating either a very low resisting capacity in the red cells or some abnormal opsonic relation in the serum which makes these a prey to white cells. The rapid haemolysis taking place in these cases would naturally be expected to result in a hurried attempt on the part of the blood-forming organs to compensate for the loss. Hence the appearance in the blood of large numbers of embryonic or of premature or irregular forms of cell—megaloblasts, cells with little or no haemoglobin, irregular mitoses, cells with more than one resting nucleus, etc.

While not proposing to enter on a discussion of the limited literature bearing on this subject, we should like in conclusion simply to refer to the fact that accounts of cases of jaundice at birth, apparently, in some instances at least, associated with anaemia and splenic enlargement, tending to occur in certain families, have been recorded. There
are also accounts of conditions more or less similar in older children and even in adults. We would specially mention the remarkable series of cases recently published by Herbert P. Hawkins and Leonard S. Dudgeon (1909), which have many features in common with the four we have described, and others by Auden (1905), Chauvettard (1908), and Pollak (1908). We would now simply leave our cases on record, in the hope that, with further observations, they may form a step in the investigation of certain pathological conditions affecting the liver and haemopoietic system, which have not as yet been fully correlated.

Table giving Summary of Blood Changes.

<table>
<thead>
<tr>
<th>Date</th>
<th>Sex</th>
<th>Hæmoglobin.</th>
<th>Blood Corpuscles per cmm.</th>
<th>Differential Count of Five Hundred White Corpuscles.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total number of Nucl.-</td>
<td>Polynuclear Leucocytes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>painting Red Cells.</td>
<td>Neutrophil Polynuclears.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percentage of Cells in</td>
<td>Basophilic Polynuclears.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Missiles.</td>
<td>Eosinophilic Polynuclears.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in Karyorrhexis.</td>
<td>Basophilic Myelocytes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Basophilic Monoocytes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large Mononuclears.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lymphocytes.</td>
</tr>
</tbody>
</table>

1. This disease appears to affect, in general, several members of one family in which the father and mother are quite healthy. It may, however, occur in a single member of a large family.

2. There is no evident connection with syphilis or other infective condition.

3. Its essential features are jaundice, splenic enlargement, anæmia.
CONGENITAL ANÆMIA WITH JAUNDICE.

with great reduction in the number of red cells in the blood and the presence of great numbers of normoblasts and especially of megaloblasts.

4. The characters of the blood are associated with evidences of increased corpuscle production in the liver, and of destruction in the circulating blood and spleen.

5. The jaundice is associated with obstruction in the bile passages.

6. There are distinct changes in the thyroid gland.

7. The rationale of the disease is probably either (a) the occurrence of a more or less complete obstructive jaundice causing unusual effects in a person possessed of congenitally fragile blood corpuscles; or (b) the effect of some unknown toxic agent which has a selective action upon the liver to alter profoundly its blood-forming function and to produce irritative biliary materials.

REFERENCES.


**DESCRIPTION OF PLATES LI.–LIII.**

**PLATE LI.**

(Obj. Zeiss Apochr., 8 mm.; Oc. comp., 4; T.L. 160.)

**Fig. 1.**—Film of blood from umbilical cord. Child A 1. Leishman’s stain. Showing appearance of normal blood at birth. Two white blood corpuscles in left part of field; one normoblast in right. (× 125.)

**Fig. 2.**—Film of blood from umbilical cord. Child A 3. Leishman’s stain. Showing large numbers of nucleated red cells. (× 125.)

**Fig. 3.**—Film from blood of umbilical cord. Child A 4. Leishman’s stain. Showing large numbers of nucleated red cells. Large lymphocytes in the field. (× 125.)

**Fig. 4.**—Film from blood of umbilical cord. Child B 9. Leishman’s stain. Showing large numbers of nucleated red cells. An irregular mitosis in centre of field. (× 125.)

**Fig. 5.**—Naked-eye view of under surface of liver with interior of duodenum exposed to show the great enlargement of Vater’s papilla in Case B 9.
Fig. 6.
CONGENITAL ANÆMIA WITH JAUNDICE. 413

PLATE LII.

(Obj. Zeiss oil immers. Apochr., 2 mm.; Oc. comp., 8; T.L. 160 mm. × 1000 in all cases.)

**Fig. 6 (a).—**Phagocyte engulfing red blood corpuscles. Blood from umbilical cord. Child A 4. Stain, Leishman.

**Fig. 6 (b).—**Phagocyte with two red corpuscles in the upper part, a purple staining inclusion in the lower. Blood from ear. Child B 9. Stain, Leishman.

**Fig. 6 (c).—**Phagocyte with digestive vacuole and a dark body (remains of red cell?) in the centre. Blood from ear. Child A 3. Stain, Leishman.

**Fig. 6 (d).—**Large mononuclear leucocyte containing dark granular masses, probably the result of phagocytosis; resembling cells found in spleen. Blood from umbilical cord. Child A 4. Stain, Leishman.

**Fig. 6 (e).—**Megaloblasts. In the centre a red cell in early stage of karyorrhexis; appearance simulating amitotic division. Peripheral blood. Child A 4. Fixed in methyl-alcohol. Stain, Ehrlich haematoxylin; watery eosin.

**Fig. 6 (f).—**Megaloblasts. Blood from umbilical cord. Child A 3. Stain, Jenner.

**Fig. 6 (g).—**Red cells with double nuclei. In upper part to left a cell of megaloblastic size, its nuclei, however, showing more pyknosis than do those of the smaller cell in the lower part of the field, whose nuclei are definitely of megaloblastic type. Blood from ear. Child A 4. Stain, Ehrlich’s haematoxylin; watery eosin.

**Fig. 6 (h).—**Mitosis (skein) in megaloblast. Stippling of cytoplasm. Blood from ear. Child A 3. Stain, Leishman.

**Fig. 6 (i).—**Mitosis in megaloblast. Stippling of cytoplasm. Blood from umbilical cord. Child A 4. Stain, Jenner.

**Fig. 6 (j).—**Mitosis in megaloblasts. No stippling of cytoplasm. Blood from umbilical cord. Child A 3. Stain, Jenner.

**Fig. 6 (k).—**Irregular mitosis in megaloblast. Cell dividing into three or four (!). Stippling of cytoplasm. Blood from ear. Child B 9. Stain, Leishman.

**Fig. 6 (l).—**Red cell dividing into three or two; in the latter case, one retaining double nuclei. Blood from umbilical cord. Child A 3. Stain, Jenner.

**Fig. 6 (m).—**Nucleated red cell (megaloblast?), undergoing phagocytosis. The nucleus had a different staining reaction from the nuclei of surrounding cells. Blood from ear. Child A 3. Stain, Leishman.

**Fig. 6 (n).—**Karyorrhexis in red cell, presumably megaloblast. Blood from ear. Child B 9. Fixed in methyl-alcohol. Stain, Ehrlich’s haematoxylin; watery eosin.

**Fig. 7.—**Liver from Case B 9. The islands of blood formation. (× 100.)

**Fig. 8.—**Liver from a healthy full-term child (delivered by craniotomy), showing the normal size of blood-formative islands at time of birth. Note that they are only about one-half or one-third the diameter of those in Fig. 1. (× 100.)

**Fig. 9.—**Liver from Case A 3, to show the dilatation and filling up with bile of the canaliculi consequent on obstruction. (× 500.)

**Fig. 10.—**Spleen from Case B 9, to show the great numbers of phagocytes loaded with pigment found in this organ. (× 500.)

**Fig. 11.—**Kidney from Case A 4, to show the very slight extent to which these organs were affected in all the cases. (× 60.)

**Fig. 12.—**Thyroid from Case A 4, to show the absence of colloid material and general character of the gland in all the cases. (× 75.)