Blood pictures : an introduction to clinical haematology / by Cecil Price-Jones.

BLOOD PICTURES

CECIL PRICE-JONES

BLOOD PICTURES

AN INTRODUCTION TO CLINICAL HÆMATOLOGY

BY

CECIL PRICE-JONES, M.B. (Lond.)

WITH 5 COLOURED PLATES AND 7 ILLUSTRATIONS IN THE TEXT

THIRD EDITION

BRISTOL: JOHN WRIGHT AND SONS LTD.
LONDON: SIMPKIN MARSHALL LTD.

1933

PRINTED IN ENGLAND
BY JOHN WRIGHT AND SONS LTD., BRISTOL.

PREFACE TO THIRD EDITION

A THIRD edition of this book is called for by the advances in hæmatological knowledge and in the methods of interpretation of blood examinations which have been made since the second edition was published twelve years ago.

In fitting the new material to modern needs I have kept the style and arrangement of the first edition, believing that this has most usefully appealed to students and workers in clinical laboratories.

I have therefore restricted the book to its original limits, avoiding as far as possible clinical descriptions and treatment; and, as before, I have omitted, with only a few exceptions, references to the vast literature of the subject, which may be found in text-books of hæmatology.

I have again to thank my many friends and critics, and hope this new edition may be as useful and favoured as its predecessors.

C. P.-J.

London,
April, 1933.

PREFACE TO FIRST EDITION

THE following pages have been written in response to the frequent request by clinicians for some guide to the interpretation of reports on blood examinations, and also for some simple method by which general practitioners can assist their diagnosis by making examinations of the blood.

For these purposes it was not desirable to write a complete hæmatological text-book, and accordingly the theoretical aspect of hæmatology has been omitted, and the descriptions of the numerous apparatus and methods, most of which have now only antiquarian interest, have been avoided.

A few examples of 'blood pictures' from actual cases have been given, but these are not to be regarded as fixed standards. They are only to be considered as conforming to the type of which they are examples.

When an observer has made a blood picture he should in every instance express it in terms of the normal picture.

With the exception of those diseases which are known as 'blood diseases', a diagnosis should not be made from a blood picture alone. The appearances in the blood are only to be used as a part of the general clinical picture.

C. P.-J.

1917.

CONTENTS

PART I

THE COLLECTION AND EXAMINATION OF MATERIAL

PART II

BLOOD PICTURES IN THE DIAGNOSIS OF DISEASE

APPENDIX

COLOURED ILLUSTRATIONS

BLOOD PICTURES

PART I

THE COLLECTION AND EXAMINATION OF MATERIAL

Chapter I

TECHNIQUE OF BLOOD EXAMINATION

A BLOOD picture is an expression in numerical terms of the cytological constituents of the blood.

It comprises, for routine purposes, the number of red cells per cubic millimetre, the hæmoglobin percentage and colour index (the coefficient of hæmoglobin per corpuscle), the number of white cells per cubic millimetre, and the relative percentage and absolute numbers per cubic millimetre of the different varieties of the white cells. It indicates the abundance or scarcity of blood-platelets, which in some cases may need enumeration. It also notices the presence or absence of abnormal cell forms.

The use of a blood picture is chiefly diagnostic, but also to some extent prognostic.

It is first of all essential to establish a 'normal' or healthy blood picture; the values of any blood picture may then be expressed by the signs +, −, 0 (being increases, diminutions, or no change respectively), relative to the corresponding figures of the normal picture.

The second essential is to employ, if possible, uniform methods and technique in the examination of samples of blood. Much confusion has arisen from the so-called 'personal factor' introduced in blood examinations, and possibly to a certain degree this is unavoidable; but endeavour should be made to reduce it to negligible proportions by the adoption of a fixed scheme. In the following account this has been attained as the result of long personal experience based on the work of well-accredited modern hæmatologists; though not professing to any finality, and possibly open to academic criticism, it will serve all the practical purposes required by the clinical pathologist.

THE COLLECTION OF SAMPLES OF BLOOD

Blood is most conveniently collected by puncturing the lobe of the ear with a clean straight Hagedorn needle. The puncture is best made about the middle of the length of the auricle, just inside the margin; this is preferable to puncturing the lobule. The collection of blood from the finger is often unsatisfactory. The auricle should be gently massaged, but not rubbed; cleaning with iodine, ether, etc., is not necessary, and should be avoided in view of the artificial hyperæmia, the possible leucocytic attraction, and introduction of tissue juice and cells, likely to be set up thereby.

The first drop of blood being discarded, collect for red and white cell-counts in a Thoma pipette, make films on glass microscope slides, and finally collect for hæmoglobin estimation in a hæmoglobinometer pipette.

Some persons bleed with difficulty, and in these cases it is often tempting to encourage the hæmorrhage by squeezing the ear, but this is not advisable. It is much better to make a second puncture which may possibly tap a more readily bleeding vessel. Some persons, especially pernicious anæmia patients, bleed very freely, so that the blood quickly runs to the edge

of the lobe, away from the site of the puncture; it is preferable not to take these hanging drops, but to take a fresh drop from the puncture site itself.

All collecting apparatus should be thoroughly cleaned with water, alcohol, and ether before use and be quite dry. Glass slides should be free from grease (it is well to rub the glass with emery paper), and should be straight and of level surface.

THE ENUMERATION OF RED CELLS AND WHITE CELLS

The best apparatus for this purpose is Bürker's hæmocytometer. It has many advantages over the old-form Thoma-Zeiss. The modification supplied by Messrs. Hawksley, and known as the Bürker-Hawksley counting chamber (*Fig.* 1), consists of two cells worked in solid glass, closed by a cover-slip placed centrally

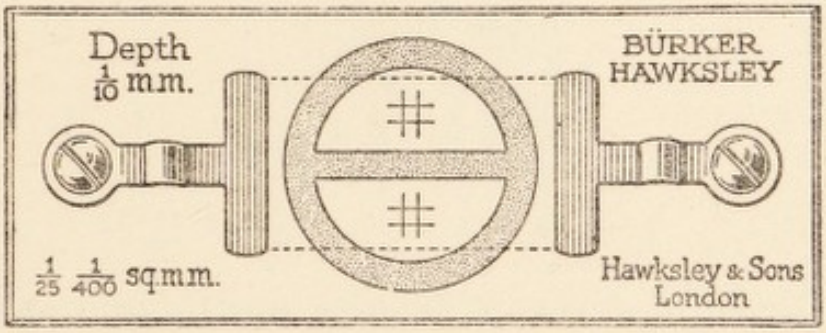


Fig. 1.—Bürker-Hawksley Counting Chamber.

and held in position by two spring clips. A portion of each cell platform projects beyond the edge of the cover-slip (see dotted line). The advantages of the two cells lie in the possibility of obtaining a control count from the same drop of blood, and the facility of counting two different cases without deranging the apparatus. The depth of each cell beneath the cover-slip measures 0·1 mm. On each of the counting stages is a ruled counting scale; this measures 3 mm. by 3 mm.; it is marked by vertical and transverse lines

into accurate subdivisions, columns, and squares of 1 mm., $\frac{1}{20}$ mm., $\frac{1}{40}$ mm., etc. (*Figs.* 2, 3). If a single column (a) is chosen, it has a width of $\frac{1}{20}$ mm., a length of 3 mm., and a depth (or space between it and the cover-slip) of 0·1 mm., so that it has a cubic measurement of $3 \times \frac{1}{20} \times 0{\cdot}1$ c.mm. $= 0{\cdot}015$ c.mm. If the whole scale is counted, the cubic measurement is $3 \times 3 \times 0{\cdot}1$ c.mm. $= 0{\cdot}9$ c.mm.

The whole apparatus being thoroughly cleaned and dried, the cover-slip is applied, and fixed in place by the two lateral clamps.

The red and white cells are counted from the same drop of blood on the same counting stage. The blood

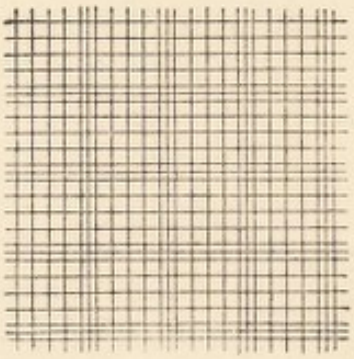


FIG. 2.—Bürker Counting Scale.

is collected in a Thoma diluting pipette, containing to the top mark above the bulb 101 parts, the stem to the mark below the bulb containing 1 part, marked into subdivisions which are only rarely required; they are useful in cases of polycythæmia, when it is more convenient to deal with a higher dilution of the blood samples.

The best diluting fluid is 0·8 per cent saline containing 10 per cent formalin (0·8 per cent saline 90 c.c., formalin 10 c.c.), coloured by the addition of a few drops of a saturated aqueous solution of gentian violet. By this means the white cells are stained violet, and can be readily distinguished.

The blood is sucked up to the mark 1 c.mm. on the stem of the pipette, and diluting fluid is at once sucked up to the mark 101 above the bulb. The pipette is thoroughly shaken, a stemful is expelled, and the point applied to the projecting portion of the cell platform. The fluid quickly runs under and fills the space between the counting stage and the under surface of the cover-slip. The slide is then examined under a $\frac{1}{6}$-in. objective.

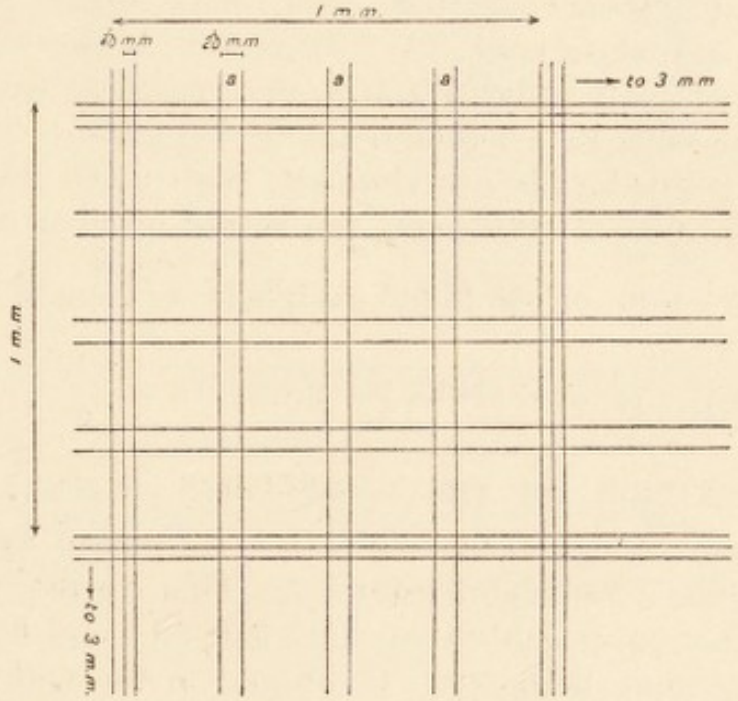


FIG. 3.—Part of Bürker Counting Scale Magnified.

Counting Red Cells.—In counting red cells it is convenient to take one of the single $\frac{1}{20}$-mm. columns, and count all the red cells throughout the length (3 mm.) of the column. Suppose n red cells are counted, this will represent the number of red cells in 0·015 c.mm. of fluid; therefore the number per c.mm. of fluid $= \frac{n}{0{\cdot}015} = 100n \times \frac{2}{3}$; and since the blood was diluted 100 times, the number of red cells per c.mm. of blood is $100 \times 100n \times \frac{2}{3}$, or 10,000 times the number

of cells counted, multiplied by 2 and divided by 3. If $n = 750$, then the cells number $750 \times 10{,}000 \times \frac{2}{3}$, or 5,000,000, per c.mm.

In practice, it is better to count two of these columns, add together the number obtained from each, divide by 3, and multiply by 10,000.

Counting White Cells.—The white cells are seen stained violet. As a rule their numbers are relatively very few, so that any single column, such as was chosen for enumerating the red cells, may quite possibly contain no white cells. It is therefore better to count all the stained cells in the entire counting area, i.e., all those cells in a cubic space of 0·9 c.mm.

If n stained cells are counted, then since the blood has been diluted 100 times, the actual number of white cells per c.mm. of the blood sample is $\frac{1000n}{9}$. If $n = 70$, the number of white cells per c.mm. is $\frac{70{,}000}{9}$, or 7700.

ESTIMATION OF THE HÆMOGLOBIN PERCENTAGE

The percentage of hæmoglobin is estimated by means of Haldane's hæmoglobinometer. This consists (*Fig.* 4) of two similarly calibrated glass tubes (A and B) of the same internal diameter. The liquid in the sealed standard tube (A) is a 1 per cent solution of blood containing an amount of hæmoglobin having an oxygen capacity of 18·5 c.c. per 100 c.c. of blood as determined by the ferricyanide method. It has been saturated with coal gas (carbon monoxide) in order to change the unstable oxyhæmoglobin solution into the stable solution of carboxyhæmoglobin for the purpose of securing a permanent colour standard.

Into the empty tube (B) are poured a few drops of tap water—say up to the mark 30. The blood is carefully collected in the pipette (D) up to the mark 20 c.mm.; the point is wiped in order to remove any

excess of blood on the outside, the blood is then blown out into the tube (B), thoroughly mixed with the water, and the pipette washed out with the water in the tube.

The tube (B) is now connected up with a gas supply by means of the tube (G), which is passed down to near

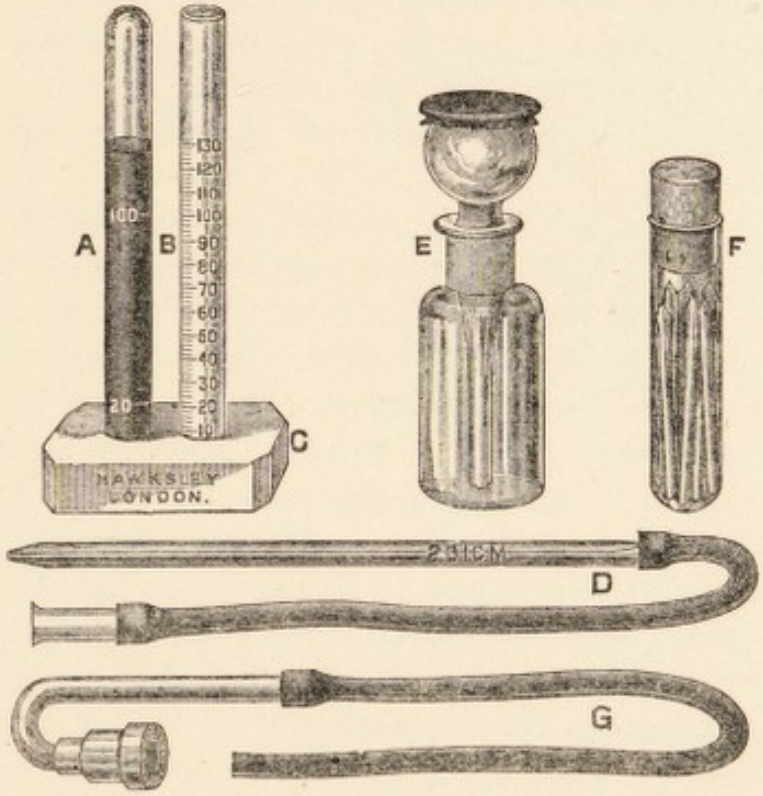


FIG. 4.—Haldane's Hæmoglobinometer.

A—Glass tube containing blood solution of standard tint.
B—Graduated tube.
C—Rubber stands for tubes A and B.
D—Capillary pipette and suction tube; wires for cleaning the pipette are supplied.
E—Bottle with pipette stopper.
F—Glass tube holding 6 lancets.
G—Tube and cap for fixing over ordinary gas-burners.

the level of the diluted blood, and gas is allowed to pass for a few seconds. As the tube (G) is withdrawn, with the gas still passing, the end of the tube (B) is closed with the finger, and the liquid is made to pass up and down the tube at least a dozen times, so as to saturate the hæmoglobin with carbonic oxide. Water is then

added drop by drop from the pipette stopper, the tube being inverted after each addition, until the point is reached at which the tints of the liquids in the tubes (A) and (B) are just equal. The diluting and mixing should be done gently to avoid the formation of air-bubbles.

In judging the equality, the tubes should be held against the light from the sky, or, if artificial light be used, against an opal glass shade; and it is absolutely necessary that the tubes should be repeatedly transposed.

The level of the liquid is read off on the graduated tube (B), after half a minute has elapsed since the last drop of added water was mixed with the rest of the liquid by inverting the tube. The observation is repeated after the addition of another drop of water, and if necessary another, until a point is reached at which the tints are again unequal; the true result is the mean of these readings. The error in any single determination ought not to exceed 2 per cent.

The result obtained is the percentage actually present of the amount of hæmoglobin contained in a solution of blood having an oxygen capacity of 18·5 c.c. per 100 c.c. of blood. Assuming the reading of tube B is 100, the amount of hæmoglobin contained in the sample is 100 per cent and has an oxygen capacity of 18·5 c.c. per 100 c.c. of blood; if the reading is 110, the amount of hæmoglobin contained in the sample has an oxygen capacity of $\frac{18{\cdot}5 \times 110}{100} = 20{\cdot}35$ c.c. per cent; if the reading is only 90, the oxygen capacity of the sample is 16·6 c.c. per 100 c.c. of blood.

Since the function of hæmoglobin is to carry oxygen, a measurement of the oxygen-carrying capacity is the only useful method of expressing the amount of hæmoglobin in any sample of blood, and is the essential principle of all reliable hæmoglobinometers.

Having estimated the percentage of hæmoglobin in

a sample of blood, the colour index, corpuscular value, or coefficient of hæmoglobin per corpuscle is obtained by dividing the hæmoglobin percentage by the percentage of red cells :—

$$\frac{\text{Hb. percentage}}{\text{R.C. percentage}} = \text{C.I.}$$

For example, assuming 5,000,000 red cells per c.mm. is normal, or 100, then, if 4,500,000 red cells are enumerated, the red-cell percentage is 90 ; let the hæmoglobin percentage as estimated above be 90 ; then the colour index $= \frac{90}{90} = 1$, or normal. Again, assuming the average red-cell count of a woman to be 4,450,000 per c.mm., or a corpuscular percentage of 89, then for a colour index of 1 the hæmoglobin percentage in a woman will be 89.

FILM PREPARATIONS

The relative proportions of the different varieties of white cells are estimated by means of film preparations. Films are best prepared in the following way. Two clean microscopic slides are taken ; a drop of blood is caught on one of the end edges of one slide, and this edge is at once applied square to the upper surface of the other slide. When the blood drop has taken a line transverse to the length of the slide, draw the first slide firmly along the surface of the second slide.

Some workers recommend drawing the slide with a jerky movement, and so producing a series of alternating thin and thick bands on the blood film. When leucopenia is present and the white cells are only sparsely distributed through the film, then the thicker bands are often serviceable for accelerating the counting, as more white cells will be accumulated in these areas. For most purposes, however, and especially for the careful examination of red cells, searching for parasites, etc., it is preferable to deal with as thin and as evenly-spread a film as possible.

Having made several films, allow them to dry on the table. Do not fix them by heat or any other agent. When they are dry, apply the stain. The best for most routine work is Jenner's stain. Some pathologists prefer Leishman's, which is especially to be recommended for the examination of blood parasites. Others use Giemsa's stain, which is also preferable to Jenner's in the examination of parasites; but for ordinary work it is not so serviceable, and requires a longer time.

Jenner's Stain.—This is conveniently made by dissolving 3 or 4 tabloids of Jenner's stain (B. W. & Co.) in 30 or 40 c.c. of pure methyl alcohol.

By keeping Jenner's stain in a wide-mouthed stoppered vessel of sufficient size to admit a microscope slide, the films can be immersed in the stain, which is thereby economized, and can be used over and over again to stain any number of specimens. If kept well stoppered, the stain remains unaltered.

The films are allowed to stand in the stain for two to three minutes; they are then well washed in ammonia-free neutral distilled water, dried with blotting paper, and examined under a $\frac{1}{12}$-in. oil-immersion objective.

Examination of Stained Films.—In examining stained films it is important to observe consecutive microscope fields. The routine adopted is as follows: starting from the lower margin of the film, successive vertical fields are examined, and the different varieties of cells are noted and enumerated. It is best, especially in incomplete pictures (*see p.* 31), to count at least 1000 white cells; if, however, the film is good and even, and the counts of successive 100 cells have approximately identical values, it is probably sufficient to count only 500 white cells.

The appearance of the red cells should be noted, and any abnormal forms enumerated and classified. Every white cell must be counted and classified, and any

abnormal appearance noted. The different forms of abnormal red and white cells are enumerated as percentages of the number of white cells counted on the stained film.

PLATELETS.—The prevalence or otherwise of platelets (thrombocytes) should be noted. These are small refractile bodies 1·5 to 3 μ in diameter; stained by cresyl blue they appear as collections of minute violet granules surrounded by faint blue areas; they have a strong tendency to agglutinate and arrange themselves in clumps, which influences their accurate enumeration. In healthy blood they number about 300,000 per c.mm. (250,000 to 450,000).

Enumeration of Platelets.—The method described by Howel Evans* is recommended: (*a*) Pour embedding paraffin into cold water, and while still soft mould the mass on the finger to form a cup of about 2 to 3 c.c. capacity—to admit the tip of a finger readily; (*b*) Prepare an anti-coagulant solution of 2 per cent sodium citrate in 0·29 per cent sodium chloride, sterilized in tubes in doses of 10 c.c.; (*c*) Just before use shake a small pinch of cresyl blue into a tube of the solution, which should then be filtered; (*d*) The patient's finger-tip is cleaned, dipped into the fluid, and pricked through the dependent drop, and one or two drops of blood are collected in the paraffin cup; (*e*) Mix the blood and cresyl blue solution thoroughly by suction and expulsion in a glass pipette, and transfer a drop to a red-cell counting chamber. After an interval of 20 minutes for the platelets to settle, count 2000 red cells and corresponding platelets. This gives the ratio $\frac{P}{R}$ and the absolute value of platelets per c.mm. is obtained from the red-cell count per c.mm.

---

* *Jour. Pathol. and Bacteriol.*, 1928, xxxi, 815.

Chapter II

DESCRIPTION OF THE BLOOD-CELLS

RED CELLS (*Plate I*)

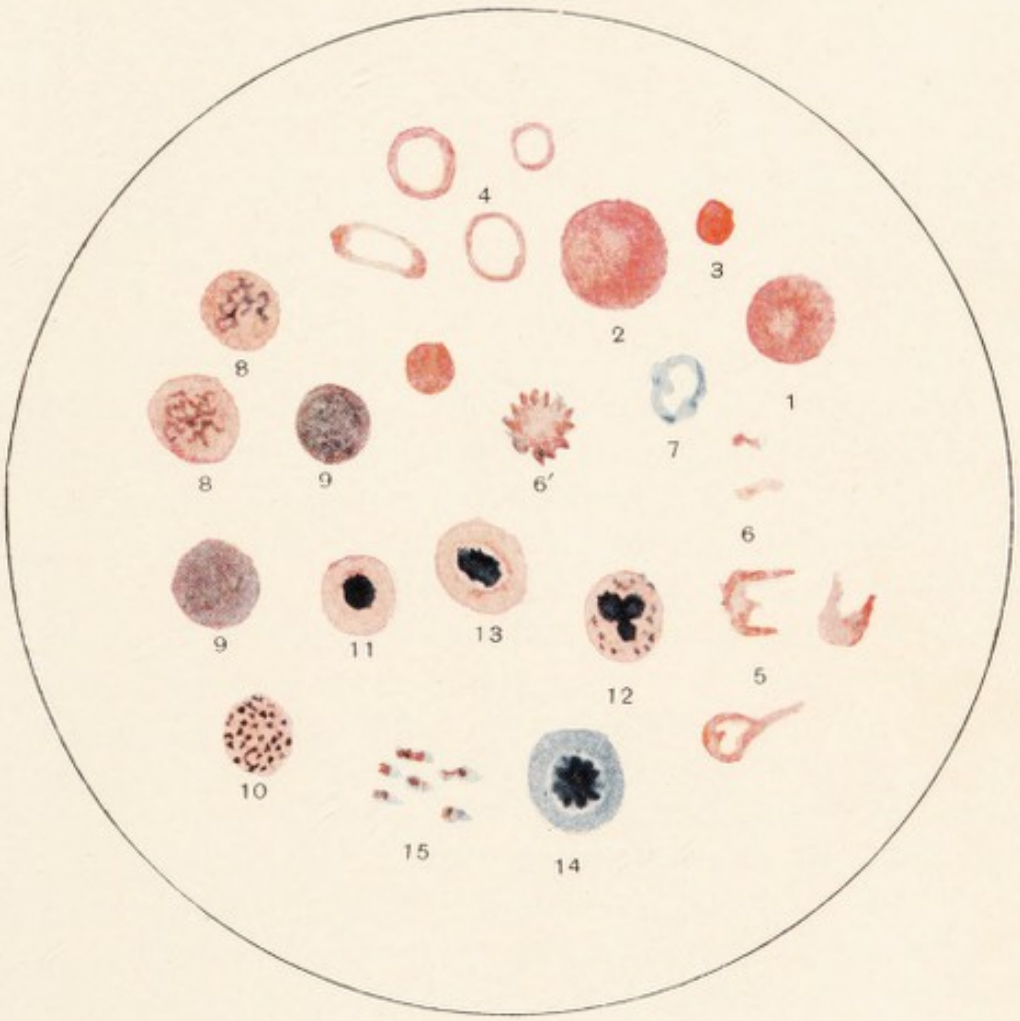
In Jenner-stained films healthy red corpuscles appear as round pink discs, varying from 6 μ to 9 μ in diameter. They are biconcave in form, so that the stain is often less intense at the centre than at the periphery. The pink colour of these cells is due to the eosin of the stain which has been taken up by the oxyphil selection of the hæmoglobin, and the amount and intensity of the colour is directly related to the hæmoglobin content of the cell.

In some varieties of anæmia the amount of hæmoglobin is deficient and the discs are pale, often mere colourless rings with pink-stained periphery—these are *hypochromic cells*; when the pink colour is entirely absent the cells have a grey shadow-like appearance and are referred to as *skiacytes*; when the periphery is distorted into various pear-shaped, battledore-like, and other grotesque forms the cells are known as *poikilocytes*; these must not be confused with *crenated cells* with wavy irregular periphery, which are artefact productions. Sometimes fragments of red cells are met with, which are known as *schizocytes*; a red cell may be fragmented without losing its hæmoglobin content.

Variation in the size of red-cell diameters is known as *anisocytosis*; it is always present; the degree of this variability can be estimated (*see p.* 70), and is often a useful diagnostic sign.

The most important abnormal forms of red cells found in the circulation are *nucleated red cells*, and

PLATE I



1, Normocyte. 2, Megalocyte (macrocyte.) 3, Microcyte. 4, Hypochromic cells. 5, Poikilocytes. 6, Schizocytes. 6′, Crenated cell. 7, Shadow cell (skiacyte). 8, Reticulocytes. 9, Polychromasic cells. 10, Punctate basophilia. 11, Normoblast. 12, Megaloblast. 13, Megaloblast. 14, Gigantoblast (metrocyte). 15, Platelets.

other immature cells showing *polychromasia* and *punctate basophilia*, which normally occur in the blood of the newborn and in the bone-marrow of adults, and represent stages in the development of red cells from primitive forms.

Nucleated red cells—erythroblasts—do not occur in healthy blood, and are rarely met with in ordinary routine blood examinations. In some cases of anæmia they are abundant, and reflect the activity of the bone-marrow. There are several forms of these cells. A normal-sized red cell with a round compact deep blue-black staining nucleus is a *normoblast*. Larger forms, often with dividing nuclei—showing '*buds*' or '*wheel spoke*' appearance—are *megaloblasts* and *metrocytes* (*gigantoblasts*). The cytoplasm of these cells often shows polychromasia and basophilic staining.

Polychromasia—a diffuse purple staining of the cytoplasm—and *punctate basophilia*—when the red cell is studded or stippled with blue-black granules of varying degrees of coarseness or fineness—were at one time regarded as degeneration effects, and were thought to be nuclear remnants. They are now recognized as the remains of the spongioplastic network of the cytoplasm of the primitive cell, retained even after the nucleus of the cell has been lost.* These cells represent stages in the maturation of the red discs after removal of the nucleus.

Owing to the varying degrees of polychromasic and basophilic staining seen in Jenner-stained films, it is usually difficult or impossible to make an accurate

---

* Pappenheim (*Folia Hæmatologica*, 1910, ix, part 3, 572) has shown that the constituents of a cell are to be regarded as *cytoplasm*—composed of *spongioplasm* and *paraplasm*—and *nucleus*—composed of *chromatin* and *parachromatin*.

Spongioplasm is indifferent cyto-reticular ground substance; in young and more primitive forms it is relatively abundant and stains strongly basophil; in older or more evolved cells it stains only faintly basophil, and is diminished in amount, or even absent.

estimation of the number of these immature cells; by employing a vital-staining method (cresyl blue) the spongioplastic network of the cells is broken up and detached from the cell periphery, and after counter-staining with Jenner stain appears as a collection of deep-blue fragments arranged in clumps, or wreaths and skeins about the centre of the clear normal-stained pink cytoplasm. These cells are now known as *reticulocytes*, and can be readily counted and expressed as percentages of the red cells. In healthy blood there are 0·1 to 0·5 per cent of these cells. Reticulocyte estimation is a valuable sign in the diagnosis and prognosis of cases of anæmia.

Method for Staining Reticulocytes.—Equal quantities of blood and brilliant cresyl blue solution (1 part saturated alcoholic solution of cresyl blue to 5 parts 1 per cent sodium citrate in normal saline) are mixed on a paraffin slide and incubated in a moist chamber for 15 minutes at 37° C. Films are then made in the usual way and counterstained with Jenner stain. The number of reticulocytes to 1000 red cells is now counted.

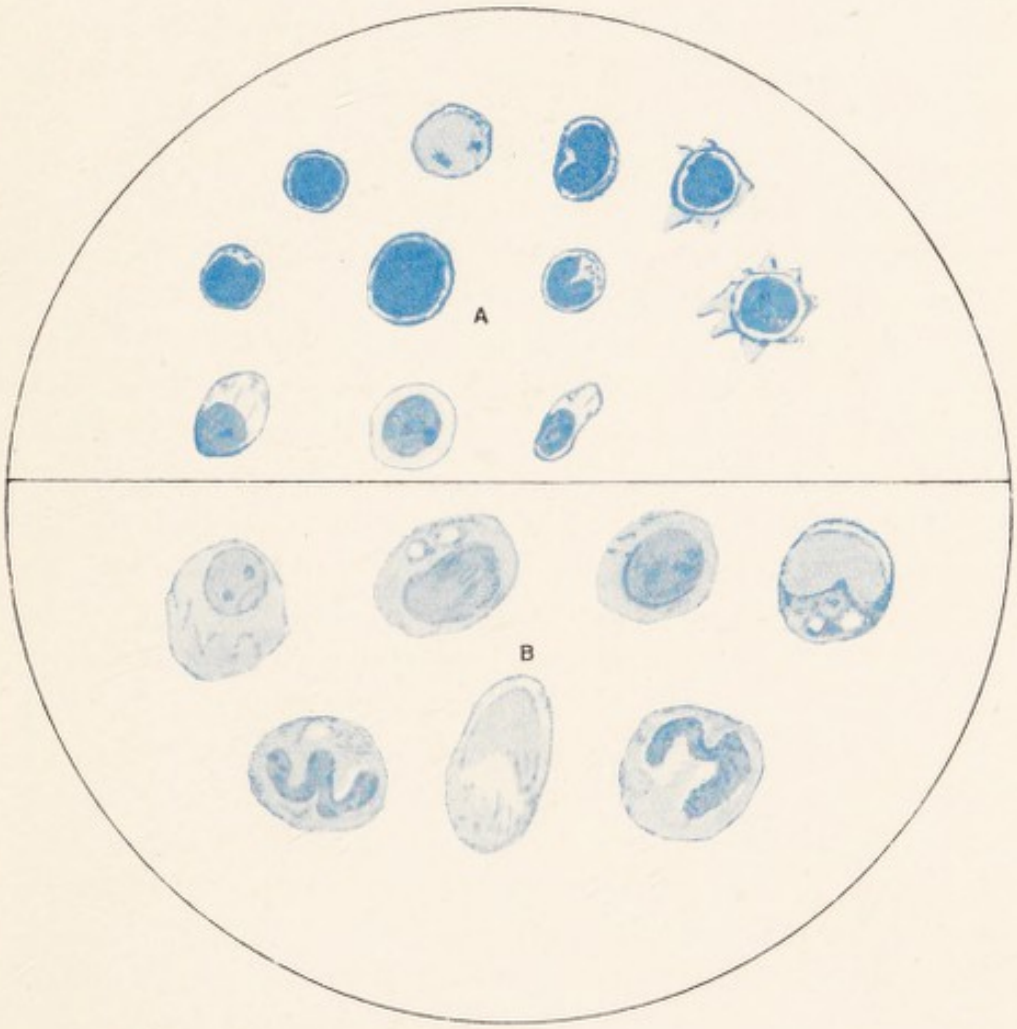
WHITE CELLS

There are many varieties of white cells. They may be grouped into two classes: (1) *Lymphoid*—non-granular—cells, which include the lymphocytes and large mononuclear cells; (2) *Leucoid*—granular—cells, which include polymorphonuclear leucocytes, eosinophils (coarse granular leucocytes), and mast cells (basophil granular leucocytes). *Abnormal forms* of white cells must also be searched for in stained films.

1. Lymphoid Cells (*Plate II*).—*Lymphocytes* (A) are non-granular cells, varying in diameter from that of a normal red corpuscle to nearly twice that size, viz., from 7 to 12 μ. The smaller-sized of these cells are known as *small lymphocytes*, the larger as *large*

PLATE II

LYMPHOID CELLS



A. Lymphocytes. B. Large mononuclear cells.

lymphocytes. The two varieties are, by some observers, quite arbitrarily classed as two distinct kinds of cells ; they are more usefully to be regarded as varying sizes of the same class of cell, and both named lymphocytes. The large lymphocyte is generally accepted as a younger form of the small lymphocyte.

The lymphocyte has a relatively large round nucleus staining deep blue (strongly basophil), is surrounded by a narrow concentric border of more or less reticulate protoplasm, and usually has a well-stained periphery. The protoplasm may sometimes have the appearance of containing deep-blue-stained granules ; these are not true granules, but are derived probably from the cyto-reticular ground-substance (spongioplasm) of the cell, and are known as 'azurophil granules'.

When the nucleus is less deeply stained a nucleolus may be seen, often placed eccentrically. Occasionally the nucleus is indented at one side as if about to undergo division by amitosis ; mitotic figures are not observed in the nuclei of these cells.

In film preparations, lymphocytes may assume various appearances, often of artefact nature. The cell wall may present short irregular projections, or the protoplasm may be extended to one side or all round the nucleus, thereby altering the proportions of the nucleus and protoplasm, often making it difficult to distinguish these cells from the large mononuclear cells ; this is especially the case with the larger lymphocytes. But attention to the actual size of the nucleus and to its deeply basophil staining should prevent mistakes in classification.

In the circulating blood of a healthy man, the lymphocytes number from 20 to 30 per cent of all the white cells. If the average total white count be regarded as 7500 per c.mm., the absolute number of lymphocytes per c.mm. will vary from 1500 to 2250.

Large mononuclear cells (*Plate II*, B) are much larger

than the preceding—three to four times the size of a red cell, having diameters of 12 to 20 μ. They assume many different appearances, owing to variations in size, in the proportions of nucleus to protoplasm, in the degree of nuclear staining, in the shape of the nucleus, and whether the protoplasm is almost unstained clear hyaline or is scattered with granules. These granules, like those occurring in the protoplasm of the lymphocyte, are of spongioplastic origin, and are therefore not to be regarded as true granules.

There are three chief varieties of these cells :—

a. The large hyaline cell, with a relatively large amount of very faintly stained hyaline protoplasm ; it shows an indistinct reticulum, a round or oval, rarely indented, eccentrically situated nucleus, which is more faintly basophil than the nucleus of the lymphocyte, and commonly contains one or more nucleoli.

b. A cell of similar size to the preceding, in which the protoplasm is relatively less in quantity, is stained more deeply, and has a distinctly granular appearance.

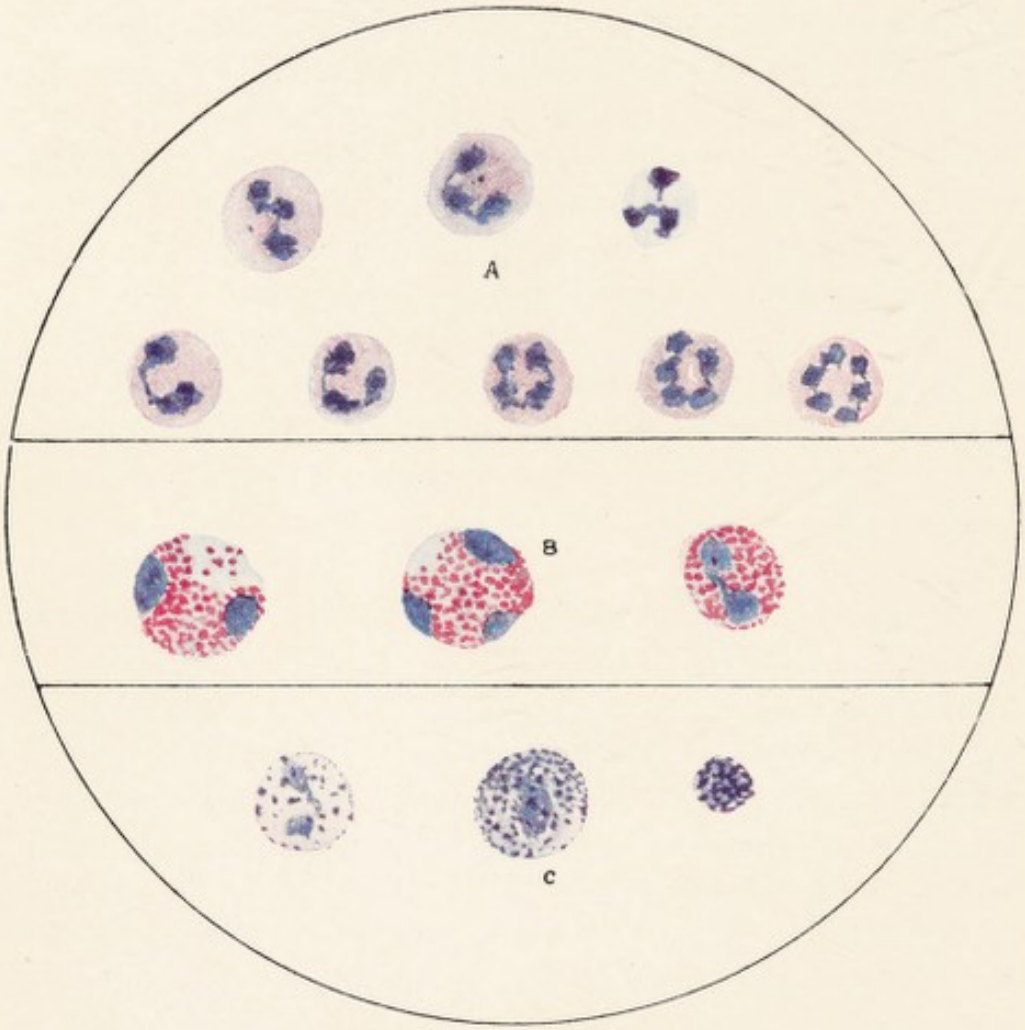
c. Cells in which the nucleus is deeply indented, apparently dividing into two parts, or bent or twisted into polymorphous shapes. These cells were formerly regarded as forms intermediate between the lymphocyte and the granular polymorphonuclear leucocyte, and received the name of 'transitional' cells. This term has now fortunately passed out of general use.

Of the many varieties of these cells, some have received specific names; but as their origins and functions are still unknown and subjects of controversy, little reliance can be usefully placed on these classifications.

It is generally supposed that the large mononuclear cells are of endothelial origin. They are active phagocytes, taking up bacilli, coccal bacteria, protozoa, disused red cells and leucocytes, etc. They are sometimes referred to as *macrophages*.

PLATE III

LEUCOID CELLS



A. Polymorphonuclear leucocytes. B. Eosinophils. C Mast cells.

In the circulating blood of healthy men, these large mononuclear cells number from 6 to 8 per cent of all the white cells. The absolute numbers vary from 450 to 600 per c.mm.

2. **Leucoid Cells** (*Plate III*).—*Polymorphonuclear leucocytes* (A) are the most numerous of all the white cells in the circulation. In fresh unstained specimens of blood they are colourless and exhibit active amœboid movement. They are about half as large again as the red cells, though often they appear very much bigger. The protoplasm is relatively abundant, and stains very faintly basophil, or appears unstained. The spongioplastic reticulum is not apparent, being occupied by varying numbers of fine granules which stain a pale-pink—neutrophil to oxyphil—colour. These granules are more especially concentrated about the nucleus; they are sometimes very numerous and seem to fill the cell; often they are very few or appear to be absent.

The nucleus is stained deeply basophil, and assumes a great variety of shapes, being twisted or partially divided into two, three, four, or more portions. It more commonly resembles a small ribbon of nuclear substance twisted three times or more; sometimes these divisions are seen to be held together only by fine nuclear threads; sometimes the portions seem to be completely separated. The nuclear substance has a 'clotted' aspect, and nucleoli cannot be detected. Distinct from the nucleus it is very common to observe a small basophil granule-like body; this is the centrosome of the cell, and must not be confused with a foreign-body cell-inclusion.

Some observers claim a diagnostic value for the classification of these cells according to the number of nuclear divisions, which are thought to express the age of these cells. Excepting the broad distinction of myelocytes, metamyelocytes, and mature

polymorphonuclear leucocytes this principle is not universally accepted. For practical purposes such classifications are too arbitrary and personal and too unreliable to be of much importance.

These cells are active phagocytes of coccal bacteria, and under certain conditions also of bacillary forms. They are referred to as *microphages*.

In the circulating blood these cells number 55 to 65 per cent of all the white cells; the absolute numbers vary from about 4000 to 5000 per c.mm.

Eosinophil cells (B) are generally rather larger than the preceding. The protoplasm is usually tightly packed with coarse, deep-pink, oxyphil granules; it is therefore not uncommon to find that some of the cells have ruptured in the film preparation, the granules being scattered. When the protoplasm contains fewer granules, it will be seen to have taken a basophil stain.

The granules are readily distinguished from those of the polymorphonuclear leucocyte, being very discrete and several times their size, and as seen in the intact cell they suggest the appearance of spores.

The nucleus commonly appears in two parts, situated at or toward the periphery, on either side of the cell. Occasionally the nucleus has three divisions; these nuclear portions are round or oval in shape, and have a 'clotted' appearance like the nuclear substance of the polymorphonuclear leucocyte. Nucleoli cannot be detected. The centrosome of the cell is hidden by the granules.

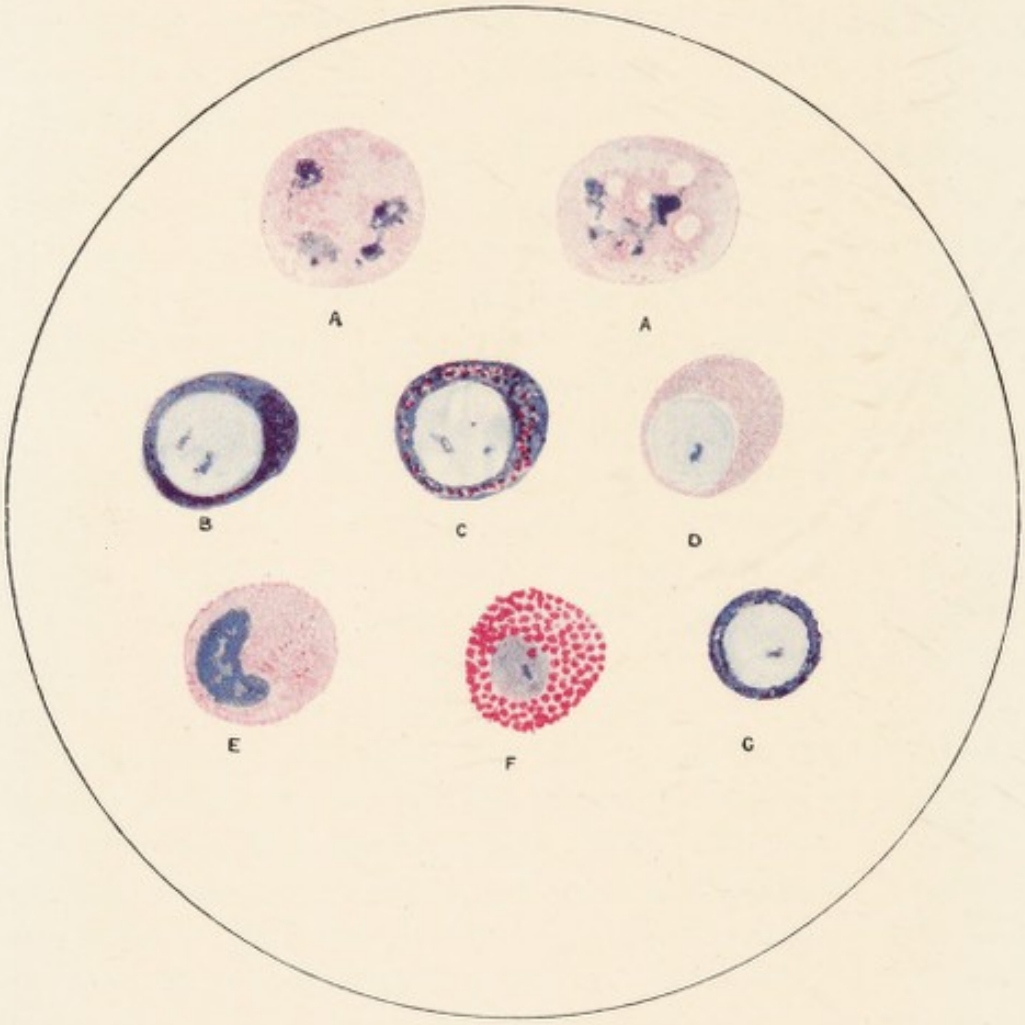
These cells are phagocytes of coccal bacteria, but their functional significance is as yet not fully understood.

In the circulating blood of healthy man the number of these cells is 3 to 6 per cent of all the white cells; the absolute numbers vary from about 200 to 400 per c.mm.

Mast cells (C) are about the same size as polymorphonuclear leucocytes. The nucleus is stained

PLATE IV

ABNORMAL WHITE CELLS



A, Degenerate (œdematous) polymorphonuclear leucocytes. B, Myeloblast. C, Promyelocyte. D, Granular myelocyte. E, Proleucocyte or metamyelocyte. F, Eosinophil myelocyte. G, Lymphomyelocyte.

faintly basophil, is often indistinct, and is usually divided or polymorphous. The cytoplasm consists of homogeneous unstained paraplasm and spongioplasm, in which appear variously scattered granules. These granules are situated chiefly at the periphery of the cell and away from the nucleus ; they are irregular in size and shape, some being quite powdery, others very coarse and often rod-shaped. They are commonly not very numerous, and show a violet or metachromatic staining. This staining reaction has been regarded as an indication of the presence of mucin. It has been suggested that these cells are derived from large mononuclear endothelial cells, the granules representing a mucoid degeneration of the spongioplastic network.

It is clear, however, that these cells do not belong strictly to the leucoid or granular leucocyte group. They are always present in healthy circulating blood.

Often their number is very small, less than 0·1 per cent of all white cells, though a percentage of 1·5 is quite common.

Abnormal White Cells (*Plate IV*).—These are of two kinds : (1) Degenerated cells ; (2) Immature cells.

1. *Degenerate forms* of all the white-cell varieties are met with. Lymphocytes show vacuoles in their protoplasm, and badly-staining nuclei ; similar degenerations are even more common in large mononuclear cells. Polymorphonuclear leucocytes appear swollen (œdematous) to twice or three times their normal size (*Plate IV*, A) ; the nucleus or some one or more of the nuclear divisions may stain badly, and vacuoles may be present in the protoplasm. Similar changes may occur in eosinophil cells.

2. *Immature white cells* are derived from the bone-marrow, and are known as *myelocytes*. The chief of these are the myeloblast, promyelocyte, granular myelocyte, and proleucocyte (metamyelocyte).

The *myeloblast* (B) is a large cell, 10 to 20 μ in diameter. It consists of a large, faintly-stained nucleus, surrounded by a deeply-stained homogeneous margin of very variable width, measuring an eighth to a sixth or more of the entire cell diameter. The nucleus shows one or more nucleoli.

The *promyelocyte* (C) resembles the preceding, from which it is derived. In the peripheral margin there are faintly-oxyphil-stained spaces, which are seen to contain definite granules, the oxyphil staining of which is sometimes masked by the strongly basophil spongioplasm in which they are held.

The *granular myelocyte* (D) is a further development of the preceding. Here the basophil margin is replaced by fine neutrophil-oxyphil granules. The nucleus remains unchanged, though in some cells it may be seen to be dividing by amitosis.

The *eosinophil myelocyte* (F) is a similar cell, containing coarse oxyphil granules.

The *proleucocyte* or *metamyelocyte* (E) resembles the granular myelocyte, but has a more deeply stained nucleus, which no longer has a homogeneous appearance, and in which nucleoli cannot be detected. Often the centre is more faintly stained or unstained, giving the appearance of a ring nucleus, which may be folded on itself, so as to present a horseshoe shape.

The lymphomyelocyte, or lymphoblast, is indistinguishable from the myeloblast described above. It occurs in the lymphoid tissue of the bone-marrow, but is especially found in lymph nodes, spleen, thymus, etc.

The *prolymphocyte* is derived from the lymphomyelocyte by a modification of the nucleus, which is no longer homogeneous and stains deeply basophil. This cell gives rise by division to the lymphocyte.

Immature white cells are met with especially in the blood of leukæmia, and generally indicate some exaggerated activity of the bone-marrow.

Peroxidase Reaction.—To differentiate the cells of the myeloid series (cells originating in the bone-marrow) from those of the lymphoid tissue, the so-called 'peroxidase' staining method has been devised. This depends on the oxidation of benzidine by hydrogen peroxide with an oxidizing ferment present in myeloid but absent in lymphoid cells. The result is shown by a deposition of a blue-green pigment in the granules of the myeloid cells. Of several methods employed for this purpose, the copper peroxide method of Sato and Sekiya is to be preferred.*

Reagents :—

Solution A : Copper sulphate solution 0·5 per cent.

Solution B : Rub 0·2 grm. of benzidine with a few drops of water in a mortar ; add 200 c.c. of water at room temperature and filter ; to filtrate add 4 drops of hydrogen peroxide (3 per cent).

Solution C : A counterstain—1 per cent aqueous safranin.

Use.—To fresh dry blood-smear apply solution A ; pour off most of it and apply solution B for two minutes. Wash thoroughly with water. The peroxidase granules of leucocytes are stained deep bluish-green which does not fade.

Or pour off peroxidase stain and without rinsing add solution C at once and let stand for two minutes before washing. Cytoplasm of myeloid leucocytes stains blue, lymphoid elements show no trace of blue or green but appear red because of their red-staining nuclei. Myeloid leucocytes, eosinophil and basophil granules are stained most intensely blue and appear large ; monocytes are mostly faintly stained and their granules appear small, though distinctly blue.

Red cells and platelets are always unstained.

---

* *Tohoku Jour. of Exper. Med.*, 1926, vii, 111.

Chapter III

THE NORMAL BLOOD PICTURE

This is an ideal standard picture derived from values observed in 100 healthy men and 100 healthy women.

1.—THE NORMAL BLOOD PICTURE.

Red Cells per c.mm.	4,000,000 to 6,400,000
Hæmoglobin per cent	85 to 117
Colour Index	0·84 to 1·11
White Cells per c.mm.	6000 to 9000

Differential Count of White Cells.

Lymphocytes per cent	20 to 30
Large mononuclears ,, ...	6 to 8
Polymorphonuclears ,, ...	55 to 65
Eosinophils ,, ...	3 to 6
Mast cells ,, ...	0·1 to 1·5
Lymphocytes per c.mm.	1500 to 2700
Large mononuclears ,, ...	450 to 720
Polymorphonuclears ,, ...	4000 to 6000
Eosinophils ,, ...	200 to 500
Mast cells ,, ...	7 to 135
Nucleated red cells	not present
Abnormal red cells or white cells	,,

The observed average red-cell count for men is 5,400,000 per c.mm. The range or limits of health calculated from the standard deviation of the distribution of these observations is from 4,510,000 to to 6,350,000. For women the average count is 5,000,000 and the calculated limits 3,940,000 to 6,080,000; so that the limits for all healthy persons are roughly 4,000,000 to 6,400,000 per c.mm. Counts outside these limits should be regarded as not healthy.

The average hæmoglobin percentage is 105·4 per cent for men, the calculated limits being 95·6 to 117·2 per cent. For women the average is 98·2 per cent and the limits are 85 to 111·5 per cent.

For healthy persons the colour index ranges from 0·84 to 1·11.

In new-born infants, and children under twelve months, the number of red cells is often very high—6,000,000 per c.mm.

The number of white cells is very variable, 6000 to 9000 or higher being quite healthy limits, depending on the individual and also on the time of day.

The so-called leucocytosis of digestion, especially after a meat meal, may show in healthy persons an increase of 30 to 40 per cent, up to 10,000 or more white cells per c.mm. This usually commences within the first hour, and reaches a maximum about four hours after the meal. One observer records an increase of 95 per cent four hours after a meal following on a twenty-four hours' fast. This phenomenon is not perfectly understood. It is ascribed to the effects produced by the absorption of food on the mononuclear cells in the adenoid tissue throughout the gastro-intestinal tract, and to an increased outpouring of lymph from the thoracic duct during digestion. Most observers find that this is a 'mixed' leucocytosis, the relative proportions of the lymphoid and leucoid cells not being greatly changed—in fact, the leucoid cells are more often relatively increased; therefore the marrow must furnish a considerable number of polymorphonuclear leucocytes, and the chemiotactic properties of the absorbed albumin derivatives must be regarded as a possible cause of the increase in number of the leucoid cells in the circulation during digestion.

Digestion leucocytosis is not constantly met with. It has received considerable attention in connection with the diagnosis of cancer of the stomach, and was

noted by some observers to be absent in these cases. More recent reports show that it is often present, and it is now generally considered to be quite untrustworthy in the diagnosis of malignant disease of the stomach.

Leucocytosis has also been noted after violent exercise or intense mental exertion.

The relative proportions of the white-cell varieties given in the standard picture show the usual ranges of these cell values in healthy adults; but it should be noted that in children, even up to puberty, the relative percentage number of lymphocytes is usually much higher than 30 per cent, more commonly about 40 per cent. In quite young children, six months to two years old, the lymphoid cells may number over 50 per cent, the picture approximating to that of the lower vertebrates. In healthy women the lymphoid character is often pronounced, the lymphocytes numbering over 35 per cent. On the other hand, in the healthy, meat-eating trained athlete, the percentage of polymorpho-nuclear leucocytes is usually high, 68 to 72 per cent. These figures may perhaps explain the high percentage values given for these cells in normal blood by earlier observers.

During menstruation the red cells and hæmoglobin percentage are usually diminished, and the white cells are increased in number to a slight degree. Many observers have recorded a leucoid leucocytosis in the late months of pregnancy. More commonly this leuco-cytosis is 'mixed', the relative proportion of the various white cells remaining unchanged. A few days after parturition this leucocytosis disappears, unless compli-cations ensue, when it persists and has a definite leucoid character.

The normal blood picture is of a *leucoid* type; that is to say, the leucoid cells are preponderant. In describing blood pictures the terms *lymphoid type* and *leucoid type* are applied respectively to those pictures

in which the lymphoid and leucoid cells are relatively more numerous than in the normal picture. The values are expressed by the signs +, —, and 0 (increase, diminution, and no change) relative to corresponding figures of the normal picture, slight increases or decreases being expressed by + and —, greater or exaggerated changes being written as + + or + + + and — — or — — —.

For example, a white-cell picture which shows :—

				Normal
Lymphocytes	per cent	35	+	(20–30)
Large mononuclears	,,	15	+ +	(6–8)
Polymorphonuclears	,,	45	—	(55–65)
Eosinophils	,,	4	0	(3–6)
Mast cells	,,	1	0	(0·1–1)

is a *lymphoid* picture.

A white-cell picture which shows :—

Lymphocytes	per cent	15	—	(20–30)
Large mononuclears	,,	3	—	(6–8)
Polymorphonuclears	,,	77	+ +	(55–65)
Eosinophils	,,	4	0	(3–6)
Mast cells	,,	1	0	(0·1–1)

is a *leucoid* picture.

INCOMPLETE PICTURES

The examples just given are *incomplete pictures*, obtained only from the examination of film preparations, but they are often serviceable in cases where a complete blood examination has not been made and a rough and rapid estimation is required.

Provided the preparation has been evenly made, further examination of the film may also enable one to fill in some of the other gaps of the complete picture, e.g.—

1. If the white cells are manifestly neither too numerous nor too few, it is sufficient to write 0 or normal ; if they are more numerous (+), there is leucocytosis ; if fewer (—), a leucopenia. With practice, it is quite

possible to estimate the actual numbers of the white cells with approximate accuracy.

2. The presence or absence of abnormal red cells, anæmic or polychromasic cells, cells showing any punctate basophilia, nucleated red cells, etc., indicating or not the existence of anæmia, may be noted.

3. The presence or absence of abnormal white cells will be observed.

PART II

BLOOD PICTURES IN THE DIAGNOSIS OF DISEASE

Chapter IV

INTRODUCTORY

Speaking broadly, a leucoid type of blood is associated with a *coccal* infection, a lymphoid type of blood with a *bacillary* infection, and a lymphoid plus large mononuclear type with a *protozoal* infection. When a mixed infection is present, doubtful and misleading pictures occur, one type masking the other. In one and the same case the blood picture may change completely during the course of the illness, so that a diagnosis from the blood picture must always be guided by the clinical evidence, by the seat of the disease, by its period and history, and by any complications that have arisen.

The so-called blood diseases proper, various forms of anæmia and leukæmia, malignant disease, and other morbid conditions of unknown etiology and not coming into the category of either coccal or bacillary infection, do not necessarily show any definite type of white-cell picture, and attention has to be directed to the red-cell and hæmoglobin aspects, to the presence of abnormal red and white cell forms, and to the general character of the complete blood picture.

An opinion of a blood specimen should never be formed from only one or two characteristics, but, as far as possible, from a consideration of all the aspects of the complete blood picture.

Although a single blood examination may be of great value, and frequently may even suffice for diagnostic purposes, it cannot be too strongly urged that a true and satisfactory diagnosis and prognosis of a disease can only be arrived at by repeated complete blood examinations.

It will be convenient for our purpose to consider diseases as bacterial infections—coccal and bacillary,—protozoal infections, blood diseases, and malignant new growths.

Chapter V

BACTERIAL INFECTIONS

COCCAL INFECTIONS

Without entering into the bacteriological aspect of the question, it may be stated that, in general, the majority of acute inflammatory conditions are due to infection by some variety of coccus. When the inflammation is very severe or prolonged, it proceeds to suppuration, ulceration, or abscess formation.

According to the situation of the inflammation, the condition is referred to as pneumonia, pleurisy, empyema, appendicitis, meningitis, endocarditis, tonsillitis, dermatitis, infected wounds of various parts, conjunctivitis, urethritis, cystitis, etc. In all these morbid states the blood picture has a similar type, varying only in degree with the seat of the infection, its limited or more extensive area, its chronicity, and its severity. For example, the inflammation of a single acne pustule would not be shown in the blood picture, though the picture of severe furunculosis would be typical. Conjunctivitis or urethritis may not show any deviation from the normal picture.

As mentioned above, however, the effect of a second infection has more influence in changing or masking a blood picture than anything else. This is well shown in pneumonia and pleurisy of bacillary origin (tubercle), and in appendicitis of *B. coli* or typhoidal origin.

Probably the most extreme type of leucoid blood picture is met with in cases of acute lobar pneumonia (*No.* 2, *p.* 36). This picture exhibits an extreme leucoid leucocytosis, often showing myelocytes, and later associated with anæmia.

A similar picture is met with in cases of empyema, though it is generally less marked, and free from abnormal red cells and white cells.

2.—COCCAL INFECTION. (Leucoid Type.)
(*ACUTE LOBAR PNEUMONIA.*)

		Example
Red Cells per c.mm.	0 (later −)	4,800,000
Hæmoglobin per cent	0 (later ⌐)	88
Colour Index	0 (later −)	0·91
White Cells per c.mm.	+++	25,000
Differential Count of White Cells.		
Lymphocytes per cent ..	−−	10
Large mononuclears ,, ..	−	3
Polymorphonuclears ,, ..	++	84
Eosinophils ,, ..	0 to +	2
Mast cells ,, ..	1	0
Lymphocytes per c.mm. ..	0 to +	2500
Large mononuclears ,, ..	0 to +	750
Polymorphonuclears ,, ..	++++	21,000
Eosinophils ,, ..	+	500
Mast cells ,, ..	0 to +	250
Nucleated red cells		
Normoblasts per 100 white cells ..	0 (later ?+)	2
Megaloblasts ,, ,, ..	0	0
Metrocytes ,, ,, ..	0	0
Immature white cells		
Myeloblasts per 100 white cells ..	0	0
Promyelocytes ,, ,, ..	0	0
Myelocytes ,, ,, ..	0 (later ?+)	2
Proleucocytes ,, ,, ..	0 (later ?++)	8
Abnormal red cells		
Anisocytosis	0 (later+)	absent
Anæmic cells	0 (later+)	,,
Poikilocytes	0 (later+)	,,
Polychromasia	0 (later ?+)	,,
Punctate basophilia	0 (later ?+)	,,

No. 3, *p.* 37, is a picture of leucoid type from a case of abscess of the liver.

Incomplete pictures are often employed in the examination of the blood for acute appendicitis. Two

cases are illustrated in *Nos.* 4 and 5, *pp.* 37, 38, and will serve as examples.

Generally speaking, when there is a leucocytosis of over 10,000 per c.mm., and the polymorphonuclear

3.—COCCAL INFECTION.

(*ABSCESS OF THE LIVER.*)

Red Cells per c.mm.	.. ..	4,370,000	(−0)
Hæmoglobin per cent ..	.. ..	80	(−)
Colour Index	.. ..	0·92	(0)
White Cells per c.mm.	.. ..	17,500	(+++)

Differential Count of White Cells.

Lymphocytes	per cent	.. 10·4	(−−−)
Large mononuclears	,,	.. 3·5	(−)
Polymorphonuclears	,,	.. 86·0	(+++)
Eosinophils	,,	.. 0·0	(−)
Mast cells	,,	.. 0·0	(−)
Lymphocytes	per c.mm.	.. 1820	(0)
Large mononuclears	,,	.. 612	(0)
Polymorphonuclears	,,	.. 15,020	(+++)
Eosinophils	,,	.. 0	(−)
Mast cells	,,	.. 0	(−)
Abnormal red or white cells		.. not present	

4.—COCCAL INFECTION. (Estimated Leucocytosis, from Films.)

(*ACUTE APPENDICITIS.*)

White Cells per c.mm.	.. ..	++	? over 15,000

Differential Count of White Cells.

Lymphocytes	per cent	.. −−−	.. 5·0
Large mononuclears	,,	.. −	.. 3·5
Polymorphonuclears	,,	.. ++++	.. 90·5
Eosinophils	,,	.. −	.. 1·0
Mast cells	,,	.. ..	.. 0·0

Operation showed an acute gangrenous appendix and pus formation.

leucocytes number 75 per cent, and, excepting the corresponding relative decrease in the lymphoid cells, there are no other deviations from the normal blood

picture, a diagnosis of acute coccal infection can be made. When the polymorphonuclear cells number 80 to 90 per cent, it is almost certain that suppuration is present.

As mentioned above, blood pictures of similar coccal-infection leucoid type are met with in malignant endocarditis, meningitis, tonsillitis, etc. The blood picture of epidemic cerebrospinal meningitis is characterized especially by the extraordinary diminution of both the relative and absolute numbers of lymphocytes. In many cases less than 1 per cent of these cells was

5.—COCCAL INFECTION. (Estimated Leucocytosis, from Films.)

(*ACUTE APPENDICITIS.*)

White Cells per c.mm.	..	++	? over 15,000

Differential Count of White Cells.

Lymphocytes	per cent	..	−−−	..	11·6
Large mononuclears	,,	..	−−	..	2·6
Polymorphonuclears	,,	..	++++	..	85·6
Eosinophils	,,	..	−	..	0·0
Mast cells	,,	..	..	..	0·0

Operation showed acute appendicitis with suppuration.

counted, the absolute numbers per c.mm. being only 100 to 200. This picture forms a strong contrast with that of tuberculous meningitis, in which condition the lymphocytes are markedly increased. In cerebrospinal meningitis the large mononuclear cells have a normal or even slightly raised relative number, and, absolutely, are often enormously increased in number per c.mm.

Skin diseases are often due to mixed infection, but the coccal element is dominant. Leucocytosis is usually only slight; relative counts of lymphoid and leucoid cells may be masked by the presence of eosinophilia; often the blood picture may present only very slight variations from the normal.

6.—SKIN AFFECTION.

(URTICARIA INDURATA.)

Red Cells per c.mm.	4,970,000	(0)
Hæmoglobin per cent	98	(0)
Colour Index	1	(0)
White Cells per c.mm.	10,800	(+)

Differential Count of White Cells.

Lymphocytes per cent ..	16·9	(−)
Large mononuclears ,, ..	5·2	(0)
Polymorphonuclears ,, ..	61·7	(0)
Eosinophils ,, ..	15·8	(++)
Mast cells ,, ..	0·4	(0)
Lymphocytes per c.mm. ..	1825	(0)
Large mononuclears ,, ..	561	(0)
Polymorphonuclears ,, ..	6663	(+)
Eosinophils ,, ..	1706	(++)
Mast cells ,, ..	43	(0)

Abnormal red or white cells .. not present

7.—SKIN AFFECTION ACCOMPANYING BACILLARY INFECTION.

(ENTERIC FEVER, MASKED BY FURUNCULOSIS.)

White Cells per c.mm.	20,000	(+++)

Differential Count of White Cells.

Lymphocytes per cent ..	19·0	(−)
Large mononuclears ,, ..	2·6	(−)
Polymorphonuclears ,, ..	73·0	(+)
Eosinophils ,, ..	5·3	(0)
Mast cells ,, ..	0·0	
Lymphocytes per c.mm. ..	3800	(++)
Large mononuclears ,, ..	520	(0)
Polymorphonuclears ,, ..	14,600	(+++)
Eosinophils ,, ..	1060	(+)
Mast cells ,, ..	0	(+)

Abnormal red cells
- Polychromasia .. .. .. present
- Punctate basophilia .. .. .. ,,

A case of long-standing urticaria indurata gave picture *No.* 6, *p.* 39. This shows a mild leucoid leucocytosis, masked by a high degree of eosinophilia.

Eosinophilia.—Increase in relative and absolute numbers of eosinophil cells is sometimes met with in skin affections, as in the example quoted (*p.* 39). It is also reported as occurring in some cases of asthma and in carcinoma of the lung, also in Hodgkin's disease; feeding raw liver is followed by varying degrees of eosinophilia.

The condition is especially characteristic in patients suffering from intestinal worms, and is perhaps most developed and constant in cases of ankylostomiasis, due to the presence of *Ankylostoma.* The eosinophil cells in these cases often reach 30 per cent of all white cells, and cases showing 62 to 72 per cent of these cells have been recorded. This infection may or may not be associated with leucocytosis. The large mononuclears are usually slightly increased in number. Anæmia of a chlorotic type is generally present, and often to an extreme degree.

In some cases a skin infection, by its leucoid type of blood, may mask the lymphoid picture of bacillary infection. Picture *No.* 7, *p.* 39, was made from the blood of a patient with enteric fever; the *B. paratyphosus B* was isolated from the stools and from the urine. For some time previous to this he had suffered from multiple boils. Unfortunately only an incomplete picture was obtained. As polychromasia and punctate basophilia were present, there was probably some anæmia.

BACILLARY INFECTIONS

These include infections by the tubercle bacillus and its allies, the coli-typhoid group of organisms, diphtheria, etc.

The inflammation set up by these organisms is,

generally speaking, of a less acute nature than that caused by coccal organisms; it is often of a catarrhal character, and associated with fibroblast scar-tissue formation. Suppuration occurs only in the later stages of the inflammation, and is then due either to the introduction of some secondary coccal infection or to slow tissue necrosis. It is rather a foreign-body suppuration than a rapid toxic destruction such as follows a coccal infection.

The blood picture in all these infections is of a lymphoid type, which, however, very often becomes masked by the leucoid influence of a secondary coccal infection. Leucocytosis is not usually of high degree, and is often absent; a lowered number of white cells—leucopenia—is not uncommon in uncomplicated cases.

In quite early stages the red-cell count and the hæmoglobin percentage are found to be unaltered, but before long a chlorotic anæmia supervenes.

The picture of an early tuberculosis of the lung is shown in *No.* 8, *p.* 42.

In cases of acute phthisis resembling acute lobar pneumonia, the absence of leucocytosis, and the lymphoid character of the blood picture, are diagnostic.

Example *No.* 8 will, at a later stage, show the introduction of a coccal (often pneumococcal) infection. The white cells show a + + leucocytosis; the lymphocytes are absolutely +, but not relatively changed from normal; the large mononuclears still show both relative and absolute increases; the polymorphs show relatively no variation from, or slight increase on, the normal, and an absolute increase, depending on the degree of leucocytosis (*No.* 9, *p.* 42). This picture shows the gradual masking of a lymphoid by a leucoid type owing to a coccal infection.

Infection by the coli-typhoid group of organisms also presents a marked lymphoid blood picture, especially in early uncomplicated stages. There is often no change

8.—BACILLARY INFECTION.

(EARLY TUBERCULOSIS.)

Red Cells per c.mm.	0 to −
Hæmoglobin per cent	0 to −
Colour Index	0 to −
White Cells per c.mm.	− to 0

Differential Count of White Cells.

Lymphocytes	per cent	+ to ++
Large mononuclears	,, ...	+ to ++
Polymorphonuclears	,, ...	0 to −−
Eosinophils	,, ...	0 to −
Mast cells	,, ...	0
Lymphocytes	per c.mm.	0 to +
Large mononuclears	,, ...	0 to +
Polymorphonuclears	,, ...	− to −−
Eosinophils	,, ...	− to 0
Mast cells	,, ...	0
Abnormal red or white cells	.. .. ..	not present

9.—BACILLARY INFECTION.

(TUBERCULOSIS, WITH SECONDARY COCCAL INFECTION.)

		Example
Red Cells per c.mm.	−	3,500,000
Hæmoglobin per cent	−	62
Colour Index	−	0·88
White Cells per c.mm.	++	16,000

Differential Count of White Cells.

Lymphocytes	per cent ..	0 to +	24·2
Large mononuclears	,, ..	0 to +	4·4
Polymorphonuclears	,, ..	0 to +	69·6
Eosinophils	,, ..	0	1·6
Mast cells	,, ..	0	0·2
Lymphocytes	per c.mm. ..	++ to +	3872
Large mononuclears	,, ..	+ to 0	704
Polymorphonuclears	,, ..	0 to ++	11,130
Eosinophils	,, ..	0 to +	256
Mast cells	,, ..	0	32

in the red-cell element, though chlorotic anæmia is common later. Leucocytosis is not usual, and generally leucopenia is found in these cases. The same type of blood is met with in intestinal stasis, and in chronic catarrhal appendicitis and colitis; it closely resembles the picture of early tubercle, and the diagnosis must be guided by the clinical symptoms. The picture may be written as shown in *No.* 10, *p.* 43.

This example of a case of intestinal stasis gives a picture very similar to that of chronic appendicitis.

10.—BACILLARY INFECTION.
(*INTESTINAL STASIS.*)

		Example
Red Cells per c.mm.	0	5,160,000
Hæmoglobin per cent	0	100
Colour Index	0	0·98
White Cells per c.mm.	0 to −	5300
Differential Count of White Cells.		
Lymphocytes per cent	+ to ++	35·3
Large mononuclears ,,	+ to ++	9·0
Polymorphonuclears ,,	− to −−	55·0
Eosinophils ,,	0 to −	0·6
Mast cells ,,	0	0·0
Lymphocytes per c.mm.	+ to 0	1870
Large mononuclears ,,	+ to 0	477
Polymorphonuclears ,,	0 to −	2915
Eosinophils ,,	0 to −	31
Mast cells ,,	0	0

When an acute attack supervenes in these cases, it is often the result of some coccal infection. Picture *No.* 11, *p.* 44, is that of a man who, after several slight attacks and dyspeptic symptoms, had a severe acute attack, and the appendix was removed by operation. The example was obtained from a film. From this picture, owing to the high percentage of large mononuclear cells, a diagnosis of chronic inflammation was made, but the high polymorphonuclear count suggested acute coccal infection. On examination after

removal, the appendix was large and doubled on itself by old adhesions; there were three recent patches of ulceration. An organism which resembled the pneumococcus, and also a Gram-negative bacillus, were found in smear preparations, but cultivations were not made.

11.—MIXED INFECTION.

(ACUTE SUPERVENING UPON CHRONIC APPENDICITIS.)

White Cells per c.mm.	probably over 10,000

Differential Count of White Cells.

Lymphocytes	per cent	9·3
Large mononuclears	,, ...	12·0
Polymorphonuclears	,, ...	77·0
Eosinophils	,, ...	1·3
Mast cells	,, ...	0·3

12.—BACILLARY INFECTION.

(ENTERIC FEVER.)

Red Cells per c.mm.	5,206,000		(0)
Hæmoglobin per cent	102		(0)
Colour Index	0·95		(0)
White Cells per c.mm.	2000		(– – –)

Differential Count of White Cells.

Lymphocytes	per cent ..	26·0	(0)
Large mononuclears	,, ..	6·4	(0)
Polymorphonuclears	,, ..	67·6	(0)
Eosinophils	,, ..	0·0	(–)
Mast cells	,, ..	0·0	(0)
Lymphocytes	per c.mm. ..	520	(– – –)
Large mononuclears	,, ..	128	(– – –)
Polymorphonuclears	,, ..	1352	(– – –)
Eosinophils	,, ..	0	(–)
Mast cells	,, ..	0	(–)

It is instructive to compare the picture of intestinal stasis and chronic appendicitis on *p.* 43 with the pictures of acute appendicitis on *pp.* 37, 38; the value of blood pictures in the diagnosis of these cases is well shown.

No. 12, *p.* 44, is an example of a picture from a case of enteric fever; *B. paratyphosus B* was isolated from blood and stools. Here the chief characteristic is the leucopenia; the usual lymphoid type is not present, and the relative proportions are normal.

The blood picture in *B. paratyphosus B* infection may sometimes be distinguished from that of *B. typhosus* by a normal or even raised white-cell count which may have a leucoid character.

The blood picture of coli-typhoid-group infections may show no change in the red cells, and only slight diminution of the hæmoglobin percentage; but when diarrhœa is severe or hæmorrhage occurs there may be great variation in the red-cell picture. After severe and prolonged diarrhœa, the number of red cells and the hæmoglobin percentage may be increased; after hæmorrhage they are diminished, and abnormal red cells may be present, depending on the degree of anæmia produced.

The complications of bronchitis, pneumonia, and hæmorrhage, in early and late stages of the infection, influence the leucopenia, which is often not present, and may be replaced even by a leucocytosis. The lymphoid type then assumes a coccal leucoid character, as was described in the case of tubercle infection. Cases complicated with abscess formation will show a polymorphonuclear count ascending day by day, even to 85 per cent or higher, but the relative diminution of lymphocytes is more marked than the relative diminution in large mononuclear cells. A pure coccal suppuration generally shows a marked relative diminution of these cells (e.g., *No.* 7, *p.* 39, and *No.* 11, *p.* 44).

More commonly, however, in enteric-group infections the lymphoid type of blood picture is continued into convalescence, leucopenia being maintained into the second and third weeks of the disease.

In the rare cases of abscess formation of pure *B. coli* etc. (bacillary) origin, the blood may retain its lymphoid type, and leucocytosis may be absent. A case of liver abscess in the course of enteric fever (*B. typhosus*) showed only a slight leucocytosis (11,000 white cells per c.mm.), with 50 per cent of lymphocytes.

Diphtheria is a toxæmia from a bacillary infection, and the blood picture has a lymphoid character, usually associated with some red-cell change. When, as often

13.—BACILLARY INFECTION.

(*DIPHTHERIA.*)

Red Cells per c.mm.	..	+ to ++	(later 0 to −)
Hæmoglobin per cent	..	0 to +	(later 0 to −)
Colour Index	..	−	(later −)
White Cells per c.mm.	..	+ to +++	(later 0 to +)

Differential Count of White Cells.

Lymphocytes	per cent	..	++	(later +)
Large mononuclears	,,	..	+	(later +)
Polymorphonuclears	,,	..	− to 0	(later 0 to +)
Eosinophils	,,	..	−−	(later − to 0)
Mast cells	,,	..	0	0
Lymphocytes	per c.mm.	..	+++	(later ++)
Large mononuclears	,,	..	++	(later +)
Polymorphonuclears	,,	..	0 to +	(later + to 0)
Eosinophils	,,	..	−−	(later −)
Mast cells	,,	..	0	0
Abnormal red cells		..	..	polychromasia later

happens, the throat affection is associated with some coccal infection, the lymphoid type may be masked. A tonsillitis or pharyngitis of purely coccal origin has the usual leucoid blood picture of those infections. It is, however, often possible to make a rapid diagnosis by means of a blood picture in these cases.

In the early stages of diphtheria there may be polycythæmia; red cells numbering up to 7,500,000 per c.mm., the hæmoglobin percentage not being proportionately increased, have been recorded. Later,

the red cells are diminished, a chlorotic anæmia may supervene, and polychromasia and other red-cell abnormalities may be present.

Leucocytosis is usually high. The blood picture may be expressed as in *No.* 13, *p.* 46.

In cases of influenza there is a lymphoid type of blood. Leucocytosis is rarely noticed, leucopenia being more common. Even an influenza-bronchopneumonia may not show any leucocytosis. When complicated with a pneumococcal infection, and especially with a condition of lobar pneumonia, the usual high leucocytosis of that affection is present.

Chapter VI

PROTOZOAL INFECTIONS

In hæmatozoal and spirochætal infections, such as malaria, syphilis, etc., the blood picture is usually definite. The red cells and hæmoglobin may or may not be altered, but generally there is some anæmia, oligocythæmia, and lowered hæmoglobin percentage, together with signs of destruction and regeneration (high reticulocyte count) of the red cells, and slightly lowered colour index.

The presence of the parasite in the circulating blood is sufficient for diagnosis. When, however, parasites cannot be detected in the blood, the white-cell picture is often of great help. It has a lymphoid type, with or without leucocytosis, and shows increased number, often of very high degree, both relatively and absolutely, of the large mononuclears.

In the early stages of syphilis, anæmia is usually absent; in the secondary and tertiary forms, and also in congenital syphilis, anæmia is commonly present. Lymphocytosis—both relative and absolute increase in the number of the lymphocytes—associated with relative and absolute increase of large mononuclear cells, is present from the commencement, and persists usually through the entire course of the disease, though in certain complicating skin affections there may be masking by a secondary coccal infection which encourages some increase in the number of polymorphonuclear leucocytes. In papular eruptions especially there may be some increase in the number of eosinophil cells, which, however, does not seriously mask the general lymphoid type of the blood picture. The large mononuclear

leucocytosis found in syphilis is not usually of the high degree that is met with in the blood of malarial patients.

14.—PROTOZOAL INFECTION.

Red Cells per c.mm.	− to 0
Hæmoglobin per cent	− to 0
Colour Index	− to 0
White Cells per c.mm.	0 to + +

Differential Count of White Cells.

Lymphocytes per cent	+ +
Large mononuclears ,, ...	+ + +
Polymorphonuclears ,, ...	− − −
Eosinophils ,, ...	0 to +
Mast cells ,, ...	0
Lymphocytes per c.mm.	+ +
Large mononuclears ,, ...	+ + +
Polymorphonuclears ,, ...	− − −
Eosinophils ,, ...	0 to +
Mast cells ,, ...	0
Nucleated red cells .. .. ?	present
Abnormal red cells	
Anisocytosis .. .. ?	,,
Polychromasia .. .. ?	,,
Punctate basophilia .. .. ?	,,

Chapter VII

BLOOD DISEASES

CHLOROTIC ANÆMIA

This form of anæmia is met with in the later stages of most infections, in the cachexias of phthisis, syphilis, and malignant disease, in lead poisoning, and after severe hæmorrhage. It may also occur as an independent disease known as *chlorosis*, which formerly was very common but has been met with only rarely in recent years. Chlorosis depends on a diluted state of the blood, the volume of which is increased; the oxygen capacity of the hæmoglobin per unit of volume of the blood is therefore diminished and the number of red cells per c.mm. of this diluted blood is lowered.

Generally, *chlorotic anæmia* is a term used to express a type of anæmia characterized by a diminution in the number of red cells per c.mm., and by a relatively greater diminution of the hæmoglobin percentage, whereby the colour index is lowered. The red cells are *hypochromic*, though irregularly stained, a few deep-stained (*orthochromic*) cells being usually present together with the colourless discs. The sizes of the cells are smaller than in health, and anisocytosis is often considerable. In severe cases and in the later stages of the condition regeneration forms of red cells are commonly seen.

In the recovery from an attack of chlorosis it is not uncommon to find polycythæmia—an increased number of red cells over the normal.

The white cells may show no variation from the normal, though leucocytosis may be present in a slight degree. The blood picture is usually of a lymphoid

type, the lymphocytes and large mononuclear cells being relatively increased in number, but there is rarely any absolute increase in the number of these cells.

In the anæmia which follows hæmorrhage slight leucocytosis is generally found, and this is associated with relative and absolute increase in the number of polymorphonuclear leucocytes.

Microcytic Anæmia (Witts).*—This condition is a 'secondary' or 'chlorotic' anæmia resulting from a deficient production of hæmoglobin. Whereas the red-cell count is only moderately reduced, the hæmoglobin percentage is remarkably lowered, so that the colour index may be as low as 50 per cent of its normal value.

This form of anæmia occurs more usually in women ; it is confined to the reproductive epoch, and persists in varying intensity throughout the child-bearing period ; it is much aggravated by pregnancy, and tends to spontaneous cure after the menopause. It is frequently associated with *hypochlorhydria* or *achlorhydria*. Cases are reported as occurring in men.

The hæmatological features of this disease are anæmia, microcytosis, anisocytosis, and changes in the staining reaction of the red cells. In blood films from untreated cases, stained and fixed with Jenner and superstained with 10 per cent aqueous eosin, most of the red cells appear as unstained discs enclosed by pink rings of varying widths, often barely distinguishable ; many of the cells are oval or biscuit-shaped, the stain being limited to the ends of the cell ; distributed irregularly among these pale (hypochromic) cells there are always a few (1 to 5 per cent) deep-stained (orthochromic) cells, which appear to be normal cells, though on measurement they are found to be too small.

---

* *Jour. Pathol. and Bacteriol.* 1932, xxxv, 759.

The most remarkable feature of this anæmia is the rapidity and degree with which it reacts to large doses of iron ; in the course of a few weeks the microcytosis is removed, and with a return to a normal colour index the orthochromic cells replace the hypochromic cells.

PERNICIOUS ANÆMIA

The blood picture of pernicious anæmia shows a diminution in the number of red cells per c.mm., and in the hæmoglobin percentage, but a raised colour index, the diminution in the number of red cells being relatively greater than the diminution of the hæmoglobin percentage. There is usually an extreme degree of anisocytosis, and megalocytes, microcytes, poikilocytes, schizocytes, and skiacytes are almost invariably present.

A feature constantly found is the increase in the average diameter of the red cells. The megalocytes usually show polychromasic staining, and punctate basophilia is very commonly seen.

Nucleated red cells are frequently present, but not invariably, and may be of all types. The fact that megaloblasts are often more numerous than normoblasts has been regarded by some as of diagnostic importance. Metrocytes (gigantoblasts) are also met with occasionally.

Generally, the red-cell picture has the appearance of active red-cell regeneration, associated with that of red-cell destruction.

The white cells may show no change from the normal, but commonly there is leucopenia, and the picture has a lymphoid type. The nuclei of the polymorphonuclear leucocytes may show extreme lobulation, but this is not a constant sign.

The introduction of liver therapy for pernicious anæmia has profoundly influenced the progress and indeed also the diagnosis and blood picture of this disease, since many anæmia patients have been treated

with liver before the confirmation of diagnosis by a blood examination. The effect of liver treatment is to make the bone-marrow turn out healthy red cells. At the commencement of this treatment the cells

15.—BLOOD DISEASE.
(*PERNICIOUS ANÆMIA.*)

		Example 1	*Example* 2
Red Cells per c.mm.	− − −	900,000	1,440,000
Hæmoglobin per cent	− −	29	38
Colour Index	+	1·6	1·35
White Cells per c.mm.	− − to 0	2600	2800
Differential Count of White Cells.			
Lymphocytes per cent	+ to + +	36·6	68·4
Large mononuclears ,,	0 to + +	5·3	8·4
Polymorphonuclears ,,	− to − −	54·6	24·0
Eosinophils ,,	0 to −	3·0	0·2
Mast cells ,,	0	0·3	0·0
Lymphocytes per c.mm.	− to 0	950	1915
Large mononuclears ,,	− to 0	137	235
Polymorphonuclears ,,	− to − − −	1719	672
Eosinophils ,,	0 to −	78	5·6
Mast cells ,,	0	7·9	0
Nucleated red cells			
Normoblasts in 100 white cells may be present		0	3
Megaloblasts ,, ,, ,, ,,		3	0
Metrocytes ,, ,, ,, ,,		0	0
Abnormal red cells		*Example* 1	*Example* 2
Anisocytosis always present		extreme	extreme
Anæmic cells ,, ,,		numerous	numerous
Skiacytes ,, ,,		,,	,,
Poikilocytes ,, ,,		,,	,,
Schizocytes (?) ,, ,,		,,	,,
Polychromasia ,, ,,		present	present
Punctate basophilia ,, ,,		,,	,,

hurried out are immature and are shown on staining to be reticulocytes. This effect is known as the *reticulocyte reaction*; failure of this reaction following adequate doses of liver is generally regarded as against the diagnosis of pernicious anæmia. By enumerating

the reticulocytes (*see p.* 20) it is possible to estimate the value of the liver treatment. The reaction commences on the third to fifth day after starting 'liver', and varies inversely with the red-cell count, being greatest when the red cells are fewer. The reaction continues for ten to twelve days or more—it may attain a value of 30 to 40 per cent—and after about three weeks of treatment it falls to 1 per cent; during this period the red-cell count has risen probably to over 3,000,000 per c.mm.; the hæmoglobin has also risen, but as a rule not so quickly as the red-cell count, so that at this stage there is a temporary lowering of the colour index.

The blood picture of pernicious anæmia may be expressed as in *No.* 15, *p.* 53. *Example* 1, before the introduction of liver therapy, was a severe case, and the patient died two months later. The red-cell picture is typical. Of the white cells, the large mononuclears, indeed, show no relative increase in number, but although the lymphocytes, owing to the extreme leucopenia, are not absolutely increased, yet relatively they will be found to be increased, and the picture has a lymphoid type.

Many cases are met with, however, which present a less pronounced picture, and are generally of less severe nature. The red-cell count may be about 2,000,000 per c.mm., the hæmoglobin percentage about 60, the colour index being 1·5. The white-cell picture is normal. Nucleated cells are absent, but there is a marked anisocytosis, with poikilocytes, and polychromasic megalocytes. The chief and all-important diagnostic signs are: (1) The raised colour index; (2) The presence of megalocytes (*see Fig.* 6, *p.* 69); (3) The high degree of anisocytosis.

As mentioned above, the blood of these patients is often thin and watery. They bleed very readily, and it is sometimes difficult to check the hæmorrhage,

corresponding with the thrombopenia (diminished number of platelets).

APLASTIC ANÆMIA

The blood picture of aplastic anæmia, which is often erroneously diagnosed as pernicious anæmia, is characterized by extreme diminution of red-cell count and a proportionately lowered hæmoglobin percentage, so that the colour index has a normal value. There is a marked leucopenia of lymphatic type, the myelogenic leucocytes being especially affected ; there is a diminution in the number of platelets.

The red cells show a raised mean diameter, but the variability (anisocytosis) is not usually so high as in pernicious anæmia. Nucleated red cells, polychromasia, and basophilia are absent, and in consequence reticulocyte reaction does not take place with liver treatment.

AGRANULO-LEUCOCYTOSIS

This is an acute aplasia of the leucopoietic elements of the bone-marrow. The erythropoietic element is not at all or only slightly affected, so that during the short course of the disease the red-cell count, hæmoglobin, and colour index may remain normal. Polychromasia and basophilia of the red cells are absent. The platelets may or may not be reduced in number. The condition is often associated with severe angina, and may be fatal in the course of a week or less. The chief feature of the blood picture is diminution or even total absence of the granular leucocytes, with both relative and absolute increase in the number of lymphocytes and large mononuclear cells.

LEUKÆMIA

This is a morbid condition of the blood in which there is a persistent and progressive increase in the number of white cells, which include, besides the

varieties normally present, a variable number, often a preponderance, of immature white cells derived from the bone-marrow.* Leukæmic blood does not always present the same histological picture; but although there are many transitional states, it is convenient to recognize two main varieties, viz., (1) *lymphoid*, (2) *leucoid*, depending on the particular class of marrow cell that predominates.

1. **Lymphoid Leukæmia.**—The histological appearance of the blood depends on the period of the disease, on its severity, and the rate of progress. The clinical terms *acute* and *chronic* have no fixed relation to the type of blood.

In this condition the red cells are diminished in number, as a rule, to about 2,000,000 per c.mm., and commonly include a few normoblasts and other forms from accelerated marrow activity. The hæmoglobin and colour index are both lowered. The white cells number about 100,000 on first examination, and may rise to over 600,000 per c.mm. In quite early cases, which only come by chance under examination, the white-cell count may be much lower than 100,000. It is probable, however, that the onset of the leucocytosis is sudden and considerable.

In the early stages the white cells are composed chiefly of lymphocytes, with a few prolymphocytes and large mononuclear cells, the granular (leucoid) leucocytes being reduced to 5 per cent or lower; mast cells are not usually found in increased numbers in the blood of this variety of leukæmia. In later stages the lymphocytes are relatively fewer, whereas the prolymphocytes are increased in number, and the blood contains large numbers of lymphoblasts. Finally, in

---

* For a detailed description of the phylogeny of white blood-cells the reader is referred to *Guy's Hospital Reports*, lxv, p. 85 (and *see* Appendix, *p.* 72). The descriptions of immature white cells are given on *pp.* 25, 26.

the extreme stage of the affection, lymphocytes are only rarely seen, the microscopic field being occupied with lymphoblasts which are not distinguishable from myeloblasts, though in some cases they may be differentiated by the peroxidase reaction.

2. **Leucoid Leukæmia.**—As in the preceding variety, the number of red cells, the hæmoglobin percentage, and the colour index are lowered, normoblasts being commonly met with, even in the early stages of the disease. The white cells are enormously increased in number per c.mm., and include different varieties of marrow cells according to the period at which the examination is made.

In the early stage the polymorphonuclear leucocytes are predominant. They are of several characteristic forms: (*a*) The normal leucocyte, of which there are relatively few; (*b*) Cells resembling the normal, but much larger, twice or three times the size; (*c*) Degenerated forms with badly stained and swollen nuclei, and often with vacuoles and fewer granules in the cytoplasm. There are usually a number of proleucocytes with horseshoe-shaped nuclei, and a few typical granular myelocytes. The eosinophil cells are also increased in number. The number of lymphocytes is relatively greatly reduced, and so also is that of the large mononuclear cells; the mast cells on the other hand are relatively enormously increased in number.

At a later stage the normal leucocytes are few, the predominant elements being the proleucocytes and myelocytes, and a few promyelocytes; lymphoid cells are rarely met with; mast cells are very numerous. At a yet later stage myeloblasts are present. Finally a condition may be reached in which the microscopic field is almost entirely occupied with myeloblasts, and only occasional granular myelocytes and mast cells are to be seen. This appearance is almost identical with that of the final stage of lymphoid leukæmia, the finding of

a few granular cells and mast cells, and the complete absence of mature lymphoid cells, being the only signs which distinguish the final stage of the leucoid from that of the lymphoid variety.

Leucoid leukæmia is often called splenic leukæmia, splenomedullary leukæmia, or myelogenous leukæmia.

PSEUDOLEUKÆMIA

This is a general term used to include a number of conditions, clinically similar but probably very different pathologically, such as lymphoma, lymphadenoma (Hodgkin's disease), lymphosarcoma, Banti's disease, splenic anæmia, etc., various diseases characterized by inflammation or enlargement of lymph nodes and structures, and usually associated with enlargement of the spleen and liver.

These diseases are not strictly diseases of the blood at all, and have been called pseudoleukæmia from the fact that the lymph nodes and spleen are sometimes enlarged in leukæmia ; but at the same time the blood is not in any sense leukæmic.

Whether any true relationship exists between leukæmia and pseudoleukæmia has not been definitely determined, but from the point of view of the hæmatologist there is no apparent resemblance between these two conditions.

The blood picture of pseudoleukæmia belongs to no particular type. Usually the red-cell picture remains normal, a chlorotic anæmia being present sometimes in late stages. There is often no leucocytosis, and the white-cell picture varies in type, being lymphoid in lymphadenomata, and often leucoid in lymphosarcomata. In typical Hodgkin's disease the large mononuclear cells are frequently increased in both relative and absolute numbers.

The chief value of blood examinations in these cases is the possibility of eliminating other morbid conditions,

such as tuberculosis, syphilis and protozoal infections, suppuration and coccal infections, leukæmia, and malignant growths.

VON JAKSCH'S ANÆMIA

Anæmia infantum of von Jaksch has also been regarded as a pseudoleukæmia or splenic anæmia ; but from a hæmatological standpoint it is more allied to leukæmia or to lymphanæmia. There is usually enlargement of the spleen and liver, and sometimes also of the lymph-glands. It occurs only in quite young children of from six months to four years, and may be regarded as a regression in the blood of the child to an embryonal type.

The blood picture shows a marked, often an extreme, diminution in the number of red cells and in the hæmoglobin percentage, the colour index being either lowered or slightly raised. The chief characteristic is the presence of large numbers of nucleated red cells almost entirely of normoblast type, megaloblasts being found in some cases in small numbers.

There is usually a leucocytosis of about 20,000 per c.mm., but this may be much higher, 100,000 and over. The type of white-cell picture is *lymphoid*, the lymphocytes, more especially the large mononuclear cells, being both relatively and absolutely increased in number. Bearing in mind that this type of blood is generally associated with some protozoal infection, it is interesting to note that many of these cases have been traced to a syphilitic origin.

Occasionally myelocytes have been found in the blood of these cases, but never in such numbers as to suggest a true leukæmic blood picture.

FAMILIAL (ACHOLURIC) JAUNDICE

This is a widespread familial anæmia due to the inheritance of a special abnormal type of red cell.

These cells are microcytic, showing diminished diameter measurement but a normal cell volume, suggesting that the thickness of the cell is increased; and the discs, which do not show the usual biconcavity, are spheroidal. Megalocytosis does not occur, but owing to the extreme degree of anisocytosis and the presence of microcytes the larger cells can sometimes be mistaken for megalocytes.

Apart from these morphological characters, the red cells show a much diminished resistance to hypotonic solutions, which favours their destruction, whereby the spleen becomes enlarged and the activity of the bone-marrow is stimulated to produce fresh red cells; so that films show much polychromasia and basophilia, and 20 to 30 per cent of reticulocytes may be present.

The colour index in these cases is usually normal or may be slightly riased. The white-cell count may be normal, or slightly raised owing to a relative and absolute increase in the number of polymorphonuclear leucocytes; occasional myelocytes and metamyelocytes may be thrown out by the extreme activity of the bone-marrow.

Removal of the spleen lessens the degree of microcytosis, and the diminished resistance to hypotonic solutions may be lessened though not removed: indicating that the primary factors of the disease are the abnormal form and constitution of the red cell, the anæmia, jaundice, and enlargement of the spleen being secondary symptoms.

Chapter VIII

MALIGNANT DISEASE

The blood picture of malignant disease is not of constant type. It varies with the period of the disease, and with its situation, and is modified by the presence or absence of metastasis, and whether or not any secondary infection or complication such as ulceration, hæmorrhage, or interference with the natural processes of the body, has supervened.

The blood from a case of early carcinoma, before any cachexia has developed or any obvious metastasis has appeared, shows no change in the red-cell count or hæmoglobin percentage, but the white cells are usually slightly increased in number. The relative count of lymphocytes may be either unchanged or lowered, but the absolute numbers of these cells may be increased or unchanged. The large mononuclear cells are increased both relatively and absolutely, and the polymorphonuclear leucocytes, though to a less degree, are also increased in relative and absolute numbers. The general type of the picture is a *large mononuclear and polymorphonuclear leucocytosis.*

No. 16, *p.* 62, illustrates the picture of early uncomplicated malignant growth. The example was taken from a case of scirrhous carcinoma of the breast.

In the later stages of the disease, the red cells may be lowered in number, and chlorotic anæmia may supervene (*No.* 17, *p.* 63), but this is by no means constant, and in many cases, even up to the fatal termination, the number of red cells and the colour index are quite inappreciably lowered. The leucocytosis may become more pronounced, but this also is not at all constant,

depending chiefly on the presence and degree of ulceration or secondary coccal infection with which it is connected. The leucocytosis is never at any time very high ; 25,000 is quite exceptional, the average count of white cells being about 12,000 to 15,000 per c.mm. The number of large mononuclear cells is usually raised both relatively and absolutely, but their proportional and absolute numbers may be entirely masked by the increased numbers of polymorphonuclear leucocytes,

16.—EARLY UNCOMPLICATED MALIGNANT DISEASE.
(SCIRRHOUS CARCINOMA OF THE BREAST.)

			Example
Red Cells per c.mm.	.. ..	0	5,050,000
Hæmoglobin per cent	.. ..	0	98
Colour Index	.. ..	0	0·9
White Cells per c.mm.	.. ..	+ to ++	10,000

Differential Count of White Cells.

Lymphocytes	per cent ..	0 to −	11·6
Large mononuclears	,, ..	+ to ++	15·0
Polymorphonuclears	,, ..	+ to ++	71·2
Eosinophils	,, ..	0	1·8
Mast cells	,, ..	0	0·4
Lymphocytes	per c.mm. ..	− to +	1160
Large mononuclears	,, ..	− to ++	1500
Polymorphonuclears	,, ..	+ to ++	7120
Eosinophils	,, ..	0	180
Mast cells	,, ..	0	40

especially if metastases have developed, or if there is much suppuration or general coccal infection.

In cases of gastric carcinoma it has been noted that when the polymorphonuclear leucocytes have progressively increased in number, metastases of the liver are probably present. This sign may possibly be of use as a guide in operating for these cases. *No.* 17 is a good example of this ; many nodules were found in the liver. The figures in the second column are those of

a count taken a month later than the first. Usually, however, before this stage is reached, the clinical diagnosis of probable malignant growth is manifest.

In some cases of gastric cancer, the aspect of the patient and the blood picture present resemblances to

17.—MALIGNANT DISEASE.

(CARCINOMA OF STOMACH.)

	First count	*Second count*	
Red Cells per c.mm. ..	3,400,000	3,206,000	(−)
Hæmoglobin per cent ..	60	40	(−)
Colour Index	0·88	0·62	(−)
White Cells per c.mm. ..	12,000	20,200	(+)
Differential Count of White Cells.			
Lymphocytes per cent ..	19·6	15·6	(− −)
Large mononuclears ,, ..	6·6	7·6	(0)
Polymorphonuclears ,, ..	70·0	76·0	(+)
Eosinophils ,, ..	0·3	1·0	(−)
Mast cells ,, ..	0·0	0·0	(− 0)
Lymphocytes per c.mm. ..	2352	3151	(+)
Large mononuclears ,, ..	782	1535	(++)
Polymorphonuclears ,, ..	8400	15,352	(++)
Eosinophils ,, ..	36	202	(0)
Mast cells ,, ..	0	0	(− 0)

18.—MALIGNANT DISEASE WITH BONE METASTASIS.

Red Cells per c.mm.	3,800,000
Hæmoglobin per cent	50
Colour Index	0·66
White Cells per c.mm.	10,400
Differential Count of White Cells.	
Lymphocytes per cent	15·5
Large mononuclears ,, ...	1·0
Polymorphonuclears ,, ...	81·5
Eosinophils ,, ...	0·0
Mast cells ,, ...	0·5
Nucleated red cells per c.mm.	832
Reticulocytes per cent	6·2
Myelocytes per cent*	1·5

* Of white corpuscles.

19.—DIAGNOSIS OF NON-MALIGNANT FROM MALIGNANT DISEASE.

(GASTRIC ULCER: CLINICALLY RESEMBLING CARCINOMA.)

Red Cells per c.mm.	.. ..	5,140,000	(0)
Hæmoglobin per cent	.. ..	54	(−)
Colour Index ..	.. ..	0·53	(−)
White Cells per c.mm.	.. ..	9100	(+)

Differential Count of White Cells.

Lymphocytes	per cent ..	25·1	(0)
Large mononuclears	,, ..	5·7	(0)
Polymorphonuclears	,, ..	66·2	(+0)
Eosinophils	,, ..	2·4	(−0)
Mast cells	,, ..	0·6	(0)
Lymphocytes	per c.mm. ..	2275	(0)
Large mononuclears	,, ..	455	(−0)
Polymorphonuclears	,, ..	6005	(0)
Eosinophils	,, ..	218	(0)
Mast cells	,, ..	54	(0)
Abnormal red or white cells	..	not present	

20.—DIAGNOSIS OF NON-MALIGNANT FROM MALIGNANT DISEASE.

(INTESTINAL STASIS: CLINICALLY RESEMBLING CARCINOMA OF THE STOMACH.)

Red Cells per c.mm.	.. ..	5,020,000	(0)
Hæmoglobin per cent	.. ..	90	(0)
Colour Index ..	.. ..	0·9	(0)
White Cells per c.mm.	.. ..	8100	(0)

Differential Count of White Cells.

Lymphocytes	per cent ..	36·6	(+)
Large mononuclears	,, ..	6·3	(0)
Polymorphonuclears	,, ..	55·0	(0)
Eosinophils	,, ..	1·6	(0)
Mast cells	,, ..	0·3	(0)
Lymphocytes	per c.mm. ..	2964	(+)
Large mononuclears	,, ..	510	(0)
Polymorphonuclears	,, ..	4455	(−0)
Eosinophils	,, ..	130	(0)
Mast cells	,, ..	24	(0)
Abnormal red or white cells	..	not present	

those of pernicious anæmia. The number of red cells is often extremely lowered, though never to the degree of oligocythæmia met with in fatal cases of pernicious anæmia. Cases with 1,460,000 and 1,168,000 red cells per c.mm. have been recorded, but the hæmoglobin percentage is lowered more in proportion, so that the colour index in these cases is reduced. The abnormal red cells are very numerous, and include almost all varieties; of the nucleated red cells, those of the normoblast type are more common. The presence of nucleated red cells in malignant disease suggests secondary deposits in bone, especially when associated with immature white cells (No. 18, *p.* 63).

21.—DIAGNOSIS OF NON-MALIGNANT FROM MALIGNANT DISEASE.

(EMPYEMA OF GALL-BLADDER: CLINICALLY RESEMBLING CANCER OF LIVER.)

Lymphocytes	per cent	..	— —	..	10·0
Large mononuclears	,,	..	—	..	3·2
Polymorphonuclears	,,	..	+ + +	..	86·0
Eosinophils	,,	..	—	..	0·2
Mast cells	,,	..	0	..	0·6

It has been stated that megaloblasts are not met with, but a case is recorded in which a large number of nucleated red cells were present, and 37 per cent of these were of the megaloblast type. The mean diameter of the red cells is not increased but is often diminished.

The blood picture of these cases is further distinguished from that of pernicious anæmia by the presence of leucocytosis of 10,000 to 20,000, and by the leucoid character of the white-cell picture, the leucocytosis and polymorphonuclear leucocyte count being always higher when metastases have developed or any ulceration is present.

The effect of digestion leucocytosis in cancer of the stomach has been referred to above.

No distinguishing character of the blood picture indicates the diagnosis between carcinomatous and sarcomatous growths. Both varieties conform to the general type and account given above. The chief points to be considered are: (*a*) Slight leucocytosis; (*b*) Increased number of large mononuclear cells; (*c*) Increased number of polymorphonuclear leucocytes; (*d*) The masking of the whole picture by complications; (*e*) The occasional onset of a cachectic anæmia.

It may be of interest to give here some examples from cases in which malignant growth was suspected clinically, but in which the diagnosis was negatived by the blood picture (*Nos.* 19, 20, 21, *pp.* 64, 65). *No.* 19 was a suspected carcinoma of the stomach. From the blood picture, the diagnosis was "probably not a malignant growth". Operation showed gastric ulcer, not malignant. In *No.* 20, another case of suspected carcinoma of the stomach, the diagnosis was "suggestive of intestinal stasis", and the patient was being treated for this condition two years after. The third, *No.* 21, a suspected growth of the liver, was an incomplete picture made from a film preparation. The red cells appeared healthy. There was undoubtedly high leucocytosis. A diagnosis of suppuration was made. On operation, pus was found in the gall-bladder.

Chapter IX

MEASUREMENT OF THE SIZE OF RED BLOOD-CELLS

Blood films made in the usual way are dried in the air without heat, fixed and stained in Jenner stain for two minutes, and afterwards for two minutes in a 10% aqueous solution of eosin to intensify the stain. Some convenient form of projection apparatus, adjusted to a magnification of 1000 diameters, is used to project the image of the microscope field on to a sheet of paper lying on the table. Having chosen a thin portion of the film, the red cells, being well separated, are outlined in pencil; for each cell two diameters, maximum and minimum, are measured to 0·5 mm. with a millimetre scale, and the mean of these measurements is accepted as the diameter of the cell, and expressed in terms of μ. The cells are classed in groups progressing by 0·25 μ, and the mean diameter of 500 cells is taken to represent the mean diameter of the red cells for any specimen of blood.*

In healthy blood the diameters of the red cells vary from 6 to 9 μ. The average mean diameter of 500 cells taken from each of 100 healthy persons (50,000 red cells) was found to be 7·202 μ, and the individual means actually varied from 6·8 to 7·49 μ.

The mean diameter of 500 red cells taken from the

---

* This classification of diameter values represents the distribution of the various-sized red cells in the sample of blood. From this distribution it is easy to calculate the 'mean' (μ), the 'standard deviation' (σ), and the 'variability' (degree of anisocytosis) (v), by the method described in Yule's *Introduction to the Theory of Statistics*, pp. 108–112, and which I have used in *Red Blood Cell Diameters*, Oxford Univ. Press, 1933.

same person at different hours of the day is variable. On waking in the morning the diameter is less, often as much as 0·5 μ, than at the end of the day. It is interesting to note that this variation occurs even if the subject remains in bed all day. This diurnal

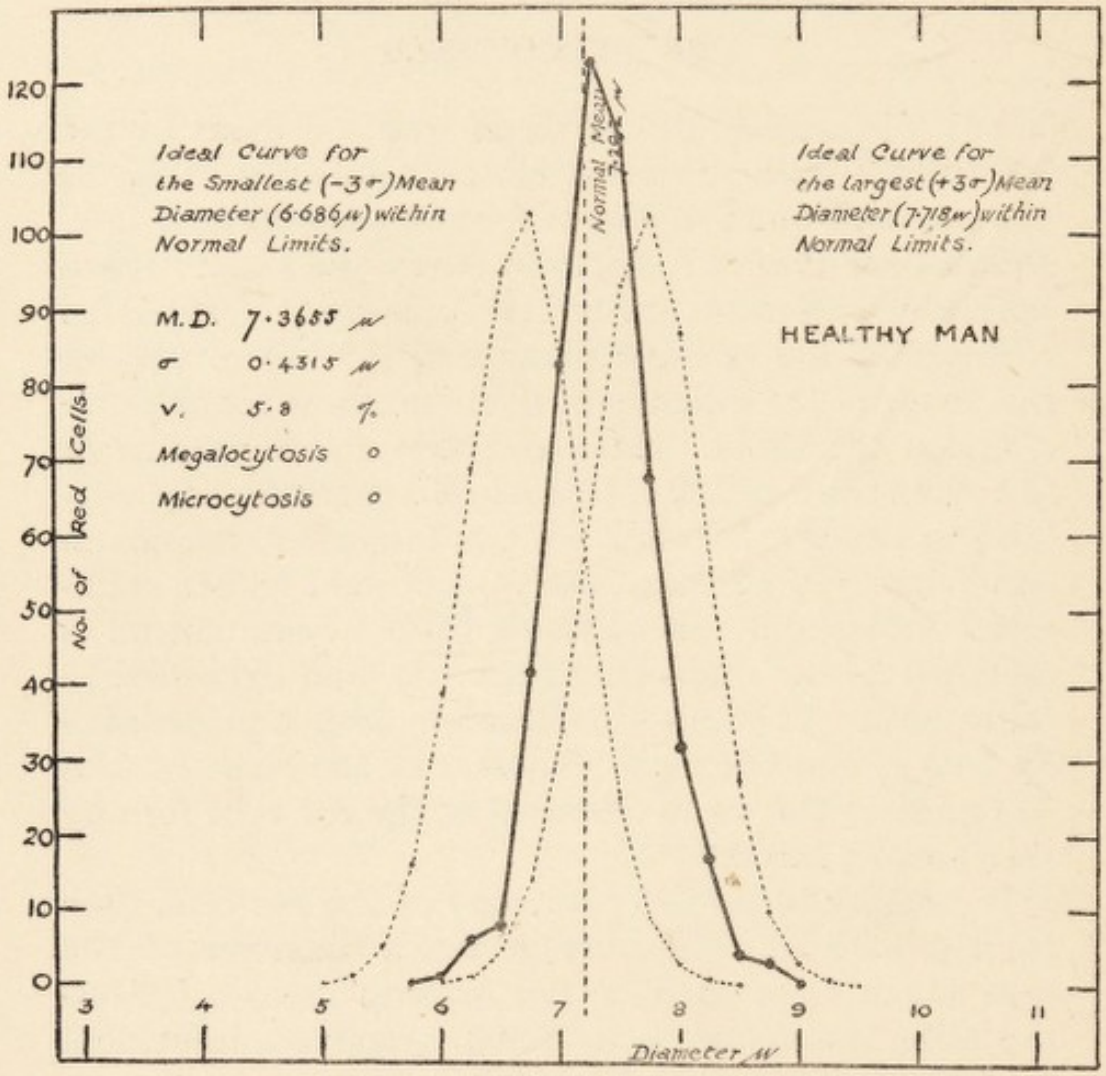


FIG. 5.—Red-cell-diameter distribution curve for healthy man.

variation is not increased by gentle exercise, but violent exercise will cause an increase in the diameter in the course of a few minutes. After forced breathing for five minutes, sufficient to produce some apnœa, the diameter is diminished.

It has been shown that increased or diminished

diameters correspond with increased or diminished volume of the red corpuscles.

It has also been demonstrated that these variations are associated with changes in the reaction of the blood. When the alkalinity of the blood is reduced, the diameter of the red cells is increased; and when the alkalinity is greater, the diameter is less.*

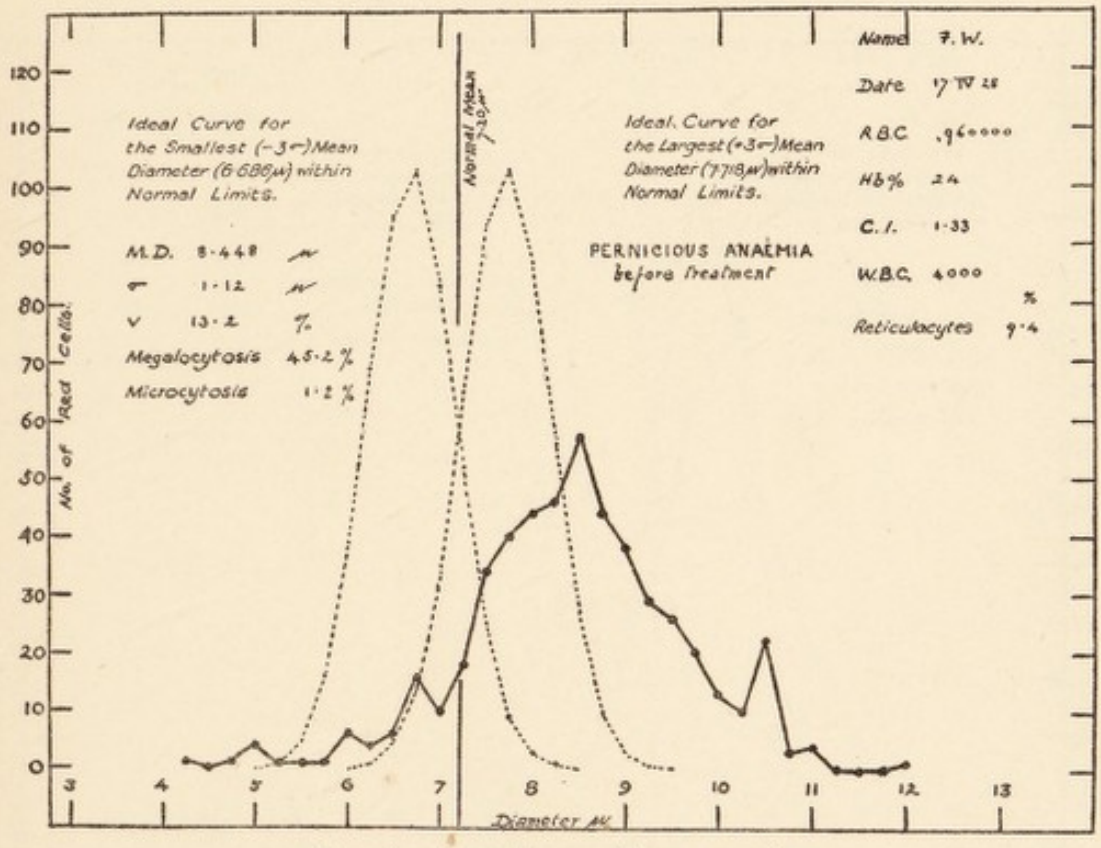


FIG. 6.—Curve in pernicious anæmia.

The measurements of red-cell-diameters are conveniently demonstrated by curves. *Fig.* 5 expresses the distribution of 500 cell diameters in the blood of a healthy man. The mean diameter is 7·3655 μ and the variability of the measurements is 5·8 per cent. The dotted curves in this figure exhibit the calculated maximum and minimum 'ideal' curves within healthy

* *Jour. of Pathol.*, 1920, xxiii, No. 4.

limits; these two curves therefore include an area within which the diameters are normal or healthy. Cells outside the area to the left would be too small, and those outside the area to the right would be too large; by enumerating these outside cells it is possible to estimate the percentage megalocytosis or microcytosis as the case may be. (*See Red Blood Cell Diameters*, Oxford Univ. Press, 1933).

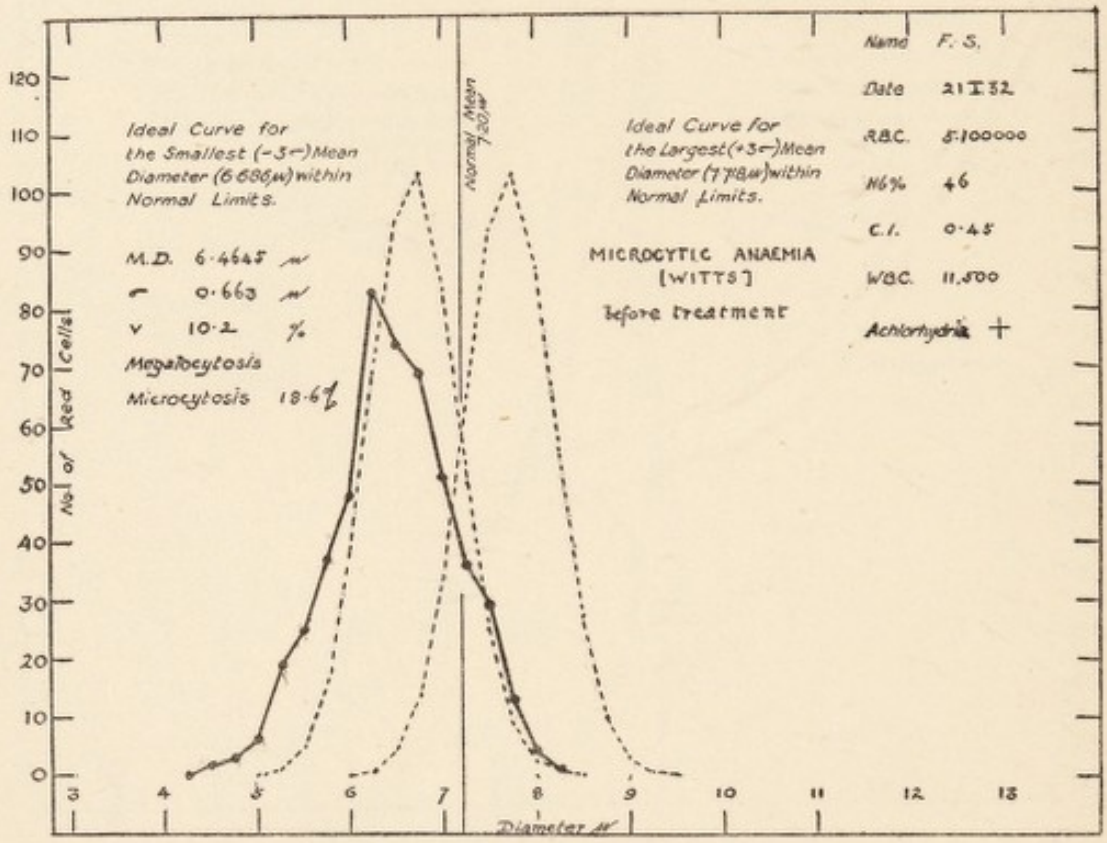


FIG. 7.—Curve in microcytic anæmia.

In the blood of pernicious anæmia the diameters of the red cells vary from 4 to 13 μ, and the mean diameter of 500 cells varies from 7·5 to 8·5 μ. The degree of anisocytosis (variability) is greatly increased over that found in healthy blood; this sign is even a more constant feature than the increased mean diameter (megalocytosis) of the red cells in this disease.

Fig. 6 expresses a red-cell-diameter distribution curve of pernicious anæmia—showing a shift of the curve to the right of the normal mean, and an extended base indicating the range of variability.

Fig. 7 expresses a red-cell-diameter distribution curve from a case of microcytic anæmia (Witts). It shows a shift of the curve to the left of the normal mean, and an increased variability.

1535.33 JOHN WRIGHT AND SONS LTD., STONEBRIDGE HOUSE, BRISTOL.

APPENDIX

PHYLOGENETIC DIAGRAM OF BLOOD-CELLS

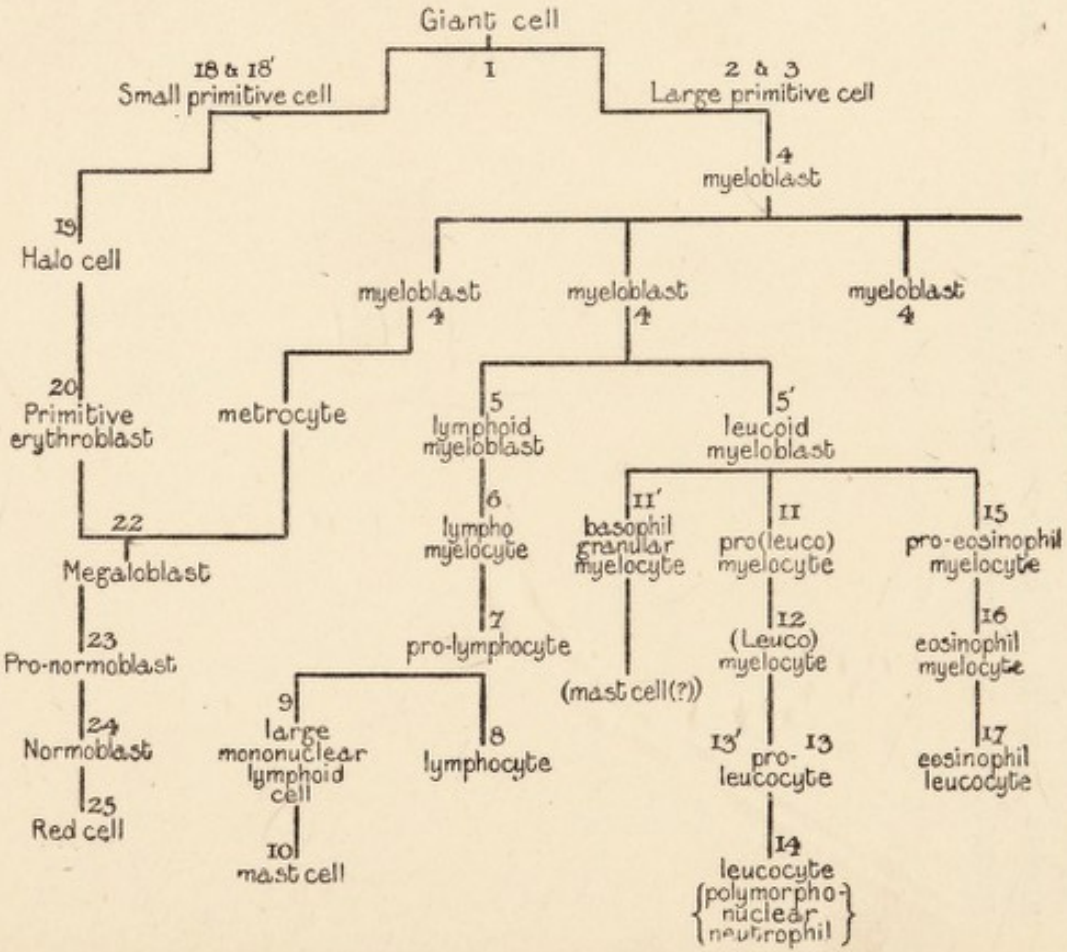
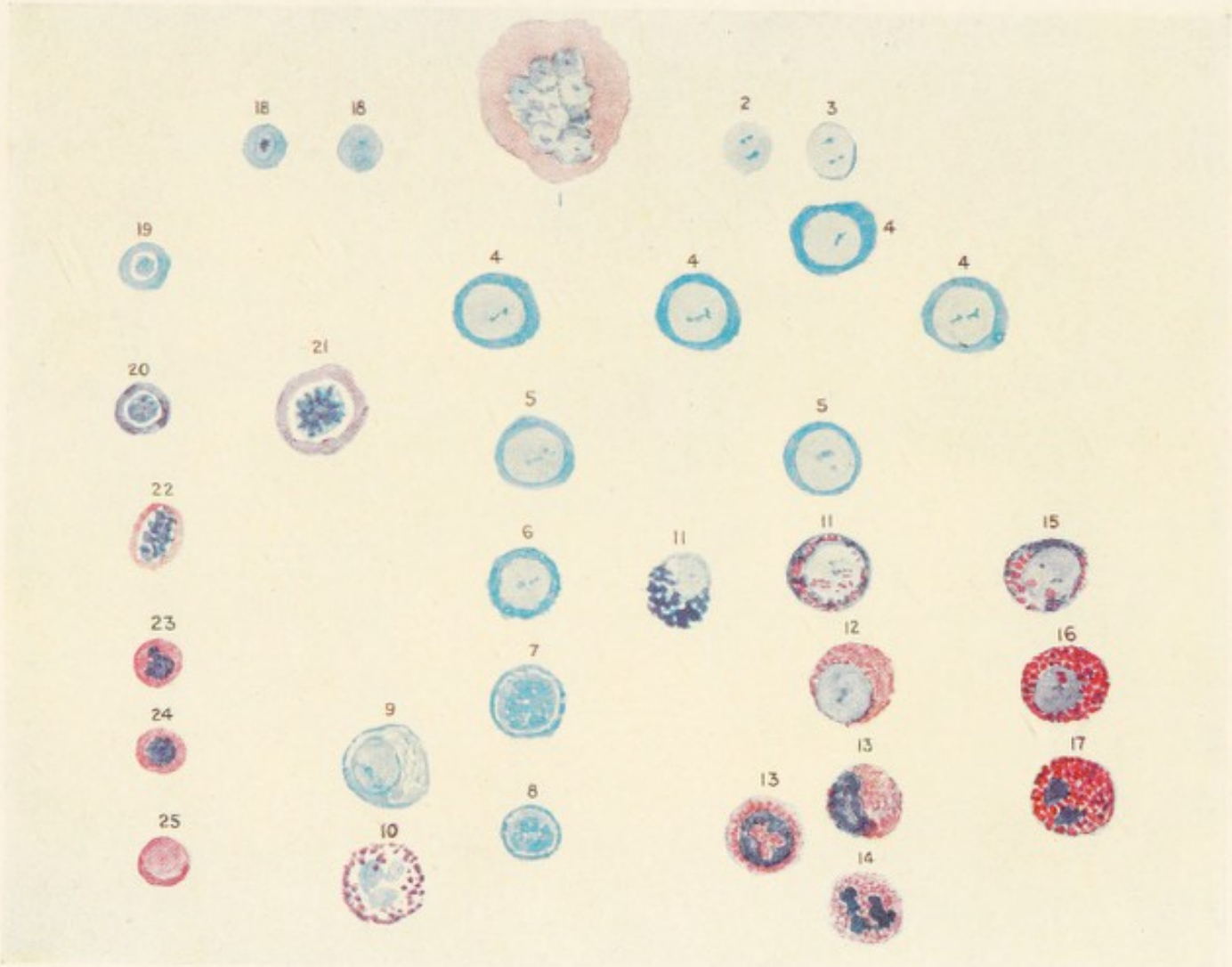


PLATE V

MARROW CELLS



7/10