SANDOZ ATLAS of HAEMATOLOGY

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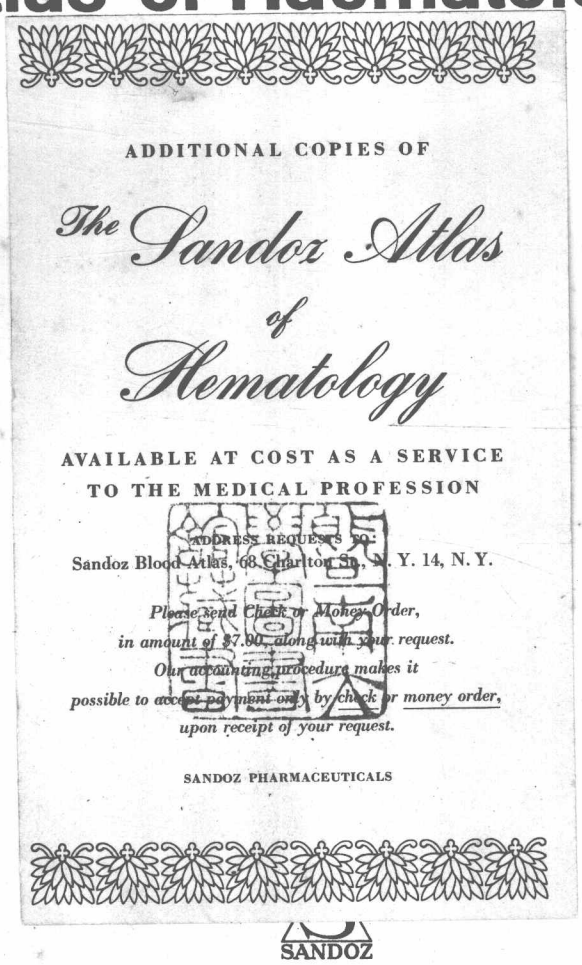

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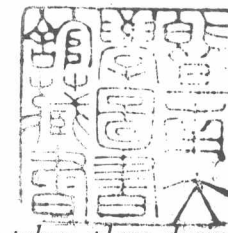
Preface



The rapid advances in haematology which have taken place during the last few years have been matched by the publication of so many new text-books and atlases that the literature has been kept well up-to-date. Despite the excellence of the existing works, however, it seemed to us that there was still room for another atlas of haematology designed to meet the needs of the practising physician. Nowadays, haematology is no longer the hobby of a few specialists, but has become an indispensable diagnostic aid to the modern physician. It is important, therefore, that he should possess an atlas which will enable him to identify without difficulty the corpuscles of the blood and haemopoietic organs. The coloured drawings usually employed almost inevitably suffer from the disadvantages of subjective interpretation. Our aim has been to produce an atlas in which the blood cells are faithfully portrayed and the appearance is that actually seen when a well prepared film is examined under the microscope. This has been accomplished by taking colour photomicrographs of the various preparations, by using modern techniques of colour printing and by avoiding artificial combinations of cells from different parts of films. In this way, we have been able to achieve an authentic reproduction of the form and colour of the blood cells in their natural surroundings.

The reception accorded to the first edition of the "Sandoz Atlas of Haematology", which was published in 1949 in French and German only, was extremely favourable and completely justified the undertaking. In a short time, the entire edition was exhausted, and the continued demand for the atlas made it necessary to prepare a second edition. It was decided that this new edition should appear not only in French and German but also in English and Italian, and that the atlas should be revised and enlarged. This has been done and a further 34 illustrations, consisting of 70 separate photographs, have been added.

With a few exceptions, a magnification of 1 : 1200 has been employed. The magnification of 1 : 500, usual in microscopic work, although employed for actually taking the colour photographs proved too low for purposes of reproduction. In order to obtain the necessary clarity and the same wealth of detail seen in a transparent slide, a higher magnification is needed for reproductions to be examined under incident light. In the case of a few particularly large elements, such as megakaryocytes, stroma cells and osteoclasts, however, a lower magnification was used in certain photographs in order to show the cells in their entirety.

The atlas is divided into three sections, each of which follows the same general plan. The first part of each section deals with the development of the nine species of blood cells in the haemopoietic tissues, particularly in the bone marrow, and this is followed by a description or

photographs of the cells in the peripheral blood under normal and pathological conditions. As no international agreement on the question of terminology has yet been reached, the classical nomenclature has been employed as far as possible.

Part I gives a brief account of the basic principles of haematology and of the technique of preparing and staining blood and bone marrow films. At the end of this section, will be found drafts of forms suitable for recording the results of blood and bone marrow counts, followed by the normal values of haematological data.

Part II is devoted to a systematic description of the various groups and species of blood cells and their development.

Part III contains 44 plates comprising a total of 256 illustrations of normal and pathological elements found in the blood and haemopoietic organs. Apart from Figures 78 and 79 C, which show leucocytes in rabbits with Pelger-Huët's anomaly, and Figures 248 B and 248 C showing trypanosomes in guinea pig blood, all the photographs are of human blood cells. Facing each plate will be found descriptions of the individual photographs.

Since the atlas is intended primarily to fill practical needs, every effort has been made to include all known cells of the blood and haemopoietic organs, whether normal or pathological, for the general practitioner is just as likely as the specialist to encounter the rarer elements.

Many cells, for example tissue basophils and certain stem cells, are only rarely seen in healthy persons, but under pathological conditions their numbers may be increased without qualitative changes, and even in leukaemic patients, the blood corpuscles may be normal in appearance. It was therefore possible to overcome the difficulty of obtaining photographs of some of the rarer elements by using preparations from pathological cases.

Of the 579 photographs which go to make up the 256 illustrations, 346 are of preparations in our own collection, while the preparations used for the remaining 233 photographs were kindly placed at our disposal by clinicians in Switzerland and other countries. We should like to record here our gratitude to the undermentioned for the help they have given us in this connection (individual acknowledgments will be found in the descriptive text facing the illustration).

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We are especially indebted to Dr. Käthe Schäffer who selected the specimens containing blood parasites and arranged the photographs on plates 42 and 43.

Our appreciation and thanks are also due to Messrs. Frobenius Ltd., Basle, for their skill and willing co-operation in the difficult and laborious task of reproducing the colour photographs.

The "Sandoz Atlas of Haematology" has been written and compiled by Dr. E. Undritz of the Sandoz Pharmacological Research Laboratories, under the direction of Prof. E. Rothlin.

The atlas has been translated into English by Dr. A. M. Woolman. We are greatly indebted to Dr. A. Piney, London, who kindly read through the manuscript of the English translation and made a number of valuable suggestions.

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PART ONE

General Considerations

I. Fundamental Principles of Haematology

This general section is devoted to a brief discussion of the terminology and classification of the blood corpuscles, followed by a description of their formation, reproduction, maturation, functions, and destruction (lysis), both under normal and under abnormal conditions. An account is also given of the cellular elements which are found in the bone marrow but are not concerned in haemopoiesis. Detailed descriptions of the individual blood cells will be found in Part Two. While the atlas accurately reflects the present state of our knowledge of haematology, no claim can be made to completeness, for there are many questions still to be answered.

1. TERMINOLOGY

Haematology possesses no uniform terminology, partly because there are still gaps in our knowledge and partly because not all authors interpret the findings in the same way. In the following pages, we shall adhere to the classical nomenclature, both for the two large *groups* of blood corpuscles—the erythrocytes and the leucocytes—and for the individual cell species: normocytes and megalocytes, basophils, eosinophils, neutrophils, monocytes, lymphocytes, plasma cells and the elements of the megakaryocyte-platelet system. Each of the individual cell species undergoes various stages of development to which numerous synonyms have been applied. We have selected those names which appear to agree best with the specific properties of the elements they describe and which are least likely to be misunderstood. For the ripe neutrophils, for example, the term "polynuclear" is incorrect, since they possess only one nucleus. On the other hand, the description "segmented" is accurate, though it naturally refers only to the nucleus and not to the entire cell. Similarly, we have preferred the older term "myelogenous" to the now more generally adopted term "myeloid", since the latter strictly speaking means "resembling marrow" and not "derived from marrow". By employing only classical terms and those derived from them, we hope to have arrived at an internationally acceptable nomenclature and, as far as possible, we have used the same terms in all four languages. Terms which differ from these but are in common use in certain countries have also been added in brackets to facilitate understanding. For cell stages which have only recently been recognized, we have used terms which fit in well with the classical terminology, such as

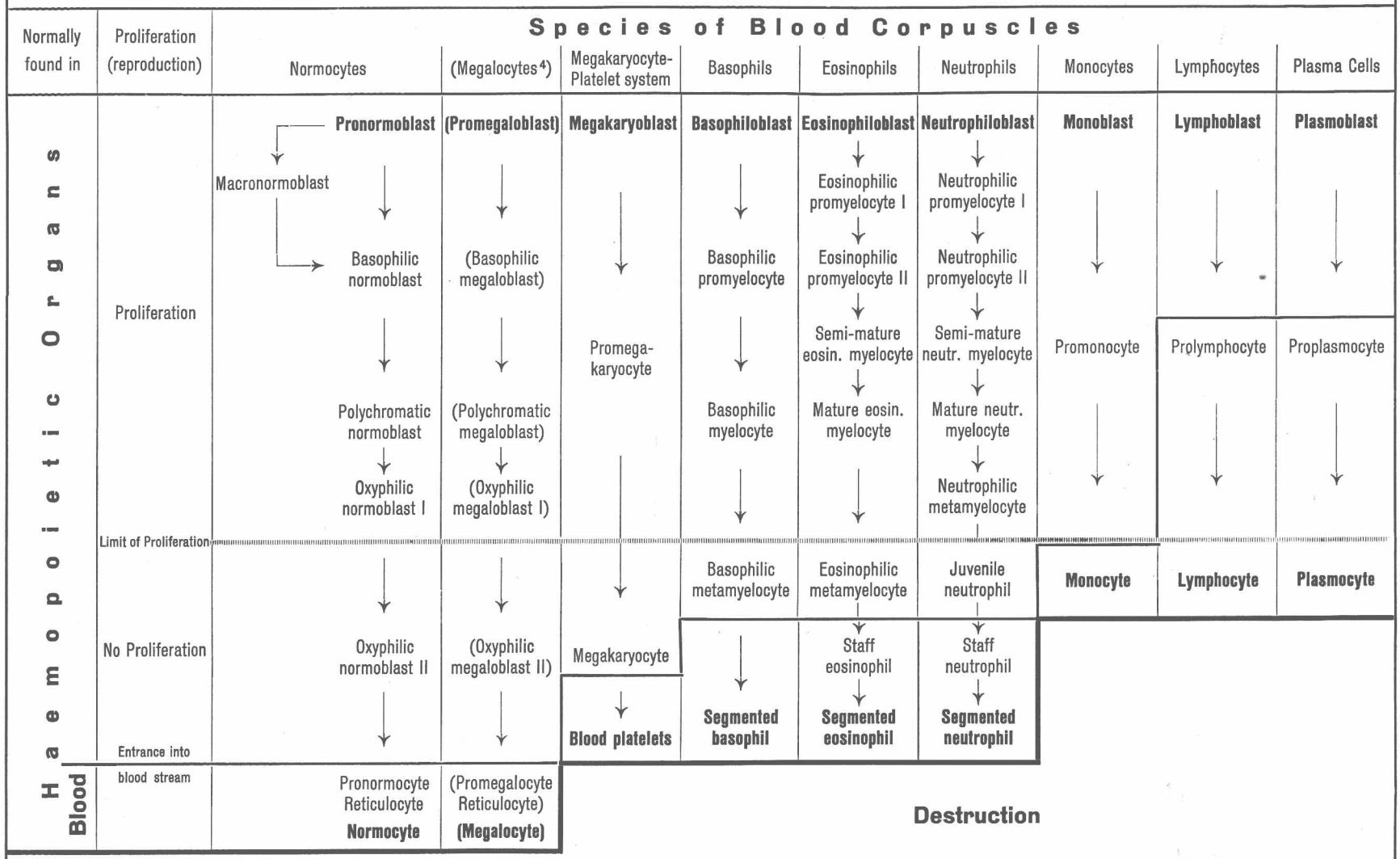
Table 1

The Genealogical Table of the Blood Cells[1]

A. Primary Formation in the Embryo[2]

Fertilized ovum → mesoderm → mesenchyme → specific stem cells

B. Somatic Regeneration[3]



[1] See text on p. 3. [2] Commencing with the fertilized ovum. [3] Commencing with the specific stem cells. [4] Cells in brackets are not normally found in adults.
The stem cells and the definitive forms are printed in heavy type.

basophiloblast, eosinophiloblast and neutrophiloblast, to describe the ungranulated stem cells of the corresponding species of blood corpuscle. Naegeli's "myeloblast" and Ferrata's "haemocytoblast" are now known to be collective terms covering a variety of stem cells. Since the introduction of bone marrow puncture, it has also proved necessary to subdivide many of the more mature stages of development. Thus the promyelocytes of the basophils, eosinophils and neutrophils are now subdivided into promyelocytes I and promyelocytes II. The promyelocytes I are the same size as the blast cells but already contain sparse granulation (corresponding to Ferrata's basophilic, eosinophilic and neutrophilic myeloblasts), while the larger cells with more abundant granulation are known as promyelocytes II (the promyelocytes of Naegeli or the immature myelocytes of Rohr). These terms also fit in well with the classical nomenclature and are not likely to lead to misunderstanding. Instead of the misleading term "reticulocyte" we speak of "proerythrocyte", which conforms better to the classical terminology. Certain terms, such as "staff form", although not classical have found general acceptance, and these have been retained. Others, such as "Türk's irritation cell", have been dropped, since it is no longer certain to which cells they were originally intended to apply. To facilitate understanding, however, the most widely employed synonyms have also been given.

2. CLASSIFICATION OF THE BLOOD CELLS INTO GROUPS, SPECIES AND STAGES OF DEVELOPMENT

Table 1 shows the genealogical table of the blood cells. Two distinct processes are shown: (a) the *primary formation* of the specific stem cells in the embryo, starting from the fertilized ovum, and (b) the *somatic regeneration* of the different species from their stem cells, which sets in after the latter have been elaborated in the embryo.

The following phases in the process of development are indicated: the limit at which proliferation ceases (broken line), the threshold at which the various blood corpuscles enter the blood stream (thin, continuous line) and the stage of development at which the death and destruction of the cells eventually occurs (thick, continuous line). Stages which correspond to approximately the same degree of maturity are shown at the same level. It will be seen that the stage of development at which entrance into the blood stream and death of the cell occurs varies according to the species of blood corpuscle to which it belongs. The plasma cells and lymphocytes do not reach the same stage of maturity as, for example, the neutrophils, while the destruction of the latter takes place at an earlier stage than that of the normocytes.

With regard to the nomenclature of the red blood corpuscles, confusion can be avoided if the two species, normocytes and megalocytes, are referred to collectively as erythrocytes. The introduction of new terms is thus rendered unnecessary. By employing the prefix "normo-" systematically for all the stages of development of the one series, from pronormoblast to normocyte, and the prefix "megalo-" for the other series, from promegaloblast to megalocyte, a clear differentiation between the two series can be made (see Table 1). The prefix "erythro-" should only be employed when a differentiation is unnecessary, and conveys no more than "red blood corpuscle".

Table 2

CLASSIFICATION OF THE BLOOD CORPUSCLES INTO GROUPS AND SPECIES

Groups	Species or systems	Synonyms
Erythrocytes	Normocytes	(Erythrocytes in a restricted sense, rubricytes)
	Megalocytes	
Leucocytes	Basophils with soluble granulation	Blood basophils (blood mast cells)
	Eosinophils	(Acidophils)
	Neutrophils	(Microphages)
	Monocytes	(Large mononuclear and intermediate forms, macrophages; vaguely related to histiocytes, migratory cells, clasmatocytes, reticulo-endothelial and endothelial cells, etc., see p. 58)
	Lymphocytes	(Small mononuclear forms)
	Plasma cells	Plasmocytes (plasmacytes, Türk's irritation cells [?])
	Megakaryocytes Blood platelets	Giant cells of the bone marrow Platelets (thrombocytes)

Terms in brackets are those not employed elsewhere in the atlas.

Table 2 shows how the blood corpuscles are divided into two *groups*, the erythrocytes and the leucocytes, which are then subdivided into 9 *species (polyphyletism* according to Undritz, 1934). The most common synonyms are also given.

Classification of the species into stages of development*

A. THE SYSTEM OF THE NORMOCYTES (Plates 2 and 6, and parts of Plates 1, 3, 4 and 5): Pronormoblast, macronormoblast (macroblast)**, basophilic normoblast, polychromatic normoblast, oxyphilic normoblast with nuclear structure, oxyphilic normoblast with structureless (disintegrating) nucleus, *pronormocyte* (normocytic reticulocyte, normocyte with vital granulation, granulofilocyte), *normocyte.*

B. THE SYSTEM OF THE MEGALOCYTES (Plate 7 and parts of Plates 1, 3, 4 and 5): Promegaloblast, basophilic megaloblast, polychromatic megaloblast, oxyphilic megaloblast with

* The stages which normally pass into the blood stream from the haemopoietic centres are printed in italics.

** The macronormoblast or macroblast is an intermediate stage which does not invariably occur.

nuclear structure, oxyphilic megaloblast with structureless (disintegrating) nucleus, promegalocyte (megalocytic reticulocyte), megalocyte.

C. THE SYSTEM OF THE BASOPHILS WITH SOLUBLE GRANULATION (*Blood basophils*, Plate 11): Basophiloblast (myeloblast of the basophilic series), basophilic promyelocyte stage I (basophilic myeloblast of Ferrata), basophilic promyelocyte stage II, basophilic myelocyte, basophilic metamyelocyte, *segmented basophil.*

D. THE SYSTEM OF THE EOSINOPHILS (Plates 12 and 13): Eosinophiloblast (myeloblast of the eosinophilic series), eosinophilic promyelocyte stage I (eosinophilic myeloblast of Ferrata), eosinophilic promyelocyte stage II, eosinophilic myelocyte, eosinophilic metamyelocyte, staff eosinophil, *segmented eosinophil.*

E. THE SYSTEM OF THE NEUTROPHILS (Plates 14—19): Neutrophiloblast (myeloblast of the neutrophilic series), neutrophilic promyelocyte stage I (neutrophilic myeloblast of Ferrata), neutrophilic promyelocyte stage II (immature myelocyte), semi-mature neutrophilic myelocyte, mature neutrophilic myelocyte, neutrophilic metamyelocyte, juvenile neutrophil, *staff neutrophil, segmented neutrophil.* (Metamyelocytes and juvenile forms are usually grouped together and described simply as "metamyelocytes" or simply as "juvenile forms". Arneth subdivides the segmented forms into those with 2, 3, 4, 5 and more segments).

F. THE SYSTEM OF THE MONOCYTES (Plates 20—23): Monoblast, promonocyte, *monocyte.*

G. THE SYSTEM OF THE LYMPHOCYTES (Plates 24 and 25): Lymphoblast, *prolymphocyte, lymphocyte.*

H. THE SYSTEM OF THE PLASMA CELLS (Plates 26—28): Plasmoblast, *proplasmocyte, plasmocyte.*

I. THE SYSTEM OF THE MEGAKARYOCYTES AND PLATELETS (Plates 29—31): Megakaryoblast, promegakaryocyte, megakaryocyte, *blood platelet.*

The precise characteristics of the individual groups, species and stages of development of the blood cells are described in Part Two.

3. ORIGIN OF THE BLOOD CELLS

Certain cells of the adult organism, such as the nerve and muscle cells, no longer possess the power of proliferation and hence, under normal conditions, they cannot be replaced. In the case of other cells, such as those of the skin and the glands, however, there is a steady formation of new cells to take the place of those constantly being used up. The blood cells belong to the class of proliferative cells.

In the embryo, the blood cells are formed in the mesenchyme which is derived from the mesoderm. The sites of formation of the blood cells vary in a definite order during the period of intra-uterine development. At first situated outside the embryo, in the yolk sac and abdominal pedicle, and later within the embryo, chiefly in the liver and spleen, they finally become localized in the bone marrow and lymphatic tissue. At birth, this process of development is already complete.

Despite its name, the lymphatic tissue is not solely concerned with the formation of *lymphocytes*, although lymphopoiesis is strongly evident in it. From the same tissue arise the *monocytes* and the *plasma cells* as well as the *basophils with insoluble granulation* (tissue basophils) although, in man, the latter do not properly speaking belong to the blood cells. Lymphatic tissue is found not only in the lymph glands, the lymph follicles and the spleen, but also in vascular sheaths throughout the body.

The bone marrow is the site of formation of *basophils with soluble granulation* (blood basophils), *eosinophils, neutrophils, megakaryocytes* and *normocytes*. However, *lymphocytes, monocytes, plasma cells* and *basophils with insoluble granulation* are also produced in the bone marrow in the vicinity of the vessels.

In certain primary and secondary diseases of the blood, the blood cells which are normally formed only in the bone marrow can also arise in other organs, particularly in the spleen, the liver and the lymph glands. On the other hand, it may also happen that lymphocytes, monocytes, plasma cells, and basophils with insoluble granulation are formed in excessive quantities in the bone marrow. In man, the megalocyte is unique in that it appears for only a brief period during one particular stage of development. It is found in the embryo from the second week of pregnancy, when blood formation commences, up to the third month of pregnancy, its formation being entirely extra-embryonic. According to Naegeli, megalocytes reappear in adults in pernicious anaemia, and are then formed principally in the bone marrow.

Many authors have assumed that the supply of new cells in the adult organism is derived, as in the embryo, from multipotent mesenchymal cells. It seems more probable that, after the initial embryonic period, each species of blood cell has its own particular stem cell *(polyphyletism)*, for each cell species follows its own independent line of development, beginning with the stem cell and ending with the mature form which is released into the blood. Although there are many points of resemblance among the different cell species with regard to the form, structure and staining reactions of the cells, and of their nuclei and cytoplasm, each individual species of cells exhibits a number of specific characteristics by which it may be distinguished from other species. Typical features are also to be found in the chemical composition of the cells, and in their enzyme content and functions. Above all, it has so far been impossible to provide conclusive proof of the existence either of intermediate forms between one species and another or of mitoses or polyploid bastards of different cell species. There is thus no evidence that cells from different species can be derived from common stem cells.

4. THE BLOOD CORPUSCLES UNDER NORMAL CONDITIONS

a) **Reproduction and maturation.** All blood cells reproduce by mitosis. The number of consecutive mitoses is limited, for when the cells mature they eventually lose their power of division. No longer capable of proliferation, they enter the blood stream, fulfil their functions and are destroyed. In healthy individuals, it is only in extremely rare instances that cells in mitosis are found in the blood, but dividing plasma cells, or perhaps lymphocytes, may very occasionally be seen (Figs. 155 A, 155 B).