**Part V.—The hæmolytic (erythronoclastic)
anæmias of later infancy and childhood :
with special reference to the acute hæmolytic anæmia
of Lederer and the anæmia of von Jaksch**

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The destructive diseases of the erythron which fall for consideration under this heading show many points of general similarity although individual variations are frequent. In Part IV emphasis has been laid upon the fact that the erythron may be affected adversely either in the bone marrow or in the circulation; further, that for this reason the term hæmolytic anæmia was probably incorrect because it stressed the destruction of red blood cells, but that the title of erythronoclastic anæmia was more correct because it indicated that the erythron may be affected in the circulation or in the marrow or in both situations. Moreover, this is not the whole story, because not only may the erythron itself be affected in either the circulation, the marrow or both, but also the other elements of the blood, the thrombocyte system and the myeloid leucocyte system, may suffer damage. Again, in the latter months of the lactation period the child's supply of iron for hæmoglobin-building is somewhat precarious; a disturbance of the erythron is therefore likely to render manifest any iron deficiency and thus a deficiency anæmia may develop in the course of a hæmolytic anæmia. For these reasons a variety of clinical and hæmatological syndromes may occur, and it is possible that some conditions which hitherto have been regarded as quite distinct from the hæmolytic anæmias have, in reality, a close relationship to them.

If the examination of an anæmic child discloses an anæmia of the hyperchromic type, associated with a positive indirect van den Bergh reaction in the blood, and the presence of an excess of urobilinogen and urobilin in the urine, the fact that hæmolysis has occurred cannot be doubted. The coincidental presence of thrombocytopenia or agranulocytosis, or even of both, suggests that they also have been produced by the same causal agent acting respectively on the thrombocyte system or the myeloid leucocyte system. The degree of marrow response observed indicates the amount of

damage suffered by the erythronic cells and those of the other systems in the marrow. If the marrow has received only a moderate injury a good regenerative response will be found; whereas if it has suffered severely, complete destruction or irrecoverable paralysis of marrow function may occur and this will produce an increasing anæmia and death. The marrow, however, may be only temporarily paralysed, and after a day or so, or perhaps after a blood transfusion, active regeneration occurs. Further, if the child does not come under observation until some time after the onset of the hæmolytic, the hyper-bilirubinæmia may have ceased owing to excretion of the bilirubin, and then the blood serum will not give a positive indirect van den Bergh reaction.

Cases in which the thrombocytes are markedly affected may be diagnosed as thrombocytopenia, whereas those in which a marked decrease in myelogenous cells occur are liable to be classified under the heading of infective agranulocytosis (or leukopenia). Since one, two or all three blood cell systems may be affected, and in all grades of severity, we agree that all these conditions should be regarded as a single entity as suggested by Lescher and Hubble²⁰, and although we have grouped them under the heading of destructive diseases of the erythron (erythronoclastic anæmias) it could be argued that they should all be classed under the heads of either primary myelogenous or primary platelet diseases.

The cases which we have observed can be divided into four groups:—

- Group 1. Acute hæmolytic anæmia (Lederer type).
- Group 2. Sub-acute hæmolytic anæmia.
- Group 3. von Jaksch's syndrome (subchronic hæmolytic anæmia).
- Group 4. Acholuric jaundice.

Group I.—Acute hæmolytic anæmia (Lederer type).

In a paper published by one of us in 1931¹ were described four cases in which anæmia developed with great suddenness; the children were acutely ill and showed enlargement of the liver and spleen, a severe degree of anæmia with an intense marrow reaction, and in some cases a leucocytosis of 20,000 to 40,000 per c.mm. All the children made a rapid, and in some instances a spontaneous, recovery. This condition was regarded as due to an intestinal infection because abdominal pain and diarrhœa or vomiting were associated symptoms. Dr. Lederer kindly drew our attention to the fact that these cases were examples of a symptom complex of which he had seen three examples and which he had described in 1925 as 'a form of acute hæmolytic anæmia probably of infectious origin.'² He had been unable to find any earlier description of this form of anæmia in the literature and hence its designation as 'the Lederer type' seems justified. In 1930³ he reported three additional cases, and of this total of six cases three occurred in children aged three years, sixteen and six months respectively. All the children, but not all the adults, showed some gastro-intestinal symptoms, and since such symptoms have been absent in other children seen by us, we have come

to the conclusion that if these cases are infective in origin the infection is not necessarily intestinal. The condition is a rarity; thus O'Donoghue and Witts⁴ have been able to collect only thirty-six cases, of which eleven were between the ages of two and thirteen years. These writers do not mention the cases described by us, and exclude from their survey children under the age of two years, and the acute hæmolytic anæmia of pregnancy. Further, they point out that many of the cases are reported under varying headings such as acute febrile anæmia. We have now had a further series of five cases, bringing the total number we have seen in children up to nine.

The following case is a typical example of the severest form of this condition:—

Case 1.—A. S., male, aged 2 years and 7 months, was admitted to hospital on May 23rd, 1932, with a history that he had always been rather pale, but never ill until three days previously, when he became feverish and vaguely unwell. Thirty-six hours before admission he was noticed to become extremely pale, and on the day before admission he was observed to be yellow and to pass blood in his urine. His bowels had not been opened for 2 days, and there had been no vomiting.

On admission he was found to be a well-built and well-nourished child who was profoundly ill. He was stuporose, somewhat dyspnoëic, and deeply jaundiced; his mucous membranes were very pale. A few purpuric spots were present on the trunk and limbs and there was hæmoglobinuria. The spleen was enlarged, the edge being 1 in. below the costal margin; enlargement of the liver was not demonstrable.

The details of the blood examination at this date are given in the accompanying lists. The Arneth count was as follows:—I, 64; II, 35; III, 1 per cent. Weighted mean 1.37. Anisocytosis and poikilocytosis were present.

Date	25.5.32.	26.5.32.	27.5.32.	28.5.32.	4.6.32.	30.6.32.
Red cells, per c.mm. ...	1,100,000	1,510,000	1,070,000	1,560,000	1,590,000	4,200,000
Hæmoglobin, p.c. ...	32	35	28	28	42	88
Colour index ...	1.5	1.1	1.4	0.9	1.3	1.1
Reticulocytes, p.c. ...		3.5	3.5	2.1	29.5	
Leucocytes, per c.mm.	26,900	28,300	29,200	37,100	6,500	9,000
Myelocytes ...	0	3	3	1	0	0
Neut. metamyeloc.,						
immature, p.c.	7	3.5	4	4	1	
mature, ,,	15	9.5	3	6	1.5	
Neut. polymorph., ,,	41	54	56	55	33.5	39.5
Eosinophil ,,	0	0	2	3	2	5.5
Basophil ,,	0	0	1	2	0.5	
Lymphocytes, large, ,,	13	13	14	16	31	} 49
small, ,,	13	10.5	13	10	25	
Monocytes, p.c. ...	3	6.5	5	3	4	5.5

COURSE. Shortly after admission the boy was given a transfusion of 4 oz. of blood which produced an immediate improvement both in the general condition and the colour of the mucous membranes; twelve hours later, however, he again became desperately ill and stuporose, apparently having hæmolyzed all the donor's blood. At this time jaundice and pallor were still marked, the size of the spleen was unchanged but the liver was just palpable. Therefore, another 4 oz. of blood were transfused fifteen hours after the first transfusion: nine hours after the second

transfusion hæmoglobinuria was still marked and so a third transfusion of 4 oz. of blood was given. On the following day, May 27th, the urine still contained a considerable amount of hæmoglobin and a fourth transfusion of a similar amount of blood was given. Later, on the same day, the urine still showed albuminuria, but became free of hæmoglobin and red blood cells. After this date the urine was found to show hæmoglobin on one occasion only, and even then another specimen passed later in the same day was free from hæmoglobin although a faint haze of albumin, urobilinogen in excess, urobilin and a trace of bilirubin were present. On May 29th, the child was still ill and pale, but the jaundice was distinctly less, the lower border of the liver was felt half an inch below the costal margin in the mid-clavicular line; and the spleen had slightly diminished in size. On May 31st a purulent nasal discharge occurred which lasted for twelve hours. From this time forward improvement became more and more obvious. On June 3rd, pallor was still present, but jaundice was no longer obvious, the liver had become normal in size and the spleen was only just palpable. On June 7th the spleen could no longer be felt, the child's general condition was good, and the pallor was obviously diminishing. The improvement continued until on June 24th the child appeared to be a perfectly normal child and on June 25th, less than six weeks from the start of the illness, the hæmoglobin was 88 per cent. and the red cells 4,200,000 per c.mm.

It will be noticed that a reticulocytosis was present on admission to hospital and on the fourth day of the illness, and ten days after admission reached 29·5 per cent. Another interesting feature is that the fragility of the red cells was increased and that this gradually diminished until on discharge it had reached a normal level. This variation, which has been noticed by others, is somewhat difficult to explain unless the hæmolytic agent had affected all the red cells rendering them more fragile, but not completely hæmolyzing all of them.

Attempts were made to find out any possible causal infection. The only indication of any infection was the occurrence of a nasal discharge which lasted for a period of twelve hours on May 31st and cultures taken on this day showed numerous micro-organisms none of which was hæmolytic.

Here, then, is a case which shows the dramatically sudden onset of a severe hyperchromic anæmia associated with jaundice and hæmoglobinuria, in which there is an intense marrow reaction, and which, after a series of blood transfusions, shows a recovery almost as dramatic in character as the onset. No other form of treatment whatever was given with the exception of a single dose of potassium bromide.

The clinical picture in this type varies in details in different cases, but in its essentials remains the same. Thus although hæmoglobinuria and intense jaundice have only been seen in the foregoing case, the rapid onset often with a quite dramatic suddenness and the production of severe anæmia tending to be of a hyperchromic type is characteristic of them all. Sometimes the condition is so severe that not only is the erythron destroyed, but the damage to the marrow also is so great that the myeloid and platelet system suffer, and there is little or no evidence in any of the three systems of a bone-marrow reaction. This state of affairs is exemplified in the following case:—

Case 2.—I. W., female, aged 6 months, who, her mother said, never had any colour and for 3 to 4 weeks before admission to hospital had been getting yellower.

On admission she was obviously anæmic and examination of her blood showed that the hæmoglobin was 35 per cent.; red blood cells 1,850,000, leucocytes 5,300, and platelets 75,000 per c.mm., colour index 0.95; reticulocytes 1.4 per cent. There was a considerable degree of anisocytosis. No abnormal white cells were seen and the myelogenous cells were few in number. The fragility of the red cells was normal. The urine showed urobilinogen in excess and a slight positive reaction for urobilin; a positive delayed direct van den Bergh was present, and the indirect reaction was also positive to the extent of 0.9 units of bilirubin.

It is obvious from this description that not only was there an almost complete absence of regenerative response on the part of the bone marrow portion of the erythron, but also that the myeloid and platelets systems had been damaged, the circulating elements being destroyed and their precursors in the marrow paralysed.

COURSE. In this case there never was any response by the bone marrow, the child became progressively weaker and the pallor increased, and 8 days later the blood revealed a definite increase in the anæmia, thus:—hæmoglobin 27 per cent.; red blood cells 1,250,000, leucocytes 9,250, and platelets 22,400 per c.mm.; colour index 1.08. No reticulocytes were seen, anisocytosis was still marked, there was some stippling of the red cells and some erythrocytes showed Cabot's rings. Except for a very few basophil cells polychromasia was not present, and only one or two normoblasts were seen. On the day following this blood count 2 oz. of blood were transfused, but this was unavailing and the child died a few hours later. An autopsy was not permitted.

There can be little doubt that this case was an example of a true aplasia of the marrow (aplastic anæmia) due to the action of some noxious influence on the circulating cells of the blood and on the marrow cells. We believe that we are right in regarding this case as an example of acute hæmolytic anæmia. We should not hesitate to do so had the child recovered, or had we not carried out an autopsy on another child who clinically was a typical example of an acute destructive disease of the erythron, myeloid, and platelet systems with practically complete absence of marrow response.

The case to which we refer was of extreme interest, not only because it illustrated the difficulties of diagnosis, but also because on microscopical examination it proved to be an instance of non-leukæmic reticulo-endotheliosis, a condition described by German writers and hitherto unrecognized in this country. Here we give a short description of the clinical details; it will be more fully discussed in a later paper (Part IX).

Case 3.—J. W., male, aged 21 months, was said always to have been pale; three months before coming under observation he had developed an abscess in the neck which had been evacuated and healed normally. He remained well until 10 days before admission to hospital, when a small abscess over the bridge of the nose and a swelling below the right eye developed, and three days later a swelling in the region of the left parotid gland. After these foci had developed he gradually became paler and was noticed to bruise easily. On admission there was marked waxy pallor, bruises on both legs, a small abscess in the lower right eyelid and an abscess in the left parotid. The spleen was palpable 1 in. below the costal margin, the liver was not enlarged. The mucous membranes were pale, hæmic murmurs were present over the heart, and the lymph glands in the neck, axillæ and inguinal region were very slightly enlarged. There was no jaundice. The urine showed an excess of urobilinogen and of urobilin, but no bilirubin; the blood gave a slight delayed direct van den Bergh and a positive indirect reaction (0.4 units of bilirubin). Fragility was

normal. The hæmoglobin was 26 per cent., red blood cells 1,360,000 leucocytes 950. and platelets 21,300 per c.mm; colour index 1.0, reticulocytes 0.2 per cent. The films did not show nucleated red cells, anisocytosis or polychromasia and there were no abnormal white cells. Of the leucocytes only 8 per cent. belonged to the granular series.

This child died a little over three weeks later and during this period the bone marrow showed very little evidence of regenerative action. At one time there was a slight increase in hæmoglobin, red and white blood cells and platelets; also a reticulocytosis of 5 per cent. and a degree of polychromasia and anisocytosis occurred, and 1 and 1.5 respectively of normoblasts and megaloblasts per 100 white cells were seen. The temperature was raised for 6 days before death, and reached 105° shortly before death occurred.

Nutritional anæmia associated with acute hæmolytic anæmia.—In other instances, although after transfusion there has been evidence of a good marrow response, a return to a normal blood picture has not occurred, but in its stead the picture of a nutritional anæmia has developed and only after the exhibition of iron has a complete recovery been effected. These are obviously instances either of the lighting up of a latent nutritional anæmia by an acute hæmolytic anæmia, or of the supervention of hæmolysis in the actual course of a nutritional anæmia. The following is a good example of such an occurrence.

GRAPH 1.—Case 4: nutritional anæmia associated with acute hæmolytic anæmia.

Case 4.—K. H., male, aged 5 years; had suffered from asthma for about 6 months during which time it was noticed that he was rather pale. For 2 weeks

before admission the pallor had become more marked and he had vomited once, but he had not been confined to bed until the day of admission to hospital. On this day he became extremely ill and complained of pain in the upper abdomen.

On admission he appeared very ill and intensely pale, the skin being of a waxy, slightly yellowish, colour resembling that of a child with acute leukæmia; the mucous membranes were blanched, but the conjunctivæ did not show any icteric tint; dyspnoea was marked and air-hunger extreme. He was restless and complained of upper abdominal pain due to a tender liver which extended 2 in. below the ribs in the mid-clavicular line. The spleen was not enlarged, nor was there any glandular enlargement. There were hæmic murmurs over the heart, but no petechiæ nor retinal hæmorrhages were seen. The temperature was 100°, pulse rate 150, rising in a few hours to 180, and respirations 35 per minute. An examination of his blood revealed that the hæmoglobin was less than 20 per cent., the red cells 1,240,000, leucocytes 15,800, and platelets 570,000 per c.mm.; poikilocytosis, anisocytosis, and very slight polychromasia were present, but the white cells did not show immaturity.

In the course of the first 4 days after admission the child was given three blood transfusions, 3, 7, and 6 oz. respectively. These relieved the urgent dyspnoea; the respirations, which had reached 54, dropping to 24 and the pulse rate to 100 per minute one week after admission. On the 8th day a definite reticulocytosis was present and thereafter considerable clinical and hæmatological improvement occurred, but although as shown in Graph I, five weeks after admission the red cells had reached 4,880,000 per c.mm. the hæmoglobin hovered between 40 and 50 per cent. for a month. It seemed obvious, therefore, that the original hæmolytic anæmia had been replaced by a definitely hypochromic, possibly nutritional, anæmia. At this time the stomach contents were examined after a barley gruel test meal, because it was thought the condition might be an achlorhydric anæmia; free hydrochloric acid was found to be present in the gastric juice although in small amount. Iron was now given in the form of reduced iron, 9 grn. a day; a fresh reticulocyte 'kick' occurred and the child went on to make a complete recovery.

Sometimes although the onset of the disease may be acute and the resulting anæmia considerable, the child does not appear as acutely ill as those described above and recovery occurs spontaneously without any treatment.

Case 5.—B. M., female twin, aged 14 months. When first seen this child gave a positive indirect van den Bergh reaction (0.95 units of bilirubin) in the blood; urobilinogen in excess and urobilin were present in the urine. She also showed severe marrow damage by the presence of leucopenia and thrombocytopenia. During recovery it was obvious she had suffered from actual or latent nutritional anæmia

Date	28.6.32.	2.7.32.	5.7.32.	27.7.32.	19.8.32.	2.9.32.	14.9.32.	3.10.32.
Red cells, per c.mm.	1,613,000	2,036,000	2,893,000	4,267,000	3,537,000	4,293,000	5,027,600	6,340,000
Hæmoglobin, p.c.	32	42	46	48	47	55	70	80
Colour index ...	1	1.05	0.8	0.57	0.67	0.64	0.7	0.65
Reticulocytes, p.c.	2	13.2	4.8	3.6	4.3	2	2.6	
Platelets ...	76,000				227,000	plentiful		
Leucocytes, p.c.	5,100				10,750	13,550	16,800	
Normoblasts, „				1 seen	.5			
Anisocytosis ...	+	+++	+++	+++	++	++	++	
Poikilocytosis ...		++	++	+	+	+		
Polychromasia ...	+	+++	+++	+++	++	++	++	
Punctate basophilia		+	+					

before the hæmolytic anæmia developed, in that, as in the previous case, the hyperchromic anæmia changed under treatment into a hypochromic anæmia (see blood counts) requiring iron for its complete cure. The observation is of interest because this child was not noticed to be pale until a week before admission, and the pallor had increased rapidly during the three days prior to admission. Her twin brother admitted on the same day, had been pale for months. He also presented a hæmolytic anæmia, but of the sub-acute type, superimposed on a nutritional anæmia (see Case 8).

Relapse from intercurrent infection.—One case was noteworthy in showing that an infection developing in the course of treatment may produce a relapse and delay recovery until the infection is cured, and thereby perhaps contributes something to the discussion on ætiology.

Case 6.—D. A., female, aged 11 months who, although always a pale baby, had become paler and slightly jaundiced four days before admission. On admission the blood showed the changes characteristic of a severe hæmolytic anæmia, the red cell count being only 800,000, and the white cell count 14,100 per c.mm. of which 86 per cent. were lymphocytes, the hæmoglobin was 18 per cent. and the colour index 1.12. Anisocytosis was very marked, polychromasia and poikilocytosis were also present but to rather a lesser degree and the halometer reading was 7.84μ . The child was well nourished, not jaundiced, but extremely ill and had a temperature of 100, pulse rate 180 and respirations 70 per minute. On the second day after admission the urine showed urobilinogen and urobilin in excess, and gave a positive test for bilirubin. The van den Bergh test gave negative direct and indirect reactions with the blood serum. Shortly after admission 40 c.cm. of blood were transfused and 18 hours later a second transfusion of 50 c.cm. was given. As a result the temperature fell, the respiration and pulse rates diminished and the child's general condition improved. The blood also showed an improvement, but only up to a certain point, since the red cell count and hæmoglobin remained at about the same level (two millions and forty per cent. respectively) until the twelfth day after admission. Four days later (16th day) the child became worse, vomited, and had three loose green offensive stools in 24 hours. The temperature rose to 102° , pulse to 180 and respirations to 70 per minute: coincidentally the red cells fell to 1,490,000 per c.mm. and hæmoglobin to 28 per cent. Examination of the urine next day showed the presence of a dense cloud of albumin, pus, and red blood cells. Another blood transfusion of 60 c.cm. of blood produced considerable improvement, the temperature, and the frequency of the pulse and respirations diminished and the blood was restored to its former level. The blood, however, did not show any further improvement until the urinary condition had completely cleared up, after which steady progress occurred until cure was complete. It is interesting also to note that the spleen was not palpable until after the relapse when it reached to $1\frac{1}{2}$ in. below the costal margin.

Results.—Of the nine cases we have seen, eight recovered. Five were transfused, these being the most severe cases and their response to treatment was remarkable; one of the transfused cases died, but we believe that in this instance the transfusion was delayed until too late. The beneficial effects of transfusion in hæmolytic anæmia may be due, as suggested elsewhere, to the supply of some missing factor and thus bring the hæmolytic into the category of deficiency diseases of the erythron; or it may be that it allows the bone marrow time to recover from the injury, tiding it over the acute part of the attack until such period as it is able to repair the damage by sending forth new cells into the circulation.

By way of contrast to these results we report the following case which, in its inception and response to treatment by blood transfusion, appeared to be a typical case of acute hæmolytic anæmia, but which, three weeks after what had appeared to be a complete recovery, relapsed, and on re-admission to hospital soon showed evidence of acute leukæmia which rapidly proved fatal.

Case 7—J. E., male, aged 4 years, was admitted on September 25th, 1929. Until a month previously he had been perfectly well, but had then become listless and somewhat pale. Ten days before admission he had had a rigor, a temperature of 105° and passed frequent watery dark brown and offensive stools, and afterwards his pallor and weakness had increased.

When admitted to hospital his temperature was 100°, pulse rate 156 and respirations 40 per minute; he was intensely pale, his face being of a café-au-lait colour, and there were a few small glands in the neck, groins and axilla. The spleen was not enlarged and a systolic murmur was audible over the heart apex. His red blood cell count was 1,600,000 per c.mm., and the blood film showed marked variations in size and shape of the erythrocytes but no nucleated red cells, nor was there any obvious increase in the number of leucocytes. On September 28th he was given a transfusion of 40 c.cm. of blood and thereafter showed slight improvement. On September 30th numerous hæmorrhages were present in both retinae, but on October 4th his red blood count was lower than on admission, being 1,400,000 and his platelets 11,800 per c.mm. There was nothing abnormal in the differential white count. On October 6th he was again transfused, this time with 60 c.cm. of blood, and on the following day urobilinogen in excess and urobilin were present in the urine. From this time he improved continuously, and on October 11th the red blood cell count was nearly two millions and the leucocytes 7,600 per c.mm., the hæmoglobin was 29 per cent. On October 24th his colour was quite good, the apical systolic murmur had disappeared, but urobilinogen and urobilin were still present in the urine on the 30th. He was discharged from hospital on November 14th, having apparently made a complete recovery, although he still had a slight anæmia, the red cell count being 4 millions and the hæmoglobin about 70 per cent. In addition to the blood transfusions he had been given two drachms of dried lettuce and a quarter-tube of liver extract daily.

After discharge from hospital he remained well for three days, then he lost his appetite and his weight declined. He was therefore readmitted on December 7th, looking thin and pale. There was no rise of temperature; the abdomen was considerably distended, the superficial veins being very prominent; the liver reached half-way to the umbilicus, and the spleen was just palpable. An examination of the blood count on December 10th showed a hæmoglobin of 64 per cent., red cells just under 4 millions, white cells 7,800, and platelets 350,000 per c.mm., a count very similar to that on his discharge from hospital. A week later he appeared much paler, the liver and spleen had increased in size, the left kidney was enlarged and lymphatic glands were palpable in the neck, axilla and groins; the red cell count had fallen to 2,750,000, and the platelets to 56,000 per c.mm., but the leucocytes had increased to 18,160 per c.mm. of which 82 per cent. were large lymphocytes and 18.1 per cent. lymphoblasts the latter reaching 61 per cent. a week later. It was now obvious that the boy had a lymphatic leukæmia and from this time he went rapidly downhill, hæmorrhages occurred, the left renal tumour increased in size, as did the lymphatic glands, and he died on December 28th. The diagnosis of acute leukæmia was confirmed at autopsy.

Group 2.—Subacute hæmolytic anæmia.

The differentiation of subacute from acute hæmolytic anæmia is based entirely on the more gradual onset of the illness, the clinical history therefore

lacking the dramatic character noted in the acute group. The members of this group show variations in the degree of acuteness of the illness; some closely resemble the acute hæmolytic anæmias, and others show characteristics approaching those found in the third group (von Jaksch's syndrome). The following is an example of a case very similar to an acute hæmolytic anæmia.

Case 8.—A. M., male twin, aged 14 months who, like his twin sister (see Case 5) was admitted to hospital on the same day, showed a hæmolytic anæmia superimposed on a nutritional anæmia which was unmasked when the former was cured. The boy had not been well since an attack of broncho-pneumonia at 5 months. He had never had much colour, but was said to be 'paler than when born.'

On examination he was found to be apyrexial, somewhat poorly developed and pale, but not jaundiced. There was clinical and radiographical evidence of healing rickets, but no enlargement of liver or spleen. The urine contained a slight excess of urobilinogen, but no urobilin nor bilirubin. Examination of the blood showed hæmoglobin 40 per cent., red blood cells 2,018,000, leucocytes 11,900 and platelets 130,000 per c.mm.; colour index 1.0; reticulocytes 6 per cent.; average diameter of red blood cells (halometer) 8.19μ . Polychromasia and anisocytosis were well marked and there was some poikilocytosis and punctate basophilia. Two normoblasts per 100 white blood cells were present. The Arneth index gave a weighted mean of 3.20 and the fragility was normal.

The red cell count but not the hæmoglobin improved, until after one month in hospital the figures were 3,187,000 and 39 respectively, the colour index being 0.6. There was still very definite polychromasia but only a slight degree of poikilocytosis, the anæmia now being of the nutritional type. Up to this point radiostol only had been given with a diet of cows' milk, but from this time onwards 3 grn. of reduced iron were given daily and a mixed dietary started. Improvement was continuous and in 6 weeks the blood was practically normal.

In view of the fact that the child and his twin were both in hospital at the same time with a hæmolytic anæmia, the possibility of lead anæmia was considered, but neither child showed a lead line at the ends of the long bones nor the presence of lead in the urine.

As an example of subacute hæmolytic anæmia showing a picture which approximated to that of the von Jaksch's syndrome the following case may be cited.

Case 9.—D. W., male, aged 11 months, was admitted to hospital with a history of having been well until 3 weeks before admission, during which time he had lost weight.

On examination he was found to show definite signs of rickets, was pale and showed some bruising of the forehead; the liver and spleen were enlarged to 3 in. below the costal margin in the mid-clavicular lines. The urine showed a slight excess of urobilinogen but was free from urobilin and bilirubin. The blood gave an indirect van den Bergh reaction (0.5 units of bilirubin) and the fragility of the corpuscles was normal. Hæmoglobin was 61 per cent., the red blood cells 2,818,000 and leucocytes 10,650 per c.mm.; colour index 1.09, reticulocytes 6.8 per cent. The blood film showed marked polychromasia, anisocytosis, poikilocytosis and megalocytosis; there was a slight degree of stippling. One megaloblast and two to three normoblasts were counted for each 100 white blood cells. The platelets were greatly reduced in number and a differential leucocyte count showed the presence of 2.6 per cent. of myelocytes, metamyelocytes and myeloblasts.

On the third day after admission the child developed chicken pox, and two days later the anæmia was slightly more marked, but by four days later a great improvement had occurred, his red cells having increased by about 1,000,000 per c.mm. and the hæmoglobin by 10 per cent. At this time vitamin D was administered and 3 weeks later the child had made a complete recovery.

Discussion of acute and subacute hæmolytic anæmia.

The variations in symptoms occurring in acute and subacute hæmolytic anæmia are well illustrated by the foregoing cases. It may be thought that the division into acute and subacute groups is both arbitrary and unnecessary. Although it may be admitted that there is no sharp differentiation between the two groups, yet in practice it is quite possible to distinguish some cases which develop more speedily and which show a more dramatic clinical picture than others.

Acute hæmolytic anæmia.—In this group the onset may show symptoms suggestive of an acute intestinal infection; thus in some cases there occurred pyrexia, diarrhœa, vomiting, and in two cases even abdominal pain, due in one to a sudden enlargement of the liver. In others, although the initial symptoms may suggest the occurrence of an acute infection, there is nothing to indicate that this infection is from the intestine. This onset is followed by the development of a severe degree of pallor which may reach its maximum in one or two days, or take as long as two or three weeks. The pallor not infrequently has the curious yellow waxy appearance so characteristic of acute leukæmia, or at other times it is of a café-au-lait tint. Associated with the onset there may be severe respiratory distress manifested by rapid respirations and sometimes air-hunger, both due to anoxæmia from the rapid onset and severe degree of the anæmia. The degree of pyrexia varies. In the most severe cases of the series, the temperature only rose to 99°, but in one case it reached 105°. The majority, however, only showed a mild degree of pyrexia. When these children were first seen it was obvious that they were desperately ill, some indeed being in extremis. In the most severe case (Case 1), intense jaundice and hæmoglobinuria occurred; the others were not obviously jaundiced although some were thought to show a faint icteric tinge, and three showed bilirubinuria. The spleen was palpable in six of the nine cases, although in Case 6 it only became so after a recrudescence of the hæmolysis. The degree of enlargement varied very considerably from a state in which the spleen was only just palpable to one in which the edge reached to a distance of 3 in. or more below the ribs. The liver was only enlarged in three cases: in two of these both liver and spleen were enlarged; in the third there was no splenic enlargement, but the liver was very tender on palpation. Glandular enlargement, and that only to a slight degree, was noted in one case. Bruising or petechiæ were present in three cases, and the urine contained red blood cells in two others. Hæmic murmurs were frequently noted.

At the time when the children first came under observation their blood showed hæmoglobin values varying from under 20 to 50 per cent.; the red cell count from 800,000 to 2,800,000 per c.mm., and the colour index from 0.7 to 1.45. In seven instances the index was unity or above and only in one case, where the index was 0.7, could the condition be regarded as a hypochromic anæmia. The other was over 0.8, a figure which in an

infant under fifteen months is equivalent to an index of unity in children above that age. Signs of an intense marrow reaction were present in the cases which recovered, either at the time of coming under observation or following a blood transfusion; thus reticulocytosis rising in some cases to a high degree, and a marked degree of immaturity of the red cells were present in the film. Anisocytosis, poikilocytosis, polychromasia, punctate basophilia were pronounced, and this is the only form of infantile anæmia in our series in which punctation and Cabot's rings have been seen. Nucleated red cells were present in six, and megaloblasts in three instances. The anæmia has constantly been of the megalocytic type as shown by the high colour index and the presence of megaloblasts and megalocytes in the peripheral blood. We regret that we have no Price-Jones curves of our cases but in all cases the halometer readings, if any value can be attached to them, have shown the presence of megalocytosis. We are aware that megalocytosis has been said by O'Donoghue and Witts not to occur in the acute hæmolytic anæmia of Lederer, but we can only say that in addition to the halometer findings we have found megaloblasts, although not in large numbers, in the peripheral blood in two cases and Lederer himself reported this occurrence in some of his cases. A reference to the Price-Jones curve reproduced in Fig. 2 will show that megalocytosis occurs in the subchronic form of hæmolytic anæmia. The fragility of the red cells was increased in one case only, and gradually returned to normal as the child's condition improved.

The leucocytes varied from 5,100 to 45,000 per c.mm. In the instances where low counts occurred they were in great measure due to diminution in the cells of the marrow series, an indication that these myeloid cells of the marrow as well as the marrow portion of the erythron had been affected. In some cases, in Case 1 in particular, there was a large number of immature cells of the myelocyte series. The platelets varied from 14,000 to 130,000, the lower figures showing that these were also damaged at their origin in the marrow exactly as were the red and granular white cells. In six of the eight cases in which the tests were carried out additional evidence of the occurrence of hæmolysis was found in the presence of an indirect van den Bergh reaction in the blood, or in the presence of an excess of urobilinogen or urobilin in the urine, and sometimes of all of these. We have already pointed out that if the child is not seen until some days after the hæmolysis has occurred it may have had time to deal with and excrete the excess of blood pigments, and in such cases the blood serum does not give a positive indirect van den Bergh reaction nor the urine show an excess of urobilinogen or urobilin.

Of the nine cases, four recovered without transfusion. These, however, were not so extremely ill as the other five, of which four recovered after transfusion. The fatal case (Case 3) was interesting because when first seen there was evidence of damage to all the marrow systems, erythron, myeloid cells and blood platelets, and we think it is probable that transfusion was

delayed until too late. From our further experience we believe that repeated transfusions might have saved this child. Since an autopsy was not allowed this case might be classed as an aplastic anæmia, but, for reasons already given, we believe that it is more correctly regarded as an acute hæmolytic anæmia in which the marrow was so badly damaged that recovery under the treatment given was impossible. It is, of course, possible for the marrow to be so damaged that it will not respond to any form of treatment and the symptoms progress until death occurs. In spite of the fact that the less seriously ill children who show a good reticulocytosis may recover spontaneously, we have no hesitation in saying that immediate, and if necessary repeated, blood transfusions should be given in every case. This may act simply by tiding the patient over the time of inhibition of the bone marrow, or it may have some stimulating effect on the marrow, possibly supplying something in which it is deficient. In whichever way it acts there is no doubt that it is frequently a life-saving measure.

Progress towards recovery naturally varies in different cases. It tends to be rapid at first and considerably slower in the later stages. Slight relapses are not uncommon, and in one instance (Case 6) rather a marked relapse occurred. Nevertheless, considering the great severity of the illness, recovery really takes place with considerable rapidity and, what is even more important, appears to be permanent. In very severe cases the hæmoglobin will reach 60 per cent. or even higher before the colour index falls below unity and the megalocytes disappear. In one severe case (Case 1) the child reached and maintained a normal hæmoglobin for its age (80 per cent.) although the megalocytic process was still present. In two cases (Cases 4 and 5) in our series recovery occurred from the hæmolytic anæmia but a nutritional anæmia either developed or was unmasked, for the cure of which iron was required; and it is interesting to note that one of these children, aged five years, showed a considerable degree of hypochlorhydria. Bearing in mind the usual tendency to iron deficiency at the end of the lactation period it is always advisable to give iron to infants under a year or fifteen months who are suffering from acute hæmolytic anæmia.

ÆTIOLOGY.—Speculation on the ætiology of acute hæmolytic anæmia is interesting, but of certain knowledge as to its cause there is none. The picture suggests that the illness is the result of some infection, but like all other writers on this subject we have been unable to discover the infecting agent. It is possible that the same picture can be produced by more than one ætiological factor. In one of our series a recurrence of hæmolysis occurred coincidentally with the development of an attack of pyelitis (*B. coli*) and recovery began directly the pyelitis was cured, but whether the two incidents were related it is impossible to say.

The age incidence of our cases has been from seven months to five years: six of them being under two years old. The latest paper on the acute hæmolytic anæmia of Lederer with which we are familiar is that by O'Donoghue and Witts⁴ who dismiss from consideration 'cases under the

age of two years and also cases in pregnancy as the reactions of the blood-forming organs at these times are poorly understood and often extreme.' This sacrifice they say is made 'in the interests of clarity, as there is much to suggest that the acute hæmolytic anæmia of Lederer does occur in the infant and the pregnant woman.' We fail to see how the subject is clarified by the exclusion of infants and it may be accepted without question that this form of anæmia does occur under two years, if for no other reason than that two of Lederer's own cases were actually under that age.

The difficulties in separating acute hæmolytic anæmia from leukæmia are well illustrated in our series. On the one hand, in Case 1 the immature cells of the granular series reached 30 per cent. of a white cell count of 26,000, which suggests the possibility that some cases which have been recorded as recoveries from acute leukæmia were examples of acute hæmolytic anæmia. On the other hand, Case 7 appeared to be a typical acute hæmolytic anæmia with recovery, but three weeks after his supposed recovery was found to be suffering from acute lymphatic leukæmia. A further difficulty in diagnosis is illustrated by Case 3 of our series, which appeared to be an example of an acute destructive disorder of the erythron, and myeloid and platelet systems, without marrow response. Yet at autopsy there was found a non-leukæmic reticulo-endotheliosis. In our opinion, a diagnosis of acute hæmolytic anæmia should always be viewed with suspicion unless the patient recovers or the diagnosis is confirmed by autopsy.

Subacute hæmolytic anæmia.—We have seen four cases which we should classify under this heading. Three of these were admitted to hospital. Of these four children, two were members of two pairs of twins; in one instance the other twin had an acute hæmolytic anæmia, and in the other the corresponding twin had a nutritional anæmia.

The differences in the onset and the clinical picture between this and the acute group have been mentioned. Only one of these children had pyrexia and this child also had rapid respirations; all the children were pale, one showing the café-au-lait complexion. The spleen was palpably enlarged in two cases, in one to a considerable degree, and in this child the liver also showed definite enlargement. Urobilinogen in excess was present in the urine in two and an indirect van den Bergh in one case. The fragility of the red cells was normal. The colour index varied from 1.0 to 1.14. In each case the red cells showed a considerable degree of anisocytosis and polychromasia; to a lesser degree poikilocytosis was present in three cases, as also were nucleated red cells. Reticulocytosis was present in the three patients admitted to hospital and in one a considerable degree of megalocytosis. The red cell counts varied from 1,409,000 to 2,818,000, the white cells count from 9,000 to 11,000 per c.mm. All the cases made a good recovery without transfusion, but the remarks made under acute hæmolytic anæmia on the advantage of giving iron and the value of blood transfusions, if the anæmia be severe and without evidence of reticulocytosis, apply to subacute hæmolytic anæmia.

It may be noted that one of the children in this group had suffered from whooping cough before coming into hospital and developed pneumonia during its convalescence. Another was incubating chicken pox, and it could be objected that herein lay the cause of its anæmia. This is a possibility, but against such an explanation are the facts that the syndrome produced was similar to the other cases and, further, that there is no evidence as yet forthcoming specifically to connect chicken pox with a hæmolytic anæmia.

Group 3.—von Jaksch's syndrome (subchronic hæmolytic anæmia).

During recent years much controversy has centred round the syndrome known as von Jaksch's anæmia, splenic anæmia of infants, or anæmia pseudo-leukæmica infantum. This condition, which is insidious in onset, is confined to the first three years of life, and the majority of the patients are under two years of age. Some writers assert that it is a disease *sui generis*, which others as stoutly deny. Many agree with the view of Naegeli that it is a special form of biological response on the part of the blood to any injury—infectious, toxic, alimentary, etc.—a response which can only occur during the first months of life.

There is a lack of clear definition as to what is, and what is not, included in the term von Jaksch's anæmia. For example, American writers seem to have a somewhat different conception of this syndrome from British writers, and regard it as an 'anæmia with splenomegaly, leucocytosis, and a moderate number of immature leucocytes and erythrocytes in the blood,' manifestations which, as pointed out by Blackfan, Baty, and Diamond⁵, may be produced by a number of known morbid processes. Amongst British pædiatricians it is customary to regard the following clinical picture as that of von Jaksch's anæmia. The child, usually well nourished, shows marked pallor of rather waxy type. Œdema of the ankles may be present and not infrequently petechiæ on the limbs and trunk. The liver and spleen are enlarged; the latter may reach even to the iliac crest and to the right of the umbilicus. As a result the abdomen is markedly enlarged and large veins may be seen on its surface. The lymph glands are as a rule not palpable. In many instances clinical signs of rickets are obvious, and both rickets and syphilis have without any real evidence been regarded as causative factors. The prognosis is good, and recovery, when it occurs, is complete.

The blood changes which are usually accepted as characteristic are well summarized in the following quotation (Thursfield⁶):—

The red cells are diminished to 2,500,000 per c.mm. or less. There is always poikilocytosis, and polychromatophilia and nucleated cells are common. The hæmoglobin shows a decrease to 40 per cent. or less, sometimes as little as 12 per cent. The colour index is from 0.5 to 0.7. At some time during the illness there is a leucocytosis, never very great, rarely reaching 30,000 per c.mm., and at other times the number may be less than normal. A moderate increase is, however, more usual than a leucopenia. The feature of the blood film is the constant presence of myelocytes in numbers greater than those found in any other condition except leukæmia, though never in the ratio common in that disease. An average percentage

of these cells is from 2 to 6 per cent. Nucleated erythrocytes are always present, sometimes in large numbers. The blood platelets are present in normal number and the fragility of the red corpuscles is not increased.

Undoubtedly cases answering to this description are seen from time to time although they are much less frequent than twenty years ago, a fact for which no satisfactory explanation is forthcoming. The syndrome is indeed now a rarity, and during the last three years we have seen only four cases which we would unhesitatingly accept as falling in this category.

It is interesting that the foregoing description differs considerably from that given by von Jaksch himself in his original paper⁷ published in the year 1889. The anæmia, he said, occurred not very infrequently and was associated with 'great swelling of the spleen, of the liver, of the glands and a persistent very remarkable leucocytosis (proportion of white cells to red 1:20, 1:17, 1:12), nevertheless the examination of the sections shows no leukæmia.' The differential diagnosis from leukæmia he described as follows:—'Blood findings, gland swelling, enlargement of the spleen are present in both affections. In leukæmia the liver and spleen increase equally in proportion to their original volumes, in the affection described by me as anæmia infantum pseudoleukæmica there is certainly a disproportion between the liver and spleen, in the sense that the volume of the liver is relatively less increased when compared with that of the spleen; further the liver is not, as in leukæmia, palpable as a plump tumour with thick plump edges, yet nevertheless an increase in volume is definitely indicated by (the position of) its lower sharp border.' He regarded the prognosis as better than leukæmia: 'at least I have observed an undoubted case which recovered.' In the following year he reported⁸ two further cases; one, a girl aged eleven months who died and at the autopsy no evidence of leukæmia was found in the liver, spleen, kidneys or heart; the other, a child aged nineteen months, whose red cell count when first seen was 1,380,000 and leucocyte count 114,500 per c.mm. and who made a complete recovery. In this paper he stated that this anæmia differed from leukæmia in the almost complete absence of eosinophil cells.

It seems possible that he actually excluded cases which many would now regard as von Jaksch's anæmia. In his view anæmia pseudoleukæmica infantum could be distinguished from the anæmia accompanying severe rickets by the slight leucocytosis and non-progressive character of this change in rickets; whereas now not a few authorities regard the presence of rickets as an important point in the diagnosis of von Jaksch's anæmia. In our opinion rickets is not characteristic of the von Jaksch syndrome, although of course both conditions may be combined in the same child; the occurrence of a nutritional anæmia is, however, quite possible in rickets, because a diet defective in one dietetic factor is likely to be defective in others.

In neither of these two papers did von Jaksch mention the occurrence of nucleated red cells, or lay stress on the presence of the marrow series of white cells. The credit for the first description of the appearance of

nucleated red cells in the circulating blood in this syndrome is usually ascribed to Hayem. This is probably erroneous because, although Hayem drew attention to this occurrence in the blood of a child suffering from anæmia, he regarded the anæmia as due to leukæmia. Under the heading of 'leukæmia of the new born' he described⁹ the case of a child aged ten months who had nucleated red blood cells in her blood and of whom he says that the alteration in the blood and the hypertrophy of the liver and spleen make it difficult to doubt that the case was otherwise than one of leukæmia, but that since he was unable to follow up the case, details of the after-history could not be given. He goes on to say that leukæmia in the new born has peculiar characters, the white count being about 30,000, but the blood has the unique characteristic that it contains numerous nucleated red cells. This case may have been an example of the syndrome which von Jaksch had in mind, but Hayem certainly did not recognize it as such, nor did he appear to be aware of von Jaksch's paper. Nevertheless, it is only fair to say that Hayem's observations were published in the same year as the original paper by von Jaksch, and it may have been that Hayem's work was published earlier in the year than that of von Jaksch.

Far the best account of this syndrome given in these early days was that published in 1891 by Luzet¹⁰, a pupil of Hayem. His description tallies very closely with the clinical picture we have described, and if the name of anyone is attached to this syndrome it should in all justice be that of Luzet. According to Luzet there is a form of anæmia which is akin to, if not identical with, leukæmia, to which the name of anæmia pseudoleukæmica infantum has been given, and in which there are splenomegaly, moderate leucocytosis, and large numbers of nucleated cells, many of which show mitosis, in the circulating blood. It is obvious that he also recognized the presence in the blood of immature cells of the marrow series, and he pointed out that in children suffering from this condition the hæmatopoiesis took on a foetal character. Further, he stated that cure might occur, or the leucocytosis increase and the condition change into a leukæmia. He also described intermediate forms between this anæmia and true leukæmia the existence of which he regarded as evidence in favour of the identity of the two diseases.

Cooley¹¹ who has made a special study of this anæmia states that one of the best descriptions of it is given by Eppinger who emphasized its gravity and chronicity, the remarkable degree of splenomegaly, the moderate degree of enlargement of the liver, the appearance in the blood of numerous normoblasts and megaloblasts, the occurrence of a moderate leucocytosis and the frequent occurrence of cells of the marrow series. Eppinger regarded the disease as chronic, progressive and often fatal, and made no mention of any tendency to recovery. He apparently held the view that it was a secondary hæmolytic anæmia.

One striking point of difference in the various descriptions of the disease relates to prognosis. Some writers regard the prognosis as good, others as bad. Again some writers describe a hyperchromic, others a hypochromic anæmia.

An instance of the confusion which may be caused by the use of the term von Jaksch's anæmia is found in a recent paper by Åkerrén¹² on primary anæmic states in early infancy. One of his cases which was clearly an example of the hæmolytic anæmia following icterus gravis (erythroblastosis of the new born), is described as showing a pronounced Jaksch-Hayem's complex of symptoms; and in the paper on hæmolytic anæmia of the neonatal period there is described a case which, had it been seen in later infancy, would certainly have been accepted as an example of von Jaksch's anæmia.

Again, although the syndrome has been called anæmia infantum pseudo-leukæmica we have had the experience so clearly described by Luzet of seeing a case which originally presented the signs and symptoms of this syndrome, eventually develop into an acute leukæmia. In our opinion such cases are in all probability leukæmic from the beginning, although it is possible that they are examples of leukæmia engrafted on the anæmia in much the same way as a malignant growth may arise from a focus of chronic irritation.

It is obvious, therefore, that many additions have been made to the original description so that a clinical picture such as we have given has not a great deal in common with that drawn by von Jaksch, and thus the syndrome has come to include rather a heterogeneous and motley collection of anæmias. Cooley has rendered great service by pointing out that amongst the various forms of anæmias, many of which he regards as 'secondary anæmias,' reported as von Jaksch's anæmia there is a special group to which he has applied the name of erythroblastic anæmia of childhood.

Erythroblastæmia of childhood (Cooley).—Other writers have suggested that this form of anæmia should be called Cooley's anæmia, family hæmolytic anæmia (Wollstein and Kreidel¹³), thalassæmia or mediterranean anæmia (Whipple and Bradford¹⁴). The characteristics of this group are worth considering since cases have not been observed in this country although we venture to think that the condition would not have been regarded by British writers as von Jaksch's anæmia. These are:—an anæmia with familial and racial tendencies and limited almost entirely to children of Syrian, Italian and Greek stock, which begins in infancy and runs a chronic and progressive course to a fatal termination. Splenomegaly is very marked and there is some degree of icteric discoloration of the skin. There may be progressive enlargement of the malar and cranial bones due to marrow hyperplasia which gives both characteristic radiographs and also a somewhat mongolian facial appearance. The red cells showed marked variation in size but less in shape, nucleated red cells are likely to be seen in unusual numbers, and megaloblasts are common. The anæmia varies from a moderate to a severe degree, and the colour index is usually low. Polychromasia and reticulocytosis are marked. Leucocytosis to about 20,000 cells per c.mm. is usually present; lymphocytes are likely to predominate, and myelocytes and other immature cells of the marrow series are usually seen. Platelets show no characteristic change. Fragility of the red cells is normal, and there is

evidence of increased hæmolysis in a high icteric index and a positive indirect van den Bergh reaction. Following splenectomy a marked and sustained increase in nucleated red cells occurs. Urobilinogen and urobilin may be present in excess in the urine.

This form of anæmia was originally regarded by Cooley as being hæmolytic in nature and displaying a congenital diathesis allied to that seen in congenital hæmolytic jaundice and sickle-cell anæmia. In his latest article¹⁵, however, he states that although hæmolysis is a constant and important feature he no longer regards the disease as primarily hæmolytic in origin in the same sense as congenital hæmolytic icterus; rather he believes that the apparent relationship is greater to pernicious anæmia and sickle-cell anæmia, and that it is probable that the urge to put forth quantities of immature cells and the resultant hyperplasia of erythropoietic tissue is the result of a metabolic process which compels these tissues to make 'bricks without straw.' If this thesis be correct Cooley's anæmia might also be classified under the deficiency anæmias. The occurrence of a form of erythroblastic anæmia in adult coeliac disease as described by Bennett, Hunter and Vaughan¹⁶ is of interest in this connection, because it would appear to furnish evidence in favour of Cooley's latest thesis. The erythroblastic anæmia of coeliac disease, however, differs from Cooley's anæmia in that these authors were able to report a cure in one instance.

Discussion of von Jaksch syndrome (subchronic hæmolytic anæmia).

In our opinion it is advisable altogether to drop the use of the name of von Jaksch in describing this anæmia for the following reasons:—

(1) He did not describe any clear cut or characteristic entity; nevertheless it is only fair to say that when the clinical features described by Luzet are added to his meagre description a picture results which is similar to that regarded in this country as von Jaksch's anæmia.

(2) Other writers, in recording what they thought von Jaksch described, have unconsciously added details to the syndrome with the result that more than one form of anæmia has been included under this head.

(3) The syndrome accepted by British workers as von Jaksch's anæmia shows many features undescribed by him, and in our opinion really represents a hæmolytic anæmia of a rather more chronic form than the group of subacute hæmolytic anæmias which has been considered above.

Evidence of hæmolytic nature.—The following case may be cited as evidence of our thesis that this syndrome is in reality a subacute hæmolytic anæmia.

Case 10.—A. G., male, aged 9 months; breast fed for 2 weeks and after that given a cows' milk mixture; was said to have been pale since he was 2 months old. On examination he was found to be a pale but not badly nourished child; there was some bruising on the head and legs; the abdomen was enlarged; the spleen showed marked enlargement reaching below the umbilicus, and the liver was palpable for 3 inches below the costal margin. The Wassermann reaction was negative, in child and mother. Radiographs of the skull and long bones did not

show any suggestion of the changes described by Cooley, nor any evidence of rickets. The child was given iron and yestamin, and was under observation for a period of two months. During this time a series of blood counts showed the changes consistent with those usually accepted as the von Jaksch syndrome.

Date	14.9.32.	16.9.32.	5.10.32.	10.10.32.	18.10.32.	28.10.32.	7.11.32.
Red cells, per c.mm. ...	1,618,000	2,009,000	2,409,000	3,244,000	4,370,000	4,962,000	5,490,000
Hæmoglobin, p.c. ...	30	50	57	68	86	96	80
Colour index ...	1.0	1.25	1.19	1.06	1.0	0.96	0.73
Reticulocytes, p.c. ...	4.6	6	17.2	14	5	1.7	
Platelets, per c.mm.	157,000	14,000	53,000				163,000
Leucocytes, ,,	6,000	12,000	22,000	15,400	15,000	29,400	
Myeloblasts, p.c. ...	0.3	0.5	0.3				
Myelocytes, ,,		1	1.6	1			
Neut. metamyeloc., p.c.	0.3		3.6	2	1.5		
,, polymorph. ,,	35.0	35.0	27.6	35.6	60.5	53.6	
Eosinophil ,,	1.3	3.5	1	3	1	0.3	
Lymphocytes, p.c. ...	54.3	46.5	60.3	50.6	23.5	30.3	
Monocytes, ,,	8.0	10.5	5	7	12	13.3	
Plasma & Türk cells, ,,					0.5	1.3	
Mast cells, p.c. ...		3.0	0.6	0.6	1	1	
Normoblasts,							
p.c. leucocytes	5.6	8.5	50	10	0		
Megaloblasts,							
p.c. leucocytes	1	1.5	9	1.6	0.5		

The red cells varied from 1,600,000 to just over 5 millions; the white cells from 6,000 to 29,000, the platelets from 14,000 to 163,000 per c.mm. The hæmoglobin varied from 30 to 96 per cent., and the colour index from 1.25 to 0.73. Normoblasts and megaloblasts were conspicuous features in the film during the first month in hospital and at one time reached 11,000 and 1,980 per c.mm. respectively. At this stage reticulocytes, which were always a feature during the first month in hospital, reached the high point of 17.2 per cent. Polychromasia, anisocytosis, punctate basophilia, and to a lesser degree poikilocytosis, were marked during this period, and megalocytosis was present. At the same time cells of the myelocyte type (myelocyte, metamyelocytes, myeloblasts) were evident and formed 5.5 per cent. of the white cells at the time when the erythroblastæmia was most marked. On admission to hospital urobilinogen was present in excess in the urine, the clotting and bleeding times were normal, but there was a slight increase in the fragility of the red cells. On discharge from hospital the fragility had become normal.

It seems to us that the hyperchromic anæmia, the presence of a high reticulocytosis, of megaloblasts, of anisocytosis, polychromasia, poikilocytosis and punctate basophilia, of megalocytosis and finally the occurrence of an increased amount of urobilinogen in the urine, are changes which, although quite different from those found in the deficiency nutritional diseases of infancy, are typical of a hæmolytic anæmia with a marrow response. The clinical signs were also those accepted as typical of the von Jaksch syndrome. We admit that, since this child had been given iron, it could be argued that the reticulocytosis was the result of that drug and that therefore the condition was a nutritional anæmia. On the other hand the coincidental hæmatological and urinary changes are strong evidence of

the occurrence of hæmolysis, but of even greater importance is the fact that reticulocytosis to the extent of 6 per cent. was present before iron was exhibited, and such reticulocytosis could not possibly have occurred if a shortage of iron were present. The similarity of the blood picture, particularly in some of the subacute hæmolytic anæmias, both to Thursfield's description of the blood changes quoted above, and to that in this case is, we submit, striking evidence in support of our conception that the syndrome is a chronic or subchronic hæmolytic anæmia.

We have recently had under observation an infant of eleven months who developed the clinical and hæmatological pictures accepted as typical of the von Jaksch's syndrome whilst in hospital, and in whom evidence that hæmolysis had occurred was obtained by another method.

Case 11.—A. A., was 11 months old when admitted to hospital on December 8th, 1932. She was small but well nourished and occasional petechiæ were seen. A few lymph glands were palpable; the liver was slightly, if at all, enlarged, and the spleen was just palpable. The red cells numbered 2,100,000 and the white cells 7,800 per c.mm. The hæmoglobin was 42 per cent., the colour index unity, and only one reticulocyte was seen. The Price-Jones curve was normal (Fig. 1). Shortly after admission to hospital the abdomen became protuberant and the spleen enlarged until it reached to the iliac crest and almost to the middle line. The blood, as the accompanying lists show, had the cellular characteristics of anæmia pseudo-leukæmica infantum. The Price-Jones curve moved to the right towards the macrocytic zone (Fig. 2), and a definite megalocytosis developed.

Date	18.12.32.	23.2.33.	20.3.33.	13.4.33.
Red cells, per c.mm.	2,170,000	3,220,000	4,200,000	4,340,000
Hæmoglobin, p.c.	46	64	92	94
Colour index	1.09	1.0	1.1	1.08
Reticulocytes, p.c.	13.3	6.2	2.3	2.6
Platelets	scanty	25,000	150,000	450,000
Leucocytes, per c.mm.	15,450	14,700	11,600	10,600
Myeloblasts, p.c.		0.5		
Myelocytes, p.c.	1	0.5		
Neut. metamyeloc., immature, p.c.	1.5	1.5		
" " mature, "	1.5	0.5	1.5	
" polymorph, p.c.	34	33	20	29
Eosinophil polymorph., p.c.	0.5	2	1	
Basophil polymorph., "		0.5	0.5	
Lymphoblasts, p.c.		0.5	2.5	
Lymphocytes, large, p.c.	30	50	53	51
" small, "	21.5	8	13.5	7
Monocytes, p.c.	7.5	4.5	0.5	12
Plasma and Türeck cells, p.c.	2.5		1	1
Normoblasts, p.c. leucocytes	3	3	1	1
Macronormoblasts, p.c. leucocytes	4	12	3	
Megaloblasts, " "	0.5	9	1.5	
Anisocytosis	+++	++++	+++	++
Poikilocytosis		++	+	
Polychromasia	+++	++	+	
Punctate basophilia	+++

FIG. 1.—Case 11: Price-Jones curve, Dec. 11th, 1932, showing normal characters ; for comparison with Fig. 2.

FIG. 2.—(Case 11 : Price-Jones curve, Feb. 8th, 1933, for comparison with Fig. 1 ; showing shift to right ; anisocytosis and some megalocytosis have developed.

FIG. 3.—Drawings of blood cells.

No. 16 and 26-42 from Case 11 ; von Jaksch anaemia. No. 1-15 and 17-25 from Case 6, Part IV ; anaemia of late neonatal period developing into picture of von Jaksch anaemia.

1. Eosinophil leucocyte with a few basophil granules.	21. Histiocyte type of cell: hæmo-histioblast of Ferrata.
2-12. Erythrocytes showing aniso- and poikilocytosis, polychromasia and megakaryocytes : (2, a reticulocyte).	22. Megaloblast.
13. Myelocyte.	23. ? Histiocyte, somewhat similar to cell 21.
14. Plasma cell.	24. Normal lymphocyte.
15. Immature lymphocyte: nuclear oxy- and basi-chromatin, rather fine.	25. ? Lymphoblast: heavier nuclear membrane and nuclear structure which, though fine, is coarser than cells 6 and 7; cytoplasm translucent.
16. Megaloblast: cytoplasm more grey and opaque than in cell 3.	26 and 27. Megaloblasts.
17. Megaloblast.	28. Lymphocyte with immature nuclear structure.
18. Myeloblast.	29. Normoblast.
19. ? Myeloblast: nuclear texture very fine, but no nucleoli; delicacy of nuclear structure unlike that of lymphatic cell.	30. Megaloblast.
20. Normoblast.	31. Türk cell.
	32-42. Erythrocytes showing changes similar to cells 2-12; (cell 34, a reticulocyte).

Iron in the form of ferrous sulphate was administered during the first two months of this child's stay in hospital, but in spite of the fact that a very definite reticulocytosis occurred, little if any improvement in the anæmia followed, showing that although many new red cells were being formed they were being destroyed quite as rapidly, i.e., that a hæmolytic process was keeping up the anæmia. The reticulocytosis was certainly not due to the administration of iron for the following reasons:—(1) reticulocytosis did not occur until seven days after iron was started; (2) a 'reticulocytic kick' which is so characteristic of successful iron therapy, did not occur, i.e., a reticulocyte response appearing up to four days after administration of iron and gradually fading away a few days later; (3) reticulocytosis continued after the administration of iron had been stopped for fourteen days. An interesting event in this case is that when iron administration was stopped improvement commenced, and in spite of the subsequent development of an attack of measles, complete recovery occurred after the child had been five months in hospital.

Further evidence in favour of our view of the origin of von Jaksch syndrome is that in two other ways it shows similarity to the acute and subacute hæmolytic anæmias. First, as has already been mentioned, the syndrome sometimes ends as an acute leukæmia, and we have already described an example (Case 7) of exactly the same sequence in acute hæmolytic anæmia. Secondly, we have observed in the same child at two different periods the von Jaksch syndrome and a nutritional anæmia, exactly as in some children with acute or subacute hæmolytic anæmia, nutritional anæmia has occurred during the period of recovery.

Ætiology and treatment.—We are quite in the dark as to the cause of this form of anæmia; it is said to be more common in twins and is undoubtedly often associated with rickets. It is not due to rickets because it occurs in its absence, and there is no characteristic response to treatment with vitamin D. Syphilis has also been suggested as a factor, but the same remarks apply to it as to rickets.

In view of our ignorance of ætiological factors treatment has to be on general lines. Any dietetic or hygienic errors should be corrected and in severe cases blood transfusion may be helpful. Coincidental disease such as rickets, syphilis, or nutritional anæmia, should of course receive appropriate treatment. Splenectomy has been recommended and practised in this country by Ashby and Southam¹⁷ as a method of affording a more rapid cure. In view of the fact that the eventual prognosis is good, such drastic treatment appears too high a price to pay for a possible shortening of the illness.

Prognosis.—The prognosis of this form of anæmia is good. Recovery nearly always takes place, although the illness may be lengthy. Death from intercurrent disease is, of course, always a possibility. It is also possible that the marrow portion of the erythron may ultimately cease to regenerate, either from fatigue or from the effect of the factor which is producing hæmolysis: in other words, an aplastic anæmia may develop and death result. We have not encountered this sequence of events, but in view of what may happen in other forms of erythronoclastic anæmia we believe that the possibility should be borne in mind,

Group 4.—Other forms of hæmolytic anæmia.

There are two other forms of hæmolytic anæmia which may be encountered in infancy and childhood:—(a) sickle-cell anæmia, and (b) that disease which is described under the various titles of congenital or acquired hæmolytic jaundice, acholuric family jaundice and congenital family cholæmia. Both these forms of anæmia are regarded by Boycott as congenital malformations of the erythron. Sickle-cell anæmia which is almost entirely confined to the negro races has never been recorded in England.

We do not propose to enter here on any detailed discussion of acholuric family jaundice and would only refer to two or three points concerning the disease. It appears to us that apart from the familial and hereditary nature of the disease there is a sort of gradation from the acute hæmolytic anæmias,

FIG. 4.—Price-Jones curve in acholuric jaundice, showing microcytosis and anisocytosis.

through the subacute and subchronic forms, to this, the most chronic of the hæmolytic anæmias. It differs from the other forms of hæmolytic anæmias in that whilst anisocytosis, macrocytosis and microcytosis are characteristic of them, anisocytosis with microcytosis is characteristic of acholuric jaundice, as is shown in the Price-Jones curve of one of our cases reproduced here (Fig. 4). This feature of acholuric jaundice was stressed by Gännslen, but it is worthy of note that a few macrocytes are sometimes present. Even more important than the microcytosis is the fact that the cells are more globular than normal and therefore when the volume of packed cells is estimated in the hæmatocrit they show a higher volume index than normal.

Another difference from the other forms of hæmolytic anæmia is that whilst the fragility of the red cells is usually normal in them, fragility in acholuric jaundice is usually increased, although both these statements are subject to exception. For instance, we have recorded above one case (Case 1) of acute hæmolytic anæmia in which the fragility was increased, and we have met one case of acholuric jaundice in which fragility was normal. The occurrence of normal fragility in acholuric jaundice was pointed out by Dawson¹⁸, and our colleague A. P. Thomson informs us that he has observed the fragility in such a case increase after splenectomy. It is important to recognize that in acholuric jaundice there are always some cells that are more resistant to saline solutions, although there are many that are less resistant, the really important observation being, as pointed out by Hillier¹⁹, that in this disorder the range of fragility is increased.

Probably the reason why jaundice is so much more conspicuous in acholuric jaundice than in other forms of hæmolytic anæmia, is because in it there is not only a more constant but also a greater destruction of red cells. This is due to the fact that here the marrow is always active and turning out more cells than normal; whereas in, for instance, the acute hæmolytic anæmias, the marrow may be completely paralysed during the period of hæmolysis.

Summary.

In a review of the hæmolytic (erythronoclastic) anæmias of later infancy and childhood nine cases of acute hæmolytic anæmia of Lederer, and four cases of subacute hæmolytic anæmia have been discussed, and emphasis has been laid on the necessity of regarding these syndromes as a destructive disease of the erythron and not of the red blood cells alone.

It has also been stressed that the same disease may affect not only the erythron but also the myeloid and platelet systems.

The co-existence of nutritional, with acute or subacute hæmolytic anæmia in the same individual, has also been described.

Finally, it is recommended that the title 'von Jaksch's anæmia' should be discarded and the thesis has been brought forward that the syndrome which has been regarded in Britain as an anæmia of this type is really a rather chronic form of hæmolytic anæmia.

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