ANÆMIA AND LIVER THERAPY IN INFANCY AND CHILDHOOD

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In recent years, considerable attention has been directed to the effects of liver therapy in the anæmias of adults, but the application of this in infancy and childhood does not appear to have received the attention it deserves; and while it is the object of this paper to give a general review of the anæmias occurring in early life, haemolytic anæmias, in which liver therapy has been successful, are discussed in greater detail.

In discussing the measures essential in a given case, it is necessary to have a clear conception of the types of anæmia met with in infancy and childhood, and of the manner in which the reaction of the patient to the pathological process may affect the blood picture.

It is well recognized that in infants trivial causes may affect the temperature to a considerable extent, whereas in the adult the variation would not be noticed. This juvenile reaction is true of almost every system, but it may not be out of place to stress its importance in relation to the haemopoietic system,—a slight infection, for example, may cause a degree of anæmia which would be alarming if met with in an adult. Whilst, in the main, the causes of anæmia are essentially the same in infants and adults, the violence of the reaction in children may cause a grave anæmia; whereas in adults the fall in haemoglobin may be so slight that it is a matter of only minor importance. In premature infants, this reaction is especially marked.

In this paper, the following arrangement has been adopted:

In Part 1, haemolytic anæmias are discussed in some detail, under the following headings:

(a) True pernicious anæmia,
(b) Acholuric jaundice,
(c) Haemolytic anæmias obviously of infective origin,
(d) Congenital, or occurring in the early months of life.

In Part 2, a somewhat brief account is given of non-haemolytic anæmias:

(a) Anæmia due to haemorrhage,
(b) Chlorotic anæmias,
(c) Grave secondary (aplastic) anæmias,
(d) Splenic anæmia,
(e) Anæmias associated with metabolic disturbances,
(f) Anæmias of infective origin,
(g) Anæmia associated with Hodgkin's disease, leukaemia, chloroma, and glandular fever,
(h) Anæmia associated with malignant disease.
Normal variations of the blood in infancy and childhood.

For purposes of comparison with anæmic states it is useful to review the normal variations of the blood picture as found in infancy and childhood. Considerable differences have been found by various workers, some of whom, however, have based their averages on comparatively few cases. A further difficulty is encountered in deciding what is to be regarded as a normal child. In discussing her findings in infancy, Helen Mackay\(^1\) arrived at the conclusion that the majority of babies are anæmic, on the ground that the value of the haemoglobin can be raised by the administration of iron. Her observations were chiefly on babies in London clinics. She remarks that 'no evidence concerning other areas of the British Isles is given, the appearance of London infants compared with those in other parts of Britain would not suggest that London is peculiar in its anæmic babies.' As the remarks in this part of the paper are introduced for comparison with states showing a considerable degree of anæmia, it appears to us that the normal should be regarded as that found in the average infant, apart from drug treatment; and these figures are given, though for purposes of further comparison the figures given by the above writer as those obtainable after the administration of iron, are also inserted.

\textbf{Haemoglobin.}—All authorities are agreed that at birth the value of the haemoglobin is high, the average being about 110 per cent. After birth this falls, reaching a value of about 70 per cent. in the third week. In some cases there may be a slight fall after this to the seventh or eighth week, after which the value remains steady until the second year (see Fig. 1). Then there appears to be a slight rise, the value at the sixth year being 75 to 80 per cent., after which it rises to the adult value. According to Helen Mackay, the values...
in artificially fed babies are about 5 per cent. lower than in those breast-fed.

The following figures are taken from her paper.

Fig. 2 shows the average in breast-fed and artificially fed babies not treated with iron; Fig. 3 contrasts this with the values obtained with the administration of iron.

Fig. 2. Hemoglobin values in breast-fed and artificially-fed infants.

Fig. 3. Hemoglobin values in infants with the administration of iron.
Red cells.—Fig. 4 (after Lippmann) shows the changes in the red cell count during the first two days of life. According to most observers blood taken from the umbilical cord at birth gives rather higher values than those given by Lippmann for the new born. Allumbaugh, for example, gives 5·52 millions as the average in 50 babies: Lucas gives 5·51 as the average in 36 cases and these figures are in remarkably close agreement with our own findings. From the second week onwards till the sixth year, the count appears to remain at about 5,000,000, that for both sexes being about the same (Fig. 1). During the first few days a few nucleated cells are found: some cells are irregular in shape and the variations in size are rather greater than those found in later life. Engelsen states that the size of the cells in the new born is greater than in later life. We have found considerable variations, the mean diameter ranging from 7·3\mum to 7·9\mum at birth, the average being 7·6\mum (normal adult value 7·23\mum).

According to de Vicaris the resistance of the red cells to hypotonic salines is increased at birth, but Lippmann records the opposite finding. In a large series investigated by one of us, the resistance of the cells was invariably found to be decreased.

White cells.—At birth the total white count averages just over 16,000, but there is a considerable variation in different individuals. Fig. 5 (after Lippmann) shows the course of the total white count, and the values of the polymorphonuclears and lymphocytes during the first five days; and Fig. 6 (after Carstanjen) gives similar values up to the 6th year, after which the values are those found in adults. It will be noticed that there is a fairly sharp rise in the total white count during the first twelve hours after birth: this is due entirely to an increase in the polymorphonuclear count. This rise is followed by a
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Fig. 5. Changes in white-cell count in first week of life (after Lippmann).

Fig. 6. Number of polymorphonuclears and lymphocytes in early childhood (after Carstanjen).
fall which continues throughout the first week of life—again due to an alteration in the polymorphonuclear count: indeed, at the end of the first week, the number of lymphocytes shows a slight rise. After the first week, the number of polymorphonuclear cells remains fairly steady at about 5,000, while the lymphocytes increase to a maximum at about the sixth month. During the first three years of life, with the exception of the first week, the number of lymphocytes is greater than that of the polymorphonuclears; after the age of three, the number of lymphocytes continues to fall up to the age of six when adult values are obtained. This tendency to a lymphocytosis is important and it will be shown later in this paper that even in children over the age of three, stimuli which tend to produce a high white count often give rise to a relative lymphocytosis. The variations in the eosinophils and monocytes (hyalines) do not appear to be of importance. Basophils are present in small numbers during the early days of life, but by the fifth day are only occasionally observed.

**Platelets.**—The variations in the platelet count during the first 48 hours are shown in Fig. 4. After this time the values are approximately those found in adults.

Individual variations are least in the red cell counts, and greatest in the platelet counts. This will be seen from the coefficients of variability calculated by Lippmann from 71 infants, the variations being:—red cells 11 per cent., total white cells 25 per cent. (polymorphonuclears 35 per cent., lymphocytes 46 per cent.), platelets 48 per cent.

1. **Hæmolytic Anæmias.**

Since the introduction of recent biochemical tests, it has been possible to separate the anæmias of adults into two classes, viz., those in which there is excessive hæmolysis, and those in which this is not present. This same procedure can be applied to the anæmias of children, and it is necessary to discuss briefly the main features common to hæmolytic anæmias.

In hæmolytic anæmias there is an increase of bile pigment in the blood plasma which stains the skin and the scleroties a lemon yellow colour. This pigmentation must not be confused with the creamy yellow tint which is often so striking, particularly in the cheeks, the ears and the extremities of children suffering from anæmia of non-hæmolytic origin. Though the spleen is enlarged in the majority of children with anæmia, it is more constant and more striking in the hæmolytic group. In the case of the liver, enlargement is much more likely to occur in the presence of hæmolysis. In contrast to icterus of obstructive origin, the stools of these cases are of normal colour. The urine is usually dark from the presence of excess of urobinline, but very rarely contains bile pigment. It should be remembered that in the early days of life, bile salts and bile pigments are commonly found in the urine as a normal phenomenon. In doubtful cases, van den Bergh's test gives a negative direct and a positive indirect reaction in the plasma, a reaction which varies in intensity with the severity of the hæmolysis. Cases of obstructive jaundice give an immediate direct reaction.
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(a) Pernicious anaemia. Many writers include as cases of pernicious anaemia any grave anaemia occurring in childhood, and Still even goes so far as to say that 'whether pernicious anaemia as seen in adults ever occurs in childhood is doubtful.' After a careful investigation, we feel convinced that such cases, though rare, are encountered. Notes on one of four such cases which we have personally investigated are given (Case 1), and a further case is described later (Case 7). In all of the four cases the onset was very sudden, the child becoming extremely anaemic within a few days. With suitable treatment recovery was rapid, but the rapidity of onset and recovery is not to be regarded as differentiating the disease from that occurring in adults, but rather as an illustration of the juvenile reaction referred to above.

Case 1. Baby O., 4 months old, was admitted to hospital in July 1925 for extreme anaemia, restlessness and dyspnoea. He had been quite fit until a week previously when he was noticed to become pale, and the pallor had rapidly increased without apparent cause. On examination, the mucous membranes were pale and the skin and conjunctivae tinted a light yellow colour;

![Diagram](https://example.com/diagram.png)

**Fig. 7.** Diameter of red blood corpuscles in Case 1.

the spleen was palpable ½ in. below the costal margin; there was a systolic murmur at the apex and there were systolic and diastolic murmurs at the base: the rectal temperature was 100°, pulse 150, respirations 45 per minute. The blood picture showed Hb. 25 per cent.; red cells 900,000; colour index 1·4; white cells 5,300 (polymorphonuclears 27 per cent., lymphocytes 71 per cent., hyalines 2 per cent.). The red cells showed great irregularity in shape and size and the mean diameter was 10·67 µ (normal 7·23 µ). Many cells showed polychromasia, and a few punctate basophilia. The fragility of the red cells was normal and van den Bergh's reaction gave a negative direct and a marked positive indirect reaction. On the morning after admission the haemoglobin had fallen to 18 per cent. and it was decided to transfuse the patient. Seven ounces of citrated blood were given into the median basilic vein, and immediately there was decided improvement in the child, the distressing dyspnoea was relieved and the pulse rate fell to 120. From this time improvement was uninterrupted: the child has been seen on a number of occasions up to a year ago and there has been no repetition of the anæmia. The only abnormality found has been a constantly increased mean diameter of the red cells (9·23 µ), although the anisocytosis has not been so great. Since the initial attack of anæmia the condition has been similar to that found in adults in the intervals between the haemolytic crises. Fig. 7 shows the red cell distribution curve on admission and two years later.
(b) **Acholuric jaundice.**—Occurring in childhood this is almost invariably of the familial type. Thus in 69 members of a family\(^1\) there were 19 known to have had this condition. Of these, 8 were known to have had it before the age of 15 years, 3 died of it before reaching the age of 3 years. The principal features of acholuric jaundice as occurring in childhood are illustrated by Case 2.

**Case 2.** Allen H. was deeply jaundiced at birth and the urine was dark: this lasted for some weeks. At the age of 6 years he again became jaundiced. Three months after this he contracted diphtheria and this was associated with a recurrence of jaundice. The following year he became anaemic rather suddenly, the pallor being associated with another attack of jaundice. On examination at this time the spleen was palpable 1 in. below the costal margin: Hb. 50 per cent.: van den Bergh’s test gave a negative direct and a marked positive indirect reaction. The red cells showed slight hemolysis in 0-06 per cent. saline solution: the membrane potential of the red cells was 29 millivolts (normal 8 millivolts). The boy’s father gave no history of the complaint, but on examination the sclerotics were found to be rather yellow and the spleen was just palpable: his Hb. was 88 per cent., van den Bergh’s test gave a very marked positive indirect reaction, and estimation of the fragility of the red cells showed commencing hemolysis in a solution of NaCl as high as 0-72 per cent.: the membrane potential of the red cells was 18 millivolts.

(c) **Hæmolytic anaemias obviously of infective origin.**—In the early months of life sepsis of the umbilicus and infection of the alimentary tract are the commonest causes of this group of anaemias: more rarely parasitic infection may be the cause.

(d) **Hæmolytic anaemias, congenital or occurring in the early months of life.**—Cases of haemolytic anaemia are not very uncommon in the early months of life. In some the anaemia appears to be due to an exaggeration of the normal haemolysis encountered after the fifth month of intra-uterine life and which is normally especially marked immediately after birth\(^2\). When carried to excess, this becomes of pathological significance. In these cases, the red cells and haemoglobin are reduced at first in approximately the same proportion, but soon the haemoglobin falls out of proportion to the fall in the number of the red cells (and so the colour index falls): in the early stages the cells are of remarkably regular size and shape suggesting that the haemolysis is of primary importance. Later the blood picture changes: the cells becoming much more irregular in shape and size, the anaemia becomes non-hæmolytic in character, and this later stage may be due to a shortage of iron. In support of this view, it is found that the van den Bergh reaction in the earlier stages gives a strong positive indirect reaction, which disappears in the later stages. It is important to note that at no time is the mean diameter of the cells increased. It has already been suggested that the later stage is associated with an iron shortage, and in confirmation of this, administration of iron is often of value. In connection with the earlier hæmolytic phase, it may be noted that in cases of icterus gravis neonatorum in which the fatal issue is postponed, a considerable degree of anaemia is encountered. In another and more severe type the haemolysis is evident throughout. These cases are often described as ‘pernicious’ but they show obvious differences from the true pernicious anaemia described above, and therefore we feel that this term should not be used for this group. A study of these cases suggests that they may be sub-divided into several different groups. In many, the character of the disease suggests an infection, but in
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none, either before or after death, has any evidence of this been found. Some of them show an irregular pyrexia, but more often this is only terminal. In nearly all, there is a considerable enlargement of the spleen. Of these severe haemolytic anaemias, there is one class which is worthy of special mention. It appears to be more common in the months of June to August, and is marked by a sudden onset, the haemoglobin often falling within 48 hours to a value as low as 20 per cent. Unless immediate treatment is adopted, the child rapidly becomes restless, comatose, and dies. A single adequate transfusion of blood often leads to a recovery almost as dramatic as the onset.

Case 3. S.J., aet. 6 months, was admitted in August, 1926, with a history of having suddenly become anaemic. The child was well nourished, the mucous membranes were pale and the skin and conjunctive showed a light yellow colouration. Examination of the blood showed:—Hb. 23 per cent., red cells 1,500,000, colour index 0·77, white cells 12,200 (polymorphonuclears 60 per cent., lymphocytes 32 per cent., hyalines 6 per cent., eosinophils 2 per cent.). There was irregularity in shape and size of the red cells, but the mean diameter was within normal limits, being 7·18 μ. The fragility of the red cells was normal, and van den Bergh’s test gave a negative direct and a positive indirect reaction. The child was transfused with 6 oz. of citrated blood, and after this progress though slow was uninterrupted.

In the following case the onset of the haemolytic crisis was just as sudden, but it is distinguished from the others by the recurrent nature of the attacks.

Case 4. Severe haemolytic anaemia, with splenomegalia, controlled by liver treatment. Sylvia K., aet. one year eight months, was first seen in August, 1928, for severe anaemia and jaundice. There was no family history of any condition resembling this. There was one other child, who was quite healthy. The patient’s mother was rather anaemic, and said she had always been so: her haemoglobin was 74 per cent., and the red and white cell counts and the fragility of the red cells were normal. On physical examination, nothing abnormal could be found, and there was no palpable enlargement of the spleen.

The patient was breast fed until seven months old, and had broncho-pneumonia at seventeen months. She had always had an adequate mixed diet. She had been rather pale since birth, but had been more so for the six weeks prior to being seen. Her mother had noticed that she seemed rather yellow at times, but said she had never been deeply jaundiced. Her bowels were open one to four times daily, and sometimes the faeces were of a rather pale yellow colour, but had never been white.

She was admitted to hospital, and was evidently very anaemic. Her skin had a light yellow pigmentation which also showed slightly in her sclerotics. On systematic examination, her weight was 25 lb. 1 oz., and temperature normal. The whole abdomen was rather distended with gas, the liver was of normal size and consistency; the spleen was uniformly enlarged and rather firm, extending downwards to the level of the umbilicus. The faeces were normal, and the urine showed no abnormality, there being no bile salts or bile pigments present.

The blood count showed:—Haemoglobin 32 per cent., red cells 2,060,000, colour index 0·75: white cells, 9,100 (polymorphonuclears 51·5 per cent., lymphocytes 45·5 per cent., large hyalines 3·0 per cent.). There were anisocytosis and some polychromasia. No nucleated red cells or abnormal white cells were seen, and the mean diameter of the red cells was normal.

Other investigations produced the following results:—fragility of red cells in saline solutions normal (haemolysis commencing in 0·45 per cent. NaCl); Wassermann reaction in the blood negative; urobilin in urine strongly positive; van den Bergh’s reaction in serum negative direct, and strongly positive delayed direct and indirect; the faeces showed no occult blood or abnormal micro-organisms present.

She improved until November 1st, 1928, on iron ammonium citrate, gr. 5, t.d.s., and the haemoglobin rose to 60 per cent. On this date she had a haemolytic crisis, became very anaemic, and the skin and sclerotics became tinted a pale yellow colour. The haemoglobin dropped to
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20 per cent. on November 3rd, and the blood contained many nucleated red cells. On November 6th, the haemoglobin was 18 per cent. From November 1st to November 6th she ran an irregular temperature up to 101°. She was given three transfusions of blood (total 285 c.c.m.) between November 6th and November 12th, when the haemoglobin was 24 per cent. She was evidently still haemolyzing her red cells at a fast rate.

From November 7th, liver extract equivalent to 1/4 lb. of fresh liver was given. On December 3rd the haemoglobin was 34 per cent, but the patient was still rather yellow; 1/4 lb. of fresh liver was then given in addition. On December 28th the haemoglobin was 42 per cent., and on February 12th, when she was discharged from hospital, the haemoglobin was 66 per cent., the yellow pigmentation had disappeared and there had been no haemolytic crisis since the liver extract was started.

She developed whooping cough in March 1929, during which time her mother said she became slightly yellow. Otherwise she has remained perfectly well and has taken the same quantity of liver regularly during the whole time.

On examination on January 27th 1930, at the age of 3 years 2 months, she had gained 8½ lbs. in weight, and looked extremely healthy: the liver was normal, and the spleen had decreased in size so that it was just palpable at the end of a deep breath.

The blood showed:—haemoglobin 72 per cent., red cells 5,120,000, colour index 0·70; white blood corpuscles 10,600 (polymorphonuclears 55 per cent., lymphocytes 40 per cent., large mononuclear cells 4 per cent., eosinophils 1 per cent.) Anisocytosis and poikilocytosis were within normal limits; the red blood corpuscles of the “ring” appearance; no polychromasia or punctate basophilia; no nucleated red cells or immature white cells seen; van den Bergh’s reaction—direct negative, indirect less than 0·5 units.

The essential feature of this case was a severe haemolytic jaundice occurring in a child one year old, with an enlarged spleen reaching to the level of the umbilicus: the anaemia and jaundice were not due to Addison’s anaemia or to acholuric jaundice. This was controlled by liver treatment, and at the end of nineteen months’ treatment, the spleen was only just palpable. The dose of liver necessary to control the abnormal haemolysis was equivalent to 1/4 lb. of fresh liver. On half this dose, the haemoglobin was rising very slowly, and the yellow pigmentation of the skin persisted. The full quantity, which is the full dose normally given to an adult, was taken without any ill effect for fifteen months, and the haemoglobin rose to a normal value of 72 per cent. The quantity of liver has since been reduced to 2 oz. daily and the patient so far has shown no signs of increasing haemolysis.

It will be noted that whooping cough was associated with a mild relapse, and we take this opportunity to point out that in many of the cases of haemolytic anaemia the onset of any acute infection may be associated with a severe haemolytic crisis. This also applies to the administration of anaesthetics. This association, of course, occurs also in adults, but the reaction in children is usually more severe.

Case 5 is another case of the same nature.

Case 5. Grace B., aged 10 years, was admitted to hospital in March, 1930, on account of severe anaemia and jaundice. There were nine other children in the family, none of whom had ever had this trouble. The father and mother were quite healthy, had no splenie enlargement and the fragility of the red cells was normal in both of them. The patient was said to be rather deeply jaundiced at birth and had been pale since then. She had had about twelve attacks of severe anaemia associated with jaundice: five of these had been very severe and had necessitated admission to hospital. The first severe attack followed measles at the age of eighteen months. The attacks were all similar: in the course of a few hours the child became very feverish, anaemic, and the skin tinted a light yellow colour. In most of the attacks vomiting occurred. On ex-
amination the skin was a lemon yellow colour but the conjunctivæ were very little affected. She was very anemic; the spleen was enlarged to one inch below the subcostal plane and was very firm. The liver was not enlarged and the stools were of normal colour. She had a temperature ranging up to 101°. Investigation of the blood showed:—haemoglobin less than 20 per cent., red blood cells 1,210,000, white blood cells 5,000 (polymorphonuclears 45 per cent., lymphocytes 47 per cent., hyalines 8 per cent.). There were no abnormal forms of red or white cells and the reticulocyte count was 0·4 per cent. van den Bergh's test in the blood serum gave a negative direct reaction, and a positive indirect reaction (2·25 units). The fragility of the red cells was normal. The urine contained no bile pigments, but excess of urobilin. The Wassermann reactions of the child and of her father were negative. The average size of the red cells showed a mean diameter of 6·72 μ (range 5·0 μ to 8·2 μ) as compared with the control average 7·37 μ (range 6·2 μ to 8·8 μ). She was very little improved by blood transfusions of 850 c.cm. as she haemolysed the blood cells very rapidly. On the equivalent of ¼ lb. of liver the reticulocyte count rose to 26·4 per cent. on the 26th day and the haemoglobin to 32 per cent. Re-examination of the blood on June 25th 1930 showed:—Hb. 52 per cent., red cells 2,630,000, C.I. 1·00, white cells 9,000 (polymorphonuclears 53 per cent., lymphocytes 40 per cent., hyalines 6 per cent., eosinophils 1 per cent.). van den Bergh's test showed a negative direct and negative indirect reaction (less than 0·5 units). She is still under treatment.

Differential diagnosis of haemolytic anæmias.

It has already been mentioned that in anæmias of doubtful origin, van den Bergh's test becomes of diagnostic importance in differentiating the haemolytic anæmias from those of non-haemolytic origin. For this test, a large quantity of blood is unnecessary. It can be demonstrated satisfactorily by drawing blood from a finger prick into two capillary tubes, using a minute amount of heparin as an anticoagulant. The tubes are sealed and centrifuged: the ends are broken and the cells expelled: the plasma of one is mixed with an equal amount of van den Bergh's reagent, and of the other with an equal part of van den Bergh's reagent and 2 ½ volumes of alcohol. The mixtures are drawn up into the tubes which are again sealed and centrifuged. The colours of the supernatant fluids are compared with the series of standard solutions in similar capillary tubes.

Red cells.—While in non-haemolytic anæmias the haemoglobin is fairly uniformly distributed in the red cells, in haemolytic anæmias 'shadow cells' are common. In fact, these 'shadow cells' are more common than in adults because the haemolytic crises are more sudden. Polychromasia, punctate basophilia and nucleated red cells are present in many anæmias, and are not of diagnostic value.

Size and shape of red cells.—In true pernicious anæmia, in children as in adults, there are marked poikilocytosis and anisocytosis: and the average diameter of the red cells is always raised as illustrated in Fig. 8. The colour index is high and usually above unity. In acholuric jaundice poikilocytosis and anisocytosis may also be present, and the average diameter is considerably less than normal 14 as illustrated in Fig. 8. This has been confirmed by Masters, Zerfas and Mettel 15. The colour index is usually normal in spite of a considerable degree of anæmia; it never rises above unity. The explanation of this apparent anomaly is that in acholuric jaundice the red cells are of much greater thickness than in other anæmias, as may be clearly seen by examination of the
cells seen floating on their sides in the haemocytometer chamber. In the other
haemolytic anæmias the mean diameter of the cells is about normal, and poikilo-
cytosis and anisocytosis not so marked except in the cases mentioned above
as occurring in the first few days of life.

An examination of the fragility of the red cells to hypotonic solutions of
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For this purpose blood is drawn into a small quantity of a solution of sodium
citrate and centrifuged. The plasma is pipetted off, the red cells are washed in
0.90 per cent. NaCl, and the suspension again centrifuged. This process in
repeated, the final supernatant fluid being withdrawn as completely as possible.

In each of a series of small tubes 2 c.cm. of saline solutions are introduced. The
concentrations of these solutions range from 0.30 to 0.84 per cent. with intervals

![Graph](http://adc.bmj.com/)

**Fig. 8.** Comparison of size of red blood corpuscles.

...of 0.03 per cent. To each tube 0.1 c.cm. of the washed corpuscles is added and
the tubes are inverted several times to ensure even suspension. An equal
quantity of corpuscles is similarly added to tubes containing 0.90 per cent.
NaCl and distilled water. As a control, the blood of a normal individual should
be treated in the same manner. The tubes are allowed to stand for 12 hours:
the percentage haemolysis in each tube is estimated by colorimetric comparison
of the supernatant fluids with the 100 per cent. haemolysis in the tube which
contained distilled water. Fig. 9 illustrates curves plotted in a case of acholuric
jaundice and in a normal individual. It will be observed that in normal persons
slight haemolysis occurs about 0.48 per cent. but haemolysis is not quite complete
at 0.30 per cent. It is often stated that in solutions weaker than 0.40 per
cent. haemolysis is complete, but when accurate quantitative methods are used
the lower limit is found to be much below this. In acholuric jaundice haemolysis commences in solutions stronger than 0·48 per cent.; it has even been observed at 0·84 per cent: and in this disease, haemolysis is complete in concentrations of NaCl higher than in the normal. In very young children, where large quantities of blood cannot be obtained, the test can easily be performed in a modified manner by allowing a drop of blood to fall into tubes containing 0·51 and 0·48 per cent. NaCl. This gives a ready qualitative method of diagnosis. It is worthy of note that in other haemolytic anaemias the resistance of the red cells is usually increased and not diminished.

As shown by Hampson and Maizels in cases of pernicious anaemia and acholuric jaundice, the reaction in the red cells is more acid than in the normal. This appears to be associated with a high content of ester phosphate in the red cells and leads to a high potential on the membrane of the cells. This has since been shown to be the case in other varieties of haemolytic anaemia.

Fig. 9. Fragility of red blood corpuscles in saline solutions.

(as for example in Case 4 where on Nov. 6th a value of 40 millivolts was found). It has not been found in other conditions: in cirrhosis of the liver, for example, a positive indirect van den Bergh's reaction is found, but the electrical charge (or membrane potential) of the red cells is normal (Case 6).

Case 6. Peter B., at 12 years, had been subject to bilious attacks, occurring about once a month, for about as long as he could remember. He had had two operations at four months' interval for bilateral undescended testicile at the age of 10. Following the first operation, in November 1927, he became slightly jaundiced for 2 days. In September, 1928, he was again jaundiced for three weeks, this time accompanied by abdominal pain and vomiting. In February 1929, he had a sore throat. Two weeks later he was again noticed to be jaundiced: with the onset of the jaundice he had an attack of vomiting and the jaundice lasted a week. At this time he was admitted to hospital. On enquiry, he stated that although the jaundice became more marked in February 1929, he did not think the yellow colour had ever quite cleared since September 1928. On examination, the liver edge was just palpable and the spleen could be felt for about two fingers' breadths below the costal margin. The sclerotics were tinged with yellow
The urine contained a slight excess of urobilin: the Wassermann reaction was negative: van den Bergh's test gave a positive indirect (12 units) but a negative direct reaction; the fragility of the red cells to hypotonic saline solutions was normal; the membrane potential and the phosphate content of the red cells was normal: haemoglobin was 86 per cent., red cells 4,452,000, colour index 0-94, white cells 7,200—polymorphonuclears 62 per cent., lymphocytes 31 per cent., hyalines 5 per cent., eosinophils 2 per cent.; the red cells were normal in size and shape. Between April 1929 and 1st February 1930, he had periodical attacks of nausea and vomiting; in three of these attacks the jaundice was noticed to increase in intensity. The liver now extended 1 ½ in. below the costal margin, while the size of the spleen appeared to be the same. Examination of the blood as regards van den Bergh's reaction, fragility, and phosphate content gave similar results to those obtained in February 1929. The Hb. was now 70 per cent. A luvulose tolerance test gave the following results:—blood sugar fasting 0-118 per cent., one hour after 50 grammes luvulose 0-130 per cent., after two hours 0-130 per cent. He was treated with mercury inunctions and was given glucose by the mouth, with injections of insulin. On the 7th March the haemoglobin rose to 85 per cent., van den Bergh's test became negative, the liver showed slight decrease in size, and a luvulose tolerance test gave the following results:—blood sugar fasting 0-102 per cent., one hour after 50 gms. luvulose 0-110 per cent., two hours 0-110 per cent.

White cells in hæmolytic anæmias.—In true pernicious anæmia it is usual to find a low white count with a relative lymphocytosis. This is also true in grave anæmias of infective origin. In the other types, a high white count is more commonly encountered, and on the whole the presence of this is associated with a better prognosis. In all severe anæmias of the types under consideration, there is a tendency for immature white cells to be found: this is especially the case when the white count is high and is more constant in very young children. It is probably to be regarded as another example of the reaction of the infant's hæmopoietic system to stimulation. As pointed out already, as compared with adults, the percentage of lymphocytes is high in the normal infant, and in older children almost any stimulus to the formation of white cells results in a reversion to the infantile type of reaction and so to a lymphocytosis. Very rarely in this group of anæmias does the lymphocytosis exceed 65—70 per cent., a point of considerable importance in diagnosis, to which reference will again be made.

Treatment of hæmolytic anæmias.

Liver therapy.—Following the work of Minot and Murphy showing the value of the therapeutic administration of liver and extracts prepared from it in cases of pernicious anæmia, it has now become a generally recognized form of treatment for this disease. The application of this in infancy and childhood appears to have been neglected, but as is shown by the following case it is of equal value in true pernicious anæmia even in early infancy.

Case 7. Rose S., had pneumonia at the age of 8 months, since when she had been noticed to be slightly yellow. One month later it was noted that she was becoming anæmic. At the age of 11 months she was brought to hospital. The skin and conjunctivæ were then distinctly yellow, and the mucous membranes were pale. The spleen was palpable three fingers' breadths below the costal margin. No other abnormality was detected on physical examination. The urine contained an excess of urobilin. Examination of the blood gave the following results:—Hb. 37 per cent.; red cells 1,800,000; colour index 1-06; white cells 7,000 (polymorphonuclears 42 per cent., lymphocytes 53 per cent., hyalines 1-5 per cent., eosinophils 0-5 per cent., myelocytes 3 per cent.). There were marked anisocytosis and poikilocytosis, the mean diameter of the red cells was 8-7 μ. Normoblasts were fairly numerous and occasional megaloblasts were present.
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van den Bergh’s test gave a negative direct and a positive indirect reaction. The fragility of the red cells was normal. A test-meal showed the absence of free HCl in the resting juice and one hour after a feed. The Wassermann reaction was negative. The baby was given liver extract and a fortnight later the haemoglobin had risen to 54 per cent., and anisocytosis and poikilocytosis were less marked. van den Bergh’s test was negative. A month after treatment was first commenced the blood picture was—Hb. 70 per cent.; red cells 3,900,000; colour index 0-9; white cells 6,200 (polymorphonuclears 40 per cent., lymphocytes 57 per cent., hyalines 2 per cent., myelocytes 1 per cent.): van den Bergh’s test was negative and no abnormality was detected in the urine.

Although the administration of liver is still common in many anæmias in adults, in the majority of cases the results are totally unsatisfactory, and apart from pernicious anæmia no clear idea appears to exist as to when it is likely to be of value. The following remarks, based on investigations on anæmias occurring in adults are introduced into this paper with the object of showing the application of the knowledge so gained to the anæmias of infancy and childhood. In 1927 it was shown by Hampson and Maizels that in both pernicious anæmia and acholuric jaundice there is an increased electrical charge on the membrane of the red cells, and this was shown to be proportional to the degree of haemolysis as measured by van den Bergh’s reaction. On investigating the effects of the administration of liver in such cases, it has been found that proportional to the decrease in haemolysis the electrical charge becomes normal. This is illustrated by the values obtained in a patient and shown in the following table:

<table>
<thead>
<tr>
<th>van den Bergh’s reaction</th>
<th>Membrane potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before liver feeding</td>
<td>5</td>
</tr>
<tr>
<td>One week after liver feeding</td>
<td>4</td>
</tr>
<tr>
<td>Three weeks</td>
<td>1</td>
</tr>
<tr>
<td>Ten weeks</td>
<td>0.5</td>
</tr>
</tbody>
</table>

In a large series of cases of anæmia of many different varieties, the only cases which have materially benefited by the administration of liver have been those in which there has been a raised electrical charge. Practically all such cases have shown evidence of increased haemolysis.

From these results it appeared worth while to try the effect of liver feeding in cases of hemolytic anæmia occurring in childhood, and we are convinced that it is of considerable value in these cases even when the condition is not that of pernicious anæmia. The response in a case of acholuric jaundice is illustrated by the following case.

Case 8. George A. The child was admitted in 1922 at the age of 1 year and 6 months for anæmia. The abdomen was large and the spleen extended below the umbilicus. There was slight beading of the ribs with no other evidence of rickets. The onset of the anæmia had been gradual, but on admission to hospital, the blood showed Hb. 23 per cent., red cells 1,300,000; colour index 0-9; normoblasts were numerous and a few megaloblasts were seen. There was much poikilocytosis and polychromasia. White cells were 30,000 per cubic mm.—polymorphonuclears 21 per cent., lymphocytes 70 per cent., hyalines 3 per cent., myelocytes 6 per cent. During the next two years, the child showed gradual improvement and the case was diagnosed as von Jaksch’s anæmia. In 1922 the child had slight jaundice and further examination of the blood showed...
marked increase in fragility of the red cells (Fig. 9) and the cells themselves were small in diameter (Fig. 10), and showed the typical dumb-bell shape of acholuric jaundice. Between 1922 and 1928 there were numerous recurrences of anaemia accompanied by icterus, and the liver gradually increased in size. In 1928 it was found that the membrane potential and the phosphate content of the red cells were high. He was given liver extract and the haemoglobin rose rapidly to 80 per cent., following a sharp rise in the reticulocyte count. The membrane potential and phosphate content of the red cells became approximately normal, and there was some increase in the resistance of the red cells—whereas formerly on numerous occasions laking had commenced at 0-76 per cent. NaCl, laking now commenced at 0-66 per cent. NaCl. After discharge the patient was instructed to take liver regularly. This he failed to do, and as there appeared no likelihood of the régime being effectively carried out, splenectomy was performed. Although the anaemic state persisted at intervals during the seven years the child was under observation, the appearance of the blood film gradually changed. White cells became less numerous, myelocytes disappeared, the differential count became more normal, and nucleated red cells were only found on rare occasions.

![Graph showing size of red blood corpuscles in a case of acholuric jaundice (Case 8).](http://adc.bmj.com/)

**Fig. 10.** Size of red blood corpuscles in a case of acholuric jaundice (Case 8).

Case 4, quoted above, showed haemolytic crises occurring at an early age. This was neither a case of pernicious anaemia nor acholuric jaundice, but the electrical charge (40 millivolts) was the highest we have met. The value of liver therapy in this case was most striking. We have been impressed by the fact that in order to control haemolysis in children, it is necessary to give a dose of liver which is relatively greatly in excess of the amount required by an adult. Doubtless this is partly to be explained by the greater demands on the haemo-poietic system in a growing child; thus in Case 4, the dose of liver necessary to control the haemolysis was equivalent to ½ lb. of fresh liver. On half this dose the haemoglobin percentage was rising very slowly, and the yellow pig-
mention of the skin persisted. The full quantity, which is the full dose normally given to an adult, was taken from the age of 1 year and 11 months for 15 months and the haemoglobin value rose to 72 per cent.—a normal value for this age. Again, in Case 5 the equivalent of $\frac{1}{2}$ lb. of liver only partially controlled the haemolysis, but $\frac{3}{4}$ lb. did so completely.

The initial fall of haemoglobin in the haemolytic crises in children is often of great severity (Cases 1, 4, 5 and 7). The beneficial effects of liver therapy do not become apparent until after the elapse of at least a week, and it becomes of vital importance to tide the patient over this period: it is here that blood transfusion becomes of special benefit.

The beneficial effects of splenectomy in cases of acholuric jaundice are now well recognized. Although after splenectomy the resistance of the red blood cells to hypotonic saline solutions is increased, it is certainly not our experience that the fragility ever becomes normal as it sometimes stated. This is confirmed by Masters, Zerfas and Mettel. In infancy splenectomy is an operation attended by a very high mortality. The administration of liver extract during this early period of life may tide the patient over to a later age when, if thought advisable, splenectomy can be performed in comparative safety.

**Blood transfusion.**—In selected cases we are firmly convinced of the efficacy of blood transfusion. In children as in adults it is just as essential that great care should be taken over the correct grouping of the donor and recipient, and it may be necessary to allow corpuscles of an infant to stand with the sera for half an hour, as agglutination may be delayed. It is always our practice to give the transfused blood into one of the peripheral veins such as those in the antecubital fossa and not into the superior longitudinal sinus. We have seen three fatalities following the latter procedure. As this is a method which has been in common use we would emphasize that it is a simple process to withdraw blood from the sinus, but this cannot be taken as proof that the bevel of the needle lies entirely within the sinus: and in delivering blood, part may be delivered into the lumen of the sinus and part into the meningeal spaces.

In most severe cases of haemolytic anaemia of the infective type, we consider blood transfusion of great value, and in the type which has been described as occurring with sudden onset particularly in the summer months, a single transfusion may be all that is necessary. It has already been remarked that in cases where liver therapy has been adopted, it may be necessary to give an initial transfusion.

In delivering blood into a vein in the antecubital fossa, the process is of necessity slow, and this gives an opportunity for watching the pulse rate and for any signs of cardiac dilatation. It is therefore possible to give relatively large transfusions, and provided the process is carefully watched the results appear fully to warrant them in preference to small transfusions. On several occasions we have given 200 c.c.m.s. to a child only a few weeks old.

In addition to special treatment, attention to the usual hygienic measures is of course essential. Even in the normal infant the reserve of iron is low, and it is therefore important to attempt to remedy this deficiency by the administration of suitable iron salts.
II. NON-HÆMOLYTIC ANÆMIAS.

(a) Anæmia due to hæmorrhage.—As compared with adults hæmorrhage is a relatively rare cause of anæmia in infancy and childhood, but when bleeding does occur the loss of comparatively small quantities may readily endanger life. It is encountered in the early days of life in the form of melæna neonatorum.

Case 9. Eliz. B. was admitted to hospital at the age of seventeen days on account of abdominal pain. The child had been seized with sudden abdominal colic and became very blanched. She then started to vomit large quantities of partly altered blood and to pass large quantities of blood per rectum. The abdomen became very distended and in spite of treatment she succumbed within 18 hours of the first symptoms. Post mortem the whole of the stomach and intestines were tremendously distended with blood which originated from profuse oozing of the whole alimentary tract.

It is also met with in hæmorrhage from the umbilical cord, usually associated with sepsis. Very rarely in rather older children hæmorrhage from the gastro-intestinal tract may be due to duodenal ulceration.

Case 10. James W., at 6 months, was admitted on account of vomiting, and the first vomit after admission contained a large amount of partially altered blood. He died quite shortly afterwards. Post mortem the child was wasted and the thymus unduly large. The stomach was distended and contained mucus and blood. The intestines contained a large amount of blood. Just distal to the pylorus there was a duodenal ulcer with a ruptured vessel in the base of the ulcer which had been the cause of the hæmorrhage.

Hæmophilia. This cause of bleeding may be met at all ages. In some cases it is readily recognized by the family history, but in others this may be obscured owing to the disease having missed two or three generations. Occasionally sporadic cases occur, and atypical cases may be met with in females as well as in males as is illustrated by the following case.

Case 11. Jean P., at 12 months, was admitted in June, 1929, for bleeding from the socket of an extracted tooth. The bleeding had been profuse and on admission the haemoglobin was 18 per cent. Numerous red cells showed diffuse basophilia: the white cells were 19,400—polymorphonuclears 53 per cent., lymphocytes 26·5 per cent., hyalines 12 per cent., eosinophils 1·5 per cent., basophils 1·5 per cent., myelocytes 2·5 per cent., transitional cells 3 per cent. The blood platelets were numerous. A fortnight later the haemoglobin had risen to 38 per cent.; the red cells were 2,800,000: the white count had fallen to 5,000—polymorphonuclears 37 per cent., lymphocytes 51 per cent., hyalines 11 per cent., eosinophils 1 per cent., and no abnormal cells were present. In December, 1929, she was readmitted for intractable hæmorrhage from her lip which had been cut 14 days previously. In the interval the child was said to have regained her normal colour. This time the haemoglobin was 40 per cent., white cells 18,500—polymorphonuclears 40 per cent., lymphocytes 56 per cent., hyalines 2 per cent., eosinophils 1 per cent., basophils 1 per cent. The blood platelets were 220,000, and the blood calcium 9·8 mgrm. per cent. Both bleeding and clotting times were very much prolonged. On enquiry it was found that there was rather diffuse hæmorrhage from the cord after birth and that the child had always bruised very readily. There was no history of any similar condition in the family.

There are instances in which this condition has led to bleeding from the umbilical cord which may be of alarming extent or even fatal. Such a family is illustrated in Case 12.

Case 12. Jack L. was admitted for a hæmatoma in the left thigh. He had had three previous attacks of hæmorrhage in the same position. At the age of eighteen months he had bleeding from the gums and at the age of four a severe epistaxis. He had always bruised very easily and very frequently suffered from painful swellings under the skin following slight injuries.
Although the parents did not give a history of abnormal bleeding two other children had died from bleeding from the umbilical cord at birth. Investigation showed: Hb. 74 per cent., red cells 4,320,000, white cells 9,100, differential count normal, blood platelets 170,000 per c.mm., blood calcium 9.37 mgm. per cent., and bleeding and clotting times 3 days after admission within normal limits.

This case illustrates the fact that if the blood be examined repeatedly there are periods between the attacks of hæmorrhage when the clotting time may be normal, whereas during the attacks this may be very delayed and at such times trivial injuries may lead to serious hæmorrhage. Some closely allied cases show a lowered platelet count in addition to the typical characters of hæmophilia. Although in many of these cases the hæmorrhage is subcutaneous and of small extent, when there is an open wound (even with dental extraction) the amount of hæmorrhage may be serious.

PURPURA.—In this paper we are only concerned with anæmia occurring in infancy and childhood, and purpura as a cause of anæmia during this period is rare. The anæmia is usually secondary to hæmorrhage from the nose, kidneys or intestines. There may be purpuric spots scattered over the body especially on the limbs, though if the patient has been kept in a recumbent position the petechiae may be more evident in the sacral region and over the buttocks. Troublesome bleeding sometimes occurs from the gums and may suggest scurvy. During the attacks some degree of pyrexia is often encountered, and in a case of renal bleeding the pyrexia with hematuria and the presence of blood-casts in the urine present a picture strongly suggestive of acute nephritis. Often, too, there is albumen in the urine somewhat in excess of the amount of blood. During the attacks there is a low platelet count and the spleen may be enlarged, though this is not invariable. Considerably reduced platelet counts may be found in cases of aplastic anæmia and in leukaemia, and when hæmorrhages occur in these conditions the diagnosis may be difficult. Reference to this will be made again when these conditions are under discussion.

Case 13 is an example of purpura occurring in a child ten years old.

Case 13. Grace D., wt. 10, gave a history of repeated epistaxis and bleeding from the gums for six weeks. Although the epistaxis had been most marked during this time, for some years there had been a tendency to slight bleeding from the nose. On examination the child was very pale: petechiae were scattered over the body but were most marked on the lower limbs, except that after the blood pressure had been taken, a crop of petechiae occurred below the area of compression by the arm-band. Slight pressure on the gums produced bleeding which continued for hours, and purpuric spots were present on the tonsils, but otherwise the tonsils were not abnormal: the temperature on a few occasions reached 99°, but otherwise was normal: the spleen was palpable one inch below the costal margin. Examination of the blood showed: Hb. 30 per cent., red cells 2,900,000, colour index 0.52: white cells 4,900—polymorphonuclears 59 per cent., lymphocytes 41 per cent.: platelets 90,000: coagulation time 1' 40" (Dale and Laidlaw): bleeding time much prolonged: van den Bergh’s test negative. Transfusion of blood followed by splenectomy led to almost immediate cessation of bleeding. On the day after splenectomy the patient was again transfused, and thereafter recovery was uninterrupted.

Although in the majority of cases of thrombocytopenic purpura the results of splenectomy are very satisfactory, it appears to us that the cases in which there is a family history belong to a different group. In our experience of these cases the platelet count does not rise after operation, with the consequence that
the bleeding continues into the peritoneum and in the abdominal wall, and the results have been invariably fatal within a few hours, in spite of transfusion.

(b) Chlorotic anaemias.—Anaemias of the chlorotic type are by no means uncommon. As with the true chlorosis occurring in the adolescent female, so in childhood, the cause may be very difficult to find. The anaemia with low colour index is perhaps due to a variety of causes such as prematurity, diet insufficiencies, unhygienic conditions, minor infections, overwork and lack of sleep. It has been described by various writers as due to each of these conditions. In severe cases the child presents a peculiarly white waxy appearance, which is in marked contrast with the yellowish colour of the skin found in so many anaemias in young people. Although gain in weight is unsatisfactory the child appears well covered, probably due to an excess of water in the tissues. An examination of the blood shows a fall in the haemoglobin greater than the reduction of the red cells, and consequently a low colour index. The haemoglobin may fall to below 20 per cent. While a fatal termination to the anaemia is rare, the resistance of the patients to infections is impaired and they may succumb to some intercurrent condition which would not be considered grave in otherwise healthy children. It is perhaps of interest here to note that in anemic adults it is fairly common to obtain a history of anaemia of the chlorotic type occurring in early life. In a study of infants attending out-patient departments and welfare centres, Helen Mackay came to the conclusion that some degree of anaemia was the rule in children under the age of two. The anaemia she described was improved in almost every case by the administration of iron. She pointed out the importance of early treatment in these cases. Shortage of iron is undoubtedly an extremely important factor in chlorotic anemias; and where the food has contained only traces of iron, an anaemia insidious in onset may become extremely marked. In a case recently seen by one of us, a child had been fed on the breast without supplementary feeding for 2½ years. The value of the haemoglobin was 22 per cent. Dietetic treatment with the administration of iron led to rapid improvement. Transfusion is usually neither necessary nor desirable unless there is some accompanying infection which renders a rapid rise of haemoglobin almost imperative. Failure to respond to treatment is almost always due to insufficient dosage of iron. Relatively large amounts are necessary. For the first few days the dose should be increased gradually or somewhat troublesome alimentary symptoms may present themselves, but after this, large doses are almost always well tolerated. In agreement with the findings of Helen Mackay, in our opinion iron ammonium citrate is the best form for administration, and leads to the most rapid improvement (up to 20 grains being given per diem at the age of one year).

Case 14. Eric P., aged 4 months, was admitted on January 31st, 1930, for severe anaemia. At birth the weight was 4 lb. 3 oz., and he had been fed on dried milk with the addition of cod liver oil. He had always been pale; there had been no haemorrhage. On admission he was extremely anaemic and of a pale waxy colour. Blood examination showed: Hb. 35 per cent., red cells 3,400,000, C.I. 0.01, white cells 7,000 (polymorphonuclears 34.5 per cent., lymphocytes 48.5 per cent., histiocytes 7.5 per cent., eosinophils 4.0 per cent., basophils 0.5 per cent.) There were no abnormal red or white cells present. He was given saccharated carbonate of iron in one-grain doses, thrice daily: the haemoglobin was only 40 per cent. on March
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4th, 1930. The dose of ferri carb. sacchi. was then raised gradually to 10 gr., t.d.s., and in spite of an intercurrent attack of measles, on May 28th, 1930, the hemoglobin was 63 per cent.

In the paper referred to above, Helen Mackay noted that in a group of cases with rachitic manifestations, the hæmoglobin values were approximately the same as in those without rickets. In older children we are of the opinion that rickets is associated with a fall in the value of the hemoglobin.

Anemia of a similar type may be found in association with other diseases—as, for example, in coeliac disease.

(c) Grave secondary (aplastic) anæmias.—There is a group of anæmias which although rare in early childhood becomes increasingly common in older children. Similar cases occur in adults, and now that pernicious anæmia in adults has become sharply defined, and in the majority of cases responds so readily to liver therapy, the cases under consideration have shown themselves to be of an obviously different nature. We wish to stress this because the literature on the subject is very confusing. In the past, various authorities have grouped these cases with the haemolytic anæmia described by Addison as pernicious. Writing on this subject, Poynton, Thursfield and Paterson¹⁴ say, ‘although writers have insisted upon the wide differences between anæmia gravis in childhood and pernicious anæmia in the adult, we are inclined to think that the essential resemblance is much more convincing, and to believe that the differences do not lie so much in the nature of the disease as in the fact that we are dealing in the one case with an adult, and in the other with a child.’ We have already drawn attention to differences in reaction between adults and children (most marked, of course, in infancy) but we do not think that the condition under discussion is an example of such reaction. We agree with the above writers when they say, ‘it is certain that most of the cases reported under this heading (pernicious anæmia) are examples of other forms of severe anæmia’; but we feel convinced that true pernicious anæmia does occur in very young children and cases of this disease, fully investigated, have been recorded above. In these cases, the picture showed a remarkable resemblance to the disease as it occurs in adults, and contrasts strongly with the ‘anæmia gravis’ at present under consideration. Moreover, the anæmia gravis has its counterpart in the adult in a form similar to that found in children, and very different from true pernicious anæmia. Probably this group is a composite one, but apart from the fact that spontaneous improvement occurs in occasional cases, they are all entitled to the name of grave anæmia in that treatment appears to have very little effect on the course of the disease. General treatment, iron, arsenic, liver therapy, and blood transfusion appear to exert very little influence on the course of the disease—indeed transfusion in some cases appears to lead to an exacerbation of the condition. Many of the cases are said to have been anaemic for years, but the condition has not previously caused anxiety. In a few cases the anæmia appears to have occurred so soon after whooping cough or diphtheria as to suggest a causal relationship. There is often irregular pyrexia and this suggests a possible infective origin, though usually none can be discovered except near the end when it appears probable that the infection may be due to a lowered resistance. A tendency to bleed is common to all
of these cases, though considerable haemorrhages are rare. Associated with this there is a low platelet count. All the cells of marrow origin are reduced—there is a low red cell count and a low white count, the polymorphonuclears being especially reduced in number. The degree of reduction in white cells and platelets appears to be of prognostic significance. No evidence of increased blood destruction is found post-mortem, Perle's reaction on liver and spleen being negative. The whole picture suggests an aplastic anaemia and post-mortem examination reveals a white marrow. Occasional slight improvements in the blood condition associated with marrow activity are not incompatible with a condition which in the main is aplastic. The diagnosis may offer considerable difficulties. We have seen such cases diagnosed as purpura, but the degree of anaemia is altogether out of proportion to the amount of haemorrhage when such occurs. In other cases 'aleukemic leukemia' has been suggested, but in the condition under consideration the number of immature white cells is always under 1 per cent. The superficial glands are not more enlarged than in many otherwise normal children. Hodgkin's disease may present a very similar clinical picture, and this should always be carefully considered. At times the picture, with anaemia, pyrexia, purpura and splenic enlargement, may closely simulate that of malignant endocarditis. In addition the heart often shows some degree of dilatation: there is a systolic murmur at the apex, and often a diastolic murmur at the base: the latter is frequently harsh in character and may be fairly prolonged; it may often be accentuated by extending the neck or by drawing the chin forward.

Case 15. Joan B., at 11, was admitted for anaemia. There was a rather indefinite history of lassitude during the preceding year. During this time there had on several occasions been bleeding from the nose, but not sufficiently severe to account for the anaemia. There had been no sore throats and there was no history pointing to infection. On examination she was found to be extremely pale. There was no yellow coloration of skin or sclerotics. The gums bled easily. The glands were palpable in the neck and the spleen could be felt about one finger's breadth below the costal margin. There were a few scattered purpuric spots and slight oedema over the legs. Systolic and diastolic murmurs could be heard at the base of the heart. Examination of the blood showed a negative reaction to van den Bergh's test: Hb. 23 per cent., red cells 1,200,000, C.I., 0·96: white cells 2,700 (polymorphonuclears 21 per cent., lymphocytes 77 per cent., hyalines 2 per cent.): platelets 120,000. In spite of treatment by transfusion, and by administration of iron and arsenic the patient became more anemic and died. At autopsy, there was no evidence of endocarditis, the only finding of importance being a white marrow.

The following notes on a case in an adult (Case 16) show that there is no essential difference between the disease in adults and children.

Case 16. Percy J., at 27, a glass bottle maker, was admitted to hospital in 1928 for extreme anaemia. In 1912 he had appendicectomy, followed by peritonitis and abscess in the right lung. He made a complete recovery from this. Five weeks previous to admission he had pain in the left shoulder, followed shortly afterwards by pain in the right shoulder. Then he had dyspnoea on exertion, his legs felt weak, and the pallor of his face which had been noticed for the previous 3 years became much more marked. On admission he was extremely anaemic, and had marked purpura on the left arm and shoulder, with a sub-conjunctival haemorrhage in each eye. There was a soft systolic murmur at the base of the heart, the spleen was not palpable, and blood examination showed: Hb. 19 per cent., red cells 1,040,000, colour index 0·94, white cells 4,200 (lymphocytes 61 per cent., polymorphonuclears 39 per cent.). Other investigations showed: no occult blood in the stools, van den Bergh's reaction negative, Wassermann reaction negative, and the fractional test meal showed acid within normal limits. Later, bleeding from the gums
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occurred, and a blood count 6 weeks after admission showed: Hb. 17 per cent., red cells 766,600, white cells 3,222 (lymphocytes 69 per cent., polymorphonuclears 31 per cent.). In spite of two transfusions of blood he died 2 weeks later, and autopsy showed complete absence of hemopoietic activity in the bone marrow, petechial hemorrhages on the epicardium and pleura, and diffuse fatty degeneration of the heart.

(d) Splenic anæmia.—Considerable enlargement of the spleen is often associated with anæmia in children, but very few of these cases are examples of true splenic anæmia. Many writers deny the occurrence of the disease in childhood, but on enquiring carefully into the history in adults, it is not uncommonly found that anæmia has been present during childhood. We are of the opinion that the disease may be diagnosed at an early age. Points especially to be noticed in clinical diagnosis are the firmness of the spleen, the occasional occurrence of small hæmatemesis, and the slowly progressive character of the anæmia. In the later stages the liver becomes involved, with cirrhosis and portal obstruction. The blood picture shows a low hæmoglobin value and a low colour index. The red cells are pale; there is moderate anisocytosis and the mean diameter is not raised. The fragility of the red cells is not increased, and in the later stages when cirrhosis is present may actually be diminished. There is usually leucopenia with a relative lymphocytosis. There is only a slight increase in the amount of bilirubin in the blood as shown by an indirect reaction to van den Bergh’s test, unless the liver is severely damaged. The platelet count in this condition is usually low, but in a condition presenting closely similar features is high. In this latter type, thrombosis is common in the veins of the portal system, and associated with this a transient ascites occurs at an early stage. Case 17 illustrates the features in an advanced case.

Case 17. J.F., aged 9, was admitted on May 21st, 1929, for abdominal enlargement and drowsiness. The parents and six other children were alive and well. He had measles when four and diphtheria recently, having been discharged from a fever hospital on May 12th, 1929. The abdomen had always been rather large but became much more so while he was in the fever hospital. The doctor there found ascites and splenomegaly, and during the latter part of his stay he had hæmaturia as well. This had persisted but had become much less up to the time of his being seen by one of us. There was no history of any hæmaturia before the diphtheria. On examination he was distinctly drowsy, the abdomen was much distended and the abdominal wall tense (circumference at umbilicus 32½ inches). The distension was due to fluid as there was a marked fluid thrill and shifting dullness; on dipping through this an enlarged spleen could be felt reaching nearly to the umbilicus. On deep palpation a very small and very hard liver could be felt extending just below the xiphisternum. It was evidently cirrhotic. Examination of the chest showed markedly distended veins extending up from the abdomen, and there were signs of fluid at the bases of both lungs. This was confirmed by X-ray examination, which also showed a very large heart shadow suggesting some pericardial effusion. The urine showed the presence of blood and albumen; the amount of albumen was not in excess of that due to the blood. Microscopically, red cells but no casts were seen. There was slight oedema of the legs, and the blood pressure was 140 mm. systolic and 105 mm. diastolic. At no time was there any pyrexia. Investigations showed: Hb. 62 per cent., red cells 3,487,000, C.I. 0·89, white cells 4,000 (polymorphonuclears 85 per cent., lymphocytes 10 per cent., hyalines 4 per cent., and eosinophils 1 per cent.). No abnormal forms of red or white cells were seen. Platelets 160,000 per c.mm. A little ascitic fluid was withdrawn for examination, and showed some blood (?) contamination) and 530 leucocytes—mainly lymphocytes—per c.mm. The protein content was 0·8 per cent. The Wassermann reaction in the blood and the ascitic fluid gave negative results. On June 1st, 1929, the liver tolerance test after 30 grm. of lactulose showed blood sugar
values of:—fasting 0·105 per cent., ½ hour later 0·173 per cent., at 1½ hours 0·120 per cent., at 2½ hours 0·114 per cent., an extreme degree of liver deficiency. The faces contained no occult blood. A diagnosis of splenic anaemia with cirrhosis of the liver (Banti's disease) was made. With complete rest in bed on an ordinary diet with the addition of as much glucose as he could take, the general condition of the patient improved, and the blood disappeared from his urine. The ascitic fluid was absorbed almost completely, so that on June 20th, 1929, the abdominal girth was 25½ inches. On July 1st, 1929, Mr. R. C. B. Ledlie operated on the patient, and in view of his previously serious condition, it was decided not to perform splenectomy, but to tie the splenic veins instead. Mr. Ledlie confirmed the diagnosis and found a very large, hard spleen and a small cirrhotic liver. He was able to tie at least 9–10ths of the splenic veins, the only difficulty throughout being the bleeding from the enlarged vessels in the anterior abdominal wall and the gastro-splenic omentum. The patient made a rapid recovery from this operation: there was a little coffee ground vomit on July 4th, 1929, and also epistaxis. The blood reappeared in the urine for six days and then finally disappeared. The spleen temporarily enlarged to the level of the umbilicus. Recovery was otherwise uneventful. On July 8th, 1929, blood examination showed: Hb. 53 per cent., red cells 3,125,000, C.I. 0·86; white cells 6,230 (polymorphonuclears 73 per cent., lymphocytes 16 per cent., metamyelocytes 11 per cent.); platelets 500,000 per c.mm. There were no abnormal forms of red or white cells present. On July 13th, the platelets were 870,000. On readmission on September 16th, 1929, he looked the picture of health, was very active and had gained 5 lb. in weight. There was no sign of any fluid in the abdomen. The lower margin of the spleen was now 1 inch above the umbilical level, and the liver felt unchanged. Blood examination showed: Hb. 84 per cent., red cells 5,100,000, C.I. 0·82; white cells 6,400 (polymorphonuclears 73 per cent., lymphocytes 21 per cent., metamyelocytes 4 per cent., eosinophils and basophils 1 per cent. of each): platelet count, 350,000: the liver tolerance test with 50 gms. of levulose showed resting 0·104 per cent., ½ hr. later, 0·118 per cent., 1 hr. later, 0·116 per cent., 1½ hrs. later 0·106 per cent,—a normal result.

Re-examination on 12th May, 1930, showed that the patient had gained 7 lb. in weight, and he looked extremely well. There was no fluid in the abdomen, the veins on the upper abdominal wall were very much smaller, and the liver and spleen had remained unchanged. The blood showed:—Hb. 60 per cent., red cells 4,980,000, white cells 6,300 (polymorphonuclears 60 per cent., lymphocytes 29 per cent., metamyelocytes 8 per cent., eosinophils 2 per cent., basophils 1 per cent.): platelets 337,000. The blood sugar before 50 grm. of levulose was 0·119 per cent., ½ hour after was 0·129 per cent., 1 hour after 0·137 per cent., and 1½ hours after was 0·137 per cent.

It may be difficult to differentiate splenic anaemia from biliary cirrhosis especially when this is of the type described by Gilbert and Fournier, in which enlargement of the spleen is more marked than that of the liver. In biliary cirrhosis, jaundice occurs in the early stages and is of a remittent character, being usually deeper in each successive attack, and for this reason often presents a similarity to acholicuric jaundice rather than to splenic anaemia, though the fragility of the red cells is never increased. In discussing treatment the advisability of splenectomy arises. An effect of splenectomy is to produce a rise in the platelet count, and if before operation the count was normal or high, there is a grave danger of subsequent thrombosis in the portal system, and in our opinion a high platelet count constitutes a definite contra-indication to this procedure. When the count is normal the risk is still considerable. When the platelet count is low, splenectomy in the majority of cases will effect a cure. In young children the operative risk is considerable, and in very slowly progressive cases it may be desirable on this account to postpone operation to a later age. In Case 17, the patient was not considered in a fit condition for splenectomy, but it was felt that as his condition was so serious, some operative procedure with the object of limiting splenic activity was desirable. In the light of the work of R. M. Pearce, it seemed that this object might be attained.
by ligature of the splenic veins. The operation in this case was found to be simple and was not attended by any severe surgical shock. The clinical results were extremely satisfactory and whereas the liver function as demonstrated by the laevulose tolerance test was grossly impaired before operation, six weeks later a normal result was obtained. It will be noted that as with splenectomy the platelet count rose from a pre-operative figure of 160,000 to 870,000 per c.mm. thirteen days later. It would appear from this that ligation of the splenic veins is only indicated when the platelet count is low. The operation has the great advantage that it is rapidly performed and the dangerous procedure of dividing splenic adhesions is avoided.

(e) Anæmias associated with metabolic disturbances.—Perhaps the best known example of this is the anæmia associated with thyroid deficiency. This may be very severe, is accompanied by a low colour index, and usually responds readily to thyroid medication, although it may be advisable in some cases to give iron salts as well.

Less well recognized is the fall in haemoglobin met with in cases of catarrhal jaundice, although this is seldom sufficiently severe to necessitate treatment. In another group of cases periodic attacks of mild jaundice of hepatic origin are associated with cyclical vomiting, and in these a troublesome degree of anæmia may be encountered. In this condition there is a low colour index, with frequently a moderate leucocytosis.

Clinically the attacks are marked by pyrexia and extreme prostration, and the picture may be very similar to that of leukæmia, a point to which we shall return later. The attacks of jaundice, pyrexia and anæmia also present points of similarity to the biliary cirrhosis referred to above. For treatment, in addition to the well-known effects of administering glucose and allied preparations, it is usually advisable to give adequate doses of a readily assimilated form of iron such as iron ammonium citrate.

Case 18. Joseph B. developed a slight cold at the age of 15 months and was noticed to become pale and restless. A month later he suddenly became much more anæmic. After a few weeks the condition improved and an attempt was made to ‘feed the child up’ to make up for the period of illness. This was rapidly followed by vomiting, and the child became fretful, pale and restless. A month later there was a further attack of vomiting, again associated with anæmia. After 3 weeks’ interval there was yet another attack. In January 1928, the child was seen by one of us, and blood examination showed:—Hb. 32 per cent., red cells 2,100,000, white cells 7,800. The red cells showed anisocytosis and poikilocytosis, but the mean diameter was normal. There was at this time distinct jaundice. Fats were largely omitted from the diet and the amount of sugar was increased: after this there were only one or two mild attacks of vomiting and he fairly rapidly recovered from his anæmia. Two years later he is still in perfect health.

(f) Anæmias of infective origin.—It is well known that the acute specific fevers and sepsis are frequently associated with anæmia (Case 19). That occurring in infective endocarditis has already been referred to, though the latter condition is rare in childhood and very rare in infancy.

Case 19. Lilian E., age 6 weeks, became jaundiced on the first day after birth, and had become progressively so until admitted to hospital. When 5 days old she had convulsions and when 3 weeks old there was a watery umbilical discharge. On admission the child was deeply
jaundiced, and had large subcutaneous hematomata on the face, scalp, and body. She was in a condition of tetany which yielded to injections of calcium chloride. A blood count showed: --
Hb. 34 per cent., red cells 1,800,000, colour index 0-94, white cells 22,400, platelets 53,000.
The liver was regularly enlarged and was firm; it reached nearly to the level of the umbilicus.
van den Bergh's reaction gave a strong positive immediate direct reaction and a positive indirect
reaction. The urine contained sugar and albumen, and the blood-sugar value was 0-209 per
cent. She improved for a time, the effusions of blood disappeared, the jaundice became less
marked, the liver became smaller and the child gained in weight. Later she became weaker and
died, and post mortem the umbilical vein was found thrombosed and full of pus, and there
were multiple abscesses in the liver which was itself becoming cirrhotic.

In the anaemia associated with diphtheria, myelocytes are not uncommonly
found. In Still's disease, there is often a moderate degree of anaemia which is not
so severe as the pallor suggests. The enlargement of the spleen and of the glands
may at first sight suggest a blood disease but the condition of the joints is
diagnostic. Other conditions producing pallor and anaemia are acute rheuma-
tism, particularly with pericarditis or endocarditis, and nephritis. Rarer
causes of anaemia of this type are congenital syphilis and tuberculosis: in all
these the associated clinical picture is usually so evident as to leave no doubt
as to the cause of the anaemia.

(g) Hodgkin's disease, leukæmia, chloroma, and glandular fever.—The pre-
sence of glandular enlargement, splenomegaly, recurrent bouts of pyrexia and
severe anaemia are so common in childhood as to present considerable difficulties in
diagnosis.

In Hodgkin's disease anaemia is not often one of the earliest symptoms.
When present it is marked by a low colour index, and the white cells are either
increased or decreased according to the stage of the disease. Some cases show
eosinophilia, but taken as a whole the blood picture is not diagnostic. The
glands are discrete, of elastic consistency, and the enlargement frequently starts
in the upper cervical region. In children, moderate enlargement of the spleen
is usual. When there is an intermittent pyrexia the glands and the spleen
frequently enlarge still further, and then subside with the temperature. The
disease is not seldom associated with tuberculosis as illustrated by the following
case.

Case 20. Douglas C., at. 9, since November, 1925, had been noticed to be irritable and had
developed a dry cough and nocturnal enuresis. On examination in March 1926, he was distinctly
anæmic: Hb. 30 per cent., red cells 2,000,000, C.I. 0-75; white cells 5,200 (polymorphonuclears
61 per cent., lymphocytes 31-5 per cent., hyalines 6 per cent., eosinophils 1 per cent., basophils
0-5 per cent.). The spleen was firm and enlarged to the level of the umbilicus, and there was an
enlarged tender gland above the right clavicle. There was a well marked water-hammer pulse
(B.P. 115/40) and capillary pulsation, but no aortic bruit could be heard. A well marked harsh
systolic bruit was heard over the whole precordium. During the stay in hospital he had inter-
mittent bouts of pyrexia lasting 2 to 3 weeks, and reaching 104° in the rectum for several days
at a time. During these bouts the supravaculicular gland and other glands in the neck and axillæ
and also the spleen became much larger and more tender, subsiding again with the decline of
the temperature. He had a splenic rub and pleural rubs on two or three occasions. During
one of the relapses he developed epistaxis and purpura, and died. Post mortem miliary tuber-
culosus was found in the lungs, and the glands and spleen proved to be typical of Hodgkin's disease.
The heart muscle was very fatty but no valvular lesion was found.

ARCHIVES OF DISEASE IN CHILDHOOD
ANÆMIA AND LIVER THERAPY IN INFANCY

Leukæmia is much more common than is generally recognized, and although usually of the lymphocytic variety, may be myelocytic. Its onset may be insidious but much more usually is dramatic and may only be recognized on routine blood examination after excessive haemorrhage from slight trauma. In three of our cases such haemorrhage had occurred after extraction of a tooth. Considering the ready tendency of lymphoid tissue to hypertrophy in children it is remarkable that the glands, although numerous, are usually small. Glands of this nature are found in the neck, axillæ and groins and have usually appeared simultaneously in these situations, a point of importance in differentiation from Hodgkin's disease. As in this latter condition, there may be a slight irregular pyrexia, but at intervals this becomes much more pronounced and is associated with further enlargement of the glands, the liver and the spleen, which subsides with the pyrexia. During these phases there is profound prostration and the haemoglobin falls to a very low level. At such a time blood transfusion may be followed by a remarkable improvement and the haemoglobin may rise 30 or 40 per cent. The improvement is only temporary, and a fatal issue is not long delayed. This is well illustrated by Cases 21 and 22, and three similar cases are instanced by McLean and Caffey*.

Case 21. John B., set. 2 years 4 months, was admitted on 9th February, 1930. In September 1929, he had whooping cough of mild type. Since October, 1929, he was noticed to be weak, particularly in his legs, and in December he became irritable, sleepless and unsteady on his feet. He was treated with antipyrin and developed a purpuric rash. On admission he was extremely pale and very irritable and had haemorrhagic sordes round the mouth; he had slight general enlargement of the glands in the neck, axillæ and groins and the spleen was palpable one inch below the costal margin. There was also moderate enlargement of the liver. Blood examination on the 22nd January, 1930, had shown Hb. 60 per cent., red cells 5,440,000: white cells 24,000 (polymorphonuclears 2-7 per cent., lymphocytes 83 per cent., pro-lymphocytes 14 per cent., eosinophil myelocytes 0-3 per cent.). The red cells showed some anisocytosis and poikilocytosis, and 5,000 nucleated red cells per c.mm. were present. On the 10th February, the Hb. had fallen to 30 per cent., and the red cells to 2,500,000; the white cells numbered 4,000 (polymorphonuclears 2 per cent., lymphocytes 63 per cent., pro-lymphocytes 11 per cent., lymphoblasts 22 per cent., eosinophil myelocytes 1 per cent., basophils 1 per cent.). The blood platelets were very scarce. On 13th February, the Hb. fell to 23 per cent., and on the 15th Feb.

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Fig. 11. Temperature and pulse rate in leukæmia (Case 21).
ruary 12 oz. of citrated blood were transfused. On 24th February, the Hb. had risen to 65 per cent., and this was maintained until 28th February. The white cells still numbered 4,000 (polymorphonuclears 6 per cent., lymphocytes 62 per cent., pro-lymphocytes 23 per cent., lymphoblasts 7 per cent., hyalines 2 per cent.). During this time the spleen became impalpable, but subsequently became very large again. The Hb. rapidly fell to below 20 per cent. before death ensued. During the whole course of the disease there were periods of irregular pyrexia illustrated by Fig. 11.

Case 22. Margaret D., et. 3, was admitted on 12th February, 1930, for generalized painful glandular enlargement and anaemia. In December, 1929, there was pain in the right arm with inability to use it. Later the left thigh and knee became painful and tender to touch. A series of pyrexial attacks occurred each lasting three to five days, with intervals between, which, occasionally were as long as sixteen days. During the attacks the glands on both sides of the neck, in the axilla and groins became more enlarged and tender; these subsided when the temperature settled. On 14th February 1930, the blood count showed Hb. 62 per cent., red cells 3,510,000, white cells 5,600 (polymorphonuclears 20 per cent., eosinophils 2 per cent., lymphocytes 65 per cent., hyalines 12 per cent., basophils 1 per cent.). On 24th February, during another severe pyrexial attack with a temperature up to 105°, there were again pains in the joints especially in the hips, and blood examination showed white cells 2,800 (lymphocytes 98 per cent., hyalines 2 per cent.). Shortly after this the child died in an extremely anaemic state. The irregular pyrexia during the course of the illness is illustrated by Fig. 12.

The tendency of hæmorrhage to occur at an early stage has already been mentioned. The slightest trauma results in bruising and bleeding from the gums, and may lead to confusion with scurvy. The tonsils are enlarged, ragged, ulcerated and bleeding. Subconjunctival and cerebral hæmorrhages are not rare and purpuric spots may be scattered all over the body. Any drug which tends to produce a rash may precipitate widespread purpura. This
abnormal tendency to bleed is associated with a low platelet count. The importance of this has been demonstrated by McLean and Caffey*, who showed that in a series of nearly 200 cases of diseases in children the platelet count was abnormally low in six. These included the three cases of leukæmia. Apart from the clinical picture, the blood is diagnostic but needs expert examination. The value of the hemoglobin is always low but shows considerable fluctuation. The colour index is very variable and may be as high as 1·0, or as low as 0·4. The red cells show moderate anisocytosis, poikilocytosis and polychromasia: nucleated forms are often present in considerable numbers. The white cell count may be very high indeed, and we have encountered a figure as high as 1,450,000 per c.mm. in a case of lymphocytic leukæmia. This is exceptional, but figures of 200,000 are more common. In adults the count is usually high and low counts are rare, but in children low counts are common. The differential count of the white cells is of more importance than the absolute value. High white counts are of course found in other conditions, notably in whooping cough where a count of 60,000 is not infrequent, and even higher counts have been recorded. In lymphocytic leukæmia it is the rule to find immature white cells such as lymphoblasts and pro-lymphocytes in considerable numbers. In grave secondary anaemias it has already been mentioned that immature forms such as myelocytes or lymphoblasts may be met with, values up to 5 per cent. being common, but in leukæmia the values are commonly between 10 per cent. and 20 per cent. Any case in which the percentage number of lymphocytic forms is over 70 is strongly suspicious of leukemia, and when any considerable number of immature cells is present in addition, the diagnosis may be regarded as certain. In such cases examination of blood films at intervals will usually show periods during which the lymphocytic forms reach a total of over 90 per cent.

In myelocytic leukæmia the spleen is very much enlarged and usually reaches well below the umbilicus. Perisplenitis, manifested clinically by a rub, is very common. The glands are usually enlarged, particularly in the abdomen, where they may be felt by bimanual examination with one finger in the rectum. Purpuric eruptions are common, as also is intermittent pyrexia. There is often a vague history of general ill health during the preceding one or two months, but the general course after the case comes under observation is usually very rapid. Examination of the blood shows changes in the red cells as described in lymphatic leukæmia, although there is in this case a greater proportion of nucleated forms. The white cell count, in contra-distinction to lymphocytic leukæmia, shows a high count from an early stage, the number rapidly rising to over 100,000. The differential count shows a high percentage of true myelocytes and transitional forms.

Chloroma may be regarded as a special variety of leukæmia. It is a rare form and is best illustrated by Case 23.

Case 23. S.H., set. 6, was admitted to hospital on account of recurrent bouts of pyrexia, pains in the limbs and vomiting. He was treated with large doses of sugar, and improved markedly. Two months later the attacks recurred, and were accompanied by drowsiness and slight neck rigidity. The cerebro-spinal fluid was normal. Shortly after, he was noticed to

* McLean and Caffey, J. A. M. A., 1921, xlix, 1.
become anaemic, and blood examination showed: Hb. 70 per cent., red cells 5,800,000, C.I. 0.6; white cells 6,000 (polymorphonuclears 50 per cent., lymphocytes 37 per cent., eosinophils 4 per cent.). The anaemia and the drowsiness increased, and blood examination 6 weeks later gave 59 per cent. haemoglobin, the white cell count remaining the same. At this time (6 months after admission) slight proptosis of the right eye was noticed, and this steadily progressed. Shortly afterwards the haemoglobin value was 22 per cent., and the red cells showed considerable anisocytosis, some polychromasia, and a few nucleated forms were seen. The white cells were now 1,400 (lymphocytes 78 per cent., pro-lymphocytes and lymphoblasts 4 per cent., polymorphonuclears 18 per cent.). He was transfused with only a temporary effect. The proptosis was much more marked and a definite tumour could be felt in the temporal fossa. A week later the C.S.F. showed 0.089 per cent. protein with an increase in the globulin, and 2 cells per c.m.m. The total white cells were now 19,000 with 83 per cent. lymphocytes and 8 per cent. of immature lymphocytic forms. At autopsy a week later typical deposits of chloroma were found in the right orbital fossa, extending into the temporal fossa.

Glandular fever tends to occur in epidemics and is characterized by a sudden onset of fever, with tender enlargement of the lymphatic glands, and an enlarged spleen which is often tender and rather soft. The liver is slightly enlarged but never to the extent met with in leukæmia. The temperature may be intermittent and after an acute course of two or three weeks tends to subside. Minor relapses are common, and it is often six or seven weeks before the temperature becomes normal. The blood shows moderate anaemia, the main points of interest being in the white count. There is moderate leucocytosis of 15,000 to 30,000, and in six cases which we have observed the differential count has invariably shown a rise in the number of mononuclear (hyaline) cells. Immature hyaline cells are often present in considerable numbers.

Malignant disease is a rare cause of anaemia in childhood. It includes such forms as sarcoma of the kidney, teratomata and tumours of the suprarenal glands. The cause of the anaemia is usually obvious, but a left renal sarcoma has been mistaken for an enlarged spleen, and tumours of the suprarenals with secondary deposits in the temporal fossæ may be thought to be the deposits of chloroma.

**Von Jaksch's anaemia pseudo-leukæmia infantum.**—In 1889, von Jaksch drew attention to a form of severe anaemia occurring in infants associated with considerable enlargement of the spleen, and a blood picture showing a high white count, a relative and actual lymphocytosis and fairly numerous myelocytic cells; normoblasts and megaloblasts were also described as being present. Authorities have differed in regarding this condition either as a definite entity or as a type of infantile reaction not necessarily due to any single cause. Poyn- ton, Thursfield and Paterson, for example, hold the former view, but admit that one of the cases they describe 'affords some support to the arguments of those who, unlike ourselves, believe that von Jaksch's disease is not a clinical entity, but an unusually severe stage of any infantile anaemia, the uncommon features being merely an expression of the severity of the intoxication.' Krumbhaar, on the other hand, states that the anaemia 'is in all probability not an independent condition, but represents an atypical response of the infantile haemopoietic system to one or other of the primary diseases of the blood.' While not subscribing to the view that the condition is 'an unusually
severe stage of any infantile anaemia,' from the material at our disposal we are strongly of the opinion that the picture described by von Jaksch may be found in a number of conditions, certainly not entirely dependent on severity, for the picture may be maintained for a long time during recovery, whereas others rapidly proceeding to a fatal termination may never exhibit the characteristic features. Aschenheim and Benjamin found rickets in their cases: we have encountered the association, but it is by no means invariable. Giffint thinks the condition is the infantile form of splenic anaemia: in discussing the latter condition we have shown that splenic anaemia may occur in childhood without the picture described by von Jaksch. Von Jaksch himself appeared more concerned in differentiating the disease from true leukaemia, and was impressed by the number of illnesses showing a picture closely related to that of leukaemia.

The discussion is not of purely academic importance, for if the view we take is correct, the prognosis and treatment become those of the underlying conditions. This perhaps accounts for the varying statistics given by different writers as to the effects of treatment. Case 8 is that of a child suffering from acholuric jaundice which presented the features described by von Jaksch. In infancy the picture was that of von Jaksch's anaemia but later the characteristic features of this condition largely disappeared leaving the underlying condition unmasked. Had an estimation of the fragility of the red cells been made in the early stages, a diagnosis of acholuric jaundice would almost certainly have been made. We feel that most, if not all of the cases described under this heading could be classified in one of the groups described earlier in this paper.

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