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FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, EDINBURGH; MEMBER OF THE ROYAL COLLEGE OF PHYSICIANS, LONDON; VICE-PRESIDENT, ROYAL MICROSCOPICAL SOCIETY; DIRECTOR OF THE PATHOLOGICAL DEPARTMENT, ROYAL INFIRMARY, WIGAN; CONSULTING PHYSICIAN, LEIGH INFIRMARY, ETC.

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PREFACE.

THE title suggests the aim of this small addition to the students' library, written at the request of many undergraduates and graduates, and teachers of clinical medicine.

That some of the views expressed herein will not gain universal acceptance is only to be expected, for hæmatology is a controversial subject. This may not detract from the main object, which is to present to the student and practitioner a summary of the diseases of the blood in the light of recent advances in clinical hæmatology.

I must express my gratitude to Professor John Hay for many valuable suggestions, to Mr. C. F. Hill for his enthusiastic and invaluable assistance in the preparation of the photomicrographs, and to the Editors of the *British Medical Journal* and *Journal of the Royal Microscopical Society* for permission to use some of the illustrations.

Coloured drawings have not been used (the illustrations are photomicrographs) because it is the first essential that students should recognise structure rather than colours.

The photomicrographs were taken with a Watson's camera, Watson's 2 mm. apochromatic objective, and the oil immersion condenser made by the same firm. The magnification in each case is 1000 diameters.

W. E. C.

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ELEMENTARY HÆMATOLOGY.

CHAPTER I.

INSTRUMENTS AND METHODS.

It is outside the scope of this student's manual to describe all the various instruments and methods used in hæmatology; only those that have been found useful to the beginner will be mentioned.

The Microscope is the most important piece of apparatus in hæmatology and some knowledge of its use is essential. There are many good books on microscopy,

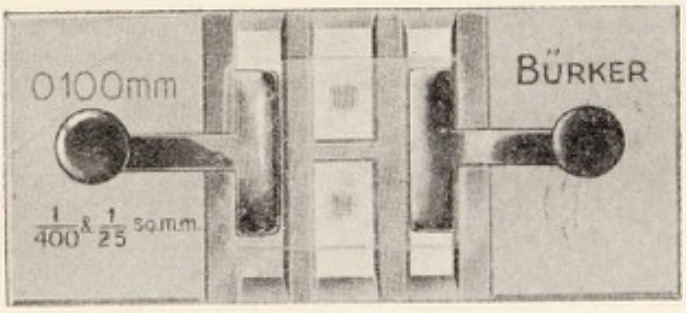


Fig. 1.—The Bürker or open type of hæmocytometer, showing coverslip clamped into position.

by the aid of which the student will, in a short time, be able to manipulate the instrument intelligently.

Micrometry may be learned from the same source, or by practical demonstration, in a few minutes.

The Hæmocytometer.—The most convenient and the most accurate is the Bürker type of instrument. This consists of a table, cut out of solid glass, on which are two counting chambers separated by a trench (fig. 1). The table on which the counting chambers are etched is 0·1 mm. lower than the rest of the slide. Over the

counting chambers a coverslip is applied and clamped into position.

The rulings of Thoma and Neubauer are most commonly used. The Neubauer ruling (fig. 2) consists of 9 squares, each 1 mm. square. These are sub-divided, and the central square millimetre divided into 400 small squares each $\frac{1}{20}$th mm. square, and arranged by triple ruled lines into 16 groups of 16.

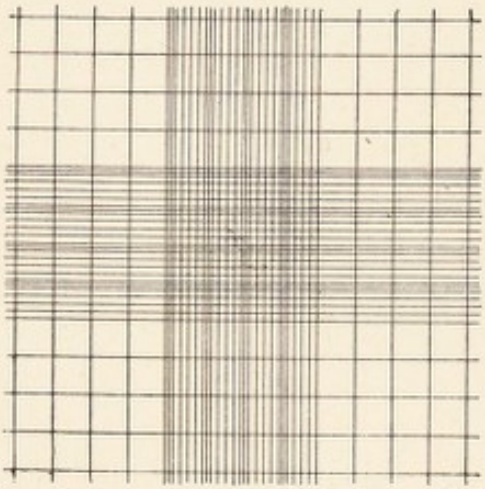


Fig. 2.—Neubauer's ruling.

The area of each of the large 9 squares is 1 sq. mm., and as the depth with the coverglass in position is $\frac{1}{10}$th mm., the cubic capacity is $\frac{1}{10}$th of a c.mm. The small squares in the centre which are used for the enumeration of red corpuscles are a $\frac{1}{400}$th of a sq. mm. in area, and their capacity with the coverslip in position is $\frac{1}{4000}$th of a c.mm.

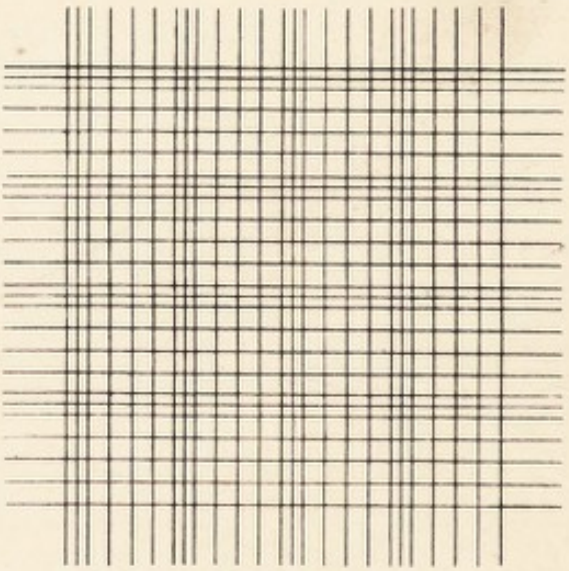


Fig. 3.—Neubauer's ruling.
(Central square mm. magnified.)

Fig. 3 is the central sq. mm. used for counting red corpuscles. The centre square millimetre is subdivided into 400 small squares, each fifth of which is divided by a median line for convenience in counting.

Hæmocytometers made of solid glass can be cleaned with acid if necessary and kept in a mixture of alcohol and ether without damage to any part.

Enumeration of Erythrocytes.—The pipette with 101 engraved above the bulb is used. The skin on the patient's finger is cleansed with alcohol and dried and a puncture made on the palmar surface with a No. 1 straight Hagedorn needle. The first drop of blood is wiped off and the pipette filled up to the mark 0·5 from the second. Should the blood go beyond the mark it can be drawn back by wiping the tip with a clean piece of linen. Plunge the tip of the pipette into the diluting fluid and draw it up to the mark 101. This gives a dilution of 1 in 200. Take the ends of the pipette between the thumb and middle finger and shake until the blood and fluid are well mixed. The diluting fluid is Hayem's solution :

Perchloride of mercury . .	0·5 gm.
Sodium sulphate . . .	5 ,,
Sodium chloride . . .	1 ,,
Distilled water	200 c.c.

Blow out nearly half the contents of the bulb and place the tip of the pipette to the angle between the edge of the coverslip and the counting chamber of the hæmocytometer. The diluted blood will flow by a capillarity over the counting platform. If bubbles are present or if the blood overflows into the ditch the process must be repeated. The hæmocytometer is placed on the microscope and a $\frac{1}{6}$th in. or a 4 mm. objective with a long working distance used.

The red corpuscles in 80 small squares are counted. In counting, corpuscles which lie on the left hand and upper lines should be counted as within the squares, those on the lower and right-hand lines are not counted; It is convenient to take 5 sets of 16 small squares that are bounded by the triple lines.

Calculation.—Suppose the numbers counted in the 5 sets of 16 were :

The first set of 16 squares . .	100
,, second ,, ,, ,, . .	110
,, third ,, ,, ,, . .	95
,, fourth ,, ,, ,, . .	106
,, fifth ,, ,, ,, . .	112
The total in 80 small squares	=523

To find the number per cubic millimetre of undiluted blood, take the average, in this case $\frac{523}{80}$, multiply it by 4000 (the cubic capacity of each small square being $\frac{1}{4000}$ c.mm.) and 200, the amount of dilution; in other words by 800,000. In the example the number per cubic millimetre would be 5,230,000. With the dilution of 1 in 200 the number in a cubic millimetre of undiluted blood is obtained by adding 4 cyphers to the total counted in 80 small squares.

Enumeration of Leucocytes.—The pipette with 11 engraved over the bulb is used. The technique for collecting the blood is the same as for erythrocytes. Blood is drawn into the pipette 0·5 mark, and the diluting fluid to mark 11, this gives a dilution of 1 in 20. The diluting fluid is 0·5 per cent. of glacial acetic acid in distilled water. This fluid hæmolyses the red corpuscles and makes the leucocytes stand out as refractile bodies with their contour well defined. About half the contents of the bulb are blown out and a drop placed in the other division of the hæmocytometer.

Counting.—With the Thoma ruling at least four or five preparations must be made, and the leucocytes counted in the centre square millimetre and averaged. With Neubauer's ruling the leucocytes in all the 9 sq. mm. can be counted with one operation. The average for

1 sq. mm. is found, and the figure multiplied by 10 gives the number of leucocytes in 1 c.mm. of diluted blood, and this figure multiplied by 20 (the dilution) gives the number per cubic millimetre of undiluted blood.

For example, if 270 leucocytes were counted in the 9 sq. mm. then $\frac{270}{9} \times 10 \times 20 = 6000$ leucocytes per cubic millimetre in undiluted blood.

Hæmoglobinometers.—There are many hæmoglobino-

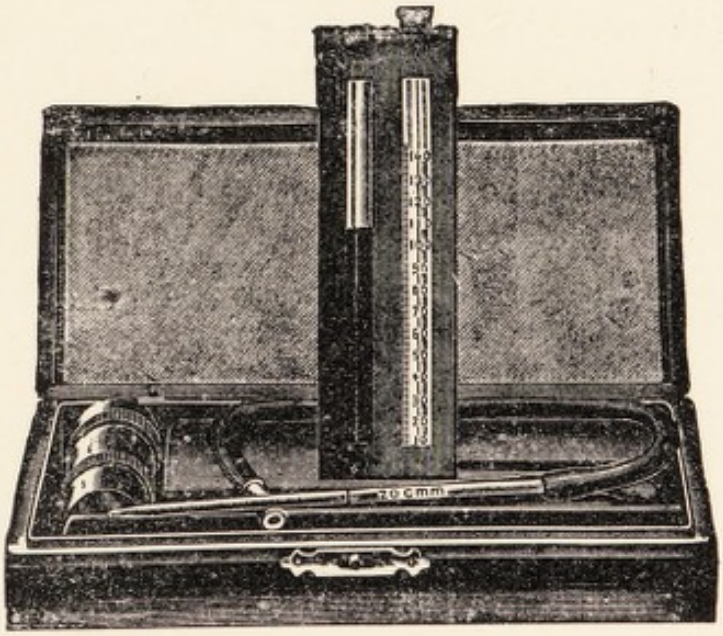


FIG. 4.—The Sahli hæmoglobinometer.

meters in common use, and the student must be guided by the advice of his teacher in clinical pathology as to which type he uses.

It will be sufficient to mention two that are accurate for clinical work.

The Sahli Hæmoglobinometer (fig. 4) consists of a pipette to measure 20 c.mm. of blood, a standard colour tube containing a 1 per cent. solution of acid hæmatin, a bottle and dropper for distilled water, and a graduated tube for diluting the blood to be examined. The graduated tube is filled up to the mark 10 with decinormal hydrochloric acid. Blood is taken up to the 20 c.mm

mark on the pipette and added to the acid. In a few minutes the hæmoglobin is converted into acid hæmatin. Distilled water is added until the colour matches the standard, and the percentage of hæmoglobin is then read off. The apparatus should be kept in the dark when not in use, as prolonged exposure to light alters the colour of the standard.

Dare's Hæmoglobinometer.—In this, undiluted blood is allowed to flow by capillarity into a slit between two small plates of glass clamped in a metal holder. One piece of glass is clear, the other opal. The holder is placed, with the opal glass towards the source of light, into a receiving slot in the instrument and the colour compared with that of a graduated glass disc, and the percentage of hæmoglobin read off at the side. This instrument is expensive, and the examination must be made rapidly before clotting occurs.

Colour Index.—The colour index indicates the amount of hæmoglobin in each red corpuscle compared with the normal amount taken as unity. The normal number of erythrocytes is taken as 5,000,000 per cubic millimetre, so that in a case with that count and a 100 per cent. hæmoglobin, the colour index would be 1. The colour index is obtained by dividing the percentage of hæmoglobin by the percentage number of red corpuscles. For example, if the red-cell count is 2,500,000, that is 50 per cent. of the normal, and the hæmoglobin 40 per cent., the colour index would be $\frac{40}{50}=0{\cdot}8$. In red-cell counts of 1,000,000 and over, the percentage of corpuscles is obtained by multiplying the first two figures of the count by 2.

The Hæmatocrit.—This is an instrument for the determination of the relative volumes of corpuscles and plasma. It consists of a graduated capillary tube of uniform bore in which the specimen of oxalated blood is

placed and centrifuged at 7000 revolutions per minute until the sedimented corpuscles do not show further shrinkage. The height of the column is read off on the millimetre scale and the percentage relation to the normal calculated. The volume index expresses the average size of the red cell compared with the normal size. It is the quotient obtained by dividing the volume of red corpuscles obtained by the hæmatocrit by the number of red corpuscles per cubic millimetre, both expressed in percentages of the normal. The volume index runs parallel to the colour index. The following are averages given by Larrabee :—

	Erythrocytes per c.mm.	Hæmoglobin per cent. by Sahli instrument.	Colour index.	Volume index.
Normal males .	5,267,250	103·0	0·98	1·007
Normal females .	4,968,667	106·0	1·06	1·001
Addison's anæmia	1,712,166	50·0	1·47	1·270
Secondary anæmia	3,737,160	61·0	0·81	0·790
Chlorosis . .	3,205,000	34·5	0·55	0·695

It has been found that the corpuscular volume varies directly, not only as the number of corpuscles but also as the concentration of hæmoglobin. There is no great change in the hæmoglobin concentration in each corpuscle even in disease. The hæmoglobin-content also depends on the size of the corpuscles, so that the colour index may be taken as a guide to the average size of the corpuscles.

Enumeration of Thrombocytes.—1. *In Blood Films.*—A drop of a 14 per cent. magnesium sulphate solution is placed on the skin of the finger-tip, and the needle pushed through the drop. The blood is mixed on a slide with a

glass rod coated with paraffin, and a film made in the usual manner, fixed and stained with Giemsa. The ratio of platelets to red cells is determined. The number of red cells per cubic millimetre is counted in the hæmocytometer at the same time, and the number of platelets per cubic millimetre calculated.

2. In the next method, the platelets are counted in the hæmocytometer in a dilution of 1 in 100. The diluting fluid consists of two parts of an aqueous solution (1 in 300) of brilliant cresyl blue and three parts of 1 in 1400 aqueous solution of potassium cyanide. The solutions are kept separate and mixed immediately before using. The blood is taken up to the mark 1 in the red-cell pipette and diluted to 101 with the diluting fluid, and shaken. A drop is placed in the counting chamber and allowed to stand for ten minutes, and the count made with $\frac{1}{6}$th in. objective. The platelets appear as rounded lilac-coloured bodies.

Prothrombin Time.—The estimation of prothrombin time is important in the diagnosis of hæmophilia. In this disease the prothrombin time is lengthened from eight to thirty times the normal.

Howell's Method.—Decalcification and subsequent recalcification activate the maximum amount of prothrombin present in the blood and the inhibitory action of antithrombin is overcome.

Take 2 or 3 c.c. of blood from a vein, and place it in a centrifuge tube which contains 0·25 c.c. of a 1 per cent. solution of sodium oxalate in normal saline. Invert several times and centrifugalise for ten minutes. Take four small test-tubes, and to each add five drops of the clear plasma and a 0·5 per cent. calcium chloride solution; two drops in tube 1; three drops in tube 2; four drops in tube 3; and five drops in tube 4. Invert each tube two or three times. Repeat this with a specimen

of normal blood as a standard. The coagulation time of the tube which clots first is the prothrombin time. The "prothrombin quotient" is found by dividing the time of the unknown blood by that of the normal standard.

Reticulated Red Cell Count.—The stain is made by adding two drops of a 2 per cent. potassium oxalate solution and one drop of a 1 per cent. aqueous solution of brilliant cresyl blue to 5 c.c. of 0·85 saline. Take up blood in the pipette for counting leucocytes to the 0·5 mark and draw up the solution to the 11 mark. Shake the pipette for two or three minutes and place a drop on a slide, spread and allow to dry, and examine with a 2 mm. objective. The percentage of reticulated cells in 1000 erythrocytes is calculated.

Preparation of Blood Films.—The first essential in making a satisfactory blood film is to render the slides fat free. This is done by placing them in a mixture of chromic acid one part, strong sulphuric acid eight parts, for twenty-four hours; thoroughly wash under the tap and transfer them to a mixture of alcohol and ether. They are dried with a cloth rendered fat free by boiling in sodium carbonate solution and rinsed in several changes of water and dried, but not ironed.

The Spreader.—A spreader may be made by cutting an ordinary 3×1 microscope slide in half, or a special spreader [1] used. The spreader is a piece of glass measuring 5 cm. by 19 mm., the edges of which are very finely ground and square (fig. 5). A drop of blood the size of a large pin-head is placed half an inch from the end of a slide; the spreader is held at an angle of approximately forty-five degrees and moved backwards until it touches the drop; the motion is then reversed, the spreader drawing the blood behind it and distributing

[1] Made by Watson & Sons, 313 High Holborn.

it evenly in the centre of the slide. The great advantage is that the blood does not spread to the edges of the slide. If the blood overflows the edges most of the leucocytes are lost and the film is valueless for the differential and

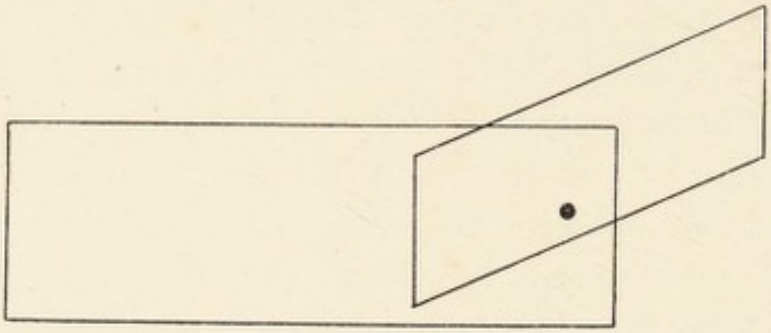


Fig. 5.

polynuclear counts. The completed film should look like fig. 6.

The Stain.—There are many modifications of the Romanowsky stain in use and most of them are satisfactory for human blood. The important point for the student is to get accustomed to any one of the modi-

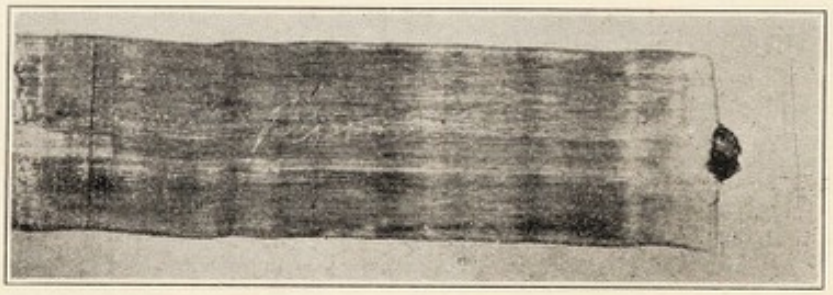


Fig. 6.

fications. For routine clinical work one of the most satisfactory is Giemsa. The film is dried in air, fixed for ten minutes in methyl or absolute ethyl alcohol. The stain is diluted 1 to 10 with distilled water and the film stained for twenty minutes, washed under the tap, and dried between filter paper. The film may be examined unmounted with a 2 mm. objective, but must be mounted if a 4 mm. be used. The distilled water must not have an acid reaction, and it would be better

to use solution of potassium carbonate 1 in 40,000 in distilled water. The objection to Giemsa is that the time required in staining films is longer than with Wright's or Leishman's stain.

The Peroxydase Reaction.—The use of this reaction is to differentiate between lymphocytes and myeloblasts, as these two cells may be indistinguishable morphologically. There are several methods, but Goodpasture's stain is as satisfactory as any:

Sodium nitroprusside . .	0·05 gm.
Benzidine	0·05 ,,
Basic fuchsine . . .	0·1 ,,
Hydrogen peroxide . .	0·5 c.c.
Alcohol (95 per cent.) . .	100·00 ,,

Make a blood film and allow to dry. Cover the slide with the stain for one minute; then add an equal quantity of distilled water and let the diluted stain act for three minutes, wash and dry. Intense blue-black granules are seen in the polymorphs, eosinophils, myelocytes, and myeloblasts. Monocytes show a few blue-black granules. Lymphocytes stain a light red colour and do not show any granules (fig. 7).

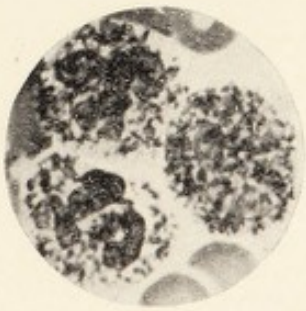


Fig. 7.—The peroxydase reaction in three polymorphonuclear leucocytes.

Coagulation Time. — The normal coagulation time of blood taken from a skin puncture is about three and a half minutes. The time is influenced by many factors — temperature, cleanliness of instrument, size of the drop, and admixture with tissue lymph. Coagulation time of blood taken directly from a vein varies, according to the method used, from five to twenty minutes. The simplest method of estimating coagulation time is to place several drops of blood on a

clean slide and draw a needle through one of the drops at one-minute intervals. When shreds of fibrin cling to the needle coagulation has taken place. Coagulation time is shortened in infections by pneumococcus and b. typhosus. Coagulation is delayed in hæmophilia, in some cases of Addison's anæmia, and in obstructive jaundice.

Bleeding Time.—*Duke's Method.*—Make a slight cut in the lobe of the ear with the point of a scalpel. At half-minute intervals blot with a piece of filter-paper all the blood which has flown out from the cut. The rate of decrease in the size of the blot indicates the rate of decrease of the hæmorrhage. Normally there are three to six blots in the bleeding time of one to three minutes.

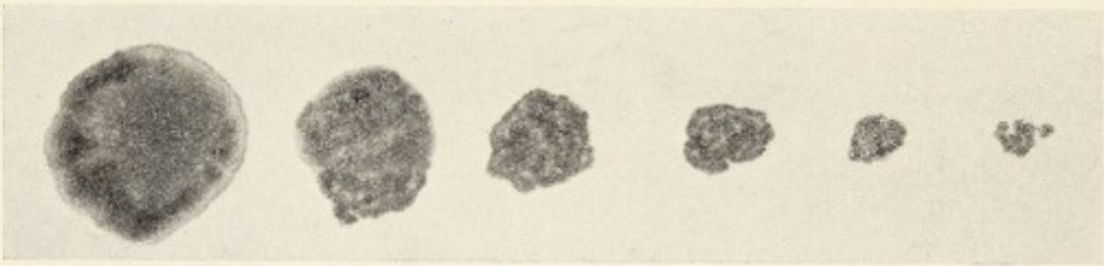


FIG. 8.—A row of blots made at half-minute intervals from a case where the bleeding time was normal.

There is slight increase in the bleeding time in severe anæmia, and very great prolongation in conditions in which the thrombocytes are diminished in numbers, viz. thrombocytopenic purpura, in chloroform and phosphorus poisoning, and in some cases of lymphatic and myeloblastic leukæmia.

Fragility of Red Corpuscles.—An accurate 1 per cent. solution of NaCl is necessary. A double row of small test-tubes is placed in a rack and filled as follows:—

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1 per cent. saline, c.c. . .	0·6	0·7	0·8	0·9	1·0	1·1	1·2	1·3	1·4	1·5
Water, c.c. .	1·4	1·3	1·2	1·2	1·0	0·9	0·8	0·7	0·6	0·5
Percentage of NaCl . .	0·3	0·35	0·4	0·45	0·5	0·55	0·6	0·65	0·7	0·75

To each tube of the front row is added 0·1 c.c. of the patient's corpuscles after washing and centrifuging, and to the back row the same quantity of normal corpuscles. Normal corpuscles hæmolyse in the 0·45 per cent. tube, but there are always intact corpuscles at the bottom of the tube, indicating that hæmolysis is incomplete. At 0·35 per cent. hæmolysis is complete. The striking example of increased fragility of the red corpuscles is acholuric jaundice in which hæmolysis commences at 0·7 per cent. and is complete at 0·5 per cent. Slight increase in fragility is found in some cases of streptococcal infections and in von Jaksch's anæmia. Increased resistance is found in obstructive jaundice, splenic anæmia, and after removal of the spleen.

Care of Instruments.—Scrupulous cleanliness is essential. The hæmocytometer pipettes should be cleaned immediately after use by drawing through them successively two changes of water, alcohol, and ether, or acetone. If a clot has formed in the pipette it may be dislodged with a horsehair, but never with a wire, and the pipette should stand overnight in a test-tube of strong sulphuric acid. From time to time it is advisable to fill the pipettes with liquor potassæ and let them stand for a few hours. The counting chamber must be cleaned with water and a little acetone applied with a fat-free cloth, and if the instrument is of the solid type it can be kept in a jar of alcohol and ether together with the coverslips.

CHAPTER II.

EMBRYOLOGY.

THE part of the mesoderm that concerns hæmatology is the mesenchyme or primitive connective tissue from which are developed:

1. The blood-stream cells.
2. The endothelium of the vessels.
3. The specialised endothelium and reticular cells of the reticulo-endothelial system, viz. the lining of the sinusoids of the liver, lymphatic glands, spleen, marrow, and medulla of the suprarenals.
4. Free histiocytes, the wandering macrophages of connective tissue, some of which develop granules and become tissue-mast cells.

Blood-Stream Cells.—In the first few days of embryonic life, the cells in scattered areas of the mesenchyme become differentiated into endothelium, surrounding free cells floating in plasma. These are the early blood-vessels and primitive blood-cells. They appear first in the yolk-sac, and in a short time, about three weeks, the vessels of the sac have communicated with those formed in the embryo. Later, about two and a half months, mesenchyme cells have invaded the cartilages of the long bones and the tissue from which the flat bones will ultimately develop and take on hæmatogenic functions, but for a large portion of fœtal life the liver is the chief seat of blood formation.

The early fœtal red cell is a megaloblast whose nucleus undergoes endolysis resulting in the non-nucleated megalocyte, a corpuscle much larger than the normal

erythrocyte. At about five and a half to six months erythrogenesis becomes normoblastic in type, and the manufacture of blood-stream cells is gradually transferred from the liver to the marrow. The other mesenchyme descendants have developed into lymphatic tissue, reticular tissue, spleen, etc.

In post-natal life blood-stream cells are formed from several descendants of the mesenchyme. The specialised endothelium of the marrow gives rise to the marrow hæmocytoblast, and from this are developed erythroblasts and erythrocytes, myeloblasts, and granulocytes, and the giant marrow cell—the megakaryocyte.

Similarly, the lymphatic endothelium gives rise to the lymphatic hæmocytoblast, which, owing to its environment, has become somewhat altered in function and confines its activities to the production of lymphoblasts, which develop into lymphocytes.

The reticulo-endothelial system gives rise to the monocytes through an intermediate form, the monoblast or pre-monocyte. It must be remembered that although these descendants of the indifferent mesenchyme cells, called indifferent because they can undergo metaplasia, have normally specialised functions they still retain the potentialities of their ancestors. For instance, in a rabbit rendered anæmic by repeated bleeding the endothelium of the splenic sinusoids may be seen undertaking the production of normoblasts, and in Addison's anæmia the liver endothelium attempts to revert to its early hæmogenic function. The striking example of this reversion is the myeloid metaplasia of the endothelium of the spleen and lymph glands in myeloid leukæmia.

The term "cell potential" is used to indicate the possibilities of its line of development. It is governed by many complex factors, but once a cell becomes a

parenchymatous cell—of the brain or pancreas, for example—its potentiality is fixed and does not change. The mesenchyme descendants with which we are dealing, however, retain their early potentiality as in the examples above, and *in vitro* this can be altered by alteration of the environment. In tissue culture of embryonic spleen it is possible by altering the environment of the cells by chemical changes in the surrounding fluid to cause at one time an output of erythroblasts, and at another the leucocytic series of cells; and in cultures of lymph nodes the deeper cells develop into multinucleated giant cells, but if fresh embryonic extract be added they revert to normal growth.

There is no reason why the marrow should not undertake the production of all the blood-stream cells, and no doubt it does under certain conditions, but the balance of evidence is in favour of the multiple origin suggested above in normal post-natal life.

The Hæmocytoblast.—*The Marrow Hæmocytoblast.*—The blood-stream marrow cells arise to a large extent from pre-existing normoblasts and myeloblasts. The stock is replenished in one or other group, according to body requirements, from the primary division of the marrow endothelium—the hæmocytoblast. Rarely, in cases of intense marrow activity, in the leukæmias for example, the hæmocytoblast is found in the peripheral blood.

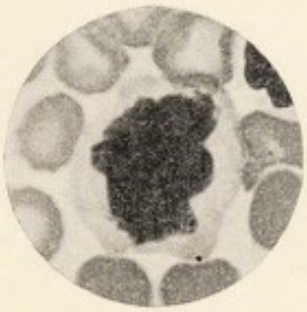
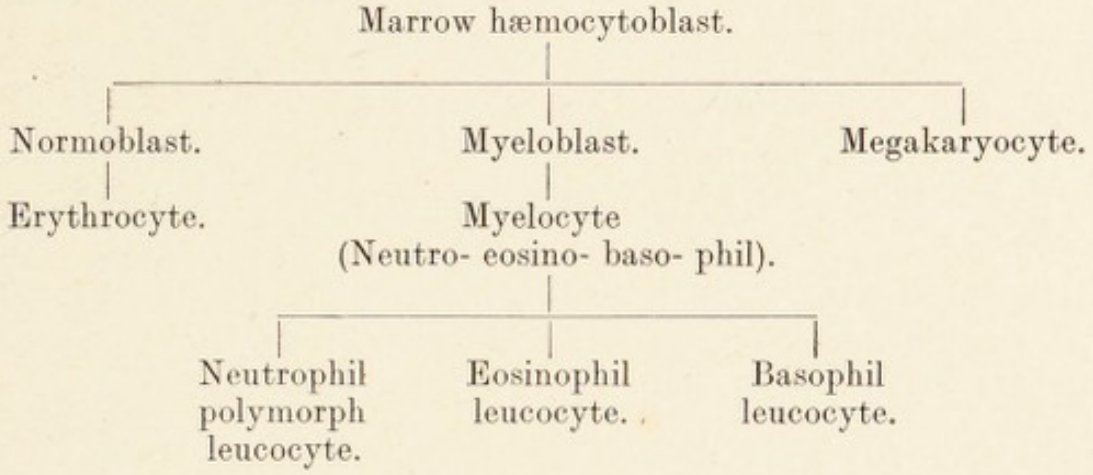


Fig. 9.—Marrow hæmocytoblast from a blood film in myeloid leukæmia.

It is a large cell, round or ovoid, with an ill-defined contour. The cell protoplasm is homogenous and faintly basophilic. No granules are present. The nucleus stains feebly with Giemsa and shows a very fine delicate reticulum, poor in chromatin. In addition to

blood-stream cells, it is the parent of the multi-nucleated giant cell of the marrow—the megakaryocyte.



These leucocytes contain granules and are grouped under the term "granulocytes."

The Lymphatic Hæmocytoblast.—This is indistinguishable morphologically from the marrow hæmocytoblast. It gives rise to the lymphoblast of the germ centres of lymphatic tissue, which in turn supplies the lymphocytes to the blood-stream.

Lymphatic hæmocytoblast.
|
Lymphoblast.
|
Lymphocyte.

The lymphoblast and myeloblast can only be differentiated by special nuclear stains and the peroxydase reaction. (*Note.*—The peroxydase reaction is not present in the earliest myeloblast.)

The monocyte, as mentioned above, arises through the monoblast from the endothelium of the reticulo-endothelial system, chiefly in the spleen.

CHAPTER III.

THE ERYTHROCYTES.

Origin.—In post-natal life the bone marrow is the sole source of erythrocytes. They arise from the primary division of the marrow endothelium, the hæmocytoblast, whose daughter cells, normoblasts, undergo active proliferation. The normoblast is approximately the same size as the erythrocyte. The nucleus is round and consists of densely packed chromatin, which in its early stage has a curious radial arrangement (fig. 16). Later, the nucleus becomes contracted into a deeply staining mass in which no structure is visible. The cytoplasm of the early normoblast is basophil, but hæmoglobin is soon metabolised. The nucleus undergoes endolysis, but is never extruded, and the resulting erythrocyte, ceasing to be a cell, becomes a mere mechanical carrier of oxygen and CO_2. Normoblasts are never found in the blood-stream in health except in the first few days of life.

Numbers.—The average numbers of erythrocytes in health in males is from 5,000,000 to 6,000,000 per cubic millimetre, and 4,500, 000to 5,000,000 per cubic millimetre in females. There are physiological increases during the first few days of infancy in persons living at high altitudes, and local increase due to vasomotor influences, such as the application of cold to a finger. Pathological increase occurs in congenital and acquired valvular disease, in conditions accompanied by marked loss of fluid, such as profuse sweating, vomiting and

diarrhœa, cholera and diabetes. A great increase in numbers is characteristic of erythræmia or splenomegalic polycythæmia and erythro-leukæmia.

Diminution in numbers occurs in all conditions causing anæmia—hæmorrhage, infective conditions, malnutrition, etc.

Size.—The mean diameter in health measured in plasma under conditions approximating those of the circulation is 8·8 microns. When a blood-film is dried and stained, shrinkage takes place and the diameter becomes 7·6 microns. The extreme variations in health in stained films are 5·5 and 9·5 microns. The erythrocyte measures 2 microns in depth through its thickest part. The mean diameter is somewhat diminished in secondary anæmias, but increased in Addison's anæmia owing to the presence of megalocytes.

Shape.—Erythrocytes are biconcave discs. They assume this shape even before the nucleus has undergone complete solution and before they leave the marrow. The shape is due to the resultant of stresses in the physico-chemical complex of the envelope and stroma, and is a definite advantage because it gives the largest area for exchange of gases and allows all parts of the interior to become saturated at the same time. No point of the corpuscle is more than 0·85 micron from the surface. If the erythrocyte was spherical the centre would be 2·5 microns from the surface and the surface area 20 per cent. smaller.

Rouleaux Formation.—In shed blood the red cells adhere together by their broad surface in groups of three to forty. Not only is this true of shed blood, but the condition may be seen in the capillaries of the mesentery in the living animal. The causes of rouleaux formation are complex. It is a property of normal human serum and plasma which is increased on heating to 60° C. and

is rapidly lost at room temperature. Alteration in the cohesive forces between the cells is not explained altogether by differences in electrical potential.

Rouleaux formation is deficient in the severe anæmias when there are large numbers of poikilocytes and cells of various sizes present.

Reticulated Red Cells.—These are present in normal blood in numbers varying from 0·3 to 1 per cent. They are demonstrated only by vital staining which shows up a basophilic reticulum (fig. 10). This reticulum is not the final remnant of the nucleus, but is indicative of immaturity. Reticulated red cells, or reticulocytes, are increased in any condition associated with abnormal marrow activity, as in recovery from the anæmias and in hæmolytic jaundice, in which disease they may be present to the extent of 10 to 20 per cent. There is a marked reticulocytosis in Addison's anæmia during the first few days of treatment by liver.

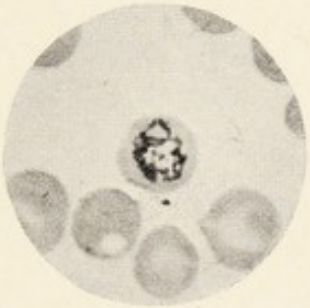


Fig. 10. Mag. = 1000.

Length of Life of the Erythrocytes.—The length of life has been estimated on the rate of bilirubin excretion, but it is impossible to arrive at a definite conclusion. According to the bilirubin estimation the length of life is from thirty to forty days. By transfusion methods the results would place the life at from twenty-eight to one hundred days.

Fate of the Erythrocyte.—The chief sites in mammals of blood destruction are the reticulo-endothelial cells of the spleen and liver. Here the erythrocytes are phagocyted and hæmoglobin disintegrated. Iron is split off from hæmatin in the form of hæmosiderin and retained, and the remainder of the molecule converted into bilirubin.

PATHOLOGICAL HÆMOGLOBINIFEROUS CELLS.

Achromia.—This is the term given to red cells deficient in hæmoglobin, and is shown in the blood-film by pallor of a larger central portion of the stained cell than normal.

Anisocytosis is the term used to indicate marked variations in the sizes of the red cells. It is found in all anæmias of any severity.

Megalocytes are large non-nucleated red cells measuring up to 16 microns in diameter.

Microcytes are cells smaller than normal erythrocytes and measure 2 to 4 microns in diameter.

Poikilocytes are misshapen erythrocytes and appear pear-shaped or angular.

Schizocytes are fragments of red cells and are seen most frequently in Addison's anæmia.

Figs. 11 and 12 are from two adjacent fields in a blood-film from a case of Addison's anæmia. Aniso-

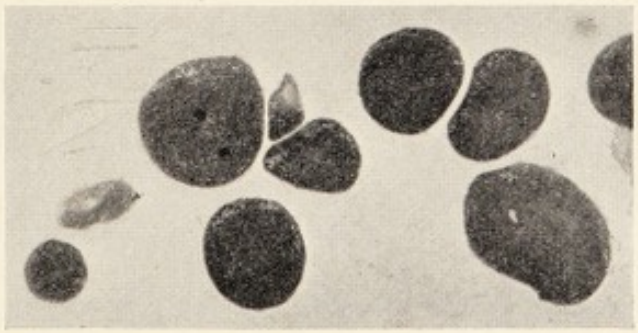


Fig. 11.

cytosis is well illustrated and several megalocytes (one containing Howell-Jolly bodies), a large poikilocyte also showing these bodies (fig. 12), and several small poikilocytes and microcytes are seen. A fragment of a red cell or schizocyte is seen close to a megalocyte in fig. 11.

Fig. 12.

Polychromatophilia or Diffused Polychromasia.—By these terms is meant that certain red corpuscles have an unusual affinity for basic dyes and stain a bluish colour with eosin-methylene blue preparations. The condition is seen in fœtal blood, and in conditions where active red-cell regeneration is taking place, as in the remissions of Addison's anæmia and in recovery from secondary anæmia. It represents an early stage in the formation of hæmoglobin.

Punctate basophilia is the term given to the presence

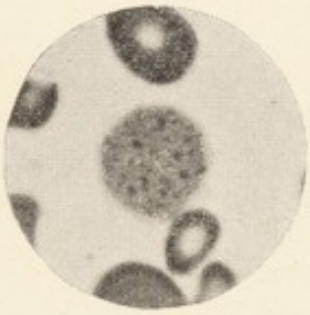


Fig. 13.

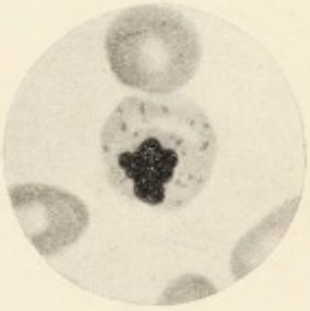


Fig. 14.

of scattered blue-black granules in erythrocytes. The granules are situated beneath the envelope, do not stain with methyl green, and have no relation to the nucleus. The granules may be very fine, or very coarse. The condition is seen in orthochromasic and polychromasic erythrocytes with and without Howell-Jolly bodies, and in cells with intact nuclei (figs. 13 and 14). They are never seen in fœtal blood nor in normal blood, and the

condition may be accepted as a sign of defect in the envelope.

Punctate basophilia is seen in severe anæmias, Addison's anæmia, and is a prominent feature in lead poisoning.

Howell-Jolly Bodies and Cabot's Rings.—Howell-Jolly bodies are nuclear remains and appear as small purple-stained masses in the erythrocytes. They stain with methyl green and chromatin stains. Cabot's rings are made up of very fine dots arranged in circles or figures of eight and have the same staining reaction. They are

Fig. 15.—Howell-Jolly bodies in a megalocyte.

Fig. 16.

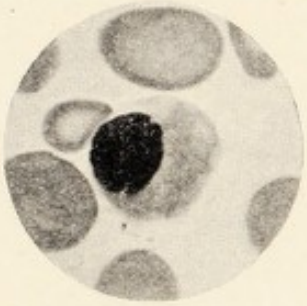


Fig. 17.

found in any condition where nucleated red cells are present in the circulation, especially in Addison's anæmia.

Normoblasts.—The parent cell of the erythrocyte, the normoblast, is found in the blood-stream in many pathological conditions, notably in severe secondary anæmia from whatever cause, in the leukæmias, and in Addison's anæmia. The cell is usually the same size as the erythrocyte. Fig. 16 is a normoblast of usual size. Occasionally large normoblasts are found. These large cells are given the title "macro-normoblasts" (fig. 17) to distinguish them from the megaloblast. The nucleus has the characters mentioned on p. 18, and, as will be seen from the photomicrographs, is quite different in structure to the nucleus of the megaloblast.

Megaloblasts.—These are nucleated cells measuring up to 24 microns in diameter and approximate the embryonic type of parent red cell. The title is unfortunate, because not all megaloblasts are large; some are very small, microblasts, others no larger than normoblasts, and others again have distorted cell bodies, poikiloblasts (fig. 23). The nuclear structure distinguishes them from normoblasts. The nucleus is vesicular, the chromatin strands appear widely separated, and in stained films the cytoplasm of the early cell is basophilic and shows a clear perinuclear zone due to retraction of the nucleus. Fig. 18 is a megaloblast,

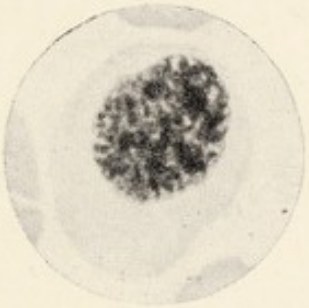


Fig. 18.

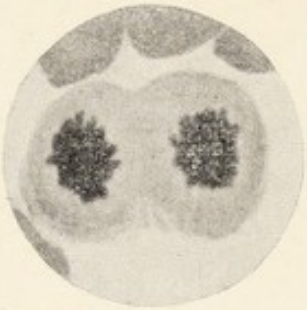


Fig. 19.

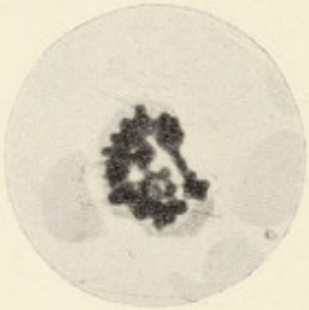


Fig. 20.

showing the characters mentioned above. They are frequently found in mitosis.

Fig. 19 is a megaloblast in telophase, and fig. 20 is a megaloblast daughter cell in late telophase. All stages of solution of the nucleus, karyolysis, down to the production of Howell-Jolly bodies, and all stages of pycnosis or clumping of the nuclear chromatin and fragmentation of the nucleus, karyorrhexis, are seen.

Figs. 21 and 22 illustrate solution of the nucleus or karyolysis.

Figs. 23 and 24 illustrate the condition of pycnosis and karyorrhexis in a poikiloblast and a small megaloblast. A schizocyte is present in fig. 24.

Eventually the nucleus disappears and the cell becomes a megalocyte, microcyte, or poikilocyte.

Vacuolation of the endoplasm is a frequent occurrence in red cells in Addison's anæmia. This has been termed

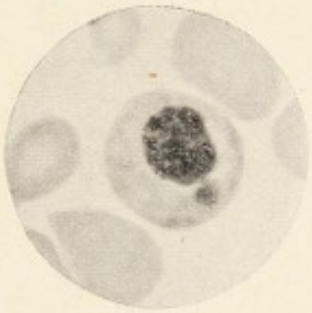


Fig. 21.

Fig. 22.

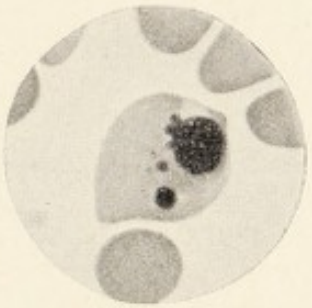


Fig. 23.

"endoglobular degeneration." The condition is not a degeneration, but due to shrinking of the endoplasm in the course of preparation of chemically defective cells.

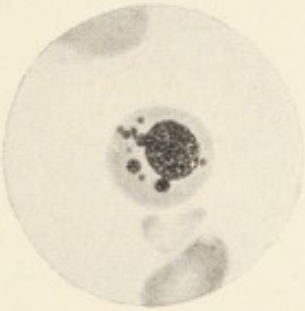


Fig. 24.

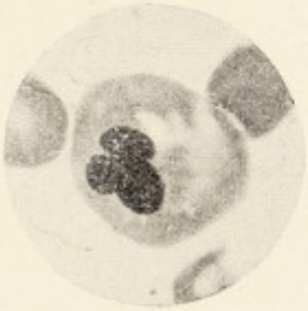


Fig. 25.

Fig. 26.

Fig. 25 is a megaloblast showing this condition, and also a fairly late stage of solution of the nucleus.

Fig. 26 shows the condition in a misshapen megalocyte. Note the minute microcyte in the figure.

Megaloblasts are characteristic of Addison's anæmia.

CHAPTER IV.

THE LEUCOCYTES.

Origin.—In post-natal life several tissues are responsible for the blood-stream white cells, as we saw in Chapter II. The marrow endothelium through the hæmocytoblast and myeloblast gives rise to the neutrophil myelocyte, eosinophil myelocyte, and the basophil myelocyte, which become the neutrophil polymorph, the eosinophil, and the basophil leucocytes. The lymphocytes originate in lymphoid tissue from the lymphatic hæmocytoblast, and the monocytes from the reticulo-endothelial system, chiefly of the spleen.

Numbers.—The average number in health varies from 6000 to 9000 per cubic millimetre, the proportions of the different kinds being approximately :

Neutrophil polymorphonuclears .	65 to 70 per cent.
Lymphocytes	20 ,, 30 ,,
Monocytes	2 ,, 5 ,,
Eosinophils	1 ,, 4 ,,
Basophils	0 ,, 1 ,,

Lymphocytes.—The small lymphocyte is a little larger than a red corpuscle, and has a large deeply staining nucleus, with a small amount of basophilic non-granular cytoplasm. Fig. 27 is a small lymphocyte. Large lymphocytes have the same densely staining nucleus, but possess more cytoplasm. The cytoplasm is pale blue and translucent, and may contain a few large pinkish granules. Fig. 28 shows two large lymphocytes

with granules in their cytoplasm. Lymphocytes are increased in numbers in lymphatic leukæmia, whooping-cough, glandular fever, congenital syphilis, tuberculosis, smallpox, chicken-pox, mumps, and typhoid fever.

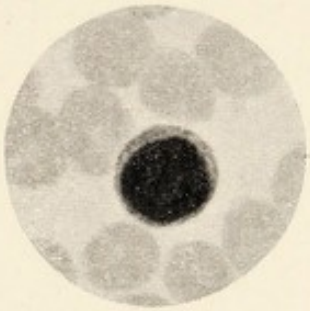


Fig. 27.

Fig. 28.

Actual reduction in the number of lymphocytes occurs in measles.

Monocytes.—These are large cells whose nuclei are often situated eccentrically.

The nucleus may be round, irregular, or horseshoe shape, and stains less intensely than the lymphocyte nucleus. Figs. 29 and 30 are typical monocytes. Fig. 29

Fig. 29.

Fig. 30.

illustrates the difference between the polymorph and this cell. The cell body has a large amount of protoplasm, which appears foamy owing to the wide meshes of its reticulum, and may contain a few azurophil granules.

Monocytes are increased in numbers in protozoal infections such as malaria and trypanosomiasis, in vaccinia and smallpox, dengue, and in any chronic microbic infection, and frequently in Banti's and Hodgkin's diseases.

It is interesting to note here that several facts point to the origin of the monocyte from the reticulo-endothelial system. Injections of colloidal silicic acid produce in rabbits changes in the endothelium of the spleen. These cells proliferate and coincidently monocytes appear in the blood-stream in enormous numbers. The same results are obtained by experimental infection of rabbits with b. monocytogenes. The virus of vaccinia acts especially on the reticulo-endothelial cells and causes an increase of monocytes in the blood-stream.

The Eosinophil Leucocyte.—These cells measure from 8 to 12 microns in diameter, and have either a single or

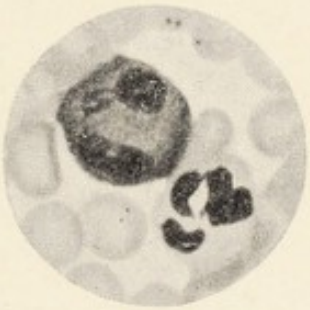


Fig. 31.

Fig. 32.

multi-lobed nucleus. The cytoplasm contains coarse, round, or oval granules, which have a strong affinity for acid stains. With eosin the granules stain bright red.

Fig. 31 illustrates an eosinophil and a polymorph. The granules in the polymorph are scarcely visible in the photograph, whilst those in the eosinophil are large and prominent.

Eosinophils number 1 to 4 per cent. of the leucocytes.

They are increased in many conditions, notably myeloid leukæmia, infections by animal parasites such as oxyuris vermicularis, trichinella spiralis, the tape worms, ankylostoma, bilharzia hæmatobia, and echinococcus; in fact, in infection by any of the worms. There is slight increase also in scarlet fever, and a very

marked increase in some cases of bronchial asthma, and in many skin diseases.

The Basophil Leucocyte or Mast Cell.—These are found in about 60 per cent. of normal people to the extent of 0·3 per cent. of the total leucocytes. They are rather smaller than the eosinophils. The nucleus may be round or indented or clover-leaf in shape, and is partly obscured by the coarse granules which stain deep purple with eosin-methylene blue preparations (fig. 32). Basophils are increased in numbers in myeloid leukæmia, sometimes in measles, diphtheria, and infections by staphyloccus aureus.

The Neutrophil Polymorphonuclear Leucocyte.—The polymorph measures 10 to 12 microns in diameter. The cytoplasm contains very fine granules which are oxyphil and stain a reddish tint with Giemsa. Fig. 33 illustrates a normal polymorph with five lobes in its nucleus united by fine chromatin filaments. The nucleus has 1, 2, 3, 4, or 5 lobes, according to the age of the cell in the blood-stream. This is of practical importance, as will be seen in the chapter on the Polynuclear Count.

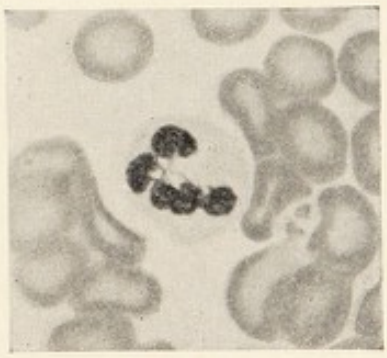


Fig. 33.

A physiological increase in the polymorphs occurs in the first few days of life, in the last few months of pregnancy, during digestion, after a cold bath, exposure to ultra-violet light, and exercise.

A pathological leucocytosis occurs in all infections *except* the following: measles, mumps, malaria, rubella, influenza, typhoid and para-typhoid fevers, uncomplicated tuberculosis (except tuberculous meningitis), and leprosy.

A polymorph leucocytosis occurs in certain toxic

conditions, such as malignant disease, uræmia, cirrhosis of the liver; after general anæsthetics, especially ether; after the injection of antitoxic sera and preparations of nucleic acid, and after hæmorrhage.

Leucopenia, or diminution in the number of leucocytes, mainly affects the polymorph, and occurs in some of the acute fevers, such as typhoid and para-typhoid fevers, measles, influenza, tuberculosis, whooping-cough (although the lymphocytes are increased), and smallpox in the early stages. Leucopenia is also common in malaria and trypanosomiasis, in pernicious anæmia and splenic anæmia. An infection may be so virulent—in some cases of pneumonia, for example—that the marrow is simply overwhelmed and ceases to function, and instead of the usual leucocytosis, diminution in numbers is found.

There is very marked diminution in polymorphs in aplastic anæmia, lymphatic and myeloblastic leukæmias.

PATHOLOGICAL LEUCOCYTES.

Myelocytes.—The presence of myelocytes in the blood-stream is always pathological. These are large cells with single, round, faintly staining nuclei, which in the

Fig. 34.

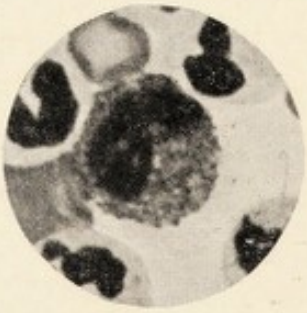


Fig. 35.

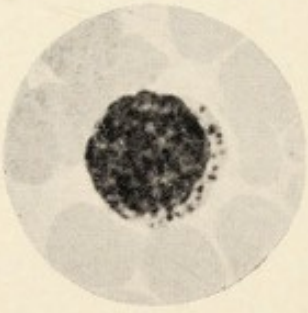


Fig. 36.

early forms have two or more nucleoli. The cytoplasm contains neutrophil, eosinophil, or basophil granules. Fig. 34 is a neutrophil myelocyte of the small type. Nucleoli are seen in the nucleus as pale areas surrounded

by denser rings of chromatin. Fig. 35 is an eosinophil myelocyte, and fig. 36 a basophil myelocyte. Myelocytes are frequently present in the blood-stream when there is a marked leucocytosis, and are always present in considerable numbers in myeloid leukæmia. They are constantly found in von Jaksch's anæmia and in malignant disease when metastases have occurred in the bone marrow.

Myeloblasts.—The myeloblast is the parent cell of the myelocyte and differs from it in two important points. The first is that the myeloblast has no granules in its cytoplasm, and the second that the nucleus is poor in

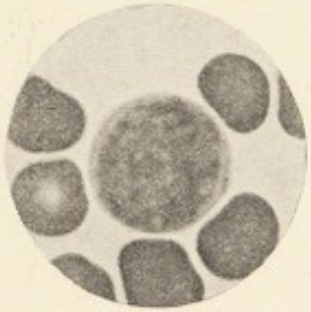


Fig. 37.

Fig. 38.

chromatin, has a finely reticular structure, and frequently contains three or four nucleoli.

Fig. 37 illustrates a myeloblast with several nucleoli in its nucleus. The cytoplasm is not so abundant as in the myelocyte and is basophilic. Myeloblasts are present in the blood-stream in acute myeloblastic leukæmia and in acute and chronic myeloid leukæmia.

Lymphoblasts or Pathological Large Lymphocytes.—In lymphatic leukæmia large immature lymphocytes appear in the blood-stream in enormous numbers. They are identical with the large cells of the germ centres of lymphatic glands and correspond to the myeloblast of the marrow. Some are indistinguishable from myeloblasts except by the oxydased reaction which shows the presence of blue-black granules in the myeloblast, but not

in the lymphoblast. The nucleus is sometimes lobulated and the cell termed a "Rieder" cell. Fig. 38 is an example of a Rieder cell.

Macropolycytes.—Giant polymorphs, or macropolycytes, are of two distinct types. Macropolycytes of the first type are found in Addison's anæmia, tuberculosis, cancer, septic conditions, malaria, and general septicæmias. They measure 18 to 20 or more microns in diameter and frequently have hypersegmented nuclei. The staining reaction of the nucleus and cytoplasm is

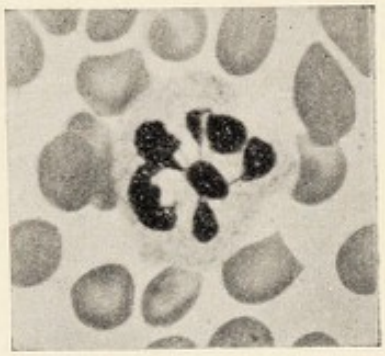


Fig. 39.

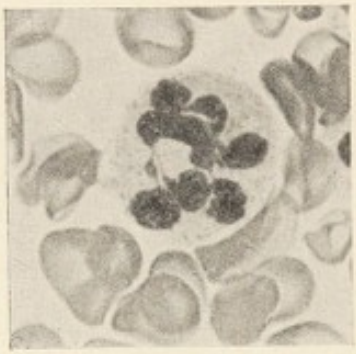


Fig. 40.

the same as that of the other polymorphs in the blood film.

Figs. 39 and 40 are examples of this type of macropolycyte. The explanation of the presence of this cell is that an occasional polymorph has been locked up in a tissue space and lived beyond its allotted span of life, three weeks, and developed into a giant. The other type, which resembles the megakaryocyte of the marrow, is found in the terminal stages of Addison's anæmia. Fig. 41 illustrates this cell. The megakaryocyte type contains coarse granules, some of which are not oxyphil, as in the normal polymorph, but azurophil. This cell represents abnormal reversion to embryonic type and is probably the result of aberrent metaplasia of the endothelium of the liver sinusoids.

The Plasma Cell.—This cell, of the lymphoid type, is

not infrequently found in the blood-stream. It exists in small numbers in the connective tissues, and is present in areas of chronic inflammation, such as the infectious granulomata. It is found in the blood-stream in the acute and chronic leukæmias, Addison's anæmia, lymphadenoma, tuberculosis, and many other conditions. Fig. 42 is an example of a large plasma cell.

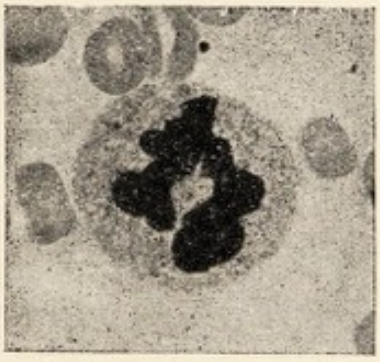


Fig. 41.

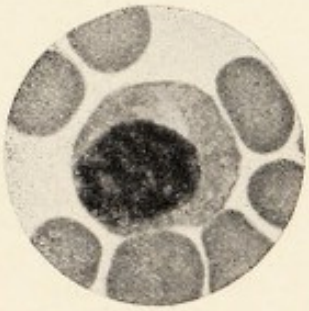


Fig. 42.

These cells vary in size, some are large, as in the illustration, but smaller forms little larger than a lymphocyte are seen. The nucleus is eccentric and shows a radial arrangement of its chromatin. The cytoplasm is strongly basophilic.

THE THROMBOCYTES OR BLOOD PLATELETS.

Thrombocytes in stained films appear as irregular ovoid granular bodies 1 to 4 microns in diameter, and stain a reddish violet with eosin-methylene blue preparations. Their numbers show considerable variation, but an average of about 300,000 per cubic millimetre is found in normal persons. Their origin is uncertain. They have been considered as fragments of white-cell nuclei, the remains of the normoblast nucleus, and detached portions of the cytoplasm of the megakaryocytes. Whatever their origin, they play an important

part in coagulation. The coagulability of the blood seems to vary as the number of platelets present.

They are diminished in numbers in essential thrombocytopenic purpura, in many cases of malnutrition associated with deficiency in vitamin A, in diphtheria, and in certain symptomatic purpuras, *q.v.* They are increased after hæmorrhage, in septic conditions, and in some other secondary anæmias.

CHAPTER V.

THE POLYNUCLEAR COUNT.

As mentioned in Chapter IV., the polymorph in health has a number of nuclear segments varying from 1 to 5. In bone marrow the young polymorph, as it develops from the myelocyte, has a single-lobed nucleus; only occasionally is one found with two lobes. It enters the blood-stream with one lobe, and as it grows older the nucleus becomes more segmented and split up into separate masses which are united by fine chromatin filaments. The polymorph is classified according to the number of these nuclear segments. In Class I. are placed cells with single-lobed nuclei, in Class II. those with two lobes, and so on to Class V.

In making the count a nucleus is not considered divided if there is any band of nuclear material, except a thin strand of chromatin uniting the various lobes. The diagram on p. 37 explains this.

The first figure represents a polymorph, and the five lobes its nucleus. The thick lines represent bridges of nuclear tissue connecting the lobes. Although the nucleus shows five distinct masses, the connecting threads are too thick for it to be termed anything but a cell of Class I. The second figure represents a cell of Class II. The portions of the nucleus connected by the thick bands must be counted as one piece. The end-piece, joined only by a filament, is counted as a separate part. The third figure represents a cell of Class III.,

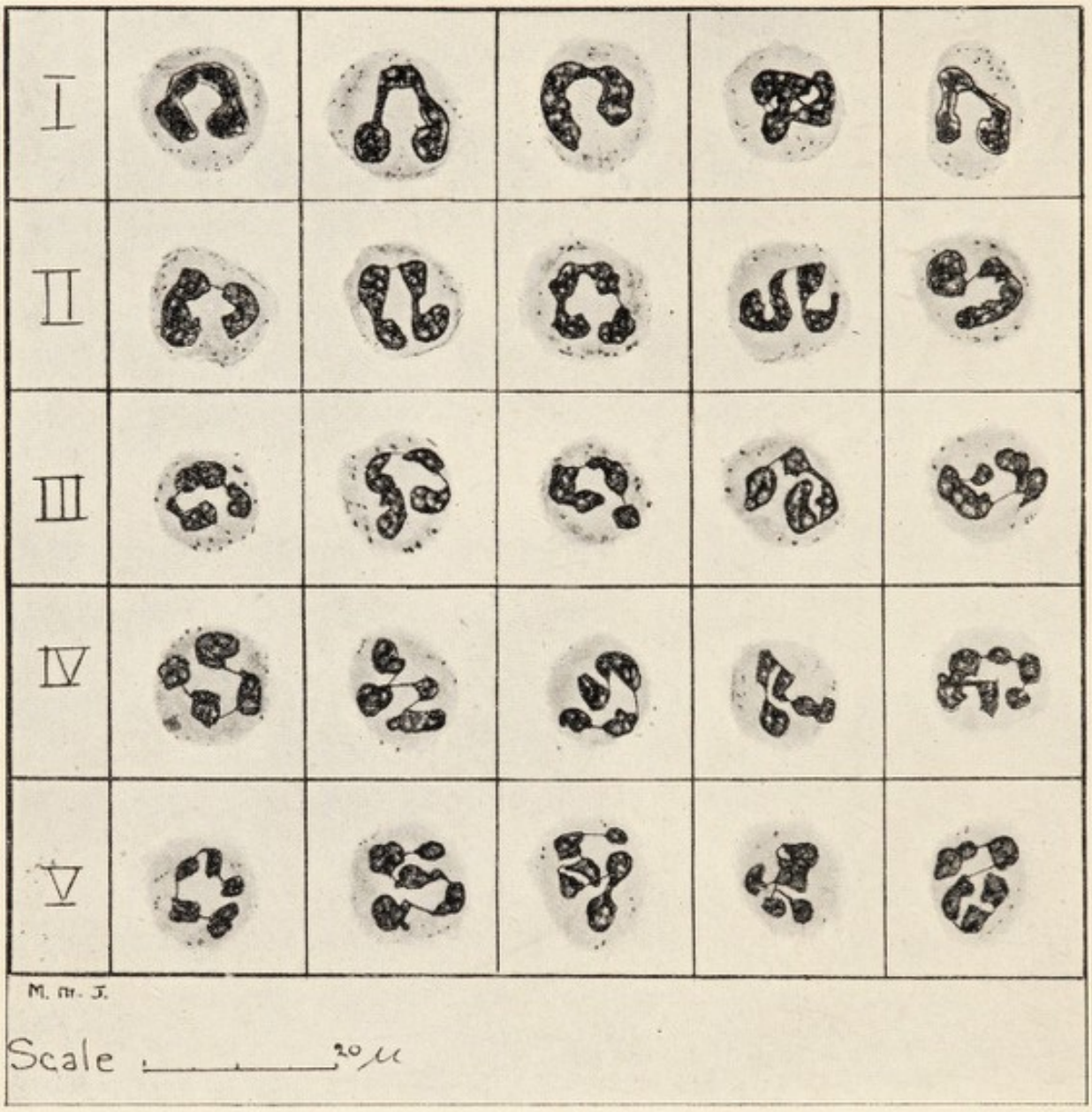


FIG. 43.—The five classes of the Polynuclear Count. If there is any band of nuclear tissue, except a chromatin filament, uniting the nuclear masses, those parts must not be considered as separate segments.

I., No. 2; II., Nos. 3 and 4; III., No. 4; and IV., No. 5, illustrate this point.

In V., No. 4, the upper segment of the nucleus overlies the segment below it, but the thin chromatin filament uniting them can be seen on the left.

the fourth a cell of Class IV., and the fifth a cell of Class V. A blood-film is made and stained in the usual way and examined with a 2 mm. objective. A hundred

FIG. 44.

polymorphs are counted and classified according to the number of nuclear segments they contain.

In health the numbers in the various classes are:

I.	II.	III.	IV.	V.
10	25	47	16	2

The length of life of the polymorph in the blood-stream has been worked out by injecting a single dose of a marrow stimulus, such as thyroid extract, and following the count daily until it returns to normal. The duration of its existence in the blood-stream is about three weeks.

In all cases of infection the older cells of Classes IV. and V. and some of Class III. are quickly killed off and removed from the circulation and there is an increase percentage of the younger cells of Classes I. and II. The count has a left-handed appearance, as shown in the table on the following page (38).

This left-handed drift occurs whether there is a leucocytosis or a leucopenia. A leucopenia in infective conditions does not mean aplasia of the marrow, but is consistent with marrow activity.

As the patient recovers, the polynuclear count gradually returns to normal, but takes longer than three weeks because recovery from infection is a gradual process, and so long as there is any toxic absorption the

	I.	II.	III.	IV.	V.
Typhoid fever . . .	54	31	15	0	0
Scarlet fever . . .	44	43	13	0	0
Measles	45	39	16	0	0
Erysipelas	45	40	14	1	0
Diphtheria	41	39	17	3	0
Rubella	30	35	32	3	0
Varicella	33	35	28	4	0
Pertussis	34	39	27	0	0
Puerperal sepsis . . .	42	37	21	0	0
Gonorrhœa	20	31	40	8	1
Acute anterior poliomyelitis .	39	27	27	7	0
Dental sepsis . . .	26	38	30	6	0
Cerebrospinal fever . .	40	45	14	1	0
Streptococcal septicæmia .	64	36	0	0	0
Staphylococcal osteomyelitis .	47	41	12	0	0
Chronic nasal catarrh . .	28	31	37	4	0
Lobar pneumonia . . .	57	26	15	2	0
Chronic bronchitis . .	25	45	23	7	0

count will remain left-handed. An example of this in the following case:—

INFECTIVE JAUNDICE.

Date.	I.	II.	III.	IV.	V.
29/10/26	46	46	8	—	—
5/11/26	22	56	22	—	—
12/11/26	18	40	34	8	—
19/11/26	18	32	42	8	0
8/12/26	12	30	44	12	2
15/12/26	10	28	44	16	2

It will be evident that the count is useful in ascertaining the presence of an infection and its severity, and is a guide to the progress of the case. If a case is recovering the count will tend to become more normal, but if the count shows an increasing left-handed drift there is increasing toxæmia.

CHAPTER VI.

ANÆMIA.

The Normal Blood Picture.

The following may be taken as the normal blood picture :—

Hæmoglobin . .	90 to 100 per cent.
Erythrocytes . .	5,000,000 per c.mm.
Leucocytes . . .	7500 ,,
Thrombocytes . .	300,000 ,,
Colour index . .	0·8 to 0·1

Differential Count—

Polymorphonuclears .	68 per cent.
Lymphocytes . .	26 ,,
Monocytes . . .	3 ,,
Eosinophils . . .	2 ,,
Basophils . . .	0 to 1 ,,

Polynuclear Count—

I.	II.	III.	IV.	V.
10	25	47	16	2

The term " anæmia " implies a reduction in the erythrocytes or hæmoglobin, or both. Less than 5,000,000 erythrocytes and 90 per cent. hæmoglobin constitutes anæmia. The causes may be removal of blood from the body, defective formation of erythrocytes and hæmoglobin, or excessive destruction of red cells within the body.

The anæmias may be divided into primary and secondary.

Primary Anæmia.

The primary anæmias are those in which no recognised cause has been found for the condition, and include :

1. Chlorosis.
2. Addison's anæmia.
3. Primary aplastic anæmia.
4. Sickle-cell anæmia.

Secondary Anæmia.

In the secondary anæmias recognisable causes are present, amongst the most common of which are the following :—

1. Hæmorrhage. There may be one large hæmorrhage, or the continual loss of small amounts of blood due to trauma, gastric or intestinal ulceration, uterine hæmorrhage, hæmoptysis, hæmatemesis, hæmaturia, hæmorrhoids, and hæmophilia.

2. Acute and chronic infective conditions, *e.g.* typhoid fever, acute septicæmia and pyæmia, chronic sepsis, tuberculosis, malaria, syphilis, rheumatic fever, etc.

3. Cachectic conditions, *e.g.* chronic nephritis and carcinoma.

4. Infection by certain animal parasites, *e.g.* schistosomiasis and ankylostomiasis.

5. Diseases of the blood, *e.g.* splenic anæmia, the leukæmias, acholuric jaundice, etc.

6. Occupations, *e.g.* workers in badly ventilated rooms and factories, and workers with lead and T.N.T.

7. Starvation and badly balanced diets, *e.g.* scurvy and pellagra.

8. Myelophthisic anæmia. This is the term given to the anæmia supposed to be due to a crowding out of erythroblastic tissue by such diseases as secondary

carcinoma deposits in bone, multiple myeloma, leukæmic infiltration, and sclerosing osteitis.

Any cause of secondary anæmia is capable of precipitating the cessation of function of the marrow and leading to aplastic anæmia.

Symptoms of Anæmia.—The symptoms common to all anæmias, primary and secondary, are :

1. Muscular and mental weakness.
2. Dyspnœa.
3. Palpitation.
4. Headache.
5. Vertigo.
6. Tinnitus.
7. Anorexia.
8. Œdema.

Physical Signs.—Pallor of the skin and mucous membranes, soft pulse, low blood-pressure, and hæmic murmurs.

Acute Secondary Anæmia.—This is always post-hæmorrhagic and follows the rapid loss of a large amount of blood. The symptoms are as above, with the addition that nausea and vomiting, and convulsions due to anæmia of the brain may occur.

The Blood.—Within twelve hours the blood shows a diminution in the number of erythrocytes depending upon the amount of hæmorrhage, reduction in hæmoglobin, a low colour index, and a polynuclear leucocytosis. There is achromia with anisocytosis and polychromatophilia, and a few normoblasts and myelocytes may be present in the blood-stream.

Treatment.—Arrest the hæmorrhage. Fluid by the mouth. Rectal salines. Saline and gum arabic intravenously (500 c.c. of ·85 per cent. NaCl solution and 6 per cent. gum arabic) or transfusion of blood.

Later treatment is considered under chronic secondary anæmia.

Chronic Secondary Anæmia.—The symptoms and physical signs are those of anæmia.

The Blood.—Erythrocytes are diminished in numbers, sometimes to 2,000,000 or less per cubic millimetre, but the hæmoglobin shows an even greater reduction and the colour index is low, 0·4 to 0·6. There is achromia and sometimes marked anisocytosis and poikilocytosis. Normoblasts are absent or very scanty. In lead poisoning there is marked punctate basophilia. The leucocyte picture varies according to the causation. In the chronic infections the polymorphs may be increased, normal in numbers, or decreased; the monocytes are increased and frequently also are the lymphocytes. The polynuclear count shows an increase of Classes I. and II.

Treatment.—The cause must be sought out and removed. Rest, fresh air, and a diet prescribed which contains 125 gm. of liver daily, with fresh fruit and vegetables, but with a low fat content. If liver cannot be taken, then concentrated liquid extract of liver must be given. In experimental anæmias in dogs it was found that recovery took place very rapidly if liver was added to the diet.

Specific treatment by anti-sera and autogenous vaccines must be considered. Good results are obtained by combining dietetic and specific therapy with ultra-violet light.

THE PRIMARY ANÆMIAS.

1. Chlorosis.

Definition.—An anæmia of unknown origin occurring only in females between the ages of fourteen to twenty-five years. The disease is now a relatively rare condition.

Etiology.—A large proportion of cases occur in domestic servants, or at the age when country girls take up city life. Poor air, overwork, and constipation are important factors, and there seems to be some relationship between menstruation and the disease.

Possibly there is a defect in the absorption and metabolism of iron.

Pathology.—The number of post-mortems on record is very small. In those recorded the bone marrow appeared normal, and the commonest cause of death was thrombosis of the cerebral sinuses. Thrombosis of the veins of the legs is not very rare.

Symptoms.—The patient is fat and pale, often of a greenish tint, with blue sclerotics. The symptoms and physical signs are those common to all anæmias, and in addition, dyspepsia and constipation, and there may be a morbid appetite with a craving for pickles and vinegar, or even slate pencils and wood.

Nervous symptoms such as headache, insomnia, and neurasthenia are frequent. Menstrual disorders—amenorrhæa, dysmenorrhæa, or menorrhagia—are usual.

The Blood.—In common with many other forms of anæmia the total volume of the blood is increased. The characteristic change is that the erythrocytes are only slightly reduced in numbers, but there is a marked reduction in the hæmoglobin content, and the colour index is low, frequently below 0·5. The erythrocytes in a great proportion of cases number between 3,000,000 and 5,000,000 per cubic millimetre. In stained films, beyond marked achromia no other abnormality of the red cells is seen. Normoblasts are rarely, if ever, found. The leucocyte count may be normal, or in exceptional cases increased to 12,000 per cubic millimetre. An increased percentage of lymphocytes is common.

Prognosis.—The usual duration of the disease under

treatment is from three to six months. Recurrences are common and may last into middle life and be the cause of chronic ill-health.

Diagnosis.—The diagnosis is established by a blood count. The diseases for which chlorosis is most frequently mistaken are: tuberculosis, nephritis, anæmia due to hæmorrhage, *e.g.* peptic or intestinal ulcer, hæmorrhoids, etc., and hyperthyroidism.

Treatment.—Rest, fresh air, a mixed diet containing liver ($\frac{1}{2}$ lb. daily), fresh fruit, and green vegetables. The constipation must be treated by magnesium sulphate. This diet, with magnesium sulphate, results in rapid improvement. Iron may be given in some form, such as Pill Ferri grs. V, beginning with 1 pill t.d.s.p.c., increasing in seven days to 2 and at the end of a fortnight to 3 t.d.s.

2. Addison's Anæmia.

Synonym.—Pernicious anæmia.

Definition.—An anæmia of unknown origin characterised by the presence of megaloblasts in the blood-stream, increase in the average diameter of the red corpuscles, hyperplasia of the bone marrow and achlorhydria.

Etiology.— *Age.*—Most common over thirty-five years, but may occur at earlier ages.

Sex.—The disease is twice as common in men as in women.

Pregnancy and Parturition.—A megaloblastic anæmia indistinguishable from Addison's anæmia occurs in connection with pregnancy. The course of the disease in these cases was, before the liver diet, progressive, and without the usual remissions.

Heredity.—Many remarkable hereditary and familial cases are on record.

Of the many supposed etiological factors a few may

be mentioned. "Infections and hæmolytic toxins" still have support, but the causative organism varies with the observer—oral sepsis, non-hæmolytic and hæmolytic streptococci in the duodenum, b. coli, b. Welchii, or the hæmoglobinophilic bacillus of Pritchett and Stillman. Many cases are recorded in association with syphilis, malaria, sprue, dysentery, ankylostomiasis and bothriocephalus latus infections. Certain occupations have been suspected—plumbers, gas workers, and workers with T.N.T.

Defective detoxicating power of the liver has been suggested, and Schneider's theory, hypersplenisation leading to opsonisation and phagocytosis of the erythrocytes, has had support.

Atrophy of the gastric and intestinal mucosæ, absorption defects, and intestinal putrefaction, are other supposed causes, and, of course, vitamin deficiency has been blamed.

Recently, a phytotoxic substance has been demonstrated in the serum in Addison's anæmia.

From cytological evidence it is possible that the primary etiological factor lies in the abnormal hæmocytoblast.

Hæmatogenesis proceeds in an apparently normal manner, but probably never quite so chemically, until abiotrophy of the hæmocytoblast occurs. The failing parent produces chemically abnormal erythrocytes which are readily phagocyted by cells of the reticulo-endothelial system; the intracellular hæmolysis resulting in alteration in the constitution of the plasma and anæmia. At the same time abnormal granulocytes appear, and from their morphological appearance and behaviour it would be reasonable to conclude that they too are not functionally normal. The alteration in the environment of the hæmocytoblast thus produced results in further

embarrassment of that cell, and as a compensatory measure the mesenchyme descendants in the liver and hæmolymph glands undergo metaplasia and attempt to revert to their embryonic function. The vicious circle may be broken by the reticulo-endothelial cells becoming refractory and temporarily incapable of further phagocytosis, or the environment is altered by dietetic means. The products of hæmolysis are excreted and to a large extent disappear from the plasma, and the hæmocytoblast partially recovers. Its inherent defect remains, however, and sooner or later the circle is again completed, and a relapse occurs. The condition is not a simple reversion to embryonic type, but, as we shall see later, an abnormal reversion.

Pathology.—The colour of the body is extremely pale with a faint icteric tinge. There is little or no wasting. The subcutaneous fat is yellow, and the muscles bright red. There may be petechial hæmorrhages in the skin, mucous and serous membranes.

The tongue may be smooth and the superficial layers of epithelium atrophied. No constant changes are found in the stomach and intestines.

Liver.—The liver is fatty and pigmented. Histologically the pigment is seen as golden-brown granules in the liver cells and endothelial cells at the periphery of the lobules. The pigment is hæmosiderin and gives the reaction for free iron with hydrochloric acid and potassium ferrocyanide. The liver cells may be necrotic in areas, and fatty degeneration is common. There is evidence of myeloid metaplasia, and the capillaries are dilated and contain megaloblasts, myelocytes, and large cells which resemble the megakaryocyte of the marrow.

Spleen.—The spleen is often enlarged. Histologically there is excess of fibrous tissue, and the cells of the pulp consist of lymphocytes, megaloblasts, red corpuscles,

and endothelial phagocytic cells, with an occasional megakaryocyte type of giant cell. The spleen gives the free iron reaction.

Kidney.—Interstitial nephritis is the rule, and the epithelium of the tubules shows granules of iron-containing pigment.

Heart.—Fatty degeneration is constant and marked.

Bone Marrow.—The ordinary fatty marrow of the long bones is replaced by dark red marrow, and the marrow throughout the body is increased in amount. Histologically there is marked erythroblastic activity, and sections and smears show an enormous number of megaloblasts. In addition, and equally as striking, is the leucoblastic activity, and in many cases the white cells outnumber the red. The white cells are for the great part neutrophil myelocytes. An occasional hypersegmented polymorph is seen. Basophil myelocytes are numerous in some cases. Large endothelial phagocytic cells containing nucleated and non-nucleated red cells are frequent. The marrow gives the free iron reaction.

Central Nervous System.—Petechial hæmorrhages are constantly found on the meninges, and there may be minute hæmorrhages in the brain substance. In the cord the same conditions are found, together with postero-lateral sclerosis.

Hæmolyph Glands.—The prevertebral lymph glands are large and dark red in colour, and histologically large endothelial phagocytic cells containing red corpuscles are seen. These glands also give the free iron reaction.

Symptoms.—The symptoms are those of anæmia, added to which are those peculiar to Addison's anæmia—gastro-intestinal crises with epigastric pain, vomiting and diarrhœa, glossitis and hyperæsthesia of the tongue and mouth.

Fever is rarely absent at some stage of the disease.

Hæmorrhages.—Large hæmorrhages from mucous membranes are distinctly rare, but petechial hæmorrhages in the skin are frequently seen. Retinal hæmorrhages occur in 80 per cent. of cases.

Nervous System.—Tingling and numbness with spasticity or tabetic gait are indications of postero-lateral scleroses.

Physical Signs.—The patient has a lemon-yellow colour, but there is no loss of weight.

Circulatory System.—Some cases show hyperthrophy and dilation of the heart. The systolic pressure is very low, frequently under 100 mm. Hg. Hæmic murmurs are the rule. Œdema and effusions into the pleura and peritoneum occur in 40 per cent. of cases.

Spleen.—The spleen may be normal or slightly enlarged, the edge being just palpable.

Test Meal.—Achlorhydria is a constant feature, free HCl is absent, the total acidity very low, and there may be complete achylia.

Urine.—The urine contains pathological amounts of urobilin and urobilinogen, and very frequently albumen and granular casts.

Serum.—The serum contains pathological quantities of urobilin as shown by the Van den Bergh reaction and the high icterus index.

The Blood.—Rouleaux formation is very defective, but autoagglutination is frequently seen. The total number of red cells is greatly reduced, sometimes below 1,000,000 per cubic millimetre. Hæmoglobin is also reduced, but not in the same ratio as the corpuscles, and the colour index is high, 1·1 to 1·6. A leucopenia is the rule, counts of 4000 or less per cubic millimetre being common, but it must be remembered that cases of Addison's anæmia react to infections, and a leucocytosis does not negative the diagnosis.

Changes in the Blood-cells.—Red Corpuscles.—The average diameter is large, 8·6 to 8·8 microns in stained films, and the volume index greater than normal. In fresh preparations by dark-ground illumination many erythrocytes do not show the normal bi-concave shape, some are bi-convex, and some almost globular in form. In films they assume various shapes, the endoplasm separates from the cell membrane and frequently shows irregular fissures. The cell membrane is wavy and irregular. This suggests an abnormal physico-chemical composition of the red cell. The fragility of the corpuscles is normal. In stained films anisocytosis is very marked, megalocytes, poikilocytes, and microcytes being usual (figs. 11 and 12). Diffuse polychromasia and cells showing Howell-Jolly bodies and Cabot's rings are frequent, and punctate basophilia is a prominent feature in some cases (figs. 13, 14, and 15). Nucleated red cells of various generations and in various stages of mitosis are found (figs. 16 to 26). The striking cell is the megaloblast with its characteristic nucleus. Normoblasts are frequent at the beginning of a remission and after a few days on a liver diet.

It must be remembered that many blood-films do not show nucleated red cells, and the only alteration in the red cells may be the presence of a large number of megalocytes.

Leucocytes.—As a rule the polymorphs are diminished in numbers, and the percentage of lymphocytes high. Myelocytes are usually present, and may be as numerous as 10 per cent. of the total leucocytes. Many of the myelocytes are abnormal, and extremely small forms are seen. Plasma cells are not infrequent. The polymorphs show remarkable variations from the normal. As mentioned in Chapter V., the normal polynuclear count is:

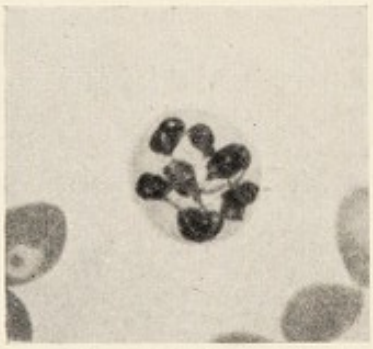
I.	II.	III.	IV.	V.
10	25	47	16	2

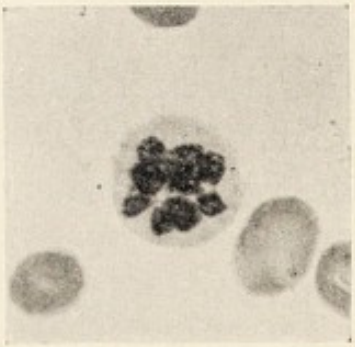
In infections the percentage of cells in Classes I. and II. is increased, and the count is left-handed as in the examples given on p. 38. In Addison's anæmia the polynuclear count frequently shows an increase of Classes IV. and V., as in the following examples :—

Case.	I.	II.	III.	IV.	V.
1	8	20	39	22	11
2	6	27	40	22	5
3	7	20	44	24	5
4	7	16	29	39	9
5	20	31	17	16	16
6	16	22	32	16	14
7	10	15	38	24	13
8	12	34	26	20	8
9	6	20	42	20	12
10	6	18	36	24	16

The count appears to be right-handed.

Polymorphs with more than five lobes are so uncommon in normal blood that no class is made for them





FIGS. 45 and 46.—Polymorphs of normal size, showing hypersegmentation of the nucleus.

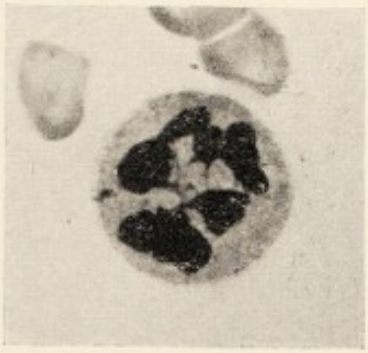
in the polynuclear count, and any containing six or more nuclear segments are placed in Class V. In Addison's anæmia, however, large numbers of polymorphs are found with six, seven, or as many as fourteen nuclear segments in a cell of approximately normal size

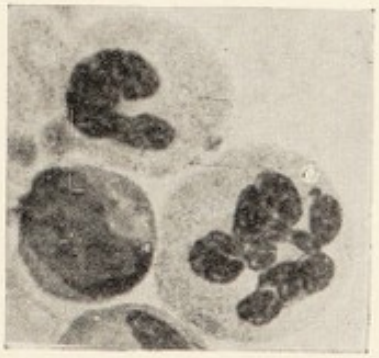
(figs. 45, 46). In addition to these cells of normal size with hypersegmented nuclei, macropolycytes of both types are found.

Type I. is seen in fig. 47. Except for size and hypersegmentation of its nucleus, the cell resembles the other polymorphs in the film. The megakaryocyte type is shown in figs. 41, 48, and 49, and, as pointed out in Chapter IV., resembles the megakaryocyte of the marrow and the large cells found in the liver in Addison's anæmia.

Fig. 47.—Type I., macropolycyte.

The only feasible explanation of these abnormal red cells and leucocytes is that the parent cell, the hæmocytoblast, either from an inherent defect or on account of some alteration in environment, has undergone an abnormal reversion. Many of the





Figs. 48 and 49.—The megakaryocyte type of macropolycyte.

cells produced are not found in embryonic or post-natal blood or tissues.

Thrombocytes.—The number of thrombocytes in relapses is almost invariably low, and counts of less than 90,000 per cubic millimetre not uncommon, and the bleeding time is prolonged to seven to thirty-five minutes or longer. The platelets are larger than normal and may measure 6μ in diameter. At the beginning of a remission

the platelets rise to normal numbers, and in some cases are actually above the average.

Remissions.—In the majority of cases the disease is not progressive but characterised by relapses in which the classical picture is present. These last for a varying length of time, when for some reason unknown the tide turns, a remission occurs, and the patient improves. Before the advent of the liver diet the disease terminated in death usually after two remissions, but four or five have been recorded. With the liver diet patients begin to improve in a few days, are apparently well in two or three months, and do not have a relapse so long as they take a sufficient quantity of liver.

Complications.—Subacute combined degeneration of the cord is a very frequent complication. The common type is that of postero-lateral sclerosis with spasticity, paresis, and sensory changes. Very much rarer is the tabetic type.

Pyelo-cystitis due to b. coli is fairly common.

Sepsis in the form of boils is not very uncommon.

Pneumonia or nephritis may be terminal events.

Aplastic anæmia. Not infrequently Addison's anæmia terminates by aplasia of the marrow.

Circulatory System.—Pericarditis, auricular fibrillation, Stokes-Adams syndrome, arterio-sclerosis, and angina pectoris have been recorded. Coma is not at all uncommon, many of the cases being uræmic.

Diagnosis.—The diagnosis rests upon the results of an accurate total blood examination with, if necessary, estimation of the volume index, or measurement of the red cells.

Treatment.—Rest in bed for three weeks. A generous diet including liver (150 grammes a day), fresh fruit and vegetables, with a low fat content. Medicinally the only

obvious indication is to replace the hydrochloric acid of the gastric juice, and the dilute acid may be given in 20 minim doses t.d.s.p.c. Larger doses have been advocated, but few patients can tolerate them. If the patient cannot take liver, then the concentrated fluid extract must be given in doses equivalent to the above amount of fresh liver substance. When the red-cell count has reached 4,000,000 per cubic millimetre the amount of liver may be reduced to 125 grammes three times a week. The liver diet brings about a prompt remission, and in some cases the return of the erythrocytes to normal diameters.

3. Primary Aplastic Anæmia.

Definition.—A fatal anæmia due to aplasia of the bone marrow, characterised by progressive diminution in the numbers of erythrocytes and leucocytes in the blood.

Etiology.—The majority of cases occur under forty years of age, and the disease affects the sexes equally. No etiological factor has been found.

Pathology.—*Bone Marrow.*—All the erythroblastic tissue has disappeared from the long bones and been replaced by fat. In the flat bones also the red marrow has to a large extent atrophied and been replaced. One of the last remaining places where red marrow is found is in the angles of the ribs.

No constant changes are found in any other organs.

Symptoms.—These are the usual symptoms of anæmia. There is a tendency to hæmorrhages from the mouth, intestine, and into the subcutaneous tissues. The disease runs a progressive course without remissions, and death takes place in from three to six months.

The Blood.—The erythrocytes are markedly diminished, and final counts as low as 400,000 per cubic millimetre

are not uncommon. The colour index is generally about 0·8. The leucocytes may number less than 800 per cubic millimetre, the decrease being most noticeable in the granulocytes (polymorphs, eosinophils, and basophils). The red cells are normal in size and in appearance, no nucleated forms nor poikilocytes, etc. being present. Reticulated red cells and polychromatophilia are entirely absent.

The thrombocytes are very scanty, and the bleeding time prolonged even up to two hours. The serum does not show any pathological increase in urobilin by the Van den Bergh and icterus index reactions.

Diagnosis.—The diagnosis depends upon the progressive diminution of erythrocytes and leucocytes as shown by repeated blood examinations, and the absence of any etiological factor.

Treatment.—The cases are hopeless from the start, and no line of treatment has been of benefit. Liver extract has not the slightest effect on the course and termination of the disease.

Secondary Aplastic Anæmia.

As mentioned under secondary anæmia, aplasia of the marrow may terminate any secondary anæmia, and may occur as the final phase of Addison's anæmia. The commoner causes are excessive exposure to radium and X-rays, poisoning by benzol and T.N.T., following repeated hæmorrhages and chronic sepsis.

The post-mortem appearances of the marrow are identical with the primary form.

4. Sickle-cell Anæmia.

A hereditary disease in negroes characterised by a curious change in the shape of the red cells when the

blood is allowed to stand. It affects negroes of both sexes, and appears to be a defect of the marrow and spleen, resulting in the production of chemically abnormal red corpuscles which are readily phagocyted.

Pathology.—The bone marrow and lymphoid tissues are hyperplastic, the spleen is small and shows active phagocytosis of red cells by the endothelial cells. The liver is sometimes large, and contains deposits of brown iron-free pigment.

Symptoms.—The symptoms are those of anæmia with enlargement of lymphatic glands. The blood shows characteristic sickle-shaped red cells after standing for twenty-four hours, and an increase in the reticulocytes and thrombocytes. The serum contains an excess of bilirubin. The red cells are reduced in numbers to 1,500,000 to 3,000,000 per cubic millimetre. Polychromasia and nucleated red cells are frequent. There is a leucocytosis of moderate degree, and myelocytes are usually present. The disease shows remissions and relapses.

Diagnosis.—The diagnosis depends upon the blood examination. The disease must be differentiated from acholuric jaundice by the sickle-cell and the absence of increased fragility of the red cells.

Treatment.—The treatment is that of secondary anæmia. Splenectomy has been performed with good results.

CHAPTER VII.

SPLENIC ANÆMIA.

Synonyms.—Banti's disease. Primary splenomegaly with anæmia.

Definition.—A chronic disease of unknown origin characterised by splenomegaly, a tendency to hæmorrhages, anæmia, and, in the later stages, cirrhosis of the liver.

Etiology.—The cause of splenic anæmia is unknown. The theories are, first, that it is a primary disease of the spleen. This is based on the fact that splenomegaly is the earliest sign, and that splenectomy apparently cures the disease. Another view, that phlebitis of the splenic vein is the primary factor, is based on experimental results which have shown that damage to the spleen can cause lesions in the liver similar to those found in splenic anæmia, which disappear with the removal of the spleen. Infection also is said to be another cause, but no constant organism has been found. On account of the proliferation of the splenic endothelium it has been suggested that the reticulo-endothelial system is primarily at fault. The disease begins in young adults of either sex.

Pathology.—*Spleen.*—The spleen is enormously enlarged, and may weigh 15 to 20 lbs. The capsule is thickened, and there is great increase of fibrous tissue throughout the organs, both pulp and follicles becoming fibrosed. Infarcts are common, and phlebitis and thrombosis of the splenic veins invariable. The sinus endothelium shows proliferation, sometimes in a marked degree.

Liver.—There is peri-portal cirrhosis, and the liver may be pigmented. Both the spleen and liver frequently give the free iron reaction.

Bone Marrow.—Beyond a certain amount of erythroblastic activity the bone marrow shows no constant change.

Symptoms.—The course of the disease is divided into three periods: (1) the anæmic or pre-ascitic stage; (2) the intermediate stage; (3) the cirrhotic stage.

(1) The anæmic or pre-ascitic stage. The duration of this stage is from three to five years or longer, and is characterised by anæmia and enlargement of the spleen. Hæmorrhages occur from the gastric and œsophageal veins, nose, and gums. The patient has the usual symptoms of anæmia, with enlargement of the left side of his abdomen with pain due to peri-splenitis.

(2) The intermediate stage lasts only a short time. The symptoms increase in intensity. Vomiting and diarrhœa occur, the spleen becomes larger, the anæmia more marked, and hæmorrhages—epistaxis, hæmatemesis, hæmaturia, and purpura—more frequent.

(3) The cirrhotic stage is characterised by symptoms of cirrhosis of the liver-recurrent ascites, slight jaundice, increased anæmia, and emaciation. Death may occur from a large hæmorrhage, cholæmia, or an intercurrent infection.

The Blood.—The red corpuscles are reduced in number, counts of 2,000,000 to 3,000,000 being the rule, hæmoglobin is reduced still more proportionately, and the colour index is low. The condition is a secondary anæmia. Normoblasts are found in a great many cases, as well as polychromasia and sometimes punctate basophilia.

The Leucocytes.—There is an early leucopenia which becomes more marked as the disease progresses. In the

early stages counts of 3000 per cubic millimetre are common, while later the leucocytes may be reduced to below 600.

Thrombocyte counts seem to place cases of splenic anæmia in two classes—those with normal or reduced counts, and those in which the thrombocytes are increased. Counts of over 1,000,000 per cubic millimetre are not uncommon. This is of importance in treatment, as it has been found that splenectomy is almost invariably fatal in cases with a high count, death taking place from thrombosis of the mesenteric veins.

The Van den Bergh and icterus index reactions show pathological amounts of bilirubin in the serum, evidence of hæmolysis.

Diagnosis.—The presence of a leucopenia and splenic enlargement with anæmia of the secondary type are the basis of the diagnosis. The differential diagnosis must be made from all causes of hæmatemesis, purpura, hæmaturia, cirrhosis of the liver, and from all other causes of splenomegaly.

Prognosis.—The disease is gradually progressive, but may last twenty years. Death may result from thrombosis of the splenic vein, large hæmorrhages, or an intercurrent infection.

Treatment.—Medicinal treatment must be symptomatic, as no known agent has the slightest effect on the course of the disease.

Splenectomy (the advisability depending upon the thrombocyte count) performed before there is evidence of cirrhosis of the liver holds out the best hope.

VON JAKSCH'S ANÆMIA.

Synonym.—Infantile splenic anæmia.

Etiology.—*Age.*—The disease begins in children of six months to two years, rarely up to four years of age.

No predisposing factor has been found, but rickets frequently, and syphilis occasionally, are associated with the condition.

Pathology.—The spleen is large, often reaching to the umbilicus, smooth, and red owing to venous congestion. There is diffuse connective tissue overgrowth and the follicles are indistinct. Myeloid metaplasia has been described in some cases. The splenic sinuses contain large numbers of nucleated red cells, numerous leucocytes, and large mononuclear cells. The liver is slightly enlarged, and here again there may be evidence of myeloid metaplasia. The bone marrow is hyperplastic.

Symptoms.—The onset is gradual, and attention is arrested by general ill-health and the pallid, waxy, and apathetic appearance. Gastro - intestinal disturbances with slight fever, anæmia, and enlarged spleen may be the first signs. The liver is often palpable. The spleen may reach below the umbilicus and across the middle line.

The Blood.—The erythrocytes are reduced, frequently below 2,000,000 per cubic millimetre, and the colour index is low. Polychromatophilia is usual, and normoblasts may number 2000 per cubic millimetre. Megaloblasts may be present. Thrombocytes are much reduced in numbers, and the bleeding time is prolonged.

A leucocytosis of between 14,000 and 60,000 per cubic millimetre is a constant feature. The differential count shows an increase in the monocytes, which may reach 24 per cent., and lymphocytes, which may number 70 per cent. of the total leucocytes. Myelocytes are constantly present.

Prognosis.—The majority of cases recover in six to twelve months. Cases with severe rickets or congenital syphilis frequently die from some secondary infection such as broncho-pneumonia.

Diagnosis.—The combination of age, splenomegaly, an anæmia with large numbers of normoblasts, and the characteristic leucocytosis are diagnostic.

Treatment. — Concomitant disease, *e.g.* rickets or syphilis, must be treated. Liquor arsenicalis 1 to 2 minims four times a day, together with a suitable diet, results in cure in most cases. Liver extract does not influence the course of the disease, nor does it have any beneficial effect.

Splenectomy should not be advised, and X-rays and radium are dangerous.

CHAPTER VIII.

ACHOLURIC JAUNDICE.

Synonyms. — Acholuric family jaundice. Congenital spleno-megalic jaundice. Hæmolytic jaundice.

Definition.—A chronic congenital or acquired disease characterised by increased fragility of the erythrocytes, splenomegaly, anæmia, and jaundice, with absence of bile in the urine.

Etiology.—There are two types of the disease—the congenital and the acquired.

The congenital or familial form is the commoner, and can be traced through three or four generations. It is transmitted by either parent. The acquired form begins in early adult life and may have no obvious cause, but cases have been found in association with syphilis, tuberculosis, carcinoma of the gall-bladder, toxæmia of pregnancy, dysentery, septicæmia, and cholangitis.

Pathogenesis.—Two views are held. Firstly, a primary weakness of the red blood corpuscles; secondly, hæmolytic activity in the spleen. Neither view covers the facts, but there is destruction of the abnormal red cells by the spleen, which results in its enlargement. The excessive hæmolysis is shown by the bilirubinæmia, but the renal threshold for bilirubin is raised and the urine does not contain bile.

Pathology.—Post-mortem, the chief characteristic is the greatly enlarged spleen which shows marked congestion of the pulp and sinuses, perisplenitis, and

fibrosis. No constant changes have been found in the liver or marrow.

Symptoms. — There may be good health over long periods, with jaundice varying from time to time. The jaundice does not produce the usual symptoms, the patients being "more icteric than sick." The fæces contain bile pigment and salts. The urine does not contain bile. The serum gives a pathological indirect Van den Bergh's reaction, and the icterus index is high. Hæmoglobinæmia and paroxysmal hæmoglobinuria are sometimes present.

Pyrexial attacks occur at some stage in the disease and are associated with intestinal colic and bile in the urine. There may be cholecystitis, and gall-stones have been recorded in several cases. The spleen is enlarged and may be tender.

Epistaxis and retinal hæmorrhages have been recorded.

The Blood.—The blood shows the characteristics of secondary anæmia. The erythrocytes show marked variations in size, large numbers of small cells—microcytes—being present. The average diameter of the corpuscles is diminished. Polychromasia is frequent and reticulocytes are very much increased in numbers, and may reach 10 to 20 per cent. of the red cells, instead of the normal 0·7 per cent. The pathognomonic sign of the disease is the increased fragility of the erythrocytes. Normally, hæmolysis begins at 0·44 per cent., and is complete at 0·34 per cent. NaCl. In hæmolytic jaundice it begins at 0·7 per cent., and is complete at 0·5 per cent. There are no constant changes in the leucocytes.

Diagnosis.—The characteristics—increased fragility of the red cells, marked increase in reticulocytes, the jaundice with absence of bile in the urine, with the splenic enlargement—should differentiate the disease from hypertrophic cirrhosis of the liver, congenital syphilis,

Addison's anæmia, splenic anæmia, and other causes of splenomegaly with anæmia.

Prognosis.—In mild cases good health may be maintained without treatment. In the majority the damage to health is very considerable, and death may occur during an exacerbation.

Treatment.—Splenectomy may be said to cure the disease. No other treatment has the slightest effect.

CHAPTER IX.

GAUCHER'S SPLENOMEGALY.

Definition.—A disease of unknown origin characterised by splenomegaly and alteration in the reticulo-endothelial cells of the spleen, liver, lymph glands, and bone marrow.

Etiology.—The cause of the disease is unknown. The endothelial hyperplasia is not neoplastic in origin, but due either to some metabolic defect or to some inherent deficiency in the reticulo-endothelial system.

The disease is frequently familial in occurrence and affects females more often than males.

Pathology.—The distinctive lesion is the presence of Gaucher cells in the spleen, liver, lymphatic glands, and bone marrow. Gaucher cells are reticulo-endothelial in origin, large, 20 to 40μ in diameter, with small eccentric nuclei, and foamy cytoplasm. The swollen appearance is due to the presence of a phosphorous-containing protein. They are grouped in alveoli surrounded by connective tissue. Iron-containing pigment—hæmosiderin—is present in the cells and connective tissue.

The spleen is large, smooth, and greyish-pink in colour, with small translucent areas scattered uniformly over the cut surface. The liver and internal lymphatic glands are also enlarged, the bone marrow hyperplastic, and sections show the same translucent areas, consisting of masses of the cells, as the spleen.

Symptoms.—The disease begins in childhood, usually before the twelfth year. The first symptoms are those

of anæmia with progressive enlargement of the spleen. Later, the liver is enlarged, but the superficial glands rarely show increase in size. There may be a brownish-yellow discoloration of the skin and thickening of the conjunctivæ. · Purpura is not uncommon.

Blood.—The anæmia is never very severe, the average red-cell count being 3,700,000 per cubic millimetre, and hæmoglobin 55 per cent. There is a definite leucopenia, counts as low as 500 leucocytes per cubic millimetre having been recorded. Thrombocytopenia is constant.

Prognosis.—The average length of life is about twenty years, but cases are on record where the course has been extremely rapid. Death is due to intercurrent infection.

Diagnosis.—The diagnosis can only be made with certainty by examination of material obtained by splenic puncture, or by removal of the spleen. The clinical features described above—the chronicity, pigmentation of the skin, thickening of the conjunctivæ, the large spleen, without the ascites and jaundice—may suggest the condition.

Treatment.—The condition is improved in many cases by splenectomy.

CHAPTER X.

HODGKIN'S DISEASE.

Synonym.—Lymphadenoma.

Definition.—A disease characterised by painless and progressive enlargement of groups of lymphatic nodes, a secondary anæmia, and, in most cases, splenomegaly.

Etiology.—The disease is commonest in early adult life, males preponderating in the proportions 2 to 1 female.

Pathogenesis.—The exact etiology is unknown. There are two schools of thought upholding the following views:—

1. That the condition is an infectious granuloma. (Neither syphilis nor tubercle are related to the primary condition, but a secondary infection with tubercle bacilli is of frequent occurrence.) Several organisms have been isolated—a gram-positive granular bacillus and a gram-positive diphtheroid—but inoculation experiments have failed to produce the lesions in laboratory animals, even in the rhesus monkey or chimpanzee.

2. That the condition is a neoplasm of the hæmopoietic tissues commencing in some part of the reticulo-endothelial system—a reticulo-endothelioma. In support of this view it is pointed out that all grades of transition between aleukæmic and leukæmic lymphatic tumours and new growths of the bone marrow, and Hodgkin's disease are seen. The primary growth may be situated in any part of the reticulo-endothelial system, and although clinically commonest in the cervical glands, cases of Hodgkin's cirrhosis of the liver are recorded.

The condition may commence in the marrow, skin, thymus, or spleen.

Pathology.—*Histology.*—Microscopically the lymph nodes show loss of normal structure, the lymphoid tissue being replaced by proliferation of the reticulum and the endothelium of the germ centres and sinuses. In these areas are seen plasma cells, monocytes, lymphocytes, and eosinophils (the latter may be present in large numbers), with enormous masses of endothelial cells, some of which have developed into giant cells and contain two, four, or as many as ten nuclei, and resemble the megakaryocyte of the marrow. Areas of necrosis are often present. The later stages show marked increase in the reticulum, which becomes converted into dense fibrous strands which undergo hyaline degeneration. Periadenitis is constant in this stage. The secondary nodules in various organs are faithful replicas of the picture in the lymph nodes.

Macroscopically, the distribution of the enlarged glands and secondary deposits are:

1. The superficial cervical glands, and next in order of frequency, the axillary and groin glands.

2. Mediastinal and abdominal glands and lymphoid tissue in the intestinal wall.

3. The spleen is almost always enlarged owing to the presence of secondary growths, which appear as grey areas as large as a walnut. These areas have the same histological structure as the primary growth. The condition is sometimes called the "hardbaked spleen."

4. The liver is often enlarged for the same reason, or there may be a Hodgkin's cirrhosis.

5. The kidneys and lungs show secondary deposits.

6. Destruction of bone may be present through medullary or periosteal deposits, and there may be pressure on the cord from invasion of the vertebræ, or signs of intracranial tumour from affection of the skull bones.

Symptoms and Signs.—The first sign in a large proportion of cases is a painless enlargement of one or more superficial lymphatic glands. Anæmia with its signs and symptoms, slight in the early stages, increases in intensity. The spleen is enlarged in 80 per cent. of cases, and the liver may extend below the costal margin.

Pigmentation of the skin is common with enlargement of the abdominal glands, and pruritus and boils fairly frequent.

Pyrexia always occurs at some stage. The temperature may be slight and irregular, or of the Pel-Ebstein type. The Pel-Ebstein syndrome is the term given to the relapsing type of pyrexia seen in lymphadenoma. The temperature rises to a maximum of 103° to 105° F., and gradually falls to normal; the pyrexial period lasting from seven to fourteen days. This is followed by an apyrexial remission of the same duration, which is again succeeded by another febrile attack similar to the first. These attacks may recur for many months.

Lymphatic Glands.—The glands are discrete, never adherent to the skin, never caseate nor suppurate unless they are the seat of a secondary infection. The rapidly growing glands are soft, the more chronic ones hard. The earliest enlargement is most frequently noticed in the cervical glands; successive groups are affected, and finally large masses are produced throughout the body as mentioned under Pathology. Pressure signs occur, viz.:

1. Cervical glands, causing cough and dyspnœa and distortion of the trachea, dysphagia from pressure on the œsophagus, pressure on the cervical sympathetic causing inequality of the pupils and unilateral exophthalmos or enophthalmos, and paralysis of the recurrent laryngeal nerves.

2. Mediastinal glands, the pressure of which cause cough, dyspnœa, cyanosis, dilatation of the intercostal

and neck veins, and œdema of the face and neck. Pleural effusion occurs, and a case of invasion of the thoracic duct causing a chylous effusion has been recorded. Cardiac displacement is common, and hypertropic pulmonary osteoarthropathy may be extensive.

3. The axillary and groin glands cause pain and œdema of the arms and legs.

4. Abdominal glands. Abdominal lymphadenoma may cause ascites and may simulate tuberculosis or even acute abdomen. Pressure on the bile ducts causes jaundice.

5. Invasion of the vertebræ produces signs of extradural tumour of the cord, and implication of the cranial bones may resemble intracranial tumour.

6. Deposits in the lung parenchyma give signs of pulmonary neoplasm.

The Blood.[1]—The blood picture is not diagnostic. There is a progressive anæmia of the secondary type. The red cells are reduced to 2,500,000 or less per cubic millimetre and hæmoglobin to 30 or 40 per cent.

Leucocytes. In the very early stages there may be a leukopenia from reduction in the numbers of polymorphs; but when the disease is established a leucocytosis is invariably present, usually from 10,000 to 20,000 per cubic millimetre, with polymorphs numbering from 70 per cent. to 90 per cent. of the total leucocytes. Occasionally eosinophils are numerous—5 per cent. to 15 per cent., and in early cases with a normal or only a slightly raised total leucocyte count the increase in monocytes is striking.

Thrombocytes are increased in numbers, and very large forms are frequently seen.

[1] Local congestion results in a local polycythæmia; therefore it is of vital importance that a blood count should not be taken from a congested part.

Prognosis.—The duration of the disease, invariably fatal, is usually from two to three years, but cases living as long as ten years are recorded. Death may be due to progressive anæmia, pressure on important structures, or to a secondary infection.

Types of Hodgkin's Disease.

1. *The classical type* outlined above.

2. *The acute type* with rapid involvement of all lymphatic tissue, resulting in death in from two to six months.

3. *The localised type,* in which one group of glands enlarge and no further generalisation occurs for months.

4. *The peritoneal type* with abdominal discomfort, temperature, and enlarged spleen, which may resemble typhoid fever or abdominal tuberculosis, or at times acute abdomen. Actual perforation of the intestine has occurred.

5. *The osteo-periostitic type* is very rare. Tumours of the sternum, ribs, vertebræ, and other bones leading to destruction and pathological fracture are recorded.

Diagnosis.—The diagnosis rests upon the histological examination of a gland.

Hodgkin's disease must be differentiated from the various forms of splenomegaly, the leukæmias, lymphosarcoma, Banti's disease, and general lymphadenitis due to tubercle and syphilis.

Treatment.—Arsenic by the mouth, intravenously or intramuscularly, X-rays and radium, cause the glands to become smaller but do not have a material effect on the condition.

Surgical interference is inadvisable except in cases where a removable group of glands is causing pressure signs.

CHAPTER XI.

PURPURA AND HÆMOPHILIA.

PURPURA.

THE term "purpura" is given to spontaneous hæmorrhages in the skin and mucous membranes. Several terms are in common use; petechiæ are purpuric spots less than 10 mm. in diameter; larger areas are called ecchymoses, which in turn, if extensive, are designated suggillations. Purpura is a symptom occurring in many diseases.

Classification.—The conditions under which purpura is seen are best classified according to the blood-platelet count. The following classification is modified from Leschke:—

I.[1] *Essential Thrombocytopenic Purpura.—Synonyms.*—Essential thrombopenia, purpura hæmorrhagica, Werlhof's disease.

II. *Symptomatic Thrombocytopenic Purpura.* — This occurs in:

1. Blood diseases—lymphatic and myeloblastic leukæmias, Addison's and aplastic anæmia, acholuric jaundice.

2. Infections—sepsis, smallpox, typhoid fever, scarlet fever, tuberculosis, rheumatic fever, measles, diphtheria, cerebro-spinal fever, typhus, and any of the acute exanthemata.

3. Anaphylaxis.

4. Diets deficient in vitamins.

[1] For brevity, thrombocytopenia is commonly called thrombopenia.

III. *Non-thrombocytopenic purpura.*

1. Anaphylactoid purpura, or the Schonlein-Henoch disease.

2. Capillary weakness. In this group are included the purpura of old age, of cachectic conditions, and mechanical purpura.

3. Infection—capillary emboli in septicæmia and pyæmia and endothelial damage due to toxins in sepsis.

4. Intoxications—iodine, potassium iodide, mercury, benzol, pyridine, and snake venom.

IV. *Hæmophilia.*

In all cases of purpura, in addition to the usual blood examination, the following tests should be performed :—

1. Enumeration of the thrombocytes.

2. Determination of the bleeding time by Duke's method.

3. Estimation of the coagulation time.

4. Determination of increased permeability of the capillaries.

(*a*) The Rumpel-Leede test. This is a capillary-resistance test and is of considerable value in the diagnosis of essential thrombocytopenic purpura. The armlet of a sphygmomanometer is applied above the elbow, and a pressure about midway between the systolic and diastolic applied for five minutes.

The pressure is released and the skin of the forearm examined for hæmorrhages. In scarlet fever and other streptococcal septicæmias, and in some other infectious diseases, a few small petechiæ are found in the anticubital fossa. In essential purpura the hæmorrhages are extensive over the entire forearm.

(*b*) Inject, subcutaneously, one c.c. of 0·2 per cent. NaCl solution. If there is a tendency to bleeding a hæmatoma will form.

ESSENTIAL THROMBOCYTOPENIC PURPURA.

Definition. — A disease characterised by purpura, hæmorrhages from mucous membranes, and a diminution in the number of thrombocytes.

Etiology.—The disease is most common before puberty, but no age is exempt. It occurs equally in males and females. Heredity does not play any part in the etiology, only one case of transmission from mother to child being on record.

Pathology.—There is extreme anæmia of all the organs. Petechiæ and ecchymoses are found universally—in the peritoneum, pleuræ, pericardium, endocardium, and retina. Hæmorrhages may be found in any organ, the adrenals, meninges, brain, muscles, and occasionally into the serous sacs.

Symptoms.—The onset is usually abrupt with malaise, and occasionally fever. There are usually severe and extensive ecchymoses in the skin, and hæmorrhage from mucous membrane, the gums, epistaxis, and occasionally hæmaturia.

The Blood.—The striking feature is the diminution in the number of platelets, which may fall to less than 4000 per cubic millimetre. The platelet count is very low preceding the hæmorrhage, and rises as the bleeding ceases.

There is increase in the bleeding time, as measured by Duke's method, and so important is this test that the bleeding time is looked upon as a measure of functional activity of the platelets.

Subcutaneous injection of 1 c.c. of a 0·2 per cent. NaCl solution results in a hæmatoma.

Non-retractility of the clot is another constant sign. In thrombocytopenic purpura the clot is firm but fails to retract, and there is no extrusion of serum.

The blood picture is that of secondary anæmia. Normoblastic crises have been recorded, but are not common. After an attack of hæmorrhage there is a great increase, amounting in some cases to 15 per cent., of reticulated red cells. There is a polymorphic leucocytosis, and myelocytes may be present in the peripheral blood.

Pathogenesis.—There are probably two factors. (1) A destruction of thrombocytes, or lack of production ; and (2) change in the capillary walls. These two factors are probably related in some way.

What part the spleen plays in the disease is not certain. Removal of the spleen leads to a rapid increase in the thrombocytes, and a thrombolytic action has been ascribed in this organ. Increase in this function has been suggested as the cause of the disease.

Diagnosis.—The purpuric spots, bleeding from the mucous membranes, the diminution in the thrombocytes, the increase in the bleeding time with non-retractility of the clot, and the Rumpel-Leede test are the diagnostic features. The absence of urticaria, arthritis, and abdominal pain differentiate it from the Schonlein-Henoch disease.

Treatment.—During an attack absolute rest in bed is essential. No drug seems to have the slightest effect in checking the hæmorrhages. If the loss of blood is great transfusion should be performed, or intramuscular injections of defibrinated blood. Good results have been reported from the injection of 30 c.c. of citrated blood intramuscularly at weekly intervals.

Many successes have been reported from splenectomy, but occasionally the symptoms return.

Recently good results have been obtained by the mercury-vapour lamp. By this treatment the thrombocytes rapidly rise and the bleeding stops.

THE SCHONLEIN-HENOCH DISEASE

(Anaphylactoid Purpura).

Schonlein's purpura or purpura rheumatica and Henoch's purpura or purpura with colic are merely different types of the same disease.

Etiology.—The disease is probably an intoxication by histamine or like substances.

Age and Sex.—It is more common in early life and in males. The type with joint pains is more frequent in young adults than in children.

Symptoms. — Onset. Temperature, 101 to 103° F. Sore throat. Joint pains. Usually many joints are affected and there may be some swelling, but bleeding into the articulations never occurs. There may be albuminuria. Abdominal colic with diarrhœa and vomiting may be severe. Acute abdomen may be simulated, and cases are by no means rare in which exploratory operations have been performed.

There may be melæna.

The Rash.—In addition to the purpuric spots on the extensor surface of the legs, arms, and body, urticaria and erythema are often present. There may be œdema of the angioneurotic type. Epistaxis, bleeding from the gums, and hæmatemesis may occur, but are less frequent than in essential purpura. Acute nephritis may be a serous complication. The capillary-resistance test does not give rise to petechiæ, but may result in urticarial wheals.

Foreign proteins such as tuberculin and casein give very marked cutaneous reactions.

Blood.—The thrombocytes are present in normal numbers. The bleeding time and coagulation time are normal.

Diagnosis.—The diagnosis is based on the presence of

arthritis or abdominal colic with purpura, and urticaria, erythema, or œdema, with a normal thrombocyte count, normal bleeding time, and the Rumpel-Leede test.

Prognosis.—The dangers are nephritis and cerebral hæmorrhage, not loss of blood. Relapses are the rule.

Treatment.—On the theory of histamine absorption from the intestine 20 grms. of animal charcoal may be given daily. Good results are reported from the injection of 4 c.c. of novocaine-sodium chloride solution (·05 per cent. novocaine) intrathecally, on the grounds that the condition is a central trophoneurotic disturbance.

Injections of foreign protein, old tuberculin, casein, or milk have been used. Calcium lactate by the mouth, and calcium chloride solution, 25 c.c. of a 10 per cent. solution, intravenously daily have given good results.

HÆMOPHILIA.

Definition.—An hereditary disease limited to males, but transmitted by females, characterised by a tendency to excessive hæmorrhage and by a marked delay in the coagulation time of the blood.

Etiology.—Hæmophilia occurs only in the male, and is only transmitted by the female. Careful enquiry into the family history will show a large number of cases in the same family. The women in bleeder families are remarkably fertile.

Symptoms.—The liability to excessive hæmorrhage from slight injuries commences in early infancy, but tends to diminish with age and varies from time to time. The hæmorrhage is always traumatic in origin. The site of the hæmorrhage may be external—tooth extraction, epistaxis, cuts ; or internal—hæmatomata, in the joints, especially the knee, or the spinal cord, resulting in a transverse myelitis.

The Blood.—The thrombocytes are present in normal numbers, but are deficient in pro-thrombin or its precursor. Coagulation of the blood is delayed, due to delay in the formation of thrombin. There is a marked prolongation of the prothrombin time. The coagulation time of blood taken from a vein is lengthened to four or five hours. In blood taken from skin wounds the time varies from thirty to eighty-five minutes. Normal blood clots by skin puncture in about eight minutes at 20° C.

There is some increase in the bleeding time from a skin puncture in hæmophilia, but it is never as prolonged as in thrombocytopenic purpura. Usually the delay does not exceed five minutes. The Rumpel-Leede capillary-resistance test is negative. If there has been hæmorrhage of any severity the blood will show a secondary anæmia with a leucocytosis.

Diagnosis.—The essential facts are (1) repeated and prolonged hæmorrhages on slight trauma, commencing in infancy, in males only ; (2) delayed coagulation time ; (3) exhibited by males and transmitted by females only. The disease must be differentiated from essential thrombocytopenic purpura.

Treatment.—In hæmophilic families the children should be protected from injury. Residence in a warm climate during the winter months is advisable. The disease is rare in warm climates, and cases are recorded who bled profusely in cold countries but ceased to bleed when taken to warmer places.

Local Treatment.—Wash the clot from the site and apply cephalin. Normal human blood also frequently checks the bleeding.

General Treatment.—Intravenous injection of fresh horse serum in doses of 20 c.c. monthly has given good results, and 20 c.c. of a 5 per cent. Witte's peptone

every two or three days for a fortnight has been advised.

Transfusion is the most satisfactory method of checking severe bleeding in hæmophilia, and should be employed before any operation. Either citrated blood or unaltered blood may be used.

CHAPTER XII.

THE LEUKÆMIAS.

Definition.—Leukæmia is a disease characterised by hyperplasia of the leucocytic elements of the hæmopoietic system and the persistent presence of abnormal white cells in the blood-stream.

Varieties.—The leukæmias, for descriptive purposes, are divided into myeloid and lymphoid types, but it must be remembered that in both types the whole hæmopoietic system — marrow, lymph glands, and reticulo-endothelial system—is involved. In cases of lymphatic leukæmia, for example, the marrow is almost completely transformed into tissue identical with that of the lymphatic glands, and cases are on record which have had the blood changes of lymphatic leukæmia, but in which there was no enlargement of the lymphatic glands, the pathological changes being confined to the marrow. And in cases of myeloid leukæmia examination of the spleen and lymph glands shows that they have undergone myeloid metaplasia, and have been transformed into structure identical with the marrow. Although the various parts of the hæmopoietic system are widely separated anatomically (marrow, spleen, lymph glands, etc.) and structurally different, they are all descended from the same mesenchyme cells, and retain the multi-potentiality of their embryonic prototypes.

Pathogenesis.—Nothing is known of the factors which produce the intense activity of the leucopoietic tissues,

nor can any definite explanation be given why one element predominates in the several types of leukæmia.

Neoplasm of the hæmopoietic system and infection are two suggestions. The arguments for and against these theories will not be considered here, because neither accounts for the findings in the disease.

One may suggest that physiologically each section of the hæmopoietic system plays its part by the production of its own type of blood-stream cell ; the several portions react according to body requirements, the stimulus being hormonic in character—some subtle addition to or subtraction from the chemistry of the plasma. The same reaction is seen intensified in infections by different organisms and in pathological and experimental toxæmias. When the stimulus is removed the parent cell in the particular blood-forming organ ceases hyperactivity and resumes its normal career because its environment has returned to normal.

The leukæmias and erythræmia may be due to a similar biochemical defect—either excess or deficiency of some constituent of the plasma.

The leukæmias may be classified as follows:—

1. Acute Leukæmia.

(*a*) Acute myeloblastic leukæmia.
(*b*) Acute lymphatic leukæmia.
(*c*) Chloroma.
(*d*) Acute myeloid leukæmia.
(*e*) Acute monocytic leukæmia.

2. Chronic Leukæmia.

(*a*) Chronic myeloid leukæmia.
(*b*) Chronic lymphatic leukæmia.

ACUTE LEUKÆMIA.

All types of acute leukæmia agree in certain clinical manifestations.

Etiology.—*Age.*—The age of the patient is usually under twenty years, except in the rare condition of acute myeloid leukæmia, which occurs at any age.

Sex.—Acute leukæmia is nearly twice as common in males as in females.

No predisposing or causative factor is known.

Symptoms and Signs.—1. *Anæmia.*—This may be the first sign to attract attention and is always extreme.

2. *Hæmorrhages.*—Hæmorrhage—from the gums, tonsils, nose, stomach, rectum, and vagina—is frequent, together with swelling and ulceration of the gums.

3. *Purpura.*—Extensive petechiæ, very often generalised, may be the first sign.

4. *Enlargement of Lymphatic Glands.*—The glands are enlarged in the great majority of cases. The more chronic the course of the disease the greater is the affection of the glands.

5. *Enlargement of the Spleen.*—The liver and spleen are usually both enlarged. The spleen is palpable in 75 per cent. of cases, but the enlargement is never great.

6. *Fever.*—Almost all the cases have an irregular temperature, varying from 102° to 104° F.

Blood Changes.—The changes in the red cells common to all acute cases are extreme anæmia, the red-cell count may fall to 700,000 per cubic millimetre in a few days, and normoblasts are constantly present and may be very numerous. The colour index is low, but in the later stages may reach unity.

Leucocytes.—The total number is increased in the vast majority of cases, with one type of cell predominating.

Prognosis.—All acute leukæmias are invariably fatal, many within fourteen days and all within six months.

Diagnosis.—If a blood film is examined the disease is recognised at once. Clinically the condition may be mistaken for:

1. Essential thrombocytopenic purpura, and purpura of other origin, *e.g.* septicæmia.

2. Vincent's angina, and other causes of ulceration of the tonsils and mouth.

3. Scurvy. The swelling and ulceration of the gums have led to the diagnosis of scurvy.

4. The hæmorrhagic forms of the exanthemata, especially cerebro-spinal fever, typhoid, typhus, and scarlet fever.

Treatment.—No treatment has the slightest effect on the course of the disease.

(*a*) ACUTE MYELOBLASTIC LEUKÆMIA.

The symptoms are those common to all acute leukæmias.

The Blood. — In addition to the red-cell changes

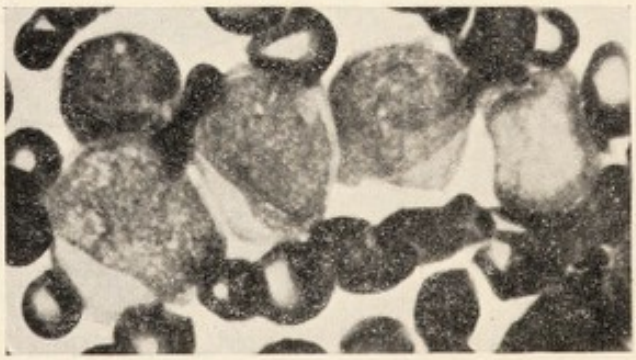


FIG. 50.—Myeloblasts—Acute myeloblastic leukæmia.

described above, the leucocytes are increased, common counts being from 10,000 to 150,000 per cubic millimetre, of which usually 95 per cent. are myeloblasts. Fig. 50

is a photomicrograph of large myeloblasts from a case of myeloblastic leukæmia. A small type of cell is seen in the upper left-hand corner.

Cases are on record with counts as low as 2000 per cubic millimetre, but the characteristic proportion of myeloblasts is always present. The oxydase reaction alone differentiates the cells from lymphoblasts, but some of the very young myeloblasts do not give the reaction.

Pathology.—*Alimentary System.*—The lymphatic tissues of Waldeyer's ring are usually enlarged. The walls of the stomach and intestine are infiltrated with myeloblasts.

Liver.—The infiltration may reach an extreme degree. Masses of cells may be visible under the capsule and the portal tracts. There is a deposit of hæmosiderin, which gives the free iron reaction, at the periphery of the lobules.

Heart.—Fatty degeneration is the rule, and infiltration with myeloblasts may be so marked that the muscle fibres are separated.

Kidneys.—The kidneys are enlarged and show considerable infiltration.

Spleen.—The spleen is somewhat enlarged, but is never very big. The Malpighian bodies are atrophied and the pulp is packed with myeloblasts.

Lymphatic Glands.—These are enlarged in the majority of cases and their structure lost owing to the dense aggregation of myeloblasts.

Bone Marrow.—The marrow of the long bones is replaced by red marrow, the predominating cell being the myeloblast, with red corpuscles and normoblasts the next most numerous elements.

(*b*) ACUTE LYMPHATIC LEUKÆMIA.

In addition to the symptoms of acute leukæmia the blood shows the following changes:—

Leucocytes.—Number.—Leucocyte counts vary from 2000 to 200,000. A leucopenia or a normal number is not at all infrequent, but the important point is that the percentage of lymphocytes is very high, usually over 90 per cent. and may reach 99·5 per cent. of the total leucocytes.

The type of cell in acute lymphatic leukæmia is the

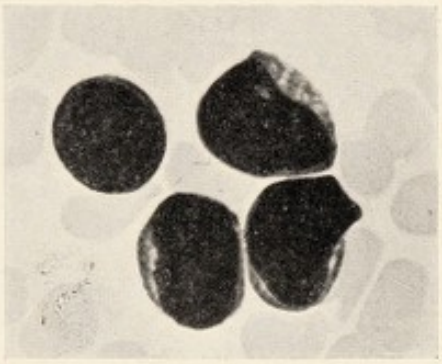


Fig. 51.

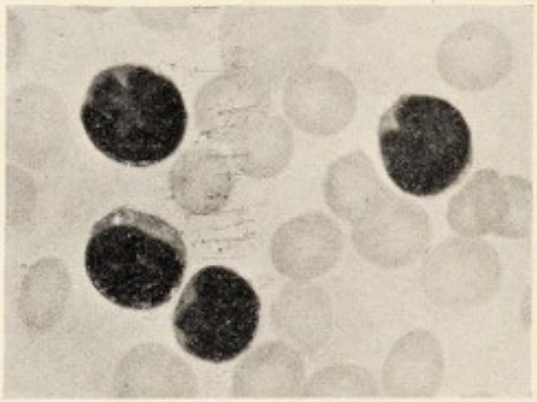


Fig. 52.—Acute lymphatic leukæmia.

large lymphocyte, indistinguishable except by the oxydase reaction and special nuclear staining from the myeloblast.

Fig. 51 shows typical large lymphocytes from a case of acute lymphatic leukæmia.

In some cases the cells are of mixed types—some large, some small, and others intermediate in size (fig. 52).

In less acute cases there is always a considerable proportion of small lymphocytes.

Pathology.—The only difference in the morbid anatomy between myeloblastic and acute lymphatic leukæmia is the histological difference in the two cells. The changes described under acute myeloblastic leukæmia are the

same in the lymphatic type, with the substitution of "lymphocyte" for "myeloblast."

(*c*) CHLOROMA.

Definition.—An acute myeloblastic leukæmia characterised by infiltration of the subperiosteal tissues with myeloblasts resulting in the formation of tumours, especially in the skull bones. The tumours have a green colour on section.

Pathology.—The tumours are masses of myeloblasts. The green tint is not invariably present, but when present may be quite bright, fading on exposure to air.

The sites commonly affected are the orbit and temporal bones and vertebræ, but any bone may show the tumours. The lymphatic glands, skin, and kidneys are constantly affected.

Symptoms.—The symptoms are those of acute leukæmia plus pressure signs. The characteristic pressure signs are protrusion of the eye from growth in the orbit, blindness, sometimes deafness, and the presence of tumours on the bones of the skull. The blood changes are those of acute myeloblastic leukæmia, and the duration of the disease the same.

(*d*) ACUTE MYELOID LEUKÆMIA.

This condition is very rare. The blood changes and symptoms are those of chronic myeloid leukæmia, but the anæmia is very rapid, and the spleen is not so enlarged.

The duration of this acute type is usually from fourteen days to six months.

(*e*) ACUTE MONOCYTIC LEUKÆMIA.

A few cases of leukæmia are on record in which monocytes have been as numerous as 40 per cent. of the

total leucocytes. There is little, if any, involvement of the bone-marrow series of cells, the granulocytes. There may or may not be an increase in the total number of leucocytes, the essential point, as in other leukæmias, being the high percentage. Clinically the cases have been characterised by severe anæmia, glandular enlargement, hæmorrhages, and a very acute course.

CHRONIC LEUKÆMIA.

(*a*) CHRONIC MYELOID LEUKÆMIA.

Synonyms. — Spleno - medullary leukæmia, chronic myelogenous leukæmia.

Definition.—A fatal disease characterised by the persistent presence of bone-marrow cells in the blood-stream and enlargement of the spleen.

Etiology.— *Age.*—The disease is most common between twenty and fifty. A few cases have been recorded in infancy, and even congenital cases have been known.

Sex.—More frequent in males than in females, in the proportion of two to one.

No predisposing factors are known.

Pathology.—*Bone Marrow.*—The marrow of the long bones is pink, the fat being replaced by myelocytes and red cells. Smear preparations and sections show many myeloblasts, myelocytes, and normoblasts.

Spleen.—The spleen is always enlarged, and may weigh from 15 to 20 lbs. Perisplenitis and thickening of the capsule are constant. There may be scars of old infarcts, and the veins in the hilus are enlarged. On section the cut surface is red, and there is a considerable degree of fibrosis. Histologically no Malpighian corpuscles remain, and the splenic pulp is packed with enormous numbers of polymorphs and myelocytes. The splenic endothelium has undergone myeloid metaplasia.

Liver.—The liver is constantly enlarged, and microscopically the portal spaces and capillaries are densely infiltrated with leucocytes and myelocytes. Giant cells are sometimes found.

Lymphatic Glands.—The superficial glands are usually macroscopically unaffected, but the mesenteric glands are frequently enlarged and histologically show the same myeloid metaplasia as the spleen.

Kidneys.—The kidneys show infiltration with leucocytes and myelocytes.

Symptoms.—The onset is insidious, attention being drawn to the condition by enlargement of the abdomen due to the increased size of the spleen, or pain from perisplenitis. Rapid loss of weight may be the first sign of the disease. Anæmia is not a prominent feature in the early stages, but later becomes extreme, with dyspnœa and œdema of the legs. Wasting may be extreme. Slight irregular pyrexia is constant. Retinal hæmorrhage, "leukæmic retinitis," is frequently found. Meniere's disease from hæmorrhage into the semi-circular canals sometimes occurs. Skin tumours, transverse myelitis, osteosclerosis, and priapism have been recorded in many cases.

Hæmorrhages, chiefly from the nose and gums, and gastro-intestinal symptoms, vomiting and diarrhœa, are frequent terminal events.

Enlargement of the spleen. The spleen usually reaches below the umbilicus. The edge and notch are readily felt, and the surface is smooth and often tender.

The liver is usually palpable, and sometimes the axillary glands are enlarged.

Urine.—There is an enormous increase in the uric acid output due to the destruction of leucocytes.

The Blood.—Erythrocytes.—In the very early stages anæmia is not marked, but blood films show striking

numbers of normoblasts. As the disease progresses the secondary anæmia becomes more conspicuous, the red cells reduced to 1,500,000 or less per cubic millimetre, and hæmoglobin to 20 or 30 per cent. Normoblasts may number 40,000 per cubic millimetre.

Thrombocytes.—The platelets as a rule are greatly increased, often to more than 1,000,000 per cubic millimetre.

Leucocytes.—The total number may reach 500,000 or more per cubic millimetre, but counts varying from

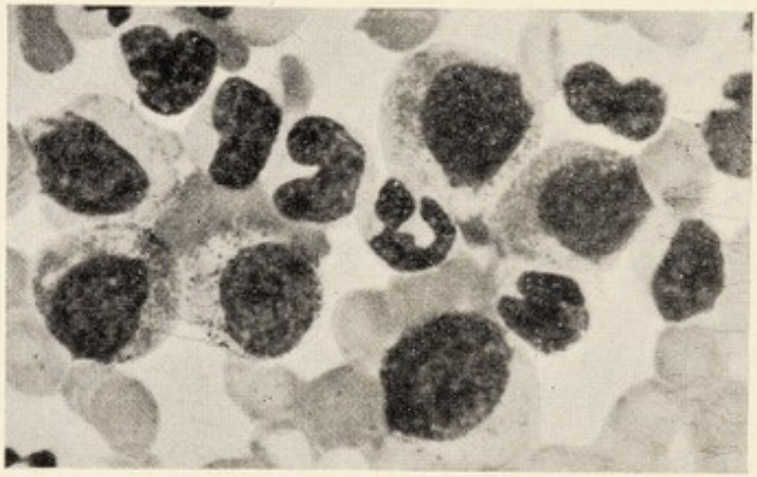


FIG. 53.—Chronic myeloid leukæmia.

20,000 to 350,000 are the usual figures. The characteristic feature is the presence of large numbers of myelocytes—neutrophil, eosinophil, and basophil—but it must be remembered that all the normal leucocytes are increased, although the percentages of lymphocytes, monocytes, eosinophils, and basophils are low owing to the numbers of myelocytes and polymorphs. The predominant myelocyte in most cases is the neutrophil, but either the eosinophil or basophil may be present in large numbers.

Fig. 53 is a field from a case of chronic myeloid leukæmia, showing a group of neutrophil myelocytes and polymorphs.

The percentages of the types of various myelocytes present wide differences in films from the same case taken at various times. The following may be taken as typical white-cell variations:—

Total leucocytes . .	20,000 to 350,000 per c.mm.
Polymorphs . .	20 to 60 per cent.
Eosinophil leucocytes .	0·2 ,, 5 ,,
Basophil leucocytes .	0·2 ,, 5 ,,
Myeloblasts . .	2 ,, 25 ,,
Neutrophil myelocytes .	10 ,, 60 ,,
Eosinophil myelocytes .	0·2 ,, 20 ,,
Basophil myelocytes .	0·2 ,, 20 ,,

The total number of leucocytes varies almost from day to day, and may fall to normal, but myelocytes still constitute a considerable percentage of the total.

Myeloblastic Termination.—Some cases, either in the natural course of the disease or as the result of X-ray treatment, suddenly show a marked increase in the number of myeloblasts. The percentage of myeloblasts may be as high as 80 to 98 per cent., and the total leucocyte count may remain as high as 100,000 per cubic millimetre, but usually falls and counts as low as 5000 per cubic millimetre are recorded, with the percentage of myeloblasts high.

Course and Prognosis.—Recovery never takes place, and probably all cases die within five years. The disease is not uniformly progressive, but remissions occur. The remissions are never complete, and even in aleukæmic intervals blood-films still show the presence of myelocytes. Acute infections such as influenza and sepsis may cause a sudden drop in the white-cell count. A high percentage of myeloblasts is a grave sign, and cases which show sudden large increases of these cells rarely live beyond a few weeks.

Treatment.—The general treatment is that of anæmia. Iron, arsenic, atoxyl, and many other remedies have been tried, without affecting the course of the disease.

X-rays often cause a rapid diminution in the size of the spleen and in the number of circulating leucocytes, and seem to prolong life. Subsequent applications of X-rays, however, have less and less effect.

Benzol in doses of 10 minims twice a day, increased to 50 minims a day, in capsules with olive oil, in occasional cases gives results similar to X-rays.

During treatment by X-rays or benzol the blood must be examined regularly, and treatment discontinued if the total leucocyte count falls to 20,000, or if there is an increase in the percentage of myeloblasts.

(*b*) CHRONIC LYMPHATIC LEUKÆMIA.

Etiology.—The disease is rare, occurs after the age of forty, and is found most frequently in males.

Pathology.—The pathology and histology correspond to chronic myeloid leukæmia, except that the tissues and marrow are packed with small lymphocytes, instead of myelocytes.

Symptoms.—The onset is always insidious, with enlargement of groups of superficial lymphatic glands. In some cases every superficial gland is involved, but cases are recorded where there has been no superficial glandular enlargement. Skin tumours are not infrequent. The spleen is usually palpable. Weakness, wasting, and anæmia are the only symptoms. Acute termination with hæmorrhages, purpura, and marked thrombopenia may take place.

The Blood. — *Erythrocytes.* — These are normal in numbers at the beginning of the disease, but there is a progressive secondary anæmia towards the termination.

Leucocytes.—The leucocyte count varies considerably. Counts as low as 2000 and as high as 500,000 per cubic millimetre may occur. Small lymphocytes constitute over 90 per cent. of the white cells (fig. 54).

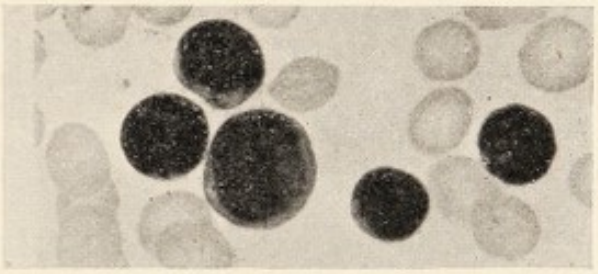


FIG. 54.—Shows four small lymphocytes and one larger type, in a film from a case of chronic lymphatic leukæmia.

Prognosis.—This is the most chronic leukæmia, the duration being five to ten years. Death occurs from pneumonia or other inter-current infection or from progressive anæmia.

Treatment.—There is no response to X-ray treatment, but a great improvement has been recorded by radium. Arsenic, naphthalene tetrachloride, in five- to ten-grain doses, and benzol may be tried.

CHAPTER XIII.

ERYTHRÆMIA.

Synonyms.—Polycythæmia vera, Osler's disease, Vaquez's disease.

Definition.—A disease characterised by hyperplasia of the erythroblastic tissues, cyanosis, enlargement of the spleen, and an increase in the number of red cells in the circulation.

Etiology.—The disease occurs equally in both sexes between the ages of thirty-five to sixty. There is no known etiological factor.

Pathology.—The bone marrow is purplish-red in colour, the fat of the long bones being replaced by red marrow to such an extent that the compact bone may be encroached upon and rendered brittle. Many myeloblasts and myelocytes are present.

Enlargement of the spleen, general dilatation of the veins and arteries throughout the body, and marked arteriosclerosis are constant.

The pathogenesis is uncertain. The appearance of the marrow suggests a primary hyperplasia of the erythroblastic tissue corresponding to the white-cell increase in leukæmia. On the other hand, it is suggested that the loss of splenic function leads to abnormal stimulation of red-cell production.

Symptoms. — 1. Appearance. — Brick-red to plum-coloured face, with lips and ears purple.

2. Symptoms of cerebral congestion, headache, and vertigo. High blood-pressure is common, though not invariable.

3. Hæmorrhages.—Daily or weekly hæmorrhages are not uncommon—epistaxis, hæmatemesis, hæmoptysis, or hæmorrhage from the rectum and genital tract. Cerebral hæmorrhage is not infrequent.

4. Splenic enlargement.—The enlargement is usually of moderate dimenisons, the spleen rarely reaching below the umbilicus.

5. *Blood.*—The blood volume is often double the normal. The erythrocytes number 7,000,000 to 12,000,000 or more per cubic millimetre. A few normoblasts are constantly present, and reticulocytes are in greater numbers than normal. The hæmoglobin percentage is high, 120 to 180 per cent., but the colour index is below 1. The shape and size of the red cells are normal.

There is always a leucocytosis of 20,000 to 30,000 per cubic millimetre, due to increase in numbers of the polymorphs. No abnormal leucocytes are present.

6. Vaso-motor instability is marked. On raising the hand above the head the colour becomes white immediately, and on lowering it the change to brick-red is equally sudden.

7. Gastro-intestinal disturbances.—Dyspepsia, thirst, constipation, and abdominal pain, and tenderness over the spleen are common.

Two interesting changes in the blood picture may take place. Erythropoiesis may diminish in intensity, the red-cell count falling from perhaps 12,000,000 to 3,000,000 per cubic millimetre, and the condition pass into an anæmia in which anisocytosis and poikilocytosis and large numbers of normoblasts are prominent features, or the anæmia may be of the secondary type without these characteristics.

The second alteration that may occur shows the close relationship between erythræmia and leukæmia. The

red-cell count remains high, but myelocytes appear in the blood-stream in increasing numbers, and the condition becomes erythro-leukæmia.

Diagnosis.—Erythræmia must be differentiated from other causes of splenomegaly and polycythæmia. An increased number of red cells, erythrocytosis, occurs in conditions hindering the supply of oxygen to the tissues, and is compensatory, *e.g.*:

1. High altitudes.
2. Erythrocytosis due to chronic pulmonary disease, *e.g.* emphysema.
3. Congenital heart disease.
4. Thrombosis of the portal vein.

Prognosis.—The disease lasts from six to ten years or longer. Death occurs from cerebral hæmorrhage or arterio-sclerosis with cardiac failure.

Treatment.—Bleeding, forty to sixty ounces, gives marked temporary relief. X-ray treatment reduces the size of the spleen and the number of red cells per cubic millimetre, and has given the best results.

CHAPTER XIV.

ERYTHRO-LEUKÆMIA.

Definition.—A disease characterised by the clinical and pathological findings of both erythræmia and myeloid leukæmia. The condition is a pan-myelosis.

Etiology.—The few cases on record have an age and sex incidence similar to myeloid leukæmia. As mentioned in the previous chapter, cases of erythræmia sometimes pass on to the combined disease. No causative factor is known.

Pathology.—There is hyperplasia of the erythroblastic and granuloblastic elements of the marrow. The stimulus would appear to cause the hæmocytoblast to produce both red and white cells indiscriminately.

Bone Marrow.—Macroscopically, the marrow of the long bones shows marked hyperplasia and appears a whitish-yellow studded with red islets. Microscopically, sections show an enormous increase in all the marrow constituents.

Spleen.—The spleen is always large, as in myeloid leukæmia, and may weigh twelve or more pounds. Perisplenitis and infarcts are present. On section, the Malpighian bodies are invisible and the splenic pulp is mottled and congested. Microscopical examination shows extensive myeloid metaplasia, with the lymphatic elements almost completely absent.

Liver.—The liver is enlarged and yellowish in colour. Microscopically, atrophy of the liver cells and diffuse myeloid metaplasia are seen.

Lymphatic Glands.—The abdominal glands are often enlarged and also show myeloid change.

Kidneys.—These and other organs show leukæmic infiltration.

Symptoms.—The signs and symptoms are those of each of the combined diseases. Cyanosis and vascular engorgement of the veins of the cheeks, enlargement of the liver and spleen, and in some cases of the superficial lymphatic glands. Pain over the spleen from perisplenitis is usual. Epistaxis, bleeding from the gums and other mucous membranes, although present is not so marked as in pure erythræmia. Cardiac failure with œdema is the usual terminal event.

Blood.—The erythrocytes number from 6,000,000 to 8,000,000 per cubic millimetre. The counts are somewhat less than in erythræmia. Normoblasts are present in numbers, and there may be anisocytosis and poikilocytosis, punctate basophilia, and many cells showing diffuse polychromasia.

The hæmoglobin figure is high, 96 to 120 per cent., and the colour index 0·6 to 0·8.

Leucocytes.—Total leucocyte counts vary from 10,000 to 90,000 per cubic millimetre. Myelocytes are always present, and may reach 40 per cent. of the total. The thrombocytes are increased in numbers.

Diagnosis.—The red-cell count suggesting erythræmia and the total leucocyte and differential counts approximating those of myeloid leukæmia, together with the marked splenic enlargement and cyanosis, make up the picture of this composite disease.

Prognosis.—Invariably fatal in from two to five years.

Treatment.—The treatment is that of erythræmia and myeloid leukæmia.

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