STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham).

Part IV. The hæmolytic (erythronoclastic) anæmias of the neonatal period; with special reference to erythroblastosis of the new born

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In Part I of this series we have emphasized the fact that anæmia must be regarded as a disease of the erythron, that is, as a disease which not only may affect the red cells in the circulating blood, but also their precursors in hæmopoietic centres of the marrow and elsewhere, although both portions of the erythron do not necessarily suffer to the same extent nor even at the same time. Such a conception is of particular importance in the consideration of the destructive diseases of the erythron. These disorders are usually spoken of as the hæmolytic anæmias, and although we shall make use of this term, it is, in our view, not sufficiently embracing. It stresses the destruction of red cells in the blood stream (hæmolysis), whereas often there is also evidence of damage to, or sometimes paralysis or destruction of, the hæmopoietic centres (aplastic anæmia). Therefore we suggest that these destructive diseases of the erythron should be called 'erythronoclastic anæmias' as a more correct, if less euphonious, title than hæmolytic anæmia. These anæmias are of the hyperchromic type and show marked anisocytosis and poikilocytosis. If the hæmopoietic centres are not too severely damaged to respond to the call for new cells, reticulocytosis, polychromasia, megaloblastosis and normoblastosis occur. The presence of megaloblasts and normoblasts in the peripheral circulation has not the same significance as in the deficiency anæmias, because in them the maturation of the erythrocyte cannot take place unless the missing factors are supplied, whereas in the erythronoclastic anæmias these immature cells appear in the peripheral circulation only because blood formation is extremely active.

A

For the sake of convenience and clarity we have divided the erythronoclastic anæmias into two main groups:—(a) those occurring in the neonatal period (first four weeks of life) which are described in this paper, and (b) those occurring in later infancy and childhood (see Part V). Damage to the marrow, and to the extra-medullary hæmopoietic portions of the erythron if still in existence, is more frequent in the latter group, but it occurs in both.

The erythronoclastic anæmias of the neonatal period may be classified as follows:—

Group 1. Hæmolytic anæmia of the new born.

- A. With hydrops foetalis;
- B. With icterus gravis;
- C. Without œdema or icterus gravis.

Group 2. Hæmolytic anæmia later in the neonatal period without œdema or icterus gravis.

In the following pages these groups are first described clinically, after which a description is given of the pathological changes found in association with each group.

Group I. Hæmolytic anæmia of the new born.

In many examples of this form of anæmia, whether associated with dropsy or grave jaundice or not, there is a high degree of erythroblastæmia; for this reason they have recently been grouped under the head of 'erythroblastosis of the new born,' and the suggestion has been made that they are clinical varieties of the same underlying 'erythroblastic process.' The evidence in favour of this view has been based upon:—(a) the similarity of the pathological appearances and the blood picture in the three varieties; (b) the presence at birth of jaundice in some cases of hydrops foetalis; (c) the occurrence of a mild degree of œdema in some cases of icterus gravis; (d) the incidence in the same family both of hydrops foetalis and icterus gravis. This hypothesis will be discussed later, but here it may be stated that sometimes hydrops foetalis shows little or no pathological evidence of an 'erythroblastic process'; that in some cases of anæmia of the new born, in our opinion hæmolytic in nature, erythroblastæmia does not occur at any rate until recovery begins; and that grave familial jaundice may not show erythroblastæmia at birth.

A. Hæmolytic anæmia with congenital hydrops foetalis (Erythroblastosis foetalis).—The infant suffering from this condition is most frequently still-born; it may, however, be born alive to survive only a few hours or days. The degree of dropsy is variable, and although perhaps more marked in one part of the body than another, it is usually generalized. Ascites is usually present and may be of such degree as to obstruct labour; indeed, sometimes the infant's abdomen has to be perforated before delivery can occur. Not infrequently fluid in considerable amounts is present in the pleural and pericardial cavities, and the placenta and umbilical cord may be œdematous. There is marked enlargement of the liver and spleen accounting

in part for the abdominal distension, and Clifford and Hertig¹ found in their cases that the heart was enlarged to twice its normal size, an observation we can confirm. Jaundice may be present but only to a slight degree, and there is marked pallor. Examination of the blood shows a severe anæmia, the red blood count having been recorded as under half a million cells per c.mm., and there is a striking erythroblastæmia, the number of nucleated red and white cells found by different observers varying from 5,000 to 297,000 per c.mm., of which the greater number are nucleated red cells. In some instances the myelogenous series of cells is also increased, and myeloblasts and myelocytes have been reported as present in abnormally large numbers. In view of these findings the condition has also been called 'erythroleukoblastosis foetalis.' The œdema is usually regarded as secondary to the anæmia, but it has been suggested that the heart hypertrophies as the result of the anæmia and that later cardiac failure leads to a generalized œdema.

We have only seen one case of hydrops foetalis during recent years.

Case 1.—B. M., male, was admitted to hospital on the day of his birth and died in a few hours. He was the third child in the family the second having been a premature child who lived six hours. The patient weighed 5 lb. 9 oz., and was said to be seven weeks before term. He was pale, showed rapid respirations and great distension of the abdomen.

B. Hæmolytic anæmia with icterus gravis (Erythroblastosis of the new born).—Icterus gravis is a severe, usually fatal, jaundice occurring in the new-born baby, and should be sharply differentiated from those forms of severe or fatal icterus which are associated with infection, syphilis, sepsis or congenital malformation. It is often familial, and the infant suffering therefrom is not infrequently slightly jaundiced at birth. Icterus usually occurs a few hours after birth although it may not be present until the end of the first or beginning of the second day. It deepens rapidly and reaches an intense degree so that by the third day the child's skin has become almost a mahogany brown colour. Later the child becomes drowsy, the respirations rapid, and subcutaneous hæmorrhages or petechiæ, convulsions, cyanotic and collapse attacks may develop. Unconsciousness supervenes and deepens, and death usually occurs on the fourth or fifth day. If the child recovers the jaundice gradually disappears but takes three to four weeks or even longer to clear completely. During this period of decreasing jaundice the colour becomes more and more of a lemon yellow tint, and from the appearance of the child it is obvious that a severe degree of anæmia is present. Examination at or shortly after birth may reveal slight enlargement of the liver and sometimes of the spleen, and the latter organ may increase in size during the period of intense jaundice. The urine shows urobilinogen, urobilin in excess, and bile pigments, but the stools are not always acholic. The placenta is not infrequently hypertrophied.

A high degree of erythroblastæmia directly after birth has been reported: thus, Buhrman and Stanford² have recorded two cases. In one the blood five hours after birth showed:—hæmoglobin 50 per cent., red cells 2,950,000, and nucleated red cells 213,300 per c.mm. In the other the blood

picture six hours after birth was:—hæmoglobin 47 per cent., red cells 1,510,000 per c.mm., of which 139,500 were nucleated. These authors did not refer to the presence of megaloblasts or megalocytes. On the other hand, in a case described by Hart³, the blood examined on the third day showed 4,200,000 red cells and 9,000 leucocytes per c.mm., the hæmoglobin was 85 per cent., and the blood film showed no abnormality of white or red cells. The following case also did not show erythroblastæmia.

Case 2.—B. A., born by Cæsarean section, developed icterus gravis on February 20th, 1933. The blood examinations on February 22nd and 28th were as follows:—

Red cells	...	...	3,650,000 per c.mm.	4,400,000 per c.mm.
Hæmoglobin	...	...	95 per cent.	94 per cent.
Colour index	...	...	1.3	1.07
Reticulocytes	...	...	5.7 per cent.	3.8 per cent.
Leucocytes	...	...	7,500 per c.mm.	10,700 per c.mm.
Myelocytes	...	...		1 per cent.
Neut. metamyeloc. : immature				0.5 " "
" " mature				1 " "
" polymorph.	...	...		56 " "
Eosinophil polymorph	...	...		4 " "
Lymphoblasts	...	...		1 " "
Lymphocytes: large	...	...		19 " "
" small	...	...		2 " "
Monocytes	...	...		16 " "
Plasma and Türck cells	...	...		0.5 " "

FIG. 1.—Case 2: Price-Jones curve.

A Price-Jones curve (Fig. 1) of this case taken on February 28th, showed a definite megalocytosis, but this is normal at this age according to van Creveld, and this curve is identical with his curve for normal babies of this age⁴.

Examination of the blood when the jaundice is fading as a rule shows a profound anæmia of the hyperchromic type, the red cells being diminished out of proportion to the hæmoglobin, and the colour index being unity or higher. A considerable degree of polychromasia and anisocytosis is present, as are normoblasts and reticulocytes. Megaloblasts may also be found. The platelet count may be normal, but usually is slightly reduced. The white cell count may be raised, but this is not a constant feature nor of great importance. It is interesting that an eosinophilia is present, especially during recovery. As the child improves the normoblasts quickly disappear, and the blood picture gradually returns to normal.

The hæmatological details in a typical case of anæmia following icterus gravis, 18 days after the onset of jaundice, were as follows:—

Red cells ...	2,147,200 per c.mm.	Lymphocytes ...	35 per cent.
Hæmoglobin ...	36 per cent.	Monocytes ...	7.1 „ „
Reticulocytes ...	28 „ „	Plasma cells ...	0.8 „ „
Platelets ...	320,000 per c.mm.	Normoblasts	
Leucocytes ...	23,420 „ „	(per 250 leucocytes)	16
Premyelocytes ...	1.1 per cent.	Macronormoblasts	
Myelocytes ...	3 „ „	(per 250 leucocytes)	2
Neut. metamyeloc.	2 „ „	Anisocytosis ...	+
„ polymorph.	48.2 „ „	Poikilocytosis ...	+
Eosinophils ...	2.8 „ „	Polychromasia ...	+++

The presence of abnormal megalocytosis, or of megaloblastosis, is to be regarded as the response to a great demand on the marrow and extra-medullary hæmopoietic centres. All of these still possess embryonic qualities and their ability to cope with the demand for new cells is shown by the presence of a reticulocytosis. In assessing the degree of megalocytosis it is necessary to bear in mind that, as has been already mentioned, megalocytosis normally occurs in the new born.

The anæmia following icterus gravis therefore differs clinically from nutritional anæmia of the new born in the following respects:—

(1) A severe hyperchromic anæmia becoming obvious as a severe attack of icterus is clearing up.

(2) The presence of a positive indirect van den Bergh reaction in the blood which may not be obtained if the icterus has all disappeared.

(3) The presence of an excess of urobilinogen and of urobilin in the urine, which also may not be found after the disappearance of the icterus.

(4) A spontaneous effort at recovery as shown by marked reticulocytosis and progressive improvement.

(5) A macrocytic response and in some cases the presence of megaloblasts in the peripheral blood, an occurrence almost unknown in nutritional anæmia.

(6) Frequent occurrence of eosinophilia.

This late anæmia of icterus gravis does not really call for treatment because if the child survives until the anæmia is obvious spontaneous

recovery will occur. The treatment of the anæmia present at birth and the prevention of the severest degrees of the later anæmia are best carried out by efficient treatment of the icterus gravis. We have found the method of treatment outlined by Hampson⁵, in which intramuscular injections of about 10 c.cm. of parental blood serum are given daily for several days, has been very successful if commenced sufficiently early. If the administration of serum is delayed until after the second day of life it is doubtful whether recovery will occur; indeed, one of our cases which received treatment before the end of the second day ultimately developed a considerable degree of spasticity (kernicterus). Icterus gravis has also been successfully treated by intramuscular injections of whole blood, but we prefer to give serum. Frequent small blood transfusions have also been given. We have not had any experience of this form of treatment, but in view of the results we have obtained in the treatment of acute hæmolytic anæmia of later infancy we are not surprised that good results have been reported. Hampson's method, however, has the great merit of simplicity. Blood transfusions are likely to be more helpful than serum in combating the early anæmia, and in hydrops foetalis. In any case the essentials for success are early diagnosis and treatment, and to this end it should be pointed out that Clifford and Hertig lay stress on the peculiar yellow colour of the vernix caseosa in erythroblastosis of the new born.

C. Hæmolytic anæmia without œdema or icterus gravis.—These cases should perhaps be classified under Group 2, and in any case they form a connecting link with that group. Infants which can without hesitation be classified under this heading are examples of erythroblastosis of the new born, but may not show any erythroblastæmia. This condition must be one of extreme rarity, but we believe that we have seen one case, and have pathological material from two.

Case 3.—B. O., male, aged 6 days, died within an hour of admission to hospital and before any extensive examinations had been carried out. He was the third child in the family; no miscarriages. He was born at term and was very pale at birth; the umbilicus was healthy, no bleeding from the cord. On the 3rd day he was faintly jaundiced, but this was not evident by artificial light when he was seen. The spleen was enlarged; respirations were 40 and pulse 120 per minute and temperature was 97°. He died without further examination, but blood drawn from the heart by a syringe ten minutes after death was pale pink of the colour of dilute strawberry jam. This fluid gave a red cell count of 320,000 and leucocyte count of 15,200 per c.mm. The hæmoglobin was too low to estimate, being under 20 per cent. The serum was bile-stained. Films showed an excess of large lymphocytes, but the staining properties of the cells were very poor. Erythroblastæmia was not a feature of the film. A differential leucocyte count gave the following percentages:—

Neut. polymorph	2	Basophil polymorph.	0.5
„ metamyeloc., mature ...	5	Lymphocytes, large	82.5
„ „ immature	3	„ small	0.5
Eosin. polymorph.	2	Monocytes	1.5
„ metamyeloc., immature ...	1.5	Monocytes (?)	1.5

At autopsy slight bile-staining of the lungs, pleural exudate and liver was observed,

The other case was that of a child who was born in one of the Birmingham municipal maternity homes and is to be reported in detail elsewhere by Dr. Mary Crosse. The following is a brief note of it:—

Case 4.—B. W., developed slight jaundice on the 2nd day of life. This soon disappeared. At 7 days the child was noticed to be pale, and the following day the spleen was palpable, the red cell count 2,600,000 per c.mm., and hæmoglobin 42 per cent. A day later the red cell count was below a million and the hæmoglobin 20 per cent. The child died on the 12th day.

Group 2. Hæmolytic anæmia later in the neonatal period without œdema or icterus gravis.

In the course of our investigations we have found a few examples of severe anæmia of the hyperchromic type in infants varying in age from a few weeks to two or three months. The history and examination may or may not reveal jaundice, and even when jaundice has occurred it may have made such a slight impression on the mother's mind that to obtain any history of it a direct question has to be asked; certainly there is never any history suggesting the occurrence of icterus gravis. Usually the child is normal at birth and during the subsidence of icterus neonatorum it is noticed to be pale. Advice may be sought at this time, or not until some weeks later. On examination the child is found to be extremely pale and, if in the neonatal period, a slight icteric tint may still be noticeable. Frequently some enlargement of the spleen is found. Its degree is, however, rarely marked and in any event slight enlargement of the spleen is no great help in classifying the anæmias of infancy. Urobilinogen and urobilin are in excess in the urine.

The following case illustrates the history and clinical findings in this type of hæmolytic anæmia:—

Case 5.—W. S., a male breast-fed child aged 4 weeks, was brought to hospital for anæmia with a history of jaundice of five days' duration during the first week of life. Since that time he was said to have become increasingly pale. On admission he was obviously very anæmic. There was no pyrexia, and no trace of jaundice; the liver was slightly and the spleen considerably enlarged; the stools were deeply pigmented and urobilinogen was present in the urine in considerable quantities. The blood examination corresponded exactly with that already described in the anæmia following icterus gravis; there was an anæmia of the hyperchromic type showing a considerable degree of polychromasia, anisocytosis, macrocytosis, reticulocytosis and megaloblastosis. The white cells were very slightly increased and showed some immaturity of the myeloid series.

From the time of admission to hospital this child showed a steady progress to complete recovery and during this time an eosinophilia developed. Recovery was complete and spontaneous; indeed the blood picture when first seen indicated that the marrow was active and healthy. The details of the blood counts are given in the accompanying list,

	6.10.31.	14.10.31	21.10.31.	25.11.31.	23.12.31.	20.1.32.
Red cells, per c.mm. ...	1,090,000	2,103,000	2,510,000	3,450,000	4,547,000	4,890,000
Hæmoglobin, per cent.	18	43	40	52	70	76
Colour index ...	0.9	1.02	0.8	0.75	0.78	0.76
Reticulocytes, per cent.	5	5.8	2.2	0.8	0.4	0
Platelets, per c.mm. ...	250,000	330,000	310,000	338,000	400,000	plentiful
Leucocytes ,, ,, ...	14,000	9,800	5,500	12,300	8,900	17,100
Myelocytes, per cent.	0	1.5	2.5	0	0	0
Neut. polymorph.						
per cent.	45	21.5	18.5	13	15.5	37
,, metamyeloc.						
per cent.	4	3	5	0.5	0	0
Eosinophils. ,, ,,	1	4.5	6.5	1	1	1.5
Basophils. ,, ,,	1	1	0.5	0.5	1.5	1
Lymphocytes,						
large ,, ,,	49	54	43	} 81	73.5	53.5
small ,, ,,	1	8	17.5			
Monocytes. ,, ,,	2	6.5	6	4	8	7
Normoblasts						
(p.c. of leucocytes)	3	0.5	0.5	1	1	0
Macronormoblasts						
(p.c. of leucocytes)	3	6.5	1.5	0	0	0
Megaloblasts						
(p.c. of leucocytes)	27	4.5	0.5	0	0	0

We have at present under observation another child suffering from this form of anæmia, in which the clinical and hæmatological findings are similar to those found in older infants in the syndrome described as von Jaksch's anæmia; indeed, were the child over six months of age and the history unknown, the anæmia would be unhesitatingly classed in that group.

Case 6.—B. M., female. According to the history obtained from the mother this infant was pale when born, although otherwise normal, and two weeks after birth she was very slightly yellow for a period of three days. The pallor, which was very noticeable during the first few weeks of life according to some observers, had increased somewhat when the child was about 12 weeks old. At the age of 17 weeks she was admitted to hospital.

On examination she was found to be well nourished and intensely pale. The skin showed the yellowish waxy appearance so characteristic of acute leukæmia or severe pseudo-leukæmica infantum, and there was a doubtful icteric tinge in the conjunctivæ. Two petechial spots were found and there were a few shotty glands in each axilla. The abdomen was distended; the liver reached 1 in. below the costal margin in the anterior axillary line, and the spleen was greatly enlarged, reaching to the level of the anterior superior iliac spine. The red cells were only 1,450,000, leucocytes 18,700 and platelets 60,000 per c.mm. The hæmoglobin was 21 per cent., and the colour index 0.72. Anisocytosis was extreme, with a moderate degree of poikilocytosis and polychromasia. Reticulocytosis was present to the extent of 7.3 per cent. of red cells. Nucleated red cells were also obvious, normoblasts and macro-normoblasts amounting to 1.5 and 9.5 per cent. of the white cells respectively. Immaturity of the granular leucocytes was present as is obvious from the detailed counts given in the accompanying lists. A drawing of the various cells seen in the blood films from this case will be found on page 206.

On the day following admission the child's condition was slightly improved by a transfusion of 60 c.cm. of blood. Fourteen days later 80 c.cm. were transfused and

this produced definite though not great improvement. The slight tinge of icterus disappeared. This improvement was not maintained, for after three weeks the child became slightly icteric again, two purpuric patches appeared and there was a considerable drop in the blood count.

	2.2.33.	15.2.33.	1.3.33.	11.3.33.	10.4.33.
Red cells, per c.mm. ...	1,450,000	1,950,000	2,360,000	1,370,000	2,100,000
Hæmoglobin, per cent.	21	32	42	29	45
Colour index ...	0.72	0.82	0.9	0.8	1.07
Reticulocytes, per cent.	7.3	4.1	3.7	5.0	1.8
Platelets, per c.mm. ...	60,000	115,000	400,000	50,000	30,000
Leucocytes „ „ ...	18,700	41,000	19,000	8,000	8,900
Myeloblasts, per cent.	0.5	0.5	4.5	4	
Myelocytes „ „	3	1.5	1.5		3
Neut. metamyeloc., immature, per cent.	0.5	4	0.5	1.5	2.5
mature „ „	3	2	1	0.5	0.5
Neut. polymorph., per cent.	18.5	22.5	43	27	33
Eosinoph. polymorph., per cent.	1	0.5	2.5	1.5	1
Basophil. polymorph., per cent.	0.5		0.5		
Lymphoblasts „ „	1.5	1.5	0.5	3.5	
Lymphocytes, large, „ „	54	60	23	40	22.5
small „ „	9.5	4	9.5	11	32.5
Monocytes „ „	11	3.5	11	8	5
Plasma and Türk cells „ „	0.5		2.5	0.5	
Normoblasts (p.c. leucocytes)	1.5	2	1.5	2	2
Macronormoblasts (p.c. leucocytes)	9.5	10	6.5	4	2
Megaloblasts (p.c. leucocytes)	0	2	1.5	8.5	1.5

Three days after admission the blood gave a slightly delayed positive direct van den Bergh reaction, and a positive indirect reaction (1 unit bilirubin). Urobilin in excess was found twice, and urobilinogen in excess once in the urine. The stools, which were deeply pigmented, showed an excess of urobilin. A Price-Jones curve (Fig. 2) showed the marked degree of anisocytosis noted above, and the presence of a few megalocytes.

This case is one of extreme interest and we regret that we cannot complete its record as the child is still in hospital. Although the spleen is now, eight weeks after admission, smaller than when first seen and the Price-Jones curve shows that the anisocytosis is less and the curve tending to approximate more to the normal, the child is still very ill. Blood transfusions have been performed from time to time but no permanent improvement in the degree of anæmia has occurred. The interest lies in the fact that although this is an example of hæmolytic anæmia which dates from the neonatal period, it is obvious that destruction of the erythron is still occurring. We have already pointed out the similarity to the von

Jaksch's syndrome presented by the clinical picture of this child; it is probable that the clinical course of the case indicates the mode of development of that syndrome and so lends support to the view that the anæmia of von Jaksch is a sub-chronic hæmolytic anæmia.

FIG. 2.—Case 6 : Price-Jones curve.

Although in our experience in this group of cases recovery after a varying time is the rule, yet death occurred in one instance.

CASE 7.—R. L., male, was aged 3 months at the time of his death and had been noticeably pale from the first week or so of life, but had never suffered from jaundice or œdema. A week before his admission to hospital he had become paler. When examined it was obvious that he had severe anæmia; there were some purpuric patches on the head; the spleen and liver were enlarged but the lymphatic glands were normal. Examination of the blood revealed the presence of a very severe anæmia, the red cell count being under one million, and the hæmoglobin 20 per cent.

Red blood cells per c.mm ...	810,000	Eosinoph. polymorph. ...	...	2.5
Hæmoglobin per cent. ...	20	Basoph. polymorph. ...	...	1.0
Colour index ...	1.25	Large lymphocytes. ...	...	18
Leucocytes per c.mm. ...	15,850	Small lymphocytes ...	...	47.5
Reticulocytes per cent. ...	1.0	Lymphoblasts ...	...	1.5
Myeloblasts ...	0.5	Türk cells ...	...	0.5
Neut. polym., segmented		Monocytes ...	...	1.5
per cent. ...	20	Normoblasts } per 100 {	...	3
„ „ non-segmented		Megaloblasts } leucocytes {	...	5.5
per cent. ...	7	Polychromasia ...	...	++
Metamyelocytes, mature		Anisocytosis ...	...	+++
per cent. ...	1.0	Poikilocytosis ...	...	+

Fig. 3 is a composite drawing and Fig. 4 is a photograph of the cells present in the blood films. He died five days after admission and the details of the autopsy are given in the section on pathology (page 176).

FIG. 3.—Case 7 : Composite drawing showing large numbers of megaloblasts.

1. Megaloblasts. 2. Basophilic lymphocytes. 3. Lymphocyte.
4. Lymphoblast, possibly myeloblast. 5. Chromasomes in mitotic red cell. 6. Mast cell. 7. Mature metamyelocyte.
8. Mature neutrophilic polymorphonuclear. 9. Polychromasia.
10. Platelets.

FIG. 4.—Case 7 : Blood film ($\times 390$) : mitosis in erythroblast on right, premyelocyte below, lymphocyte to left,

Pathological changes in hæmolytic anæmia of the new born.

Pathological changes in icterus gravis.—We have had material from four fatal cases, and the following were the chief macroscopic abnormalities found. All the organs, with the exception of the central nervous system and cerebro-spinal fluid which were only slightly tinted, showed general icteric staining, often of an extreme degree. Deep bile staining of the basal ganglia (kernicterus) and degeneration of the nerve cells are described in the literature, but unfortunately we have not had an example of this in our series. The liver was slightly enlarged, deeply bile stained, and did not show any cirrhosis. The gall-bladder contained either a normal or small amount of bile; sometimes little more than mucus. The spleen was slightly enlarged. The bone marrow was of a rich red colour throughout, tinged with the general icterus, which sometimes stained the epiphyseal line a greenish hue. A little oozing of blood from the umbilical stump has been noted but without any evidence of infection.

HISTOLOGICAL EXAMINATION: LIVER (Fig. 5, 6 and 7). The principal finding has been the presence of embryonic blood formation in the hepatic sinusoids which produced a striking low power picture. The liver cell columns were broken up by wide sinusoids, in which were found many small clumps of fairly deeply staining round and oval cells possessing prominent nuclei somewhat vesicular in type. Much bile pigment was present, chiefly lying free in the sinusoids, but also occurring in the liver cells, in phagocytic histiocytes in the sinusoids and sometimes as small thrombi in the bile canaliculi. There was no obvious fatty degeneration in the central areas of the lobules which is so common in many toxic affections in children. This picture of the packing of the liver sinusoids with immature cells closely simulates a leukæmic process and careful examination of the cells was therefore required. This was carried out on well-cut sections with the twelfth-inch immersion objective. Most of the larger cells were about 8 or 10 μ in their longest diameter, and possessed round or oval nuclei of about 7 μ in size and surrounded by a moderate amount of cytoplasm. The nuclei were vesicular, a well defined nuclear margin enclosing a pale interior in which one or two nucleoli might be found; the knots of karyomitone were rather distinct although not numerous and tended to lie mostly near the nuclear membrane. Such characters are very similar to those of the myeloblast and premyelocyte when these cells are seen in histological sections. A careful comparison of our specimens (stained with hæmatoxylin and eosin; eosin and methylene blue; Giemsa) with those of myeloid leukæmia has shown that cytoplasm, nuclear margin and chromatin network tend to be definitely darker in staining reaction than those of the myeloid cells; the cytoplasm too is more basophilic. Moreover the real nature of these cells was revealed by the large number of erythroblasts scattered in their vicinity and throughout the sinusoids. Extruded erythroblastic nuclei were common and erythroblasts of larger size with karyorrhectic polymorphic

FIG. 5.—Liver in icterus gravis; projection drawing ($\times 1000$): showing pro-erythroblasts with cytoplasm darker than in myelocytes; darker small cell with them appears to be a type of megaloblast, the nucleus is larger than in the usual normoblast.

FIG. 6.—Liver in icterus gravis ($\times 90$): showing wide sinusoids with haemopoietic foci.

nuclei were not uncommon and required differentiation from polymorphonuclear granulocytes, which they superficially resemble in sections. These prominent dark cells are in fact erythropoietic in character being pro-erythroblasts*. Further search of the sections revealed cells some of which appeared to be less and other more mature than pro-erythroblasts. The less mature consisted of a few larger and paler cells with similar, but lighter vesicular nuclei (probably hæmohistioblasts), which appeared to be derived from swollen endothelial cells either partially or wholly detached (proliferated Küpffer cells). On the other hand, cells of similar general characters, about 8 μ in size, but with a darker, strongly and evenly stippled nucleus throughout, were seen, and these were probably megaloblasts. Nuclear forms and types between these and the recognizable erythroblasts have been found, though many of the erythroblasts have, on the whole, rather large nuclei. Other cells observed included some polymorphonuclear granulocytes and some large phagocytic histiocytes. Sections stained by the Turnbull-Hueck process revealed the presence of a considerable amount of hæmosiderin.

SPLEEN.—The presence of the above described cells and erythropoiesis was variable: recently one of our cases showed these, but the next case did not. The reticular cells always showed evidence of activity: proliferation in some cases and phagocytosis in others. Lymphocytes were numerous.

MARROW.—In our cases the marrow has shown considerable activity, especially on the myeloid side, but it does not appear to have any distinctive characters. One marrow, which was decalcified and hence did not reveal its cellular characters well, showed a diminution in normoblasts, and a smear made from this marrow revealed many immature granulocytes but no normoblasts. The significance of this finding is not understood, but it is possible that the embryonic hæmopoietic function of the liver is maintained in activity partly because of some failure of the erythropoietic function of the developing marrow.

Pathological changes in hydrops foetalis.—In hydrops foetalis very similar changes have been recorded, and the erythroblastosis evident in the organs has been regarded as one proof of an inherent relationship between icterus gravis and hydrops foetalis. De Lange and Arntzenius¹⁰ and others have described a breaking up of liver cell columns by erythroblasts and cells like lymphocytes (? megaloblasts), with and without a few bile thrombi, and a positive iron reaction by the Turnbull-Hueck process. We have had the opportunity of examining only one case in recent years (Case 1 above).

* 'Erythroblast' designates any form of nucleated red cell (i.e., either megaloblast or normoblast). 'Pro-erythroblast' is a more immature cell which appears to be developing into a nucleated red cell. In Sabin's terminology, 'erythroblast' does not include 'megaloblast.'

FIG. 7.—Liver in icterus gravis ($\times 850$): PE, proerythrocytes with lighter nuclei and dark cytoplasm (the cytoplasm is darker and the chromatin masses in the nuclei slightly darker than in myeloblasts): M, megaloblasts with darker, heavily dotted nuclei: N, normoblasts.

FIG. 8.—Case 1: Liver in hydrops foetalis ($\times 75$): showing severe toxic change and necrosis in liver cells; E, erythroblasts.

FIG. 9.—Case 1; Liver in hydrops foetalis ($\times 700$): showing great disorganization, only a few hepatic cells (H) being recognizable; the scattered dark round cells are normoblastic nuclei or small erythroblasts; PE, ? large proerythroblast.

FIG. 10.—Case 4; Liver ($\times 700$): showing more mature erythroblasts, mostly with nuclei of normoblastic type.

The autopsy in this case showed generalized œdema; slight bile staining of the pleural and peritoneal fluids; obvious enlargement of the heart and swollen and œdematous kidneys. The following features were found on microscopical examination. The architecture of the liver was largely lost and the columns of cells were so broken up that it was somewhat difficult even to recognize that the section was one of hepatic tissue (Fig. 8 and 9). There was extreme fatty degeneration and areas of necrosis were scattered throughout the lobules, especially in the central areas; the sinusoids were greatly widened and filled with erythrocytes, scattered nuclei, debris and prominent irregular eosinophilic masses (basophilic with methylene blue). Examination under a higher magnification showed that these masses contained nuclear remnants and were in fact necrotic cells which on account of their strong affinity for eosin were possibly hepatic cells. Although erythroblast nuclei were fairly numerous, megaloblasts and pro-erythroblasts, which were such a characteristic feature of icterus gravis, were scanty. The section, therefore, showed extreme toxic and necrotic changes with evidence of some erythropoiesis, which in its turn also appeared to be affected by the toxic process. Sections stained by the Turnbull-Hœck process for iron showed the presence of considerable amounts of hæmosiderin.

The renal glomeruli were swollen and filled the capsules; there was cloudy swelling of the tubule cells with œdema and fragmentation of the tissues and also much eosinophilic material in the tubule cells.

The myocardium showed nuclear chromatolysis, œdema and fragmentation of the fibres.

These findings do not entirely correspond with those recorded by some observers since there was only slight evidence of erythropoiesis, the outstanding feature being the presence of changes which were obviously due to a severe toxæmia.

Pathological changes in hæmolytic anæmia of the new born without œdema or icterus gravis.—We have examined the organs of two cases of this type (Cases 3 and 4), of which the clinical details have already been described.

Cases 3 and 4.—Both showed a pathological picture in the liver similar to that detailed under icterus gravis, except that bile thrombi were absent and granules of bile pigment fewer; the cells were identical in form although in Case 3 the cells which we have called pro-erythroblasts, and in Case 4 (Fig. 10) megaloblasts and normoblasts, predominated. In the spleen clumps of pro-erythroblasts, normoblasts and extruded nuclei were common. In Case 3 the thymus was normal; the myocardium showed fragmentation of the fibres; small hæmopoietic foci were present in the adrenal medulla but none in the kidney. The bone marrow in both children was cellular and sections showed plentiful myeloid cells and also normoblasts with a few doubtful megaloblasts.

The only features common to these cases of icterus, hydrops foetalis, and severe hæmolytic anæmia of the new born are:—foci of embryonic hæmopoiesis; a varying degree of toxic change; and considerable deposits of hæmosiderin in the liver.

It must, however, be remembered that hæmopoiesis in the liver is by no means uncommon in healthy new-born children, and occurs in most premature infants; thus, a set of sections, taken from a case of prematurity of about eight months to serve as standards, was found to show extensive erythropoiesis in the liver. The cells were similar to those already described, except that the larger immature cells were somewhat less numerous and pro-erythroblasts plentiful,

Embryonic extra-medullary hæmopoiesis.—The earliest paper which we have consulted on the subject of extra-medullary hæmopoiesis is one published in 1909 by Buchan and Comrie⁶ on ‘congenital anæmia with jaundice and enlargement of the spleen.’ The microphotographs in this paper are good, and one of a section from a liver of a full-term child shows blood-forming islets, which are only one-half or one-third the size of those present in the cases of jaundice. Ferguson⁷ found hæmopoiesis in the livers of six out of nine premature infants examined, but in much less amount than that in three cases of icterus gravis, two of hydrops foetalis, and one of anæmia without jaundice or œdema. From the description he gives of the cells and from his illustrations, it is clear that the changes are similar to those which we have described above; further, he also found megaloblasts and normoblasts in the peripheral blood of cases of icterus gravis. Ferguson also states that the term erythroblastosis was first applied to the hæmopoietic foci in hydrops foetalis by Eichelbaum who also said that erythroblastosis might occur without œdema; further, that prior to Eichelbaum’s contribution Sanger had described congenital anæmia with leukæmia, and Pereg and Jacob had reported congenital œdema without any adequate anatomical basis. Ferguson therefore came to the conclusion that the hæmopoietic foci may be either erythropoietic or leucopoietic (i.e. leukæmic) in character, but we think that it is highly probable that Sanger mistook the immature pro-erythroblasts for myeloblasts.

Some observers, as Schmidt and Lobenhoffer, have described the hæmopoietic foci as lying between the endothelial and liver cells, but this relationship was not clear in our cases. Schridde, according to Capon⁸, was the first to draw attention to the hæmatological features of hydrops foetalis and he also described pointed greenish-yellow particles in the renal epithelium, which Fischer compares with those found in experimental poisoning. Capon himself noticed that in hydrops foetalis the villi in the placenta were crowded to a degree which was out of proportion to total epithelial surface, and suggested that this produced compression of the chorionic vessels with consequent impairment of nutrition and a rise of blood pressure in the foetus; to these changes the foetus responds by an increased blood cell formation, which, however, does not suffice for tissue metabolism and therefore exudation of fluid into hypertrophied placental villi and subcutaneous tissue occurs. This hypothesis is ingenious, but as will be seen later we think that a simpler one will cover the observed facts.

De Lange⁹ has collected striking examples of the incidence of still-births, icterus gravis and hydrops foetalis in foetuses of the same mothers, some of whom had evidence of toxæmia during pregnancy, and has pointed out that in all probability a maternal toxæmia is the cause of these conditions. She states that family histories may show œdema of pregnancy in sisters, and instances of the occurrence of icterus gravis and hydrops foetalis in the families of their brothers: facts which she believes strongly suggest a hereditary factor. Arntzenius and she¹⁰, argue that a toxin is a likely cause of icterus

gravis and of hydrops foetalis, and that the hæmopoiesis is reparative in character. They also say that the presence in the liver in hydrops of a positive action for iron when stained by the Turnbull-Hueck method is evidence of moderate hæmolysis; further, that the œdema may be caused by the influence of the toxin on the blood vessels; and they point out that, although extra-medullary blood formation occurs in most cases, it is not present in all. In their view, therefore, there is no relationship between grave icterus and hydrops, except that they are both due to the action of a toxin of an unknown nature. Rantmann, on the other hand, holds that the erythroblastosis is not a reaction, but a primary factor.

We agree with Salomonsen that the finding of considerable quantities of hæmosiderin in the liver by the Turnbull-Hueck process cannot be regarded as evidence of an abnormal degree of hæmolysis. The livers in our cases of icterus gravis, hydrops foetalis, and hæmolytic anæmia of the new born showed considerable quantities of iron; nevertheless we have found as great a degree of iron present in the liver of a premature child who died when one day old and in that of a full-term child who died when eighteen days old, although, on the other hand, the liver of a child one month old was practically free from iron.

Extra-medullary hæmopoiesis in later infancy.—In a full review of the subject of extra-medullary hæmopoiesis, Brannan¹¹ reported the case of a male infant of 7½ months showing many normoblasts and a few megaloblasts in the peripheral blood with reduction of platelets and changes in the skull bones. This child had tumour-like deposits of hæmopoiesis in the hilum of the kidneys and in the falx cerebri. He also quoted instances of such marrow deposits in the broad ligaments, in the breasts, and in relation to sweat glands in the soles and palms, and considered it probable that these myeloid elements are constantly present in the spleen of adults. We consider that there is some histological evidence for this process, since in sections of splenic tissue we have found scanty cells of myeloid type with erythroblasts, the latter being more numerous than in other organs (except the marrow). In a case of lymphatic leukæmia, recorded in the article on leukæmia (Part VI) a small focus of marrow formation was discovered in the hilum of a kidney. This type of extra-medullary hæmopoiesis has been referred to in order to demonstrate how it differs from the embryonic form which we have described as occurring notably in the liver of the premature and new-born baby. It differs in its activity, its occurrence in later infancy, its focal distribution, and its relatively greater activity in the formation of myeloid cells.

Pathological changes in hæmolytic anaemia later in neonatal period without œdema or grave jaundice.

The chief findings at the autopsy on the only fatal case of this type that we have seen were as follows:—

Case 7.—R. L. The organs were pale, especially the liver and kidneys. The liver weighed 265 grm., the spleen was uniformly enlarged and firm, epicardial ecchymoses were present, and the bone marrow of the left femur was red throughout,

FIG. 11.—Case 7; Liver ($\times 90$): showing wide sinusoids filled with pro-erythroblasts and normoblasts; some fatty degeneration, no peri-portal infiltration.

FIG. 12.—Case 7; Liver ($\times 590$): showing erythroblastic focus with pro-erythroblastic (PE); M, megaloblast.

FIG. 13.—Case 7; Liver ($\times 700$): showing sinusoid: PE₁ is a very immature cell, PE₂ is more mature and probably an early normoblast; K normal Kupfer cell, K₂ swollen. The erythroblastic focus does not lie between the Kupfer and liver cells,

FIG. 14.—Case 7; Bone marrow ($\times 700$) showing erythropoiesis, resembling similar foci in liver. PE, pro-erythroblasts.

All sections were taken from specimens fixed in formalin; the autopsy was performed 8 hours after death in the month of September.

LIVER (Fig. 11, 12 and 13). Sections stained with hæmatoxylin and eosin when examined under the low power showed the liver cell columns broken up by wide sinusoids filled with large and small dark cells; some fatty degeneration of the cortical areas was present and the portal tracts were inconspicuous. Under the high power many of the cells in the sinusoids were large, about 13μ in diameter, and possessed pale oval light vesicular nuclei, 10μ in diameter which showed fine dots of chromatin and sometimes one or more nucleoli. All grades of deeper nuclear staining were found up to cells which were apparently megaloblasts and normoblasts as already described in the various forms of hæmolytic anæmia of the new born. Swollen Küppfer cells and free histiocytes were common. Moreover, the differentiation of the cells appeared to be preponderatingly on the erythrocyte and not on the granulocyte side.

SPLEEN. Low power magnification:—the lymph follicles were rather small, the pulp was very cellular and showed many fairly large round and oval cells; there was some increase of reticulum in the less cellular parts. High power magnification:—a proliferation of reticular cells was clearly seen and these cells had swollen light oval and spindle-shaped nuclei. In the meshes of the reticular there were large vesicular nucleated cells, similar to those in the liver, and scattered everywhere were many darker cells differentiating towards normoblasts. Generally distributed also were lymphocytes of normal type whose nuclei were slightly larger ($4-5\mu$) and more finely dotted and streaked than those of the normoblasts (nuclei of normoblasts are usually about $2\frac{1}{2}-4\mu$); also the nuclear contour, though fairly regular, tended in many cases to be slightly polygonal as against the more constantly round normoblastic nuclei. The normoblastic cytoplasm was eosinophilic when stained with hæmatoxylin and eosin. With eosin and methylene blue the nuclear features were clearer, but the cytoplasmic process not so well defined. Normoblastic cytoplasm with this stain was bluish with a tinge of pink.

LYMPH GLANDS. In the hilum considerable endothelial proliferation was present and, as in the liver, amongst apparent histiocytes were many large vesicular cells with accompanying normoblasts. In a mesenteric gland endothelial proliferation was less marked.

MARROW (Fig. 14). After decalcification the cellular characters did not show well, but there were many immature cells similar to those already described and myelocytes were fairly common but not more mature granulocytes. Erythroblasts were also fairly numerous.

The erythropoietic foci seen in the organs of this case were strikingly similar to those found in icterus gravis and hæmolytic anæmia of the new born. Taking into consideration the fact that this child showed marked megaloblastosis of the peripheral blood stream it appears clear that these foci were preponderatingly erythropoietic and were part of a response to the call for erythropoiesis because of the hæmolysis. The hæmolysis commencing before the regression of the embryonic form of the erythropoiesis in the liver had taken place had the effect of retaining this type of erythropoiesis in activity.

Discussion.

From time to time reports of instances of 'anæmia of the new born' appear in the literature. We have given reasons in the paper on the hæmatopoietic anæmias (Part III) and elsewhere¹² for maintaining that sometimes anæmia of the new born is a congenital nutritional anæmia;

nevertheless, in our opinion, the majority of cases of anæmia of the new born are hæmolytic in nature, being examples either of the present class (hæmolytic anæmia of the new born or of the later neonatal period, unaccompanied by severe icterus or œdema), or of the anæmia following icterus gravis.

The clinical manifestations of anæmia of the new born have been described by A. F. Abt¹³ as follows:—

The infants are born of healthy parents, in normal spontaneous labour, and from their history has been excluded all evidence of birth injury, hæmorrhage, hæmorrhagic disease, infection or pre-natal poisoning. Within the first two weeks of life these infants while thriving and behaving in every way as normal new born infants, become extremely pale. This pallor is a sheet-like whiteness . . . The infants nurse well, are afebrile, have normal periods of sleep and wakefulness, cry lustily and vigorously, and aside from the marked and startling pallor, show no sign of ill-being. Recovery has been observed, both without and with treatment, and infants who have been followed for several years have shown no residual effects.

Whilst accepting with considerable reluctance the possible existence of an anæmia which is neither nutritional nor hæmolytic in origin, we nevertheless think that Abt has not sufficiently excluded the possibility of hæmolysis, since we cannot understand how a new-born infant can suddenly become intensely pale except as a result of hæmorrhage or severe hæmolysis. For instance, the infant described by Abt had a pink colour at birth and the pallor was noted on the eighth day, whereas on the following day without any evidence of hæmorrhage 'the child seemed as white as the sheet on which it lay.' Several of the cases from the literature accepted by him are also open to the same criticism, as is one published by Pasachoff and Wilson¹⁴. The case reported by these authors differed from that of Abt in that pallor was noted on the second day of life, and the evidence of hæmolytic anæmia in this particular instance appears to be complete. Nutritional anæmia of the new born may be distinguished from the hæmolytic group by the fact that it is a hypochromic anæmia, by its response to treatment by iron, and by the absence of those characters of a hæmolytic anæmia which have already been detailed.

The question may be asked:—Why are some hæmolytic anæmias associated with severe jaundice, while others are either free from jaundice or exhibit it only in a slight degree? The same curious difference is seen in the hæmolytic anæmias of later infancy and childhood. It is, of course, well known that severe hæmolysis may occur without severe jaundice, such, for instance, as that which sometimes follows blood transfusion.

The occurrence or non-occurrence of severe jaundice in association with hæmolysis probably depends on the condition of the liver, and the degree and suddenness of the hæmolysis. After severe hæmolysis an excessive bilirubinæmia results, and the liver being unable to excrete all this bilirubin, a hæmolytic jaundice develops—the so-called 'retention jaundice.' In this form of jaundice the colour is not a deep yellow but a lemon tint, the blood gives a positive indirect van den Bergh reaction, and there is an increase in fæcal urobilinogen. Urobilinogen or urobilin, or both, are present in excess

in the urine, but neither bilirubin nor bile salts are found in the urine. Retention jaundice is particularly likely to occur when the hæmolytic process is gradual in onset. If, however, there is necrosis of the liver cells, or obstruction to the outflow of bile, bilirubin after passing through the liver cells is regurgitated into the blood stream, and under such conditions a much deeper jaundice, guinea gold in colour, develops. In 'regurgitation jaundice' the blood serum gives a positive direct van den Bergh reaction, bilirubin and bile salts appear in the urine, urobilinuria may occur but the fæcal urobilinogen is reduced in amount. This form of jaundice is also likely to occur when a severe and sudden hæmolytic process produces an intense bilirubinæmia because the resulting bile is likely to be viscid and produce a degree of biliary obstruction. An interesting parallel to these cases occurs in acholuric familial jaundice, in which in most of the hæmolytic crises the jaundice is only of a moderate degree, but occasionally with a severe crisis the jaundice becomes greatly increased and bile pigments may appear in the urine, because bilirubin is secreted in such large quantities that the bile becomes thickened and a degree of biliary obstruction results followed by regurgitation jaundice. In icterus gravis the blood gives an indirect van den Bergh reaction; the urine contains increased amounts of urobilin and moreover also shows bile pigments. In other words, there is evidence of retention and of regurgitation and, as would be expected, at autopsy bile stasis and in some instances necrosis of the liver cells are found. In those examples of hæmolytic anæmia in which there is a history or evidence of a mild degree of jaundice, or even in those which have become anæmic without jaundice, the findings are an indirect van den Bergh reaction in the blood and an excess of urobilinogen and urobilin in the urine. However, even these findings may be absent if the child does not come under observation until some time after the occurrence of hæmolysis.

Another subject for discussion is the exact relationship existing between icterus gravis, hydrops foetalis, and severe hæmolytic anæmia of the new born. Are they, or are they not, all manifestations of an erythroblastic process (erythroblastosis of the new born)? For the purposes of this discussion it should be accepted that the term erythroblastosis implies an active bone marrow and active extra-medullary hæmopoietic centres, but that these may or may not be associated with erythroblastæmia. From the remarks made in the section on pathology, it is clear that hæmopoietic foci in all three of these conditions are usually to be found in positions where blood formation occurs in the embryo, notably in the liver and spleen; and it is reasonably certain from histological appearances alone that these foci are chiefly erythropoietic, and not leucopoietic in type. In some cases of hydrops foetalis, however, such foci are present only to a very limited extent (as in Case 1), or may even be absent (de Lange); thus providing strong evidence that they do not represent the origin of these disorders, but are only a concomitant feature or response. It is most probable that they do in fact represent a response to an increased call for erythropoiesis. In icterus

gravis there is no doubt that this call is the result of excessive hæmolysis, possibly commencing before birth; and in hydrops foetalis there is evidence of a hæmolyzing process in the occurrence of slight icterus and the presence in the liver of a positive iron reaction by the Turnbull-Hueck process. A process similar as regards hæmolysis, though no doubt different as regards its cause, in that it acts after birth, is at work in those forms of hæmolytic anæmia of the new born which do not show grave jaundice or œdema. The factor of hæmolysis in varying degree is thus common to these disorders, and the resultant response is also varying in degree and common to them all.

This response, embryonic erythropoiesis, is hence a symptom and not a cause of the disease. Further, the frequent presence of this form of erythropoiesis in premature and some full-term infants is evidence against the assumption that the cells produced by such hæmopoiesis are so abnormal in their action or structure as to initiate hæmolysis and its effects. Extra-medullary hæmopoiesis is, in short, a process which in young infants may readily be retained in activity and may be intensified by the provocation of increased hæmolysis. Given the existence of embryonic blood-forming tissue in such organs as the liver and spleen, its activity will be governed by the extent of the demand for its function. If by the time a hæmolytic process in post-natal life occurs the embryonic blood-forming tissue in the liver and spleen has atrophied, then this form of response to the increased demand for hæmopoiesis cannot occur in these organs, and the marrow has to shoulder the burden alone. We have seen this response after hæmolysis occur as late as the eighth month of life. Believing, as we do, that von Jaksch's anæmia is a chronic hæmolytic process occurring in later infancy, the presence of extra-medullary hæmopoietic foci in this condition will depend on whether the embryonic blood-forming foci have atrophied or not at the time when the hæmolysis begins. The consequent histological variations in the response to hæmolysis may account for the confusion of some instances of this syndrome with leukæmic metaplasia, a condition which, as we have pointed out, may closely resemble embryonic erythropoiesis.

The nature of the hæmolyzing factor in the hæmolytic anæmias of the new born, and the relationship between the hæmolysis thus produced and the hæmolysis which normally occurs at birth, are both unknown. Hæmolysis occurs constantly in intra- and extra-uterine life, but normally is kept within bounds by some mechanism. Hampson has suggested that hæmolysis may be controlled in intra-uterine life by something produced by the mother and passed on by her to the foetus, which in extra-uterine life is elaborated by the infant itself; for at birth a considerable degree of hæmolysis occurs owing to alterations in the oxygen tension of its surroundings, which is prevented from becoming excessive by the anti-hæmolytic agent. If this factor is absent or insufficient, excessive hæmolysis with the production of anæmia, and perhaps severe jaundice may occur; this may, however, be prevented if the anti-hæmolytic factor is given by administration of blood

serum. This is the basis of the treatment of icterus gravis by injections of blood serum, a treatment which we owe to Hampson, and which has proved a great success. On this hypothesis it is possible that in icterus gravis the maternal anti-hæmolytic factor supplied to the foetus becomes deficient towards the end of intra-uterine life, and that in extra-uterine life the infant fails to produce sufficient to keep the hæmolysis of birth within reasonable limits, and that the injection of blood serum remedies the deficiency. In hæmolytic anæmia of the new born, on the other hand, it is possible that the deficiency is entirely a post-natal one, or that the anæmia is due to a factor similar to that which initiates the acute hæmolytic anæmia of Lederer seen in older children. The fact that hæmolysis after birth is more severe in the premature child than in the normal child can be explained on the ground that the anti-hæmolytic factor has not been elaborated to the degree which it would have been if the child had gone to term. Such an hypothesis would furnish an adequate explanation of the fact that jaundice is more frequent and severe in premature than in full-term children; also of the development of hæmolytic anæmia in prematures, and of its prevention by blood transfusion. If this hypothesis is correct, the hæmolytic anæmias of the neonatal period, with the exception of that associated with hydrops foetalis, may be classified as deficiency anæmias, although they differ from the other deficiency anæmias in that the deficiency is of a temporary character only.

This hypothesis does not cover the whole ground because it leaves out of account any damage to the hæmopoietic portion of the erythron which may, and quite possibly does, occur. It thereby fails adequately to explain hydrops foetalis and those cases of icterus gravis which develop spastic diplegia in later life and those which show necrotic changes in the liver. Hæmolysis occurs in hydrops, and in addition there are extensive toxic changes in the parenchymatous cells and the capillary walls, which strongly suggest that the condition is due to a toxin which has some hæmolyzing influence, and the changes which occur in the liver and central nervous system in some cases of icterus gravis also strongly suggest that a toxin plays some part in the causation of that disease.

Summary.

In this paper the clinical and pathological characters of the erythronoclastic (hæmolytic) anæmias of the new born are described and the view put forward that the embryonic erythropoiesis (erythroblastosis of the new born) present in them is a result and not a cause of these anæmias. Attention is also drawn to the existence of a group of erythronoclastic (hæmolytic) anæmias which arise late in the neonatal period; are unconnected with severe jaundice or œdema; and may not be recognized until the children are some weeks old. The similarity between the clinical picture presented by some of the older children of this group to that of the anæmia of von Jaksch, and the light that this may throw upon the causation of the latter syndrome, is commented upon.

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ERRATA (PART III).

- Page 128, line 19: '1 mgrm. per cent.' read '0.1 mgrm. per cent.'
 line 22: for '11.25 grn.' read '11.25 grm.'
 line 23: for '1 grn.' read '1 grm.'