THE

BIOLOGY OF THE BLOOD-CELLS

WITH A GLOSSARY OF HÆMATOLOGICAL TERMS:

FOR THE USE OF PRACTITIONERS OF MEDICINE

BY

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PREFACE

THIS work is intended to serve as a companion to any of the larger text-books on Hæmatology. Special stress has been laid upon the close relationship between changes in the blood-forming organs and the blood picture as the clinician sees it, and also upon the minute morphology of the various blood-cells, whether sessile or free-floating. Above all, the attention of the student has been directed to the fundamental unity of design which is the basis of hæmopoiesis from birth to death throughout the animal kingdom.

The names of hæmatologists whose works have been consulted appear in a special index, but the author wishes here more particularly to acknowledge the great debt which he owes to PAPPENHEIM, whose writings are in so many ways an inspiration.

O. C. GRUNER.

MONTREAL, *Octobér*, 1913.

LIST OF COLOURED PLATES

I.—The Primordial Blood-cell . . *facing page* 10

II.—The Red Blood-cell . . . ,, ,, 76

III.—Author's Scheme of Lymphogenesis . ,, ,, 126

IV.—Mononuclear and Certain other Blood-cells ,, ,, 134

V.—The Relation between Pulpar Tissue and Venous Channels . . . . ,, ,, 158

VI.—The Large Mononuclear Leucocyte . ,, ,, 190

VII.—Phlogocytes . . . . . ,, ,, 250

LIST OF ILLUSTRATIONS

FIG.		PAGE
1.	T.S. of Bone, showing Trabeculæ, Marrow Tissue, Blood-vessels and Fat Spaces . . .	*facing page* 2
2.	Photograph of Three Follicles and Spleen-pulp	,, ,, 2
3.	Fragments of Trabeculæ . . .	,, ,, 3
4.	A Single Follicle showing Germ-centre Cells	,, ,, 3
5.	Diagram of Structure of the Lymphoidocyte . .	8
6.	Diagram Representing Ontogeny and Phylogeny in a Cell Series	16
7.	Mast-cell Lymphoidocyte	19
8.	Leucoblast	22
9.	Rieder Cell	22
10.	Leucosarcoma Cell	22
11.	Spermatogenesis	25
12.	Diagram showing contrast between Lymphoblast and Myeloblast	32
13.	Scheme of Cell Descent	38
14.	Leukæmic Proliferation	39
15.	Rate of Proliferation: (*a*) Normal; (*b*) Hyperplasia .	39
16.	Diagram representing Hyperplasia, Metaplasia and Anaplasia	40
17, 18.	Normal Bone-marrow . . .	*facing page* 44
19.	Bone-marrow showing Erythroblastic Reaction	,, ,, 45
20.	Pigment in Bone-marrow . . .	,, ,, 45
21.	Transverse Section of Primitive Blood-vessel . .	54
22.	Longitudinal Section of Primitive Blood-vessel . .	55
23.	Lymphoid Erythroblasts	60
24.	Diagram of the Megaloblast Forms. . . .	62
25.	Schilling's Conception of a Red Cell . . .	70
26.	Platelets escaping from Red Blood-corpuscles . .	86
27.	A Demi-lune Body	88
28.	Blood-supply of Lymph Node . .	*facing page* 113
29.	Malpighian Follicle in the Spleen . .	,, ,, 113
30.	A View of the Arterial Supply of the Spleen	,, ,, 120

FIG.		PAGE
31.	Centre of Malpighian Follicle . . *facing page*	120
32.	Anomalous Shape of Malpighian Follicle . ,, ,,	121
33.	Edge of a Capillary, showing Discharge of Lymphoid Cells from an adjacent Follicle into the Lumen *facing page*	121
34.	Central Part of a Lymphoid Follicle . ,, ,,	129
35.	Splenoid Metaplasia of Lymph-node . ,, ,,	156
36.	Transverse Section of a Pulp Cord . ,, ,,	156
37.	Fragments of Trabeculæ . . . ,, ,,	157
38.	Splenic Pulp Tissue, showing Fibrosis . ,, ,,	157
39.	Splenic Pulp Tissue of Puppy, showing Megakaryocytes *facing page*	161
40.	The Two Forms of Monocyte	175
41.	Diagrammatic, showing Morphological Differences between Lymphatic Monocyte and Leucocytoid Lymphocyte .	176
42.	Phagocytosis in Lymph-channel of a Lymph-node *facing page*	183
43.	Splenic Tissue in a case of Death from Infection by Bacillus Aerogenes Capsulatus . . . *facing page*	192
44.	Splenic Pulp in a state of Myeloid Metaplasia ,, ,,	192
45.	Chart representing Inter-relations between Follicles and Pulpar Tissue	193
46.	Graphic Record of the Cell-Formula of the Bone Marrow .	196
47.	Atrophic Marrow . . . . *facing page*	198
48.	Gelatinous Degeneration . . . ,, ,,	199
49.	Degeneration of Marrow Cell . . ,, ,,	199
50, 51.	Marrow Film . . . . ,, ,,	200
52.	Diagram of Structure of the Lymphoidocyte . .	203
53.	The Promyelocyte	206
54.	Diagram of some of the Cells of the Myeloic Series . .	210
55.	Leucocytes showing Amœboid Movement . . .	213
56.	Neutrophiles from a Case of Acute Pneumonia . .	214
57.	Graphic representation of Arneth's System. . .	215
58.	Caryorrhectic Leucocytes in an Inflammatory Area *facing page*	217
59.	Curves showing effect of certain Organisms on the character of the Cells of the Exudate	216
60.	Chart illustrating Arneth's Method	219
61.	The Neutrophile Leucocyte	221
62.	Lymphocytes in the Breast. . . *facing page*	244

FIG. PAGE

63.—Adrenal Medulla, showing Small Round-celled Infiltration *facing page* 244

64, 65.—Views in a Zone of Chronic Inflammatory Cell Infiltration *facing page* 245

66.—Chronic Inflammatory Cell Infiltration in a Case of Gonorrhœal Salpingitis . . . . *facing page* 247

67.—Portion of a Capillary Wall in an Inflammatory Area in a Case of Chronic Interstitial Appendicitis *facing page* 247

68.—Portion of an Intestinal Lymphoid Follicle, from a Case of Typhoid Fever . . . . *facing page* 273

69A & B.—Diagrams to show the Double Action of Noxious Agents on Tissues and Blood-forming Organs . . 280, 281

70.—Chart representing the Inter-relations between the Phlogocytes 283

71.—Steric Chemical Interchanges 295

72.—Splenic Pulp in a state of Myeloid Metaplasia *facing page* 302

73.—Splenic Tissue in a case of Acute Lymphatic Leukæmia *facing page* 302

74.—Mononucleate and Binucleate Forms from the Pulp Tissue of the Spleen in a case of Chronic Lymphatic Leukæmia *facing page* 305

75.—Germ-centres with well-marked Endothelioid Cells ,, ,, 305

BIOLOGY OF THE BLOOD-CELLS

INTRODUCTION.

THE classical figure, devised by Huxley, of a hypothetical Martian coming to this earth and making his investigations into the life-history of mankind by parahuman methods, is so significant that it should be ever present before the investigator. We are too apt to follow the stereotyped lines of presentation of ideas, and fail to transfer ourselves to an imaginary higher plane of life, in order to study the appearances of things from a standpoint as nearly extrahuman as is possible.

This objection applies with special force to the blood-cells. These cells, circulating blindly through the blood-vessels at the microscopic rate of thirty miles an hour, are usually only referred to during that stage of their existence; they are assiduously enumerated, and percentages are worked out ("a white-cell formula"), just as the number of fat globules might be estimated in a drop of milk to ascertain its hygienic value. If we reflect that these circulating cells must be manufactured, must pass through various phases of life during which they linger in the byways and alleys of the body, in order to fulfil definite purposes before they succumb to the death common to all cells, we see that the ordinary clinical conceptions are quite inadequate.

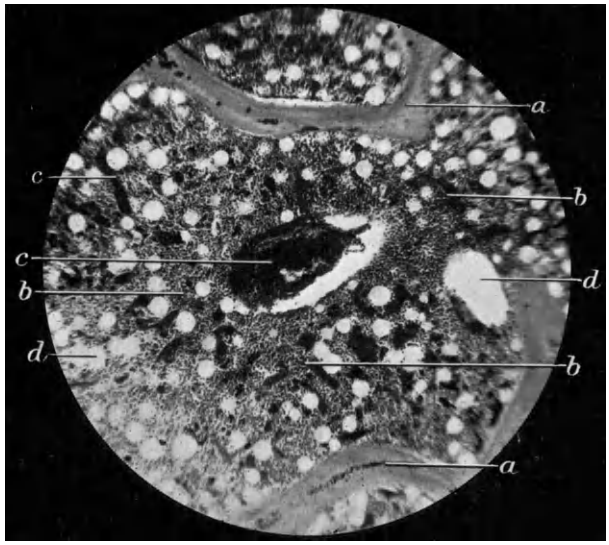
Let the reader imagine himself to be transported by magical means to the centre of an absolutely new city, inhabited by beings of a different and hitherto unknown race. How would he proceed to find out the story of these beings? He would not be content to stand at the street corner or in the gateway, and collect together five hundred of the bustling, active, hurrying toilers as they passed, and, mingling them with a few of the indolent loungers in the

vicinity, proceed to classify all these persons into percentages according to their types. From a convenient vantage-ground he would carefully note the peculiarities of each passer-by, dividing them into as many different types as he could; and he would not confine himself to a short period of the day, but would observe the different features about the people—at this time, at that; to-morrow; a month hence; by day; by night. Furthermore, it is not to be conceived for an instant but that he would look at the buildings, the roads, the material transported along the streets, and that he would feel a desire to ascertain the processes at work within those buildings; to see the factories; to see where the people came from; where they went; how they died; why they died; and what part each played in the whole fabric of life.

It is evident, therefore, that a clear idea of the blood-cells predicates more data than are supplied by taking a single drop of blood, drying it, and subjecting it to a microscopic examination. Maybe this is the only feasible procedure in a patient, but it is not the only method by which the *subject* can be studied. The structure of the blood-cell-forming organs is now sufficiently far advanced to enable definite ideas to be maintained. A knowledge of the structure of these *blood-cell factories* is all essential to a correct appreciation of the significance of the presence of the various changes found in blood films both in health and disease.

The **Factories of the Blood-cells** are of two varieties—those which are in constant requisition, and those which are only occasionally brought into action. The latter include the peri-vascular tissues in every part of the body, while the former embrace the bone-marrow, the spleen, and the lymphatic system of formative tissues. There is a remarkable family resemblance of structure exhibited by each and all of these tissues which can only have one significance, namely, that the process of manufacture is fundamentally the same in each case. Thus, to sketch out the characters of each factory broadly, we have :—

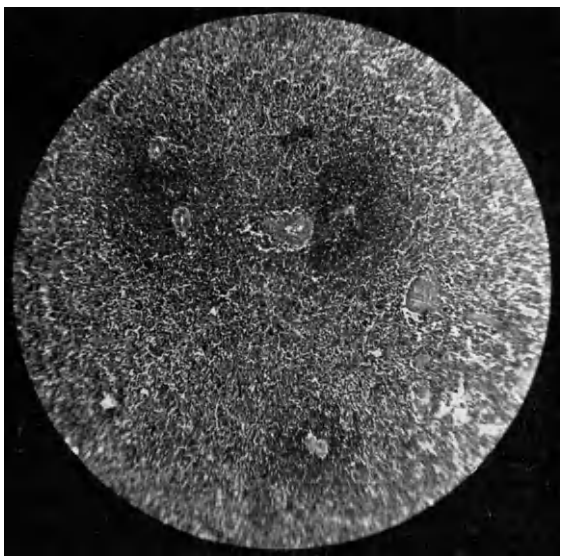
In the *bone-marrow*, intense vascularity—a veritable angioma, with numbers of formative cells completely filling up the inter-vascular spaces, save where fat-cells are interpolated in numbers varying with the degree of activity of blood-cell formation (*Fig.* 1).



" In the bone-marrow, intense vascularity . . . with numbers of formative cells, completely filling up the vascular spaces " (p. 2).

Fig. 1.—T.S. OF BONE, showing (*a*) the trabeculæ; (*b*) the marrow tissue; (*c*) the deeply congested blood-vessels; and (*d*) the fat spaces. The marrow tissue is seen to consist of densely-packed cells, which stain deeply.

(Oc. 4, Zeiss Apochrom. 4 mm.).

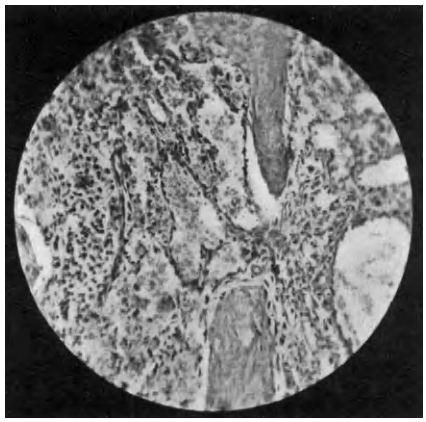


" In the spleen, the microscope reveals two series of tissues—the well-known Malpighian body and the pulp " (p. 3).

Fig. 2.—The photograph shows three follicles, which appear as darker-coloured areas. Within each is an indication of the artery which traverses it. The remainder of the picture is formed of spleen-pulp.

(Oc. 2, Zeiss Apochrom. 4 mm.).

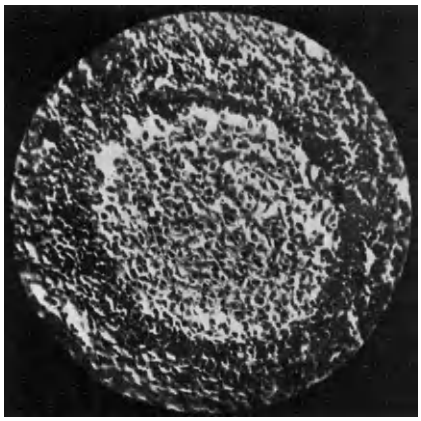
Face p. 2]



". . . the pulp tissue . . . consists of blood-channels enclosed by many varieties of formative cells " (p. 3).

Fig. 3.—The photograph shows two fragments of trabeculæ (vertical) and a number of elongated spaces marked out by the dark nuclei of endothelial cells. The intervening cells constitute the splenic pulp tissue.

(Oc. 4, Zeiss Apochrom. 4 mm.).



". . . the . . . lymphatic follicle . . . is always held to be the most characteristic feature of the lymph-node " (p. 3).

Fig. 4.—A SINGLE FOLLICLE showing the well-marked germ-centre cells, enclosed by a dark-coloured dense wall of lymphocyte-like cells.

(Oc. 4, Apochrom. 4 mm.).

The intervascular cells are nearly all free-floating, and vary much in size according as they belong to one or other generation of development. The only detail that is readily made out amongst these cells is that some contain hæmoglobin and others do not. In other words, the usual finding is one of red-cell formation with a varying amount of white-cell formation.

In the *spleen*, the microscope reveals two series of tissues—the well-known Malpighian body and the pulp. The former (*Fig.* 2) is a well-defined structure whose architecture is intimately connected with an arterial channel, while the pulp tissue (*Fig.* 3) is quite heterogeneous, and consists of blood-channels enclosed by many varieties of formative cells, whose nature is masked by the marked intermingling with cells of definitely connective-tissue type—certainly not specific blood-forming cells.

In the *lymphatic system* the structure is remarkably similar to that of the spleen. The chief difference lies in the "Malpighian body" being peripheral, while the pulp is central in situation. The Malpighian body here assumes the simple title of lymphatic follicle (*Fig.* 4), and is always held to be the most characteristic feature of the lymph-node, in spite of the fact that certain mesenteric lymph nodes never contain a follicle from the beginning to the end of life. The pulp tissue of the lymph-node is, one might say, absurdly like the pulp tissue of the spleen (*see p.* 156, *Fig.* 35), but the ordinary picture is modified by the conspicuous character of the lymphatic channels.

The *reserve factories* require no special description, since they consist of the ordinary connective tissues permeating the body, which only becomes similar in character to the pulp tissue of the named organs when such time arises that their activity is demanded. The so-called *perivascular lymphoma*, which is dealt with in Chapter VI., is understood to belong to the lymphatic system. The present series of factories belongs sometimes to the lymphatic and sometimes to the opposite series of cell-formation, the *myeloid* series. The latter term is convenient as implying the formation of cells characteristic of the bone-marrow, although it must always be remembered that cells belonging to the lymphatic series may, on occasion, be made there also.

To be more precise, we should describe three kinds of blood-cell factory: that concerned, (1) With the manufacture of red cells; (2) With the production of polymorphonuclear leucocytes; (3) With the production of mononuclear cells. But, even so, the outstanding feature of the histology of the tissue is that there is much similarity of structure between one and any other. This consideration leads to the problem of the real origin of the various types of circulating blood-cells. Are they all one, or have they different parents? It also necessitates the grouping of the subject matter according to the kind of blood-cell manufactured, and not according to the organs in which such processes occur. This is perhaps the most important feature in the problem at issue. The bone-marrow does not make only red cells and neutrophiles, the lymph-node does not make only lymphocytes, the spleen does not only destroy. Certain cells in the bone-marrow make red cells, and others make the myeloid series of cells, but sometimes the same series of cells makes lymphocytes instead. The pulp tissue of the lymph-node and of the spleen are usually concerned with the lymph follicles with which they are associated, but sometimes they make neutrophiles (the myeloic series), and at other times each of them makes large mononuclear leucocytes. Occasionally, the spleen makes red cells in large numbers.

Even though the site of formation of any of these cells may be variable, the final products (the "blood-mature" cells) are fairly easily classified. The well-known cell formula:—

Red cells	about 5,000,000 per c.mm.		
Hæmoglobin	95 to 110 per cent		
White cells	5 to 8, and not more than 10,000 per c.mm.		
Polymorphonuclear leucocytes	about 70 per cent		
Lymphocytes	,, 20	,,	
Large mononuclears	,, 8	,,	
Eosinophile leucocytes	,, 1	,,	or more
Mast cells	,, 1	,,	or less

is regarded as a list of the cell forms with their average normal numbers and proportions. As a rule, maximum and minimum limits are assigned for the leucocyte percentages. They have been omitted above for the sake of simplicity.

The study of blood films is misleading to this extent, that the cells are seen in an artificial condition. The cell forms are normally in motion, the granules within them are moving, the cell composition is changing, and the structural characters differ with the progress from youth to old age. Further, a cell-count only represents the state of the peripheral blood at the particular moment of collecting the material. The wide daily variation in the total white cell-count requires to be borne in mind. The fact of such variation being much exaggerated in certain diseases, as shown by the observations of Thomson,* Marlin,† and others, should render the practice of paying slavish devotion at the feet of " exact " total cell-counts a matter of history. A very low total white-count, or a very high one, may be of definite value, but it need not be correct " to the fourth figure." We suggest that the *preliminary* blood examination should lie in a study of *films*, the erythrocytometer being only called in later, and then, preferably, only after a hæmoglobin estimation (correct to a multiple of five) has been made. In surgical cases, however, a rapid white-count correct to the nearest thousand should be run through two to four times a day in difficult cases ; the red cell-count is a luxury in surgical work, but a necessity in chronic medical cases.

The exact nomenclature of the cell-forms varies considerably. Many writers call the large mononuclears " large lymphocytes." Others add the English term, " hyaline leucocyte," which is really only a form of lymphocyte.‡

For descriptive purposes it is, however, much more satisfactory to divide the blood-cells into primordial, red, lymphocytic, monocytic, neutrophilic and phlogocytic forms. The last named include any of those characteristic of non-suppurative inflammatory cell infiltration.

The primordial cell is understood to be the parent form of any of the other blood-cells, and it only appears in the blood stream under peculiar pathological circumstances. The word " primordial " conveniently expresses the simple idea that this cell is an ancestor several generations back in the line of development, and does not represent a morphological type, although some forms of primordial cell are actually synonymous with Pappenheim's lymphoidocyte. The term " monocyte," introduced by Pappenheim, is used in a

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* *B.M.J.*, 1911, p. 1586.

† *Journal of Clinical Research*, 1912, p. 43.

‡ To avoid repetitions and to facilitate reference, the meaning of any term used in hæmatology will be found stated in the glossary at the end of this book. Under each term is given a list of other words which have been employed to designate the same cell.

morphological sense. It is so convenient as to deserve universal adoption.

The life-history of each one of these main groups of cells will be traced out, noting the changes which occur from the time of their birth to that of their death, and the effects upon them which pathogenic or other influences produce. Our opening remarks indicate the importance of a study of the tissues in which each is formed,* both in regard to the ante-natal processes for each cell, and in regard to the mode in which the blood-cell formula reflects the morbid changes (anaplasias, metaplasias, hyperplasias, etc.) at the root of the so-called " diseases of the blood."

We shall thus find that each " blood-disease," at some stage in its course, is the outward evidence to us of a tragedy in the life-history of the particular portion of the hæmatopoietic system, and we shall dimly appreciate the fact that orderly blood formation demands constant single-hearted co-operation on the part of the other tissues of the body,† as well as co-operation with the brain, which should see that deleterious agents are not admitted by carelessness in diet and general hygiene. Withdraw such influences, and the formative blood-cells are stranded; they make desperate attempts to breed true and follow up definite harmoniously apportioned (methodised) sequences of differentiation; fail; and are irretrievably lost (because destroyed by the harmful agent) or merely maimed until such time as better conditions prevail. The individuals of the army which fight such incessant warfare under these conditions are at the same time inconstant as entities; they are ever changing, ever moving about and ever reproducing, not working together for individual purposes, but all subserving common necessities, while each still acts for himself where nutrition is concerned.

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* The various hæmatopoietic tissues which are concerned with the production of each type of blood-cell do not correspond to organs—tissue and organ are not equivalent or co-significative. The tissue which makes a lymphocyte, for instance, is not the whole of a lymphatic gland, nor is a lymphatic gland the only structure in the body which makes lymphocytes. This fact renders it logical to preface a description of any given order of blood-cells by an account of the corresponding formative tissue, and to correlate aberrations in the particular cell genealogy with metaplastic, hyperplastic, and allied changes in that tissue.

† Epigenetic stimuli.

CHAPTER I.

ON THE PRIMORDIAL BLOOD-CELL.

Section I.—THE PRIMORDIAL CELL: Where met with—Morphology—Comparative cytology—Chemical characters—The subsequent history and fate of the primordial cell: Phases in its life: Old age: Differentiative divisions: Signs of ontogenetic and phylogenetic development: Abnormal entry into the blood-stream—Differential diagnosis: Typical and atypical forms: The lymphoblastic macrolymphocyte: The leucoblast: The Rieder cell: The leucosarcoma cell—The death of the primordial cell: Degeneration forms: Changes in (*a*) nucleus, (*b*) cell-body: Irritation forms.

Section II.—Evidence pointing to the existence of a mother-cell for the adult blood-cells—The arguments in favour of (*a*) dualism, (*b*) unitarianism in hæmatology—Werzberg's and Ellermann's experiments.

Section III.—CYTOMETAPLASIAS OF THE LYMPHOIDOCYTE.

I.—THE PRIMORDIAL CELL.

WHERE met with—Morphology—Comparative cytology—Chemical characters—The subsequent history and fate of the primordial cell: Phases in its life: Old age: Differentiative divisions: Signs of ontogenetic and phylogenetic development: Abnormal entry into the blood-stream—Differential diagnosis: Typical and atypical forms: The lymphoblastic macrolymphocyte: The leucoblast: The Rieder cell: The leucosarcoma cell—The death of the primordial cell: Degeneration forms: Changes in (*a*) nucleus, (*b*) cell-body: Irritation forms.

FOR the purpose of simplicity, the parent cell of all blood-cells may be described as a "primordial cell." It is protean in function as well as in morphology, but nevertheless is amenable to definite description. The cell referred to as a "lymphoidocyte"* in hæmatological literature, may be considered representative of the primordial cell in general.

OCCURRENCE.—In all the hæmatopoietic tissues enumerated. Never in normal post-embryonic human blood, but in certain diseases it, or its immediate relatives, may circulate and, appearing in the blood-film, lead to the diagnosis of such diseases. Whether it can be identified in puncture fluids is not known; but, in the diseases referred to, these primordial cells are to be made out within different tissues.

1. **Morphology.**—(*See Plates I, IV, VI, VII,* and *Fig.* 5.)

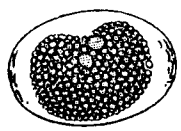

Fig. 5.
Diagram of structure of the lymphoidocyte.

Outer Form.—The absolute *size* is variable: sometimes large, sometimes small. The *shape* is round or ovoid (in cross-section), its *contour* rather ill-defined but regular.

Inner Structure of Cell Body.—Scanty, strongly basophile, homogeneous granoplasm, with feeble differentiation between spongioplasm* and paraplasm.* No granules.† There is no perinuclear zone (inconstant). A paranuclear attraction-sphere* is present (inconstant).

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* *See* GLOSSARY at the end of the volume.

† If azure and myeloic granules be present, the cell has probably passed the primordial stage.

Nucleus.—Relatively large; round, with ill-defined but regular contour. Structure—leptochromatic, vesicular, amblychromatic, not myelocytar (*see* GLOSSARY). Stains feebly with Giemsa. There is a fine, delicate, almost granular reticulum. There is little chromatin. The parachromatin is basophile.

Nucleolus.—One or more present; basophile.*

Vacuolar Structures in the Primordial Cell.—Cell-inclusions were described by Pappenheim[2]† as occurring in these cells when they appear in leukæmia. They are of the following forms: (1) Azurophile granulation; (2) Rods lying free in the cell-body; (3) Rounded or oval inclusions lying free in the cytoplasm; (4) Vacuoles with round central inclusions; (5) Vacuoles whose walls are lined or carpeted by azurophile precipitations; (6) Azurophile rods lying within vacuoles (*see Plate I, Nos.* 5, 6). Some of these structures were met with by Auer in 1906.[3] Various writers have discussed whether these are parasites or no. The consensus of opinion is that they are not, although the rod-like bodies are extremely similar to the blepharoplasts, the precursors of the flagella or motor apparatus of trypanosomes, especially as studied in avian hæmozoa.[4] Löwit suggested that these inclusions were the cause of leukæmia,[5] although Pappenheim's bodies were not like Löwit's.

Some of these bodies may be chromidial in origin; they are akin to the azure granules (*see p.* 143). (Hynek.[6])

The **Daughter-cell**, or **Micro-lymphoidocyte**, resembles the above in all respects, save that of size.

The other forms of primordial cell are described on *pp.* 60, 125, 189, 203, and 278.

2. **Comparative Cytology.**[7]—(*Plate I.*) The primordial cell is a normal inhabitant of the blood-stream in lower vertebrates, and is met with in the body fluids of invertebrates. It possesses well-marked characters, which are in accord with those given above. The most recent investigations on these cell-forms as met with in the animal series are by Werzberg,[7] from whose work we largely quote.

In the *fishes*, this class of cell is usually represented by a micro-lymphoidocyte, hardly larger than a lymphocyte, though more typical

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* This body is not an unalterable anatomical entity, any more than is the nucleus. Its structure is constantly varying with the phases of functional activity (Ferrata[1]).

† For references to Literature, see end of volume.

DESCRIPTION OF PLATE I.

1.—Wall of a small capillary in the pulp of a lymph-node, to show the adventitial cells (*adv.*), which partly fuse into a syncytial mass, and partly send out processes amongst the surrounding tissue cells. The capillary is lined by endothelial cells (*end.*) and contains a number of red blood cells (*r.c.*). One adventitial cell (*adv.'*) is free. The first generation (*L L*) is seen in the vicinity of the adventitial cells, and some grand-daughters (mesolymphocytes, *m.l.*) and microlymphocytes (*l*) are also noticed. *MWC* = Marchand wandering cell, a migrating adventitial cell.

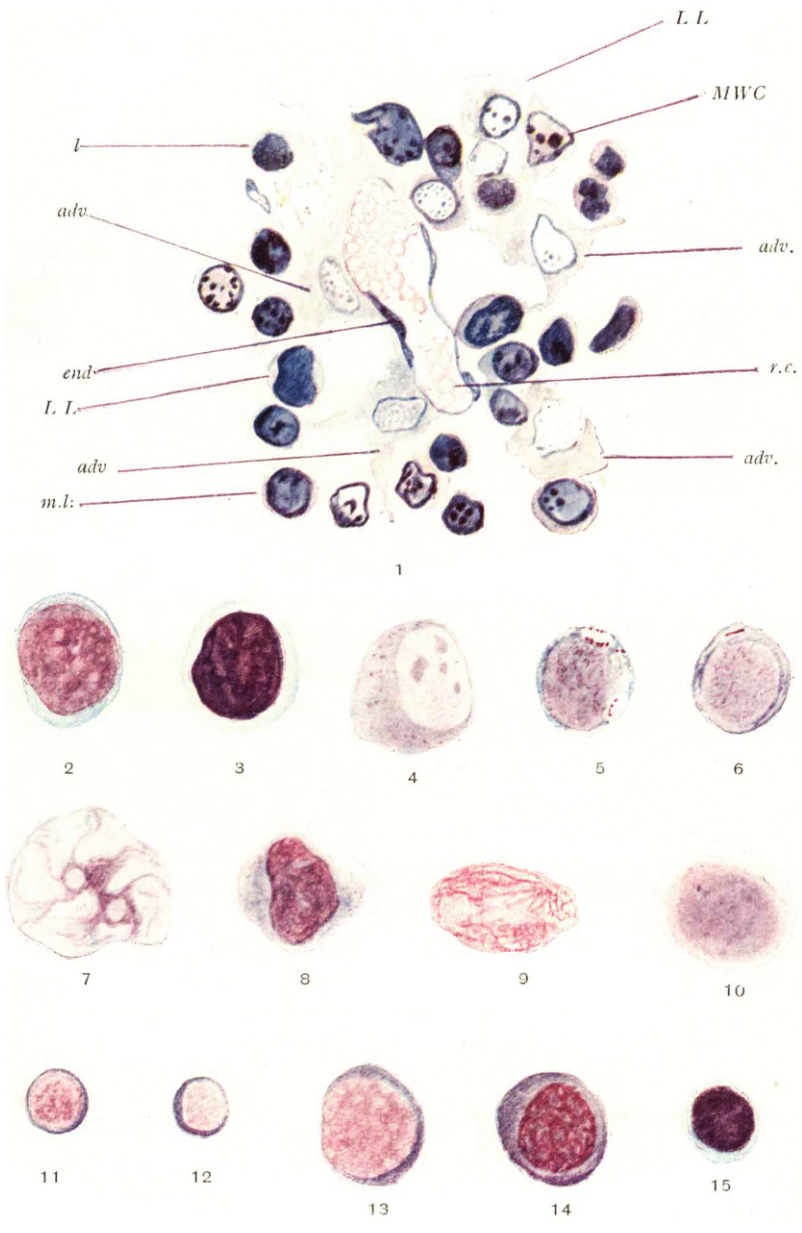
Contrast *adv.* with *Fig.* 5 in the text.

Drawn with the camera lucida, Zeiss oil-immersion, comp. oc. 12. (slightly schematic).

2.—A typical lymphoidocyte (drawn from a film preparation of bone-marrow 3.—Another form, showing commencing leucoblastic change in the nucleus. 4.—A senile form, with commencing degeneration of cytoplasm. 5, 6.—Lymphoidocytes containing vacuoles in which are azur-staining bodies. From Pappenheim's case of acute myeloblastic leukæmia. Fol. hæm. Vol. v. 7-10.—Different manifestations of degeneration and death in the lymphoidocyte. 11-15.—Lymphoidocytes in lower vertebrates: cod, sea-lamprey, frog, the lizard, gongylus, common fowl respectively. 11-14 from Werzberg, Fol. hæm. Vol. xi. 15.—From Kasarinoff, Fol. hæm., Vol. x. All stained with Pappenheim's panoptic stain.

PLATE I.

THE PRIMORDIAL BLOOD-CELL



forms are seen in tinca vulgaris, cobitis fossilis, and characteristically large cells are seen in anguilla fluviatilis, whose cell-body tends to increase in size and diminish in basophilia as the cell ages and differentiates. In this class of animals, the lymphoidocyte is present in much smaller number than is usual with the amphibia.

In the *amphibia*, typical large lymphocytes or myeloblasts are met with, whose cell body is broader and more pure blue* than in man. The nuclear network is very delicate. Transitional forms to large lympholeucocytes and small lymphocytes can be seen. The astrosphere is well seen in the salamander lymphoidocyte. Vacuoles are frequent in the cell body in siredon. Nucleoli are absent in siredon. These cells are numerous in the blood of the newt, triton, and the Mexican axolotl (siredon pisciformis) and in young frogs, but though present are rare in other amphibians.

In the *reptiles*, large lymphocytes occur in varying numbers in the circulating blood. They are large round basophile cells with an extremely fine azure granulation, a round central nucleus with delicate nuclear network and one nucleolus. In the lizard (lacerta viridis) and in gongylus ocellatus the nuclear structure is more myeloblastic. Nucleoli are absent in the tortoise-lymphoidocyte.

These cells are numerous only in algiroides nigropunctatus, the scincoid lizard, and are not found at all in ophiosaurus acanthodactylus.

Microlymphoidocytes with intensely basophile border occur in algiroides and in platydactylus mauritanicus (with azurophile granules).

Transitional forms to amphochromophile myeloblasts are seen in some of this group of animals, and apparently take the place of the missing polynuclear leucocytes; such cells have a dull violet granulation.

True myelocytes are not found in agama inermis.

In the chameleon, the lymphoidocyte has a relatively large cell body and presents a number of vacuoles, especially towards the periphery of the cell. A feebly oxyphile area may be found in the middle of the cell near the nucleus, which is the position in which the eosinophilic bodies of the descendant cells will appear. (Reptile blood-cells are largely eosinophilic.)

In the *birds*, lymphoidocytes or primordial cells are not present in the circulating blood except under abnormal (experimental) conditions. The size of the cell is typically large, its cytoplasm has a peculiar radial structure, while the nucleus stains feebly and shows a tendency to myelocytar markings. " Irritation " forms occur here with a strongly basophile peripheral zone.

3. **Chemical Characters.**—Observations upon the chemistry of the primordial cell, as an individual, depend on the careful study of preparations stained by different dye combinations. The differences in morphology are largely dependent on differences of chemical structure of the cell as a whole, and the variations in

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* Panoptic stain.

form which are observed during the course of the life of the cell are also dependent upon intra- and intermolecular changes, taking place within either nucleus, or cell-substance, or both. To a large extent, a description of the chemistry of this cell will be that of any other, but the subtle differences of morphology which obtain in the blood-cell series, to be set forth in detail, must surely mean equally subtle differences in the cytochemical arrangements, which may be read by him who understands. Of all the microchemical work which has been done in tissues, there is no one who has been so able an exponent of chemical details based on dye-chemical considerations as Pappenheim, and whatever there is to be said about the chemistry of blood-cells is owing to his expositions. It has long been known, of course, that the nuclear substance is composed of nucleic acid : but such a statement practically covers all that can be said in the way of correlation between histology and chemistry. The wealth of information about the chemistry of cells (biochemistry) is only applicable to a general concept of " protoplasm," using that term in the sense of any matter which bears the phenomenon of life ; in the sense of a collection of molecules into a giant molecule with a number of side chains of unknown composition (beyond the detecting of amino, hydroxyl, or carboxyl groups), whose stereochemical position and exact modes of interaction are not known. Not only is our knowledge of this point general in the above-indicated manner, but it is rendered more abstract still, when we reflect that space has to be found within the complex molecules in which to provide enzymes with a sphere of activity. The watery constituents, the salts, the ionic concentration of hydroxyl groups, and the surface tension phenomena produced by the colloidal substances, are all taken into account in the ordinary description of the chemical composition of cells in general. But it is not in this way only that the chemistry of cells is to be discussed in relation to blood-cells ; we wish to learn if chemico-structural differences correspond to differences in morphology. We have nuclear matter, in which are chromatin, parachromatin, chromosomes, etc. These portions react differently towards different stains, such as azure dyes or methyl-green and pyronin. On the one hand, we find that azure will stain a portion

of the substance red (prochromatin), while the remainder is basophile and stains with methyl-green (metachromatin). These two dyes have been combined by Pappenheim into a methyl-green-Giemsa-aurangeate,[8] and enable the demonstration that some nuclei contain more prochromatin (stain red), others more metachromatin (stain greener), while others contain as much of one variety of chromatin as of the other, and stain blue-violet. Again, using methyl-green and pyronin, it is found that both dyes will affect corresponding parts of the nucleus as long as it is in the resting stage, while chromosomes take up methyl-green alone (basichromatin); from this it is deduced that the chromosome is more nearly pure nucleic acid than is resting nuclear matter which contains nucleoproteid in considerable amount. The same is shown by Heidenhain's observations: (1) That the resting nucleus contains chiefly oxychromatin; (2) That the chromosomes in the intestinal epithelial cells of the salamander are the expression of regeneration of basichromatin in the nucleus.

The changes of staining reaction in the cell body, the initial basophilia (indicating the presence of organic acid) followed by oxyphilia as the cell grows older or differentiates (that is, oxyphilia increasing with each successive generation), should be translated in terms of microchemical reactions initiated from the nucleus. Metabolic changes in the nucleoproteid lead to the discharge into the cell body of basic substances, which accumulate in the first place in the astrospheric region; deposition of paraplasm in the interspongioplastic network accounts for the increasing oxyphilia of cell body which is seen as we pass from lymphoidocyte to finished polynuclear leucocyte. Prolongations of the abasichromatic nuclear network into filaments, which end in the cytoplasm, were observed by Knoll.[9] Changes in the nuclear chromatin, leading to rearrangement of molecules, account for the morphological changes in the nuclear network, which we should be careful not to lay too much stress on as permanencies. They are transient stages, and may represent part of a definite cycle of internuclear molecular changes which will return to the same phase at some unknown interval. In other words, to be less abstract, fine leptochromatic network aggregates into larger masses, either during the

life of the cell as an individual or during succeeding generations. These masses become increasingly aggregated as the nucleic acids of the cell increase towards the formation, for instance, of the typical myelocytar nucleus. Anaplasia, then, consists in the changes which lead to the breaking up of such aggregations back into the stage of fine leptochromatism—reversionary in one sense, progressive in the other. Just as a person standing outside a circular track in which a body revolves would regard that body as progressing as long as it is advancing towards him, coming nearer and nearer to his eye, and as regressing because, after passing the nearest point, it now steadily recedes farther and farther from him. The body itself, then, is only moving in a certain cycle, progressing in a sense, but always moving in the same direction. This idea is very well expressed in the phenomenon of leucocytosis to be discussed later—extreme leucocytosis, to speak paradoxically, is leucopenia. The reader is referred to later pages for the explanation of this paradox, which, like many others, is due to the errors of language, different names burdening one single idea because our minds fail to grasp the rock-bottom truth at the outset.

In discussing the chemistry of the cell we have always to divide up the substances into basophile and oxyphile, just because our only means of staining cells is by using basophile and oxyphile dyes. The basophile constituent of the nucleus is due to purin compounds or to nucleic acids; that of the cell body is due to lecithin compounds of protein with nucleohiston. Glycerophosphoric acid plus various fatty acids plus cholin, therefore, represent possible constituents of the basophile substance of the cytoplasm. Breakdown during metabolic activity would lead to the appearance of acidophile bodies in the paraplasm, or it might lead to the appearance of metachromatic bodies in the spongioplasm, starting with the assumption (borne out by oil-immersion histology) that the basophile constituent of cell-body is largely dependent on the spongioplasm. The appearance of mast-cell granules on the spongioplastic network and of eosinophile granules in the paraplasm, constitute examples of these different forms of activity, and, as we shall see later, they are evidences of functional state and not of hard-and-fast distinctions from certain other blood-cells.

From all these considerations, the view already expressed that cell substance is merely a giant living molecule is seen to be quite fallacious, and proves that biochemistry must be intimately associated with microchemistry if errors of popular conception are to be avoided.[10]

4. **Subsequent History and Fate of the Primordial Cell: Phases in the Life of the Primordial Cell.**—The primordial cell may exhibit purely nutritive or purely reproductive activity, like any other cell. When reproduction takes place the result may be two or more* similar cells, or the progeny is more or less differentiated. The latter result (less differentiated) is indicated by the term anaplastic, and the former (more differentiation) by the term metaplastic.

If we speak of nutrition and reproduction going on hand in hand, so as to introduce the idea that these two processes may go on at different rates, we refer to the effect on the *tissue* resulting from nutritive activity of one group of cells, and reproductive activity of another group of cells. The cells of the tissue may, in other words, be divided into two groups according as they present the one or the other variety of activity, classifying them regardless of their relative position in the tissue. In any such group of cells, too, sub-groups may be arranged according to the effect of the reproductive activity itself, whether with or without differentiation. Differentiation, however, may proceed at different rates in different cells. The net result—the degree of differentiation of the tissue—would depend on the relative proportions between individuals with slow rate of differentiation, individuals with rapid rate, and individuals either not differentiating at all or only presenting nutritive activity.

Old Age.—From the above remarks it is seen that a cell may *grow old* without further change; it may grow old and at the same time undergo changes leading to division without differentiation, or it may grow old and at the same time differentiate, so that its progeny are provided with new characters. Any of these variants

* Meristematic proliferation (merozoites), if a cluster of microlymphoidocytes, e.g., is produced.

may be normal (physiological) for the individual cell. On the other hand, an exactly parallel series of possibilities obtains, although in each case the change is characteristic of pathological cells. We have, therefore, to discuss, in any cell, whether the senile change is physiological or pathological, or whether (here) the differentiation is a reverse process—an exhibition of a "reversible reaction." Such possibilities are better illustrated by means of a diagram (*Fig.* 6). If the length of the ordinate is representative of differentiation

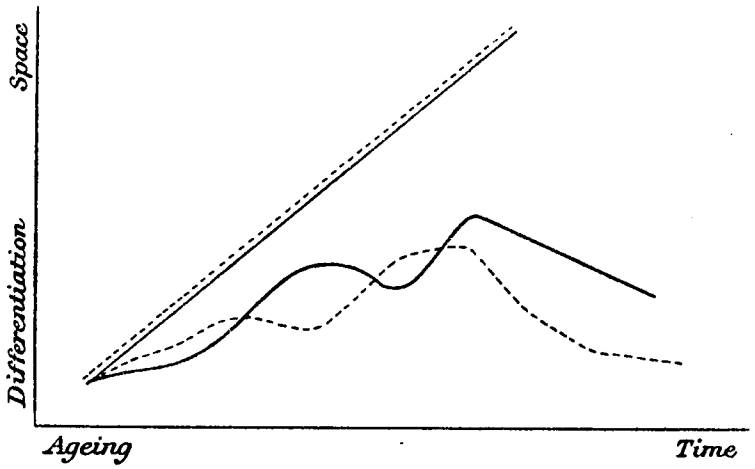

Fig. 6.—Diagram representing ontogeny and phylogeny in a cell series.

(changes in *spacial* relation), while the abscissa represents *time*, we can plot out a curve for the normal progression of cell substance (black line) and nucleus (dotted line). This curve, representing as it does the resultant between ontogeny and phylogeny, should be a straight line for cell-body as for nucleus, and the two lines should be parallel, or superimposed. A pathological change *of any kind* is at once indicated by *a deviation from the straight course*, and the two curves may be either parallel or not parallel. In each case we have a different pathological change. Let y represent differentiation of cell substance, and z that of nucleus, while t represents ontogeny, then

$$y = t \tan \alpha + b^* = z$$

* b = a constant.

in physiology, while the pathological changes in the development of the primordial cell are represented by

$$y = r \sin (qt + \epsilon^*), \text{ etc.}$$

A downward direction of the curve is representative of anaplasia. By this method of graphic representation it is evident that any given line of development presents every conceivable intermediate stage between the birth of a series of cells and the death of the last member of the race. A similar series of stages is met with in the study of any individual cell during its own life history. As a matter of fact, some portions of the curve represent changes in an individual cell while the remaining portions represent its progeny. In other words, following up the line, it represents first the newborn primordial cell, then the same cell during an apparent latent period (as regards differentiation), then the dividing cell. The curve still goes on uninterruptedly, because the daughters are merely stages of progression of the whole family. Although the differentiation of these daughter cells has involved the loss of individuality of the parent, there is yet a continuous progress along the great highway, which is consummated in the appearance of the transportable blood-mature cell proper.

Any of these intermediate stages can be seen and recognized in the tissue or in the film preparation. Many of the stages have been named irrespective of their relative positions in the line of development. Whatever be the objections to the nomenclature, they nevertheless form the only means of intercommunication of ideas on this complex subject. That such intermediate stages can occur is obvious from the above method of presentation, so that no more need be said to answer those who will not accept such minutiæ as are expressed by the extensive nomenclature devised in recent years. The fact that basophile paraplasm is becoming converted into oxyplasm during the progress of an individual cell is fortunate, because the play of colours and structure enables the detection of subtle transition forms in preparations stained with suitable acid and basic dye combinations.

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* ϵ = a variable.

A word of caution is necessary as regards the application of these general statements to clinical diagnosis : (1) Every transition form is not available for presentation, because some of the stages are passed over too quickly to avoid escaping recognition ; (2) Certain stages in the life history of different cell types may be very similar to each other, so that the personal factor may be required to differentiate them ; (3) Transition forms are likely to be met with which cannot be named, because nomenclature itself is incomplete, and because the characters are too undetermined or too transient to render definition of cell-form possible.[11]

SIGNS OF ONTOGENETIC DEVELOPMENT. SIGNS OF OLD AGE IN A CELL.—As the cell becomes older, (1) The cell body becomes relatively larger ; (2) The nucleus becomes spherical and relatively smaller ; (3) The nucleus becomes indented and polymorphous.*

A cell with a round single nucleus is younger than a cell with a polymorphous nucleus.

The explanation of 1 is that the spongioplasm becomes more and more rarefied because of intercalation of feebly-staining paraplasm in increasing amount.[13] The nuclear changes consist in a conversion of the weakly basophile parachromatin into oxychromatin (oxykaryoplastin). In proportion as these (always gradual) changes occur at different rates, so much the more are transition forms likely to appear.

The three dicta quoted above constitute Heidenhain's three *laws of cytology* whose truth is agreed upon by most authorities.

SIGNS OF PHYLOGENETIC DEVELOPMENT. SIGNS OF DIFFERENTIATION OF A CELL.—The structure of the nucleus is the main signpost indicating degree of differentiation. The evidence in favour of the view that the diagnosis of the nature of a cell must rest largely on the nuclear structure, is exactly the counterpart of the evidence which tells us that the granules are not specific. (*See p.* 222.)

This statement brings up the controversy about the diagnosis of cell-forms by Ehrlich's method. The use of Ehrlich's triacid stain and the researches upon cell granules in the circulating cells have been the basis of all modern research upon blood-cells.

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* This law does not hold good in cells whose nucleus has a wheel structure. Erythroblast nuclei undergo pycnosis with age.[12]

The defective reaction of the triacid stain on nucleus is the reason why many of the lymphoid cell forms have been lumped together, even though they have no real connection. The effective action of the named dye on the cell-plasm has therefore led to the attachment of undue importance to the cell-body as opposed to the nucleus.

Schridde's phrase, that the nucleus is the heraldic sign of the cell, has brought out the alternative to Ehrlich's mode of classification very clearly, and is the basis of the classification of cells adopted in this book. We owe the full development of this side of the subject to Pappenheim.

It will be found helpful to compare the successive stages of differentiation of the primordial cell with the various steps passed through by the nucleus of any cell during mitotic division. Just as the nuclear network is extremely dense during the resting period, so the linin is tightly arranged in the lymphoidocyte (compare diagrammatic representation of *Fig.* 5). When karyokinesis begins, the linin loosens out until a spirem with distinct convoluted threads becomes visible ; similarly, the chromatin is arranged into clumps during the leucoblast stage (granulocyte line, *see Chapter V*). As the spirem threads become thicker and shorter, an appearance is produced comparable with that seen in the myelocyte nucleus. The final cleavage of the chromosomes, the spindle-formation, and the separation of the former into two groups which move to the ends of the cell, occur rapidly, and terminate with the production of two daughter cells—just as the myelocyte rapidly forms two daughter myelocytes. The analogy ceases at this stage, because there is no counterpart in phylogenesis of any of the blood-cells with the reappearance of the close-meshed nuclear network of the resting cell.

The description of all the nuclear changes and other details of phylogenetic development which the primordial cell may present during the course of its differentiation along the various lines, is given in each successive chapter, and need not be referred to at this stage. There is, however, one form of change deserving of notice, namely *mast-cell transformation* (*Fig.* 7). Like any other cell, the lymphoidocyte may develop mast-cell granules when suitable conditions arise. The significance of these, and the mechanism of their production, are fully dealt with in Chapter VI.

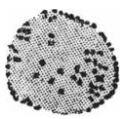

Fig. 7.—MAST-CELL LYMPHOIDOCYTE (Diagrammatic).

A change into *plasma cells* is met with in some of the perivascular lymphoidocytes, and may be here mentioned for the sake of completeness.

Duration of life.—The primordial cell usually passes its whole life within the confines of the hæmatopoietic tissues. In a very small proportion of human beings* it makes its way into the blood-stream, and gives rise to the clinical picture of (generally acute) lymphæmia. It is only in this position that its duration of life could be ascertained. It is observed to multiply even while circulating, and so give rise to more daughter cells than the simultaneous pathological phenomena in the bone-marrow supply.

5. Differential Diagnosis of the Primordial Cell or Lymphoidocyte.— Inasmuch as the lymphoidocyte is a "lymphoid" cell, its detection will depend on similar rules to those applied to the diagnosis of either lymphocytes or monocytes (which see). It will suffice at this stage to point out that the interphyletically connected cells are very similar in morphology, and that careful observation of Giemsa preparations with a high ocular and oil-immersion lens are necessary for exact study. The cells which come under consideration at this point are :—

Variants of the mother cell :—
- The microlymphoidocyte and its senile form
- The senile lymphoidocyte
- Dwarf lymphoidocytes
- The lymphoblastic macrolymphocyte (*see* table opposite)
- The leucocytoid macrolymphocytes of lymphæmic blood
- The myelæmic microlymphoidocytes.

Atypical mother cells :—
- The leucosarcoma cell of Sternberg
- The Rieder cell.

The leucoblast and its leucocytoid form.

Lymphoid hæmoblast (*see p.* 60).

The lymphæmic microlymphocytes (*see p.* 132).

The leucocytoid lymphocytes of normal blood (*see p.* 135).

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* It will be remembered that the primordial cell normally enters the blood-stream in many of the cold-blooded animals.

	Myeloic Mother Cell. (Myeloic) lymphoidocyte series; lymphoidocytar myelolymphocytes	Lymphatic Mother Cell. Lymphoblastic macrolymphocyte series
Spongioplasm ..	Dark, markedly reticular, shaggy contour	Soft, delicate, most abundant at periphery; clean-cut edge
Paraplasm ..	Feebly oxyphile, especially in the astrosphere region	Chromophobic or diffusely achromatic
Azur gran. ..	Fine, numerous, smaller, clear-cut, dusky red	Few, larger, clear-cut, bright red, more or less round
Nuclear shape ..	more or less round; may be paranuclear dimple	More or less round
Chromatin ..	Lepto-chromatic	Pachychromatic, coarse trabecular network
Parachromatin	Clean cut; distinctly basophile	Cloudy, flaky, feebly oxyphile
Astrosphere ..	Present	Absent
Perinuclear zone	Absent	Present
Nucleoli ..	Single (oligonucleolar) ..	Ditto
	Clearly defined	Ill-defined
	Feebly basophile	Slightly oxyphile

	Lymphoidocyte	Half-way	Leucoblast
Cell body ..	Scanty ..	Scanty ..	More abundant, but varies
Spongioplasm ..	Basophile contour	Basophile, commencing greyish-red	Reticulated; basophile or *grey red* (commencing oxyplasma), but darker at periphery: amphophile contour
Circumnuclear zone	o ..	Commencing	+
Azur gran. ..	Occasional	Occasional	Often myeloic
Nucleus ..	Very fine net-work, relatively large	Half fine.. Half coarse	Coarse structure Relatively smaller
Chromatin ..	— ..	— ..	Not yet completely marked off
Parachromatin	Basophile	— ..	—
Nucleolus ..	2–4 ..	One left ..	o
Senile form ..	Rieder ..	— ..	Leucocytoid leucoblast.

The RIEDER CELL has the following characters:—

Size—variable. *Shape*—rounded. The *cell-body* is sometimes relatively large, sometimes narrow; it is rather strongly basophile, and exhibits a well-marked spongioplastic structure whose meshes are small. Vacuoles may be present. The *perinuclear halo* is frequently distinct.

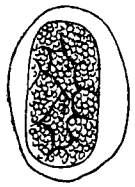

Fig. 8.
LEUCOBLAST
(Diagrammatic).*

Nucleus shows several indentations (lobate); occasionally only bi-lobed, but the division is sharp and clear-cut. Its structure is definitely leptochromatic (lymphoidocytar). A *nucleolus* is present.

Mitosis.—Division is frequently seen in these cells and is amitotic.

This type of cell varies in details according to the form from which it is derived, as other cells than lymphoidocytes may take on a Rieder form under pathological stimuli.

Fig.
RIEDER CELL
(Diagrammatic.)*

This cell is also called a Rieder leucosarcoma cell, and is really identical with the Sternberg leucosarcoma cell. It is common in leucosarcomatosis, chlorosarcomatosis, and in simple hyperplastic leukæmia. It is, however, not truly neoplastic, and is not exclusively met with in leukæmia and pseudoleukæmia (Zoja[14]).

a *b*

Fig. 10.—LEUCOSARCOMA CELL.* (*a*) Resting; (*b*) In a condition of amitosis. In (*b*) the shading indicates the position of an astrosphere (left white). Compare the nuclear markings with those in *Fig.* 5.

The LEUCOSARCOMA CELL is an atypical lymphocyte, which has arisen from a prematurely senile change of the primordial cell. It is stated that such cells develop in the lymph nodes, in the stromatic, and not necessarily in the lymphadenoid tissue by changes of anaplastic nature in the indifferent perivascular or mesenchymal cells. Such an interpretation is contradictory to the first statement that

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* The drawings are purposely diagrammatic in order to demonstrate how the main nuclear and cytoplasmic characters can be represented by a pen for the purpose of recording "bedside" microscopic findings. Compare *Fig.* 8 with *Plate I*, 3.

it is an abnormal senility of the parent cell. Since the appearance of such leucosarcoma cells is generally associated with the formation of tumour-like masses, it might be said to be a sarcoid metaplasia of the lymphatic or myeloid tissues.[15] In other words, such cells are either lymphatic or myeloic in nature.

This cell form is met with in : (1) Acute and chronic lymphatic leukæmia ; (2) Aleukæmic (sarcoid) lymphadenomatoses ; (3) Chronic and acute myeloses ; (4) Atypical (because leucosarcoma cells are preponderant) large-celled hyperplastic lymphatic or myeloic leukæmias. It is either a normal senile form of the lymphadenoid macrolymphocyte (2) or of the myelæmic lymphoidocyte (3), or an atypical cell identical with the Rieder cell. On the other hand it must not be confused with the ordinary lymphocyte of normal blood, with the lymphoblastic macrolymphocytes, nor with the large mononuclear cell of normal blood. The characters of the cell are identical with those named for the Rieder cell ; if there be any difference at all it lies in the functional ability to proliferate indefinitely.

The senile and leucocytoid forms referred to in the above list differ from the type cell only in relative preponderance of the cell-body over the nucleus.

6. **The Death of the Primordial Cell.**—While there are no data which can serve to fix the duration of the life of a lymphoidocyte, we find examples in the leukæmias which go to show that certain deleterious changes may occur, leading to the appearance in the blood of degeneration and irritation forms of the mother cell. There is no reason why one cell should present other varieties of degeneration-pictures than another, so that we should expect to find, and therefore seek for, all such phenomena as are described later under the heading " Fate of the Myelocyte " (*p.* 207), " Death of the Polynuclear Leucocyte " (*p.* 228). The following changes have been observed by the writer :—

Changes in the Nucleus.—Breaking up of the chromatin with vacuolation of the inter-chromatin substance, so as to lead to the appearance of radial floral figures, with the central or slightly excentric nucleolus left intact ; the nuclear membrane becomes more distinct, the cell-body pale (*Plate I, Nos.* 7-10).

Changes in the Cell-body.—The principal changes here consist in the formation of vacuoles of small size, lying in single file round a portion of the circumference of the nucleus. They may be of the nature of fat drops.

The formation of vacuoles has been described, in which the solitary azure granules of various forms and sizes occur. The granule or comma-shaped body is frequently excentric, and seems to be peculiar to the primordial cell (myeloblast) as it appears within the blood-stream in cases of acute leukæmia. Such bodies, while simulating protozoa, are not to be regarded as such at present, but rather as secreted products.[16 17 18 19]

Plasmolysis may occur—the separation of small buds of cell-body[20] (*Plate I, No.* 7), which may presumably become ultimately cut off from the cell. These have been thought to appear in the blood-stream as platelets. Another possible interpretation is that they are not degenerative, but evidence of amœboid movement.

Undue friability of the cell substance is a characteristic manifestation of *sub finem vitæ*.

Cytolytic forms like the Klein-Gumprecht shadows are also met with; the nucleoli are still visible, but otherwise no details of structure are discernible.

The *irritation forms* are chiefly characterized by extreme basophilia of the cell-body, increasing towards the peripheral portions. Small vacuoles also occur here and there in the bulky cell-body towards the nucleus, as if the paraplasm had been withdrawn from the periphery to appear in correspondingly conspicuous amount towards the nucleus. The process is then one of pathological sclerosis of the cytoplasm and atrophy of the functionating paraplasm.[22] Azur granules are never present. The nuclear structure differs from that of the lymphoidocyte in being distinct, well-defined, and tending to radial marking.

II.—THE PRIMORDIAL CELL (*continued*).

EVIDENCE pointing to the existence of a mother-cell for the adult blood-cells—The arguments in favour of (*a*) dualism, (*b*) unitarianism in hæmatology—Werzberg's and Ellermann's experiments.

THE question whether there are different parents for the different forms of cell, or whether one primitive cell will give rise to various forms, is best answered by a consideration of the process of cell-proliferation observed in the testis, by a study of the blood of the lower animals, and by a study of the process of blood-cell formation observed in the embryo.

1. *Cell-proliferation in the Testis.*—It will be remembered that the seminiferous tubules of the testis are lined by several layers of cells whose appearance varies according to the stage of development of the spermatozoa. It is not till puberty that morphological differences appear in the cellular strata, the components of the tubule-wall lying apparently inactive during all the preceding years. From puberty onwards, the lining cells of the tubules show differentiation into three layers, as shown in the accompanying *Fig.* 11 : (1) An outer layer, nearest the so-called basement membrane,* is comprised of cuboidal cells which vary slightly in size, the largest being called *spermatogonia*; (2) A middle

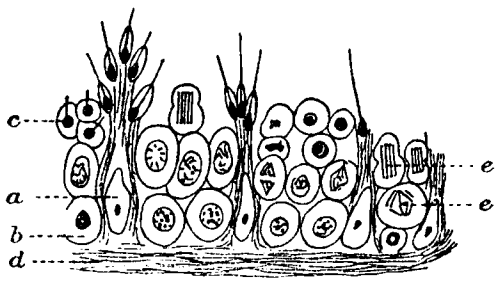

Fig. 11.—SPERMATOGENESIS.

(*a*) Sertoli Cell; (*b*) Spermatogonia; (*c*) Spermatid; (*d*) Basement Membrane; (*e*) Dividing Spermatocytes. (*Founded on Sobotta's figure, Quain, Vol. II., Pt. i.* 1912.)

* The usual definition of a basement membrane leaves a very unsatisfactory impression as to its purpose and significance. It will be borne in mind that in the cœlenterates, for instance (sea-anemone, corals, medusæ), the basement membrane constitutes a *syncytium*—a film of living substance of viscid consistence—from which the epithelial cells take their origin. In other words, this structure is a layer of undifferentiated cytoplasm giving rise to epithelial cells on the "air" or lumen side only—that away from the connective tissues. The familiar duct cells and secretory cells of the various glands are such epithelial cells. If

layer of large spherical cells—*the spermatocytes*: in active tubules these frequently show different stages of mitosis; (3) A thick inner layer of small round cells with resting nuclei—the *spermatids*; these are the immediate predecessors of the spermatozoa.

A very remarkable series of phenomena comes to notice when the development of the spermatid into the spermatozoon takes place. The spermatid contains only half the number of chromosomes present in the parent spermatocyte (homotypical mitosis), and the chromatin now becomes collected towards the head of the future spermatozoon. Adjacent spermatozoa collect together into bundles, the heads become directed towards the basement membrane, and are found to lie embedded within the columnar cells of the seminiferous tubule known as Sertoli cells (*Fig.* 11). It is the Sertoli cell that appears to play an essential part in the moulding of the spermatid into the future spermatozoon, since the cytoplasm of the one is found to blend with that of the other.

The essential point of interest in these phenomena lies in the fact that the cells nearest to the basement membrane of the immature tubule constitute the primordial cells for the spermatozoa, and become modified (by intramolecular change) to form spermatogonia only after a certain number of years of life. Previous to the puberty period their life history appears to be made up of nothing more than a maintenance of nutritional equilibrium. After the establishment of this epoch, an excess of energy becomes manifest in these cells (varying perhaps from week to week, but always present), resulting in the conversion of a certain number into spermatogonia, which, dividing into two, lose their identity, because each half is pushed on to the next layer by the new cells formed behind. The latter are arising anew by differentiation from the indifferent syncytial layer next to, and probably part of, the basement membrane.

Blood-cell formation is similar in some ways to the early stages of spermatogenesis. The adventitial cells of the bone-marrow

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the basement membrane gives rise to epithelial cells on *both sides*, but especially on that side which is directed towards the connective tissue, we should have the appearances seen in epithelial carcinoma. The basement membrane of the capillaries is also a material of the profoundest significance. Here, too, it may form a continuous living thing permeating the whole body, not always complete, but readily closing up defects by means of its semi-solid or viscid nature. The living material is rapidly destroyed after death, which accounts for its imperfect preservation in paraffin-cut material.

capillaries may be compared with the syncytial layer of the testicular tubule; the larger indifferent cells immediately adjacent to the basement membrane correspond to cells which are spoken of in hæmatology as lymphoidocytes, while the smaller indifferent cells would be comparable with blood-cells further back in the line of development—conveniently distinguished as primordial cells, although there may be so little morphological difference between them, that we have believed it justifiable to describe them as synonymous in the preceding section. The lymphoidocyte is therefore to a certain extent analogous to the spermatogonium, while the primordial or mother cell is better compared either with the (unnamed)* indifferent cell of the testis wall, or with the syncytium enclosing the whole. Under the last-named analogy, the primordial blood-cell would really be identical with the adventitial connective-tissue cell.

Now it is evident that the pre-spermatogonium of the adult cannot be the same individual that was present in the embryo. This may be regarded as an axiom, and it creates no difficulty, because cell-forms are well known to continue reproducing themselves for many generations without apparently altering their properties, just as the passions of man have been preserved unaltered through thousands of years. In hæmatology, however, there has been very much futile discussion as to whether a parent cell-form present in the embryo can persist throughout life or not. From the foregoing remarks it will be seen that there is no reason why a cell-form should not do so, provided we do not imagine that the personal identity of the cell remains. The functional, but not the corporeal identity of the primordial blood-cell, as of the pre-spermatogonic cell, persists from birth to death.

There are two striking differences between hæmo- and spermogenesis. In the first place, the spermatogonia always produce one kind of product only, while the hæmogonia must be capable (on the unitarian view) of making at least two types of cells whose functional differences are very marked, although their morphological properties are fairly similar. The only analogy between the

* Say pre-spermatogonium.

two, from the pathological side, would lie in the fact that just as the spermatogonia sometimes develop the power of unlimited non-differentiating proliferation, and produce a malignant tumour (the spermacytoma), so the hæmogonia sometimes develop powers of unlimited non-differentiating proliferation, and give rise either to the disease called leukæmia, or to the tumours variously named myeloma, chloroma, myeloblastoma, lymphoblastoma. In the second place, the spermatozoon is not the unadulterated product of division of the spermatocyte. The Sertoli cell has much to say in the matter, and we seek in vain for similarly functioning cells in the bone-marrow or lymphoid follicle.

2. The evidence afforded by *comparative anatomy* is in favour of the existence of a primordial blood-cell, because a lymphoid cell is preponderant in the blood of fishes, amphibia, and many birds. Indeed, in some fishes it is the only type of cell (Pappenheim). Limulus,* too has only one kind of blood-cell, which is non-amœbic, and has its granules at the periphery.[24] The caterpillar apparently has only one kind of cell, which is of mother-cell type.[25] A similar cell is the exclusive cell in the bone-marrow of marsupials. It is the normal inhabitant of the circulating blood in lower animals.

In spite of these accepted facts, Sternberg[26] does not consider it safe to generalize from lower animals to man, and to assume that there is therefore one common ancestor to all blood-cells in human blood.

3. *Embryology* shows us that this cell is the sole occupant of fœtal marrow and lymph-nodes, and is prevalent in the blood till the sixth month ;[27] that it is the first cell to appear in the bone-marrow, thymus, and lymph-node parenchyma.

Naegeli, however, disputes that lymphocytes appear before leucocytes,†[28] and Engel and Grüneberg[27] state that the red cells appear before the white cells, and do not even come from the vessel walls, but from the mesenchymal cells lying centrally within the solid primitive cell-strands.

The arguments *against* the idea of a primordial cell are: (1) That fully differentiated cells occur elsewhere, without any recognizable primordial cell being conditional. (2) The so-called

* The king crab. † Browning made this statement.[29]

mother-cell is a pathological cell entirely. [This is met by comparative hæmatology, and is also disproved by Zoja.[14]] (3) The arguments in favour of dualism, to be detailed presently.

Granted that there is a primordial cell for the blood-cell series, it is of importance to know whether that cell gives rise to both red and white cells or not. It is usually considered that the erythrocyte is derived from a different parent from the so-called white cells, and the discussion about the relation between the parent and daughter-cells has centered in the question as to the common origin or not of the neutrophile leucocyte, the lymphocyte, and the large mononuclear cells. Those who consider that all cells come from one, are called unitarians in hæmatology; while those who consider that the lymphocyte and the granular leucocyte come from different parents, are called dualists. The latter believe that there are two orders of cells, the lymphoblast and the myeloblast, which are not interchangeable at any time, and consider it as settled that the red cell comes from a totally different parent.

The literature on the subject is very extensive, but need hardly be gone into at length, because neither view is entirely satisfactory. The supposed contrasts between the lympho- and myeloblast, which form the mainstay of the dualist argument, are presented below in some detail, a tabular form being convenient for the purpose.*

The dualists deny that the primordial cell persists as such throughout life, but Maximow, Dantschakoff, and Neumann consider that it does.[30 31 32] It is supposed to *renew itself* from the fixed cells of the mesenchymal tissue. As we shall see later, this process can be observed in almost any surgical pathological tissue.

A third view, that the parent or primordial cell may differentiate along as many different lines as there are main orders of cells,

* In a sense, the dualist is also unitarian, because he presupposes that one given cell *does* give rise to lymphoblasts on the one hand, and to myeloblasts on the other. The difference between the two theories lies in the dualist believing that the primitive cell is only to be found in the embryo.

The unitarian, on his side, is dualist in a certain sense, inasmuch as he admits two separate lines of development for the lymphocyte and leucocyte series, after a certain stage has been reached. The strict unitarian holds that there can be no interchange between them after this stage. The transitional or modified monophyletist view, on the other hand, admits all kinds of interconnections between the lymphatic and myeloic series.

In presenting the arguments *pro* and *con*, we make no distinction between the two variants of unitarianism—because the subject is complicated enough without introducing the further subtleties of reasoning in the last-named direction. As stated below, the full argument for the modified unitarianism is the theme of this volume.

and that interchanges can and do occur between any one daughter cell and another, is more satisfactory in many ways. The lymphocyte, for instance, may revert and branch out on the other line—that of the neutrophile leucocyte—by means of a cytometaplastic process, during which the original cell acquires characters which lead to its being labelled a micromyeloblast.

This intermediate view is specially advocated by Pappenheim, and deserves wide recognition. Many of the arguments in its favour are covered by those given below in favour of unitarianism. The additional evidence is afforded during the progress of this book, inasmuch as the subject matter is arranged with this view-point foremost in the mind. The ease with which certain obscure chapters in "blood-disease" pathology can be rendered clear by this "transitional conditional monophyletism" is finally brought out in the concluding chapter.

At the present stage, therefore, we present briefly the evidence in favour of each of the two first-named prominent modern schools of thought.

Expressed more graphically, these views are:—

Dualism:—
Fixed embryonic connective-tissue cell
- Lymph vessel endothelium → Lymphoblast or macrolymphocyte → lymphocyte
- Blood-vessel endothelium
  - lympherythroblast → erythroblast → erythrocyte
  - myeloblast → myelocyte → leucocyte

Unitarianism:—
Lymphocyte → macrolymphocyte
- lympherythroblast → erythroblast → red cell
- myeloblast → monocyte → myelocyte → leucocyte

Pappenheim:—
Indifferent blood-cell → lymphoidocyte
- red-cell series
- leucocyte series
- lymphocyte series
- monocyte series

and potential interconnections.

As will be discussed later, it may be nothing more than a question of environment whether these interconnections take place or not.

The Arguments in favour of Dualism.*—Leaving out of count the problem of erythrogenesis (the development of the red cell),

* The chief dualists are: Blumenthal, Ehrlich, Helly, Lehndorff, Morawitz, Naegeli, Pincus, Schridde, Sternberg, K. Ziegler.

we find that the white cells belong to two main classes, those which appear non-granular with Ehrlich's triple stain, and those which are granular. The former are classed as lymphatic and the latter as myeloic cells. If it can be shown that there is absolute antithesis between these two groups of cells, then the assumption is that they do not come from a common ancestor.

The supposed differential characters between the myeloid and lymphatic cells are conveniently set forth as follows :—

	MYELOID	LYMPHATIC
(*a*). *Relation to vascular channels*	Only to blood-vessels, viz., in embryonic liver the myeloid tissue is perivascular. Pathological myeloid tissue in the adult arising in lymphatic tissue is still perivascular	Only to lymphatics
(*b*). *Structure of the tissue*	Disorderly (e.g., no follicles) ; cells scattered irregularly among other elements	Orderly (follicles)
(*c*). *Association with red-cell formation*	Frequent..	Never
(*d*). *Chemical features*	Contain autolytic and peptic ferments*	Do not
	Guaiac test + †	Guaiac test o
(*e*). *Biological characters*‡	Amœboid movement ..	Only slight
	Marked phagocytosis ..	No
	Chemotaxis takes place even in lymphatic leukæmia ..	No
(*f*). *Embryology*	(i). Alone present in liver ; pulp of spleen comes first	Alone present in thymus, M-bodies of spleen come last.
	(ii) Usually associated with erythropoiesis in embryo ..	Never
	(iii) Appears first	Appears last (Naegeli)[28]

* The proof of this is that in croupous pneumonia (polynuclear exudate) the tissue liquefies ; in caseous pneumonia (lymphocytes) the tissue undergoes necrosis.

† Proof—test absent (no oxydase) in lymphatic leukæmia or in a chronic lymphatic exudate. Bone marrow gives the test, but lymph glands, thymus, etc., always fail to give it. The objection to all this lies in the fact that the test is being applied to mature cells in each case, whereas the primordial cell is immature.

‡ Such functional differences are emphasized by Bergel.[33]

	Lymphoblast	Myeloblast
(*g*). *Morphological features*—		
Contour of cell	Ill defined	Well marked
Cell body (*a*)	Relatively more abundant ..	Relatively less abundant
(*b*)	Less basophile	More basophile (bright red with methyl-green pyronin)
(*c*)	No reticular structure ..	Finely reticular structure
Granulation :—		
(i) Altmann Schridde	+	o (Schridde) + (Butterfield, Heinecke, Meyer, St. Klein) ;[31] occasional : Wallgren, Maximow.
(ii) Azur ..	+	o + (Grawitz, St. Klein)
(iii) Specific	o	+
Oxydase :—	Occasional (St. Klein) ..	+ (but only in the myeloblast of myeloblast leukæmia)[32]
Nucleus :—		
Membrane ..	Dense	Delicate
Chromatin network	Dense and coarse	Delicate and fine *
Mitosis ..	Constant	Occasional
Nucleolus :—		
Number ..	1–2	2–4
With methyl-green ⅓ pyronin	Distinct, deep red	Indistinct, pale red

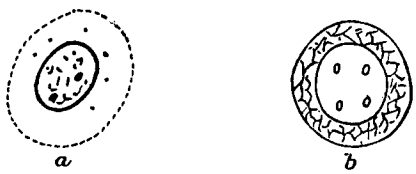

Fig. 12.—Diagram to show the contrast between (*a*) lymphoblast and (*b*) myeloblast, according to the dualist doctrine.

* Not very clearly demonstrated in Schridde's plate.[35]

(*h*). *Pathological evidence* :—

Infectious fevers cause hyperfunction of myeloid tissue first; of lymphatic system later.

Pernicious anæmia affects cytogenesis in the bone marrow but not in the lymphatic tissues.

Tuberculosis acts in the reverse way.

True lymphatic tissue never turns myeloid, but is replaced by it.

In myeloid metaplasia the follicles never show active change; they are merely compressed, and atrophy from the overgrowth of the pulp. In other words, the *myeloid and lymphatic tissues are* antagonistic. Lymphatic tissue does not turn myeloid, but is displaced by the latter.

The leukæmias are distinct (but see below).

(*i*). The dualists state that all transitions can be seen between the myeloblasts and the neutrophiles, while there are no transitions between myeloblasts and lymphocytes.

(*j*). Effect of short-circuiting the thoracic duct: there is lymphopenia. But this is due to the operation, thrombosis, and consequent interference with the lymph-flow occurring in the area. The subsequent lymphocytosis is due to the lymphocytes getting in *via* the lymph nodes direct.

(*k*). The organs used to demonstrate unitarianism were themselves pathological in character.

(*l*). Comparative cytology is misleading; it is not logical to generalize from animals to man (Sternberg).[26]

The Arguments in favour of Unitarianism* :—

(*a*). That there is no real distinction between the myeloblast and the lymphoblast; even the dualists admit that myeloblasts and lymphoblasts never occur together.†

(*b*). That in selacia‡ there is a protometrocyte which gives rise to cells with amblychromatic nuclei at one time and trachychromatic nuclei at another, and still is devoid of lipoid material in its cell body.[36]

(*c*). Maximow's observation that in amphibia and selacia there

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* The chief unitarians are—(1) *Extreme*: Arnold, Grawitz (late), Schleip. (2) *Moderate*: Dominici, Löwit, Maximow, Neumann, Türk, Weidenreich. (3) *Transitional*: Pappenheim, Hirschfeld, Eric Meyer.

† This is replied to by saying that morphological resemblances are no proof of identity of nature (Sternberg).[26]

‡ E.g., the dogfish.

are no sharply demarcated lymphoid organs in which, on the one hand, lymphocytes alone are produced, and on the other, granulocytes alone. Wherever there is lymphocytic infiltration, there one may find granulocytes occasionally formed. In other words, the blood-lymphocyte is capable of further development after leaving the blood-vessel: to wit, into a polyblast, and even into a myeloid cell under certain circumstances (Lindberg).[37] In the lower vertebrates,* at least, there is a polymorphous wandering indifferent mesenchymal cell with multiple potentialities. (See also *Plate I*, 1.). Hal Downey figures preparations from the amphibian amblystoma (the mature form of axolotl), which point in the same direction.[38] Moreover, working on the chick, Wera Dantschakoff[39] found that the intravascular erythroblasts are morphologically the same as the extravascular granuloblasts; further, that the intravascular "blasts" eventually make lymphocytes.

Certain observations by Dantschakoff[39] on the bone-marrow of fowls during hunger are of considerable importance in this connection. The changes in the marrow consist of an increase of the feebly basophile polynuclear leucocytes, vacuolation of the cell-body, and general amblychromatism of the myelocytes. The lymphoid areas become rich in plasma cells, and small lymphocytes become very much more numerous, while the edges of the areas demonstrate metaplastic conversion of lymphocytes into granular leucocytes, *pari passu* with the diminution in number of the myelocytes. The fact that the central cells of these lymphoid areas are morphologically identical with the myeloblastic cells of ordinary bone-marrow shows that the same kind of cell can turn into a lymphoid cell at one time, and a polynuclear at another.

(*d*). Granulocytes are absent in many animals, but large monocytes (Chapter IV.) and small lymphocytes are present in every animal. Moreover, while the morphology of the granular leucocyte is inconstant in different animals, that of the lymphatic cell remains uniform throughout the animal series.[15]

(*e*). The white cells and red cells are developed together in the lymphoid tissue of the kidney of the fish polyodon. Such an animal does not possess myeloid (bone-marrow) tissue at all (Drzewina,[40] Hal Downey[41]).

* Also, even as low down the invertebrate scale as the sponges.

(*f*). The observation has never been made that the lymphoid cells in an (acute leukæmic) actively proliferating lymphoid tissue (at the expense of the myeloid) are the only specific cells to exhibit mitotic figures. This would need to be definitely established before dualism could maintain its ground.[42]

(*g*). Further, in acute leukæmias we find the following peculiarities: (1) The condition is never purely lymphatic or purely myeloic ;* (2) The gland may not be enlarged, so that bone-marrow *can* make lymphoid cells ; (3) Schultze found that acute lymphoblastic leukæmias are really myeloblastic, because the cells in the spleen and lymph nodes gave an oxydase reaction and were myeloblasts.†

(*h*). Ellermann's[43] success in transplanting leukæmia of hens by means of a cell-free material, indicates that that disease is infective in nature.‡ This being so, the leukæmic process is granulomatous, and not neoplastic. The dualist view makes it neoplastic, inasmuch as the original hæmatopoietic cells are considered to be replaced or substituted by a new tissue altogether.[20]

(*i*). Werzberg's experiments with myelotoxins and splenotoxins.[44]

The following four experiments were performed: (1) Intraperitoneal injection into a rabbit of rabbit-bone-marrow-immune guinea-pig serum (the bone-marrow was extracted and injected intraperitoneally) ; (2) Same as preceding, but using smaller dose ; (3) Injected rabbit-spleen-immune guinea-pig serum ; (4) One of the animals in experiment 2 died of pneumonia. *Results*: the myelotoxic serum in large dose caused hypertrophy of the spleen follicles with myeloid metaplasia of the pulp ; the lymph nodes showed hypertrophy of the germ centres and follicles, and occasionally myeloid metaplasia of the pulp ; the bone-marrow was fatty and the liver normal. In smaller dose, the myeloid metaplastic changes failed to appear in either spleen or glands, but the other changes were as before. When associated with pneumonia, the toxin caused atrophy of the follicles of the spleen, myeloid metaplasia of the pulp, disappearance of the follicles of the lymph nodes, with appearance of large lymphocytoid cells in the interfolli-

* Example: Fleischmann's case, *Charité-Annalen*, 1909.

† This is really the same thing as saying that the lymphoblast is identical with the myeloblast. Was myeloid metaplasia excluded ? A lymphoblastic or myeloblastic leukæmia may have identical features in every particular, save the presence of myeloid metaplasia of the spleen in the latter (Pappenheim, Ziegler, Voswinckel, and Danzelt).

‡ Some authorities do not consider the leukæmia of fowls an identical disease with the human leukæmia.

cular tissue, and myeloid metaplasia in the liver. The splenotoxic serum caused myeloid metaplasia of the spleen pulp and no change in the pulp of the glands, but there was hypertrophy of the follicles throughout.

The *deduction* is that the same toxin that causes myeloid metaplasia can cause hypertrophy of the lymph follicles. The weaker toxin excited merely follicular hyperplasia. The pneumotoxin causes atrophy of the follicular tissue. On the other hand, it will be seen that the lymphatic tissue never becomes myeloid; the experiments confirm the view already expressed that the pulp tissue of the nodes and spleen are fundamentally identical:—

Primordial cell of pulp tissue → Myelocyte (myeloid metaplasia)
Primordial cell of pulp tissue → Lymphocyte, which, proliferating, becomes manifest as a misplaced lymph-follicle.*

The difficulty that lymph follicles never undergo myeloid metaplasia is explained readily enough when we come to regard the follicle cells as temporary and not primordial cells. This subject is very important, and is dealt with again later.

The conclusion of the matter is that we assume the persistence of a primordial cell throughout life, and that its after-history takes the form of one or other of the five main lines of blood-cell development—the red cell, the lymphocyte, the monocyte, the neutrophile leucocyte, and the phlogocyte. We shall take up each of these in turn in the succeeding chapters.

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* That this is correct may be readily demonstrated in the lymph nodes of any autopsy. The question will be referred to again, as so many examples from the autopsies at the Montreal Royal Victoria Hospital have been met with. It will be seen that this finding in itself strongly supports Werzberg's view, especially considering that observations on man are worth so much more than those on animals.

III.—THE PRIMORDIAL CELL (*concluded*).

The Cytometaplasias of the Lymphoidocyte.

The subject of cytometaplasia is best considered after the various blood-cell forms have been studied, but it is advisable to make some reference to it at this point in order to complete the conception of the primordial cell. It is not sufficient to describe its characters, its origin, its fate, and the *physiological transformation* into the other blood-cells which it undergoes; the fact that *it is subject to pathological processes*, under the burden of which it gives rise to granulomatous and neoplastic formations (to mention some of the most interesting of the changes), must be considered in order to complete the survey of the biology of this cell-type.

When discussing whether a primordial cell persists throughout life or not, reference was made to the process of spermatogenesis, and it was pointed out (*p.* 27) that the spermatogonium may retain its functional but not its corporeal identity during the successive generations. The same phenomenon may occur in the case of the blood-cell parents. The primordial blood-cell or lymphoidocyte may give rise to two daughter cells. These are either both lymphatic or both myeloic.* Even though the two daughter cells both belong to the same series, there still remains a necessity for assuming that one of the two retains the functional characters of the parent, the other alone being destined to differentiate. In the case of the seminiferous tubule, for instance, a certain number of the cells nearest the basement membrane always remain "primordial," (potential spermatogonia), no matter how often they have divided.

The diagram on page 38 will make the argument clearer, the successive changes in the functional character being indicated by linking (*Fig.* 13). The black spots represent juvenile or temporary stages that become more differentiated during ontogenetic development. The linked forms are actually always

* To judge by some of the mixed leukæmias, one of each variety is possible.

in the same spot, so that the primordial cell is apparently unchanging. Whether the second generation does or does not differentiate depends entirely on the presence or absence of suitable stimuli or transient influences from without. A cell which underwent myeloic differentiation yesterday, might undergo lymphatic change next week, and the latter might just as well "revert" the following week, undergoing anaplasia and then changing into myeloic cells once more. It is only in this way that one could explain the onset of an acute leukæmia with lightning-like rapidity.

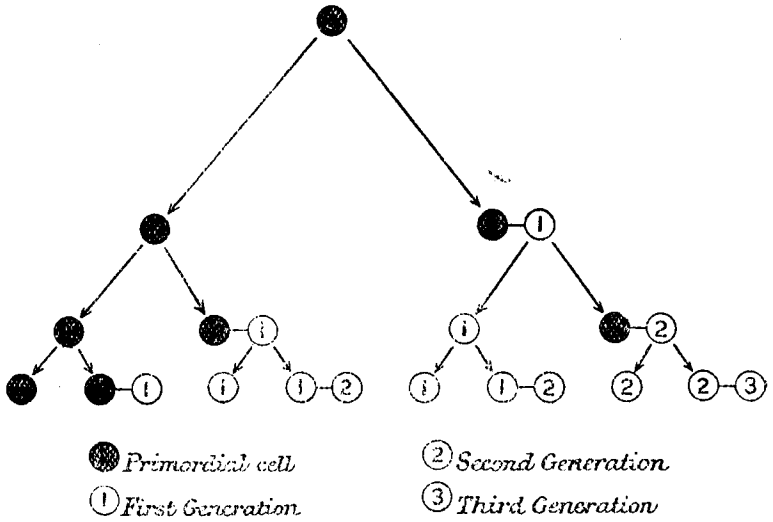

Fig. 13.—Scheme of Cell Descent.

The justness of the view is supported by the observations of Dixon and Malden, that large doses of colchicin can set up a leukæmoid blood-picture;[45] of Lüdke, that streptococci and spirochæta Obermeieri can set up similar pictures;[46] of Levy, that nitrobenzol can set up leukanæmia.[47] Zoja's observation that the active toxic agent of leukæmia also acts hæmolytically is additional evidence.[48] The fact that defective biological cell-avidity may result from deficiency in the content of proteolytic ferment[49] shows how such an aberration of development may be brought about, without calling too much on one's powers of imagination.

In leukæmia, then, the failure of successive generations to differentiate, coupled with their entry into the blood-stream, would be expressed by a diagram (*Fig.* 14) in which all the cells are drawn alike, because there is no differentiation taking place with successive generations.

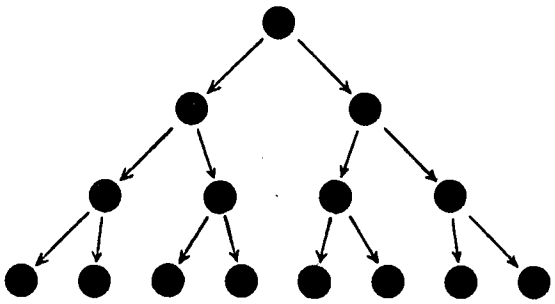

Fig. 14.—Leukæmic Proliferation.

The same method of presentation may be conveniently adopted to demonstrate the relation between this kind of proliferation and hyperplasia. Thus, in *Fig.* 15, the ordinary rate of multiplication of cells is represented by **A**, while in hyperplasia a larger number of like cells are produced in a given time, as shown in **B**. The fact that all the cells are drawn alike shows that here also there is no differentiation occurring, while their smaller size serves to show that they are not primordial but *already differentiated.*

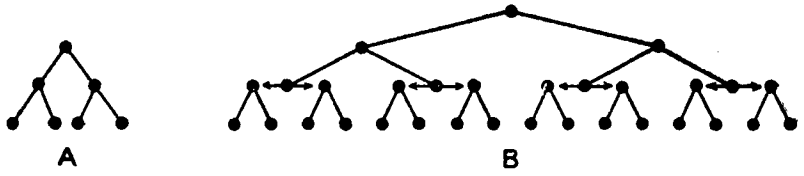

Fig. 15.—Rate of Proliferation in a Given Time. (A) Normal; (B) Hyperplasia.

Further, an application of *Fig.* 6 may be employed to illustrate the relations between hyperplasia, metaplasia, and anaplasia. In the accompanying diagram (*Fig.* 16) *a b* represents the normal progress of ontogeny and phylogeny in a cell; then, if the *rate* of multiplication be increased, we should represent the progress of the genealogy by any line such as *a c*, which has an angle more obtuse than the first. As long as the nuclear line proceeds along the same track we have simple hyperplasia, but supposing that the nuclear differentiation is more rapid than the cytoplasmic, or than the rate of reproduction, we should have two new lines somewhere between

a c and *a b*, one for the cytoplasmic growth (*a d*), and one for the nuclear (*a d'*), the latter being nearer to *a c*. These would represent metaplasia, and the more obtuse the angle with the base line, the more is hyperplasia associated therewith (metahyperplasia). Lastly, supposing that the line of development were to fall to some point *e*, instead of rising, the nuclear and cytoplasmic changes both proceeding at the same rate, we should have before us a representation of anaplasia. Here, too, the nuclear and cytoplasmic variations may not proceed *pari passu*.

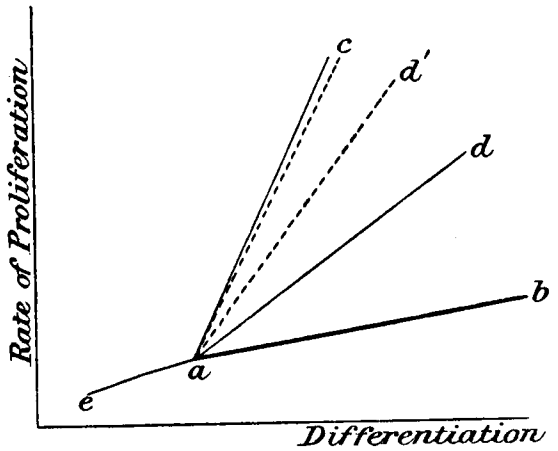

Fig. 16.—Diagram representing hyperplasia *a c*, metaplasia *a d*, *a d'*, and anaplasia *a e*; *a b* represents normal progress.

Such considerations render intelligible the occurrence of diseases like leucosarcomatosis, the large-lymphocyte leukæmias, the sarcoid leukæmias, etc. Some agent acting on the formative tissues as a whole may lead to the production of the new cells, merely by intracellular metaplasias, which take place *simultaneously throughout* the hæmopoietic organs. As Blumenthal has said, leukæmia is an anarchy of cell-manufacture,[50] but with this is the anomalous circumstance that the vessel-walls of the marrow, even the intimal cells, are actually part of the leukæmic tissue (Banti), so that the blood is circulating through a collection of discrete neoplastic cells, just as it would amongst the tumour cells in some sarcomas. This last circumstance would explain the entry of leukæmic cells into the blood—a phenomenon which may be classed as nothing more than an episode in the hæmopoietic disease.

The modern view of leukæmia* is that it is a disease produced by the action of a noxa upon the whole hæmopoietic system, and the word "leukæmia" is now understood to mean "(meta-) hyperplasia" of the tissue, and *not* simply excess of white cells in the blood-film. The diagnosis of the disease rests on a study of the tissues and not of the blood; when one meets with leukæmia plus normal blood-count, the disease is designated "aleukæmia" (formerly, pseudo-leukæmia).† While leukæmia is not the only generalized disease of the blood-forming organs, it is the only one in which there can be said to be metaplasia or hyperplasia (or both‡) involving the lymphoidocyte. The other diseases belonging to the same broad class are such as lymphosarcomatosis, lymphogranulomatosis (Hodgkin's disease, Banti's disease, Gaucher's splenomegaly, Jaksch-anæmia, kala-azar, etc.), and will be again referred to in Chapter VII.

The arguments that leukæmia is infective in nature, like septicotoxæmia (Pappenheim), are briefly given as follows: (1) The whole hæmopoietic system is affected at once; (2) Some forms are associated with anæmia (leukæmia), just as are other infections. The acute hæmorrhagic leukæmia can no longer be regarded as anything else but microbic; (3) Pyrexia is present; (4) Similar lymphomata may occur in typhoid and scarlet fevers; (5) Similar myeloid metaplasia occurs in scarlet fever, pernicious anæmia, cancerous anæmia, etc.; (6) Has been transmitted by filterable virus (Ellermann).

The arguments that leukæmia is not infective are such as these: that the leucocytosis differs from that of any other known infective disease; that fever is not necessarily microbic in origin; that the fever and apparently infective course of the disease are rather to be explained as the effect of the absence of polynuclear leucocytes in the blood-stream.

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* Pappenheim, Hirschfeld, Meyer, Domarus, Neumann, etc.

† The anomalous phrase "aleukæmic leukæmia" signifies *leukæmia* (special disease of the -poietic *tissues*) *plus* aleukæmic *blood*. The word "aleukæmic" is used in a clinical sense, while the word "leukæmia" is a histo-anatomical one.

‡ Pure hyperplasia was thought to be possible by Kundrat, Paltauf, Ehrlich-Pincus, Sternberg, Naegeli, Schridde, Türk, Lehndorff, Mosse, K. Ziegler, and others, but no known irritant will set up analogous changes by itself.

As is well known, the attempt has been strongly made to bring leukæmia into line with the sarcomas, and, further, to assume that the pathology of leukæmia is the same as that of a neoplasm.* The main argument is that in acute leukæmias, large atypical cells appear in the blood, which tend to develop tumours (Sternberg, v. Domarus[52]) with local malignancy. This is disproved, to a certain extent, by studying the properties of the cells in the two cases. In leukæmic growths, the progress is arrested by the capsule of the organ in which the tumour is situated. In leukæmias without tumour nodules, there are still the same changes in the hæmatopoietic tissues as are noted in tumour-forming leukæmias. The occurrence of transition-forms between leukæmia and Sternberg's leucosarcomatosis shows that the sarcoma theory of leukæmia is too crude.

In *lymphosarcoma*, the proliferative process begins only at one spot, and spreads to the neighbourhood, ultimately producing metastases like tumour-metastases. If the bone-marrow and spleen are affected, that is, by only metastatic action, there is no system-disease. The only resemblance between lymphosarcoma and leukæmia is met with when the tumour masses break through into the circulation and give rise to a lymphæmic picture (cases of Strausz, Virchow,[53] Palma, Drozsda[54]). The *relation between leucosarcoma and chloroma* brings out similar points. Chloroma was thought to be cancerous, until it was discovered that the blood might show an anomalous change. The disease then came to be considered as a form of leukæmia. The tumour character was indicated by the infiltration of neighbouring structures (Lehndorff[55]). Sternberg classed chloroma with leucosarcoma, although he recognized the difficulty entailed by the green colour of the tumours. The term chloroleucosarcoma was therefore introduced. Even here, however, the same generalized hyperplastic change is noted in the bone-marrow, and the report of cases in which some tumours of a case were green, and others not (Fabian,[56] Schmidt[57]) allowed these various conditions to be focussed together. The *relation between leucosarcoma and myeloma* has again been the subject of much dispute.[52] The tumour character of myelomas is well defined ; there is active invasion of the surrounding tissues, the compact bone is destroyed, and though in a few cases the tumour-formation is restricted to the bones, there are cases in which the soft parts are affected (Pappenheim's sarcomyeloma). Nodules are then noted in the liver, spleen, etc., having exactly the same structure as the bony masses. [This statement may require correction in view of the fact that such cases were reported before the days of ultra-modern hæmatology, so that the cells may not have been true myeloma cells.] Even in the case of myelomas, there are transition-forms described between tumour forms and diffuse hyperplasias without definite aggressive growth or infiltration (Runeberg, Nothnagel, Jochmann-Schumm). The blood-changes are just as undecided in myeloma as in other allied conditions—myelocytes and normoblasts occur in all.

The question is somewhat reversed if we consider whether sarcoma itself is really a neoplasm in the old sense of the word. If sarcomas are

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* Ribbert, Banti, Helly, K. Ziegler.

regarded as infective diseases, then the similarity to tumour-forming leukæmias requires no further comment. The evidence in favour of a certain number of sarcomas being due to toxoids, or organisms, or both, is accumulating, although it will never be forgotten that certain types of sarcoma—those occurring in infancy—can hardly be explained in this way. There remains the fact that there is some intimate relation between leukæmic processes and these neoplastic processes.

CHAPTER II.

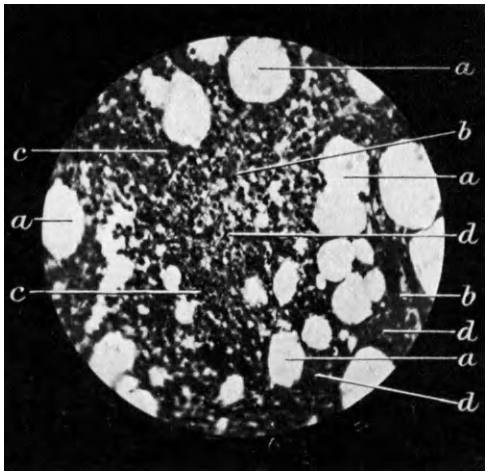
ON THE RED BLOOD-CELL.

Section I.—THE BONE-MARROW AS A RED-CELL FACTORY: The red-cell forming group—The white-cell forming group—The megakaryocyte, its significance; views as to its nature and function; occurrence—Proliferation of cells in the bone-marrow—Metaplastic and allied changes in the bone-marrow—Functions of the bone-marrow.

Section II.—THE ERYTHROBLASTIC LINE OF DEVELOPMENT: General outline of the process—Charts showing the details of erythropoiesis (*a*) in the embryo, (*b*) after birth—Red-cell formation in the liver, spleen, and lymph-nodes—Characters of the lymphoid erythroblast, and how it is formed from the primordial cell—The megaloblasts—The chemical characters of these ancestral cells—Their differential diagnosis—Views as to the nature of the megaloblast—The normoblast: its characters: its differential diagnosis—The birth of the red cell into the blood-stream—Theories of the process of denucleation.

Section III.—THE LIFE HISTORY OF THE RED BLOOD CORPUSCLE IN THE BLOOD-STREAM: Characters of the erythrocyte: the theories regarding the structure of the red cell—The chemistry of the red cell—The fate of the red cell—Degeneration phenomena—The evidence of destruction of red cells—The reticular substance—Polychromatophilia—Punctate basophilia—The Heinz bodies—Red-cell shadows—The Howell-Jolly bodies—The Cabot ring bodies—Chromolinin granules—The blood-platelets—Hyperchromia—Alterations of shape and size—The *comparative morphology* of the red cell—The spindle cell—The hæmokonia or blood-dust.

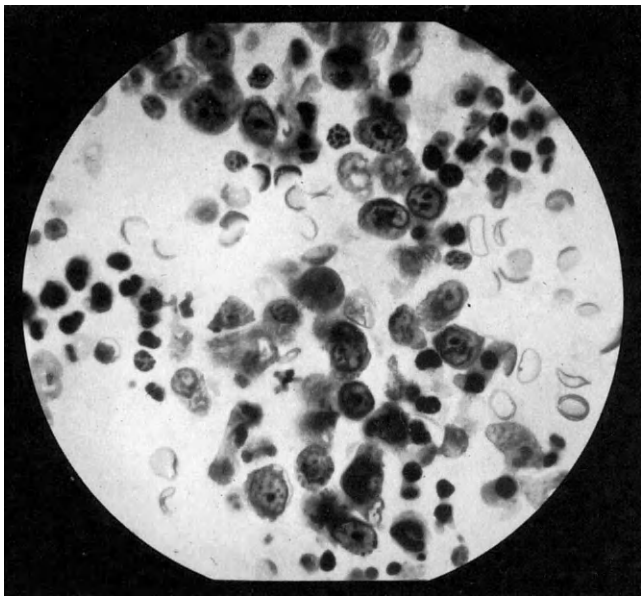
Section IV.—THE METAPLASTIC, METAHYPERPLASTIC, AND APLASTIC PHENOMENA OF ERYTHROPOIESIS: Brief discussion of the nature of anæmia—A classification of anæmias—Relation between the facts detailed in the preceding sections and clinical work—Polycythæmia.



". . . the formative cells are for the most part masked by the fatty tissue. The latter is . . . somewhat of the nature of packing" (p. 45).

Fig. 17.—NORMAL BONE-MARROW. (*a*) fat cells; (*b*) capillaries; (*c*) megakaryocytes; (*d*) formative cells.

(Oc. 6, Apochrom. 4 mm.).

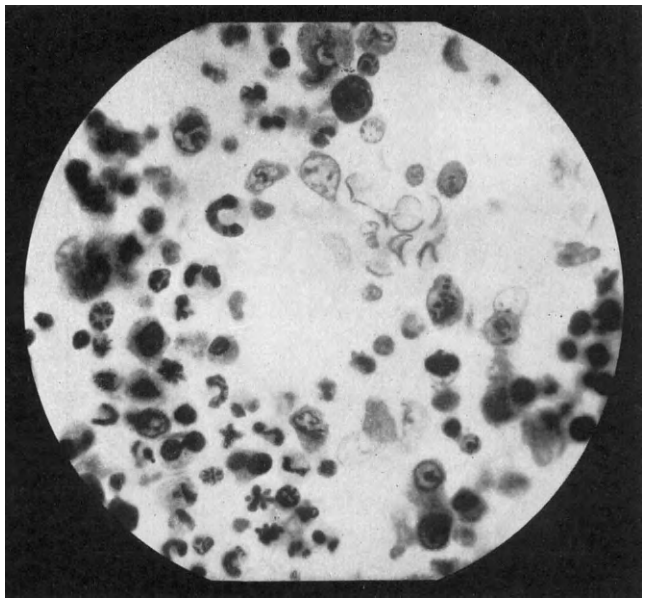


"Examined with the oil-immersion lens . . . the formative cells . . . are seen to be of various types" (p. 45).

Fig. 18.—NORMAL BONE-MARROW. The small dark cells are red cell parents, the large paler cells are white cell parents, and the ring forms are mature red cells.

(Oc. 12, Zeiss Oil-immersion).

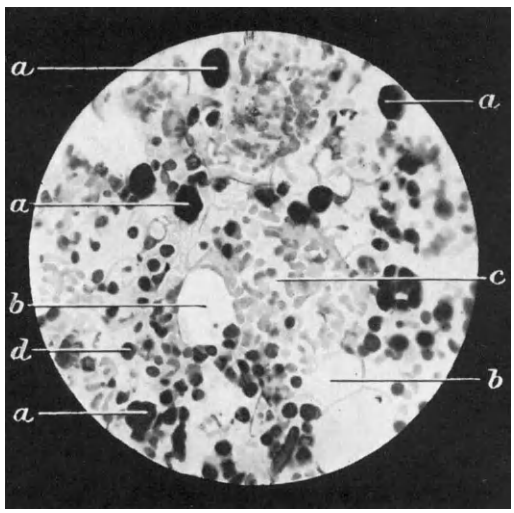
Face p. 44]



" . . . divisible into a leucocyte and a hæmoglobin-holding series" (p. 45).

Fig. 19.—BONE-MARROW SHOWING ERYTHROBLASTIC REACTION. The stellate forms are pycnotic normoblasts. The other cells are as in the preceding figure. Notice a large cell with horseshoe-shaped nucleus—a metamyelocyte.

(Oc. 12, Zeiss Oil-immersion).



" Many of the cells . . . have phagocytic properties, so that . . . pigment granules may be seen " (p. 47).

Fig. 20.—PIGMENT IN BONE-MARROW. (*a*) masses of pigment completely filling cells; (*b*) fat cells; (*c*) red blood cells; (*d*) formative cells.

(Oc. 4, Zeiss Oil-immersion).

I.—THE BONE-MARROW AS A RED-CELL FACTORY.

THE red-cell forming group—The white-cell forming group—The megakaryocyte, its significance ; views as to its nature and function ; occurrence—Proliferation of cells in the bone-marrow—Metaplastic and allied changes in the bone marrow—Functions of the bone-marrow.

ACTIVE or formative bone-marrow occurs as a reddish material in the sternum, bodies of the vertebræ, ribs, diploe of the skull, and the ends of the long bones. In bones other than these, the formative cells are for the most part masked by the fatty tissue. The latter is compensatory material, somewhat of the nature of packing, but is of importance to the parenchymal tissue by affording the nutritive means by which metabolism with differentiation can take place.

The bone-marrow, whose typical structure is shown in *Fig.* 1, is made up of a vascular connective tissue occupying the interstices of a variably dense bony trabecular framework. The blood-vessels stand out conspicuously owing to vascular engorgement, and the size of the inter-trabecular spaces relative to the small round fat cells within them is well demonstrated. Seen with a higher magnification (*Fig.* 17), these round spaces become recognizable as adipose connective-tissue cells, and the relations between them and the surrounding closely packed discrete tissue-cells become more clearly visible. The latter vary in size—some of them, the so-called megakaryocytes, being strikingly large. Small capillaries are seen here and there as small pale bands among the marrow cells, but the cytological details of the latter require still higher magnification for their detection, even such gross points as variations in intensity of staining being visible with difficulty.

Examined with the oil-immersion lens, however (*Fig.* 18), the formative cells themselves are seen to be of various types. They have been called "marrow leucocytes," and are divisible into a leucocyte and a hæmoglobin-holding series (Carnegie Dickson). A third group might be added, that of the indifferent or indeterminate cells, possessing varying or multiple potentialities

—sometimes erythropotent, lymphopotent under certain conditions, and sometimes leucopotent. In addition to these parenchymal cells there are the interstitial cells (giant cells, connective-tissue cells, and endothelioid cells).

The Red-cell Forming Group.—These include the normoblasts, the megaloblasts, and their parent cells. It was the presence of such cells in large numbers in adult bone-marrow that led Neumann[1] to discover the source of red cells during extra-uterine life, the " -blast " undergoing mitosis, its progeny losing its nuclei, or budding off portions of the cell-body.[2]

In studying microscopic preparations of bone-marrow, it is found that the parent cells of both red and white cells are difficult to distinguish. In the case of the lymphoid erythroblast, the parent of the red cell, the nuclear matter is found to be characteristically arranged along the periphery of the nucleus, with central chromatic spots. The nucleus of the lymphoidocyte never shows this structure, but presents a diffuse ill-defined variation in density of chromatin. Giemsa preparations generally show the presence of a nucleolus in the lymphocyte series, while the later generations of the parent red cell certainly do not. When the nucleus of the red cell undergoes pycnosis, there may be a superficial resemblance to a neutrophile leucocyte whose granules have been lost from degenerative changes. As a rule, a slight greenish or bluish tint is noticeable in the normoblast cell-body from the presence of more or less hæmoglobin. The megaloblast (*see p.* 61) may occasionally be mistaken for a lymphoid cell, but the structure of the nucleus is characteristic—radial arrangement of the lines of chromatin (*Fig.* 19).

The White-cell Forming Group. — This is subdivided into (*a*) non-granular and (*b*) granular cells. The latter are characteristic and well known. Granules are always clearly shown in triacid preparations, but the characteristic nuclear structure—rather coarse, but ill-defined transverse shadowing—is best seen in the panoptic preparations. The granular cells of the marrow are, of course, myelocytes of one kind or another ; that is, they have an oval, reniform, or deeply indented nucleus, as opposed to the polymorphous form in the adult leucocyte. The nuclear structure

differentiates these cells from the large mononuclear and transitional cells of Ehrlich. The presence of neutrophilic, eosinophilic, or basophilic granules affords a basis of classification.

Many of these cells are actively amœboid, and have phagocytic properties, so that red cells or pigment granules may be seen within them (*Fig.* 20). It is this fact, added to the changes due to progress of development of the bone-marrow cells, synchronously with the phenomena of active mitosis, that explains the remarkable inconstancy of structure of this tissue, not only in the different diseases, but also from hour to hour and from day to day, during the life of the individual. There is need for small wonder at the remarkable rapidity[3] of adaption to incoming morbid or physiological stimuli. We cannot fail to be impressed with the multiplicity of the changes in which one or other of a group of cells is concerned—regenerative, degenerative, reparative, aberrant. We may compare the ever-active and ever-responsive character of the blood-cell parents residing in the bone-marrow to the restlessness and excitement seen in a crowd of spectators who press forward beyond the barrier for the purpose of obtaining a better view of the object of their visit, but are forced back by the rigid rules adopted by the vigilators of the course for the maintenance of order.

The pigmentophages vary greatly in size, and contain a feebly staining oval nucleus lying in an abundant non-granular cytoplasm. They are probably derived from the endothelial cells of the capillaries as well as from the branching reticular cells.

The non-granular cells (*Fig.* 51) are crudely divisible into small, medium, and large mononuclear forms. They may be regarded as representing stages farther back in the line of development than the granular cells, the blood-mature lymphocyte, and the red cell respectively. The largest example of the former is the primordial cell already discussed, although its exact aspect in the tissue was not detailed. This is, then, the mother cell, the large lymphocyte of older authors, the lymphoidocyte of Pappenheim. Here, a small rim of basophile cytoplasm is noted, with a relatively large ovoid nucleus of variable basophilia, but characteristic structure and nucleolar content. There may be definite

peripheral chromatic marking visible in the tissue-sections. It is convenient to call this cell simply "mother cell," which serves to indicate its place in development and avoids the selection of one of the twenty-three names with which various writers have presented the same innocent cell. Between this cell and the promyelocyte it is possible to interpose a leukoblast stage (*see p.* 203). Commencing acidophilia of the cell-body, still without definite neutrophilic granules, indicates that we have a promyelocyte before us—a cell further on in the line of ontogenetic development, but also included with the non-granular cells. The leukoblast often shows azure granulation, but is not classed as a granular cell because this variety of granulation is non-specific.

Before passing on to consider in detail the red-cell forming series, it is important to refer more particularly to the *stromatic elements*. Of these, the *giant cell* is conspicuous. This is a large multinucleate cell met with in varying numbers in marrow tissue. There are two forms of giant cell: (*a*) The osteoclast, usually met with in the vicinity of bone-trabeculæ, when absorption processes are going on; (*b*) A variably large cell, constantly seen in sections of the bone-marrow, but not seen in film preparations—the megakaryocyte (myeloplax of Robin). All forms and sizes of this cell are met with, and even the nuclear characters are not stereotyped.

Characters of the Megakaryocyte. (*Plate VII*, 23, 24, *p.* 250, and *Figs.* 39, 74).

Size.—30–45 μ in the adult, smaller in embryos.

Shape.—Round in the physiological state.[4]

Cell-body.—Stains bright red with eosin, strongly red with methyl-green pyronin. It shows an outer hyaline zone, in which radial filamentous marking is visible (minute pores?), and an inner granular zone, separated from the former by a pseudo-membrane.[5] Sometimes it is deeply stainable, where the granules are numerous; at others it is only faintly stainable (few granules). A network permeates the inner zone, and contains vacuoles, clefts, or vermiform spaces.[5] The pseudopodia also show an outer hyaline margin and an inner granular zone.[6]

Granules.—(*a*) Staining by Altmann's method; (*b*) Staining with Giemsa. The latter are much more abundant, and occur

uniformly distributed through the granular layer, or in rows, or in dense patches like the tigroid patches of nerve cells.[5] The presence of these specific granules shows that the megakaryocyte has nothing to do with the lymphocytar or leucocytar series. The Altmann-Schridde granules are abundant even in the pseudopodia, which penetrate into the lumen of the capillary. Here they occur in clusters, marked off by a hyaline zone of protoplasm.

Nucleus.—This is protean in form, always vesicular. Its outline is sometimes lobate, sometimes only indented, sometimes moniliform, sometimes basket-like, or annular, or horse-shoe-like. The chromatin network is abundant and the interchromatinic substance is abundant. In the hollow of the nucleus are a number of centrioles grouped together into a small cluster, or they are scattered about in the central zone of protoplasm.

Mitosis.—Always indirect.[5] Baes and Lustig described pluripolar mitosis. C. E. Walker described division by amitosis.[10]

Motility.—Amœboid motility is present. It is therefore probably a phagocytic cell.

Differential Diagnosis.—From other giant cells—see Chapter VII.

Ancestor.—Saxer's primary wandering cell,[5] or the stellate connective-tissue cells.[4] * They are not the first cells to appear in the fœtal marrow.[4] Blumenthal and Duesberg[4] believe them to arise by fusion of lymphoid mononuclear cells, and by fusion of nuclei.

Occurrence in Marrow.—The distribution is always irregular. The numbers vary according to the degree of redness of the tissue,[4] or according to the number of isolated nuclei and pigment-containing cells,[7] but diminish with age.[4] They are more numerous towards the end of fœtal life and during the winter sleep of bats.[4] They also occur in the spleen[8] and lymph-nodes.[9]

The Significance of Megakaryocytes is not settled. Schridde states that they are amœboid but non-phagocytic. They appear to have some connection with hæmogenesis, because they are numerous in foci of active blood-cell formation, and have close relations to the blood-vessel walls, dangling their long pseudopodic

* Verson does not agree.[7]

arms into the blood-channel.[11] They are scanty in cases of tuberculosis, cancer, chronic nephritis, and all bacterial infections. They were found to be very abundant in a case of aneurysm in which leakage had taken place for a considerable time.[12] They are increased in pneumonia, septicæmia, and appendicitis. Degenerative changes in such cells are worthy of note.

VIEWS AS TO NATURE :—

1. That it is the result of proliferation of the endothelium of the vessels (Kölliker).

2. That it is produced by the fusion of several leucocytes (Sanfelice[14]).

3. That it is merely a giant leucocyte (Howell, v. Stricht, Kastanuchi, Heidenhain[15]).

4. That it is derived from the reticular cells of the bone-marrow, being a phagocyte for red cells (Ebner[16]).

5. That it is derived from the lymphoidocyte (Pappenheim[17]).*

VIEWS AS TO FUNCTION :—

1. That it destroys leucocytes which are no longer capable of functioning (Foà[18]).

2. That it is the parent of the polynuclear leucocyte, because peculiar structures are occasionally seen within it (Werigo and Jaguinow[19]).†

3. That it is the parent of red cells (Lifschitz[20]), because they are more abundant the more numerous the erythrocytes.‡

4. That it is the source of the blood-platelets (Wright,[21] Bunting,[22] Ogata,[22a] Sternberg[23]). The arguments in favour of this view are : (i) That projections from the cell-body into the lumen of the vessel can be actually seen ; (ii) That this form of cell only occurs in mammals, and the platelets are not found in the blood of any but mammals ; (iii) That the more numerous giant cells are in a tissue, the more abundant are the platelets in the blood (few in pernicious anæmia and lymphatic leukæmia, numerous in post-hæmorrhagic anæmia and myeloid leukæmia). The refutation of these arguments is to be found on *p.* 87.

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* The writer considers this view the most probable, for reasons given in Chapter VII.
† Denied by Schridde. ‡ Denied by Tomassi.

5. That it forms a ferment which acts on the extruded nuclei of the red cells, reducing the nucleohistone to nuclein and histone. The latter is subsequently utilized to form hæmoglobin in the oncoming red cells (Ciaccio[24]). This view is far more in keeping with physiological cytology, and provides an analogy in the formative organs to the Sertoli cell of the testis. Where active cell-differentiation is going on, the specialized metabolism appears to demand the presence of specialized cells.

Proliferation of Cells in the Bone-Marrow.—In mammals, the formative cells of the bone-marrow are apparently all extravascular, even the red cells making their way through (possibly) incomplete capillary walls. But in birds the walls of the capillary are complete, and the red cells are formed in dilated sinus-like portions of the blood-vascular system of the bone, the parent cells being close to the wall, while the fully-developed red cells are towards the centre of the lumen, and are washed off by the slowly circulating blood.[25] In addition to this, certain of the marrow cells without the vessels are proliferating, in order to supply fresh erythroblasts along the peripheral portion of the vascular channel, and these parent cells make their way through the vascular wall in the same way as the finished red cell is supposed to emerge in the case of the mammal.[26]

It would be of interest to determine exactly how much cell-multiplication is required hourly in order to maintain the adult's blood at average cellular richness. The accepted mechanism of red-cell formation might then be found to be entirely inadequate. Assuming that there are about five litres of blood in the body, and that the average life of a red cell is ten days,[67] we shall find that about 105 *thousand million* red cells have to be formed within the body *every hour*, both day and night. If it were possible to estimate approximately (say within 20 millions) the number of marrow cells in the body, it would be easy to see if mitosis would meet the case.* Multiplication at bacterial rate is not admissible, because this would provide a steadily increasing output. The rate

* Timofijwsky (Russky Wratsch, 1912, 24) made cell counts and found that a c.mm. of marrow tissue contains 0·674 million erythroblasts.

of red-cell destruction is to be assumed to be the same (*see also p.* 73). We should have to assume a formation of red cells by meristem methods, whereby ten, fifteen, twenty or more young cells are formed with great rapidity from one parent. On the other hand, mitosis is not so remarkable a feature of these proliferating tissues.* Formation of red cells by buds from other cells, though depicted by Maximow,[27] is not accepted as even a potential and occasional method.

Metaplastic and Allied Changes in the Bone-marrow.—These are conveniently considered in connection with the polynuclear leucocyte (*see p.* 199). The aplastic changes, however, are referred to in Section IV.

The Functions of the Bone-marrow.—These may be enumerated in this place :

1. It is hæmopoietic for red and white cells.

2. It is associated with blood-destruction and the phagocytosis of organisms. This property is increased in toxic diseases and the acute microbic infections. Agglutinins are made here, according to the observations of Azzurini.

3. It has to do with the formation, nutrition, and absorption of bone. Occasionally, the absorption of bone serves the purpose of providing more space for red-cell formation.

4. It has to do with general metabolism ; with this is associated the function loosely named " internal secretion."

5. It has to do with the preparation of fibrinogen. Müller found that there is more fibrinogen in bone-marrow in experimental staphylococcic infection, and that when defibrinated rabbit blood is injected into the same animal, marked leucocytosis occurs, with myeloid metaplasia in the bone-marrow, spleen, and liver. If hirudin blood were used (containing fibrinogen, but not coagulable) it caused leucocytosis without myeloid change.

Effect of Toxins.—Intravenous injections of saponin into rabbits (Isaak and Möchel[26a]) produces cell-complexes of normo- and megaloblasts, and indifferent marrow cells ; necroses occur here and there ; in other cases there are regressive changes present. After long-continued treatment the bone-marrow disappears, the adipose cells being replaced by connective tissue, which becomes very dense, and small foci of blood-formative cells may appear so soon as the animal has developed an immunity against the sapotoxin.

* It is usually stated that the mitotic phase is so readily passed through, that it might be missed in microscopic sections. This, however, has only a theoretical basis.

II.—THE ERYTHROBLASTIC LINE OF DEVELOPMENT.

GENERAL outline of the process—Charts showing the details of erythropoiesis (*a*) in the embryo, (*b*) after birth—Characters of the lymphoid erythroblast, and how it is formed from the primordial cell—The megaloblasts—The chemical characters of these ancestral cells—Their differential diagnosis—Views as to the nature of the megaloblast—The normoblast, its characters, its differential diagnosis—Red-cell formation in the liver, spleen, and lymph-nodes—The birth of the red cell into the blood-stream—Theories of the process of denucleation.

THE lack of uniformity noticeable in the statements made about the mode of development of the red cell is largely owing to the utilization of different material by different observers. It is not to be expected that the red cells of the chick, for instance, will be formed in the same way as those of the guinea-pig, and these in the same way as in man. Where it is possible to combine the different methods, it would be an advantage to present an account containing every variation, as a basis, because every contingency would be covered thereby. There is much objection to offering a description of the process of red-cell formation in words. It is therefore designed to show a series of genealogical tables, and allow them to speak for themselves. It is simpler to separate erythropoiesis into two stages than to endeavour to trace the continuity of development from the earliest embryonic life to the adult. The formation of the primitive blood cells in the embryonic yolk-sac is one process, that of the secondary blood-cells in the proper blood-forming organs is another.

In the *yolk-sac* we find the following sequence.[28] The mesodermal cell of the yolk-sac becomes the mesenchyme cell, which functions as an angioblast.* This is a branching cell with granular body and small nucleus, very similar to an ordinary connective-tissue cell. As soon as a number of these cells, formed simultaneously, come together,† they come to be called Pander's islands ;

* The mesenchyme cell is also called a parablast (His).[29]

† Some authorities regard them as collected into syncytial masses, but Maximow and Dantschakoff do not.

and when adjoining islands have fused, we have before us the network of primitive blood-vessels called the area vasculosa. The angioblastic cell now multiplies and gives rise to three types of cell : (i) the perivascular cell, (ii) an endothelial cell, (iii) a hæmoblast or mother cell of the erythrocyte. These form three layers, with the last-named innermost (*Figs.* 21, 22), and it will be evident that the endothelial cells will join into a membrane, separating off the hæmoblasts within from the perivascular cells without.

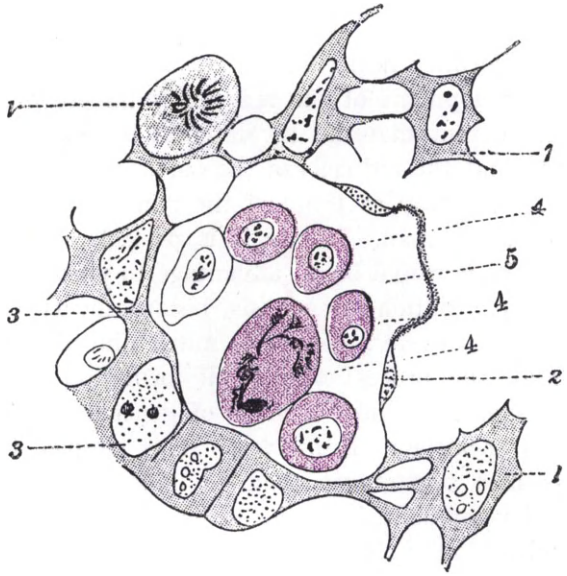


Fig. 21.—TRANSVERSE SECTION OF PRIMITIVE BLOOD-VESSEL (after Maximow).
(1) Mesenchyme cell; (2) Endothelial cell; (3) Lymphoblast; (4) Primitive erythroblast (5) Cavity of developing vessel.

The hæmoblast divides into the primitive erythroblast (lymphoid erythroblast of Pappenheim) (*see p.* 60), and the primitive lymphoblast, or non-hæmoglobin-bearing cell. All these stages are extra-embryonic. At the same time, changes are taking place within the body of the developing embryo (*see* below). The two series of vascular channels meet, fuse, and intercommunicate. Circulation is now complete.

The descendants of the hæmoblasts are carried by the

circulation into the liver* and spleen,† and proceed to give birth to a similar progeny in these regions.

Changes within the Body of the Developing Embryo. Formation of the Bone-marrow.[31]—Maximow's observations[30] show

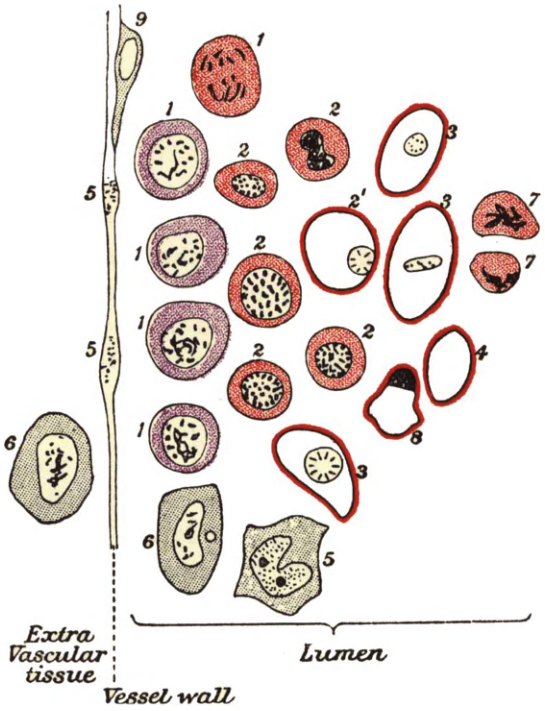


Fig. 22.—LONGITUDINAL SECTION OF PRIMITIVE BLOOD-VESSEL.

(*1*) Megaloblasts; (*2*) Megaloblasts of second generation; (*3*) Normoblasts; (*4*) Red cell; (*5*) Endothelial cells; (*6*) Lymphoid erythroblast; (*7*) Dividing normoblast; (*8*) Red cell losing its nucleus.

that as soon as cartilage is laid down, the perichondrium cells give rise to osteoblasts on the one hand, and wandering cells on the other. At the same time, connective tissue, carrying blood-vessels, grows

* The erythropoietic function appears in the liver at the tenth day, and ceases fourteen days after birth.

† The erythropoietic function appears in the spleen at the sixth week Bizzozero and Salvioli first showed that the spleen is hæmopoietic, and Dominici, Hirschfeld, and Askanazy showed that a re-assumption of this function took place in pathological states.

in and helps to form the primitive bone-marrow.* The endothelial cells of the capillaries are isomorphous with the primitive bone-marrow cells. While the endothelial cells metamorphose, some of the connective-tissue cells fuse into osteoclasts (these dissolve the newly-forming bone round the osteoblasts and later revert into the reticular bone-marrow cells), while others appear as (1) Wandering cells like the lymphocytes of the area vasculosa—massive cytoplasm, feeble basophilia, and nucleus rather rich in chromatin; (2) Small wandering cells of histogenic type; (3) Intermediate forms. The wandering cells (1) give rise to true lymphocytes.

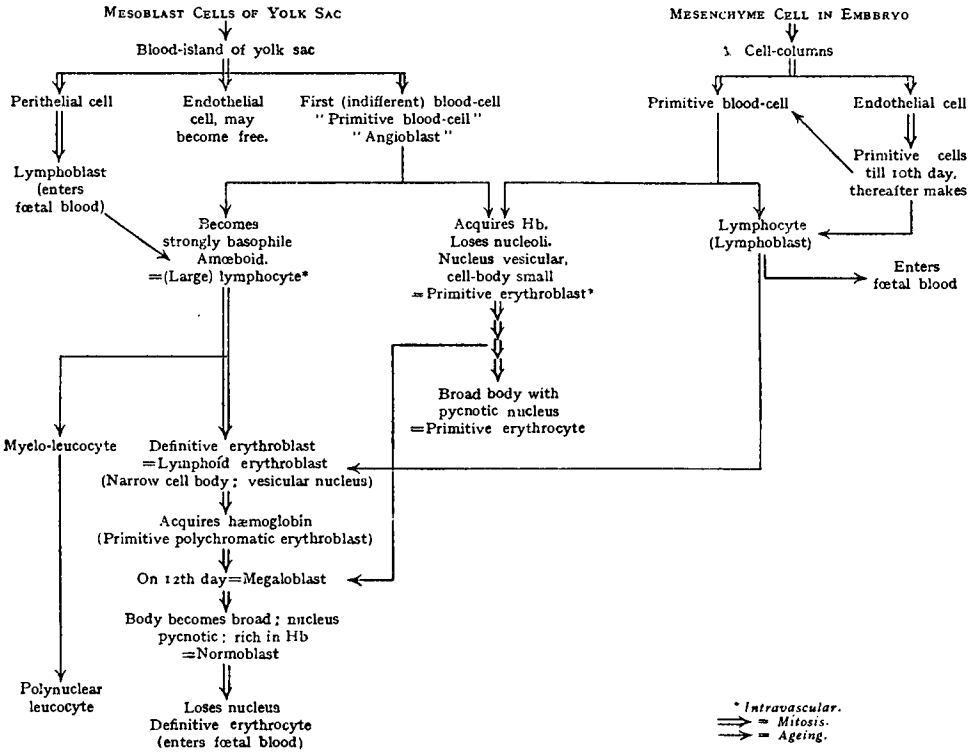
The further stages in the process of blood-formation in this region consist in the formation of erythroblasts and myelocytes from the primordial cells, which proliferate vigorously and form clumps of small polyhedral cells with homogeneous cytoplasm, smaller nucleoli, and more regular arrangement of the chromatin. The pseudopodia disappear. Hæmoglobin does not appear at this stage. Ultimately the nuclei are cast out, and are devoured by endothelial and connective tissue-cells. The endothelial cells retract from one another and allow the normoblasts (*see chart*) to separate and be washed into the circulation. Some of the cells formed from the primordial cells, and some of those formed from the wandering cells, gradually metamorphose into cells with myelocyte nucleus, and granules appear in the cell-body. At this stage, the connective-tissue cells cease making lymphocytes, but turn into fibroblasts, fat cells, and perhaps into slumbering wandering cells. True blood-cell formation is now in full swing. The finer details may vary after birth, but the essentials of the process remain the same.

The charts on opposite page will serve to make the various processes more clear.

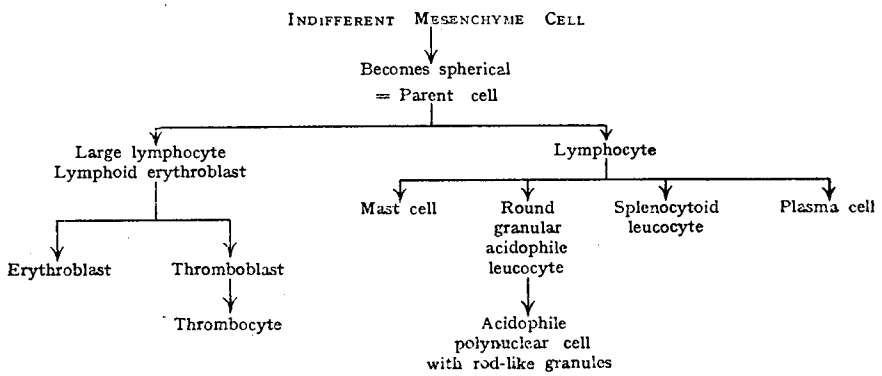
Red-cell Formation in the Liver. — The embryonic liver may be regarded as a network of rapidly-proliferating cellular trabeculæ which penetrate into a system of venous channels and give rise to bud-like processes into the lumen of the vessels, pushing

* This begins at the fourth month (Engel[31]).

SCHEME OF MAXIMOW'S ACCOUNT OF EMBRYONIC ERYTHROPOIESIS.



DANTSCHAKOFF'S VIEWS OF ERYTHROPOIESIS IN THE CHICK MAY BE SCHEMATIZED THUS:



the lining endothelial cells before them, and leaving pockets. The ultimate result is a network of epithelial cells separating a network of vascular channels called sinusoids. From the second month on, the vascular channels are found to be full of erythroblasts of all kinds. Hæmogenesis must occur somewhere in relation to the capillary channels, and it may be either within their lumen in the pockets or diverticula formed in the manner indicated above, or it may be immediately outside their walls. We thus have the following regions in which red cells can be formed :—

1. Recesses in the capillaries of the lobule. Intravascular formation.

2. The space between the capillary and the liver cell. Extravascular formation.

In these situations we meet with similar cells to those characteristic of red-cell formation in the bone-marrow. These cells have a dark cytoplasm, are of large size, and are continuous by protoplasmic processes with the reticulum. They contain no vacuoles.[31a] Saxer[31b] found that giant cells (megakaryocytes) are numerous in this tissue, and they have been considered essential to red-cell formation. According to some writers, the process of hæmogenesis in this tissue is the same in early as in late embryonic life, but Askanazy[31c] considers that there is a very definite distinction between the two.

According to Askanazy, the red cells in the liver are not made from the endothelial cells, but from migrated myeloid elements, which ordinarily spend a "nomadic existence;" wherever they settle they give rise to a local supply of red cells; at any time, however, they may pass on to other regions.

At a later epoch in intra-hepatic hæmogenesis, the primitive erythroblasts are found to have given place to a second type of cell (Mollier's hæmoblast). This is spherical in shape, has a homogeneous pale cytoplasm, and a deeply staining nucleus. An intermediate stage is passed through before the type with a very deeply staining nucleus is arrived at. Hæmoglobin then appears within the cell-body, as the basophilia diminishes. Masses of hæmoglobin may be seen within the endothelial cells at this stage, possibly from

phagocytic action on the part of these cells—but more probably from secretory action. Maximow described buds from hæmoglobin-containing mononucleate cells, projecting into the lumen of the vessel. By the time that red-cell formation has reached maturity, the reticulum in which the formative cells are situated shrinks more and more from the wall of the capillary, and leaves the new cells within the blood channel by a purely passive process. Lobenhoffer[31d] believed that the entry into the vascular channels was active, in that the space between the liver cell and the capillary becomes so filled up with colonies of young mitosing erythroblasts of varying size, that they are forced into the blood space; in this way the recesses, or the sinusoids characteristic of embryonic liver tissue, are produced. It is possible that sieve-like openings appear along the walls of the capillary.

Previous to the time of intercommunication between hepatic-formative islands and the vascular channels, the latter contain only yolk-formed red cells. After this period, it is evident that the blood in the liver contains hepatic blood-cells and marrow-cells in addition. When the yolk-cells cease to be formed, the blood contains only the hepatic and marrow red cells. By the seventh month, the sieve-like communications have closed up, and red-cell formation in the liver begins to subside.

Red cells are first formed in the liver at the tenth to the twelfth day in the rabbit; in man, at the end of the first month. The process ceases about a fortnight after birth (Kostanechi[31e]). Goodall[31f] found that red-cell formation in the liver precedes leucocytogenesis in the sheep.

Red-cell Formation in the Spleen.—The spleen commences its activity at a later period than does the liver—about the sixth week. The tissue contains numerous giant cells, and hæmoblasts, which proliferate actively. There is evidence to show that the indifferent specific splenic cells themselves give rise to hæmoblasts for a certain period of the life of the individual. This is specially marked in the lower vertebrates.[31g] There is no red-cell formation in the spleen after birth, except under pathological conditions; the later phenomena in the spleen are rather those of myeloid transformation.

Red-cell Formation in Lymph Nodes.—In one case of acute hæmorrhagic macrolymphocytar leukæmia, reported by Pappenheim,[31h] it was found that the mother cells of the venous interfollicular tissue gave rise to red cells. If this finding is to be regarded as more than of passing interest, it indicates that erythropoiesis can take place in the lymphoid tissues even in post-embryonic life.

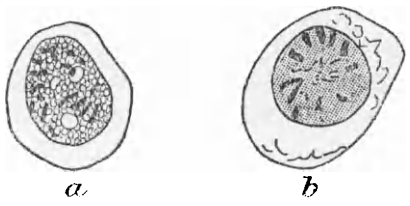


Fig. 23.—Lymphoid Erythroblasts.
a, Intermediate stage between parent cell and *b*, Lymphoid erythroblast. (See note to *Fig.* 8).

When the primordial cell acquires characters which place it with the hæmoglobin-forming series, it is found to have undergone nuclear metamorphosis. Here, as will be found to hold with the other cell series, differentiation goes hand in hand with change of nuclear character.

Characters of the Lymphoid Erythroblast.—The characters of the cell, now called lymphoid erythroblast, are as follows (*Figs.* 23 and 22):—

Size.—6–9 μ.

Shape.—Round, with regular and well-defined contour.

Cell-body.—The cytoplasm is basophile, and devoid of any granules, devoid of circumnuclear zone or astrosphere. The amount of cytoplasm is small. There is no hæmoglobin.

Cell-granules.—No azure granules.

Nucleus.—Central in position, round, relatively large (2–4 μ), clearly defined. The chromatin is arranged in characteristic form—the so-called wheel structure, since the parachromatin and chromatin alternate at the periphery of the nucleus.

Nucleolus.—None.*

* The fate of the nucleolus during the conversion of the primordial cell into the erythroblast.—The following possibilities require to be discussed: (1) That the nucleolus is cast out. In favour of this is the presence of such bodies both free and within the bodies of phagocytes; (2) That it turns into oxychromatin, and ultimately takes part in the formation of hæmoglobin; (3) That the nucleolar matter is admixed with the chromatin, thus accounting for the altered tint of the nucleus with azur staining—ordinarily purely basophile.
In embryonic myeloid tissue there are seen lymphoid erythroblasts without hæmoglobin, but with nucleolus, the nucleus already showing radial structure (promegaloblasts).

Mitosis.—Frequent. The cells are very basophilic.

Appearance with Ultra-violet Light.—The characteristic radial structure of the nucleus is well demonstrated,[32] and the dark bands are extremely opaque to the rays. The cell-body, on the other hand, is quite homogeneous (distinction from the white cells).

Characters of the Megaloblast.—This cell presents considerable variations in aspect with increasing age, owing to the fact that it is first polychromatic and finally ortho-chromatic. In other words, the amount of hæmoglobin in the cell is scanty to begin with and produces an anomalous colour effect with the ordinary dyes, while the mature cell is rich in hæmoglobin, which then stains strongly red with eosin (orthochromatic). The megaloblast is already a biconcave cell.[33] The characters are best tabulated, thus :—

	Polychromatic Megaloblast	Orthochromatic Megaloblast	
		Engel's metrocyte of the first generation	Engel's metrocyte of the second generation
Size	10–20μ ..	Less ..	Less
Cell-substance	Scanty.. ..	More abundant	More abundant
	Strongly polychromatic ..	Slightly ..	Not at all
Granules (Winkler-Schultze) ..	Present[35] ..	Present ..	Not observed
Nucleus ..	*Large*	*Large* ..	Small
	Rich in structure	*Rich in structure*	Very darkly staining
	Does not pycnose	Does not pycnose	Pycnoses
Nucleolus ..	Present[36] ..	No	No
Multiplication ..	By mitosis ..	By mitosis ..	By mitosis
Other forms ..	Gigantoblast .. Micromegaloblast*	—	—
Physiological properties ..	Amœboid† ..	No	No
Pathological change ..	Premature expulsion of the nucleus ..	Ditto ..	Ditto
Fate	Becomes metrocyte 1st gen. ..	Becomes metrocyte 2nd gen.	Becomes normoblast

* The prematurely denucleated erythroblast is an atypical form.
† Thayer.

Other cells which belong to the same group, are the secondary erythroblasts (small, medium, and large forms).

CHEMISTRY OF THE ERYTHROBLAST.—The use of vital stains reveals the presence of vivid red granules (neutral red) of acid reaction, and the nodal intersections of the reticular network (*substantia reticulosa*) stain of a brownish colour. The acidity is due to the presence of free oleic acid, probably associated with a lipoid exudate from the nucleus.[37]

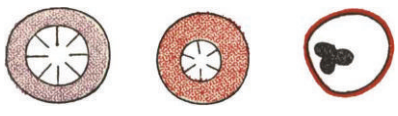


Fig. 24.—DIAGRAM OF THE MEGALOBLAST FORMS. *a*, Polychromatic; *b*, Orthochromatic form, first generation; *c*, Ditto, second generation (compare with the tabulated description).

The mechanism of the formation of hæmoglobin has been worked out to be the effect of diffusion of the parachromatin (nucleic acid) from the nucleus into the spongioplasm. The nuclear material meets with amino-bases in the latter, and combines with them to form hæmoglobin (Loele[38]). This explains why the wheel structure of the primitive cells gives place to the peculiarly densely-stained chromatic mass of the pycnotic normoblast. It is noticeable that the polychromatism becomes less and less (orthochromatism becomes greater and greater) as the nucleus becomes darker and denser. The interspongioplastic hæmoglobin appears, as the pale streaking within the nucleus disappears.

There has been much discussion as to whether the megaloblast, for instance, is rich or poor in hæmoglobin. According to Hirschfeld, this cell contains as much hæmoglobin as the other red cells, because triacid staining does not justify any other conclusion. May-Giemsa gives so polychromatic an effect that the hæmoglobin tint is masked. Pappenheim considers the megaloblast to contain little hæmoglobin, because (*a*) polychromasia means poverty in Hb, (*b*) giant megaloblasts are definitely basophile.*

* Here, as in so many subjects of dispute in hæmatology, the final conclusion is nothing more than an expression of personal opinion. There is as yet no fact which shall definitely say that polychromasia is or is not dependent on Hb-defect.

DIFFERENTIAL DIAGNOSIS OF THE MEGALOBLAST.—

From the *leucocyte*. Pycnotic megaloblasts may simulate polynuclear leucocytes. The nuclear structure should be studied. The pycnotic nucleus is quite devoid of parachromatin.

From the *Türk cell*. Note the relative size of the nucleus (compared with the cytoplasm). It is small in the Türk cell. The cytoplasm of the latter is intensely basophilic, and is vacuolated. The nucleus is amblychromatic.

From the *myelocyte*. If the megaloblast shows chromatinolysis it may simulate the myelocyte. The presence of hæmoglobin in the megaloblast would be sought for.

VIEWS AS TO THE NATURE OF THE MEGALOBLAST :—

1. *That it is degenerative*.—(*a*) That a blood-borne poison, acting on the cells, causes a change in the hæmoglobin ; (*b*) That it is the effect of a blood-borne poison acting on the marrow cells (Bönniger, Naegeli, Erik Meyer, Bloch) and causing them to make aberrant cell forms. K. Ziegler and Isaac and Moeckel regard the appearance of megaloblasts and megaloblastic degeneration of the bone-marrow as a direct result of the action of the poison on the marrow, and itself an evidence of myelotoxicosis.

2. *That it is regenerative*.—(*a*) That a blood-borne poison acts on the marrow and excites *regeneration* (embryonization, Ehrlich) without differentiation into normoblasts, etc. The progress of development is set in motion but *arrested at the megaloblast* stage. (Naegeli, Erik Meyer, Engel, Pappenheim). (*b*) That it is entirely normal erythropoiesis (Grawitz). (*c*) That it is a response to a severe injury to the bone-marrow, or, sometimes, to the blood. If these cells are *numerous* in the bone-marrow, then it must be a pathological condition (Türk). It is the product of exhaustion of an already asthenic marrow, after hæmotoxic influences. The myelotoxicosis, however, is not the cause of pernicious anæmia.[96] (*d*) That it is the normal process of red-cell formation in the embryo (Ehrlich). However, embryonic tissue contains both megaloblasts and normoblasts. Post-embryonically, too, both megalo- and normoblasts occur together.

3. *That it is a swollen erythrocyte* (Mya).—This is not likely, because it would demand a structure of cell different from that

of other cells which cannot be made to swell by osmosis. On the other hand, when the blood is rich in megalocytes, it is polyplasmic, so that some large red cells have arisen by swelling.

4. *That it is a purposeless* and inevitable result of action of some noxa (*a*) on the bone-marrow, regardless of kind, but dependent on degree; or (*b*) on the blood, with or without action on the bone-marrow, according as the latter does or does not undertake regeneration.*

The Characters of the Normoblast.—

Size.—7–9 μ.

Shape.—Spherical, not biconcave.

Cell-body.—Homogeneous, non-granular, and yellowish-green in colour (with methylene blue).

Nucleus.—Relatively small, sharply spherical and central. Stains densely, and presents the characteristic wheel structure. Pachychromatic. Nuclear membrane well marked.

Nucleolus.—Present according to Schilling.[39]

Multiplication.—By mitosis.

Degenerative Changes.—Pycnosis of the nucleus and free nucleus formation.

CHEMISTRY OF THE NORMOBLAST.—The process by which the basophile cytoplasm of the megaloblast gives place to the erythrophilic hæmoglobin-containing cell substance must lie in a chemical "metaplasia" of the paraplasm, associated with a loosening up of the spongioplastic network. In certain toxic anæmias, the basophile cytoplasm clumps up into masses which appear as punctate basophilia, during the time that the cells are circulating.[40]

DIFFERENTIAL DIAGNOSIS OF THE NORMOBLAST:—

From a *lymphoid cell.* The rule may be formulated that if a lymphoid cell have a nucleus like a wheel, or like a densely chromatic (pycnotic) mass, then it is an erythroblast or hæmoblast. This covers the difficulties of diagnosis of the parental lymphoid cell, as well as of the polychromatic or (pathological) basophile normoblasts from lymphoidocytes, large mononuclears, leucocytoid lymphocytes. The peculiar greenish tint of the erythroblast

* This view is somewhat similar to that of Türk.

cytoplasm is a frequent help in diagnosis, besides the facts that the cytoplasm is relatively more abundant, and that the nucleus is only slightly excentric, if not truly central in position.*

The Birth of the Red Cell into the Blood-stream.—We have traced the sequence of changes which take place in the process of conversion of the primordial cell into the normoblast. It has been indicated that the cell-substance becomes more and more abundant, looser in texture, and more definitely reticular in structure, while the nucleus still remains characteristically lymphoidocytar; that the nucleus† then exhibits a tendency to radial arrangement at the same time as an oxyphile parachromatin appears within it; while the cell-body develops homogeneity of structure, with alteration of staining power simultaneously with the commencement of formation of hæmoglobin. The delicate outlines of the lymphoidocytar cell become replaced by the more definite and clean-cut contour of the normoblast. Finally, the radial structure of the nucleus, ultimately well-marked, disappears again with the increase in the amount of hæmoglobin formed within the cell-body, while the shape of the nucleus alters, becomes polymorphous (pycnotic) in consequence of the shrinkage of the material within it.

Before the red cell is " born " into the circulation, it loses its nucleus.

The mechanism by which the loss of nucleus takes place is one of the subjects of controversy in hæmatology.‡ We have the following possible explanations of the process.

1. Either it is not lost at all (Schilling), only the chromatin having disappeared:

2. It is cast out:

3. It is dissolved out (chromatolysis, karyolysis): or

4. It is partly dissolved, and extruded in that condition.||

1. The first view may be correct in some instances. If chromatolysis take place, the parachromatin remains in the cell,

* This is by no means invariable.

† An alternative view (Freytag[40a]; H. C. Ross[87]), that the nucleus appears first, and develops a cell-body around it, finally giving rise to a red cell, hardly deserves mention.

‡ Probably because some observers studied healthy and others pathological blood, and considered the difference beneath notice.

|| Artificial denucleation may be induced by boric acid, urea, tannin, etc., applied to the wet preparation[40b].

and the last stage before complete loss would be represented by the Jolly body (*see p.* 83), which may never be extruded at all. The oxyphile nuclear masses which have been described as occurring in red cells would represent the parachromatin.[41] Further, the fact that a nuclear body can be demonstrated in nearly every red cell in man, by a methylene-blue-picric-acid method, is of interest. (*Plate II, No.* 7).

2. The second view was held by Rindfleisch, but was regarded by Ehrlich as holding only in the case of the normoblast, and not for all nucleated red cells. Engel accepted it only for the polychromatic normoblasts. Maximow accepted it entirely, and Pappenheim considers it is a pathological process due to errors of tonicity (anisotonia) of the serum, being met with only in the case of those erythroblasts which enter the blood-stream instead of remaining behind in the bone-marrow till their development is completed. According to this author, it is quite incorrect to assign a different mechanism for the loss of nucleus to different red-cell parents. The megaloblast is similar to the normoblast in nuclear structure, and in the senile changes to which it is liable ; it differs only in that the normal process of ageing does not go as far as the production of erythrocytes. Pycnosis, chromatolysis, and karyorrhexis only occur in the megaloblast under pathological conditions (*see chart, p.* 68), although they then follow the same rules as hold good in the normoblast. There is therefore no logic in saying that the normoblast loses its nucleus by extrusion and the megaloblast by karyorrhexis :—

Normal Process.—No megaloblasts. Normoblasts present. These show chromatolysis of pycnotic nuclei.

Pathological Process.—Megaloblasts present ; show karyorrhexis ; normoblasts also show " rhexis."

The arguments against the second theory are : the existence of Jolly nuclear rests within the red cells ; the existence of Cabot's membranes ; the absence of free nuclei in the bone-marrow.

If the nucleus be cast out, what becomes of it ? It may be subjected to phagocytosis in the bone-marrow, since macrophages are often seen there, which contain nuclei but no blood-pigment (Jolly). On the other hand, macrophages may devour whole red

cells without betraying such an event by pigment-granule deposition (R. Blumenthal). Secondly, it may break up into coarse particles (" punctate basophilia," *see p.* 78), which ultimately dissolve within the cell.

3. The third theory is accepted by Neumann, Kölliker, Engel; and by Ehrlich for the megaloblast. Pappenheim considers that this change takes place normally within the blood-cell factories, though especially marked in severe toxic anæmias (conspicuous because met within the circulating blood). It is the normal procedure after pycnosis of the nucleus has taken place, the shrinkage of the latter having ended with the formation of the small granule, the Jolly body. According to Weidenreich, this body is ultimately extruded. The loss of nucleus must occur before the cell leaves the bone-marrow at all. Blumenthal has pointed out that an alteration of osmotic relations between plasma and formative cell would account for the disappearance of the nucleus without obvious precipitation phenomena in the cell. The pressure is greater in the blood than in the areas of hæmopoiesis, and the cells are more turgescent at the time of mitosis.

4. The fourth theory is held by Engel in the case of the pycnotic normoblast.

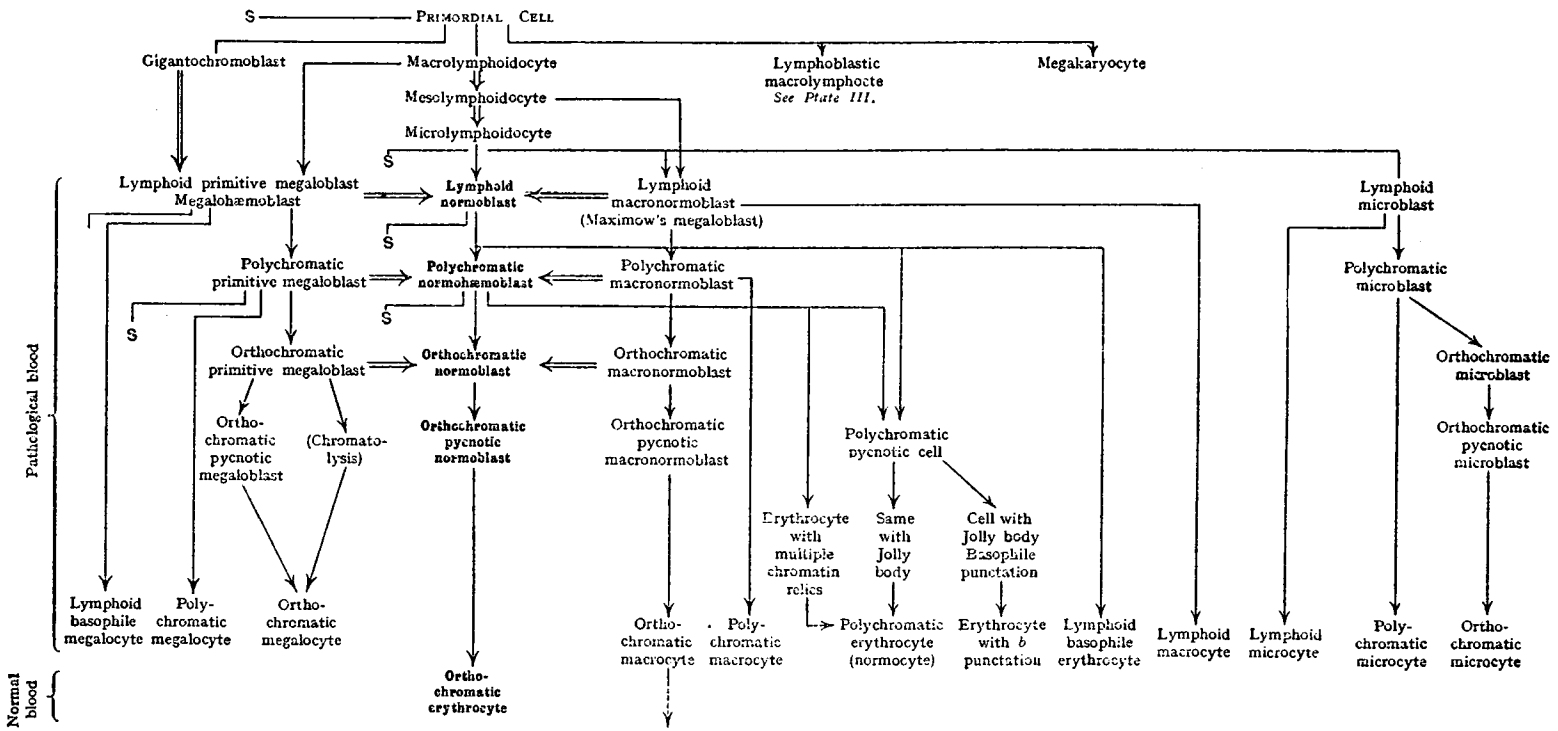
The best mode of co-ordinating these views* is as follows :—

Description	Site of Cell	State of Nucleus at the time	Last Stage	Occurs in
Normal	Bone-marrow	Pycnotic ..	Chromatolysis	Health
Abnormal	Blood ..	Partly pycnotic	Extrusion ..	Simple anæmia
Frankly patho-logical	Both blood and bone-marrow ..	(i) Pycnotic .. (ii) Juvenile and non-pycnotic	Karyorrhexis	Severe acute toxic anæmias.

As soon as this change is effected, then, the completed red cell finds itself swept into the blood-stream. Why it should be able to enter at this stage, and not before, is unknown. All that we can say is that the cell has now arrived at " blood-maturity."

* Pappenheim's exposition of these views is more graphically expressed when crystallized in the manner given.

SCHEME OF PAPPENHEIM'S VIEWS ON POST-EMBRYONIC ERYTHROPOIESIS.



III.—THE LIFE HISTORY OF THE RED BLOOD-CORPUSCLE IN THE BLOOD-STREAM.

CHARACTERS of the erythrocyte—The theories regarding the structure of the red cell—The chemistry of the red cell—The fate of the red cell—Degeneration phenomena—The evidence of destruction of red cells—The reticular substance—Polychromatophilia—Punctate basophilia—The Heinz bodies—Red-cell shadows—The Howell-Jolly bodies—The Cabot ring bodies—Chromolinin granules—The blood-platelets—Hyperchromia—Alterations of shape and size—The *comparative morphology* of the red cell—The spindle cell—The hæmokonia or blood-dust.

THE blood of the normal infant contains at birth six million red cells per c.mm. This number decreases with age to about five and a half by the end of the second week of life. The adult blood contains about five millions per c.mm. in the case of the male, four and a half millions in the case of the female.

Characters of the Erythrocyte.—The red cell, erythrocyte, or normocyte, is a thin flattened disc, slightly concave on one side, more so on the other. According to Weidenreich, mammalian red cells are dimpled on one side and slightly convex on the other (bell-form); the biconcavity usually seen is regarded by him as the result of accidents during preparation (evaporation).[42] Against this view is the observation of the cells in the circulating blood (mesentery, e.g.).*

The outline of the red cell is regular, and its surface smooth. It is very elastic. It owes its colour to the presence of hæmoglobin. According to Sapegno, it contains Winkler-Schultze granules.

Size.—This is very uniform in normal blood, 75 per cent of specimens measuring from $7\frac{1}{2}$ to $8\frac{1}{2}$ μ (·007 to ·008 mm.) by 1.7 μ in thickness.

Nucleus.—It is usually stated that there is no nucleus in the red cell of man. According to Roscoe King, every red cell has a remnant of nuclear matter within it,[51] and Schilling[52] has demonstrated that there is a definite nuclear structure in every cell, though it has so slender a connection therewith that it is lost in

* Schäfer,[45] David,[46] Jordan,[47] Jolly,[48] Orsos,[49] Löhner.[50]

the form of blood-platelets in the course of ordinary preparation. Kronberger[51] has recently shown (1912) that "nuclei" can be demonstrated in any red cell by a simple method of staining (methylene-blue, picric acid). (*Plate II, No.* 7.)

*Glass-body.**—Schilling[52] has described a peculiar structure within the swollen red cells in malarial blood, having a spherical shape, devoid of hæmoglobin, and containing a vacuole in which lay two very minute granules. The granules stain black with osmic acid, red with chromatin dyes, and are strongly refractile in the unstained condition, greenish-yellow with dark-ground illumination. These granules were regarded by Schilling as centrioles.

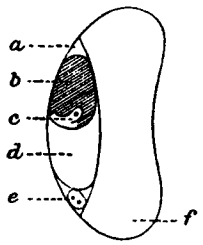


Fig. 25.—Schilling's Conception of a Red Cell (L.S.). (*a*) Membrane; (*b*) Blood platelet; (*c*) Capsule body with nucleolus; (*d*) Glass body; (*e*) Centrioles and centrosome; (*f*) Hæmoglobin-holding portion.

Subsequently he was able to detect them even in normal erythrocytes. Diazin-green demonstrated the presence of platelets adhering to the red cell by means of a delicate membrane. Lieberkühn[54] regards this as a protein spherule.†

This conception of the red cell may be expressed in the accompanying diagram (*Fig.* 25), which shows a body flat on one side, and convex on the other. The convexity is due to the "glass-body," which is ordinarily invisible, leaving an apparently biconcave hæmoglobin-bearing part. In one corner of the glass-body is the nuclear remnant, with a "capsule-body" covering in the nucleolus. Adjoining this are the centrioles, with the centrosome,‡ part of which is usually lost in preparation as a blood-platelet.

Benda and Jordan[55] consider these appearances as artefacts, even though they are seen with dark-ground illumination. Jordan's criticism is based on observations of the red cells in the living cat while narcotized with ether.

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* First found by Roberts.[53] Not accepted by Dietrich.[53a]

† A platelet may, however, be looked on as a protein spherule.

‡ Centrosome + capsule-body, by accumulating plastinoid chromatinic substances, may appear as pseudopodia (Schilling).

According to Walker, Ross and Moore,[53] 5 per cent of red cells can be made to show the presence of a centrosome if an absolutely refined technique be followed.

THE STROMA OF THE RED CELL.—The existence of a hyaline network within a red cell (substantia granulofilamentosa), made of nucleoproteid, in the meshes of which lies the hæmoglobin, has been accepted by some (Rollett[56]), and rejected by others (Schäfer[57]). The fact remains that some red cells do contain a vitally stainable substance* in the form of a network, which is the more abundant the younger the cell. It stains blue with Nile blue (*see p.* 75). Ultra-violet light, according to Grawitz and Grüneberg, shows no such reticulum in any erythrocyte. It is more satisfactory in many ways to look upon the red cell as made of a semi-permeable membrane (H. Koeppe) with a spongy network of reticular substance, enclosing aqueous hæmoglobin within its meshes. The network would be colloidal, and possibly not anatomical in the strict sense. The membrane is covered by a film of lipoid material, in which lecithin and cholesterin are prominent.

THE THEORIES RELATING TO THE SUBJECT are these :—

Griesbach :—That the red cell consists of a homogeneous structureless plasma and no membrane.

Weidenreich and Dietrich consider the red cell to be merely a bladder whose contents, the endosoma, contain the pigment, while certain agents may lead to the formation of precipitates within the envelope, and so simulate a " reticular substance." Fischer found that fixatives, such as osmic acid and mercury perchloride, would cause extracellular hæmoglobin to aggregate into flakes, thus simulating punctate basophilia and reticular matter. This view was accepted by Grawitz on the basis of observations of the red cell with ultra-violet light, wherein the cell is homogeneous.

If the red cell be only membrane + contents, the " membrane " has still to be defined. Löhner[59] divides membranes into : (1) Physical : (*a*) surface scum, (*b*) plasmatic film ; (2) Histological. He suggests that the cell membrane is only a physical one (plasmatic film).

The Stroma Theory.—Schultz expressed the view that there is a lecithin-stroma of ultramicroscopical structure, in whose meshes lie a watery solution. The jelly-like stroma maintains the hæmoglobin in an absorbed state. The full bearing of this view requires an appreciation of the phase-doctrine of Ostwald.

Schäfer is a strong opponent of this theory,[60] stating that it " must be definitely abandoned." The chief argument against it is the character of the movement of the red cell within the capillaries. In the nucleated red cell of the lower vertebrates, the nucleus is always readily displaced within the

* First discovered by Ehrlich, " Farbanalytische Untersuchungen," pp. 98, 119.

red cell, which would not be possible with a stroma. For these reasons he disbelieves even G. N. Stewart's view,[61] that the hæmoglobin is in the form of a gel.

The explanation of this divergence of opinion must lie in some such fact as was adduced in connection with the dispute about the manner of loss of the red-cell nucleus. The exact structure of the red cell may vary in normal and pathological blood; the so-called stroma may be an optical effect produced by a colloidal mixture, just as the spongioplasm of any cell may. It does not seem likely that a red cell is a sac containing anything approaching watery material, and those who are satisfied with such a view apparently overlook the laws of colloidal chemistry. The view expressed by Schultz is therefore by far the most likely.

The *red cell with dark-ground illumination.* It shows perfect homogeneity of structure under these conditions—a round bright ring with sharply-defined dark centre. Crenate, swollen or burst erythrocytes are easily seen by this method (Dietrich[62]).

The *vital staining reactions* of the red cell are best considered in conjunction with the processes of degeneration (*see p.* 75).

THE CHEMISTRY OF THE RED CELL.—It is not proposed to discuss the chemistry of hæmoglobin, since this subject belongs to the domain of pure physiological chemistry. As is well known, the gas-exchange function of the red cell depends on the presence in it of this substance. Regarding the question of the lipoid material within the cell, Overton's observations may be referred to, that the red-cell membrane is covered by a film of lipoid material, which is made up of cholesterin and lecithin* (Norris's "myelin"[63]), and encloses the hæmoglobin in watery solution. The following considerations go to show this: (1) The phenomena seen in hæmolysis by saponin. One may add, that all hæmolytic reactions are best explained in this way: ether, chloroform, immunity reactions; (2) Corpuscles melt at 52° to 60° C.; (3) The formation of rouleaux; (4) The indentation of the membrane by protozoa striking it; (5) The fact that mechanical rupture of the red cells leaves no sign of any hole; the fatty material immediately flows in around the point of rupture and obliterates it. Grawitz suggests[64] that the fine particles of fat in the circulating blood (which can be seen with dark-ground illumination) are taken up

* Drops of fluid enclosed in *lipoids* assume a flattened shape.

by the red cells and appear to us as lipoid envelope, to be afterwards given up to the tissues wherever needed (e.g., to working muscle, which requires a rapid supply of energy-producing matter). This idea of a second function of the red cells may be contrasted with Pavy's view of the function of the lymphocytes (*see p.* 139).

Percentage composition of the red cell in man (Bunge[65]):—

Water	68·2
Hæmatin	1·5
Organic compounds	29·6
Potassium salts	0·61
Sodium	0·03
Calcium and magnesium phosphates	0·016

Glucose is stored up in the red cells in cases of alimentary glycosuria (Rona and Takhaschi[66]).

The mode of formation of hæmoglobin has already been considered (*p.* 62).

The presence of oxydase in the red cells of frogs and birds was detected by Pappenheim.

The *osmotic and physical phenomena* of red cells (rouleaux formation, specific gravity, resistance of red cells in hæmolysis) do not come within the scope of this work, since their description involves the detailing of many purely physico-chemical laws.*

The Fate of the Red Cell. Degeneration Phenomena.—It is evident that in any one drop of blood, red cells of all ages must be present. If it be possible to determine the average duration of life of each, the knowledge would be of service.

The following estimation, by Zoja,[67] shows that the normal length of life of a red cell in the circulation is about ten days. Other estimations place it at three to four weeks. Assuming that the total amount of blood is $\frac{1}{13}$ of the body weight, then in an adult weighing 70 kg. there will be 5384 gm. blood (= 5080 c.c.). Again, assuming that 600 c.c. of bile are secreted daily, 0·35 per cent bilirubin is present in it, and 13·77 per cent by weight of hæmo-

* It will suffice to note that the resistance of red cells is increased (1) after injection of homologous blood, (2) after treatment with phenylhydrazin in vitro; that such increase of resistance is accompanied by an increase in the amount of stroma (Sattler; Ferrata)[66]. The last statement is disputed by Rosenthal.[66]

globin in blood; further, assuming that the total formula of bilirubin is $C_{32}H_{36}N_4O_6$, then Zinowski's equation allows an estimate of the amounts of hæmoglobin broken down and the red cells destroyed. The result is: 62·83 gram hæmoglobin and 420,000 reds per c.mm. In twenty-four hours, a tenth of the total of each is destroyed. In other words, the total cell-content is renewed every ten days.

How does the red-cell content of the blood remain constant? Roux and Driesch endeavoured to solve this problem by adducing chemical and physico-chemical data, and the biological equilibria of Centanni. If the normal equilibrium be upset, a new one arises which is more or less effective, and depends for its efficiency on the factors previously existing. The conditions depend on the circumstances which led to the disturbance of the original equilibrium, as well as on the new circumstances arising by the action of the factors inducing it (Zoja). Assuming that the destruction of the red cells gives rise to autocytolysins which excite a corresponding degree of cytopoiesis in the hæmopoietic organs, we see here an automatic mechanism for regulating the content of red cells.

The intermediate stages between "robust health" and destruction of the red cell in the liver, spleen, etc. (reappearing as bilirubin, or, pathologically, as "siderosis") are difficult to demonstrate. Some of the red cells are removed from the circulation by phagocytosis (erythrophages) in the spleen,* bone-marrow, and lymph-nodes, but there is no evident difference in the appearance of a red cell about to be phagocytosed, and one that is apparently in full activity. On the other hand, such changes may be noted as these—shrinkage, development of polychromatophilia, loss of hæmoglobin, flattening out of dimple. Pathologically, a number of changes are observable which may be interpreted as intermediate stages of breakdown, but these stages are evidently not passed through under normal conditions.

Evidence of Destruction of Red Cells.—

1. *Alterations of Morphology.*

Cesaris-Demel's reticular substance. Note the relative proportions between cells exhibiting same, and those not.

* The histolysis of red cells in the spleen passes through all stages towards a granular pigmentary detritus. In animals with nucleated red cells, the nucleus loses its affinity for basic dyes, and gradually dissolves away. At the same time, the cell-body fails to stain adequately with eosin or acid fuchsin (Blumenthal[68]).

Polychromatophilia.

Proportions between platelets and whole red cells.

Punctate basophilia.

Jolly bodies.

Cabot's rings.

Presence of normoblasts, microcytes, macrocytes, poikilocytosis, fragmentation of cells.

Alterations in the stroma: hypochromia, dyschromia (basophilia), true necrobiosis.

Alteration of the hæmoglobin: increased oxidizing power, conversion into met-hæmoglobin.

2. *Alterations of the resistance.* This is greater the younger the cell.

3. *Presence of bilinogen* in the urine and fæces (estimation by chloroform extract by Riva and Zoja's method[69]), in respect to the ratio between its quantity and that of the hæmoglobin.

THE RETICULAR SUBSTANCE.—The presence of reticular substance within red cells is demonstrated by the use of vital stains. Vital staining* is really a pre-agonic staining, because the material coloured takes up the dye just before death takes place, the staining agent being toxic in action. The reticular substance is a filamentous material beaded with granules,† the latter coming out metachromatically. Nile-blue, toluidine blue, neutral red, cresyl blue, are suitable dyes for colouring this substance, the reaction with the former showing that the material is made up of free fatty acids.[70] According to Cesaris-Demel, it is identical with basophile punctation (which see);[71] but Pappenheim, Rosin, and Weidenreich are opposed to this view, since they regard it as related to polychromatophilia—a phenomenon met with as a regenerative process, appearing as it does after repeated venesections in animals (Ferrata[72]). The material is not nuclear, but plasmatic in character, because in embryos and young animals its abundance is not associated with the appearance of changes in the nucleus.

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* Vital-staining is regarded as evidence of youth by Poggi, Vassale, Negri, Foà, Cesaris-Demel, Giglio Tos; as evidence of increased resistance of the cells by Widal, Abrami, Chauffard-Fiessinger; as identical with basophilia by Rosin, Biebergeil, Weidenreich.

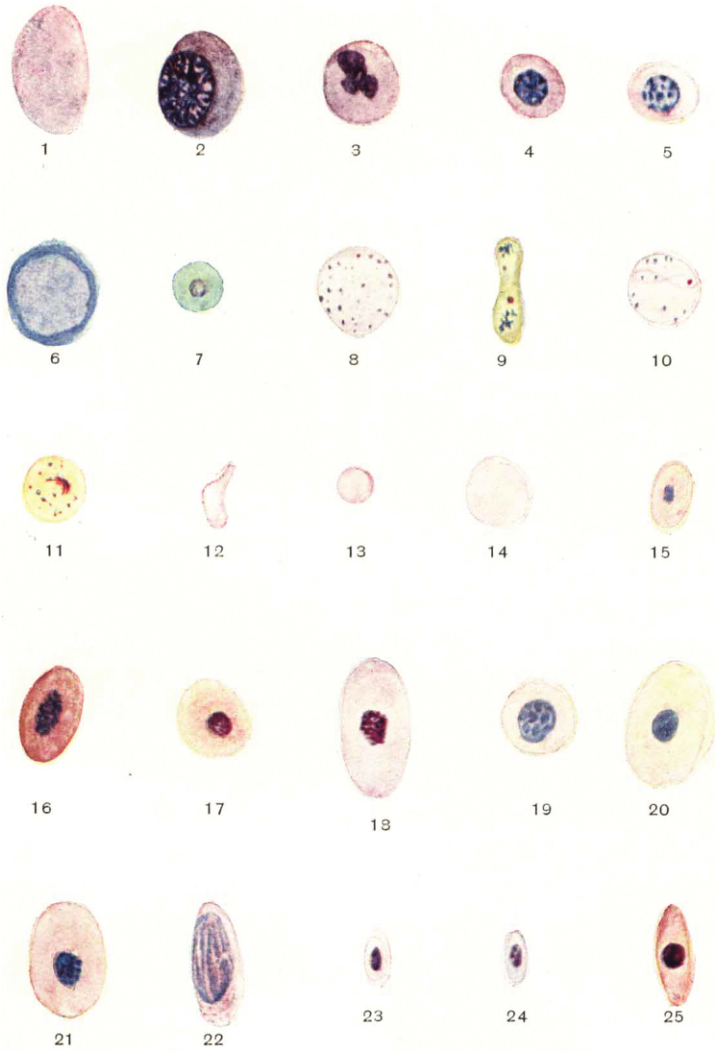
† The granules show Brownian movement.

EXPLANATION OF PLATE II.

1.—Polychromatic gigantocyte. 2.—Polychromatic megaloblast. 3.—Polychromatic pycnotic macronormoblast. 4.—Polychromatic young normobast. 5.—Orthochromatic young normoblast. 6.—Lymphoid hæmoblast. 7.—Red cell of normal blood stained to show the "nucleus" within it (methylene blue and picric acid). Figures 1 to 7 are drawn to scale. 8.—Punctate basophilia in a polychromatic red cell. 9.—Red cell showing substantia granularis metachromatica and the reticular substance. Note the metachromatic staining of the Heinz body with azur (after Pappenheim). 10.—Red cell showing a Cabot ring. 11.—Red cell showing chromatinorrhexis. (8 to 11 are highly magnified. 10 and 11 are after Ferrata and Viglioli. Panoptic stain). 12.—Poikilocyte (medium size). 13.—Microcyte. 14.—Macrocyte. (13 and 14 are drawn to scale.) *Red cells from various infra-mammalia :* 15.—From Carabus hortensis, a beetle (triacid) × 1000. 16.—Scyllium, Giemsa (after Fry). 17.—Petromyzon, Triacid. 18.—Emys lutaria, Panoptic; the hæmoglobin is polar in situation. 19, 20.—Rana temporaria. Panoptic. 21.—Triton, Panoptic. 22.—Spindle cell from Triton; stained by Unna-Ziehl. (17 to 22 after Werzberg, and approximately proportionate in size). 23, 24.—Orthochromatic and polychromatic erythroblast from sparrow, passer domesticus (× 700). 25.—Normocyte with pycnotic nucleus, from domestic fowl artificially rendered severely anæmic. After Kasarinoff. (Highly magnified).

PLATE II.

THE RED BLOOD-CELL



Pappenheim,[73] in 1907, decided that the reticular substance was rather of the nature of a *dye-precipitate* upon the surface of the lipoid membrane (adsorption of the dye by the lipoid). This view was independently arrived at by Biondi.[74] The fact that a fresh vital-stained preparation, treated with active snake-venom-lecithid, dissolves the red cells, leaving the reticular substance free,[73] is quite suggestive.

Occurrence.—Very abundant in embryonic blood, fairly abundant (30–40 per cent) in the new-born animal, and scanty in the normal adult animal. It occurs both in circulating erythrocytes and in the normoblasts of the bone-marrow. It is met with in the blood in cases of hæmolytic jaundice (Chauffard, Fiessinger[75]), and of progressive pernicious anæmia (Widal and Abrami[76]).

Significance.—As has been stated, there is evidence that the phenomenon is indicative of normal regeneration ;* it is frequently associated with polychromatophilia.† Since it can be specially well studied in the red cells of tertian malaria (Schüffner,[78] Maurer[79]), it is presumably connected with regeneration of the blood, and is not an artificial effect. The appearances described by the last-named authors have nothing to do with punctate basophilia (see below).[80]‡

POLYCHROMATOPHILIA.—By this term is meant a morphological change in the red cell whereby the basic and acid components of a dye-mixture are taken up at the same time. A mosaic work may be imagined, in which alternate minute fields are basic (the original basic material of the parent), and the remainder contain hæmoglobin.

As has been seen, this phenomenon is nothing more than a phase in the ordinary maturation of the red cell.[81] Apart from this, polychromatophilic cells may be seen in the blood of pigeons, mice, guinea-pigs, cats and dogs (Walker), frogs (Grawitz), but not in normal horse or ox blood. The close association with the reticular substance has led Schilling to regard the two as identical,[77]

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* In pernicious anæmia it is the anisocytosis and the presence of megaloblasts which indicate pathological regeneration.

† Schilling maintains that the two are identical.[77]

‡ The Maurer-Schüffner punctation is a degenerative basophile polychromatophilia. It never occurs except in intoxications, and is not an embryonic process at all (Pappenheim).

but others regard the two conditions as unrelated, although frequently met with side by side (Ferrata and Viglioli).[81]

The following *views* have been expressed: (1) That these cells are *not degenerative* (Gabritschewsky, Askanazy, Arneth, Pappenheim[82]). Proofs: (i) They are very abundant after a hæmorrhage; (ii) They occur in fœtal liver in the seventh month. (2) That they are *degenerative*—cloudy swelling, old age, etc. (Ehrlich, Engel), or, possibly precursors of punctate basophilia (P. Schmidt and Askanazy). Proofs: (*a*) Other red cells in a film show signs of degeneration; (*b*) They are abundant in starving animals, where the bone-marrow shows no signs of activity; (*c*) The strongly polychromatic cells have irregular contour; (*d*) Megaloblasts are always affected and normoblasts are not (Maragliano, Castellino, Ehrlich);* (*e*) They are very numerous after the exhibition of blood-poisons.† (3) That they are *provisional blood-cells* (Engel). (4) That the first two views may each be correct (Rechzeh, Türk, Weidenreich, Grawitz, and Pappenheim). In other words, it may be sometimes a progressive process, at others a regressive process, the latter being by far the rarer. As Weidenreich has said, if the oxyphilia be due to hæmoglobin, and basophilia to the membrane, then a deficiency of hæmoglobin makes the cell appear more basophile equally in youth and in disease. In one case the hæmoglobin has not yet appeared, in the other it has disappeared.

The so-called *azurophile polychromatophilia* is a pathological process, and is regarded as being due to fragmentation of the chromatin. In other words, it is definitely nuclear and not plasmatic in character.[83]

The polychromatophilic red cell differs from a lymphocyte in being poorly stained, in the absence of a basophile film of cytoplasm, and in the absence of a definite nucleus and nucleolus. Comparison with other cells in the blood-film will prevent mistakes.

PUNCTATE BASOPHILIA (basophile punctation, granular degeneration) is a term applied to red cells in which there are fine basophile granules of varying size. Such cells are met with in the blood of birds, of the new-born guinea-pig, mouse, and rabbit,‡ in the human embryo, and in the human adult in certain anæmias (secondary to ulcerating gastric and œsophageal cancer, lead

* But the megaloblast is an immature cell, and would naturally appear polychromatic.

† It does not follow that because blood is poisoned, regeneration of red cells does not ever develop.

‡ Denied by Grawitz, Grüneberg, Bloch, and H. König. Perhaps such embryos were diseased, and this would remove the argument that basophilia is regenerative in character.

poisoning,* poisoning by salts of tin, copper, potassium chlorate, mercuric chloride, pyrodin, phenylhydrazin, septic infections, malaria, bothriocephalus, intestinal intoxications, and in primary pernicious anæmia).†

Such cells are not met with in health, in infants, nor in such anæmias as chlorosis, post-hæmorrhagic (external), aplastic, tuberculous, syphilitic, chronic nephritic, chronic hepatic, diabetic, nor in the course of acute infections like typhoid and diphtheria.‡

Cells in which punctate basophilia may occur. (1) In polychromatic erythrocytes (as fine granules); (2) In orthochromatic erythrocytes (as coarse granules); (3) In mitosing cells.

Theories as to the nature of the condition :—

1. Is it a *true granulation*? It is not analogous to leucocyte granules, because the latter are a mature end-product of the paraplasm, and represent the functions of the cell. Leucocyte granules are analogous to hæmoglobin. Punctate basophilia, on the other hand, indicates incomplete development of the cell and is spongioplastic in character.

2. As regards *source*.

(i). Is it *nuclear*? Askanazy and Lazarus|| regard it as a karyolytic process. Ferrata[84] regards the material as parachromatin, because it is close to the nuclear membrane, and is always associated with karyolytic changes in the nucleus, and sometimes with Jolly bodies or Cabot rings. Naegeli believes it to be chromatin which has undergone a change in staining reaction, by which methyl green interacts with it.

Against Ferrata's view are the facts: (*a*) That parachromatin may be found amongst the fragments of nuclei in a cell without entering the cell-body; (*b*) That basophilia may occur without Jolly nuclear rests; (*c*) And with them. Böllke[85a] considers that the granules cannot be parachromatin, because they occur in mitosing cells (which contain none). The other

* First discovered by Grawitz and Hamel.

† Ehrlich.

‡ The condition must not be confused with the appearance of nuclear chromidial fragments arising from karyorrhexis. These stain red with azur, and blue-green with methyl-green-pyronin, purplish with hæmatoxylin.

|| Schaumann, Engel, Sabrazès, Jawein.

objections to the above theory are at the same time arguments in favour of the second view :—

(ii). Is it *cytoplasmic*? On this view it is a pathological clumping or agglutination of the lipoid katabolic basoplasm,[85] while polychromasia is a diffuse solution of lipoid matter. According to Schilling[86] and Askanazy the latter may turn into punctate basophilia, while according to P. Schmidt and H. C. Ross[87] the reverse process takes place. Hertz[88] believes the two things to be identical, because the number of basophile cells in the blood of dogs poisoned with toluylenediamine is the same as that of polychromatic cells [ascertained by making counts on films stained (*a*) vitally, (*b*) after fixation].

The following facts may be noted: (1) Basophile granules may be abundant in a red cell, and yet the nucleus be absolutely intact;[89] (2) The staining reactions are: non-staining with methyl-green, blue* instead of azur-red with Nocht's method (difference from staining reaction of Jolly nuclear rest), non-staining with the fuchsin in Pappenheim's methylene-blue fuchsin, whereas parachromatin should stain red by this method; they do not accord with the staining reactions of basiplastin, paraplasm, or basophile parachromatin, but with those of spongioplastin; (3) There are no transition forms between them and the Jolly bodies, although both structures may appear within the same cell; (4) They are not associated with karyorrhectic fragmentation of the nuclei; (5) In plumbism, the granules are excessively numerous, but pycnotic or other normoblasts are extremely rare. Ferrata's assertion that the edges of the nuclei are eroded in the vicinity of the granules is explained away as a misconception for perinuclear polychromatophilia (Grawitz); (6) They may appear in nucleated reds, but the nuclei are intact; (7) Nuclear matter is opaque to ultra-violet rays, but the basophile granules are transparent (Grawitz and Grüneberg)†; (8) These granules are seen in the bone-marrow even in cases in which the circulating cells show marked basophilia (Grawitz). This applies both to human cases and to experimental animals. (Naegeli explains this away by averring that they disappear from the bone-marrow during the agony!) (9) They may appear in entirely orthochromatic erythrocytes in which there is no nuclear matter at all.

The sequence of development of the red cell would thus be expressed as follows :—

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* Maximow stated that some granules stain red with this method, but he was confusing a Jolly body with a basophile granule.

† With dark-ground illumination the granules appear as clear spaces, differing only slightly from hæmoglobin in their refractive index (Saar, Dietrich[90a]).

Normal Process.

1. Young nucleus = senile nucleus = (pathological intermediate stage or Jolly body) = chromatolysis.

2. Young cell-body = orthochromasia.

*Pathological Process.**

1. Young nucleus = multiple nuclear fragments = karyor-rhexis.

2. Young polychromatic cell-body = finely punctate basophilia = coarse punctate basophilia = plasmorrhexis = orthochromasia (after complete loss of spongioplasm).

The pathological series of changes would be explicable as the result of lipolytic toxins or ferments acting on the red-cell envelope.[90] As soon as the intoxication ceases, the normal process of maturation would take place, unless an aplastic condition were set up. In either case the basophilia would fail to appear. The inference to be drawn is that if the clinician finds basophilic cells he will be aware that some toxic process is actually in progress. Evidence of regeneration or destruction of red cells in such a case is entirely another matter; the basophilia merely implies inhibition or delay in manufacture of red cells.

From these considerations it will be evident that the active discussion which has taken place among many hæmatologists as to whether punctate basophilia is or is not degenerative or regenerative in nature, requires no special consideration, because no one can well define what is the essential difference between the two series of processes. If it be settled that basophilia is not a stage of normal maturation, but appears temporarily under certain anæmizing conditions, the practical man has sufficient information to guide him.

COMPARISON BETWEEN VITAL STAINABLE SUBSTANCE AND BASOPHILIA.

	VITAL-STAINABLE SUBSTANCE.	PUNCTATE BASOPHILIA
Occurrence in normal blood ..	Occasional ..	No
Traumatic anæmia	Yes	No
In chlorosis	Yes	Yes
Cytoplasmic constituent concerned ..	Lipoid ..	Albuminous
Association with polychromatophilia	Yes	Sometimes

* Evidently there is no point in describing this as "embryonization."

THE HEINZ BODIES.—Like the reticular substance, these bodies stain with the vital stains, thiazin red, Nile blue, etc. Erythrocytes containing these bodies do not show any trace of them by the dark-ground illumination method until they have been stained by the pre-agonal method of brilliant cresyl blue or azur I. They then appear as brilliant phosphorescent points in the black field of each disc (Cesare Biondi[91]). Pappenheim regards them as composed of cholesterin-olein, because in phenyl-hydrazin poisoning (where they are abundant) the blood contains more cholesterin,[92] and the red cells are resistant to saponin.[93] Heinz himself regarded them as dead cytoplasm, the result of partial necrosis of the erythrocyte.[94] Hartwich[94a] found that these bodies contain protein (probably metalbumin or pure nuclein), a body allied to histone (readily soluble in acetic acid), a lipoid body devoid of cholesterin but containing free fatty acids, and some form of hæmoglobinic iron. Schwalbe and Solley's theory[95] that they are nucleoids, and become blood-platelets after being cast off, is excluded because they contain hæmoglobin and are therefore more likely to appear as microcytes. In other words, these bodies are not the same as Jolly bodies, but are identical with the intraglobular bodies* of hæmoglobinæmic blood (polymerized hæmoglobin of Ehrlich), just as are the schizocytes seen in the blood in phenyl-hydrazin poisoning. Although these bodies are hyperchromic, they do not necessarily imply that the corpuscles are diffusely hyperchromic (from conversion of Hb into methæmoglobin). They only develop in vivo.[96]

RED CELL SHADOWS.—A small number of shadow-forms occur in the normal circulating blood.[97] They present a double contour which stains reddish-blue with Giemsa, while the central portion is coloured pale lilac. They are said to give rise to irregular elongated bodies, when exposed to physical influences. Similar forms occur in pathological blood. They are demonstrable by dark-ground illumination.[98]

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* So-called "Innenkörper," seen within the erythrocyte with the ultramicroscope, and showing molecular movement. They are not artefacts, or secondary pathological granular change in the polychromatic erythrocytes, or nipping off of the lipoid basophile substrata of the discoplasm.

Nature.—They are washed-out red cells, and can be produced artificially.

Significance.—The presence of such bodies in circulating blood indicates that red-cell destruction goes on in the blood-stream, and not exclusively in such organs as the spleen.

NUCLEAR RELICS WITHIN ERYTHROCYTES.—THE HOWELL-JOLLY BODIES.—These are seen as excentric round structures as large as a nucleolus, within the red cells under certain conditions.* They stain with methyl green, which indicates their nuclear nature and distinction from basophilic granules. A mixture of methyl green and azur dyes stains the centre of the "rest" red, while the periphery is punctate. They consist of a mixture of prochromatin and metachromatin, and constitute an intermediate stage of chromatinolysis of the nucleus—a transition between the pycnotic form of nucleus and final stage of complete loss of nucleus.

Occurrence.—They may be readily demonstrated in cats after venesection or poisoning in the embryo (Pol, Schmidt, Jolly), and in human blood in cases of pernicious anæmia (Morris). They may be associated with basophilia.

THE CABOT RING BODIES[99] are seen as rings or loops within (polychromatophilic[100]) red cells. They stain with chromatin dyes, especially with Giemsa. Occasionally they present altogether an irregular shape.

Occurrence.—In plumbism, in severe anæmias,[101] in anæmia pseudo-leukæmia infantum,[102] but not in embryonic blood† or adult bone-marrow or any physiological condition.

Nature.—These bodies are regarded as the peripheral part of the erythroblast nucleus (nuclear membrane), because transition forms can be seen in which the nucleus is partly vacuolated in the centre, while the periphery is intact.[103] It may be noted that these rings may occur in basophilic red cells, and the difference of staining reaction (the ring azurophile, the granules basophile) is then sufficient to show that the granules are not derived from the nucleus.[104] It is possible that these ring bodies are the

* First described in cat blood by Howell in 1890.
† Guinea-pig, rabbit, mouse, dog, cat.

result of accelerated karyolysis in cases of hyperactive regeneration.

CHROMOLININ GRANULES.—Granules like fragments of nuclei have been described as circulating in the blood;[105] they have been regarded as chromolinin granules.

The various granular structures which can be seen within red blood-cells may be reviewed in the following tabular form, for the purpose of aiding the clinical pathologist :—

	Occur in	Visible in		Methyl-green-Pyronin	Giemsa	Hæmat-oxylin	Nuclear Matter	Plastin Matter
		Fixed Prep.	Vital Stained Prep.					
True basophile punctation :								
(*a*) fine ..	Cytes and blasts	+	+	Red	Blue	Hardly visible	o	+
(*b*) coarse	Blasts	o	+	Intense	Intense	o	o	Partly
Nuclear rests (in granular erythroblasts)	Blasts	+	o	Green	Red	+	+	o
Multiple fine acid granules*	Embryonic	o	+	o	o	o	o	o
Substantia granulo-filamentosa (alkaline granulation)†	Normal cytes	o	+	o	o	o	o	+
Substantia metachromatico-granulosa‡	Cytes	o	+	o	o	o	+	o
Maurer-Schüffner punctation	Malarial cytes	o	+	o	o	o	o	+

* Stained by vital stains: occurring in embryonic erythroblasts; coloured bright carmine with neutral red.[107] Giglio-Tos[106] thought these were degeneration-products of hæmoglobin. Pappenheim[107] considered them analogous to the keratohyalin granules of epidermal cells: a portion of the cytoplasm which is subsequently lost as the blood-discs become mature.

† Stain red, brown, or blue with neutral red thionin, or cresyl blue.

‡ Solitary, coarse.

THE BLOOD-PLATELETS.—The most easily observed phenomenon associated with the death of a red blood-cell is that of platelet formation—an agonic process occurring in a certain percentage of the erythrocytes. It need not be supposed that every platelet comes from a red cell, as will be shown below.

The blood-platelets vary much in form, some being rounded and some flagellate. The latter simulate hæmozoa.[108] Their exact shape depends considerably on the method of fixation employed for their demonstration. All stages between well-defined nucleolar bodies with a delicate cytoplasm, and nucleiform structures containing azurophile granules, can be seen.

The number of platelets is variously given at 200,000 to 778,000 per c.mm. They are less numerous in the child.[109] Reid[110] gives the average figure for the adult at 300,000. At birth, according to Morse,[111] the figures vary between 350,000 and 400,000.*

Characters.—Size : 1–5 μ. There is a protoplasmic zone, enclosing a chromatic body ("chromidium") staining with azur dyes. With osmic acid fixation, and vital staining, a capsule-body can be demonstrated, according to Schilling. Centrioles can be detected within the capsule-body (*see p.* 70). Filamentous inter-connections to red cells can also be demonstrated. A guess has been made that such filaments are the same as the so-called hæmokonia. Spodara[117a] asserted that he had seen atypical karyokinetic figures within blood-platelets, but it is more than likely that this is erroneous.

Chemical Characters.—Gross analysis shows platelets to be made of nucleo-proteins, lecithin, and cholesterin. Prothrombin is also assumed to be present in them (Schäfer[57]), and subsequently interacts with lime salts in the plasma to form the fibrin-ferment. Iodine shows the presence of a few glycogen granules. Nile blue sulphate, osmic acid, and Scharlach R do not stain them, and they contain no true nuclear material. Sapegno found that Winkler-Schultze granules are present.[35]

Attributes.—The platelet was found to be amœboid by Deetjen.[117] Their ready explosion into processes which adhere to

* Other observers are Pratt, Wright, Muir, Affanassiew, Kemp.[113, 116]

adjacent objects would enable them to plug torn vessels and stop hæmorrhage. White thrombi are made of platelets (Bizzozero,[118] Eberth, and Schimmelbusch, 1888). Schäfer points out their analogy to the large cells in the perivisceral fluid of echinoderms.[119]

According to Eminet,[120] the platelets present different and specific dye-affinities in different infectious diseases. Thus, the platelets in a case of diphtheria are different from those in a case of tuberculosis or scarlet fever. In other words, an infective agent can influence the composition of the reactive cells, and the soterocytes, as he calls them, are the manifestation of the specific anti-bodies. Diphtheritic serum, on this view, would be composed of specific diphtheritic soterocyte.* Aynaud[121] also considers that the platelets play an important part in the production of alexin and antibodies.

Brockbank[122] suggests that the blood-platelet material is a regeneration-product, and represents "potential hæmoglobin"—some protein constituent ready to enter into the production of hæmoglobin. This would explain why platelets so easily form in secondary anæmias, where regenerating power is good, and so rarely in primary pernicious anæmias, where the corpuscles themselves are damaged.

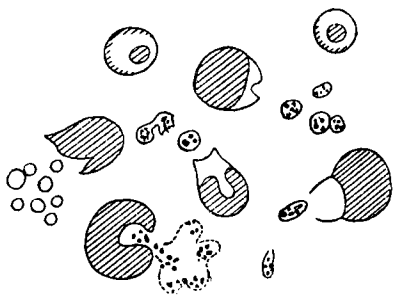

Fig. 26.—PLATELETS ESCAPING FROM RED BLOOD-CORPUSCLES (after Brockbank).

The following are the *theories as to the origin* of the platelets:

1. That they are derived *from red cells.*† Evidence: (*a*) They are more abundant the longer time is allowed to elapse after drawing the blood.‡ (*b*) Very many of these bodies can be found lying close to the "mouths" of eviscerated red cells, or even within the red cell itself[122] (*Fig.* 26). The red cell loses no hæmoglobin in the

* If the platelets be not preformed, this theory falls to the ground.

† Hirschfeld,[123] Preisich and Heim,[124] Roscoe King.[125] If they come from the red cell, they may be centrosomes or centrioles (Eisen[126]) or fragments of nuclei from the bone-marrow erythroblasts (Dantschakoff[127]), or globulin-droplets from the cell-body, or "nucleoids."

‡ In this connection the above remarks, relating to the paucity of platelets in primary anæmia,[122] and their extreme abundance in secondary[122] and post-hæmorrhagic anæmia,[129] may be noted. Mary Morse[128] found no relation between amount of menstrual flow and platelet content (platelets increased before onset).

process, and may part with several platelets. (*c*) If blood be collected directly into the gap between two closely applied cover-slips, which are then separated in the usual way, very few platelets are found (showing that contact with air is requisite for their appearance, and not contact with glass). (*d*) In those animals whose red cells are nucleated, platelets do not occur. The reason why platelets cannot be seen within ordinary red cells may be that the hæmoglobin obscures their staining property, and that special fixation might be required.

Such evidence as that which has been presented should suffice to show that the bulk of platelets is derived from the interior of normal red cells. This view is shared by Pappenheim, Hirschfeld, Schilling,[134] Maximow, Engel, Preisich, Weidenreich.[130] Perhaps the only difficulty lies in settling whether the material of which they are composed is, or ever was, nuclear matter.

The other theories are unimportant:

2. That they are derived *from breaking-down leucocytes* (Decastello and Krjukoff, 1911). Against this view is the everyday finding that platelets are extremely seldom anywhere near a leucocyte in the film preparation. Leucocytes occur in vertebrates below mammals, but platelets do not. On the other hand, the frequent finding of lymphocytes, for instance, in which constricted budding plasmoschistic fragments become detached, suggests that some platelets may come from this source.

3. That they are derived *from megakaryocytes* (Wright, Bunting).[129] This view implies that the platelets arise in the bone-marrow. If that were so, we should expect (*a*) that megakaryocytes would be excessively numerous, considering that hundreds of millions of platelets occur per c.mm. (to accept the current ideas as to the content of platelets per c.mm. of circulating blood); (*b*) That the numbers of platelets are constant. The objections to the view, even though it is accepted by Sternberg[131] and Schridde, seem to be incontrovertible, namely, they are not present in absolutely fresh preparations, or in every preparation; they are more abundant in blood-films made at the end of the operation than at the moment of the prick. This has been a frequent experience in the writer's hands, and is also emphasized by Brockbank,[122] who carried out counts at successive intervals. The evidence for the view consists in an observation that megakaryocyte pseudopodia have been found in the films (how identified as certainly megakaryocytic ?) and that platelets are absent in animals whose marrow shows no megakaryocytes. *Re* last statement, what of the platelets in crustacea, who have no bone-marrow ?

4. That they are really *separate cells* (specific cells). In favour of this view is the fact that they appear in large numbers without any evidence of destructive change in either reds or whites during clotting; that there is no

numerical relation between platelets and reds or whites.* The following experiment has also been advocated as evidence: Fill a syringe with 10 per cent sodium citrate, and take up 9 c.c. blood from a vein into it. Expel the whole into a paraffined test-tube, and put on ice for an hour. The surface layer will then be found full of platelets.†

5. That they are simply a *chemical precipitate* from the plasma.‡ Buckmaster[132] has gone thoroughly into this aspect of the subject, and concludes that platelets are artefacts. He divides them into: (*a*) Those containing hæmoglobin; (*b*) Those without hæmoglobin; (*c*) Those with an inner-body; (*d*) Those without an inner body.

6. That they are *analogous to the thrombocytes* of lower animals; because both are related to coagulation of the blood, and Romanowsky staining shows a nucleiform structure in each. The objection to the analogy is that the central azurophile granulation is not true nuclear matter.

7. Hayem's original doctrine has been finally controverted.[133] He believed that the lymphocyte or leucocyte of the blood-stream gave rise to the hæmatoblast or platelet, was then cast out into the blood-stream, and then "grew" into a red cell. The basis of this view lay in observations on pigeons (Luzet), but similar pictures have not been found in man by the majority of observers; and was supported by the fact that the blood-platelets are increased in regenerating blood.

As regards the histiogenesis of the platelets, this has been variously placed in the bone-marrow, spleen, liver, and lymph-nodes.‖

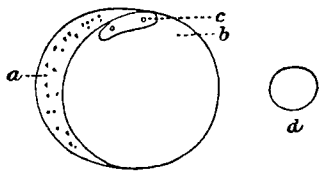

Fig. 27.—A DEMI-LUNE BODY (after Schilling). (*a*) Hæmoglobin-holding part; (*b*) Glass body; (*c*) Centriole; (*d*) Normal erythrocyte for comparison of size.

THE DEMI-LUNE BODIES.§—These vary in size up to 350 microns. They are circular bodies of extreme transparency save for a sickle-shaped structure stained with hæmoglobin. The crescent is punctated. The whole body resembles the appearance of the "old moon between the horns of the new moon" (*Fig.* 27). It is met with in malarial blood, in convalescents from typhoid (Schilling[134]), and has been noted

* But it is impossible to count platelets accurately.

† The fallacy is that the whole manipulation, including the drop of temperature, provides just the most favourable circumstances for the production of platelets.

‡ E.g., globulins (Löwit, Wooldridge).

‖ A good historical review of this subject is given by Werzberg, *Fol. haem.* 1907, Bd. x., i., p. 301.

§ First noted by Sergent;[135] later by Brumpt.[136]

by Langeron in the blood of rats and guinea-pigs, especially if they be rachitic or kept in lead cages. Schilling produced this appearance in red cells by incubating blood. The phenomenon may be looked on as an indication of imbibition in a degenerated erythrocyte whose outer layers have become " pachydermatous " from anæmia and inspissation of the serum.

Changes in the Hæmoglobin Content. Hyperchromia.—This term indicates that there is an increase of hæmoglobin in each red cell. It is the result of a chemical change in the hæmoglobin, and is associated with a lipolytic change in the stroma of the red cell. The latter explains the extreme flexibility of the cell, and the occurrence of dumb-bell forms. Hyperchromic schizocytes are produced by union of the altered hæmoglobin with the lipoid of the plasma. This phenomenon is of considerable interest in connection with the study of pernicious anæmia. In that disease, as is well known, the colour-index is increased—that is, each red cell is assumed to contain more hæmoglobin than is normal. The following experiment, devised by Pappenheim, indicates the fallacy of this conclusion. Into each of two test-tubes are placed 2 c.c. of a washed emulsion of sheep red cells. To tube A is added a drop of saline, and to tube B is added a drop of water containing a crystal of hydroxylamine. After shaking a short time, tube B turns brown. If each solution be now tested with Sahli's hæmoglobinometer it will be found that the unaltered red cells contain 23 per cent Hb, and the other tube contains 46 to 50 per cent. It is evident that the Sahli reading gives a false idea of the state of the blood, because all that has happened has been to convert the hæmoglobin into a met-hæmoglobin compound.

The conclusion is, that in pernicious anæmia the toxic agent has altered the original hæmoglobin, and converted it into a pro-met-hæmoglobin or met-hæmoglobinogen (Pappenheim), just as hæmolytic agents, animal hæmotoxins, and certain bacterial poisons may act on the hæmoglobin chemically.* If this conception of the change be correct, it is evident that any discussion as to

* Schultze explains hyperchromia on colloid chemical principles. External agents acting on the lecithin stroma alter the fixity with which the oxygen is held in by the hæmoglobin lecithin jelly.

whether hyperchromia is degenerative or regenerative is futile. It may be noted at this point that hyperchromia is often associated with macrocytosis (*see* opposite). Hyperchromic red cells occur as either megaloblasts, or normocytes, or degenerate swollen macrocytes.

It will be seen that the normal blood contains some cells which are usually spoken of as diseased. An analogy can be drawn to the familiar problem of the difference between arterial and venous blood—where the altered colour of the blood is due not to an excess of CO_2 but to a relatively greater proportion of CO_2 to O. Normal blood contains a larger percentage of " normocytes " than anæmic blood. Consequently, the best conception of the changes met with in the anæmias is to group them according as the abnormal cells are more and more abundant. A cancerous anæmia is thus 98 per cent simple anæmia + 2 per cent hyperchromic anæmia. Progressive pernicious anæmia is 98 per cent hyperchromic anæmia and 2 per cent simple anæmia. Such conditions as syphilitic anæmia, leukanæmia, malarial anæmia, Banti anæmia, are then intermediate forms showing varying proportions of hyperchromatism of the red cells. Every individual is anæmic in the strict sense of the word, but every healthy individual does not have more than 1 per cent microcytes (*see* opposite). Here, again, emphasis is laid on ideas which go to show the futility of attempting a diagnosis of anæmia on the presence of one megaloblast for instance. As will be shown presently, *our study of the blood-film is made with the object of finding what is going on in the formative tissues, or of detecting the existence of some type of toxin* (be it $-NH_2$, or $-NH$, or $-CN$, or ClO_3, or $-NOH$, etc.) actually circulating in the blood-stream. By searching for diagnostic indications on this plan the physician will never ask himself: Is this pernicious anæmia, is this chlorosis? but—Is there such and such a group in the circulation? Is there such and such a failure on the part of the bone-marrow to form red cells? Is there such and such an allomorphic change in the red-cell (chemical) components?

The condition of hyperchromia need not be considered any further. A defect of hæmoglobin in a red cell is more easy to explain than an excess of the same substance. As we have seen, the

probabilities are that there is no such thing as an " excess of hæmoglobin " in one individual cell.

Alterations of Shape of the Red Cell.—

POIKILOCYTOSIS is so familiar a phenomenon that little need be said about it. There are the following possible explanations of the production of poikilocytes : (1) Physical or osmotic changes in the serum may lead to distortion of form of the red cells. This is the only likely explanation. Some authorities have stated that it is evidence of amœboid movement ; others (2) That it is an artificial production ; others (3) That poikilocytes are fragments of red cells (Ehrlich) and serve the purpose of increasing the available hæmoglobin surface in the circulation ; and others (4) That a poikilocyte is a hastily-formed red cell.

Elongated sickle-shaped red cells were noted by Washburn in the blood of a negress suffering from an obscure anæmia.

Alterations of Size of the Red Cell.—

MICROCYTES are unduly small red cells (3 to 5 μ) ; they are round, have a deep dimple, and only differ from ordinary red cells or normocytes in their dimensions. Some authorities consider them to be immature, others believe them to be breaking down. Biernacki suggested that the normocyte contains a certain amount of plasma, and becomes a microcyte by giving up this plasma to the blood-fluid in the course of natural processes. Litten regarded them as osmotic effects, but their regular contour is against such a view.

Another view was that they are buds of ordinary erythrocytes.

MACROCYTES* are unduly large red cells (7 to 20 μ), and resemble the normocyte in other respects. They are, however, very pale, and the dimple is very shallow, if present at all. The ordinary macrocyte is really an absolutely spherical body (Plehn). The cell stains less strongly with eosin. Whereas some observers regard these cells as megaloblasts which have lost their nucleus too soon, others look upon them as being purely osmotic effects. The question as to whether they are to be looked upon as degenerative or not is superfluous, because mere reaction to physical influences is entirely another process than " degeneration."

* Very large cells (more than 20 μ) are called gigantocytes.

The view propounded by some authorities that the macrocyte is characteristic of pernicious anæmia is disproved by the detection of such cells in simple secondary anæmias. Meyer and Naegeli believed that they had detected a new sign of pernicious anæmia in the occurrence of *hyperchromic* macrocytes (increase of colour index). This is disproved by observations on experimentally produced erythrocyte destruction (met-hæmoglobin-forming poisons) and the lessons learnt therefrom (Pappenheim).

ANISOCYTOSIS is a term denoting that there are cells of a number of sizes circulating in the stream at once. They may still be classified into microcytes, macrocytes, and normocytes. This term refers to an exaggeration of variations in size, since it must be remembered that in perfectly normal blood the corpuscles are not all of the same size. Thus the proportions of cell-forms in the order just named would be 1 : 33 : 66 in normal blood, and 17 : 51 : 32 in pernicious blood (Schaumann).

The Comparative Morphology of the Red Cell.—The fact that the red cells of animals vary considerably both in shape and size has long been known. The elliptical forms are commoner in the cold-blooded animals and in birds, the round forms in the mammals. The former types possess a thicker envelope than do the latter, and fibrils are described[144] as running round the peripheral part of the red cell. The elliptical forms are biconvex, the prominence being due to the presence of a nucleus.[145]

The blood of invertebrates does not contain red blood-cells, as a rule. The plasma contains the pigment. Hæmoglobin is present in the worms and lower crustacea, but in echinoderms the pigment is different, being called echinochrom (red). Some worms contain chlorocruorin (green). The blood of molluscs and higher crustacea contains hæmocyanin (blue), in which copper is present instead of iron. It has three times as little power of binding oxygen as has hæmoglobin. Venous blood is colourless in such animals. Colourless oxygen-binding bodies called achroglobins occur in the blood of some molluscs and tunicates.

The knowledge concerning the red cells in animals below the birds is chiefly derived from the researches of Werzberg,[146] who gathered together all the information obtainable in the literature up to 1911. It will suffice to sketch out the broad outlines of the subject.

The cells to be considered fall into three groups: the orthochromatic cells, the polychromatic cells, and the megaloblasts. The hæmoblasts have been variously named by various writers, and are difficult to trace in terms of modern hæmatology. However, the ancestor of the hæmoblast appears to be a lymphoidocytar cell, having characters such as were referred to in the preceding chapter.

The red cells of the FISH are sometimes almost quite round (cyclostomes), sometimes oval, and the nucleus varies in shape from a rod to the ordinary oval form. In some instances the nucleus is round (tinca, leuciscus rutilus, esox lucius, and gadus lotus), and shows varying structure, sometimes clearly defined, at others obscure. In some cases, pycnotic forms of normoblast may be observed (carassius, cobitis fossilis, perca fluviatilis). Polychromatic normoblasts are usually scanty in the circulating blood, but in esox they are numerous, the nucleus is large, and the cell may be larger than the normocyte. Megaloblasts are sometimes abundant (roach, minnow, and cod), and in some cases, notably the perch, they are seldom seen. Platelets are absent (Fry[146a]).

In the *torpedo*,[147] the adult blood, like that of the embryo, contains granulo-filamentous red cells, orthochromatic oval macrocytes rich in hæmoglobin, polychromatic macrocytes, ortho- and poly-chromatic microcytes, occasional cells with karyokinetic figures, and lymphocytoid hæmatogonia. The latter are round, with a large vesicular nucleus, and faintly basophile cytoplasm. As the hæmoglobin appears, the tint becomes more violet (with panoptic stain). Thrombocytes are present. In this fish the red cells appear in small numbers, but their large size compensates for their paucity; they are at least five times as large as in man. The hæmoglobin-content is 21 to 22 per cent with the Fleischl instrument.

In *scyllium*, the red cells include: (1) Round bodies with round nucleus (embryonic cells); (2) Oval cells with oval nucleus (derived from bone-marrow); (3) Transitional forms to megaloblasts; (4) Normoblasts. There are no spindle cells. The fact that red-cell formation is localized to the bone-marrow, and that juvenile cells are abundant in the blood-stream along with mitosing forms, has been explained on purely physical grounds by Blumenthal.[4a] He points out that the osmotic pressure within the animal is the same as that of the medium in which it lives, and prevents the ordinary processes of cell-division, such as we are familiar with in the mammals.

The normal red cell of the cyclostome *petromyzon* is vesicular, and contains granules of hæmoglobin; it is irregularly round, variable in size, and the nucleus is a little longer than broad. Pycnotic forms occur, as well as some forms without nuclei at all—true erythrocytes. There are no polychromatic red cells, and no megaloblasts are to be found.

The blood of many AMPHIBIA contains red cells which are visible to the naked eye, but their numbers are much smaller than in other animals. They also include megaloblasts and normocytes, the former giving rise to the latter, although a certain number of normocytes arise from polychromatic normoblasts which are derived from metaplastically transformed primordial cells. The megaloblasts have a relatively large central round amblychromatic nucleus, which, in the unstained state, is strongly refractile. The normocytes occur in two forms: (1) With large round amblychromatic nucleus and polychromatic cell-body;* (2) A blood-mature cell with normoblast type of nucleus, and of large size. This is a large normocyte. A variant of this is the microcyte.

* The erythroblast of some authors. The microblast is a variant.

The sequence of development is: lymphocyte = cell with more protoplasm, and basophile flakes; nucleus larger, round, and clearly defined structure = cell with oval nucleus and commencing hæmoglobin deposit = finished red cell (Freidsohn[158]).

The blood of the *frog** contains seven varieties of red cell; there is: (1) The medium-sized, oval, orthochromatic form, whose cytoplasm is orange, whose nucleus is blue and irregular in contour (oval in the young animal) and contains a dense but distinct net-work. Some of these have pycnotic nuclei, others have none at all (Pappenheim, Engel). (2) Polychromatic normoblasts; these are of medium size, oval shape, and have a relatively large nucleus. They contain little hæmoglobin. Such forms are more numerous the younger the animal. (3) All kinds of transition forms between (1) and (2). (4) A few orthochromatic megaloblasts, with large round oxyphile cell-body and large round nucleus. (5) Microcytes (orthochromatic, with relatively large nucleus). (6) Polychromatic microblasts. (7) Cells showing punctate basophilia. It is of interest to note the seasonal periodicity of activity of red-cell formation in the frog. This is marked between May and July.

In *bombinator*, the megaloblasts are very numerous, while polychromatic normoblasts are scarce. The erythroblasts are round, flat discs with large nucleus and only a rim of cytoplasm. They are polychromatic.

Dimictylus viridescens has very large red cells, which include many megaloblasts, but very few polychromatic normoblasts.

All amphibian red cells have a characteristic nuclear structure, since the network forms broad feet which rest on the nuclear membrane all round.

The blood of *axolotl*[147] contains 300,000 red cells per c.mm., and 23 per cent hæmoglobin. The red cells show well-marked reticular substance, are of ovoid shape, and appear in two forms: the lymphocytoid, and the orthochromatic. Mitotic figures are occasionally observed. The erythroblast is round, basophile, and bears a peripheral zone of hæmoglobin. Some are polychromatic. The nucleus is round and relatively large; the chromatin is spongy and contains a substance stainable with methyl green, arranged in radial fashion; a pyroninophile substance occupies the remainder of the nucleus, with the addition of two round nucleoli, which are surrounded by a clear halo. The smaller the nucleus becomes, the nearer are the nucleoli to the surface; they finally become expelled into the cytoplasm and appear as the granules of the reticular substance (Sabrazès).

The red cells of the REPTILES are always oval, biconvex, and nucleate. They are smaller than in the amphibia. They comprise three main groups: the orthochromatic forms, the polychromatic forms, and the megaloblasts. The latter may show mitotic figures, and at times are very like lymphoidocytes. The orthochromatic cells are large, oval, and hyaline in aspect. The nucleus is variable in size, and the nuclear network does not touch the nuclear membrane in the same manner as was described for the frog, but the thick feet are replaced by slender, pointed processes of chromatin.

* Bufo, and all kinds of frog, also salamander and proteus.

The hæmoglobin is at the edges and at the poles of the cell. Some of the orthochromatic cells are small, and are called microcytes; some of the others show a pycnotic nucleus.

The polychromatic cells occur in two forms: (1) Large oval bodies whose cytoplasm appears flocculent, and surrounds a nucleus with well-marked nuclear network; (2) Very small forms, very similar to the spindle cells. There are many transition forms between these two main groups.

The megaloblasts are few in number, large in size, oval in shape, and orthochromatic in tint. The nuclear structure is blurred.

The differences observed in the different reptiles consist in the form of the nucleus, and in the relative proportions between the cell types mentioned. Thus, megaloblasts are few in tropidonotus, testudo, anolis, scincus, agama, hemidactylus, chalcides, and moderate in number in anguis, emys, lacerta. In no case are they abundant. The polychromatic forms are absent in tropidonotus, and very numerous in testudo, platydactylus, and chameleon. In testudo, the following forms of polychromatic cell have been described: (*a*) Medium-sized, round cells with large round nucleus, and rim of cytoplasm; (*b*) Similar forms with an oval nucleus which almost fills the cell; (*c*) Similar cells with round nucleus, feebly basophile cell-body, oval in shape; (*d*) Small polychromatic elongated cells with a large long nucleus; (*e*) Very small and narrow cells, poor in hæmoglobin, but not at all basophile. Large and small forms of polychromatic cell appear to be noted in all those cases in which any are to be found at all. Transitional forms are then also present, and the largest examples may appear like megaloblasts (megaloblastoid cells in lacerta).

Microblasts are noted in platydactylus, emys, and chameleon.

Lymphoid hæmoblasts have been described as occurring in platydactylus (Werzberg), and similar cells—large, round, strongly basophile—were found by the same writer in lacerta.

As regards the normocytes, rod-shaped nuclei are present in tropidonotus, lacerta, algeroides, anolis, platydactylus, and in some chameleon red cells.

Pycnosis is not often seen, but irregular nuclear forms have been described in testudo and lacerta. Microcytes are noted in some of the reptiles. In the tortoise, red-cell formation is active in spring, but very slow in winter. The erythrocyte develops from the lymphoidocyte of the bone-marrow by accumulation of hæmoglobin, as well as by mitosis of the circulating erythroblast (Eberhart[159]).

In the BIRDS, the red cells are larger than in mammals, and are relatively more numerous. Similar forms of red cells are to be found, as have been described in the preceding groups. There are flat elliptical biconvex discs with peripheral hæmoglobin, and small round, or sometimes ovoid, nucleus, in which structure is rather indistinct. There are small orthochromatic forms, or microcytes, with more clearly defined nuclear structure, since the chromatin strands are thick and impinge on the membrane with foot-like bases. Cells with pycnotic nuclei can be observed, which are otherwise like the ordinary erythrocyte, and contain much hæmoglobin. Lastly, megaloblastoid cells occur with basophile or polychromatic cell body, and relatively large ovoid nucleus in which the chromatin masses are larger and more

clearly defined than in the preceding forms. Lymphoid hæmoblasts may be detected in which the cell-body is narrow and deeply basophile, and all transitions between these and the polychromatic megaloblasts can be made out. These varieties apply to the blood of the domestic fowl.

The cells in the pigeon are similar in form. The cell types in other birds have yet to be studied carefully by modern methods.* In general, the larger the bird, the larger the red cell.

MAMMALIAN blood, with the exception of that of the camel, is characterized by the fact that the red cells are strictly round discs, and are non-nucleate.

The following list of the comparative sizes (in microns) of the red cells in various animals may prove of interest :—

Torpedo ..	20 × 88 or less†	Goat	4
Axolotl	27 × 84†	Llama	4 × 7
Proteus anguineus	62·5 × 34·5	Sheep	5
Newt	19·5 × 29·3	Horse, Ape, Rabbit,	
Amphiuma tridactylum	45 × 83	Cat, ...	6
Frog ..	14·5 × 25	Dog ..	7
Pigeon	8·5 × 14·5	Man	7·5
Finch	3·6	Elephant ..	9
Napu deer ..	2	Camel	13

The red cell content of the blood of various animals (cells per c.mm.)‡:—

Proteus	36,000	Sheep ..	14 mill.
Frog	½ mill.	Goat	10 ,,
Fish	¼–½ ,,	Man	5 ,,
Birds	1–4 ,,		

The Spindle Cell.—This form of cell, described by Recklinghausen, in 1866,[148] was first considered to be the analogue in birds of the blood-platelet in man. In point of fact, however, it occurs in all vertebrates below the mammalia, with but few exceptions, and is regarded as a cell-entity. These cells deserve mention because they appear as definite blood-cells in some animals, even though they play no part in human physiology.

The spindle cell is a pear-shaped, or almond-shaped plaque, with a central protrusion on each surface, in the position of the nucleus. The cell is sometimes rounded at the poles, sometimes very obtuse.

* The most recent works on erythrogenesis in birds are those of Wenzlaff[160] and Kasarinoff.[161]

† Sabrazès and Muratet.[147]

Size.—$\frac{1}{2}$–$\frac{2}{3}$ × $\frac{1}{3}$–$\frac{1}{2}$ the diameter of a mature red cell.

Cell-body.—Finely granular or fibrillated. The fibrils are concentric. Edge smooth. There is no hæmoglobin present, no opacity, no optical structure, no granular appearance.* Occasionally some vacuoles are present. In tropidonotus and chameleon, Unna-Ziehl staining brings out a deep red rim to the cell.

Centrosome.—Is in a dimple on one side of the nucleus. Polar centrioles are seen in testudo and birds in panoptic stain.

Nucleus.—This is oval in shape and contains no coarse chromatin fragments, but numerous granules of chromatin, which appear to lie in a lining network (Salamander[149]). On the inner wall of the nucleus in triton is a sickle-shaped clear area.

The chromatin reticulum is made up of delicate fibrils, and shows a longitudinal folding (mitochromes) of the nuclear membrane.

Nucleolus.—1–2. According to Werzberg, nucleoli are absent.

Mitosis.—Some authorities have observed this (Mondino, Sala[150]); others deny its occurrence (Meves and Werzberg).

In birds, the spindle cells are long and have an elliptical nucleus. They are regarded by some as identical in function with the mammalian thrombocyte.[149] After being shed, they become spherical, and throw out processes and adhere to one another. Fibrin filaments are seen to exude from them subsequently. In other words, they subserve a very definite function at the very time that they are in articulo mortis.

The observations made by Werzberg led him to conclude that the spindle cell is not the parent of the erythrocyte, nor yet derived from the lymphocyte (Neumann's view). While the spindle cell is endowed with the same functional powers as the platelet of the mammal, it is not morphologically related to the same; rather does this cell give off fragments of material which correspond to the mammalian platelet. The genealogy of the erythrocyte may be represented thus, following Pappenheim and Werzberg:

$$\left.\begin{matrix}\text{Lymphoidocyte}\\ \text{or mother cell}\end{matrix}\right\} = \text{hæmoblast} = \text{polychromatic normoblast} = \text{erythrocyte.}$$
$$\Big|$$
$$\text{thrombocyte}$$

* Neumann found a few tiny colourless refractile granules, which Hayem believed to be myelin, Pappenheim lipoid.

The *theories* as to the origin of the spindle-cell are fully dealt with by Werzberg.[146] It will suffice to point out that there are the following views: That they are derived from: (1) Leucocytes; (2) Endothelial cells; (3) Red cells; (4) Giant cells or megakaryocytes; (5) That they are separate entities; (6) That the red cells are the descendants.

With reference to the fourth view, advanced by Wright[151] and Rawitz,[152] it is of interest to note that the same argument is advanced as was employed to demonstrate that the platelets of man come from megakaryocytes. It has been noted by these observers that giant cells containing anything up to twenty nuclei are observed, which cells present amœboid movement, and amount to agglomerated spindle cells. In other words, the lower animals, which have no megakaryocytes, have these agglomerations of spindle cells, and give rise in due course to free spindle cells whose function is identical with that of the mammalian platelet. The latter in its turn comes from a megakaryocyte. The objections to this view have already been mentioned. The theory, from the side of the spindle-cell, is referred to by Werzberg as a "curiosity."*

The Hæmokonia, or Blood-dust.[137]—This material appears in various forms, which have been divided by Porter[138] into the following: (1) Flagellate bodies of indefinite shape; (2) Large diplococci capable of rapid movement; (3) Bodies measuring 2 to 4 μ, showing similar movement, but possessing indefinite shape; (4) Slightly round vesicular bodies with a central ruby-coloured spot, and only seldom mobile; (5) Small micrococcal forms exhibiting active Brownian movement. These bodies are all strongly refractile, and can be readily seen with the ultra-microscope (Reicher,[139] Rosenthal[140]). They can be stained with vital-staining dyes of the ammonium series (Pappenheim[141]).

It is difficult to decide upon the nature of these particles. Since they give fat reactions (sudan stain, solubility in ether), it has been supposed by Muhlmann that they are fat. They are found to be more numerous after a meal rich in fat. Thus, after a large quantity of butter has been ingested, an ultramicroscopic examination of the blood is ascertainable, according to Neumann,[142] and is useful for comparing health with cases of pyloric obstruction. These observations are contested by Wiener,[143] who believes that hæmokonia are inconstant, and are insoluble in ether. Cottin[162]

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* Other references on spindle cells are quoted in the literature under numbers 153, 157. For illustrations, see *Plate II.*

found them more abundant in the vessels leaving the intestine than elsewhere.

It has also been supposed that blood-dust is (*a*) the result of breakdown of red cells ;* (*b*) derived from proteins or lipoproteins in the leucocytes.

Hæmokonia are less numerous in the newly-born ; they are increased after radium-therapy (Cottin). They have no relation to the coagulation of the blood.

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* Porter[138] comes to the same conclusion from his observations. It is difficult to be sure that extraneous matter and post-mortem autolytic changes have not been mistaken for these bodies.

IV.—THE METAPLASTIC, METAHYPERPLASTIC, AND APLASTIC PHENOMENA OF ERYTHROPOIESIS.

BRIEF discussion of the nature of anæmia—A classification of anæmias—Relation between the facts detailed in the preceding sections and clinical work—Polycythæmia.

THE pathological changes which occur in the formative centres for red cells lead to the appearance of anæmia or polycythæmia if the erythroblastic line of development be affected. Some of these changes belong to the class of "plasias," and it is by studying them that better conceptions of the nature of anæmias can be obtained.

The ordinary blood-count is of relatively small value in elucidating the pathology of a case of anæmia. The empirical use of such a count leads to unsatisfactory results, as it tends to the erroneous belief that a certain number of reds per c.mm., a certain percentage of hæmoglobin, and a certain number of leucocytes per c.mm. will definitely decide the nature of the anæmia and the line of treatment to be followed. We would emphasize that the morphological characters of the blood-cells themselves are of vastly greater importance than the mere determination of total numbers of red cells, etc., with anything more than approximate accuracy.*

There is no such thing as a primary anæmia. Every anæmia is the effect of agents either on the circulating blood or on the bone-marrow, or on both at the same time. The agent is often of unknown nature, and, indeed is sometimes apparently of the nature of a filterable virus (Trincas[163]). Strictly speaking, anæmia is never a disease of the blood.[164] The blood is a tissue in a sense, but is better described as a transport agent, and is only temporarily damaged by any deleterious substances that happen to be taken up by it. In other words, we may say that when toxins of any kind enter the blood and damage its cells or plasma *in situ*, we have a pollution of the blood, a mechanical process exactly analogous

* This statement is not meant to imply that the counts should be hurried over; they should be reasonably accurate. The beginner requires to exercise especial care in the technique of blood-counting.

to sewage pollution of rivers. We do not say the rivers are diseased ; we know that if the pollution be prevented the river becomes wholesome once more. In the same way, if we could find out and counteract what is contaminating the blood in some anæmias, the patient would at once be restored to health. A good example of this is shown by employees who are notoriously anæmic while working in certain factories, but recover a natural white-race colour as soon as they change their occupation and come to live in other districts.

Even though the circulating blood were damaged by a noxious agent, there would still be no anæmia if the red-cell-forming organs (we assume it is the red cells that are damaged) made new sound erythrocytes rapidly enough to supersede the damaged ones. Anæmia implies that the normal equilibrium between destruction and new formation is lost ; the destruction is in excess of formation. That is to say, anæmia requires simultaneous insufficiency of the bone-marrow for its consummation. This is what Pappenheim calls myelopathy. Loss of blood, by itself, is not anæmia. Loss of blood *plus* defective renewal, from whatever cause = anæmia.

Classification.—The following groups of conditions may be met with in different cases :—

1. Stimulus to make blood is constant ; marrow inadequate. This is a *myelophthisic anæmia* (Pappenheim*). It occurs in two forms : the hæmomyelotoxic and the myelometaplastic.

2. Stimulus to make blood is excessive ; the marrow is normal. Here the excessive loss of blood cannot be replaced at once, but the anæmia ultimately disappears. If the marrow fails, and regeneration of blood is inadequate, then a myelopathy is superadded. Sub-varieties : (*a*) Pure traumatic ; (*b*) Toxogenic, e.g., morbus Werlhofii. These are all "*hæmatic anæmias*."

3. Stimulus to make blood is excessive and marrow inadequate = *aplastic* forms.

4. Hæmolysis of blood, marrow normal. This is a *hæmolytic anæmia*. It may be associated with jaundice (Widal and

* In pernicious anæmia there is destruction of the original bone-marrow and disappearance of the cytadenoid reticular tissue (Donzello[166]).

Abrami[165]). In addition to a true hæmolytic action, the red cells are found to be possessed of less resistance. *Examples*: streptococcic, staphylococcic, colon, typhoid, M. tetragenus infections may set up hæmolytic anæmias (Cicaterri-Bono[166]).

5. Hæmolysis of blood, and marrow poisoned also. This is a *myelotoxic anæmia*. Such effects are produced by experimental injection of rabbits with typhoid toxin. The bone-marrow becomes atrophic (Hirschfeld[167]).

6. Hæmolysis of the blood, the bone-marrow altogether pathological. In this case there are unusual methods of regeneration —the mother cells come to be called out as well, and perivascular tissues are called into requisition (vicarious hæmogenesis) in order to attempt to meet the demand. There is myelopathy plus defective erythrogenesis. *Example*: bothriocephalus, Biermer or pernicious anæmia, hæmo-lymph-glands.

7. Toxic action on the blood (non-hæmolytic); marrow partially adequate, but then breaks down altogether. In this case we deal with a so-called *hæmotoxic anæmia*, which may be active or passive (aplastic).

8. Toxic action on the bone-marrow. The blood reflects the changes thereby produced.

9. Failure of marrow to make cells at all. Primary aplastic anæmia. This is hypothetical, and may never be met with.

Changes which may be classed as metaplastic, meta-hyperplastic, and anaplastic and aplastic,* are met with in the lesion-groups designated 6, 7, 8, and 9. The autopsy findings can be interpreted according to the variety of "plasia," because an examination of the marrow for a cytological formula comprising all the stages of development of the red cell (and white cell, see Chapter V.) will show what has taken place. Cases with nearly every cell† a lymphoid hæmoblast, or with nearly every cell a megaloblast, or cases with hardly any nucleated red cells at all (the marrow being quite lymphadenoid)—all such would call for description or discussion. A thorough grasp of the normal and

* The exact meaning of these terms is necessarily deferred till Chapter VII.

† This phrase is really a figure of speech. It means "over 50 per cent."

pathological lines of red-cell development enables an exact appreciation of the anatomical marrow findings in the different anæmias where actual serious marrow derangement has taken place. It would almost be possible to draw up a table of the possible permutations and combinations between them.

There is, then, no specific blood-picture for pernicious anæmia (Pappenheim,[169] Krehl[170]), any more than for any other anæmia. The appearance of megaloblasts, etc., only indicates the severity of the disease, and the degree of reactive power of the patient. As Grawitz[171] said, the diagnosis of pernicious anæmia cannot be made from an examination of the blood itself. "The same degenerative and regenerative types of blood formation are equally well found in other severest anæmias, e.g., in carcinosis." The low leucocyte count and the proportionately high content of albumin are more characteristic.

The views as to the nature of pernicious anæmia have been discussed most completely by Pappenheim and the Berliner hæmatologische Gesellschaft. The theories are :—

1. That it is a specific disease primarily seated in the marrow—a functional asthenia of the marrow.

2. That it is a secondary result of toxicosis, a symptom of toxic action on the marrow (Ehrlich, Engel, Ziegler, Isaac-Möckel).

3. That some cases are primary diseases of the blood and others are dual conditions in which the blood and marrow are simultaneously diseased—myelotoxicosis + hæmotoxicosis, or hæmotoxicosis alone (Ehrlich-Lazarus view). The appearance of the megaloblast is here taken to be the absolute sign of poisoning of the marrow tissue. The cases with dual action are exemplified by the bothriocephalus-anæmia, in which the poison of the worm acts on the circulating cells first and the marrow very soon after. As soon as the marrow is involved, megaloblasts appear.

4. Pappenheim's view—that there is only a difference of degree between the primary and secondary anæmias. The so-called primary pernicious anæmias are merely cryptogenetic, the secondary pernicious anæmias are to be traced to a known causative process (tape-worm, puerperal disease, etc.). The blood shows toxicosis in each just as much as the marrow, but in some the hæmotoxicosis is more conspicuous ; in others the myelotoxicosis. If regeneration is being undertaken, then megaloblasts will appear in the circulation, otherwise not. If "not," the case is to be called "aplastic."* But

* Yet it must be remembered that one cannot diagnose aplastic anæmia with certainty till after death, because something may hold back the "blast" forms, and their absence in the blood-film may be misleading.

the fact that megaloblasts appear, and not normoblasts, is a sign that the marrow is poisoned, because that is not a natural mode of regeneration.

The following schemata are given by Pappenheim to express the differences in the hæmopoiesis met with under healthy and morbid conditions :—

Health.—

Lymphoidocyte → young megaloblast
↓
Macro-lymphoidocyte → young normoblast → old pycnotic normoblast → → normocyte with Jolly body → loss of nucleus by karyolysis → finished normocyte.

Simple anæmia.—

Lymphoidocyte → young megaloblast → old pycnotic megaloblast → macrocyte.
↓ ↓
Macrolymphoidocyte → normoblast → normocyte.

Pernicious Anæmia.—

Lymphoidocyte → young megaloblast → old pycnotic megaloblast
↓ ↓
karyorrhexis → macrocyte ← caryolysis.
↓
Young normoblast → loss of nucleus by caryorrhexis → finished normocyte.

The whole subject of the nature of anæmia is comprised in the above few charts.

The actual mechanism by which metaplasia, anaplasia, or aplasia is brought about remains unknown. It would be extremely valuable to know what atom-groups play a part in these processes. Could we influence metaplasia, or counteract aplasia ? The observations which have been made upon the action of such agents as *x*-rays, mesothorium, etc., show us that there is hope for effective work in these directions. As we shall show later, bodies containing imid-groupings can alter the rate of multiplication of marrow-cells belonging to the white cell series, so that there is a little light shed on the problem of leucocytosis and leucopenia. We require knowledge on the analogous process of polycythæmia and anæmia.

It is difficult to reconcile the classifications of anæmias which have been presented by the leading authorities of the day. That of Grawitz bore a practical stamp, that of Pappenheim a scientifically complete form. In presenting the following table, we mainly follow the latter author, inserting the names of the various " diseases of the blood " whenever they can be placed.

I.—Anæmias with primary destructive action on the blood itself (hæmatic-hæmophthisic anæmia).

1. Simple post-hæmorrhagic anæmia. This is never aplastic, only normoblastic.

Varieties.—(*a*) Acute (traumatic, puerperal, experimental, therapeutic).

(*b*) Chronic, i.e., repeated in small doses (piles, repeated hæmoptysis, endometrial hæmorrhage from fibroids).

2. Plasmogenic anæmia (drainage of albumins from plasma).

3. Hæmotoxic anæmia.—Hæmorrhages under mucous membranes.—

(*a*). The effect of simple solution of red cells (erythrolytic blood poisons). This form is hypochromic; each red cell contains less Hb than usual.

(i). With normoblasts in the blood.

(ii). With megaloblasts in the blood. This indicates that the marrow has become involved in the toxic agent.

(iii). Aplastic; no regeneration taking place:*

(*b*). The effect of agglutinating blood poisons.

(*c*). The effect of poisons causing changes in the hæmoglobin (hyperchromia), allomorphic change of hæmoglobin added to the erythrolysis.

(i). With leucocytosis: Example: pyrodin, poisoning (experimental), splenic anæmia, leukanæmia.

(ii). With lymphocytosis:

(*α*). Cause obvious (phanerogenetic anæmias). Example: cancer, puerperal anæmia, v. Jaksch's anæmia, syphilitic anæmia, tapeworm.

(*β*). Cause obscure (cryptogenetic anæmia). Example: pernicious anæmia, Addisonian.

(*d*). The effect of parasites (e.g., malaria).

(*e*). The effect of micro-organisms: morbus maculosus.

II. Anæmias with primary diseases of the marrow (myelopathic anæmias). Here there are primary or secondary hypermetaplastic changes in the bone-marrow.

This includes such diseases as Kahler's disease (multiple myeloma with blood-changes), secondary deposits of cancer in bones,

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* This is a figure of speech. Even in the most severe anæmias there must be some regeneration, because all the red cells would be dissolved, and the blood-stream be absolutely empty in ten days, unless we are to assume a simultaneous stoppage of red-cell destruction. The latter is absurd on the face of it, because the disease was first instituted by the very fact of *increased* red-cell destruction.

Aplastic anæmia is only diagnosed intra vitam by noting the presence of polychromatophilia and nucleated reds (Hirschfeld[178]). The bone-marrow may be full of micromyeloblasts.

medullary aleukæmia, acute lymphatic anæmia ; cirrhogenic poison of Banti's disease ; osteosclerosis.

Here comes chlorosis—functional derangement of Hb-manufacture.

It will be seen that such terms as chlorosis, pernicious anæmia, and Banti's disease are convenient, but they do not afford any better information to either clinician or patient. The root of the disease requires to be elucidated. Finding ourselves, as we do, in a position of being unable to decide between some of these conditions intra vitam, investigations must be made towards that very direction, so that metabolic or other methods of physical examination shall provide the required clue to diagnosis.

A new interest thus becomes attached to the blood-counting procedures. We do not find ourselves rigidly bound to count up the corpuscles to the "uttermost farthing," but we search for abnormal forms in the films, we trace out the process of hæmogenesis going on in that particular patient, and ascertain as far as possible what abnormalities there are. We ascertain the ratio between the destruction of red cells (the regenerative stimulus) and the regenerative reaction to that stimulus. Is this ratio unity less or more ? The microscopic and chemical evidence which enables the first part of this ratio to be determined has been set forth. The evidence of regeneration lies in the detection of the ancestral forms in the blood-stream, or in examination of the marrow during life. The process of regeneration is, of course, the same as the ordinary process of development, although details may be modified here and there. The rules given for the study of leucocytosis can be followed in studying anæmia ; we note that a slight grade of anæmia only leads to a call out of the reserve cells already present in the marrow, and there need be no obvious morphological change in the red cell. In cases of repeated hæmorrhages, the reserves will be drained until active manufacture of red cells is necessitated. If the production be less than the demand, nucleated forms will appear—"deviation to the left." Since the bone-marrow is a dual organ, defects in red-cell proliferation will simultaneously alter leucocytic development. Either a paresis will take place, causing leucopenia, or undue

stimulation of these cells will ensue and the anæmia will come to be associated with leucocytosis. The toxic bodies liberated by multiple hæmorrhages will suffice to produce such an effect. Briefly stated, the clinical evidences of regeneration are: (1) Appearance of nucleated red cells in the films; (2) Polychromatophilia; (3) Changes in the chemical composition of the plasma (notably the phosphorus)*; (4) Changes in the urine (bilinogen, e.g.).

Zoja[67] divides the anæmias into two groups according to the amount of bilirubin present in the urine. In the first class the amount is increased, showing that hæmolysis is more intense than usual. Two varieties may be met with here:—

1. Where (*a*) many of the erythrocytes show reticular substance; (*b*) The punctate basophilia is not present; (*c*) Where the Jolly bodies are absent, as well as normoblasts and megalocytes. The red cells showing destruction are very numerous. (The points to note are: Number of damaged red cells, excretion of bilinogen, total red-cell count and Hb-content).

2. Where (*a*) many of the erythrocytes show reticular substance with vital staining, though they are not so numerous as in (1, *b*) punctate basophilia is present, (*c*) normoblasts, and occasionally megaloblasts are seen. (Example: Plumbism, pernicious anæmia, leukanæmia, leukæmia, aleukæmia).

The explanation of the phenomena lies with the explanation of the automatic regulation of the destruction and regeneration of the red cells (*see* p. 74). In the pathological conditions referred to, a new factor of equilibrium may be set up, which can be determined by study of the blood and the bilinogen content. There are two possibilities regarding the cause of the change in the equilibrium: (1) Either the blood cells which are broken up leave auto-isolytic substances behind them, which call forth an antibody formation on the part of the organism; or (2) Some metabolic products or bacterial products are present which act as irritants for hæmopoiesis. (Cf. Ross, researches on induced cell-proliferation, referred to on p. 241.) In the first case, the autolytic substances (erythrolytic in the case under consideration) are hardly toxic, and only excite increased activity on the part of the bone-marrow cells. If the substances in question are not autochthonous, they must be of toxic or infective origin, and set up cytogenetic stimuli which bring about the appearance in the blood of immature cell elements, thus explaining aplastic anæmia or leukæmia. Foà (1910) was able to induce complete aplasia of the bone-marrow by injecting a small quantity of highly

* According to Gibelli,[173] the serum of a bled animal contains hæmopoietins, which, injected into another animal, will excite red-cell formation (regeneration). The same phenomenon is exhibited by the injection of lipoids into anæmic animals, or by the injection of lecithin alone (Kapinow[174]). In other words, the good effect on regeneration of red cells occurring after saline infusion is due to the action of the lipoids liberated by the red cells broken down by the action of the saline.

toxic serum into a rabbit or guinea-pig; he also established a similarity between infantile splenic anæmia and the hæmolytic anæmia experimentally induced by splenotoxic sera.

In the case of (2), we have the observations of Ferrata, which show that an inorganic poison or substance may be necessary before an infective agent may act. This hypothesis applies more particularly to the anæmias associated with leukæmia, aleukæmia, and Banti's disease; the blood may be damaged at the same time as is the hæmopoietic apparatus. Varying or increasing toxicity of the virus may account for the conversion of one type of leukæmia into another, or one kind of severe anæmia into another.

In this way we come to appreciate the instability of the equilibrium of the blood-forming mechanism during health. At any moment, from causes entirely beyond our ken, we may be plunged into a fatal subversion of the cytogenetic processes on which life depends. Sufficient has been said to show the logical connection between the morphological data detailed in the early parts of this chapter and the phenomena observed by the bedside. We have traced out the biology of the red cell—in other words, we have indicated the different phases of its life history under the most varied conditions, and we have seen how pathological influences modify its course. The full discussion of the individual forms of anæmia would lead us too far from the direct line which we desire to follow, and is unnecessary, because the reader has only to bear in mind that they are the result of the play between toxic action on circulating cells and toxic action on the marrow. There is then little difficulty in placing the morbid conditions into a system.

The relations between one form of metaplasia and another require brief notice. Can one form of metaplasia pass into another? We are told that cases of pernicious anæmia may apparently pass into leukæmia, and *vice versa*. Neither of these statements is true. The two diseases are merely phases of one and the same fundamental process—a condition of leukæmia, a hyperplastic or metahyperplastic disease of the hæmopoietic system. The disease may show marked anæmic signs before it becomes clinically manifest as a true leukæmia. The blood may show abnormalities in regard to the white cells without any increase in the total numbers; it is in a state of "subleukæmia," or latent

leukæmia, but the lymphadenoid change which is taking place ultimately brings about impairment of red-cell formation varying in degree from the minimal to the condition clinically known as pernicious anæmia.

Polycythæmia.—The phenomenon of marked increase in erythrocyte content of the blood is much more rare than that of anæmia, although many cases of cardiac stagnation show a certain degree of polycythæmia so long as the blood be collected from the legs (Krämer[175]). A similar blood-state is observed in the newly-born, in persons living in high altitudes, or at the sea-shore, and in some persons after high living. Such cases are spoken of as physiological polycythæmia.

Pathological polycythæmia is primary or secondary. The latter includes cases following marked loss of fluid from the body, passive congestion, and the action of certain poisons (tar preparations). Paroxysmal hæmoglobinuria, scurvy, cirrhosis of the liver, tuberculosis involving the spleen, chronic interstitial nephritis, Addison's disease, chorea, neurasthenia, are occasional causes (Senator[176]).

True *primary polycythæmia*, or erythrocytosis (*erythræmia*), resembles leukæmia only in the interminable proliferation of the blood-cells. The total volume of the blood is increased, the excretion of iron by the urine is increased, and there is found a hyperplastic condition of the bone-marrow, the whole of the fatty marrow being converted into active red marrow (Rubinstein[178]). The enlargement of the spleen which is usually associated with the disease is not primary, because splenectomy does not cure; otherwise it might be supposed that the explanation of the disease lay in an inability on the part of the spleen to destroy the red cells, or even in an active production of an antibody by the spleen which prevents erythrolysis. This view would be in favour of Luce's view that erythræmia is not myelopathic at all, but of splenic origin.[177]

CHAPTER III.

ON THE LYMPHOCYTE.

Section I.—THE FACTORIES OF THE LYMPHOCYTE : The lymph node as a whole—The lymph follicle—Cyclical changes in the lymph follicle—Metabolic changes in the lymph nodes—Regressive changes—Functions of lymph nodes—Relation to digestion—The spleen—The Malpighian follicle—The accessory factories of lymphopoiesis.

Section II.—THE LYMPHOBLASTIC LINE OF DEVELOPMENT : The morphological characters of the lymphoblast—Of the large lymphocyte —Of the germ-centre cell—Of the meso-lymphocyte—The cycle of development.

Section III.—THE LYMPHOCYTE OF THE BLOOD-STREAM : The lymphoid elements of the blood—Morphology of the lymphocyte—The differential diagnosis of the lymphocyte—The functions of the lymphocyte—Lymphocytosis and lymphopenia—The nutrioid function—The adsorptoid function—relation to phagocytosis—The chemistry of the lymphocyte ; of its azur granules—The comparative cytology of the lymphocyte.

Section IV.—THE FATE OF THE LYMPHOCYTE : Cytometaplasias.

I.—THE FACTORIES OF THE LYMPHOCYTE.

THE lymph node as a whole—The lymph follicle—Cyclical changes in the lymph follicle—Metabolic changes in the lymph nodes—Regressive changes—Functions of lymph nodes—Relation to digestion—The spleen—The Malpighian follicle—The accessory factories of lymphopoiesis.

THE term "lymphocyte" is often used in a general sense, in reference to certain cell forms met with both in the blood-stream and in the tissues. The "lymphoid cell" of Pappenheim is a uninuclear basophile non-granular cell, present in the circulating blood and also scattered throughout the body, though it appears especially congregated in the factories presently to be described. If the term "lymphoid cell" be reserved as a general one, the word "lymphocyte" comes to be applicable only to a cell-form of special function, familiarly present in the blood-stream. Although every lymphocyte is by definition a lymphoid cell, the converse does not hold good.

Two other terms are sometimes used which are apt to be misleading. These are (1) The lymphocytoid cell—applied to any cell which closely resembles a true lymphocyte in morphology, remains non-granular, but is not necessarily identical with it; (2) The lymphadenoid cell—applied to any lymphoid cell derived from a lymph-cell-forming tissue.

The word lymphocyte is ambiguous in another sense. Some hæmatologists attach a purely morphological meaning to it, while others prefer to add a genetic significance. Thus, according to Naegeli, Schridde, Helly, Ziegler, Türk, and others, every true lymphocyte has come from the lymphatic apparatus—it is a histiogenetic entity. If we define the lymphocyte solely according to its morphological characters (after Maximow and Weidenreich) it becomes inevitable to include with it a number of forms which it is hard to reconcile with the popular conception of lymphocyte. This accounts for the prevalence of the lymphocyte in the literature of hæmogenesis, and introduces an undesirable confusion into hæmatology. For the purposes of the present chapter, therefore, we disregard pre-natal lymphocytes, in order to deal more fully with the cell so well known in the blood-film. The fact that blood-lymphocytes are so much intermingled in the factories with other lymphoid cells, causes a little difficulty in describing the lymphopoietic factories according to the heading of this

section. The reader is therefore referred to the corresponding section of the succeeding chapter for a concluding survey of these tissues as a whole, as well as to the later chapters, where all manner of lymphoid cells are dealt with in perspective.

Dividing lymphoid cells (spongioplasmatic cells) into two groups according to their future history, it is possible to assign them to special tissues. We have (1) Those which remain permanently basophile; these are the lymphocytes and monocytes; and (2) Those which undergo oxyplasmasia with or without formation of specific products; these are the lymphoidocytes (*Chapter* I) and the leucoblasts (*Chapter* V).

Lymphoid cells are manufactured in the following parts of the body: the lymph nodes, the tonsils, the lymphatic follicles of the mucous membranes (e.g., solitary follicles and Peyer's patches of the intestine), the spleen, the lymphatic cell aggregations in organs (the so-called Ribbert's lymphomas[2] in the liver, kidney, lung), the mesentery (Weidenreich[1]); and indeed in the connective tissue throughout the body,* the thymus,† and the bone-marrow.‡

In using the term "lymphoid cell" in relation to these organs, we imply that the lymphocyte is not the only kind of cell made in them. The lymph node is made up of lymph follicles and medulla; the spleen is made up of Malpighian (i.e., lymph) follicles and pulp. In each case it is only the lymph follicles which are concerned with the formation of lymphocytes, although, as we shall show, it is probable that if it were not for the medulla and pulp respectively there would be no follicles at all.

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* It is this widespread distribution that accounts for the absence of blood-change after excision of masses of lymph-glands.

† While the thymus is generally accepted as an important lymph-cell factory in the embryo and infant, there are very definite features about its structure which show that the cells made in it are sufficiently distinct from the true small lymphocyte to justify them being renamed "thymocytes." It is for this reason that we shall not describe the structure of the thymus in relation to lymph-cell factories. The writer feels that at the present day there is not sufficient information about this organ to enable it to be correctly placed in the scheme of presentation adopted in this volume.

It will be noticed that Stöhr and Grawitz came to a similar conclusion—the latter because the thymus lymphocyte never contains azur granules; they occur when the thymus is not an intra-uterine blood-forming organ.

‡ It has been supposed until comparatively recently (Hedinger,[3] Schmorl, Löwit) that bone-marrow cannot make true small lymphocytes. If it does not do so, it makes cells which are at least extremely isomorphous with them. Clusters of lymphocytes with genuine germ centres (which proves their lymphatic nature) were found by Oehme in the bone-marrow of children and in cases of status lymphaticus; they were in relation to the terminal twigs of the arteries something like a Malpighian body in the spleen, but it is not known whether such nodules were pathological or not. Their structure does not enable a definite statement that they have other functional and cytoplastic potencies, because structure does not prove function.

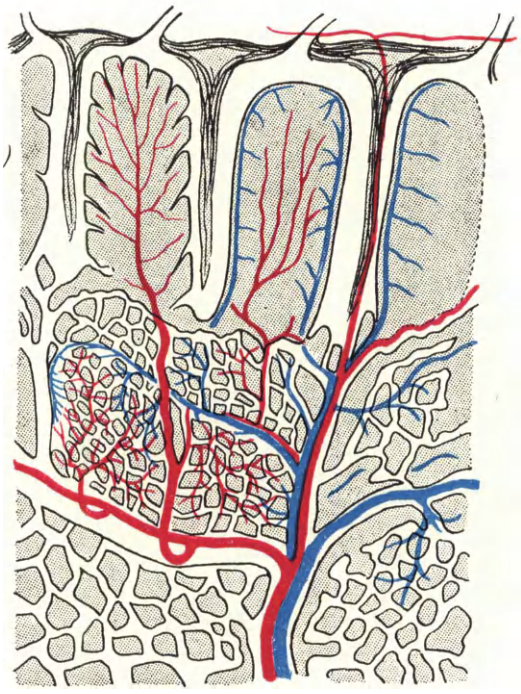
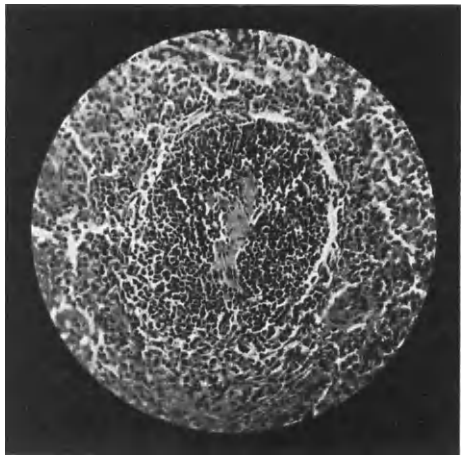


Fig. 28.—Blood-supply of Lymph Node (founded on Calvert). The red lines indicate arterial channels, the blue indicate venous blood, and the white spaces indicate the lymphatic paths. The shaded area represents the specific tissue. (*a*) follicles; (*b*) pulp cords below.



" . . . the follicle sits on the artery like an apple on a stalk " (p. 113).

Fig. 29.—Malpighian Follicle in the Spleen.

(Oc. 2, Zeiss, Apochrom. 4 mm.).

Face p. 113]

The Lymph Node.—This is made up of a number of follicles arranged peripherally to the central medullary tissue, which will in future be spoken of as " pulpar tissue." The latter is completely enclosed by the former save at one point, the point of entry and exit of the blood-vessels.

The lymphatic trunks enter over the exterior of the gland, and their channels converge to the point just named. The follicles are severally enclosed in sinuses into which the afferent vessels open.

The portion of the sinus beneath the capsule (which covers in the whole organ) is called perifollicular, and is continuous with the sinuses between the follicles (called interfollicular). These again communicate with a very irregular network of lymphatic channels, the central sinuses which separate the pulp cords from one another. The central sinuses converge to form a dense plexus of tortuous and varicose lymph-vessels from which emerge the efferent lymphatic trunks. The follicles and pulpar tissue are also permeated by the circulating lymph, since the reticular tissue which separates them from the channels is as full of perforations as if it were muslin. In consequence, their products of manufacture enter the lymph-stream easily and reach the blood-stream by way of the thoracic duct. It is probable, however, that some of them enter the blood-stream directly, and we shall find that even in the lymph-nodes a discharge of white cells directly into the pulpar blood-vessels takes place by no means infrequently, at any rate in pathological material.*

To complete the picture of the lymph node we now follow the *blood-vessels* (*Fig.* 28). Entering at the hilum, they break up into main trunks which make directly for the follicles and usually enter them at their base, so that the follicle sits on the artery like an apple on a stalk (*Fig.* 29). Passing onwards through the follicle, the artery breaks up into smaller branches (maple-tree fashion), which at once pass to the periphery of the follicle and are there gathered together into a mantle-like network of minute venous channels. These rapidly fuse into venous channels and drain towards the " stalk " of the follicle, and in their turn make

* Observations on autopsy material at the Royal Victoria Hospital, Montreal.

straight for the hilum of the gland. This is the *cortical system.* Similarly, a branch leaves at right angles to the first main vessel and supplies the pulpar tissue. It gives off branches which form a fine capillary network in the pulpar tissue in such a way that the blood-vessel is always in the centre of a pulp cord (*see Fig.* 36). In this portion of the gland the capillaries are rapidly gathered together into veins (still central with respect to the pulp cord) which steadily increase in size as they join up to form the main trunks that emerge at the hilum in their turn. Sometimes the artery to the medulla gives off a large branch which runs up to the follicle, and *vice versa.*

The architecture of the gland is thus characteristic. We have (1) follicular, and (2) pulpar tissue. The former is built up of arterial trunks, the latter is more related to venous capillaries. Running through the whole there is, of course, a delicate reticulum of connective tissue, the meshes of which are finest at the periphery of the follicle, at the margins of the pulpar cords, and along the main vascular trunks. This reticulum is covered by endothelial cells, which play a very important part in the functions of the follicle.

The Lymphoid Follicle.— In the main, the structure of the lymphoid follicle is the same whether it be in the lymph node, or tonsil, intestinal mucous membrane, etc. In many cases* there is a cluster of large cells in the centre, forming the so-called germ-centre first described by Flemming[6] (*see Fig.* 4). The remaining cells are small round cells of lymphoid character, and are more numerous at the periphery. These lymphoid cells are of two types: (1) A lymphocyte with a dark nucleus, around which one cannot distinguish a distinct cytoplasm; (2) A lymphocyte whose nucleus is larger, less darkly stained, and enclosed by a delicate protoplasmic border. Permeating amongst all the cells is a delicate connective-tissue reticulum whose meshes are open in the centre and blend with the adventitial cells of the capillaries which traverse the follicle, while they are continuously finer towards the periphery. The reticulum is everywhere covered by ramifying cells, and,

* Pappenheim points out that the germ centre is by no means as constant as is usually supposed.[5]

indeed, is derived from these. Here and there ordinary white fibrils occur in variable number, and sometimes a few elastic fibrils are also present (Bunting).[7] Many of the branching cells which go to form the reticulum are actively phagocytic, as indicated by the presence of carbon particles within them in cases of anthracotic glands. They are therefore pathologically identical with the endothelial cells which become desquamated in the sinuses in catarrhal conditions, and are also continuous with those lining the efferent lymphatic trunks. The germ-centres are not distinct in embryos, young animals, or in very old ones (Baum and Halle).[8] It is therefore believed by Naegeli[9] and others that the small lymphocyte of the resting follicles makes germ-centre cells, and that the latter mitose and give rise to new generations of lymphocytes.

Cyclical Changes in the Lymph Follicle.—The germ-centre cells, as usually described, are large and densely packed. They frequently show active mitoses, the products of their division being lymphocytes of progressively smaller size. These are pressed against the fine reticulum at the periphery of the follicle, whence they ooze into the lymph-channels enclosing them. These lymphocytes form a barrier of variable thickness round the central pale cells. However, the germ-centre only represents a transient stage in the life history of the follicle, and is always changing in form. Thus, during the fasting period, the germ-centres are specially rich in mitoses, the cell body has a granular appearance and is more basophile in reaction, the sinuses are empty, and the vascular channels very narrow. During digestion, the follicles of *any* gland—not merely the mesenteric nodes and the solitary follicles (Pirone)[10]—swell markedly, their outlines become indistinct owing to an ever-increasing amount of lymphoid cells at the periphery, the blood-vessels dilate, and the lymphatic sinuses are seen to be filled with macrophages (desquamated endothelial cells) whose cytoplasm may contain red and white cells. The phagocytes become extremely active at this period (their feeding time), their contour becomes less irregular, and their nucleus is placed to one side, while the cytoplasm of the germ-centre cells themselves becomes abundant, the nucleus becomes larger, round or oval or reniform, and its structure clearer, but mitoses are less numerous than before.

Keuthe[11] found that the germ-centre cells of the mesenteric glands take up egg-yolk from the food directly. The writer has found that human mesenteric glands are flooded with soaps in globular form for some hours after food, this fat being retained in the endothelial cells of the sinuses, to be passed on into the circulation in another form at a later hour. In other words, much of the fat received during digestion is stored in these cells until required by the organism.

Similar changes to the above take place in the endothelial lining of the capillaries.

After a certain number of hours the follicle begins to diminish its activity, its outline shrinks, and the germ-centre cells appear relatively more numerous, until finally the same appearance is reproduced that was described as present in the fasting stage. In a sense, this second appearance is equivalent to the resting stage of a secretory gland; the follicle is now empty of the lymphocytes, and the original formative cells are exposed to view, just as a secretory gland-cell loses its turbid appearance after digestion because of loss of the secretion that had accumulated during the fasting period. The explanation of the cyclical changes in such terms is misleading. Observations on the follicles in numerous cases of appendicitis have led the writer to regard the process of lymphocyte formation as continuous. In other words, there is no resting stage. The differences of appearance are due to the variations in demand upon the cells manufactured. In infections the lymphocytes may be sucked up from the follicles very rapidly, and this process may continue day after day, whereas during digestion the demand only lasts an hour or two. The richness or otherwise in germ-centre cells, therefore, depends on the demand of the tissues for lymphocytes. Germ-centre cells are of course always there, although the individuals are regularly disappearing as a result of mitosis. The phenomena are, then, exactly analogous to those observed, for instance, in a reservoir where the degree of fullness or emptiness depends upon the outflow, assuming the inflow to be constant.*

* This is not necessarily an altogether accurate representation of the processes under consideration. Pappenheim[5] points out that germ-centre cells are not always in the form of macrolymphocytes with narrow cell-body, and that in hyperplastic follicles (e.g. typhoid fever) they vary in character from the above-named form of macrolymphocyte to large

The rate of increase of the lymphocytic cells is sometimes so rapid that no other conclusion can be reached than that the intermediate stages can proliferate parthenogenetically, as it were, and produce large groups of lymphocytes in place of small ones. The appearances seen when the follicle is rich in lymphoid cells suggest this explanation, the more so as their arrangement into locules proves that they have been derived by multiplication into five, six, or more, from a small round central cell. Bearing on this view is the fact that in chronic lymphatic leukæmia the lymph-nodes show no germ-centres.[10]

Metabolic Changes in the Lymph Nodes.—Flemming[6] found that the germ centres contained rounded or semilunar bodies which have a strong affinity for basic dyes—the "tingible bodies." These are situated in the cell-body of macrophages, and some authors find them in lymphoid cells. They resist acetic acid, but dissolve in alkalies. They stain well with hæmatin and all basic aniline dyes. They stain metachromatically with thiazin dyes, and can be double-stained in some instances, the hollow of the semilunar body having an affinity for acid dyes, while the rest of it has an affinity for basic dyes. According to Ciaccio,[13] they are associated with the fact that purins are very rich in lymphoid tissue, and have something to do with the digestion of nuclear matter by macrophages. This is a katabolic process. The fixed follicle cell or the endothelial cell becomes large, its nucleus clear and round, and its cytoplasm finely granular and basophile; while as the katabolic process progresses, it becomes more acidophile and delicately reticular in structure. The ingested material now appears within the cell as the tingible bodies referred to.

In hunger, fat in the lymph nodes is always within the endothelial cells and wandering cells. The fat undergoes two changes: (1) Emulsification and saponification under the influence of the

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mononuclear forms and cells of the type of Saxer's wandering cells. In many follicles the germ-centres are reduced to a minimal perivascular envelope without any visible mitoses. He claims that normally there are no true germ centres; that the appearance of broad-bodied (leucocytoid) cells is pathological. The absence of follicles in cases of chronic lymphatic leukæmia is explained as the effect of continued proliferation by amitosis to the exclusion of the previously existing slow proliferation by mitotic methods. Similar statements are made by Schmidt. The writer would consider that the whole subject is still in a nebulous stage.

endothelial cells of the sinus; (2) Conversion into neutral fat, which appears in the form of extremely fine granules. The latter change is under the influence of the Altmann granules, the first stage being acted on to produce the second. These processes take place both in the case of autochthonous and heterocthonous fat (Stheemann).[14]

Regressive Changes.—Conversion of the proper tissue of a lymph node into adipose tissue is noticeable just as it is in the case of bone-marrow. The germ centres lose their cells, and the connective-tissue cells become adipose. This change begins in the hilum and spreads to the capsule, so that nothing is ultimately left but a narrow disconnected rim of lymphadenoid tissue. After this, fibrosis may take place in the vicinity (Rubens-Duval et Fage).[15] Conversely, adipose tissue may develop lymph-nodes in regions previously devoid of them.

Functions of the Lymph Nodes.—

1. It has long been supposed that the main function of the lymph node is to provide a *barrier to infection.** This being so, it is remarkable how seldom they prove adequate. It is only the least virulent organisms that fail to pass through them, and even here it is doubtful whether the destruction of the organism does not rather take place in the subcutaneous tissues previously. The arguments for believing that they act as a barrier to infection are such as follow: (*a*) Intravenous infection is far more dangerous than subcutaneous; (*b*) Administration of toxins subcutaneously to a guinea-pig causes necrosis in the follicles, whereas toxin, plus antitoxin, leads to increased reaction of the lymph follicles; (*c*) Streptococci taken from a wound infected with erysipelas killed a rabbit in four days. If taken from the lymph nodes in the same case, the rabbit does not die for sixty days (Labbé, Bezançon); (*d*) Maceration of lymph-node tissue at 38° C. yields a thermolabile hæmolysin, which is destroyed by 56° C. It is able to activate an inactive serum just like hæmolytic complement (Metchnikoff and Tarassewitsch,[16] and others).

2. The *absorption* of body or food *fat* by way of endothelial cells (lipophages) and conversion of the same into soaps and back again into neutral fat.

A relation of follicles to digestion is implied by their superabundance in the alimentary tract, which indicates that such function is much more important than anti-microbic action. It is therefore a matter of no surprise that recent observations of the follicles of the tonsil (MacLachlan,[17] 1912)

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* *a.* Bactericidal (Bartel, Denys, Wassermann). *b.* Antitoxic (Asher).

fail to show any evidence that this organ has anything to do with anti-microbic processes, in spite of the overwhelming belief to the contrary.

3. Formation of *macrophages* and *phagocytosis* of carbon particles, red and white cells, etc.

4. *Cytogenesis* of lymphocytes. Ehrlich thought that lymphocytes entered the circulation passively, but Jolly and others found them to be amœboid.

5. Pathologically, metaplasias of all kinds, myelopoiesis.

The Structure of the Spleen. — This differs from that of the lymph nodes, inasmuch as the follicular tissue is relatively scanty, while the pulp tissue is abundant. The organ is divided up into a number of lobes by bands of fibrous tissue, the trabeculæ, which pass inwards from the capsule. These lobes are again sub-divided into lobules, each of which is about a millimetre in diameter. This lobule is the *unit* of the organ. It is roughly pyramidal in form, the base being outwards and the apex inwards; fibrous bands traverse it and divide it into about ten compartments. The main artery of the lobule enters at the apex of the pyramid, passes straight to the base, giving off on its way a separate arteriole to each compartment (*Fig.* 30.) This arteriole ends in an ampulla (the ampulla of Thoma), the proximal two-thirds of which are lined by spindle-cells lying on a delicate reticulum, while the distal third has no definite cell boundaries and shows fibrils of reticulum passing across it. Between this imperfect terminal and the intralobular vein is the pulp cord of the spleen, so that the blood traverses the latter in its way from arterial to venous channel. The intralobular veins empty into the interlobular vein which runs along the side of the pyramid to join similar vessels from adjoining lobules, and ultimately merge into the splenic vein. Shortly after the main artery of the lobule enters the pyramid, it passes through a mass of lymphoid tissue—the Malpighian follicle. In diseased conditions, such as atheroma, this passage is well marked and conspicuous, owing to tortuosity and increased thickness of the vessel (*Fig.* 31). This main trunk bears with it a lymphatic sheath, and it is in the latter that the follicle develops.

The above sketch is completed by filling in: (*a*) A delicate fibrillar network of connective tissue throughout the organ, passing across in web fashion from one intralobular trabecula to another;

and (*b*) Sensory medullated and sympathetic non-medullated nerve fibrils, the latter being the more numerous and following the arterial ramifications to end either in the arterial muscle fibres or free in the pulp.

The Malpighian Follicle as it appears in the Spleen.—There are some slight differences of structure in the Malpighian body which require definition. The exact form of the follicle varies not only in animals but even in man.* Thus the tissue may be entirely on one side of the follicular artery, but more usually it completely envelops the artery. The artery may run exactly through its centre, or more to one side (excentric follicle). Sometimes the follicle appears as an elongated branching structure, which follows the artery through one or more branches and constitutes a tubular or sheath-like envelope to the vessel.† (*Fig.* 32).

The centre of the structure is composed of germ-centre cells, while the periphery is formed of small round lymphoid cells, just as was described for the follicle. During digestion, changes may be noted in it similar to those that are noted in the lymphatic tissues of the intestine, namely, enlargement of the follicle, increase in the size of the germ centres, and the appearance of macrophages at the periphery. Basophile cells are numerous at this time; their nucleus is characteristic—two or three large central granulations, joined by delicate chromatic filaments. The cell-body is finely granular during mitosis. Plasma cells and macrophages with abundant cytoplasm and vacuolar inclusions are noted, showing that the Malpighian bodies have something to do with hæmolysis and leucolysis during digestion (Ciaccio[13]). Conversely, during fasting, the follicles are small and sharply defined; they are then reduced to a ring of lymphocytes of small size round the central arteriole. The reticular tissue is, however, rather different. It is a very open meshwork everywhere but at the extreme periphery of the mass, where it is much more dense—denser even than at the periphery of a lymph-node follicle. As the meshwork of the lymphatic follicle communicates with the surrounding sinus, so

* Observations on autopsy material.
† This arrangement is frequent in the rat.

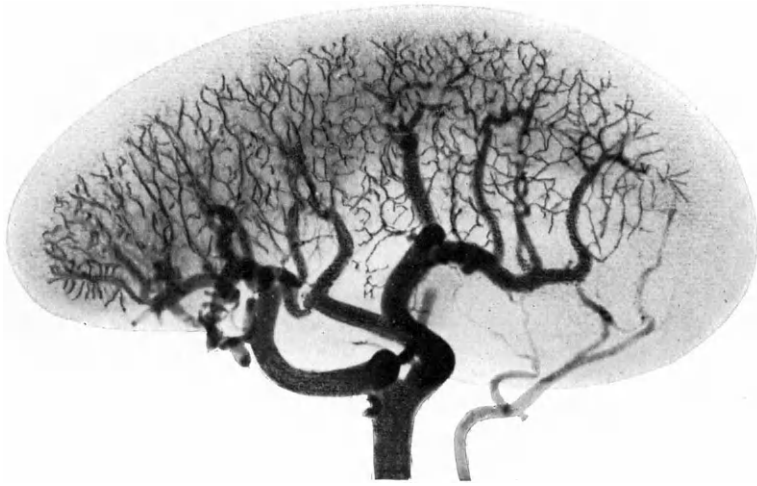
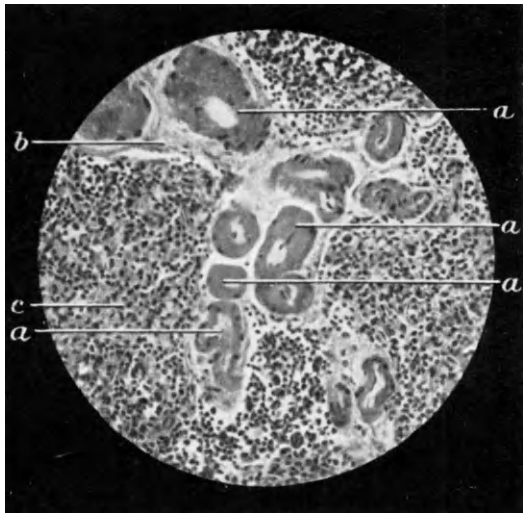


Fig. 30.—A VIEW OF THE ARTERIAL SUPPLY OF THE SPLEEN. The splenic artery was injected with barium sulphate, and the viscus photographed by means of *x*-rays. Notice the heavy trunks passing parallel to one another almost to the free surface. Each supplies a separate "compartment," and therein breaks up into a complex brushwork. (*From a photograph kindly prepared by Dr. A. Howard Pirie.*)



"In diseased conditions, such as atheroma, this passage is well marked and conspicuous, owing to tortuosity and increased thickness of the vessel" (p. 119).

Fig. 31.—CENTRE OF MALPIGHIAN FOLLICLE, with diseased central arteriole. (*a a*) sections of one arteriole. Its to-and-fro twisting causes it to be cut through several times within a short distance; (*b*) deposit of connective tissue round the vessel; (*c*) follicular cells.

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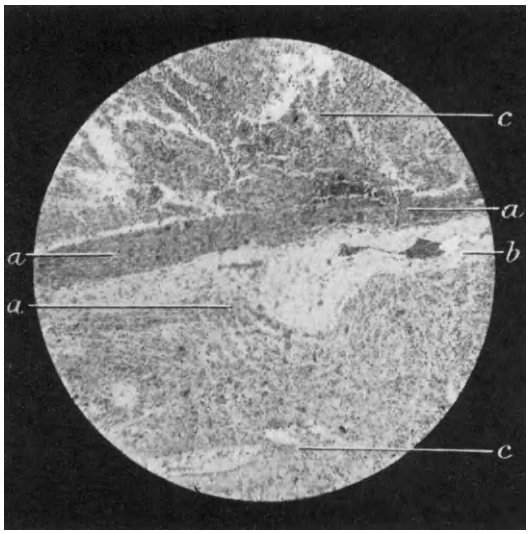
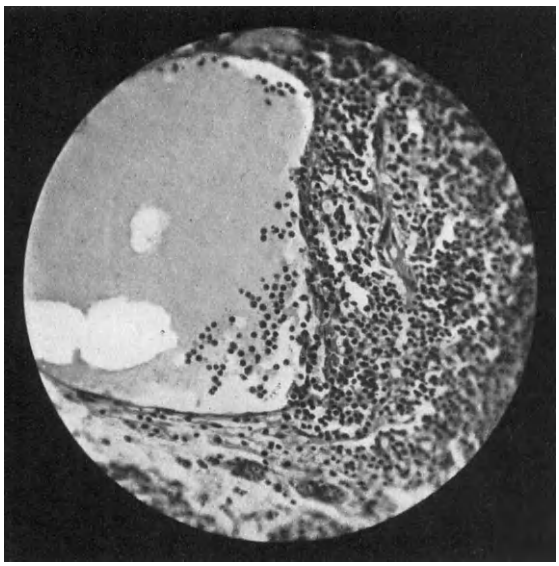


"Sometimes the follicle appears as an elongated . . . structure which . . . constitutes a tubular or sheath-like envelope to the vessel" (p. 120).

Fig. 32.—ANOMALOUS SHAPE OF MALPIGHIAN FOLLICLE. (*a a*) the follicle, surrounding (*b*) an artery cut longitudinally; (*c*) pulpar tissue.

(Oc. 2, Zeiss Apochrom. 4 mm.).



". . . such collection (of lymphoid cells) may undergo hypertrophy and give rise to a . . . focus of cytoplastic activity . . . from which some (lymphoid cells) ooze into the blood-channel direct" (p. 122).

Fig. 33.—EDGE OF A CAPILLARY SHOWING DISCHARGE OF LYMPHOID CELLS FROM AN ADJACENT FOLLICLE INTO THE LUMEN.

(Oc. 6, Zeiss Apochrom. 4 mm.).

the meshwork of the Malpighian body communicates with the spleen pulp, there being no apparent lymph-sinus system in the spleen. The vascular supply of the Malpighian follicle is also different. The mass is built round a vessel only in the sense of the perivascular lymph-sheath being dilated enormously at this particular spot. A few minute arterial trunks leave the main vessel rectangularly as it courses through the cell cluster, branch rapidly into smaller and smaller branches which make for the periphery of the follicle, and finally pass through into the pulp tissue, to end there somewhat as they do in the final compartments of the lobule.

A further distinction between the Malpighian and the lymph-node follicle lies in the character of the non-lymphoid cells which may be present. In sections of the spleen taken from subjects dying of various conditions, it is frequently noticed that the edge of the follicle may be infiltrated by certain other forms of cells which are only scanty in the lymph-node follicle. First and foremost of these is the pseudo-plasma cell, which, in some conditions, is extremely densely crowded around the follicle.[18] Eosinophile cells are also very frequent in the vicinity of these follicles, while in the lymph-node they lie in the peripheral sinuses.* The fact that the lymph-follicle cell contains phenolphilic granules while that of the spleen follicle does not, is also of interest (Loele[20]). These granules are the more numerous the nearer they are to the arterial blood. The pathological changes occurring in the Malpighian bodies are of importance and of considerable interest in so far as they provide data which would elucidate the nature of the constituent cells, but these will be referred to elsewhere.

The BONE-MARROW (*see p.* 47).—It is usually pathological for lymphocytes to be formed here.† The following evidence suggests that it may be a physiological event also. (*a*) A thoracic-duct fistula is made in the dog so that lymphocytes cannot enter the blood. The spleen is now excised. The result is lymphopenia for a short time; lymphocytosis follows (Biedl and

* In each tissue, however, the eosinophile cell is not a true eosinophile cell (blood cell) (F. W. Andrews).[19]

† According to Goodall and Gulland (*The Blood*, 1912), the bone-marrow is the chief physiological source of lymphocytes.

Decastello). The fallacy of this experiment is that lymphocytes may enter the blood directly from the lymph nodes; (*b*) Schuhmacher's counts of the cells in the efferent and afferent lymphatics and blood-vessels. The efferent lymph contains about 3000 lymphocytes per c.mm.

The Accessory Factories of Lymphopoiesis differ from the preceding tissues in their more indefinite structure. They are extremely numerous, so that, if calculated out, the cubic space occupied by the lymphatic tissues of the body would be found to be surprisingly large. This explains the unlimited possibilities of lymph-cell manufacture in any portion of the body exposed to toxic or infective influences. While it may not be certain that these accessory factories regularly discharge cells into the blood-stream, the fact that collections of lymphoid cells analogous to the Ribbert lymphoma may be met with round any vessel is suggestive.* It is evident that such collection may undergo hypertrophy and give rise to a considerable focus of cytoplastic activity. Thus the preceding illustration (*Fig.* 33) shows the edge of such a focus, perivascular in situation, taken from the subserosa of the appendix in a case of acute lacunar appendicitis. It shows the familiar collection of small round cells, from which some ooze into the blood-channel directly.

In tuberculous and syphilitic effusions, again, there is an active lymph-cell formation at the site of the disease; this is derived by hypertrophy from the existing accessory manufacturing plant.

Perivascular lymphomas enlarge in any chronic inflammatory tissue (Marcuse),[22] and their occurrence in typhoid fever, diphtheria, and scarlet fever is only noted because they are unusually large. In other words, inflammatory cell infiltration is nothing more than proliferation of a pre-existing or a potential lymphoid follicle. But the lymphocyte made in such circumstances is not necessarily the same in function as that from the lymph-node (Schridde). This conception explains the appearances in thyroid enlargement, in status lymphaticus, in Miculicz's disease, and many other conditions. In cases of enlarged thyroid in Graves' disease, lymphoid

* Such findings only require the observation of daily surgical pathological tissues for their substantiation. Pascheff found lymphoid cells in the conjunctivæ under normal conditions.[21]

follicles appear scattered throughout the organ wherever active destruction of thyroid tissue is going on, and in all such follicles germ-centres may be found. They become large and numerous after the administration of iodine to persons affected with this disease (v. Wendt[23]). The presence of diffuse collections of lymphocytes and lymphoblasts along the septa of the salivary and lachrymal glands (Hesse Thaysen[24]) forms the basis of metaplastic changes under certain conditions; that is, it is possible for lymphomas (leukæmic lymphomatoses) and lymphosarcomas to arise from them. Mikulicz's disease is nothing more than this.

It is likely, then, that the perivascular lymphoma plays some part in rendering innocuous harmful substances secreted either by the tissues themselves or by certain microbic agents (Schridde[25]).

On the other hand, M. B. Schmidt[12] does not consider that these lymphomas are always derived in the manner described, because in typhoid fever, where they appear in the liver, the collections are in the neighbourhood of the bile-ducts and capillaries, and the cells composing them are not lymphoid. They consist of foci of coagulation necrosis, infiltrated with polynuclear leucocytes. The necrosis is here associated with a direct phagocytic action on the part of the Kupffer star cells. Such observations only apply to special cases, and cannot disturb the main argument.

II.—THE LYMPHOBLASTIC LINE OF DEVELOPMENT.

THE morphological characters of the lymphoblast—Of the large lymphocyte of the germ-centre cell—Of the mesolymphocyte—The cycle of development.

THE germ-centre cell, as has been shown in the preceding pages, is ubiquitous in lymphatic tissues. Whether it is to be looked upon as the parent cell of the lymphocyte is not as clear as would be expected from the wide distribution of these cells. If we are to regard the germ-centre cell as the primordial cell for the lymphocyte, we should require to find in it the same characters as were given for the primordial cell, and it requires little investigation of lymphatic tissues to show that this is not the case. The germ-centre cell possesses different characters from those exhibited by the mother cells of the bone-marrow. The consensus of opinion is nevertheless in favour of the view that the germ-centre cell does give rise to lymphocytes, a fact which suggests that either the various blood cells are derived from different ancestors or that the germ-centre cell is only an intermediate stage between an ancestral indifferent cell and the lymphocyte as we know it. In either case, we should not use the term mother cell at all, but employ the term "lymphoblast" for the germ-centre cell.

Reference has already been made to the conflicting views concerning the nature of the germ-centre cell. We may regard this cell as either (1) The primary cell of the follicle. Against this is the fact that it is not found in embryos or young animals; that it is never seen in mesenteric lymph nodes, and is not constant even in the Malpighian bodies of the spleen. Or (2) A temporary stage derived by anaplasia of some lymphoid type, or by metaplasia from adventitial cells. Many germ-centre cells have a decidedly endothelioid aspect. Or (3) Entirely abnormal, being the result of microbic or toxic stimulus reaching such tissue. This last view would not indicate that it was a deleterious cell, but rather that special circumstances demand its appearance. It might rejuvenate the proliferating properties of the lymphoid cells ordinarily present. It would find its analogue in those protozoa which divide parthenogenetically for many generations, but eventually conjugate. Mitosis introduces a redistribution of atom-groups in a manner analogous to conjugation.

Just as in the case of the erythroblastic line of development the mother cell undergoes an intranuclear change when it becomes manifest as a lymphoid erythroblast, so in the lymphoblastic line the mother cell shows an indication of change of destiny by a re-adjustment of structure of the nucleus to form a lymphoblast, or germ-centre cell. The finely reticular structure is replaced by an almost homogeneous appearance, in which only a vague shadowing is visible. In certain phases of activity, during the process of multiplication, the nuclear structure becomes decided, with the appearance of chromatic nodal points characteristic of the Flemming germ-centre cell. With successive divisions, the cells become smaller, the nucleus becomes more and more deeply stained, the chromatin network more and more compressed, until the typical tissue-lymphocyte appears at the margin of the follicle. This lymphocyte ultimately appears in the blood-stream as a cell with characteristic morphology.

The Morphological Characters of the Lymphoblast.*—

Outer Form.—The absolute *size* is variable. The cell is, however, usually large. The *shape* is round or ovoid. The *contour* is rather ill-defined but regular.

Internal Structure of the Cell-body.—The *cell-body* is narrow, and basophile in reaction A faint reticulation can be seen within it, but differentiation between spongioplasm and hyloplasm is poor. Azur *granules* are occasionally present, as well as Altmann-Schridde granules. According to Stan. Klein, oxydase granules can be sometimes detected.

Nucleus.—This is relatively very large. The shape is ovoid, the outline clearly defined, and the chromatin network very delicate. Mitotic figures can often be seen.

Nucleolus.—One or two nucleoli may be present; they are indistinct.

This is the prevalent cell in the blood, up to the end of the fourth month of fœtal life; it persists to the seventh month.

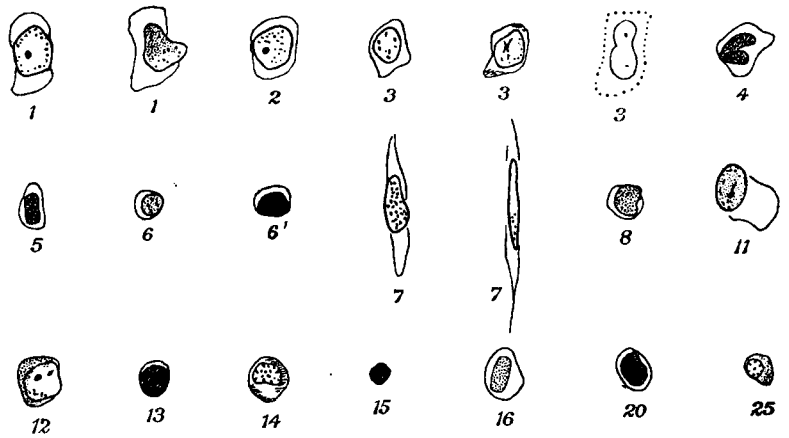
THE MACROLYMPHOCYTE is a cell apparently identical with the preceding. The myelolymphocyte is a similar cell, but more

* *See Plates III., IV.*

EXPLANATION OF PLATE III.

A diagram representing the phases of lymphogenesis, the intercellular metaplasias of the various members of the lymphatic series of cells, and their positions in the follicle, the interfollicular tissue, blood-stream, and tissue spaces. The anatomical regions are mapped out by different tints. The curved lines and arrows indicate the direction of change; single lines represent either ageing (ontogeny) or differentiation without division; double lines represent division with differentiation. Dotted circular lines indicate potential lines of development. Straight dotted lines indicate frankly pathological changes of position.

The reader will observe that each cell-form is represented as ever changing in some way, either in characters or in position. A change in position is only indicated by the appearance of a cell-form in an area depicted of another colour; change of position does not follow the curves. Thus, when 2 becomes 3 it is depicted as still on the brown-tinted rectangle. It is still in the follicle. The cell, then, has not actually moved. Again, cells 4 and 16 are both in the white area. They would both be actually on the same spot. But cell 6 has actually moved to 6'.



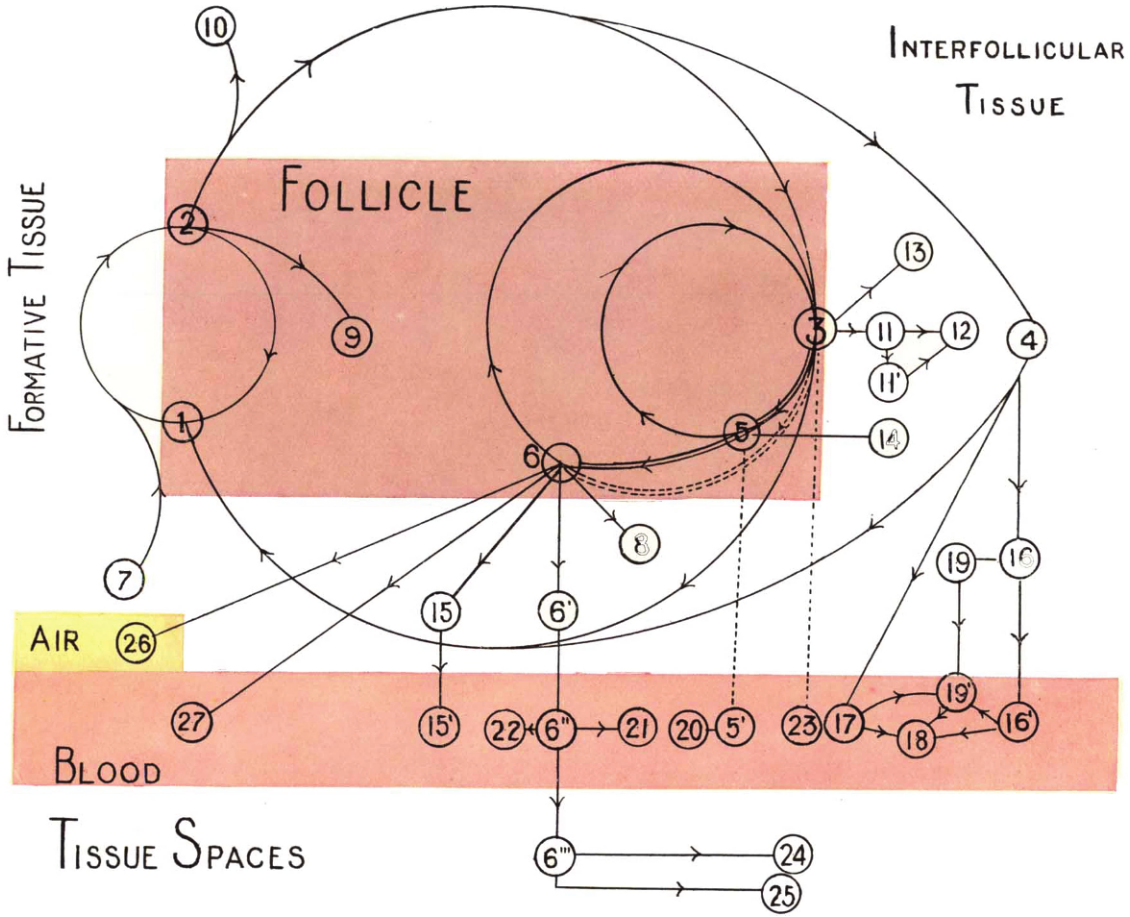
DIAGRAMMATIC OUTLINES OF CELLS REFERRED TO IN *Plate III*, drawn to scale, using a magnification Oc. 12, with Zeiss Oil-immersion lens. Panoptic stain-preparations in the author's collection.

In all these cells a white cytoplasm means feeble basophilia; a stippled cytoplasm means moderate basophilia; and line-shading implies a conspicuous degree of basophilia. Similarly, varying degrees of basophilia in the nucleus are indicated by increasing density of shading, commencing with white (represents the palest blue in the preparation), and passing to dense black (trachychromatism). The small dots in the nucleus are chromatic markings, while the larger ones, except in cell *11*, are the nucleoli. Azur granulation is not indicated.

1.—Adventitial or perithelial cell; the primordial resting cell. *2.*—Lymphoidocyte; mother cell, or wandering cell of Saxer. *3.* Lymphoblastic macrolymphocyte, or germ-centre cell. *4.*—Splenocytar monocyte, or indifferent pulp cell. *5.*—Mesolymphocyte. *5'* the same in the blood (*Plate IV*, 5). *6.*—Microlymphocyte, or tissue lymphoctye; the lymphoid cell of the follicle; *6'* the same in the interfollicular tissue; *6''* in the blood (*Plate IV*, 2); *6'''* in the tissue-space. *7.*—Stroma cell of the interfollicular tissue *8.*—Myelolymphocyte (*Plate IV*, 8). *9.*—Leucocytoid lymphoidocyte (*Plate IV*, 38). *10.*—Rieder lymphoidocyte (*Plate IV*, 40). *11.*—Leucocytoid macrolymphocyte; *11'* the same becoming plasmoid. *12.*—Macrolymphocytar plasma cell. *13.*—Lymphoma cell. *14.*—Mesolymphocytar plasma cell. *15.*—Dwarf microlymphocyte; *15'*, the same in the blood (*Plate IV*, 6). *16.*—Splenocytar monocyte, splenocyte, or large mononuclear leucocyte; *16'*, the same in the blood (*Plate IV*, 10). *17.*—Lymphocytoid large mononuclear leucocyte. *18.*—Transitional cell (*Plate IV*, 11). *19.*—Leucocytoid large mononuclear; *19'*, the same in the blood (*Plate IV*, 12). *20.*—Leucocytoid mesolymphocyte. *21.*—Lymphocyte with reniform nucleus (*Plate IV*, 4). *22.*—Leucocytoid lymphocyte ("hyaline leucocyte"), (*Plate IV*, 3). *23.*—Lymphæmic lymphocyte (*Plate IV*, 44, 45). *24.*—Myelolymphocyte (*Plate IV*, 8). *25.*—Histioid plasma cell. *26.*—Colostrum cell. *27.*—Thrombocyte of reptilian blood.

PLATE III.

AUTHOR'S SCHEME OF LYMPHOGENESIS



allied to the leucoblast series (myeloblast) than to the lymphatic. It is therefore better considered under that heading. The description of such a cell in words would leave no clear idea of any distinctions, whereas a drawing at once indicates the differences. Such cells are sometimes " large," and sometimes " small."

The Morphological Characters of the Large Lymphocyte.*—

Outer Form.—The *size* of the cell is variable. The cell may be a little smaller than the lymphoblast, inasmuch as it is a daughter cell of this. The *shape* and *contour* are as before.

Internal Structure of the Cell-body.—The *cell-body* is narrow, stains feebly basophile, and shows no indications of spongioplasm. The cytoplasm is almost hyaline in aspect. Azur *granules* are occasionally seen.

Nucleus.—The absolute size is large, and the relative size is considerable. The structure is compact, owing to lack of differentiation of the chromatin from the parachromatin. Occasionally it is indented.

Nucleoli are variable.

The Large Lymphocyte of the Tissues, the germ-centre cell, presents very definite features, which are noteworthy because they are readily made out in ordinary histological preparations of tissues. The *shape* of these cells varies markedly, from spherical through every form of polymorphism to an absolute oval. It may be said that absolutely regular forms seldom appear in the lymphatic follicles of either lymph nodes or spleen. The amount of *cytoplasm* is also very variable. In not a few instances, it is relatively abundant, but always bears the constant feature of light basophilia, and in the healthy state, homogeneity of structure. In many diseased conditions of these formative centres a vacuolar degenerative condition of the cytoplasm is noticeable, with the appearance, may be, of dusky granules between the vacuoles. With such degenerative phenomena there is associated a marked lack of distinctness of outline, and marked irregularity of contour. The extremities of the normal germ-centre cell frequently show an increase of density of cytoplasm in those cases in which a blunt

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* *See Plates III., IV.*

spindle shape is assumed, and a very faint but distinct reticular structure can be detected in the cytoplasm at these points.*

The *nuclear membrane* is always well defined in the normal cell, and strongly demarcates the basophile cell-body from the almost achromatic nuclear matter. The parachromatin in these cells is very abundant, leaving the chromatic points very plainly seen; the latter are especially abundant towards the periphery of the nucleus, where the eye sees more granules because the nuclear matter is observed at an angle. A few chromatic filaments can be observed here and there, connecting distant chromatic points. Sometimes germ-centre cells are seen which are entirely amblychromatic, the cytoplasm being itself almost achromatic. Nucleoli, or more conspicuous larger masses of chromatin, are sometimes seen. True metachromatic *nucleoli* are not always noticeable.

Mitoses are very frequently seen in the germ-centre cell, and indeed, in earlier times the phenomenon of mitosis has been largely studied in this kind of material. It is unnecessary, therefore, to discuss the mitotic forms.

The Morphological Characters of the Mesolymphocyte.*†—

Size of Cell.—This is intermediate between the preceding forms and the small lymphocyte of the blood-stream.

Shape of Cell.—Rounded. Usually oval in tissues, but rounded in the blood-stream.

Cell-body.—Feebly basophile. Sometimes rather deeply basophile. There are sometimes a few scattered azur granules, otherwise the cytoplasm is entirely homogeneous. The amount of cytoplasm varies, but it is relatively greater than in the case of the other lymphoid cells.

Nucleus.—This stains very deeply, owing to the density of the chromatin. The nucleus is absolutely large, and relatively is less conspicuous than in the preceding lymphoid cells.

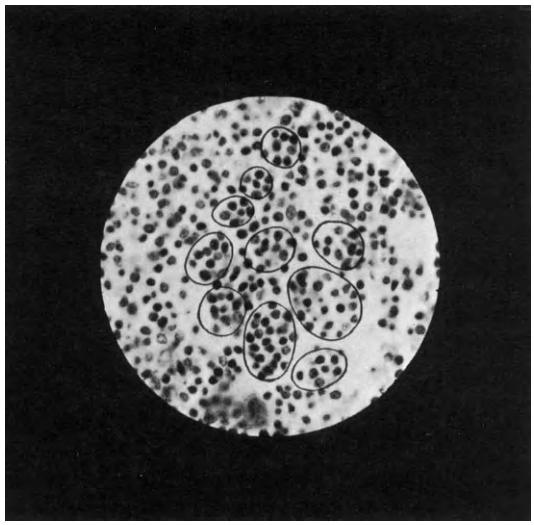
Nucleolus.—This is found in an excentric position. Single.

Mitosis.—Reproduction appears to take place by amitosis.

The Cycle of Development.—Leaving the characters of the small lymphocyte of the blood-stream on one side for the

* *See Plates III., IV.*

† Appears in the blood from the seventh month of fœtal life onwards.



" A locular arrangement of the cells may be seen, where clusters of eight or more . . . are noticed round a central lymphoblastic form of cell " (p. 129).

Fig. 34.—THE CENTRAL PART OF A LYMPHOID FOLLICLE, MAGNIFIED 400 DIAMETERS. The red lines demonstrate the cell-groups referred to. The central cell is not in focus.

(Oc. 4, Obj. 4 mm.).

Face p. 129]

moment, we have in the above brief descriptions a view of all the links of the chain of development of the cell in question—a series which is extremely simple when compared with that described for the red blood-cell, or even the neutrophile leucocyte. It is possible that this simplicity is due in part to lack of knowledge of the details, but seeing that the lymphocyte-forming centres are numerous, and so readily seen in almost any tissue, it is possible for any microscopist to find the genealogy of these cells restricted to a very small series. If the germ-centres of lymphatic follicles be studied by any of the ordinary stains—iron hæmatoxylin, eosin and methylene blue, Pappenheim's panoptic stain—they will be found to contain all grades between the germ-centre cell and the ordinary small lymphocyte. It will not be possible to fix on more than two or three definite cell-forms, because the intermediate stages differ so very slightly from one another. It is easy to point out differences in the sections, and yet there would be no definite criteria for deciding between them were they removed from their original setting. Passing through an intermediate form in which the cytoplasm is rather more basophile and much less conspicuous, while the nucleus is relatively larger but absolutely smaller, we come towards the typical lymphocyte form in which there is hardly any cytoplasmic covering to be seen.

These stages are not all seen in successive layers of follicular cells, as if the formative processes acted centrifugally in the follicle as a whole, but they can be seen to take place in many centres scattered through the follicle, each centre being in the vicinity of a capillary vessel. In well-marked cases, what may be called a "locular arrangement of the cells" may be seen, where clusters of eight or nine cells of lymphocytar aspect are noticed around a central lymphoblastic form of cell (*Fig.* 34). These clusters of cells are sometimes formed of cells with a mesolymphocytic character.

Whether the chain of development is always in the same direction or not is doubtful. It is very probable that there is a circular line, or cycle of development, by which is meant that under various circumstances the lymphocytar cell may give rise to a mesolymphocytar cell, and this to a germ-centre cell, while, on the other hand, the pulpar cell in its turn may give rise to a

lymphoblastic or to a germ-centre type of cell. This view is advanced by Pappenheim, and it is a conclusion which can be reached by anyone who has studied a large number of tissues containing lymphatic follicles. In other words, it is an axiom, and the statement requires the name of no authority for its substantiation. It is another matter to ascertain under what conditions the return of the cycle takes place, or whether the word "return" expresses a misconception. Motion round a circle is neither advance nor return.

Looking at the subject of lymphopoiesis in this manner, we see no difficulty in explaining where the mother cells come from. Whether they arise or not from connective-tissue elements (Ciaccio[13]) under certain circumstances, such as after the injection of nucleinic acid or potassium iodide, is a matter of comparatively little difficulty. As we shall see, in discussing the wandering cells of the body in general, there is always a phase in which the given cell appears as a connective-tissue cell. It is very likely that connective-tissue elements may fuse into a plasmodium, become free, and appear as cells whose nucleus is large and whose cytoplasm appears as a rim—a statement put forward by the author just named. Further, we have the pulp as a source of mother cells, since the pulpar cell, as will be shown, presents morphological and other characters which point to some genetic connection with the follicular cells of the lymph-node or Malpighian body of the spleen.

Discussion of these points is therefore deferred till the monocyte has been dealt with. *Plate III* shows a scheme of the development of the lymphocyte based on studies of lymphoid tissues.

The *development of lymph-nodes* themselves has been studied by Gulland, Saxer, Ketterer, Baum and Hille, Kling, Sabin, and others.[26] According to these observers, the lymphatic vessels appear first and mesenchymal elements cluster around them later, forming intercommunicating cell-columns which are ultimately vascularized from adjacent blood-channels. The mesenchymal tissue pouches into the dilating lymphatic vessels, and thus gives rise to the appearance already described—that of the follicle being like an apple on a stalk. The circumfollicular sinus is thus the deformed original lymphatic vessel. It is evident from a study of the adult lymph-node that some such process must have occurred during development.

In passing, it may be noted that lymph-glands may disappear during adult life, being replaced by adipose tissue, and that adipose tissue may give rise to new lymph-nodes when occasion calls.

III.—THE LYMPHOCYTE OF THE BLOOD-STREAM.

THE lymphoid elements of the blood—Morphology of the lymphocyte—The differential diagnosis of the lymphocyte—The functions of the lymphocyte—Lymphocytosis and lymphopenia—The nutrioid function—The adsorptoid function—Relation to phagocytosis—The chemistry of the lymphocyte; of its azur granules—The comparative cytology of the lymphocyte.

HAVING traced the development of the lymphoid cells up to the point of true lymphocyte formation, and having described the changes which take place within a lymphoid follicle during the phases of metabolic activity, there is no difficulty in deciding upon the mode in which the lymphocyte reaches the circulating blood. A small proportion of these cells pass directly into the blood-channels; the majority are sucked out of the follicles into the juice canals of the connective tissues and thence into the lymphatic channels till they reach the thoracic ducts on either side. Those which are made in lymph-nodes pass into the efferent lymphatics, as shown by cell-counts in experimental animals. In all cases the bulk of the lymphocytes appear to reach the veins at the root of the neck. It is a noteworthy fact that all blood-cells reach the blood through *venous* blood.

The Lymphoid Elements of the Blood-stream include several forms which it is convenient to tabulate at this point:—

1. Small lymphocytes, with their leucocytoid forms.
2. Medium-sized or mesolymphocytes.
3. Large mononuclear leucocytes (monocytes), including transitional forms, and myeloic cells.
4. Primordial cells.
5. Sarcoma cells.

The only members of this group which are normal to the circulating blood are the first, the second, and the large mononuclear leucocyte with its transitional form. If the other cells are found in a blood-film, they indicate the presence of disease.

The list may be amplified in order to bring together many of the atypical forms which may be looked for in clinical work. The

small lymphocytes may appear in dwarf form, or in amitosing forms; they may appear in the form of fatty degeneration (in acute lymphæmia, *sub finem vitæ*), in the form of the so-called Klein-Gumprecht shadows. The latter are the effect of cytolysis, and are specially numerous in acute lymphocytic and myeloic leukæmias. The *large mononuclears* or monocytes include :—

Myeloic cells, derived from the bone-marrow (= leucoblasts).
(*a*). Non-granular myelocytar cells with oxyphile cell-body.
(*b*). Non-granular metamyelocytar cells with oxyphile cell-body.
(*c*). Non-granular polynuclear leucocytes with oxyphile cell-body.
Interfollicular lymphadenoid cells, the ordinary large mononuclear leucocyte or splenocyte.
Transitional leucocyte or splenocyte.

The *primordial lymphoid cells* include :—

The large lymphocyte or macrolymphocyte (lymphoblast) with its senile and Rieder forms. This is met with in the blood in lymphæmia.
The macrolymphocyte or myeloblast, or myelolymphocyte. This may appear in senile form.
The micromyeloblast and its leucocytoid form are almost exactly the same morphologically as the small lymphocyte.
The large Rieder leucocyte.
Polynuclear leucoblasts (basophile non-granular cells with polymorphous nucleus).

Whether the sarcoma cell could be identified in the blood-stream remains to be seen. That it is possible to identify malignant cells in exudates has been established by the writer[28] some years ago, although, as with the identification of blood-cells, the personal factor is too great to allow stereotyped rules to be drawn up which shall guide the novice to a right diagnosis.

The Morphological Characters of the Lymphocyte.*—

Outer Form.—The cell has a diameter of 7·5 μ on an average. The limits of variation are 5 and 10 μ. The *shape* of the cell is almost exactly spherical.† The *contour* is regular and smooth.‡

* *See Plate III.*, 6'; *Plate IV.*

† Rosenthal considers that the *living* lymphocyte is not round; it only assumes the spherical shape when dead or dying.

‡ Specimens are sometimes seen in which the outline is jagged, and it has been supposed that: (1) Detached fragments of such spicules appear in blood-films as platelets; (2) They are flagella (so-called Flemming's bodies). H. C. Ross believed that flagella are detached from lymphocytes, and seriously put forward a suggestion that they might function as spermatozoa to other lymphoid cells in the circulation or elsewhere!

The *cell-body* is small relative to the nucleus, and with the panoptic stain is of a bright but pale blue, showing a network with varying distinctness. The paraplasm is very abundant.

Granules.—Granules are present, being often arranged into discrete clumps. They have been variously named azur, Schridde,* and Beckton granules. Possibly all these forms are one and the same in nature (see below).

Nucleus.—This is strictly spherical, and is large relatively to the cell. It is central in position in young cells, slightly excentric in old ones. The nuclear membrane is thick, the chromatin is trachychromatic in staining power, pachychromatic in texture. There is a well-marked perinuclear halo, and an astrosphere can sometimes be made out. If there be a nuclear dimple, the astrosphere is over against this.

Nucleolus.—There is generally one excentric metachromatically staining nucleolus. Occasionally more may be made out.

Appearances with Ultra-violet Light.—The nuclear substance is only very slightly permeable to ultra-violet (magnesium and cadmium) rays, and indeed is quite impermeable in some places, just as holds in the case of erythroblast nuclei (Grawitz[29]). The cell-body is never homogeneous, but is cloudy or flaky owing to the presence of irregularly distributed dusky areas. Their distribution, therefore, demonstrates that the shading does not correspond to nodal intersections of spongioplasm. A few very fine and coarse granules can also be detected—these are identical with the azur granules.

Appearances with the Ultra-microscope.—This method of study shows the middle zone of the cell to be small (compare with the appearance of the neutrophile leucocyte). Jagic claims that the azur granules are visible.

The lymphocyte of chronic lymphatic leukæmia has a very narrow cell-body; the nucleus is almost "naked." The nucleus is paler and the chromatin looser in texture than in the true lymphocyte. Azur granules are never present. The size of these cells is very variable, and there is no constant numerical relation between the small and large forms. Each case presents its own peculiarities.

The lymphocyte of the tissue is described in the fourth section.

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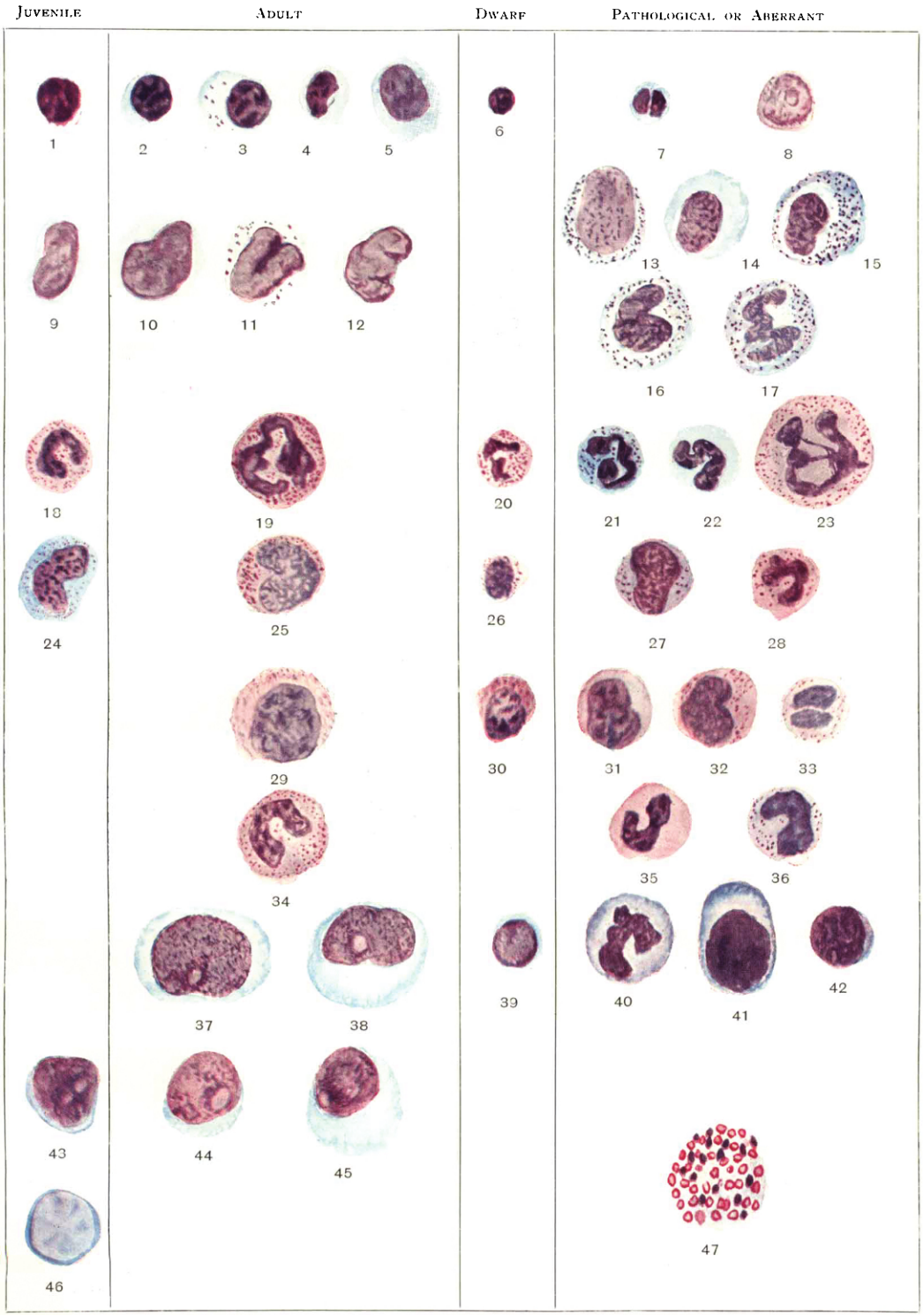
* The Schridde granules are perinuclear fuchsinophile granules.

EXPLANATION OF PLATE IV.

1.—Lymphocyte with minimal cytoplasm. 2.—Normal lymphocyte. 3.—Leucocytoid lymphocyte. 4.—Lymphocyte with reniform nucleus. 5.—Mesolymphocyte. 6.—Dwarf lymphocyte. 7.—Lymphocyte showing mitosis. 8.—Myelolymphocyte. 9.—Juvenile large mononuclear. 10.—Normal monocyte. 11.—Transitional cell. 12.—Leucocytoid large mononuclear. 13.—Leucoblastic monocyte. 14.—Myeloic monocyte without azur granules. 15.—Leucocytoid myeloic monocyte. 16.—Myeloic monocyte with indented nucleus. 17.—Polynuclear leucoblast. 18.—Metamyelocyte. 19.—Normal polynuclear leucocyte. 20.—Dwarf polynuclear leucocyte. 21.—Basophile polynuclear (granular neutrophile leucocyte. 22.—Non-granular polynuclear neutrophile leucocyte. 23.—Giant leucocyte. 24.—Leucoblast. 25.—Promyelocyte. 26.—Dwarf promyelocyte. 27.—Basophile promyelocyte. 28.—Polynuclear promyelocyte. 29.—Myelocyte. 30.—Dwarf myelocyte. 31.—Non-granular myelocyte. 32.—Rieder form of myelyte. 33.—Myelocyte with mitosis (Klein, Fol. hæm. x. p. 475). 34.—Metamyelocyte. 35.—Non-granular metamyelocyte. 36.—Basophile metamyelocyte. 37.—Lymphoidocyte. 38.—Leucocytoid lymphoidocyte. 39.—Dwarf or micro-lymphoidocyte. 40.—Rieder lymphoidocyte. 41.—Plasma-cell lymphoidocyte. 42.—Sternberg's leuco-sarcoma cell (Klein, ibid.). 43.—Juvenile macrolymphocyte (Klein, ibid.). 44.—Normal macrolymphocyte. 45.—Senile macrolymphocyte. 46.—Lymphoid hæmoblast. 47.—Hybrid eosinophile-mast cell.

PLATE IV.

MONONUCLEAR AND CERTAIN OTHER BLOOD-CELLS



Biology of Blood-cells *O. C. Gruner*

The Differential Diagnosis of the Lymphocyte. — The diagnosis of lymphocytes in blood-films is difficult owing to the lack of uniformity of description of the various lymphoid cells that can be met with in the circulating blood. Not only is it necessary to correctly name these cells, but the various degenerative forms must be recognized and recorded. The classification of mononuclear cells into small lymphocytes, large lymphocytes, hyaline and transitional cells, as is customary in much of the literature, is inadequate, and though Pappenheim's panoptic stain is advisable for much of the work of differentiation, the cell-forms can be fairly well distinguished by the ordinary staining methods in vogue at the present day (e.g., Leishman-Wright).

Pappenheim's staining method is as follows :—

Air-dried film-stain with Jenner's stain under cover for three minutes by the watch. Add five to ten drops of distilled water (same volume as the stain previously used), without rinsing ; drain (do not rinse) ; stain with freshly-prepared dilution of Giemsa, 1–10, for twelve minutes ; thoroughly wash with distilled water ; dry without heat.

The cells which may simulate the lymphocyte are as follows (*see Plate IV.*) :—

1. *Leucocytoid Lymphocyte.*—This cell resembles the ordinary lymphocyte, save that the cell-body is decidedly larger relative to the nucleus, the latter being excentric, and absolutely smaller than in the true lymphocyte. This cell is merely an older form of lymphocyte.

2. *Lymphocyte with Reniform Nucleus.*—This cell is exactly like an ordinary lymphocyte, but the nucleus is indented or reniform. The cytoplasm is paler in the vicinity of this dimple.

Both these forms are popularly classed along with the lymphocyte in differential counts.

3. *Mesolymphocyte.*—The characters of this cell have been given above. The nuclear structure is similar to that of an ordinary lymphocyte. The chief difference between this and the microlymphocyte is one of size. Sometimes the nuclear character is more defined in this type of cell, polygonal areas of deeper-stained material being present, the angles being drawn out into filamentous structures which interlace.

4. *Juvenile lymphocytes* are similar to microlymphocytes, but cell-body is practically indistinguishable. These are sometimes called " naked " lymphocytes.

5. *Dwarf lymphocytes* have already been referred to. The descriptive term is sufficient to serve for their differentiation.

6. *Lymphocytes* with nuclei in a state of *amitotic* division. It is questionable where these belong. Their nuclear characters are sufficiently distinctive.

7. *Microlymphoidocyte.*—This cell resembles the mother cell or lymphoidocyte in its nuclear markings and general characters, but is hardly larger than the average lymphocyte.

8. *Leucocytoid Microlymphoidocyte.*—This cell is also distinguished by the characteristic nuclear markings (as of the lymphoidocyte). But the cell-body is relatively more abundant.

9. *Dwarf Lymphoidocyte.*—This is smaller than 7, but otherwise identical in characters.

10. *Rieder Cell.*—This type of cell has already been fully described. Sometimes these are very small, but the polymorphism of the nucleus is sufficient for diagnosis. The only real difficulty might lie in distinguishing it from an amitosing lymphocyte.

11. *Neutrophile Pseudo-lymphocyte* (Ehrlich).—Myeloic granulopotent pseudo-lymphocyte of Pappenheim, or myelolymphocyte. This cell is as large as a lymphocyte, the cytoplasm is narrow, and the nucleus is rich in chromatin. The difference from an ordinary lymphocyte lies in the presence in the pseudo-lymphocyte of " myeloic " azur or of neutrophilic granules. Ehrlich considered that they were small polynuclears, but Pappenheim considers that they represent a metaplastic change in the lymphocyte. It is met with in pleural exudates.

12. *Lymphoid Hæmoblast.*—The characters of this cell, and the differential diagnosis, have been considered on pp. 60, 64.

13. *Plasma or Irritation Cells.*—These will be considered in Chapter VI. The main characters briefly consist in marked basophilia of the peripheral parts of the cell-body, well-marked perinuclear halo and astrosphere, and vacuolation of the cytoplasm.

14. *Aberrant mononuclear forms* of the neutrophile series

require to be borne in mind in differentiating the "lymphoid elements" of the blood-film (Chapter V.).

15. *Degenerative Forms.*—Vacuolation of the cell-body, feebleness of staining of nucleus, ill-definition of outline of the cell (indicative of cytolysis), or the presence of foreign bodies within the cells, as well as shadow forms, require to be noted.

16. *Tumour Cells.*—As already mentioned, we have yet to learn whether true sarcoma or carcinoma cells can be identified in a blood-film.

17. *Intermediate forms* between some of these types cannot be distinguished, and it would be difficult to assign satisfactory names to them.

The following "couples" are very much alike: the ordinary microlymphocyte and the microlymphoidocyte, the macrolymphocyte with narrow cell-body and the lymphoidocyte, the leucocytoid mesolymphocyte and the leucocytoid myelolymphocyte. Further examples of similar couples, which belong really to the next chapter, are: monocyte with reniform nucleus and leucoblast with reniform nucleus; monocyte with azur granules and leucoblast with azur granules. A promyelocyte with neutrophile granules may simulate the latter.

From a study of these cell forms we find that the accepted "small lymphocyte" may be one of these; the true lymphocyte, or microlymphocyte, numbers 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, also leucosarcoma cells and juvenile monocytes. The accepted large lymphocyte is really not in this series at all. The accepted hyaline cell is one of these; 1, 3, 8, 14, or monocytes.

The Functions of the Lymphocyte.—A careful study of the literature bears out the conclusion derived from the perusal of text-books of physiology—that our knowledge upon the functions of the lymphocyte is almost nil. The difficulties of direct observation are extreme, and though a number of experiments on living lymphocytes have been published by H. C. Ross, the deductions to be made therefrom are of uncertain value. A study of the causes of lymphocytosis and lymphopenia of the various tissues in different physiological conditions should afford some clue to the facts, but unfortunately the reports in the literature invariably fail to distinguish between the true lymphocyte and the leucocytoid and large

mononuclear lymphoid cell forms. The practice of gathering all lymphoid cells under one head is almost invariable, so that the whole subject must be investigated *de novo*, with much greater care and detail. Until this is done, the inferences to be drawn from a study of certain chemical considerations, and from investigations upon metaplasias in tissues, must remain our sole basis of knowledge upon the functions of the lymphocyte.

THE CAUSES OF LYMPHOCYTOSIS.—In the circulation, the lymphocyte normally constitutes about 25 per cent of the total white-cell count. In other words, there are about 2000 per cubic millimetre. In embryonic life, and in the infant, these cells number up to about 70 per cent of the total white cells.

The following are some of the possible variations from the normal: (1) The total numbers may be increased without alteration of the cell formula (absolute lymphocytosis); (2) The total numbers may be increased and the relative proportions to the other cells be also increased (absolute + relative lymphocytosis; (3) The relative proportions of the lymphocytes to the other cells may be increased, and yet the total count be normal (relative lymphocytosis); (4) The relative proportions of the lymphocytes to the other cells may be increased, but the total count be diminished (hyper-hypolymphocytosis); (5) The total count may be diminished while the proportions are maintained (lymphopenia); (6) The total count may be diminished and the proportions diminished (absolute lymphopenia).

Absolute lymphocytosis occurs in a number of conditions: (1) During the digestion of carbohydrates (increased up to 3000 per c.mm., according to Keuthe[11]); (2) During starvation or periods of hunger[30]: (3) In the course of acute fevers (typhoid, after the first week, measles, at the end of scarlet fever, during the lysis of pneumonia, in small-pox, in the acute diarrhœal diseases of infancy, and in bronchopneumonia); (4) After severe injury to the spleen (Gross). Relative lymphocytosis occurs (*a*) in certain chronic infections: tuberculosis, secondary and congenital syphilis, and the chlorotic type of syphilis); (*b*) in pernicious anæmia, chlorosis, scurvy, and hæmophilia; (*c*) in some cases of Graves' disease[31]; (*d*) in malnutrition; in rickets; (*e*) after splenectomy in animals.

Frogs react to bacterial infection by well-marked lymphocytosis just as warm-blooded animals react by polynucleosis.

Galambos[32] gives a long list, collected from the literature, of causes of lymphocytosis, from which one concludes that there is not a disease in which this condition of the blood may not arise. Such diseases may be quoted (in addition to the above) as mumps, malaria, chronic enteritis, epilepsy, tabes, achylia gastrica, acute alcoholism, asthma (inter-paroxysmal), osteomalacia, acromegaly, Addison's disease, etc., etc. (forty-eight conditions are quoted in all !). This indicates that the study of diseases in this manner is of little value. We require to know the physiological conditions obtaining.

Experimentally, lymphocytosis is induced by injections of tuberculin, pilocarpine (Rous[33]), muscarin, barium chloride (Harvey[34]), thyroid extract, staphylotoxin, etc. Bergel[35] found that mice and frogs were readily influenced by such agencies. He concludes that any infective agent of lipoid character will attract lymphocytes (e.g., tubercles). Iodine (Loebe and Michaud[36]) and mercury (Baldoni[37]) are taken up by them.

Lymphopenia occurs during the digestion of fats (Keuthe[11]) and proteids, in some cases of visceral and pulmonary tuberculosis,* and in cases where tumours block the lymph-paths (e.g., lymphosarcoma).

It will be noticed that lymphatic leukæmia is not quoted as a cause of lymphocytosis. Since the lymphocytes in this disease are not true microlymphocytes, we prefer to place this with increase in the numbers of primordial cells. In the above lists we have been unable to draw a distinction between the finer varieties of lymphocytosis and lymphopenia, owing to lack of data.

The Nutrioid Function of Lymphocytes.—This has been studied by certain workers, with equivocal results. The relation between lymphocytes in the blood-stream and digestion suggests that these cells have something to do with food-absorption. Pavy, probably quoting Pohl, considered that they took up proteid matter from the surface of the villi, or even in the stroma of the villi, incorporated it into their own cell-bodies, and, subsequently reaching distant parts of the body, finally dissolved in the tissues, thus bringing the latter a readily assimilable form of proteid.

* Compare with the fact that lymphocytosis in a puncture-fluid indicates tuberculous disease when met with in pleural or abdominal exudations.

Erdely[38] found that in rats fed on meat, the chief cells in the villi were granular—when fed on potato, the chief cells were lymphocytes—and when fed on bacon-fat, the chief cells were lymphocytes, but a few granular cells also appeared. In starvation, few granular cells could be found. Grawitz, commenting on these findings, concluded that all kinds of cells are made in the intestinal wall, and that lymphocytes play an important part in the absorption of sugar. Under the influence of meat or mixed diet, lymphocytes would turn into polynuclear leucocytes. Goodall, Gulland, and Paton,[39] in experiments on digestion leucocytosis, concluded that the increase was the result of activity—not in the intestinal wall, or spleen or mesenteric glands, but in the bone-marrow. They decided that the thoracic duct was a very unimportant source of lymphocytes, and quoted Crescenzi's[40] experiments in support of this view. Whereas the latter observer considered that the explanation of lymphocytosis after splenectomy and fistula-formation of the thoracic duct lay in a direct passage of the lymphocytes into the blood-stream, the quoted English observers interpret it as a proof that the marrow makes lymphocytes in adequate numbers all the time. The present writer, however, on the basis of observations on hundreds of lymph-nodes, agrees with Crescenzi in believing that many more lymphocytes enter the blood-stream direct than is believed, and doubts whether the bone-marrow is adequate to make hundreds of millions of red cells, of leucocytes, and also millions of lymphocytes *every day* without being always "leucoblastic." Further, if the lymph-nodes are not the chief source of lymphocytes, why should there be universal tissue-lymphocyte factories through the body ?

The observation that the blood in the intestinal veins is richer in white cells than that in the mesenteric arteries, indicates that the intestinal tract does have something to do with the formation of these cells, and that they have something to do with nutritional processes.

The presence of peptids in the small intestine may act as a stimulus to temporary hyperactivity of the lymphoid tissues there. The lymphocytes so formed may exude into the bowel lumen, devour deleterious products (Burian and Schur[40a]), and be shed

with fæcal matter, or break up food-matter further, and carry it into the villus* and so into the blood-stream (via the lacteal, or otherwise). Whether they take up carbohydrate or fat is not known. Sirensky[38] found lymphocytosis was related to carbohydrate food, while polynucleosis follows proteid food. Asher considers that lymphocytes have to do with conversion of the products of dis-assimilation brought to the lymph-nodes. (*See also under* " Fate of the lymphocyte.")

Adsorptoid Function.—Whether lymphocytes exert a bactericidal function or not is not quite clear. The large mononuclears are well-known phagocytes, but, as insisted in previous pages, we draw a very sharp distinction between the microlymphocyte and other so-called lymphocytes. From the writer's observations, the method of removing bacteria adopted by lymphocytes is largely one of adsorption of the microbe in response to some unknown force acting between the two cells, rather than one of true phagocytosis. Pfeiffer and Wassermann considered that experimental evidence was in favour of lymphocytes possessing a bactericidal action; Wanters argued against this. In favour of such a view is Bartel's finding that tubercle bacilli exposed to lymphocytes lose their virulence. Bearing indirectly on this subject is the question of whether these cells possess amœboid power or no.

AMŒBOID PROPERTIES.—Levaditi, quoting Israel, considers that the observations made by Pröscher, Wolff and Arpad, Torday and Schwartz, leave much to be desired. He considers it far from settled that lymphocytes manifest active diapedesis. It is true that the reason for the widespread distribution of lymphocytes in inflammatory exudates may lie in local production much more than in amœboid movement.

The Chemistry of the Lymphocyte. — Chemical analysis cannot be applied accurately to the study of the lymphocyte as an individual. Percentage analyses have been determined for the lymph nodes as a whole, and suffer from the unavoidable circumstance that all manner of cells are estimated together. The most recent account of the subject from this point of view is that by

* MacCallum, of Toronto.

Gerhartz.[43] The lymph-node, according to observations quoted by this author, contains 8 per cent nucleoproteid, or 0·83 per cent phosphorus.

Alcoholic extracts contain protagon, inosite, lecithin, cholesterin, some sarcolactic acid, xanthin bodies, leucin, collagen, reticulin, and elastin. These findings are common to practically every other tissue in the body. Every cell contains lipoid substances, since life is impossible without them; every nucleus gives rise to xanthin bodies as long as it remains capable of mitosis, and every interstitial tissue contains some collagen, etc.

Pappenheim[41] considers that the pathological lymphocyte poured out in Hodgkin's disease produces a " hypernomic secretion " of lipase which acts on red-cell lipoid like pancreas steapsin, and so causes the anæmia. In a paper on pseudo-leukæmia, by Tschistowitsch,[42] it is shown that the lymphocytes were enormously increased, and that fever was correspondingly conspicuous.

Nucleases act on nucleoproteid or histone of the follicle cell to make nucleic acid (= phosphoric acid, purins, etc.) plus albumin or histone. The latter may play some necessary part in mitosis (Ciaccio[13]).

The findings of arginase in lymph-nodes, by Cohnheim,[44] is of interest: the amount is small. Oxydase and paroxydase (Fischel[45]) are also found, according to a few observers. In short, as regards ferments, we expect to find each in varying quantity according to the proportions of cells within the lymph-node, whose ferment content is known. Lymphocytes, for instance, contain lipase, as they have the power of dissolving waxy material (Bergel[46]), and their cell-bodies accordingly contain no fat.[47a] Autolytic ferments are not present—a distinction from the neutrophile leucocyte.

Working with a neutral saturated aqueous solution of malachite green, Kronberger found that certain of the small lymphocytes of the blood (digestion-lymphocytes) are readily recognizable by the intense emerald-green reaction of the nucleus. From this observation and theoretical dye-chemistry considerations, it was concluded that the nucleus contained much nucleo-albumin, which is not present noticeably in the neutrophile pseudo-lymphocytes. Comparing these findings with those obtained by means of methyl-green-

pyronin, Pappenheim considered that the lymphocyte nucleus does not consist of pure nucleic acid, is less rich in certain purins than are the polynuclear leucocytes, and is richer in basic histone (nucleohistone). Thus, methyl-green-pyronin give a blue-violet with resting nuclei, green with mitosing nuclei and spermatozoon-heads; further, preliminary mordanting with alum gives different results—lymphocytes staining greenish-grey, while polynuclear leucocytes stain more reddish-violet, indicating that after mordanting the lymphocyte nucleus has a more alkaline reaction than the neutrophile.

THE CHEMISTRY OF THE LYMPHOCYTE GRANULES.—The granules of the lymphocyte are the so-called azur granules. They stain with azur dyes* (Romanowsky, Giemsa), as discovered by Michaelis and Wolff-Eisner[47] in 1902. These bodies occur in true lymphocytes, in the large lymphoid "monocytes" of normal blood, in myelolymphocytes, in lymphoblastic macrolymphocytes, in lymphoid leucoblasts, occasionally in neutrophile promyelocytes, but not in lymphoid erythroblasts, or in mature plasma cells (Pappenheim[48]).

The granule, as seen in the lymphatic series of lymphoid cells, is small, round, of scarlet-red colour, and appears sparsely scattered through the cell-body. In the guinea-pig these granules are coarser and more numerous. They increase in number as the cell becomes older.

It will be seen later that there is another form of azur granule, the myeloic azur granule. This is very similar in tint to the neutrophile granule (so-called immature stage of neutrophile granule), being of a bluish purple colour, and scattered diffusely through the cell in considerable numbers. These granules vary much in size, being sometimes very fine, at other times very coarse, and even simulate flocculent precipitates within the cell-body. It will be shown later that Pappenheim believes these myeloic granulations to be derived from part of the nuclear matter, and not from the spongioplasm.

The azur granulation is not specific. It is evident that examples of lymphocytes may occur which are devoid of azur granules. Such cells are still classed as lymphocytes. An eosino-

* Yet not by azur alone. The granules are not azurophile, as they only stain in mixtures of methylene blue, eosin, and azur.[48]

phile, on the other hand, necessarily contains eosinophile granules. In other words, the lymphocyte granule is not regarded as evidence of differentiation of a lymphoid cell.

VIEWS AS TO THE NATURE OF AZUR GRANULATION.—

1. That they are *artefact.* They may be the result of fixation; precipitation of proteins (Grawitz), or they may be the nodal intersections of the cytoplasmic reticulum (Gulland). This view is excluded by the appearance of the cells with ultra-violet light.*

2. *That they are definite entities*—

(*a*). That they are secreted or excreted *dead material.* In favour of this view are the following points: (i) that they are commoner in older cells, leucocytoid lymphocytes,† (ii) that similar bodies occur in the large mononuclears of guinea-pigs. Here they are definitely secretory (Cesaris-Demel). Against the view is Levaditi's observation that the small lymphocytes of the anthropomorphic apes are as rich in granulation as are the large forms.

If dead, are they lipoid in nature? They stain with vital stains‡ like the Kurloff bodies in large mononuclear leucocytes, and also stain metachromatically. On the other hand, they are not the same as Schridde granules, since (i) they are not confined to the perinuclear zone, (ii) are of different shape, (iii) are inconstant (Türk, Pappenheim), (iv) are visible with dark-ground illumination (Jagic[49]), and (v) also with ultra-violet light (Grawitz).

(*b*). *That they are living.*—On this view they may either constitute a preliminary phase of neutrophilic granulation, or may precede the latter without being converted into it. In either case they may be assumed to be of *ferment* character (Naegeli, Hynek, Grawitz, Weidenreich). Blumenthal considers them to be precursors of other granules besides neutrophilic granules. The arguments pro and con in this case are analogous to those brought forward under the heading of monocyte granulation (*see p.* 185), but they are not very cogent.

If they are not directly converted into neutrophilic granules.

* A similar view has been expressed regarding the neutrophilic granule of leucocytes. These granules are visible with ultra-violet light. Jagic states that he has seen them with dark-ground illumination.

† Ehrlich surmised that they were a sign of old age.

‡ According to Ferrata they are the same as the vital-staining plasmosomes.

they must be looked on as a preliminary deposit in the immature cell, indicative of a cytometaplastic change proceeding within it. The neutrophile granules eventually appear, side by side with the azur, and ultimately outshadow them when the myeloblastic change is complete. This view, advanced by Pappenheim,[48] depends for its proof upon the subtleties of microchemical staining reactions. He holds that these azur granules are a product of secretion, and are only temporarily contained within the cell. The true granulation is a bearer of cell-function (Pappenheim-Ferrata, 1911[50]). If we accept the view that neutrophilia is a specific property and that azur-granules are not specific, then we should incline to believe that the two forms of intracellular material were quite distinct from first to last, and not regard the difference to be merely that between child and adult.

THE SCHRIDDE GRANULE.—This form of granule (really an Altmann granule) is always present in every lymphocyte, is invisible both in dark-ground illumination and in ultra-violet light, and is not specific (Klein[51]). Meves[52] believes the Schridde granule to be a chondriosome.

The nature of this granule is still *sub judice*. The only certain feature about it is that it is not characteristic of a myeloblastic cell. It is very probable that Schridde's granules are identical with Altmann's and are a necessary constituent of every cell. Naturally they are more common in some than others, just as every cell does not contain the same amount of nucleic acid. There can be no question but that this granule (which Grawitz believed to be really not a true granule at all) is concentrated lipoid matter. This being so, it is evident that Beckton's claim that Altmann granules in sarcoma cells or carcinoma cells are diagnostic, is made regardless of the necessities of cyto-chemistry. On the other hand, it is possible that abundance or paucity of lipoid granules may be distinguishing factors between cells.

Comparative Cytology of the Lymphocyte.—Broadly speaking, the lower the vertebrate scale be descended, the more abundant are the lymphocytes in the blood. When studied closely, however, it is evident, from the researches of Werzberg, that while the lowest vertebrates tend to have a preponderance of mononuclears in the blood, all such cells do not belong to the category of the human lymphocyte. In many instances, the resemblance to the large mononuclear is more striking, while in others the lymphoid cell is definitely lymphoidocytar, as stated in Chapter I. On the other hand, it is not difficult rapidly to survey the lymphocyte through the animal series, because the morphology of this cell remains very constant. The

ordinary small round basophile lymphocyte is always accompanied by the form with relatively abundant cytoplasm and possibly indented nucleus (the leucocytoid form); and in all cases the characters of the cytoplasm and nucleus are the same in the leucocytoid form (save for the feature mentioned) as in the microlymphocyte form.

The matter of greatest interest, however, is the fact that many of the authorities on comparative cytology find themselves forced to the conclusion that in amphibia and reptilia the lymphocyte is actually the parent of the polynuclear leucocyte (or what serves for a " neutrophile " in such animals), the transitional stage being the large mononuclear leucocyte and the transitional cell (Freidsohn[52a]). In other words, in these lower animals, at any rate, Grawitz and Weidenreich's dictum holds good. It will be shown later how it comes about that opinions are so divided about this matter in the case of man, for we shall see that in birds the blood-cell formula changes very definitely.

In the blood of *fishes*, the lymphocytes and their leucocytoid forms are much more typical than in the amphibia and reptiles, and in certain instances—cobitis, anguilla, the perch—are so numerous that they constitute by far the greater part of the white-cell content. This finding is in keeping with the general lymphoid character of the blood and the absence of true neutrophile leucocytes. The transition from lymphocyte to large mononuclear leucocyte already referred to is well shown in this class of animals. One or two nucleoli are usually visible in these lymphocytes, the cell-body is usually only feebly basophile, and the nucleus itself is not deeply stained and shows a very delicate intranuclear structure. The torpedo-lymphocyte is amœboid (Sabrazès et Muratet[53]).

The sequence of blood-cell development in anguilla appears to be: lymphocyte = large lymphocyte = large mononuclear = polynuclear leucocyte. In petromyzon, the blood-cells all appear to arise from a lymphoidocytar mother cell, as in man.

Studies on the *lymphatic tissue* of the ganoid fish, polyodon, by Downey,[54] show that the tissue lymphocytes are here characterized by a rather thick nuclear membrane, while the outline of the nucleus is round in one type and lobulated in a second. The cell-body is strongly basophile and may show vacuolation, while the nuclear network is coarse and open. Such a cell eventually becomes a plasma cell, just as the tissue lymphocyte of the human being so often becomes " plasmoid."*

In the dog-fish, four varieties of lymphocytes are met with, according to the observations of Fry[55]: (*a*) Large, with round cell-body staining dark-blue (Giemsa) and large round reddish-purple nucleus; (*b*) Lymphocytes with small round cell-body staining dark blue with Giemsa and having a relatively large nucleus; (*c*) Spindle-shaped lymphocytes with dark-blue cell-body and oval nucleus; (*d*) Oval cells transitional between (*b*) and (*c*).

The lymphoid tissue of the torpedo is near the œsophagus (Drzewina[55]),

* This term is used by the writer as a convenient one for expressing a peculiar morphological appearance in the transitional forms of various cell-types met with in the areolar tissues.

and its primitive leucocytar elements give rise to acidophile leucocytes and lymphocytic elements, which continue to multiply by karyokinesis. In the *newt* (triton), there are transitional forms between the lymphocyte and the lymphoidocytar forms, and many of them are difficult to distinguish from spindle cells. Thiazin-staining, however, colours the cell-body of the lymphocyte blue, that of the spindle cell red. The *salamander* lymphocyte is very like the large mononuclear leucocyte. The astrosphere and the centrosome are ill-defined. In *siredon*, the cell-body of both lymphocyte and its leucocytoid form is strongly basophile. Such cells are predominant in the white-cell formula.

In the common *frog*, azur granules are observed in the leucocytoid forms. The lymphocyte figures very abundantly in this blood.

In the *reptiles*, the lymphocytes are much more variable as regards frequency. In the *tortoise* (emys), the lymphocytes form 12 per cent of the total differential count (Eberhardt), while in *anolis* lymphocytes are entirely absent (Werzberg[57]), and in *agama* (a lizard) they are very sparsely met with. They are present in scanty numbers in testudo, ophiosaurus, tropidonotus, scincus, platydactylus, and moderately abundant in the blood of lacerta, acanthodactylus, and chameleon. These cells also vary much in morphology. The nuclear structure of the emys-lymphocyte recalls that of the hæmoblast, denser chromatic masses occurring here and there at the periphery, The leucocytoid forms show one or two nucleoli. In *anguis* the chromatic markings are not so distinct, and they are more irregularly placed. In *tropidonotus*, the nuclear structure is ill-defined, and there are no definite nodal points to be seen. In *acanthodactylus*, azur granules are visible in the perinuclear halo. In *algiroides*, the nuclear structure and the degree of basophilia of the cytoplasm are very like that of the lymphoidocytes in the same animal.

It will be seen later that the blood of reptiles is largely eosinophilic.

In *birds*, whose blood has been specially reported on by Kasarinoff,[58] Niegolewski, and Hirschfeld-Kossmann, the lymphocytes are much more like the human cells, in having a more intensely basophile nucleus, and more basophile cytoplasm, than obtains in most specimens from the lower vertebrates. Under the influence of leucoblastic poisons, Kasarinoff found that the lymphocytes become smaller and basophile to an even more marked degree than in health.

It is of interest to note that Jolly, studying the tissue called the pouch of Fabricius, situated near the extremity of the avian intestine, found it to function like bone-marrow during the early life of the bird. All transitions between lymphocytes and myelocytes were observed in this tissue. The presence of epithelial cells also brings out a resemblance to thymus. Both involute in a similar manner. Further, in palmipede birds (duck, goose, teal, swan), the blood often passes into the lymphatic sinuses of the lymph-nodes.

The existence of transition forms between the lymphocyte and the large mononuclear throughout all these infra-mammalian animals has been referred to. It is evident that a certain proportion of the lymphocytes would be distinguished, for descriptive purposes, as mesolymphocytes.

There is no definite distinction between the lymphocyte of one mammal and that of any other.

IV.—THE FATE OF THE LYMPHOCYTE.

Cytometaplasias.

BROADLY speaking, it may be said that we have no knowledge upon the history of the lymphocyte from the time of its birth to the time of its death. At the present time it is not possible to draw deductions which would assign a life term to the lymphocyte on similar data to those employed for the red cell, nor is it known what region of the body is to be described as the graveyard of the lymphocyte. Davis and Carlsson[59] (1909) concluded that the lymphocytes were replaced once daily in the dog, from observations on the number of cells entering the blood by way of the thoracic duct. All that can be said is that during the course of circulation the cell-body becomes relatively larger and the nucleus relatively smaller, and that the latter may become indented. In pathological conditions, the indentation may become marked enough to cause diagnostic difficulty between this cell and the Rieder cell.

Changes with Age.—Following the usual rule, the lymphocyte body becomes more and more voluminous with age, becomes less basophile from the appearance of flakes of pseudo-oxyphile material. The nucleus become relatively smaller and more deeply stainable. Finally, the ordinary leucocytoid lymphocyte is produced.

It seems likely that the bulk of the lymphocytes dissolve up in the capillaries. *Degenerative changes* are frequently noted in blood-films ; appearance of vacuoles in the cell body ; karyorrhectic changes ; appearance of the " tingible bodies " of Flemming. Fatty degeneration is sometimes seen in acute lymphæmic lymphocytes towards the end of life. Complete death is shown by the Klein-Gumprecht shadows, which consist of ill-defined rounded masses staining somewhat like nuclear matter. A nucleolus may be visible within them.

Observations by Grawitz and Rosenthal[60], Zuntz, Schumberg, and others, led them to believe that the natural fate of lymphocytes is a conversion into polynuclear leucocytes. This is of course an

extreme unitarian view, and is not generally accepted. The facts are, however, worthy of notice. Rosenthal studied blood-films and made total counts upon healthy persons at different periods of the day, and under different phases of muscular activity. Athletes were also studied. The findings were that within the first ten minutes of muscular exertion, there was an extreme outpouring of lymphocytes into the blood-stream, but that in ten minutes the lymphocytosis had given place to a commencing neutrophilia, which became more marked as time went on. The striking character of the lymphocytosis is shown by the fact that every cubic millimetre of blood contains 3000 more lymphocytes than it did before; or, expressed in terms of total blood-content of the body, billions of lymphocytes are turned out within ten minutes. It has been thought that this increase might be the result of an accelerated lymph-flow produced by the deep respirations. The problem is a very similar one to that put forward in an earlier page—how can hundreds of thousands of red cells be poured out every hour?

In ten minutes these billions of new-comers have left the blood-stream. How is that to be explained? They do not disappear in the circulation; there are no cytolytic phenomena to be seen; and they do not accumulate in the internal organs. With their disappearance there is noted by Rosenthal an increase in the numbers of large mononuclear leucocytes, and later still, of neutrophile leucocytes. From these findings, and from Selling's observations[61] on cases of benzol-poisoning, it is argued that the lymphocyte becomes large mononuclear, and the latter becomes polynuclear, by undergoing physico-chemical change.

It is evident that if such arguments are justified, the whole fabric of white-cell hæmatology requires reconstruction. If the lymphocyte is to the neutrophile as the caterpillar is to the butterfly, it would explain the simplicity of the lympho- and monocytopoietic genealogies, but it would not explain why the bone-marrow leucocytes require to pass through a myelocyte stage. Nevertheless, the writer has no doubt but that the *functions of all lymphocytes are not the same*, that the lymphocytes seen in such numbers in the digestive tract serve one purpose, those formed in the non-mesenteric glands another, and those formed in the tonsil and

adenoids another. In each case the cells produced present similar morphological features, but are probably no more identical in function than the red cell and the neutrophile.

Observations on the differential blood-cell count during starvation, or periods of hunger, have been made by many observers (Hofmeister[62], Hammar[63], Liubomadrow, Poletaew, Källmark[30], and others). The findings are in some respects similar to those referred to as occurring during severe exercise, but there is no initial increase in the total lymphocyte count. After a preliminary fall,* the lymphocytes reach a constant figure and remain there till the starvation period is broken, when the total count rises markedly. The neutrophile leucocytes, on the other hand, steadily increase in number during the whole period. Since histological study shows an increase of activity of the lymphopoietic organs, it is evident that lymphocytes must be manufactured in larger numbers than usual. If this be so, then the lymphocytes are destroyed at a greater rate than normal during inanition, a deduction which indicates that these cells play some important part in the transference of nutritive material to the tissues.

It is therefore probable that some lymphocytes die in the blood-stream, while others do not. Those which do not die *in situ make their way into the connective-tissue spaces* (Schridde[65]), although they cannot pass through lymphatic channels lined by endothelial cells. Every blood-vessel does not allow exit for lymphocytes, but in certain regions of the body this process is readily observed, and wherever there is an infective or a toxic agent, there will be found the familiar small round-celled infiltration—i.e., infiltration with tissue lymphocytes, etc. (Chapter VI.)

The *lymphocyte of the tissue* is isomorphous with that of the blood-stream, but is not necessarily similar in function. Using the word lymphocyte in a purely morphological sense, we find ourselves able to realize that such cells are functionally distinct from one another.

The Morphological Characters of the Tissue Lymphocyte.—(*Plate III*, 6', 8).

Outer Form.—Usually small, but varies considerably (5–12 or 15 μ). *Shape*, rounded, or ovoid. *Contour*, clearly defined.

Cell-body.—Varies in amount; may be almost absent, or may be relatively rather abundant. It is practically structureless and

* According to Penny, this fall is maintained.[64]

either amphochromophile or strongly basophile. The more basophile the reaction, the younger the cell. There are no fat vacuoles.

Granules.—No azur granules. Some observers describe delicate myeloic azur granulation ; may be Schridde granules.

Perinuclear Zone.—Is present in older cells, owing to change of reaction of the cytoplasm.

Astrosphere.—Present in the indent-nucleate forms.

Nucleus.—Always lymphoidocytoid, having a very delicate leptochromatic structure. The parachromatin stains a pure blue or pale rose, while the chromation stains of an azur red-violet. It is trachychromatic. *Size,* relatively large. *Shape,* round, or, in older forms, slightly indent. *Position,* central.

Nucleolus.—Multiple, but usually single. Occasionally basophile.

Mode of Division.—By amitosis.

As the cell ages, the spongioplasm becomes less blue, the paraplasm tends to a diffuse oxyphilia, and the perinuclear zone becomes distinct.

Why is small-round-celled infiltration so common ? There is hardly a surgical tissue which does not show such a phenomenon. It is usually stated that these tissues are entirely pathological ; that this inflammatory cell infiltration is an inflammation. The name just quoted is commonly used to express it. The writer, from a careful study of thousands of tissues removed at operation, believes that this cellular infiltration is *physiological* so long as it is not excessive. In other words, these collections of cells are carrying out some definite function ; they may be altering toxic material in some invisible way, or they may be attracted thither by outside influences. The toxic material need not be morbid in the ordinary sense ; it may be metabolic material which is, in a sense, toxic. The lymphocytes which have gathered together around this material must be performing some definite action in respect to it.

The argument from the universalism of this phenomenon in body tissues, be they apparently normal, or be they inflamed, is that the so-called inflammation is only an exaggeration of what is a physiological process in the body. Be it a succession of changes occurring in a tissue as the result of an injury, it is a process different

only in degree from what is occurring in the same tissue every hour of its life. In the muscular tissues, there are waste matters poured out during activity; lymphocytes accumulate in the interstitial tissue—always around the blood-vessels; this is labelled inflammation in the microscopical laboratory, because it is assumed that because the tissue came from the operating-room it must be abnormal. The alternative view is that the waste matter attracts lymphocytes, perhaps even makes them grow locally, and these produce some definite change in it which is necessary before further activity can proceed. The accumulation of these materials at a greater rate than the lymphocytes can deal with them, leads to the sensation of fatigue. Massage, which accelerates the lymph-flow locally, and at the same time washes away the lymphocytes, relieves the fatigue.

Some such view as this would explain the *myogenic leucocytosis* already referred to. The lymphocytes are poured out in immense numbers, but are not turned into polynuclear leucocytes; no, they accumulate in the muscles where the waste matter is increasing and demanding their presence. The disappearance of the lymphocytes from the blood-stream is then easily understood. The cause of the polynucleosis still requires an explanation.

Lymphocytes, having left the blood-vessels, *wander towards mucous surfaces* when they are in the vicinity of such. This phenomenon is well known. They can be seen *in situ* between the columnar cells lining the intestine, between the goblet cells of the secretory glands, between the ciliated cells of the Fallopian tube, between the epidermal cells covering the tonsil, etc.

Other lymphocytes, in morbid states, *make their way into body fluids*. The lymphocytosis of pleural fluid has long been recognized as pathognomonic of tuberculosis. That of cerebrospinal fluid is recognized in many chronic inflammatory conditions of the meninges.

Cytoplasias.—Other lymphocytes, again, appear to possess the power of *reverting backwards along their cytoplastic lines*. Pappenheim believes that a lymphoid cell may acquire myeloic characters (i.e., become myelopotent*) after entering the connective-tissue

* See "Neutrophile pseudo-lymphocyte," page 136.

spaces, and so give rise to neutrophile leucocytes or micro-eosinophile cells. A conversion of the basophile cytoplasm into oxyplasm, with increase in amount of the latter, and perhaps a metaplasia of the chromatin (basikaryoplastin becoming oxychromatin), is not very difficult to understand.*

A well-recognized change, though perhaps not accepted by all authorities, is that from a lymphocyte *into a plasma cell.* In the tissues, the change is so constantly seen that it is remarkable for so much to have been written upon the matter. In the blood, on the other hand, there is some difficulty in following the change, because there is little resemblance between the tissue plasma-cell and the hæmatic plasma-cell. The plasma-cell, or irritation cell of Türk, is described later ; it is sufficient here to point to the deeply basophile cell-body in which are vacuolations. It is usually assumed that this cell represents a downward change, just because there are vacuoles. As already hinted, progress and regress are invidious ideas in respect to blood-cells. The biology of the blood-cell is represented by a circle or other mathematical curve, not by a straight line up or down. We see a small arc, and forget that this is not the whole. Be increase in basophilia katabolic, as it may, subsequent anabolism is not precluded. If a cell passes through plasma-cell change as part of its cycle, that should not make the plasma-cell period a degenerative one.

Conversion of Lymphocytes into Mast Cells.—Here again we have part of a cycle of changes which are everywhere spoken of as degenerative. According to Pröscher,[65] the spongioplasm of the lymphocyte may undergo mast-cell or mucoid degeneration, under the influence of certain specific toxins or toxic components. Thus, when cancer-juice is injected intravenously, a marked lymphocytosis arises, which is followed by the appearance of large numbers of mast-cell myelocytes in the blood. The author just quoted compares the mucoid change to the amyloid change which albumin

* Can lymphocytes metaplase into thrombocytes ? This question is discussed by Pappenheim,[48] who points out that contracted (round) spindle-cells are not morphologically comparable with resting lymphocytes, nor are elongated spindle-cells elongated lymphocytes, as shown by various staining-methods. The error arose from the use of aniline stains alone. The Unna-Ziehl method shows lymphocyte cell substance to be cyanophile, while the thrombocyte cytoplasm is always erythrophile, because the spongioplasm of the latter is so delicate.

undergoes. Intravenous injections of small-pox vaccine make lymphocytes diminish after a certain time, and during the fall, mast cells become much increased. The significance of this phenomenon would be that the lymphocyte has the power of binding certain toxic substances which are formed during metabolism and circulate in the blood-stream. Such bodies are made harmless in this way. The lymphocyte is therefore an antitoxic agent, and one of the manifestations of its activity lies in mast-cell production.

This view is an adaptation of the one already expressed at length. Mast-cell production is not the only result of metabolic activity, for it is not very common in either normal or pathological tissues, and such cells only form a fraction of 1 per cent of the cell-count. The other results of metabolic activity, manifested to us by changes in morphology (plasmoid change, etc.), will be dealt with much more fully in the last chapter of this book, when the relation between these processes and certain diseases—"blood-diseases"—will be discussed. It will be evident that the story of the life of the lymphocyte is incomplete unless the conversion of lymphatic tissue into adipose tissue, into fibrous material (in thymic states[66]), into lymphomata of various kinds,[24] be referred to. Such a finding, too, as that of Körmöczi,[67] that an attack of erysipelas can arrest the processes of lymphatic leukæmia, is also worthy of comment, because of the light it throws upon the pathology of these hypermetaplastic diseases, showing as it does that cytoplasias are segments of circular intracellular changes—are not progressive or regressive, but sometimes baneful to the organism. They may be coaxed along until the tissue as a whole is back once more at the same phase of healthy metabolism from which it started.

FATE IN THE TISSUE.

1. Becomes old → monocyte of inflammatory cell-infiltration
2. ,, swollen = large lymphocyte.
3. ,, polyblast } → remains so
4. Is poly(myelo)blast } → becomes myeloic cell ←
5. Becomes "eosinoid" → polynuclear eosinophile of the tissue
6. ,, micromyeloblast → ,, neutrophile ,, ←
7. ,, "plasmoid" → plasma cell (see "Chart showing fate of plasma [cell")
8. Undergoes cytorrhexis.

CHAPTER IV.

ON THE LARGE MONONUCLEAR LEUCOCYTE.

Section I.—ON THE STRUCTURE OF THE PULPAR TISSUE : The pulp-cord is the second physiological unit of the spleen and lymph-node : its structure—The giant cell of the spleen—Metabolic changes in the pulpar tissue—Functions of the spleen—The accessory pulp-cell factories : the accessory spleen ; the hæmolymph-glands.

Section II.—ON THE LARGE MONONUCLEAR LEUCOCYTE OF THE BLOOD-STREAM : The meaning of the terms : large mononuclear leucocyte, splenocyte, monocyte, lympholeucocyte—Pappenheim's monocyte : its morphology ; contrast between the two varieties of monocyte—The morphological characters of the large mononuclear leucocyte : the secretory vacuoles—The variants : the lymphocytoid, transitional, miniature, and giant forms—The differential diagnosis—The theories as to the origin of the large mononuclear leucocyte of the blood-stream—(myeloid, lymphoid, endothelial)—The birth of the cell into the blood-stream—The functions of the large mononuclear : numerical variations—Chemical characters.—The azur granules.—Comparative cytology—The fate of the large mononuclear leucocyte.—Transitional cell ; degenerative changes ; irritation changes ; reversion to tissue-spaces.

Section III.—THE PULPAR CELL AND ITS CYTOPLASIAS : The morphology of the pulpar cell—It is a multi-potential cell.—Its relation to the lymphoid follicles and to myeloid metaplasia.—Genetic interrelations.—Chart representing these, and summarizing the essential features of the biology of the cells referred to in this and the preceding chapter.

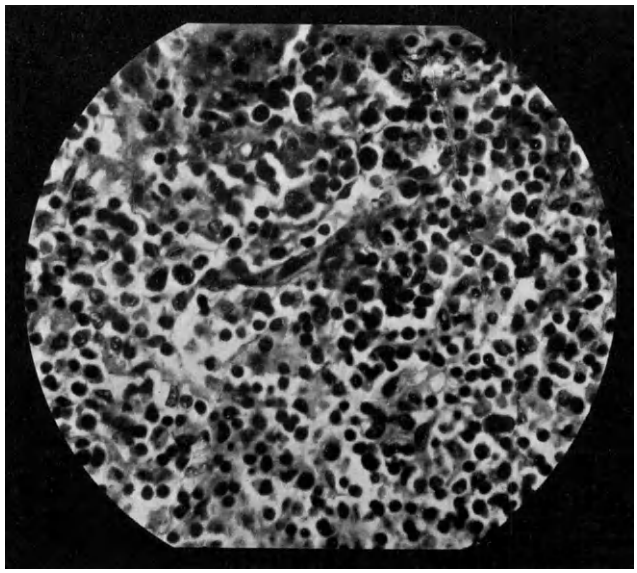
I.—ON THE STRUCTURE OF THE PULPAR TISSUE.

THE pulp-cord is the second physiological unit of the spleen and lymph-node: its structure—The giant cell of the spleen—Metabolic changes in the pulpar tissue—Functions of the spleen—The accessory pulp-cell factories: the accessory spleen; the hæmolymph-glands.

IT has been pointed out that the lymph-nodes resemble the spleen in structure to the extent that both are made up of follicular and pulpar tissue. The former is regarded as an important source of blood-lymphocytes, and is known to be a factory for tissue-lymphocytes. The pulpar tissues, on the other hand, are concerned in some obscure way with the formation of all the other lymphoid cells which may be encountered in the blood-stream, and of many forms met with in the tissues in question.

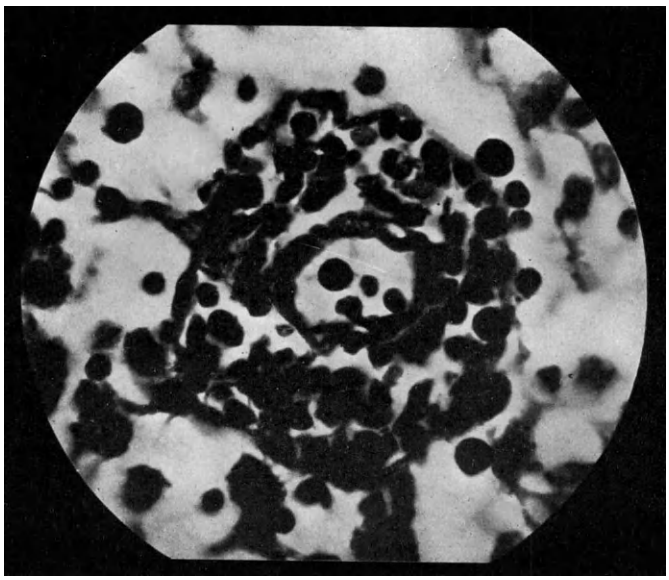
Speaking generally, it matters little whether a lymphoid follicle is in the spleen, in a lymph-node, or elsewhere. Similarly, several of the essential features of the pulpar tissue are equally well observed whether we deal with spleen or lymph-node. The anatomical position of this tissue is to a certain extent a matter of indifference, and although there is usually sufficient character about the lymph-node pulp to enable its identification from splenic pulp, there are occasions when it would be extremely difficult to decide to which organ the tissue belongs. Thus, *Fig.* 35 shows a preparation of a lymph-node which bears a remarkable resemblance to splenic tissue. Such an appearance might be regarded as pathological, and yet it is found, in lumbar glands especially, under circumstances which can hardly be placed with any given morbid condition.

It is only during recent years that the reality of such an entity as pulpar tissue has come to be recognized, with the result that a far more satisfactory view-point of the physiology and pathology of lymph-nodes and spleen is now possible. We therefore emphasize the similarity of architecture which obtains in the node and the spleen-pulp, and the close family resemblance exhibited by the cellular inhabitants of these tissues. What may be spoken of as



" . . . a preparation of lymph-node which bears a remarkable resemblance to splenic tissue " (p. 156)

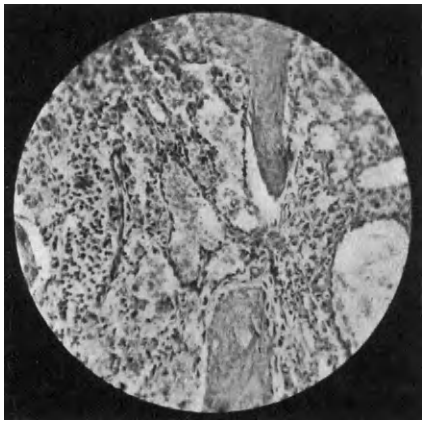
Fig. 35.—SPLENOID METAPLASIA OF LYMPH-NODE. Notice the lack of differentiation. A vascular channel traverses the field near its centre. The lymphoid cells vary in size and in staining reaction.
(Oc. 6, Obj. 4 mm.).



" The pulp-cord, when cut across. is found to contain a small central vascular channel, enveloped by a complete sheath of tissue " (p. 157).

Fig. 36.—TRANSVERSE SECTION OF A PULP-CORD. Notice the central ring, the outline of the vascular channels, the outer ring marking off the perivascular sheath filled with " free floating cells, hemmed in by a delicate meshwork of reticular tissue." The peripheral clear zone in the photograph represents the lymphatic channel.
(Oc. 8, Zeiss Oil-immersion).

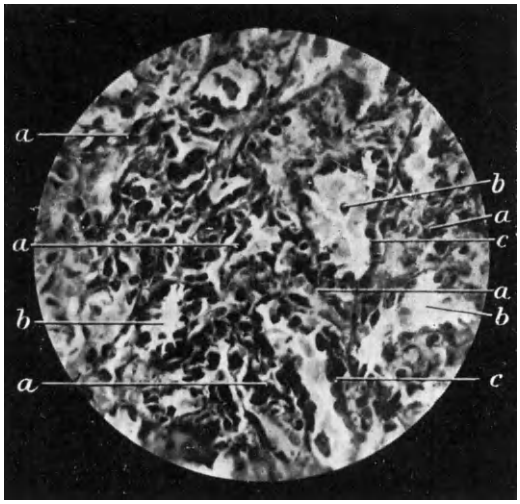
Face p. 156]



" . . . blood-channels whose walls stand out very conspicuously " (p. 159).

Fig. 37.—The photograph shows two fragments of trabeculæ (vertical) and a number of elongated spaces marked out by the dark nuclei of endothelial cells. The intervening cells constitute the splenic pulp tissue.

(Oc. 4, Zeiss Apochrom. 4 mm.).



" In cases of fibrosis of the pulp . . . the cords are found to be very rich in fibroblastic cell-forms " p. 159).

Fig. 38.—Splenic Pulp Tissue, showing Fibrosis. (*a*) spindle-shaped fibre-cells in the pulp cords; (*b*) venous channels; (*c*) endothelial cells lining same.

(Oc. 4, Obj. 4 mm.).

the splenoblastic line of development finds its theatre of action in the pulpar tissue, and its position in the anatomy is of secondary importance. This conception gives us a ready explanation for the possibility of harmless removal of the spleen.

The spleen and lymph-node have been seen to contain, as a unit of the lymphocyte-factories, the lymphoid follicle ; they also contain a second unit, the pulp cord, which appertains to the manufacture of large mononuclear cells. The two histological organs or units are closely inter-related, and are really mutually interdependent, as shown by a study of the spleen under every conceivable condition.

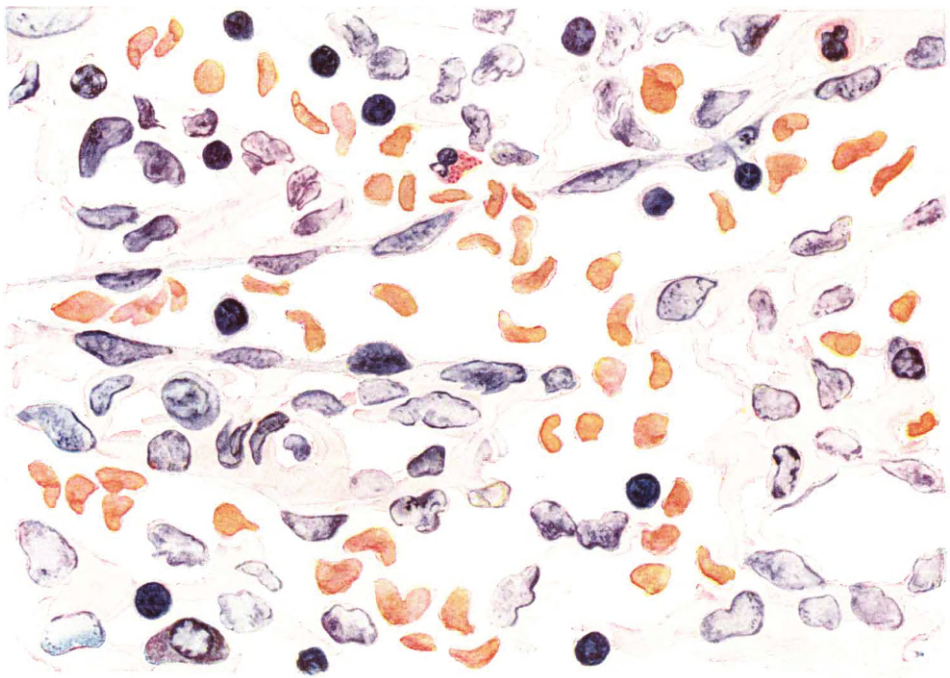
The Structure of a Pulp-cord.—In the lymph-node, it is easily ascertained that the pulp tissue is made up of a number of similar structures, forming an anastomosing network. These structures are called pulp-cords, and are best understood by reducing them to a mental picture of any one individual cord, no matter how minute it may be. Such a pulp-cord is shown in cross section in *Fig.* 36, and a careful study of such a field provides one with all the data necessary for the comprehension of the various cytometaplastic changes to which lymphatic pulp is liable. Some of the cytological details are more clearly shown in the fragment represented on *Plate I.*

The pulp-cord, when cut across, is found to contain a small central vascular channel, enveloped by a complete sheath of tissue. This sheath contains many forms of free-floating cells, hemmed in by a delicate mesh-work of reticular tissue, whose texture is loose near the capillary, but becomes increasingly dense as one passes towards the periphery, and there forms a veil-like membrane demarcating the pulp-cord from the surrounding lymphatic sinus. At the intersections of some of the trabeculæ lie the reticular cells, whose nuclei are very prominent against the slender plate-like forms of the cell-bodies. Projecting from the capillary are a few adventitial cells, whose morphology is not always easily differentiated from that of the reticular cells. Indeed, careful focussing often demonstrates that their cytoplasm runs out into branching processes which blend with similar ones from the reticular cells, and in that way forms a kind of syncytial mass pervading the whole of

the pulp-cord system. Close observation of the photograph will further reveal one or two gaps (exposed by optical section) in the outer sheath, giving free communication with the lymph-sinus beyond, so that the cells creeping amongst the reticulations of the cord can find exit into the lymphatic channels. The hall-mark of this pulpar tissue is the pulpar cell, whose morphological characters, expressed in an impressionist manner, vary from lymphoidocytar through macrolymphocytar to splenoidocytar, monocytar, and plasmoid forms. Not only does such a cell occur in the pulp-cord itself, but it will also be found to lie in the pericordal lymphatic channels.

The close *relation between pulpar tissue and venous channels* is more clearly shown in the spleen than in the lymph-node, while the splenic pulp does not show lymphatic channels in the conspicuous manner described for the lymphatic pulp-cord. While in the latter we pass from central blood-vessel through pulpar tissue to lymph-space and on to the main efferent trunk, in the spleen we pass from capillary through pulpar tissue back to capillary (*Plate V*). The sub-divisions of the splenic artery run to the respective compartments of the spleen, and break up into capillary channels, which rapidly lose a tubular character owing to the appearance of defects in their walls (elongated clefts). The lining cells of the capillary are narrow and elongated, the nucleus projecting strongly into the lumen, though covered by a film of cytoplasmic material (Mangubi-Kudrjavtzewa[1]). A central and two lateral fibrils traverse the cell-body, while circular fibrils are let in on the basal surface of the cell. Protoplasmic thickenings called basal plates occur at the cell-edges, and give rise, according to Mollier,[2] to a syncytial formation—the appearance of discrete endothelium usually seen in autopsy material being really artefact. The spaces between these branching cells constitute the meshwork of the pulp, so that the blood is really circulating amongst the cell-constituents of the pulpar tissue. Where the vascular channels can be distinguished, however, it is possible to differentiate pulp-cords by the closer network of connective tissue which permeates them. The more rapidly-flowing blood runs on each side of the sponge-work of the pulp-cord, while slowly-flowing blood gently bathes the constituent cells on its way to the

PLATE V.



Biology of Blood-cells

O. C. Gruner

channels on either side. *Fig.* 37 shows a low-power view of the blood-channels whose walls stand out very conspicuously owing to the deep-staining property of the lining endothelium, and although cord-tissue does not always intervene, fragments of loose tissue can be made out here and there, in which blood-cells are intermingling with pulpar cells, exactly as in the lymph-node. In cases of fibrosis of the pulp, such as is shown in *Fig.* 38, the cords are found to be very rich in fibroblastic cell-forms, and the blood-cells are hardly noticed.

The scene of action of the drama which is taking place amongst the cellular inhabitants of the spleen is best fixed in the mind by confining oneself to the intervascular reticular tissue and the adjacent capillary wall, and has been depicted in *Plate V* under a very high magnification, in order to make the difficult subject of spleen histology more clear. The drawing shows a vascular channel traversing the field in a horizontal direction, and communicating with another channel coming from above by a narrow opening through which a couple of red cells are passing. Below, it presents a wide opening giving access to the small bay-like terminal of a third channel. Between these various blood-vessels are strands of tissue—the pulp-cords—and these are seen to be made up of a loose fibrillar connective tissue whose meshes support several types of cell. The endothelium lining the main channel is only broken in one spot (to the right) by the passage of a lymphocyte through it, but the by-channels show many gaps in their endothelium, thus allowing free entry or exit to the various cells.*

We must now picture to ourselves the appearance of this tissue in the living state. If we could be transformed into a red cell, and follow its course through any of the labyrinthine passages, we should notice that the surface of their walls was curiously irregular, owing to the excessive prominence of the nuclei, which are apparently quite naked. In the main channel we should be moving at a considerable speed, but we should be able to linger a little in the side-paths, and observe the still greater irregularity of their sides and

* In the original specimen, the pulp-cords are actually occupied by numbers of red blood-cells, which have percolated through such apertures, but they have been omitted from the drawing for the sake of clearness.

floor, the myriad recesses into which one might retire, and the gaps here and there through which the irresistible force of suction and the pressure of the other cells about us would tend to draw us. Should we yield and drift hither or thither into the pulp-cords, we should find ourselves face to face with a wonderful variety of cellular beings : here a reticular connective-tissue cell with its bulky nucleus and spindley cell-body ; there an adventitial cell with similar characters, save that its extremities pass off into thick pseudopodia ; there, again, a similar adventitial cell, which has drawn in its processes preparatory to detaching itself from its neighbours ; again, another which has just moved from a cave-like nook, and is about to settle down again in another spot, or is about to undergo intracellular (nuclear) metaplasia ; again, another which is waiting for its prey—dying red-cells or what not—in those dim recesses, like an octopus waiting in its lair at the bottom of the rocky crannies of the ocean floor to devour any animals suitable for food that may pass by its tentacles. The octopus seizes its prey with lightning rapidity ; but the phagocyte appears to require an appreciable time for the capture of its food. Even so, there is ample time, because we can move so very slowly through all this maze of reticular tissue. Passing on further amongst the cellular inhabitants we encounter here a plasmoid cell, there a macroplasma cell, here an eosinophile cell, there a mast cell, here a lymphocyte from a neighbouring Malpighian follicle, there a cell loaded with pigment. Nor do we only experience visual impressions (as it were). In the course of our imagined passage through the pulpar strands we should experience new sensations, or whatever they may be called—chemotactic influences produced by the diffusion in different concentrations of stimulant or noxious products—waste matters derived from remote parts of the body, toxic bodies from passing unimportant organismal infections of far-off regions, changes in ionic concentration of the medium, advent of different colloidal bodies. The very presence of clusters of eosinophile, plasma, or mast cells is proof of the existence of such agents, and although as red-cell we should not necessarily become aware of them, this metaphorical description must take them into account. Ultimately, passing out of the view depicted in the plate, drawn along by the powerful

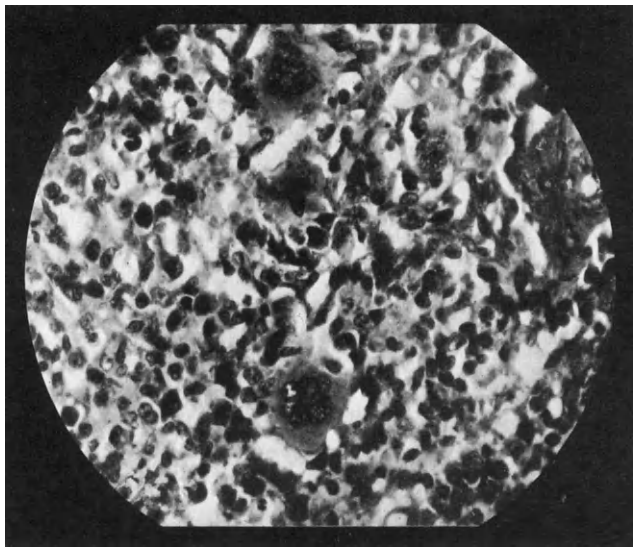


Fig. 39.—SPLENIC PULP TISSUE OF PUPPY, SHOWING MEGAKARYOCYTES. Three very large cells are shown. The nucleus has the characteristic lobed or basket form.
(Oc. 4, Zeiss Oil-immersion).

Face p. 161]

suction of the blood-stream, we find ourselves at last in a more and more rapid current as we enter the larger and larger venous channels.

The cell-constituents of the splenic pulp include the following: (1) The *reticular cells* themselves, which are at certain times actively phagocytic, as shown by the presence in them of pigment granules of various sizes. (2) The so-called *spleen phagocytes*, which are lymphoid in character, smaller than the preceding, and contain foreign bodies such as red-cells in various stages of disintegration. (3) *Endothelial cells*, already described. (4) The *true pulpar cell* and its various derivatives—the small lymphocyte, the large mononuclear leucocyte, plasma cells of various sizes, eosinophile cells of various sizes. (5) *Normoblasts* occasionally. (6) *Giant cells* or megakaryocytes. (7) Purely *stromatic cells*. (8) Kalatschnikoff[4] described ciliated cells amongst the pulp-cells, which might possibly serve to direct the blood-flow into certain districts. (9) The *cells of the circulating blood*.*

THE GIANT CELLS were first found in the spleen by Perlmeschko,[3] in 1867. They are of considerable interest, since they are very close simulators of the megakaryocyte of the bone-marrow, although forms occur which contain nuclei so lobed as to appear as multiple discrete centrally-situated bodies. They appear to be constant in young animals, such as the puppy (*Fig.* 39), and are important in relation to certain of the metaplastic processes to be discussed later.

The histology of the spleen pulp is not complete without reference on the one hand to the *elastic fibrils* which permeate it, and on the other to *nerve fibrils*. The latter end partly in the Malpighian bodies, and run in different directions to form anastomoses within them, partly envelop the brush-arteries in plexus fashion, become varicose and tortuous, and send off lateral branches to the pulp. Multipolar ganglion cells occur round the brush-arteries and vascular sheath (Asai).

Metabolic Changes in the Pulpar Tissue.—Observations on the spleen *during the digestion of albuminoids* (Ciaccio and Pizzini[5]) show that enlargement takes place at this time from hyperæmia.

* The remarks as to the cellular content of the splenic cords apply in every respect to the lymphatic cords, and in discussing the metabolic changes of the one, the other is also implied.

The nuclei of the capsular cells increase in size, and their chromatin increases in density, while the cytoplasm becomes faintly granular. The septal veins dilate, the Malpighian bodies swell, their germ centres become distinct, and their lymphoid-cell contour becomes ill-defined. The engulfing of leucocytes causes the cytoplasm of the pulpar cells to swell greatly. The endothelium of the distended venous channels becomes tumefied, and their nuclei undergo similar changes to those referred to in the case of the capsular cells. These cells may also play the part of phagocytes, become detached, and wander away from their original positions. During this phase, the vicinity of the vessels is thronged with lymphocytes, leucocytoid lymphocytes, large mononuclear leucocytes, and erythrophages. Plasma-cells occur in clusters in a similar position, while polynuclear leucocytes make their appearance after the fashion of policemen vigilating the incoming material.

The increased hæmolysis which is noticed in the spleen pulp at this time, goes hand in hand with an increased red-cell manufacture in the bone-marrow (Pirone[6]). Megakaryocytes undergo no alteration in the spleen, contrary to the expectation of the theory which has been advanced that they secrete a ferment necessary for digestive processes in the intestine. The active digestion of the nuclei of polynuclear cells and of some of the lymphocytes is manifested by a formation of nucleinic granules, which ultimately turn into purin substances (catabolic processes). The anabolism is shown by the appearance of nucleases, which are increased in amount *pari passu* with an increase of activity of lymphoid tissue and with an increase in phagocytic activity. At the same time, large mononuclear leucocytes are being made, the feebly basophile cytoplasm becoming more and more acid, and acquiring an increasingly distinct alveolar structure as liquid ferment or pro-ferment appears within its body (the macrocytase of Metchnikoff, which acts like trypsin, amœbodiastase, or actinodiastase). The connective-tissue cells run into a plasmodium with large oval nuclei and two or three central chromatic dots. A ring of basophile cytoplasm appears round the nuclear matter, and ultimately leaves the cell-complex as a lymphogonia or lymphoblastic monocyte. This becomes more and more basophile. The basophile deposit is a constructive process.

During rest the pulp tissue is found to be poor in free elements, and degenerative nuclear changes can often be observed. The ability to demonstrate increase in the purin content is also characteristic.

Pathologically, metabolic changes in the spleen are exemplified from a study of the spleen in acute infections (Ciaccio[7]). When the follicles atrophy, the pulp shows paucity of cellular elements. Nucleinic degeneration, where the nucleoproteid or nucleohistone has become converted into a nucleic acid and proteins under the influence of a ferment, is shown by caryorrhexis and pycnosis of the pulpar cell. A more advanced stage of degeneration (purinic) may occur, in which case the nucleic acid has been split into purins, phosphoric acid, and carbohydrate. A lecithinic and fatty degeneration is also observed in some cases. The reticular cells may show degenerative phenomena under these conditions.

The changes arising from metabolism are not completely covered by a consideration of the changes arising during the digestion of food-substances. This is well brought out by the careful cytochemical studies of splenic pulp by Loele.[8] The remarks which follow are largely drawn from his work. This observer, applying the Winkler-Schultze oxydase reaction, ascertained that α-naphthol alone will suffice to produce the appearance of brownish-yellow pigment within the bodies of certain of the cell constituents of the splenic pulp. The substance that renders this reaction possible is called the " phenolphilic substance," and the phenomenon itself is called " phenolphilia."

It was observed that phenolphilic substance was diminished in some cases of chronic nephritis and chronic syphilis, but increased in infective processes and in cases of breaking-down neoplasm. Expressed more fully, we find that the following groups may be constructed: (1) Cases in which there is general deficiency of phenolphilic cells through the splenic tissue; (2) Cases in which a narrow zone of granular cells occurs round the follicles, but only isolated cells are to be found in the pulp; (3) Where the perifollicular zone of cells is broad, and phenolphilic cells are fairly numerous in the remainder of the pulp; (4) Cases in which the cells are abundant throughout. The second type may be regarded as the

normal one during the stage of digestion in the adult. The first group is met with in chronic renal diseases, as mentioned above, and the third group is noted in the acute infections. The fourth group is characteristic of septic conditions (abscess of the liver, pylephlebitis, meningitis, peritonitis), cirrhosis of the liver, diabetes, and unclassifiable conditions.

Loele arrived at the following conclusions about the chemical nature of the phenolphilic substance: (1) The phenolphilic substance is an amido-aldehyde base endowed with properties resembling those of ferments. It may act as a reductase, or as an oxydase (phenolase) according to the concomitant circumstances. As a base, it is demonstrable by means of the α-naphthol reaction alone; (2) As base it may manifest itself in the form of granules, and form soluble salts with acids, or unite with phenols in alkaline solution to form colour salts (after the fashion of hydroxylamine). As an ammonium base it serves to saponify fats, and is able to dissolve albumin when combined with certain intracellular acids (lipolytic and proteolytic ferments); (3) Nitrogen bases are increased in response to electro-chemically negative stimuli (acids, phenols, alcohols), $-N = N-$ becomes $-N =$, $-N =$.

It has already been pointed out that the Malpighian follicles are built up round the arteries, while the pulp is essentially venous. The significance of this well-known anatomical point is well demonstrated by the author just named. Granted that there is phenophilic substance in the follicle cells, the effect of its presence is to take up the oxygen circulating past them, and liberate it once more in nascent form, so that coming in contact with aldehyde groups as it does, the latter become oxidized into amido-acids. Cells rich in amino-acids obviously appear "basophile" in the stained histological preparation; hence the "foci of basophilia" commonly called Malpighian bodies. Siegfried[9] pointed out that the carbon dioxide produced by metabolism would unite with the amido-acids to form carbaminic acid, which, in the presence of the sodium chloride of the blood, would give rise to hydrochloric acid and sodium carbonate. The latter is removed by the lymphatics around the follicles, while the former unites with amido-bases within the cells (e.g. of the lymphoblasts), breaks up the peptonizable

proteins—a phenomenon of autolysis—and brings about the appearance of cells with hardly anything but nucleus, the familiar lymphocytar cells. Meanwhile, the continued supply of oxygen has led to the appearance of pseudocrystalline matter within the cells, otherwise called mitotic figures, and an actual division of the cells into two.*

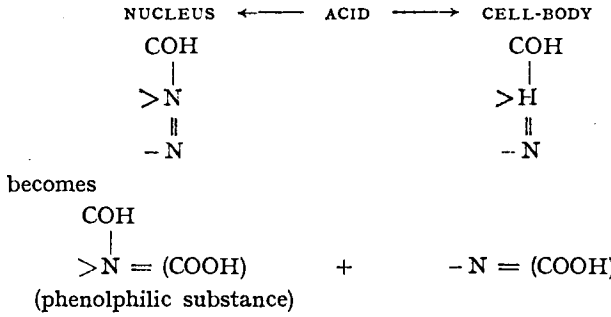
The pulpar tissue, on the other hand, is bathed in a medium relatively rich in carbon dioxide, except in the vicinity of the follicles, where the reaction of the tissue is neutral. The absence of lymphatics serves the definite purpose, or has the definite effect, of maintaining this semi-asphyxial state, for there is no opportunity of draining off the carbon compound in the form of carbonate. The surfeit of this substance leads to the accumulation of auto-oxidizable nitrogen bases—of phenolphilic substance within the cells, because the bases are attracted into the cell-body by the excess of amido-acids in the nucle-uberous cells. The further removed the cells are from the arterial zone, and the less opportunity is there for the production of basophile, differentiated cell structures, the more should one find uniformity of morphology between them. Where cells such as eosinophiles appear, which bear oxidizing granules, there will be some disturbance of equilibrium, and this is rectified, for instance, by the appearance of plasma-cells. Wherever noxæ of acid character reach the cells via a venous medium, phenolphilic granules will appear within them, whereas, as shown, they have no opportunity to accumulate in the immediate vicinity of the arterial channels. The basophile substances in the pulpar tissue tend to the formation of tryptic systems therein (in place of the peptic system characteristic of the follicles), and the effect is that oxyphilic bodies are liberated in the pulp while the autolytic macrophages are correspondingly numerous.

From these condensed remarks it is evident that the splenic pulp contains bodies which are able to make colour salts with phenols, and can neutralize acids brought to it, as well as bind decomposed phenol-like compounds to the alkaline tissue juices, and perhaps saponify neutral fats. The phenolphilic granule, in a

* Leduc's physico-chemical theory of mitosis will be recalled.

sense, acts as an amboceptor between the phenolic compound and the alkaline tissue juice, while in the process of saponification the granules play the part of complement, and cause the neutral fat to hydrolyse into a soap. Expressed in this way, the importance which the writer attaches to Loele's theories is more clearly brought out. We see that the presence of this material in such abundance in the spleen invests this organ with a new significance, in preventing the liberation into the blood of an excess of amino-bodies. Whenever metabolic processes result in the liberation of excess of acid substances by the tissues, the diminished alkalinity of the blood is rendered innocuous to the body as a whole by the phenolphilic substance formed in the spleen (also lymph-nodes and round eosinophilic zones).

The chemical structure of the phenolphilic substance has been surmised from a number of considerations. It is regarded by Loele as derived partly from the nucleus and partly from the cell-body. One would express the views under consideration by the following scheme :—



The acids diffuse into the cell-body and unite to the N group. (COOH) becomes free; and the O attacks the COH, or unites with phenols, or becomes free. The aldehyde group becomes acid (COOH), to wit an amido-acid within the nucleus. Should phenols not be present within the nucleus, the heaping up of amido-acids leads to the phenomena of mitosis. In the histological process, a phenol-ring is supplied to the cells, and with the phenolphilic substance gives rise to a colour salt of oxazin type.

The phenolphilic substance is increased by the presence of bacterial toxins, by salvarsan, and by the toxic agencies responsible for the diseases called pseudo-leukæmia. It is diminished by the presence of acidosis.

The Functions of the Spleen.—

1. Phagocytosis by macro- (not micro-) phages. R. Blumenthal[10] stated that the spleen was the battle-field between the organism and its invaders. Another author has described the organ as the graveyard of the red cell.

2. Erythrolysis—shown by the abundance of extractives in the organ.

3. Leucolysis (Blumenthal). Spleen juice destroys leucocytes.

4. Removal from the blood of abnormal products other than cells.

5. Hormonistic functions,* such as supplying an activator to the pancreatic trypsin (trypsinogenic function of Herzen,[12] corroborated by Pachon and Gachet, but not accepted by Pawlow); or supplying an activator to pepsin.†

6. Erythropoiesis during embryonic life.‡

7. Monocytopoiesis in the adult, but monocytoid cells increase in the blood after splenectomy (Pauliczek,[13] Creszenzi, Azzurini).

8. Utilization of iron (Asher,[14] Grossenbacher, and Zimmermann[15]); this is shown by the fact that after splenectomy the urine contains increase of iron, while if an iron-free diet be given at the same time, there is a very rapid development of anæmia. In leukæmia and Banti's disease there is iron-retention.

9. The functions connected with the lymphocytes (i.e., of the germ-centres). These are similar to those met with in the case of the lymph-node; e.g., relation to lipolysis and immunization against organisms which contain lipoid material.

10. Relations to immunity. These are not clear. Szokalski[16] considered that there was no relation to the formation of hæmolysins, because splenectomy does not destroy hæmolysin formation. Jungano[17] and Azzurini[18] considered that agglutinins are not made here, but Scotti[19] found very definite evidence of their manufacture in this viscus. Bergel,[20] on the other hand, found evidence that antibodies for hæmolysins were made in the pulp, because extract of spleen in a case of cancer would relieve cancer in any animal (acts as an immune serum—Braunstein).[21] Oser and Pribram[21a] found that splenectomy in rats the subject of sarcoma would cause the tumour to increase rapidly in size; while an injection of spleen-pulp would cause the growth to cease.

11. Myeloid transformation. This is considered in Chapter VII.

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* This term appears to be unsatisfactory, from the evidence afforded by the researches of Popielski[22] and others (in Russia, particularly). In other words, hormones may not be entities at all, but "chemical affinities," or, possibly, in the writer's view, stereochemical attributes, much as may hold good in the case of some amboceptors.

† Gross[11] found that the pepsin was extremely low in a case of splenectomy for trauma, while lymphocytosis appeared.

‡ The proof that enterokinase is made by the spleen lies in finding increase of the kinase after injecting nucleinic acid or pilocarpine into a dog. The source of the kinase is not the lymphocyte, because that is always present. It is not the polynuclear leucocyte, because bone-marrow itself has no such power; the macrophage must therefore be the source.

It is evident, then, that the spleen subserves a number of functions, which do not deserve contempt on the ground that splenectomy is harmless, but rather *are to be regarded as so important and necessary to the organism that they are not condensed into one organ alone, but are part of the potentialities of widely disseminated mesenchymal cellular elements.* The result of this plan of dividing risks in speculation among a number of investments is manifested by the successful (i.e., non-fatal) splenectomy referred to.

Dinkler[23] recorded a case where splenectomy was followed by polycythæmia.

The Accessory Pulp-cell Factories.—

A. ACCESSORY SPLEEN (Accessory splenoma—Faltin[25]). This body may be met with singly or in multiple. Winkler[24] and Albrecht have each reported cases in which there were hundreds present. It is usually discussed as a purely anatomical curiosity, and the situations in which it is apt to appear are stated with detail. The following brief remarks may be more suggestive—namely, that the accessory spleen is well-named : that it is truly accessory in character ; that it plays a required part ; and that it can develop at any time, and in any place, from indifferent mesenchyme cells.*

It will be evident that there is no reason why an accessory spleen should not develop at any time, if the parallel in lymphoid tissues holds good. The Ribbert lymphoma may arise into prominence at any time when occasion demands, and lymph-nodes appear in just the same way amongst the fatty tissue of the mesentery and axilla. We have, moreover, the records that accessory spleens have been noticed to be frequent after extirpation of the spleen (Litten, Tizzoni,[27] and Mosler), e.g. for rupture (Faltin[28]).

The structure of these organs is very similar to that of the main viscus. The writer has found them to be rather poorly provided with follicular tissue.

B. THE HÆMOLYMPH-GLAND.—The hæmolymph-gland is a constant anatomical feature of both man and mammals. It is particularly common in the horse (Fourgeot[30]) ; is frequent, but less conspicuous, in the sheep and rat ; but not easily seen in the dog and cat.

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* It will be remembered that the spleen itself develops from the mesenchyme of the dorsal mesentery in close connection with the mesenteric arteries. It appears as a thickening of the lymphoid tissue which surrounds the wall of the artery at an early stage (Radford[29]).

Such glands also occur as the " head kidney " of fishes (Lewis[34]), in birds (Vincent and Harrison[31]), and in swine suffering from Texas fever (Warthin[33]). It will be noted that birds possess but few lymph-nodes of the ordinary type (Quain[32]).

Briefly described, it is a lymph-node of deep-red colour owing to communications between blood, vascular channels, and lymph sinuses. In a sense, the hæmolymph-gland is nothing more than an accessory spleen. The lymphatic channels are reduced to a minimum, and do not form so definite a system as in the ordinary lymph-node, while the lymphoid cells are very irregularly arranged, and exhibit no definite follicular arrangement. In the ruminants, there are afferent and efferent lymphatics, besides a closed system of lymphatic channels. The lymph in the former is of a red colour.

It is usually stated that these bodies are normally present on each side of the aorta, but the percentage of autopsies in which this can be corroborated is rather small, and really confined to instances of microbic infection.* Other situations for these glands are : the bifurcation of the trachea, the chain of glands leading from the appendix, and the gland above the head of the pancreas.

The following types of hæmolymph-glands are often described :

1. The *splenic* type, met with in the retroperitoneal and thoracic regions. This is a small lymph-node with blood-sinuses and no Malpighian bodies. The sinuses are large, and have macrophages for red-cells and for pigment within them. This type is really an example of " splenoid metaplasia " (*p.* 308).

2. The *myeloid* type. This is only seen in the retroperitoneal region of animals. The tissue resembles red marrow in structure. Warthin termed such glands " marrow lymph-glands." The blood sinuses are smaller, and contain many basophile and sometimes giant cells. This form is also classifiable as a variant of myeloid metaplasia, a conception which brings together lymph-nodes showing myeloid metaplasia and the form of hæmolymph-gland in question.

3. *Intermediate Forms.*—Intermediate stages between (1) and (2) may occur as well as between hæmolymph-glands and glands in

* They have also been found in cases of corrosive-sublimate poisoning.

general. If the sinuses contain some lymph they are called hæmal lymph-glands (Robertson), while if they contain only blood they are called hæmal glands.

In some hæmorrhagic diseases, hæmolymph-glands are simulated by specimens through which diffuse hæmorrhage has taken place, and sometimes by specimens showing petechial hæmorrhages scattered through their substance.

As has been stated, the spleen is really a large hæmolymph-gland.

The *functions* which have been assigned to hæmolymph-glands are: (1) Making lymphocytes; (2) Making eosinophile cells by taking up disintegration products of red cells (the nuclei become polymorphous—Woltmann[36]); (3) Destruction of red cells (bilirubin formation); (4) Destruction of white cells by phagocytosis.

II.—ON THE LARGE MONONUCLEAR LEUCOCYTE OF THE BLOOD-STREAM.

THE meaning of the terms: large mononuclear leucocyte, splenocyte, monocyte, lympholeucocyte—Pappenheim's monocyte: its morphology: contrast between the two varieties of monocyte—The morphological characters of the large mononuclear leucocyte: the secretory vacuoles—The variants: the lymphocytoid, transitional, miniature, and giant forms—The differential diagnosis—The theories as to the origin of the large mononuclear leucocyte of the blood-stream (myeloid, lymphoid, endothelial)—The birth of the cell into the blood-stream—The functions of the large mononuclear: Numerical variations—Chemical characters: the azur granules—Comparative cytology—The fate of the large mononuclear leucocyte—Transitional cell: degenerative changes: irritation changes: reversion to tissue-spaces.

THE classification and enumeration of the white cells in a blood-film would be quite straightforward were the polynuclears, the eosinophiles, the mast cells, and the small lymphocytes the only variants to be considered. The existence of other lymphoid cells has been the cause of much controversy, partly because their morphology has not been clearly defined, and partly because of an absence of definite information about their source. These larger lymphoid cells were called large mononuclear leucocytes by Ehrlich, who considered that, after passing through a "transitional-cell" phase, they became neutrophile leucocytes. Metchnikoff, designating them as "macrophages" because of their power of taking up large particles of foreign matter, regarded them as identical with the wandering cells of Marchand. This view agrees to some extent with that of Naegeli, in that the latter emphasized their specific function as indicative of their belonging to a distinct order. Patella's view that they are dead cells may be put on one side, because it fails to recognize the profound biological importance of the group.

Some years ago it was thought that this cell-form was derived from the spleen, and might be correctly designated by the word splenocyte (Türk), but there are certain considerations which show that the spleen cannot be the only source of the large mononuclear leucocyte. Although the spleen pulp consists largely of such

cells, although the splenic vein is rich in them, yet splenectomy is followed after a time by a marked increase in the large mononuclears.[36] It is more probable that we should speak of these cells as being derived from the *pulpar tissues*, whether of lymph-node or spleen, not only because this procedure is more in keeping with the physiological attributes of these hæmopoietic organs, but also because the possibility, after splenectomy, of continued supply of the cells under consideration would find a natural explanation. In consequence, it would be better to speak of " pulpocytes " rather than " splenocytes," though the introduction of new terms is neither necessary nor desirable. Having once fixed what kind of a cell is a large mononuclear leucocyte, or a monocyte, further alterations of nomenclature become avoidable, even though findings from the etiological side should come to light.

It was with the object of simplifying the subject that Pappenheim introduced the term *monocyte* to group together those cells usually classified by laboratory workers as " monos " (an abbreviation of *mono*nuclear leuco*cyte*). Such cell-forms may be separated off into (*a*) the so-called normal monocyte, (*b*) the leucoblastic or granuloplastic monocyte, each of which exhibits the characteristic leucocytoid form when it becomes old. According to this method, some monocytes become definitely lymphoid in character—lipase-containing; while the others are ancestors of granular cells—oxydase and proteolase-containing. But both forms are possible functional phases of one and the same cell-form (monocyte, or its parental form, the lymphoidocyte). If the monocyte has lymphocytar characters, it persists with such; if it has granuloplastic characters, it passes on further to become a polynuclear leucocyte.

This conception tends to simplify the difficulties which the investigation of blood-films presents. Everyone has noticed how similar the basophile mononuclear cells with indented or horse-shoe-shaped nucleus are to certain pathological cell-forms called myelocytes. The distinction between them is apt to be very fine, and appears forced to the uninitiated. On the other hand, it is important to search for data which will help to detect functional differences in morphologically similar cells. The first step towards this is gained by the use of the term in question. If there is

evidence that the monocyte is leucoblastic or myeloic (forming or about to form neutrophile granules), then the blood in which it was found is abnormal and the cause of the abnormality requires to be determined. The type of monocyte natural to the blood-stream, on the other hand, is lymphoblastic if anything, and must be placed in a class apart from the other.*

The monocyte of Pappenheim is related to the mesenchymal cell of the tissues, the clasmatocyte of Ranvier, the endothelial cell, and the lymphoid wandering cell of Marchand. Present in every tissue of the body as cells with a vesicular leptochromatic nucleus, they give rise to a form with a darkly-staining nucleus which may remain latent or slumbering as the pulpar monocyte, may simply proliferate and appear as a lymphatic monocyte, or may develop along metaplastic lines to form granulocytes. The natural situation for the latter change is in the bone-marrow, but under certain circumstances it occurs in the pulpar tissues, and is then named myeloid metaplasia.†

The monocyte of the blood is a morphological entity, and it is not possible to decide whether a given cell seen in a film has come from the pulp, the follicle, the marrow, the perithelium, or elsewhere. It is certain that it cannot be derived from the lymphoid follicles directly, because we should then have to accept the existence of immature or ancestral cells in the circulating blood. Similarly, the discussion as to whether a transitional cell ends its life as a neutrophile leucocyte is superfluous, because if it were so it could not be a transitional cell but a metamyelocyte. The characters of the metamyelocyte are easily defined, and there is no need to confuse the two. Similarly, if the young transitional cell inevitably became a neutrophile, it should be called a promyelocyte (see next chapter). On the other hand, the discovery of azur granules in both series of cells has led to much confusion, although later researches have shown that the azur granules of the lymphoid cells are differentiable and distinct from those of the myeloid series.

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* The synonyms, splenomonocyte, macrolymphocytar endothelioid cell, etc., are gathered together in the Glossary.

† As will be shown later, this view of myeloid metaplasia is not universally accepted.

The Morphology of the Monocyte.—

Size.—Large, up to 25 μ.

Shape.—Rounded or ovoid.

Contour.—Fairly clearly defined.

Cell-body.—Is very feebly basophile; is transparent; may show a very fine spongioplasmic network. The leucoblastic monocyte has a distinctly basophile cell-body.*

Granules.—Very fine, numerous azur granules occur.

Nucleus.—Is rather ill-defined. Outline irregular. Size large, both absolutely and relatively. Staining power feeble.

Nucleolus.—Never present.

The term *lympholeucocyte* (Pappenheim, Coie[37]) means no more than a cell combining certain features characteristic of the leucocyte (relatively large cell-body, irregular contour of nucleus) with other characteristics of lymphocytes (especially the diffuse basophilia). It is really a senile form of the large mononuclear leucocyte, although forms occur which are not easily distinguished from the senile or leucocytoid forms of the small lymphocyte (so-called "hyaline cells" of older writers).

The alteration of terminology to indicate alterations of age in these orders of cells is best shown by the following :—

Large lymphocyte=lympholeucocyte=transitional cell.
Small lymphocyte=leucocytoid lymphocyte=lymphocyte with reniform nucleus.

This scheme accentuates the position of the transitional cell as the terminal of the lymphatic monocyte line, and should be compared with that of the polynuclear cell as the terminal of the myeloic monocyte line. In each case the law of ageing holds good; that is, the nucleus shrinks, loses its parachromatin, becomes indented or pycnotic, and relatively smaller to the cell-body.

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* The fact that the colour of the cell-body of the leucoblastic cell (panoptic stain) is better imitated by cobalt blue indicates the amphochromophilic change that is taking place in such cells.

Contrasting the two categories of monocyte, we have :—

Lymphatic Monocyte	Leucoblastic Monocyte
Bulky	Smaller
Contour rather irregular	Regular
Ovoid	Round or irregular
Contour rather ill-defined	More defined
With panoptic, cell-body stains Prussian blue	Stains cobalt blue or violet blue, or grey violet
Azur granules fine	Coarse, fewer
Nuclear markings ill-defined	Clear; more or less transverse polygonal shadows
Size of nucleus relatively small	Relatively larger, especially in young cells
Nuclear membrane definite	Not definite

These points are shown in *Fig.* 40.

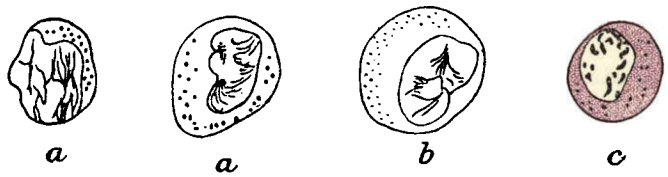

Fig. 40.—The Two Forms of Monocyte. (*a*), Leucoblast with coarse azur granules and coarse nuclear membrane; (*b*), large mononuclear leucocyte with fine azur granules, and delicate nuclear membrane; (*c*), promyelocyte with neutrophile granules and partially oxyphilic cytoplasm, indicated by purple stippling. This cell is introduced to form a contrast to *a* and *b*.

The following table will emphasize the difference in the character of the granules of various monocytes :—

Lymphoid Cells with Basophile Cytoplasm.

	Stained with Triacid	Stained with Romanowsky
Group A ..	Shows no granules ..	Shows no granules
Group B ..	Shows no granules ..	Shows some granules
Group C ..	Shows some granules ..	Shows no granules
Group D ..	Shows some granules ..	Shows some granules

Cells belonging to group A are primordial or mother cells, to group B are monocytes (in a general sense). The remaining groups are forms of promyelocyte.

The morphological differences between the lymphatic monocyte and the leucocytoid lymphocyte are shown in *Fig.* 38, wherein are to be noticed such points as centric or excentric position of the nucleus, vacuolation of cytoplasm or hyaline cell substance, size and position of azur granules.

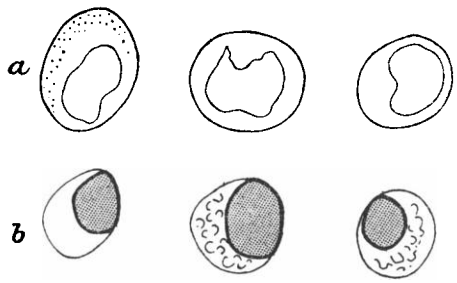

Fig. 41.—Row *a*, large mononuclear leucocytes; row *b*, leucocytoid lymphocytes. Diagrammatic drawing to emphasize the points of distinction between the two series. The heavy outline of the nucleus in *b* indicates the clearer definition of the nuclear membrane, and the shadowing indicates the more intense staining power of the nuclear matter.

The Morphological Characters of the Large Mononuclear Leucocyte.—(See *Figs.* 40, 41).

Size.—Up to 20 or 25 μ in diameter.

Shape.—Ovoid.

Contour.—Faint but regular.

Internal Structure of Cell-body.—The cytoplasm is relatively abundant, is feebly but purely basophile in reaction, is transparent, or shows a very fine spongioplastic network. Vacuoles are very rarely observable. At the periphery of the cell-body are some very minute rod-like basophile structures, but the edge is not very basophile.

Astrosphere.—There is a very feebly oxyphile perinuclear halo in some specimens.

Granules.—The following varieties are described: (1) Very fine (feebly orange) azur granules, scattered uniformly through the cell-body in considerable numbers. They may be situated more at the periphery than at the centre; (2) Ferrata's plasmosomes; (3) Kurloff bodies. These two last-named are referred to briefly under the title of secretory vacuoles; (4) Winkler-Schultze granules were observed by Sapegus.[38]

Nucleus.—This is large, both absolutely and relatively (7–10 μ). It is round or oval in shape, is usually indented or lobate to a varying degree. The position is slightly excentric. The staining power is feeble (amblychromatic), and shows an almost absolute homogeneity owing to the lack of differentiation of chromatin from parachromatin. The lining has the appearance of shadowing (woolly or flaky). The nuclear membrane is feebly defined.

Nucleolus.—Never present.

Mitoses.—Amitosis is only observable in atypical forms (Spadaro[39]).

Appearances with Ultra-violet Light.—Grawitz[40] found that various examples occur which will show all stages between flaky differentiation of cytoplasm and granule formation.

Isomorphous Cell.—Leucocytoid leucoblast.

The Secretory Vacuoles.—Secretory vacuoles occur in 15 to 20 per cent of the large mononuclear cells of the normal guinea-pig. They were first described by Kurloff.[41] These bodies vary considerably in size, are single, paranuclear, and are not readily stained by any dyes except the vital stains and the Romanowsky methods. They stain metachromatically with azur. They may include definite azur granules. Similar structures have been described and figured by Pappenheim[42] in the large lymphocytes or primordial cells of leukæmia. Views as to nature :—

1. They are parasitic (Patella[43]). *Pro*: It has been claimed that flagellate structures have been seen in them by vital staining. The Kurloff body itself has been looked on as a nucleus, the perinuclear halo being the cytoplasm. They are more numerous in animals kept under unhygienic conditions. They are absent from guinea-pigs fed on sterile food.* *Con.*: (*a*) They do not disappear with quinine or atoxyl treatment (Pappenheim[44]); (*b*) Living parasites are not vital-stainable; (*c*) Living parasites stain metachromatically with basic dyes; (*d*) The only azurophile structure in a parasite is the chromatin body; (*e*) Inoculation from one guinea-pig to another does not transmit the "disease."[45]

2. They are secretory.[46] (*a*) They are vital-stainable; (*b*) Basic dyes do not stain them; (*c*) The whole Kurloff body is azurophile; (*d*) The staining is absolutely homogeneous (except when acid fixation has been employed, when an appearance like the retracted colloid in thyroid acini is produced); (*e*) Ciaccio[47] has shown that they come from the nucleoli.

3. That they are giant azur granules formed by fusion of small ones. All transitions have been observed.

* McDonagh regards the "vacuoles" as phases in the life history of a trypanosome. Similar inclusions found in chancres are believed by him to represent phases in the life cycle of the organism of syphilis. (Proc. Roy. Soc. Med. 1912, Dec. 3, p. 85 of Pathological Section).

Variants.—

1. THE LYMPHOCYTOID FORM.—This is met with chiefly in the blood of children, and may be looked on as a juvenile form of monocyte. Its morphology differs from the main type chiefly in the fact that the cell-body is relatively scanty, and the nucleus predominant and rounded. A distinction of less striking character is the greater basophilia of the nucleus, though there is no better differentiation of chromatin than in the type form.

The question has arisen whether this is the same as the lymphoblast of the germ centre. However, they are presumably not identical, because the presence of such a cell in the blood would be pathological *ipso facto*, while the lymphocytoid large mononuclear has been met with by the writer in blood-films from apparently healthy individuals.

2. THE TRANSITIONAL CELL.—This cell appears in the blood-stream form the fifth to the sixth month of fœtal life (Grüneberg[48]). It presents many features in common with the type cell, but its essential feature is the deeply indented nucleus, which has now attained a horse-shoe form in well-marked specimens. The paraplasm remains feebly basophile, no trace of oxyphilia being ever noticeable (distinction from metamyelocyte). The more indent the nucleus, the more intensely does the cell stain with basic dyes. Azur granules are only occasionally seen. Opacity to ultra-violet light is variable (Grawitz[49]).

Isomorphous Cell.—Leucocytoid Rieder-like leucoblast.

This cell-form is regarded as a senile large mononuclear leucocyte.

3. MINIATURE FORMS occur which have the aspect of lymphocytes, but possess an irregular large vesicular nucleus. Azurophile granulation is present.

4. GIANT FORMS, either rich in, or devoid of, azur granules, are described by Ferrata and Pappenheim.[50]

The Differential Diagnosis of the Large Mononuclear Leucocyte.—This has been partly discussed in tabular form on preceding pages. It is convenient to list the similar cells at this stage :—

1. The leucocytoid lymphocyte (see *Fig.* 41).
2. The leucoblast (see *Fig.* 40).
3. The leucoblast without azur granules is similar in all other respects to No. 2.
4. The myelolymphocyte, or myeloic pseudo-lymphocyte, is really a daughter-lymphoidocyte and possesses the distinctive characters of the parent or primordial cell.
5. The lymphoblastic macro-lymphocyte (see *Table, on p.* 32).
6. The leucocytoid form of the preceding is a mere variant, in the existence of a relative abundance of cytoplasm.
7. Irritation forms. Here the chief points are the deep basophilia of the cell-body, the distinct perinuclear halo, and the tendency to radial arrangement of the main chromatin trabeculæ.
8. Promyelocyte. The oxyphilic cell-body and the neutrophile granules are distinctive.
9. Rieder forms. Here the nucleus has marked affinity for basic dyes.
10. Degenerated cells may simulate. Desquamated endothelial cells are 24–52 μ in diameter, have angular edges, and rarely show chromatin structure. The cell-body is very transparent and shows a broad-meshed reticulum. The nucleus is small, oval, and often excentric, having a feeble chromatin reticulum. Vacuoles are present, and metachromatic material may be present (Spadaro[51]).

Paremusoff[52] considered the large mononuclears of malarial blood to be degenerated lymphocytes functioning as pigmentophages.

The Theories as to the Origin of the Large Mononuclear Leucocyte of the Blood-stream.—The various views which have been advanced on this subject are most conveniently expressed in schematic form, using the following abbreviations :—

Poly = polynuclear leucocyte ; l = lymphocyte ; Tr = transitional cell ; L L = large lymphocyte ; L–L = lymphoidocyte ; L M = large mononuclear leucocyte ; L M C = lymphoid marrow cell or myeloblast : My = myelocyte ; Spl = large lymphoid cell of spleen.

a. (i) L M → Tr → Poly (ii) l

b. l → Meso-l → L M → Tr → Poly

c. l → L M → My

d. l → L–L → L M → Tr → Poly
↓ ↗
My

e. (i) L M C → L M (ii) l → L L → leucocytoid L L
↓
My

f. Spl → L M

g. Marchand Cell → L M

(*a*) is Ehrlich's original view, (*b*) is Grawitz's, (*c*) is Weidenreich's, (*d*) is the unitarian view, (*e*) is Ziegler's and Schridde's, (*f*) is Helly's, and (*g*) has been advocated by Pappenheim. The latter writer has tabulated the genetic relations somewhat after the following manner, the cells named on each line being isomorphous :—

h. macrolymphocyte ——→ lymphoidocyte
↓ ↓
monocyte ↓ ↓ leucoblast
↓ ↓ ↓
micromonocyte-microlymphocyte-microlymphoidocyte-microleucoblast ;

and

j. L L → macro-l → L M → Tr

In favour of the last-named views are the arguments used against (*b-d*) and (*e*).

Views (*b–d*), that the cell is of *lymphoid* origin (Jolly, Wolff, Blumenthal, Maximow, Weidenreich, and others). In favour of this is the fact that all the cells of the series have a basophile cytoplasm, azur granules, and nucleoli. Against it are the differences between the large mononuclear and the lymphocyte :—

Large Mononuclear	Small Lymphocyte
Form irregular	Regular
Cytoplasm very basophile ..	Feebly basophile and shows foamy structure
Azur granules very fine	Coarser, spherical, unequal
,, ,, abundant ..	Scanty
,, ,, closely packed ..	Widely separated
Nucleus of irregular shape ..	Even contour
,, stains feebly	Deeply
,, stains uniformly ..	More at periphery than centre

View (*e*), that the cell is *myeloid.* This hangs or falls on the question whether the azur granules are or are not entities, or precursors of neutrophilic granules. The arguments against the theory are :—

1. Every cell in the bone-marrow need not develop neutrophile granules.

2. Increase of large mononuclear cells in the blood bears no constant relation to neutrophilia, while decrease in the total white-cell count, or neutropenia, is not associated with increase or decrease of the monocytes.

3. There is no suggestion of any lympholeucocytes becoming eosinophilic, whereas this would be anticipated from analogy with the myelocytes.

4. Those monocytes found in myeloid tissue which are accepted as precursors of neutrophiles are called promyelocytes.

Another view-point is provided by Jagic,[53] who thought that some myelocytes fail to mature, and gradually lose their granules. Finally entering the blood-stream, they appear as large mononuclears.

(*k*).—That it is derived *from the endothelium* of the blood-vessels or lymphatics (Patella[54]).

The arguments in favour of this view are :—

1. There is an increase of these cells in the course of infections and intoxications (such as typhoid fever, chronic anæmias). In such diseases there is endarteritis and desquamation of endothelium. The amount of mononucleosis is proportional to the degree of intoxication. In such cases, tags of endothelial cells may occur in pathological blood.

2. Massage of the limbs is followed by mononucleosis.

3. It is present in chorea.

4. Rats are regarded by Patella as very active animals, and he considers that that is why their blood is so rich in large mononuclear cells.[55]

5. The morphological features of the cell. It is sometimes polygonal in contour, and shows relics of the cement substance when stained with silver nitrate. It is frequently deformed. The edges are frequently wrinkled.[56] There is a lamellar structure as if the cell had shrivelled since its detachment from its neighbours. The Kurloff bodies so frequent in these cells in the guinea-pig are evidences that degeneration has commenced. The nucleus possesses the same characters as that of normal arterial endothelium (senile form). Amitotic changes are always noticed whenever mononucleosis is marked, indicating proliferation as well as desquamation

of the endothelium. The autolytic changes which are undergone by the blood-cell are similar to those undergone by the epithelial cell.[57]

6. Their undisputed occurrence in pleural and peritoneal effusions.

The arguments against the view are as follows (Ferrata[58]) :—

1. A dead cell could not be a phagocyte.

2. It is not likely that one out of every ten white cells is a " cadaver " (Carpi[59]).

3. The proportion of these cells in the blood is constant. This would be quite unlikely if they were desquamating cells.

4. Large mononuclear leucocytes are not increased in old persons, and may occur in cases where there can be no disease of the vessel walls (Frumkin[60]).

5. Specific increase of the large mononuclears (monocytosis) due to chemotaxis cannot be due to alterations in the vessel walls.

6. True endothelial cells have quite distinctive characters (Marchiafava).

7. The irregularity of the shape of the cell and the laminated appearance are errors of technique.*

8. The Kurloff bodies in these cells are developmental changes of an azurophile secretion, and indicate progressive evolution. The nucleus is retracting, as in all ageing cells.

9. It is not accepted by reputed hæmatologists (Ferrata).*

The following questions may be asked : What *does* become of shed endothelium ? Such cells must break down, die, and be desquamated at some time. Why should *every* large mononuclear leucocyte be a genuine blood-cell ? Could one really distinguish desquamated endothelium from a lympholeucocyte ? If serosal endothelial cells are so common in pleural and peritoneal exudates, why should not one or two vascular endothelial cells occasionally occur in the circulating blood also ?

Answers to these questions may show that the endothelioid cells of Patella do actually occur in the blood-film, although they are not to be confused with the true monocyte.

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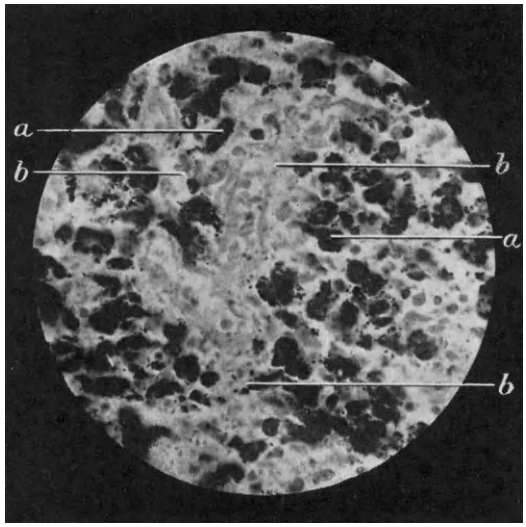
* Questionable arguments.



" The immense phagocytic cells with inclusions of inert matter are well seen " (p. 183).

Fig. 42.—PHAGOCYTOSIS IN LYMPH-CHANNEL OF A LYMPH-NODE. (*a*), endothelial cells containing black flakes and granules (carbon); (*b*), vascular channels separating the cell-groups. (Oc. 2, Zeiss Oil-immersion).

Face p. 183]

The Birth of the Cells into the Blood-stream.—There is little to be said under this heading. Granted that the majority of these cells come from the pulpar tissues, there are no laws apparent determining how many or which individuals shall be swept from their nesting-places at any given time. It must, however, be assumed that their natural habitat is in the capillary recesses, where the stream is slow.

The Functions of the Large Mononuclear Cell.—The lymphatic monocyte is best regarded as a unicellular organism endowed with motility, tactile sensibility towards cells and protozoa, and secretory and digestive functions (macrocytase).

The rate of movement is sluggish, and the pseudopodia are short and slender—properties which allow them to make their way through the capillary wall into the surrounding tissue spaces.

The power of phagocytosis was classically demonstrated[61] by injecting goose red-cells into the peritoneal cavity of a guinea-pig, after which the leucocytes were found to be apposed to them, subsequently taking them up and dissolving them, the nucleus being the last part of the red cell to disappear. The surface of contact between the leucocyte and the foreign particle is made as large as possible by means of the pseudopodia. The phenomenon is best seen in the tissue spaces, and specially well in the lymphatic channels of the lymph-nodes and spleen. The immense phagocytic cells with inclusions of inert matter are well seen in the anthracotic gland (the cells are here called pigmentophages).* Thus in the accompanying figure (*Fig.* 42) is shown a portion of such a channel as seen with the high power. Further, similar cells can be demonstrated to take up the Koch bacillus, the leprosy bacillus, and the spirillum of Obermeier. They destroy the muscular fibres in muscular atrophy and the dead nerve-cells in cerebral softening. They absorb pigment in malaria. The digestive ferment possessed by these cells is called macrocytase, which only passes into the blood itself after the cell has been destroyed. It is questionable whether the macrophage is related to Ehrlich's complement or to

* The same cells in the mesenteric nodes fix the fat absorbed from the intestine.

his amboceptor, but it is of interest to note that mononucleosis is a striking feature of all those infections which leave permanent immunity behind them—scarlet fever, enteric; also in measles (Bergel[62]).

The question of phagocytosis does not require further discussion owing to the well-known character of the phenomenon.

The existence of other functions might be indicated from a consideration of the causes of *numerical variations in the blood*. It proves, however, that though many diseases exist in which monocytosis or monopenia occurs, very little relation can be detected between them.

The normal content is represented by the following figures: up to 5 per cent of the total white-cell count according to Rieux,[63] 5–10 per cent according to other observers. This gives 240–400 per cubic millimetre.

In the newly-born they number over 15 per cent. They appear in the blood from the fifth month of fœtal life (Grünsky[48]).

Causes of increase (monocytosis):—

1. Fasting (Penny[64]).

2. Acute infections (gangrenous appendicitis, pneumonia, at the end of typhoid fever, small-pox, scarlet fever, after the tenth day of rubeola, acute lymphæmia).*

3. Chronic diseases: malaria, hepatic (dysenteric) abscess; tuberculosis; epithelioma; symptomatic anæmia, rickets, v. Jaksch's anæmia; cardio-vascular disease (Schifone[65]); leprosy with nerve lesions.

4. As an effect of certain drugs: pilocarpine, tuberculin, iodine (Lortol-Jacob), arsenic (Besredka), quinine (Bill).

Causes of decrease (monopenia):—

This is most noticeable in progressive pernicious anæmia (absolute loss in the terminal stages); chronic splenomegalies (including Banti's disease). Leukæmias.

Chemical Characters.—Reference to the existence of specific *ferments* has been considered sufficient. Macrocytase, a tryptic

* The cells in this disease are, however, pathological, and are not strictly classifiable in this list.

ferment; lipase, similar to that of the lymphocyte; and oxydase (Winkler-Schultze granules) have been met with.

The *azur granules* met with in this order of cells have excited much discussion among hæmatologists. On the one hand there is the inclination to look upon these particular granules as identical rather with the neutrophile granule of the polynuclear leucocyte than with the azur granule of the lymphocyte or leucocytoid lymphocyte, and therefore the substrates for the oxydase reaction. The grounds for the belief are:

1. That cells lymphoid according to Romanowsky staining may show neutrophile granulation with triacid.

2. That the granules disappear from leucoblasts as the cell becomes oxyphile and the specific granulation matures.

3. The monocytes found in leukæmia contain granules stainable with triacid.

The objections to the view, on the other hand, are:

1. That Romanowsky does not stain immature neutrophile granulation at all well, because the basophilia of the cell-body masks it. A cell may thus appear lymphoid and yet belong to the true myeloic series (answer to argument 1).

2. Neutrophile granules may exist side by side with azur granules.

3. The leukæmic monocytes are not lymphatic—are not lympholeucocytes (answer to argument 3).

4. Azur granulation of the monocyte is a particular kind of material unlike that of either the lymphocyte or the myeloblast, because: (*a*) Its staining reaction is different; (*b*) The granules are larger.

5. Pappenheim found azur granules in monocytes of animals which have no neutrophile leucocytes at all (amphibia, e.g.).

Intracellular Origin of the Azur Granule.—Hynek[66] suggested that the azur granule was a detached fragment of the nuclear substance, a chromidial displacement, upon which the azur material deposits, just as a fragment of organic matter might form the nucleus of a prostatic calculus. He believed that the neutrophile granule was deposited over the azurophile matter, rendering the latter invisible. Pappenheim considers that the effusion of

chromidial substance disappears in the leucoblastic monocytes as the neutrophile granules appear, being only evidence of a certain functional state of the cell.

A network of azurophile nodes also occurs in the cell-bodies of carcinoma-cells and in plasma-cells. Nay, more, every cell may show these granules if carefully studied, because azurophilia, in the opinion of the observer quoted, is merely a biological sign post of the existence of metabolic interchange between cell-plasm and nucleus.

The existence of lipoid granules was established for the cell under consideration by Ciaccio.[67]

Comparative Cytology of the Large Mononuclear Leucocyte.—The large mononuclear leucocyte appears to be widely distributed, appearing as it does in the blood of all animals in which blood-cells can be detected. The formative organs are not always easily identified. In the crustaceans, mysis for instance, there is a structure in the dorsal cephalic region of the cephalothorax,[68] in relation to the stomach, formed of groups of cells separated by fibrillæ. Division actively takes place in these clusters.

According to the researches of Metchnikoff,[61] the existence of a functionally similar cell appears to go very far back in the animal scale. The mesenchymal tissue of the lowest invertebrates includes cells which play the part of phagocytes, and are in every way analogous to the large mononuclear leucocyte of man. The presence of foreign bodies in the tissues of such animals, for instance, leads to the congregation of mesenchymal cells around the particle. A certain degree of selection is noticeable as to which foreign body is to be regarded as available for food, and which not. The classical investigations on actinia, showing the part played by these mesenchymal cells in the life-history of those metazoa, are of interest in this connection.

In some of the fish[69] the tissue analogous to the spleen is embedded in the substance of the kidney. Thus, the carp derives its large mononuclear leucocytes from such a renal tissue. In sharks a definite formative organ exists, which gives rise to numbers of macrophages. Teleosteans show definite pulpar tissue, and the vaguely suggested Malpighian bodies are found to be full of phagocytes.

While large mononuclears are met with in the spleen of triton (a newt), the main function consists in erythrolysis, and the follicles disappear from the organ as age progresses. In this animal Mestral[70] noted a remarkable periodicity of activity of blood-destruction, the organ being very vascular at one time, and ischæmic at others.

Even in amphibia there is no definite association between the splenic tissue and monocytogenesis (Maximow[71]), but in birds in the embryonic period it has been noticed by Jolly[72] that a period arises in which large mononuclears appear, apparently as a transitional stage in a myeloid metaplasia with final neutrophile leucocyte formation.

The morphological characters of this class of cells when traced through the animal scale, also show several features of interest. In the first place there is no parallelism between differentiation of the blood-cell formula and the scale according to evolution.

In some of the fish the large mononuclears do duty for the mammalian polynuclear leucocyte, while in amphibia and reptiles they appear to play the same part as the macrophages of the higher vertebrates, and while polymorphonuclear cells are absent, eosinophiles are an important feature of the blood.

In carassius[73] there are three forms of lympholeucocyte—a vacuolated form, with feebly basophile cytoplasm and excentrically-situated nucleus ; a basophile form, with a nucleus of rather polymorphous shape containing two nucleoli ; and a myeloblastic form, with a nucleus presenting features in common with those of the myeloblast.

The cell is usually conspicuously large in the tinca, leuciscus, and anguilla. In the perch it shows a well-marked astrosphere. In the cod, the cell-body is relatively large, and the nucleus is tucked in one corner of the cell. The cytoplasm shows a faintly-webbed structure.

Speaking broadly, there are two forms of lympholeucocyte in the fish—one which is feebly basophile, and the other amphochromatic. Werzberg believes the last-named to be the precursors of the granulocyte in these vertebrates.

In the amphibia the blood appears less differentiated than in the fish, and the lympholeucocytes are rather numerous. Some of them show an oxyphile cytoplasm. Azur granules are frequently noticed (especially bombinator). An astrosphere is described as present in many instances. The lympholeucocytes of the frog vary in size, and have a characteristic marking of the cytoplasm. The nucleus stains feebly, and is almost like the lymphoidocyte in structure.

As met with in the reptiles, they are found to have peculiar nuclear markings, owing to the presence of small angular discrete spots having a staining reaction like nucleoli (so-called pyrenoid marking). Some of the cells have a feebly basophile cytoplasm, and such forms contain either reniform nuclei (tortoise, lizard), or horseshoe forms (grass-snake, ophiosaurus), or polymorphous nuclei (lacerta, anolis). Others have a feebly amphophile cell-body, apparently a later stage than the preceding.

In the chameleon these cells are unusually large. In acanthodactylus there is a form of lympholeucocyte whose cytoplasm is mottled with azurophile marking. In agama some of the cells show a well-marked astrosphere.

In the birds the lympholeucocytes have a feebly basophile cytoplasm, which is usually almost filled with the rounded nucleus, whose structure is myelocytar rather than lymphocytar. Occasionally indentations are met with, and a clear perinuclear halo may be made out. Such cells were found in the blood of the Senegal finch by Hirschfeld-Kossmann.[74] Kasarinoff[75] found that administration of hæmolytic poisons led to the appearance of *pathological* monocytes in the blood.

The Fate of the Large Mononuclear Leucocyte.—As has been shown, the function of the cell-form under consideration is best exerted in those parts of the body where the circulation is specially slow. It may be, therefore, that its occurrence in the blood is more of secondary interest, and its fate—in relation to the blood-stream—may be nothing more than immigration into the honeycombed recesses of the pulpar tissues. In these situations it is enabled to exercise its powers of sluggish movement incidental to the absorption of particles with much greater facility than can be possible in the rapidly-flowing blood of the main channels. Having become detached from the trabecular network, it is swept along by the blood-current to the pulpar tissue of some other part of the body, much as a mollusc which had loosened itself from a rock might be washed away to a far-off part of the coast. It is accordingly more satisfactory to discuss the fate of the cell under the heading of the pulpar cell itself.

The ultimate conversion of this cell-form into *a transitional cell* has already been considered, and it has been pointed out that this stage represents the end-product of the particular line of development. The transitional cell may presumably pass through *catabolic changes* culminating in its disappearance as an entity, but of such phenomena we have no certain data. The lamellation of the edges, the formation of pedunculated buds of cytoplasm, loss of round contour, scattering of chromatin towards the edges of the cell, are all to be seen in blood-films from time to time.

The change into the so-called *irritation-cell* may also be noted at this point. The essential feature of this change is the great increase of basophilia of the cell-body.

After *passing back into the tissue-spaces* the cell may settle down again, and undergo any of the cytoplasias presently to be described. In making this statement, it is assumed that the returning monocyte manifests the phenomena discernible in relation to the pulpar cell. Ceasing to be locomobile in the perivascular spaces, it gives rise to other cell-forms, provided that the necessary stimuli to cytoplasia be present.

III.—THE PULPAR CELL AND ITS CYTOPLASIAS.

THE morphology of the pulpar cell—It is a multi-potential cell—Its relation to the lymphoid follicles and to myeloid metaplasia—Genetic inter-relations—Chart representing these, and summarizing the essential features of the biology of the cells referred to in this and the preceding chapter.

WERE the term splenocyte a correct one to apply to the large mononuclear leucocyte of the blood-stream, its development would be conveniently described as a splenoblastic line of development. As has been seen, however, it is misleading to take up the subject in that manner, and it becomes more effective to discuss the pulpar cell in a general sense, and regard the circulating monocyte as less important than the (relatively) sessile cell.

The pulpar cell may be looked on as the mother cell of the monocytar forms, the pulpar tissue being the factory or birth-place (and perhaps also the cemetery) of these organisms.

The embryology of the pulpar tissue is rather of secondary importance. The spleen-cells proper are carrying on the same work in the adult as they do in later embryonic life, save that there is some erythropoiesis in the embryo.

The Morphology of the Pulpar Cell.—The pulpar cell is of variable size, measuring up to about 20 μ in diameter. It has a relatively large *cell-body*, and a large nucleus whose structure is ill-defined and feebly basophile (*Plate VI*). The cell-body itself is occasionally granular, some of these being azur and others phenolphilic. The former vary somewhat in size according to the type of cell, since there is a difference between myeloic azur granules and lymphatic azur granulation. The cell-body is basophile to a varying extent, especially at its periphery.

Nucleus.—This varies in type, being usually lymphoidocytar, and includes one or two nucleoli. The structure is delicate or leptochromatic, owing to the absence of nodal intersections (in film preparations) and the feeble distinction between chromatin and parachromatin. In other examples the nucleus possesses characters which stamp it as lymphoblastic ; these have already been described.

EXPLANATION OF PLATE VI.

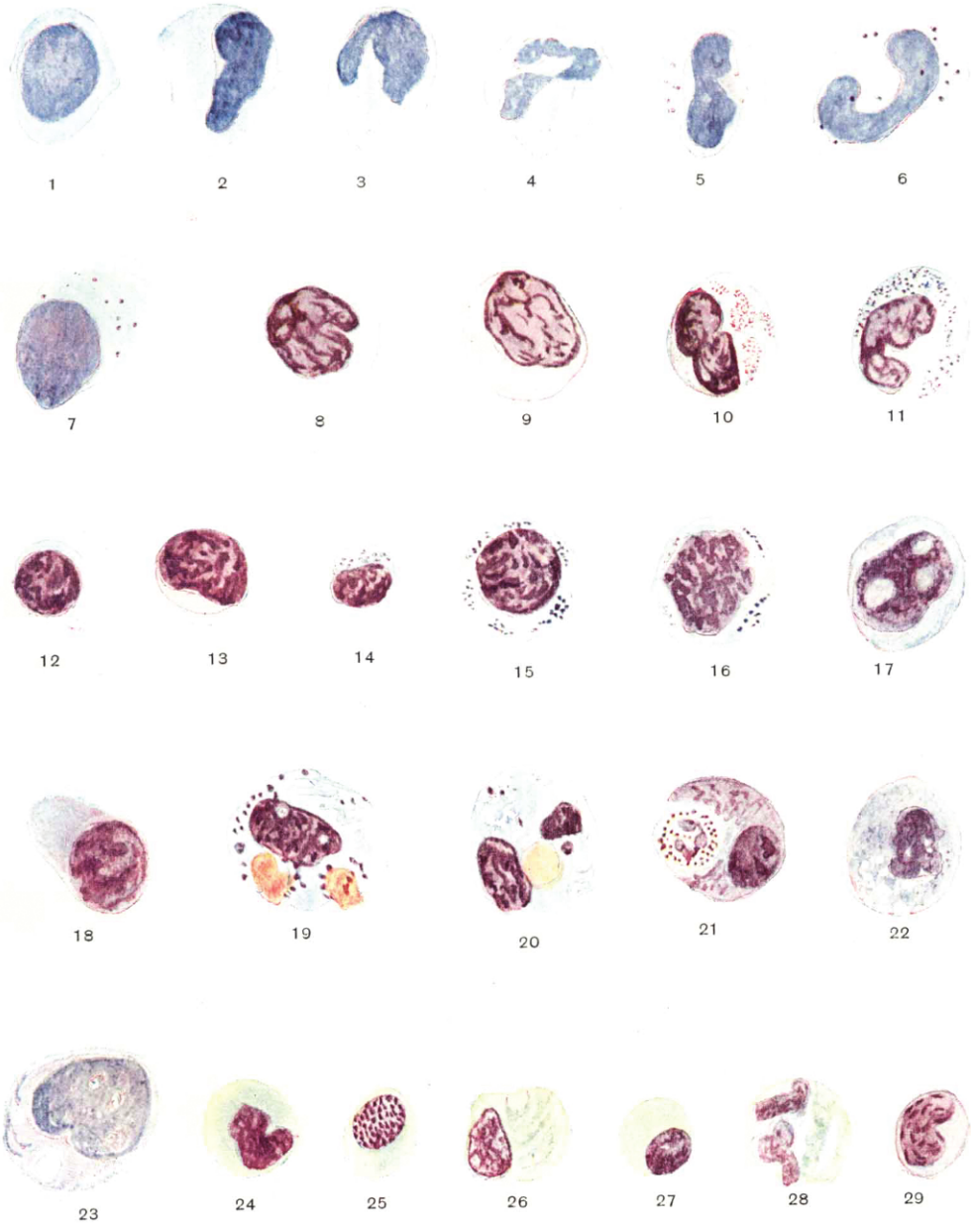
1.—Juvenile large mononuclear leucoctye, after Benjamin (Fol. hæm. Bd. vii., *Plate IV*). 2-5.—Various forms of splenic pulpar cell (Splenic film from a case of ruptured aneurysm). 6.—Transitional cell with azur granules; a senile form of large mononuclear. 7.—Leucocytoid large mononuclear leucocyte with azur granules. (This and preceding, after Benjamin). 8, 9.—Large mononuclear leucocytes from human blood. 10.—Transitional cell. 11.—Polynuclear monocyte—metamyelocyte without neutrophile granules. 12-14.—Follicular lymphocytes from the spleen. 15, 16.—Lymphoidocytar splenic cells, showing coarse myeloic azur granulation. 17.—Typical lymphoidocyte from the splenic pulp. 18.—Plasmoid form of splenic microlymphoidocyte. 19, 20.—Erythrophages, phagoctyic leucoblasts. 20.—Nucleophage. 21.—Macrophage of spleen containing polynuclear cell (8-21 after Paremusoff, Fol. hæm. Bd. xii., *Plates VIII-X*). 22.—Degenerate form of pulpar cell (vacuoles in cell-body and nucleus) from a splenic film in a case of typhoid fever; dying pulpar cell. 23-29.—Large mononuclear leucocytes (lympholeucocytes) from lower animals (23-28 from Werzberg, Fol. hæm. Bd. xi., 29 from Kasarinoff, Fol. hæm. Bd. x.). 23.—Salamandra maculosa. 24.—Rana temporaria. 25.—Emys lutaria. 26.—Lacerta viridis. 27.—Gadus lota. 28.—Anguilla vulgaris. 29.—Fowl.

Stain, "Panoptic" throughout, except 7, which is "Jenner."

Magnification, oil-immersion, oc 18.

PLATE VI.

THE LARGE MONONUCLEAR LEUCOCYTE



Biology of Blood-cells *O. C. Gruner*

Nucleolus.—More than one, occupying varying positions in the cell, and possessing the usual chemical characters of such bodies.

Mitosis is easily observed in tissue-sections.

Variations According to Age.—The varying amount of cell-body possessed by these cells enables them to be classed as juvenile (so-called naked forms), adult, and senile forms. The latter have a relatively large cell-body (" endothelioid aspect "). This classification is in accordance with Heidenhain's law.

The main interest of the pulpar cell lies in the cytometaplastic properties possessed by it. As has been indicated, it may pass along lines which tend to culminate in polynuclear leucocytes, or, far more usually, along lines which culminate in the transitional cell of the blood-stream. It is, then, the cytometaplasias that need to be referred to in studying this cell.

It may be assumed that in the first instance the pulpar cell is really a wandering cell, derived, like all other blood-cells, from perithelium or adventitial cells of capillaries. At certain times the wandering cell becomes stationary, ceases to possess phagocytic properties, and submits to the influences which changes in composition of the surrounding medium exerted upon it. In place of migration from point to point within the pulp-cords, it *settles down as an essentially multipotential or indifferent cell.*

1. It undergoes intranuclear changes, and divides, and gives rise to a progeny of lymphoid character, possessing active phagocytic properties, swept into the lymph- or blood-stream as large mononuclear leucocytes.*

2. It acquires nuclear characters which place it with the lymphoblasts of the central parts of Malpighian follicles. After one or two generations, a true lymphoblast† appears, able to give rise to clusters of large lymphocytes in the neighbourhood of the main vessels. The fate of such a process lies in the ultimate exhaustion of proliferative activity and disappearance of the follicle. The exact reason for this almost certainly lies in the advent of malign

* This explains their appearance in the lymph of the thoracic duct and in the splenic vein.

† So-called lymphoblastic macrolymphocyte. The real nature of this cell was established by the researches of Paremsusoff[76] in working on laboratory animals. He observed phagocytic properties in this cell similar to those seen in undoubtedly lymphatic cells.

influences from without, since paucity of follicular tissue in the spleen, in autopsy material, is noticed specially in association with other evidences of bacterial infection (e.g. bacillus aerogenes capsulatus, *Fig.* 43).

3. It acquires nuclear characters which indicate leucoblastic change. This phenomenon may be very conspicuous, or instances of such change may be only occasional. The former type of case is spoken of as " myeloid metaplasia " (*Fig.* 44), and is frequently noticed under the influence of certain bacterial infections (typhoid, diphtheria, etc.). It is worthy of note that this leucoblastic or myelopoietic tendency is only persisted in up to a certain point. Anti-auxetic influences appear to exist which prevent differentiation from proceeding further than the metamyelocyte stage of development. This phenomenon will be discussed later. The significance of the process may lie in an attempt by the organism to supply more antibodies than the paralyzed bone-marrow can afford.*

The genetic relations of the pulpar cell to the other cells of the spleen are more clearly indicated in chart form. Part of the subject has been included with the chart of lymphopoiesis (*Plate III*), but the chart on the opposite page, representing the inter-relations between follicles and pulpar tissue, expresses the various points more clearly.

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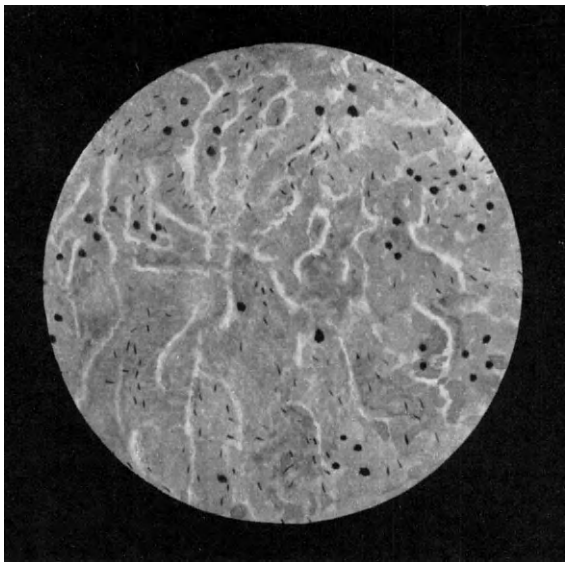
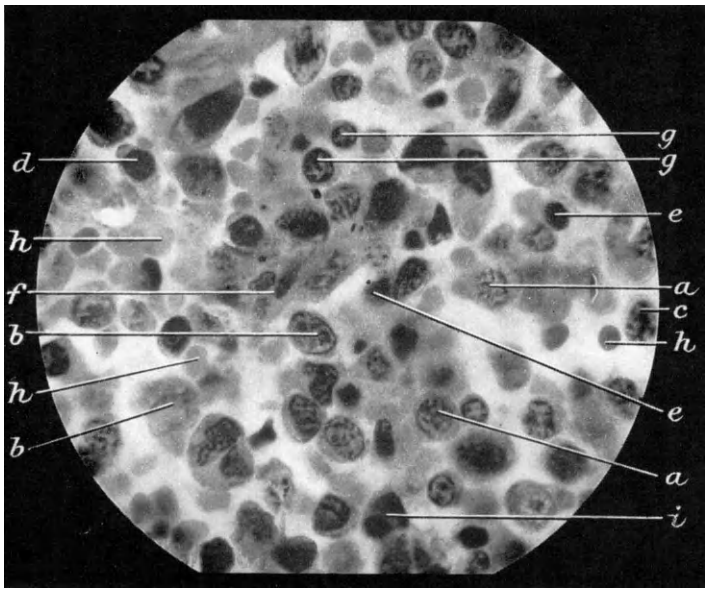
* Hæmopoiesis. The formation of erythrocytes by the spleen occurs in the human embryo during the interval between the fourth and fifth days (Lifschitz[77]), after which date the process gradually ceases. Megakaryocytes increase in number during this period. From this time onward the pulp tissue is myeloid in character, and spleen films appear exactly like marrow films.



" . . . paucity of follicular tissue of the spleen is noticed in association with bacterial infection " (p. 192).

Fig. 43.—SPLENIC TISSUE IN A CASE OF DEATH FROM INFECTION BY BACILLUS AEROGENES CAPSULATUS. The drawing shows almost complete necrosis of the tissue, the dark round spots being the only spleen cells left intact. Distinction between follicles and pulp is entirely lost. Innumerable bacilli crowd the field.

(Oc. 12, Zeiss Apochrom. 4 mm.).



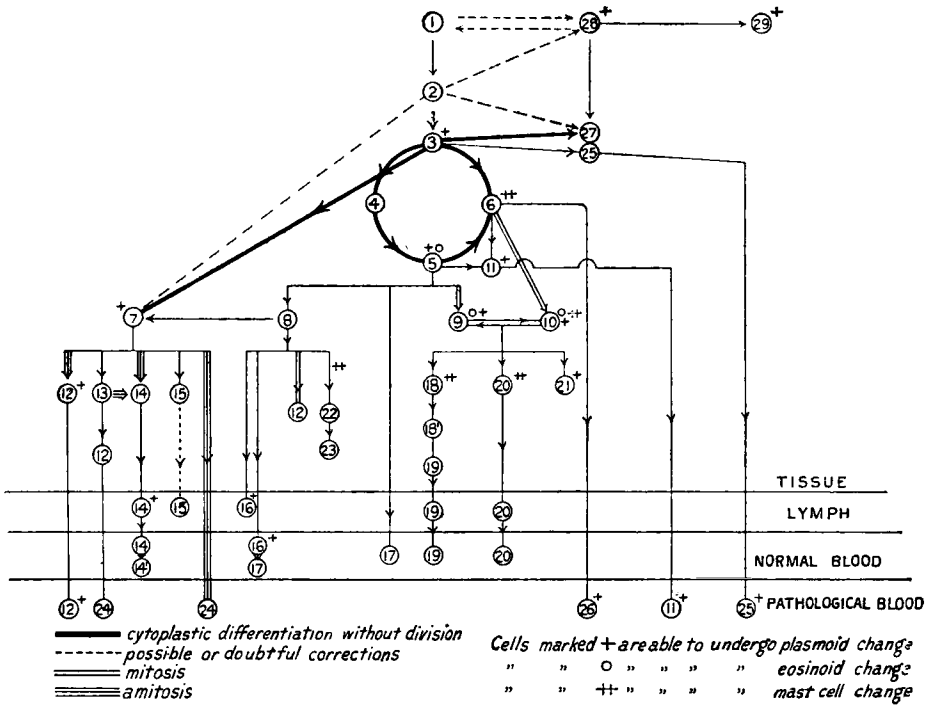
" Leucoblastic change is frequently noticed under the influence of certain bacterial infections (typhoid, diphtheria, etc.) " p. 192.

Fig. 44.—SPLENIC PULP IN A STATE OF MYELOID METAPLASIA. (*a*) myelocyte; (*b*) metamyelocyte; (*c*) lymphoblastic cell; (*d*) mesolymphocyte; (*e*) microlymphocyte; (*f*) polynuclear leucocyte; (*g*) normoblast; (*h*) red cell; (*i*) dividing plasmoid cell.

(Oc. 12, Zeiss Oil-immersion).

Face p. 192]

Fig. 45.—Chart representing Inter-relations between Follicles and Pulpar Tissue.



Explanation of Chart.

1.—Resting perithelial cell. 2.—Wandering cell of Saxer (pyrrhol cell). 3.—Lymphoidocyte. 4.—Lymphoprimitive cell. 5.—Splenic pulpar cell. 6.—Leucoblast. 7.—Lymphoblastic macrolymphocyte. 8.—Interfollicular cell. 9.—Micro-lymphoidocyte. 10.—Microleucoblast. 11.—Monocytoid macrophage. 12.—Lymphoma cell. 13.—Meso-lymphocyte. 14.—Microlymphocyte; 14′.—Leucocytoid microlymphocyte. 15.—Schridde-Hodara plasma cell. 16.—Large mononuclear leucocyte. 17.—Transitional cell. 18.—Promyelocytar eosinophile cell; 18′.—α-micromyelocyte. 19.—Eosinophile cell. 20.—Mast cell. 21.—Senile leucoblast. 22.—Plasma cell. 23.—Older plasma cell. 24.—Lymphæmic lymphocyte. 25.—Rieder cell. 26.—Leukæmic monocytoid leucoblast. 27.—Megakaryocyte. 28.—Stroma cell. 29.—Fibroblast.

CHAPTER V.

ON THE NEUTROPHILE LEUCOCYTE.

Section I.—THE BONE-MARROW AS A WHITE CELL FACTORY: The seat of manufacture of the neutrophile leucocyte—Graphic representation of varying states of activity of the marrow-tissue—Metabolic changes in the adipose tissue of the bone-marrow—Autolytic changes—Metabolism in the bone-marrow cells—Accessory factories of leucopoiesis.

Section II.—THE LIFE-HISTORY OF THE NEUTROPHILE LEUCOCYTE UP TO THE TIME OF ITS BIRTH INTO THE BLOOD-STREAM: Morphology of the cells of the myeloic series—Morphology of the leucoblast—The myeloblast—The promyelocyte—The myelocyte—The metamyelocyte—The leucoblastic line of development—Pappenheim's scheme—List of the cells normal to the blood and of those pathological to the blood—The birth of the neutrophile leucocyte into the blood-stream.

Section III.—THE LIFE-HISTORY OF THE NEUTROPHILE LEUCOCYTE IN THE BLOOD-STREAM: The morphological characters of the cell—Arneth's system—Schilling's modification—The functions of the cell—Chemical characters—The granules: neutrophilic, iodophilic, sudanophilic, phenolphilic, oxydase, myeloic azur—Theories relating to the nature of these granules—Ferments—Extractives—The death of the leucocyte—Phenomena in the cytoplasm, and in the nucleus—The comparative cytology of the neutrophile leucocyte.

Section IV.—THE CYTOPLASIAS OF THE LEUCOPOIETIC TISSUES. Leucocytosis: principles in white-cell counting; causes of leucocytosis; the phases of leucocytosis—Leucopenia—The hyperplastic and metaplastic processes of leucopoietic tissues: contrast between leukæmia and leucocytosis; auxetic processes.

I.—BONE-MARROW AS A WHITE-CELL FACTORY.

THE seat of manufacture of the neutrophile leucocyte—Graphic representation of varying states of activity of the marrow-tissue—Metabolic changes in the adipose tissue of the bone-marrow—Autolytic changes—Metabolism in the bone-marrow cells—Accessory factories of leucopoiesis

A DESCRIPTION has already been given of the structure of the bone-marrow in relation to erythropoiesis. It was pointed out that this tissue is built up round vascular channels which vary in size with variations in functional activity. As Virchow[1] expressed it, the marrow tissue is a persistent quasi-embryonic granulation tissue. The distribution of the arteries through the bone is well described by Carnegie Dickson[2] (1908), who points out that the medullary artery of the shaft usually divides into two main divisions passing to each end of the bone. They become more and more central in position, and give off radial branches on their course. Accompanying the central artery is a large very thin-walled sinus, draining blood from numerous radial tributaries, which form free anastomoses with one another, and appear to form communications with the lymphatic spaces adjoining the marrow-cells. The opinion has been expressed that the leucoblastic cells are outside the capillary channels, while the red-cell-forming cells are intravascular, but there is no very definite evidence in favour of this supposition.

The only difference in the structure of the marrow in different parts of the same bone lies in the relative preponderance of vascular channels in the central parts of the shaft and the relatively increased density of the connective-tissue reticulum towards the periphery or endosteum. It will be borne in mind that in man, the bony trabeculæ are so apt to pass through the whole thickness of the bone that a distinction into zones (mapped out by Carnegie Dickson) fails to have much importance.

As with the pulpar tissue, so with the marrow tissue, the theatre of action of hæmopoiesis may be easily defined in terms of a microscopic field, such as was shown in *Fig.* 17. This would be some distance away from the centre of a marrow-space, where the

blood-vessels are relatively more numerous than formative cells. Were the marrow-cells washed out, we should see a delicate reticular tissue formed of branching connective-tissue cells and fibrils, intermingled with the fat-cells already referred to.

In other words, we have to deal with a fatty areolar tissue, amongst the meshes of which are more or less densely packed free-

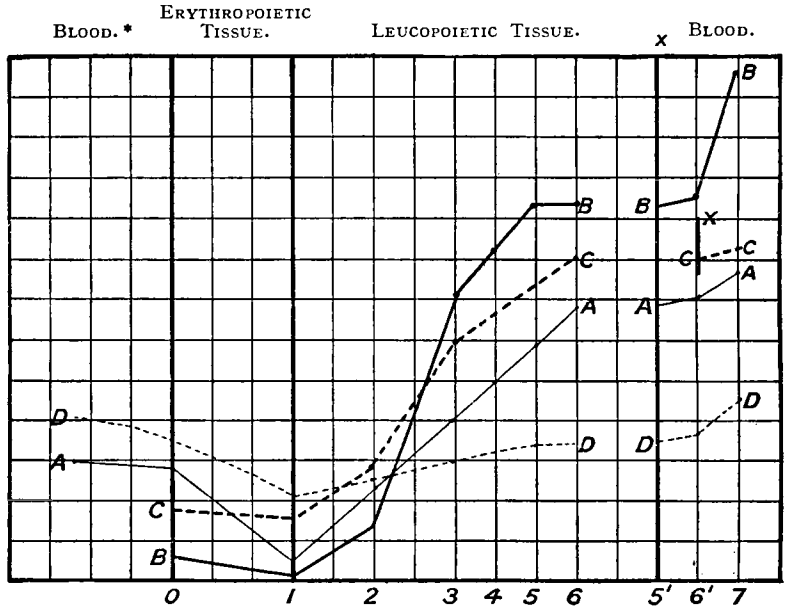


Fig. 46.—Graphic record of the cell-formula of the bone-marrow under different conditions, selected from the writer's collection. *A*, Normal infant. *B*, Case of ulcerating carcinoma, with blood neutrophilia. *C*, Case of typhoid fever with leucopenia. *D*, Case of appendix pyæmia with moderate leucocytosis.

1, Mother cell. *2*, Leucoblast. *3*, Daughter leucoblast. *4*, Promyelocyte. *5*, *5'*, Myelocyte. *6*, *6'*, Metamyelocyte. *7*, Neutrophile leucocyte. *0*, Erythroblast.

* Erythroblasts *only* represented.

floating cells of very various sizes and shapes. As was stated in dealing with the red-cell factory, these cells belong to two orders—the red-cell-forming and the white-cell-forming, which are only identifiable when the tissue is examined with a very high power of the microscope. The broad points of distinction between these specific or proper marrow cells were indicated in connection with the red-cell parents, and their exact morphology is described in the

ensuing section of this chapter. The various members of the white-cell-forming group do not always occur in the same proportions, but it is found possible to classify a given marrow tissue according to the preponderance of one or other of these cells. If smears be made from the marrow at autopsy, or during life (Ghedini-puncture of the tibia, for instance), and a differential count made, a cell-formula for the tissue may be drawn up, and used to make a graphic record somewhat in the manner shown in the figure opposite (*Fig.* 46). Here the length of the first ordinate represents the percentage of mother cells in the film, that of the second represents the percentage of leucoblasts, *the abscissa being here made to commence at the apex of the first ordinate.* The third point is found in the same manner, and represents the percentage of cells belonging to the next stage of development. The other points are marked in as explained in the figure, till finally we come to a vertical line (x), which represents the barrier between tissue and blood-stream, and allows a demonstration of the relation between white-cell manufacture and neutrophile output. If the blood contains metamyelocytes, for instance, the vertical line would require to be placed more to the left in order that the blood-cell formula should include these immature cells. In such a case we have an example of Arneth's " deviation to the left."

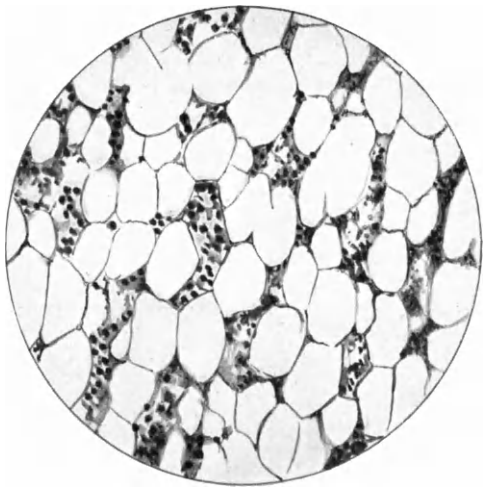
The figure shows four curves which demonstrate the effect on the marrow produced by infective agents of varying intensity or by certain forms of disease, the curve for the infant's marrow serving as a standard. The latter, rising as it does, regularly and continuously (i.e., a straight line), strikingly demonstrates the regular output of maturing cells into the marrow tissue. The curve D, on the other hand, taken from a case of appendix pyæmia, shows hardly any ascent of the line at all, while the height of ordinate 1 indicates the preponderance of parent cells in the tissue. Even the blood in this case shows only a moderate degree of leucocytosis—evidently the result of inadequacy on the part of the bone-marrow to supply the need for leucocytes in the affected areas of the body.

The presence of *adipose tissue* is an important feature of the marrow. It constitutes a variable packing material, the absorption

of which allows space for increased proliferative activity of the proper cells, while diminished activity on their part is responded to by an increase in the size of the fat cells (*Fig.* 47). Probably we have before us a co-ordinated action between the two types of tissue, the agent which causes alterations of metabolism on the side of the adipose cells also calling forth an alteration in the formative activity of the blood-cell parents. According to Maximow,[1] the fat cells of the bone-marrow are really fibroblasts. C. E. Walker,[3] working with axolotl, found that the purpose of some of the bone-marrow cells was merely to subserve the nutrition of other cells. A second group pass through many mitotic divisions to give rise to generations of cells characterized by possessing only half the number of somatic chromosomes, and ultimately form the red cells. A third group, he thought, were fertilized by conjugation, and after dividing a number of times, produced the white cells.

Metabolic Changes in the Adipose Tissue of the Bone-marrow.—The phenomena observed by Ciaccio[4] may be summarized as follows: (1) Fragmentation of the fat-globule into two or more smaller fragments; (2) An actual chemical transformation of the fat into a soluble derivative; (3) The passage of this transformed fat across the lipoid-containing cuticle of the adipose cell, with (4) The deposit of protein substances in the vicinity of the cuticle; (5) The replacement of the cell-substance of the fat-cell. The protein substances which are deposited are lipoid compounds exhibiting the property of staining with certain aniline dyes. They are soluble in feebly alkaline solutions, but not in water, alcohol, ether, chloroform, or acids (either acetic or mineral).

Autolytic Changes in the Bone-marrow.—These are of considerable importance, and have been studied by preserving the marrow in a moist chamber for several days, and examining it at intervals.[5] Within three days' time, it is found that the interstitial tissue undergoes a gelatinous change, and is associated with lack of definition of the marrow-cells. The latter lose their granules, and the nuclear matter stains uniformly, without any visible differentiation of structure. As days pass on, the cells become less and less numerous, granules become entirely absent, and the nuclei

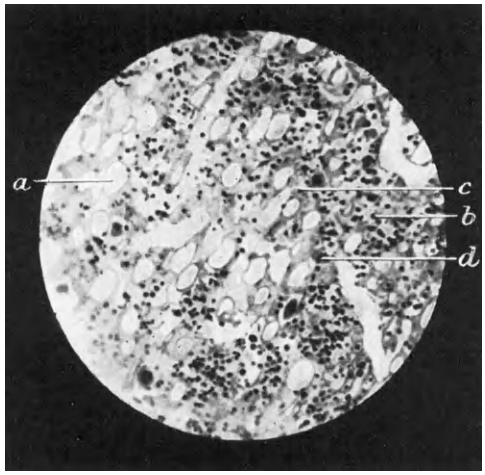


". . . diminished activity on their part" (the proper marrow cells) "is responded to by an increase in the size of the fat cells" (p. 198).

Fig. 47.—ATROPHIC MARROW. The photograph shows much larger spaces, with much fewer cells between them than are noticed in *Fig.* 17.

(Oc. 4, Zeiss, Obj. D),

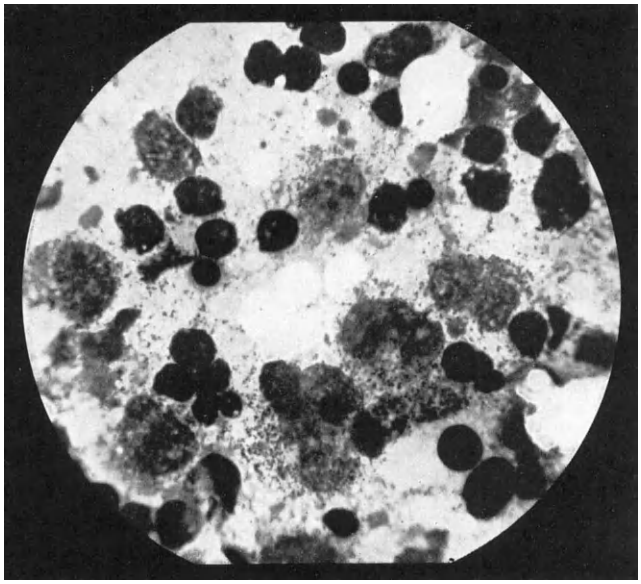
Face p. 198



" The changes . . characteristic of gelatinous degeneration " (p. 199).

Fig. 48.—" The fat spaces " (*a*) " are normal in number, but the interstitial tissue between them is changed, having lost many of the specific cells " (*b*) " and acquired a hyaline appearance " (*c*); (*d*) megakaryocytes.

(Oc. 4, Obj. Apochrom.)



". . . The field is seen to be flooded with granules from the breaking-down cells " (p. 199).

Fig. 49.—The various forms of marrow cell are here seen in various stages of degeneration. Contrast with *Figs.* 50, 51.

(Oc. 18, Zeiss Oil immersion.)

become fragmented, pass through an intermediate stage of hyperchromatosis, and disappear. The changes are complete in about twelve days, and the picture is then similar to that characteristic of gelatinous degeneration (*Fig.* 48), met with especially in cases of inanition from any cause, a fact which indicates that this change is the result of autolytic ferments becoming liberated in such individuals, from one factor or another.*

These phenomena strongly recall others which are sometimes noted in autopsies on the human subject. Routine examination of this material has shown the striking fact that sudden death occurring in the course of obscure affections[6] without marked or gross lesions, is sometimes associated with marked autolytic changes in the marrow tissue (*Fig.* 49). In this case, the field is seen to be flooded with granules from the breaking-down cells; many of the granules are neutrophile, but the majority are azurophile granules from the leucoblasts and lymphoidocytar cells. It appears as if such a change, occurring during the last hours of life, might precipitate a fatal result from sheer liberation of complement or other immune substances in excess of margins of safety, aided to the extreme by entire stoppage of red- and white-cell production.

Lucibelli[7] found that similar changes in the rabbit bone-marrow are induced by fatal injections of typhoid, colon, and paratyphoid bacilli (loss of staining power of cell, swelling of nucleus, irregular distribution of chromatin, folding of the nuclear membrane, karyolysis). Changes analogous to these were described by Longcope in cases of experimental staphylococcic infection.[8]

Metabolism in the Bone-marrow Cells.—Just as the fatty tissue of the bone-marrow presents variations of metabolic activity which are recognizable by the aid of histological methods, so the blood-forming cells can be demonstrated to undergo metabolic changes which are chiefly manifested by variations of the

* In *gelatinous degeneration* the fat spaces are normal in number, but the interstitia tissue between them is changed, having lost many of the specific cells and acquired a hyaline appearance. The change may be focal or diffuse, and may be associated with atrophy of the cancellous bone, or may occur as an almost imperceptible change amongst the fine-meshed trabeculæ of a rather ossified marrow cavity. It may or may not be associated with disseminated foci of formative or fatty marrow. This form is not identifiable in film preparations. It occurs in diseases associated with starvation, prolonged diarrhœa, carcinoma, or prolonged cases of suppuration. Foa, in 1905, found that the normal blood-serum of other species of animals would have the same effect on the marrow.

lecithin content. Ciaccio[9] noticed that a lecithin-nucleo-proteid compound is abundant in these cells, and therefore called them cellules lipo-proteo-boliques. The deposition of such material, which is derived from the nucleus, is anabolic in character. As the lecithin increases in amount, material comes to be at hand which is necessary for the development of the myeloid cells into a granulocyte progeny—a fact which throws light on the ultimate nature of the agent clinically responsible for an increase or inhibition of a leuco-blastic reaction in the marrow.

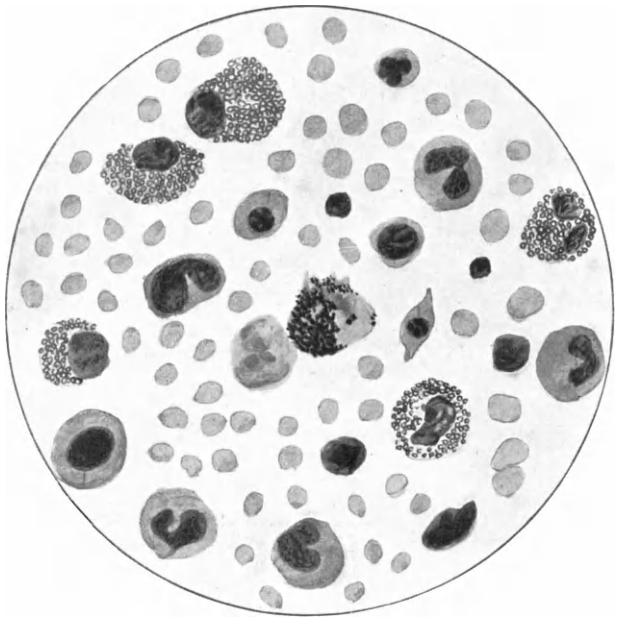
These points must be appreciated in order to understand correctly what is going on in the bone-marrow at any given time. The cells are sometimes resting and sometimes active, just as are the gland-cells of a secretory organ. When resting, the cytoplasm is ill-defined because of the accumulation within it of metabolic (anabolic) products, whereas the active cell contains pigment débris, etc., and has a smaller nucleus.

A further feature of the metabolic process lies in the appearance of oxydase ferment within the cells. This is connected physically with the nucleo-proteid constituents of the cell, although it cannot be said to be dependent on such a material, because lymphocytes do not contain oxydative ferment, and yet the nucleins are identical.[10]

While the most obvious effects of metabolic processes on morphology are most satisfactorily demonstrated when dealing with the development of erythrocytes, a similar sequence of visible changes may be traced in connection with the myeloid series of cells.* The passage of material from the nucleus into the cell-body and its transformation in this new position into other substances, account for alterations of nuclear structure, just as the passage of material out of the nucleus of the normoblast leads to the loss of parachromatin, condensation of chromatin, and the formation of a very deeply stainable shrivelled polymorphous or "pycnotic" nucleus.

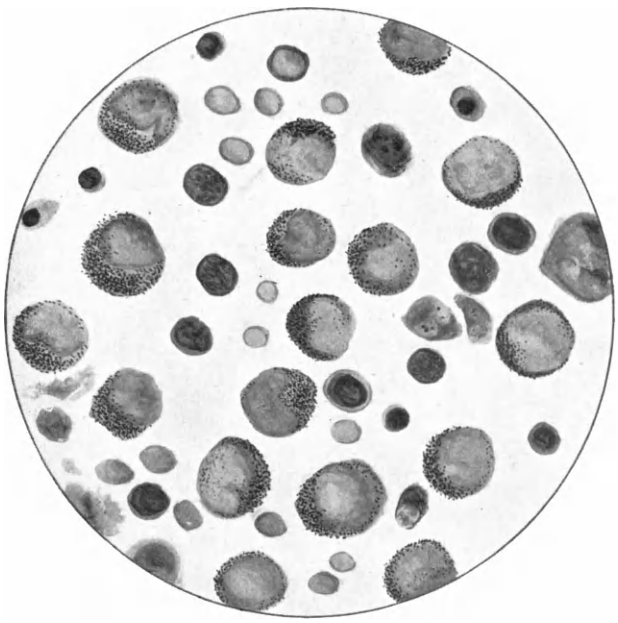
It is further helpful to remember that the cells are subjected to different stimuli even during the course of a physiological process,

* The term myeloid is conveniently applied to the group whose terminal stages are cumbered with the name polymorphonuclear leucocyte.



"The formative cells are seen to be of various types (p. 45).

Fig. 50.—MARROW FILM.—Marrow leucocytes, seen with the oil-immersion. There are five eosinophilic myelocytes, one basophilic myelocyte, four nucleated reds (one pycnotic), two free nuclei, and six metamyelocytes. Numerous red corpuscles and a few indifferent marrow lymphocytes lie in the field.



". . . a leucoblastic reaction in the marrow" (p. 200).

Fig. 51.—MARROW FILM.—The prevailing cell-form is a myelocyte with fine neutrophile granulation. Note also the uninuclear indifferent marrow cells.

Face p. 200]

and that the phenomena of cellular metaplasia arise in this way. As has been the theme in previous chapters, alterations of metabolism leading to deviations from the original line of development are the explanation of a condition of metaplasia in the cell, which is manifested in the tissue as a whole by the formation of a number of cells of a type different from that usually seen. Whereas in the spleen it is more usual to find the splenoblastic line followed to its extreme, so in the bone-marrow, the myeloblastic line (the one natural to that tissue) is usually followed. Accordingly, metaplastic change in the former comes to be manifested in what is termed myeloid metaplasia, whilst in the latter the metaplastic change is recognizable as a lymphadenoid change—to instance isolated examples.

Again, it does not follow that bone-marrow, left to itself, is always likely to produce erythrocytes and myeloid cells in just proportions. Everything, or much, depends on the presence of a suitable incoming stimulus. If myeloid cells are to be continuously produced, there must be a myeloplastic stimulus (a hormone) always available, just as the brain would cease to be conscious if it were not continuously receiving sensory stimuli from without. It is only by a conception of this kind that the remarkable suddenness of leukæmia can be intelligible. Nevertheless, we cannot shift the responsibility of successful myelogenesis entirely upon incoming stimuli; an internal predisposition to differentiate on such lines must be assumed. The phylogeny may be to a certain extent predetermined.

The effect of such a simple agent as absence of food is instructive in this connection. *During fasting*, the myelocytes are more abundant than polynuclear leucocytes;[11] but after taking in of food, the reverse holds good—the tissue becomes very vascular, intermediate or transitional forms between myelocytes and neutrophiles become very numerous, and the myelocytes inconspicuous. The megakaryocytes remain unaltered, save for the occurrence of included neutrophile leucocytes.

X-rays have been found to produce a disappearance of fat from the adipose cells, concomitantly with a marked hyperplasia of the leucoblastic formative cells. Not only is the absolute number

of myelocytes increased and abundance of mitotic figures noticeable, but the number of mature leucocytes in the tissue is very strikingly augmented. Eosinophile and mast-cell types also become inconspicuous.[12]

Accessory Factories of Leucopoiesis.—Bone with marrow spaces in it has been described as arising anew in certain of the internal organs. Thus Bilamioni found an inclusion in the lower lobe of a rabbit's lung related to the pulmonary artery. He considered the finding as evidence of the possibility of embolism of hæmopoietic tissue into the spleen, etc., from other organs. Other observers have found new bone arising in the kidney and other viscera. Such new marrow-tissue must, however, be looked upon as an anomaly, as there is no collateral evidence that it is performing a necessary part in the economy.

II.—THE LIFE-HISTORY OF THE NEUTROPHILE LEUCOCYTE UP TO THE TIME OF ITS BIRTH INTO THE BLOOD-STREAM.

MORPHOLOGY of the cells of the myeloic series—Morphology of the leucoblast—The myeloblast—The promyelocyte—The myelocyte—The metamyelocyte—The leucoblastic line of development—Pappenheim's scheme—List of the cells normal to the blood and of those pathological to the blood—The birth of the neutrophile leucocyte into the blood-stream.

Morphology of the Cells of the Myeloic Series.—The cells of the myeloic series are conveniently considered in the order of their development. Since all these cells are studied in film preparations of the marrow, their description will be found to cover that of the parenchymal cells of marrow-tissue as they appear with the oil-immersion lens. It is convenient to divide these cells into groups according as they possess specific granules or not. The former are immediately concerned with the birth of the leucocyte, the latter are more remote ancestors.

The *parent cell*, or *lymphoidocyte*, has already been dealt with at length (*Chap. I*), and it has been pointed out that it exists in two forms—the macro- and the microlymphoidocyte. In each case the nucleus is extremely finely meshed, and apparently finely granular in structure, while one or more nucleoli are constant (*Fig.* 52). A senile change in such cells, whereby the cell body becomes enlarged and the nucleus relatively smaller, is not a usual finding, and if noticed—whether in the tissue film or in leukæmic blood—may be looked on as pathological. Similar remarks may be applied to forms with deeply indented and polymorphous nuclei, or Rieder forms.

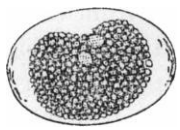


Fig. 52.
Diagram of structure of the lymphoidocyte.

Morphology of the Leucoblast.—The only other myeloid cells which may have no granules are the *leucoblasts*, already referred to as "leucoblastic monocytes," and these cells present the following morphology (*Fig.* 40).—

Shape—oval.

Size—large.

Cell-body.—Strongly basophile in reaction, the basophilia being uniform throughout. There is definite fibrillation of structure, especially towards the edge, which is accordingly rather ill-defined. The paraplasm is definitely oxyphile, and contains numerous azur granules of myeloic type. The more oxyphile the cell becomes the more amphochromophile does it appear (contrast with the polychromatophilia of the erythroblast).

Nucleus.—Round, indent, or polymorphous in shape. The structure is typical. The chromatin threads are not as broad as the parachromatin, and the appearance of transverse bands forms an easy means of identification. A circumnuclear zone is often absent, but an astrosphere is usually easily identified.

Nucleoli are absent.

The daughter generation of the leucoblast is called the MICRO-LEUCOBLAST. This cell also has a basophile cytoplasm, though the basophilia is less in degree. The paraplasm is oxyphile. This cell is analogous to the microlymphoidocyte, like it being of smaller size than the parent.

Sometimes an intermediate form can be distinguished—the MESOLEUCOBLAST, whose cytoplasm is pale blue and rather rich in spongioplasm. The nucleus is slightly indented and shows very distinct transverse shadowing. The only other respect in which it differs from the leucoblast is in point of size.

It is possible to subdivide the leucoblasts into as many groups again, according as they contain azur granules or not—it being always remembered that the mere presence or absence of such does not create a new cell, but merely indicates the existence of a certain state of functional activity. If the findings referred to in connection with lymphocytes hold good here also, we should assume that the leucoblasts without azur granules are probably younger than those with them. The azur granules are coarse, more numerous, and more uniformly scattered through the cell-body than holds in the case of lymphoid cells, and are of a bluish-violet colour.[13]

As seen in sections, the leucoblast appears to have rather a

vesicular amblychromatic nucleus, and contains one to three nucleoli. Some of the "indifferent marrow-cells" are leucoblasts.

With increasing age, the leucoblast conforms to the same law as is found in the case of the other blood-cells. It is possible to divide each of the six forms of leucoblast into as many more by classifying them into mature and senile (leucocytoid) forms. The senile forms are characterized by a relatively abundant cytoplasm. Pathologically, the senile change may be carried so far that we have actually a polymorphonuclear leucoblast, which only differs from the normal mature neutrophile leucocyte in possessing no neutrophile granules. Ordinarily, the *fate of the leucoblast* is to differentiate into a promyelocyte.

Differential Diagnosis.—Since promyelocytes may show very few, if any, specific neutrophile granules (the distinctive feature being solely a decided oxyphilia of cytoplasm), they are liable to be erroneously classified with the non-granular cells (azur granules do not count). It is possible, however, to avoid confusing the cells by noting the structure of the nucleus. If this be myelocytar in type, the cells would be correctly placed.

The Myeloblast.—This cell was so named by Naegeli, being regarded by him as the ancestor of the polynuclear leucocyte alone. The invention of the term "lymphoblast," on the other hand, led to the discussion of the identity or not of these two cells. The difference between the two has been referred to as indefinite (*Chap. I*), though emphasized by the dualists. The myeloblast of Naegeli does not actually correspond to the leucoblast of Pappenheim, but includes two kinds of cells which are really different generations of the primordial cell.

Further confusion has arisen in that different authors use the word "myeloblast" to express different cells. Thus Helly[14] came to the conclusion that the myeloblast was really the parent of red cells, at any rate in post-embryonic life, because: (1) Myeloblasts are very densely aggregated round erythroblast foci in cases of severe anæmia, instead of lying loose in the reticular tissue; (2) The conditions met with in leukæmia are no criterion, because they are entirely pathological. The answers to these statements are: (*a*) That Helly's myeloblast is not the same as Naegeli's; (*b*) The red-cell parent has a trachychromatic nucleus, while the myeloid parent has an amblychromatic nucleus; (*c*) There is a protometrocyte present in selacians which gives rise to cells with amblychromatic nuclei at one time, and cells with trachychromatic nuclei at another, and has no lipoid substances within its body.[15]

The characters of the myeloblast, as given by Naegeli, are (*Fig.* 12) :—

Shape, oval.

Cell-body very basophile, devoid of granules. Cytoplasm has a foamy structure.

Nucleus oval, and nearly as large as the cell-body, rich in chromatin, which has a delicate structure and is limited by a delicate nuclear membrane. There are no azur or fuchsinophile granules. Three or four *nucleoli* can be seen. Mitotic figures are extremely rare.

The myeloblast of Schridde, as seen in the tissues, differs rather from the above, but chiefly in being occupied by pigment granules or leucocytes till it reaches a diameter of 20–40 μ. Tsunota states that it is frequently seen in inflamed appendix tissue.[16]

The Promyelocyte.—The next stage of development of the leucoblast is the promyelocyte. This is the immediate precursor of the myelocyte, and is characterized chiefly by the halfway condition of its cytoplasm in the direction of oxyphilia, and the first appearance within its body of neutrophilic granules. These appear as very fine punctations in the vicinity of the astrosphere, which is pushed aside as they accumulate,[18] while the nucleus becomes richer in chromatin and the nucleolus diminishes in size (*Fig.* 53).

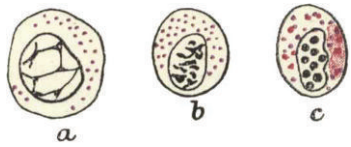


Fig. 53.—*a*, promyelocyte; *b*, *c*, myelocytes showing varying nuclear markings. Note the commencing oxyphilia (pink stippling), and the azur granules (pink) in the promyelocyte.

The cell is smaller than the leucoblast, but the other characters need not be detailed. Variants of this cell also occur, just as holds in the case of the preceding cells—senile change, undue polymorphism of nucleus, degenerative changes. Undue polymorphism of nucleus gives rise to the appearance of an immature or precocious polynuclear leucocyte, whose cell-body is only incompletely oxyphile. Such a cell is liable to be mistaken for a pycnotic megaloblast or for a true leucocyte.

A MICROPROMYELOCYTE has been described, which has an amphochromophile cell-body, with an indented trachychromatic pachychromatic nucleus. Myeloic azur granulation is still present.

The promyelocyte is a preponderant cell, according to Lossen,[17] in the marrow of children affected with bronchopneumonia, tuberculosis, and measles; in such cases the neutrophiles are diminished.

The Myelocyte.—Further differentiation of the cell converts the promyelocyte into the myelocyte, a cell well known to hæmatology owing to its characteristic presence in leukæmic blood. Until recent times it has been looked on almost as the only form of abnormal cell that could occur in the blood-stream. The characters of the (mother) myelocyte are (*Fig.* 53) :—

Shape.—Rounded or ovoid.

Size.—10–20 μ.

Cell-body.—Shows only a trace of basophilia. There is a finely reticular structure. Oxyphile or neutrophile granules have appeared, and lie chiefly towards the periphery of the cell. An astrosphere is plainly seen in some examples.

Nucleus.—Large, round, or oval, or slightly indented. There is a well-defined nuclear network, forming bands alternating with parachromatin. The nuclear membrane is sharply marked off.

Nucleolus absent.

Appearances with Vital Staining (*Plate VII.*, 54-62).—The nucleus remains hardly coloured so long as the cell lives, but a variable number of dancing blue particles can be seen in the cell-body.

Functions.—Phagocytic, when not mitosing or differentiating.*

Fate of the Myelocyte.—The natural sequence of changes which take place in the myelocyte is that which leads to its conversion into a metamyelocyte. The proof that myelocytes are precursors of neutrophiles lies in the absence of lesions anywhere else than among these cells in cases of infective leucocytosis; also the fact that drugs which set up leucocytosis (bitters, ethereal oils, camphor, blood poisons, etc.) also lead to the same phenomena in the bone-marrow.

This cell may undergo senile change, coming to have a relatively

* That they are not locomobile, and cannot make their way through the blood-vessels in the same manner as polynuclear leucocytes, is shown in the observation that only polynuclear leucocytes enter the suppurating focus when inflammation with pus formation occurs in the course of leukæmia. In new-born infants, too, the inflammatory cell infiltration never contains myelocytes, although such cells are present in the blood at that time of life.[20]

small nucleus, but ordinarily its tendency is towards polymorphism of the latter, and the production first of a metamyelocyte, and ultimately a true neutrophile leucocyte. Under abnormal influences, however, *degenerative changes* may appear, which may be summarized as follows : (1) Condensation of the chromatin into small masses situated immediately within the nuclear membrane ; (2) Swelling and vacuolation of the nucleus ; (3) Diffusion of the chromatin from the nucleus into the cell-body, with ill-definition of the nucleus ; (4) Rupture of the nuclear membrane, with disappearance of the nuclear matter; (5) Swelling of the cytoplasm, with increased staining reaction of the spongioplasm, so that the cell body appears more granular ; (6) Vacuolation of the cell-body, spaces of variable size appearing. The later the change the larger the vacuoles, until finally only a skeleton of the cell remains ; (7) Complete fragmentation of the cells.[19]

Although the myelocyte does not appear in the blood-stream until it has differentiated into a neutrophile leucocyte, there are circumstances which lead to its premature entry into the circulation : (1) In association with polynucleosis occurring in infections, notably diphtheria: the bone-marrow is then hyperplastic and hyperæmic ; (2) In association with anæmias, notably pernicious anæmia, von Jaksch's anæmia, syphilis, rickets, anæmia from neoplasm ; (3) Without associated changes in the differential count in uræmia, acute mania, and in diseases with an asphyxial condition of the blood ; (4) During the course of pregnancy (Blumenthal[22]).

Jagic's suggestion[23] that some myelocytes cease to differentiate, but gradually lose their granules and finally enter the blood as large mononuclear leucocytes, may be dismissed as quite improbable.

Multiplication without Differentiation.—A smaller form of myelocyte was described by Pappenheim, and named micromyelocyte by him. The characters of this cell resemble those of the parent, the distinction lying in the size of the cell.

The Metamyelocyte.—This is a further stage of development of the myelocyte or micromyelocyte. Its characters are easily defined, as it resembles the transitional cell already described, save that it has an oxyphile cell-body and bright neutrophilic granules

scattered through its substance. The nucleus stains more strongly and shows characteristic chromatin markings.

Atypical forms, however, have been described: (*a*) Forms with a basophile cytoplasm, producing a close resemblance to the transitional cell; (*b*) With an oxyphile cell-body but no specific granules; (*c*) Dwarf forms; (*d*) Eosinophile forms, when found, may perhaps be only functional variants from the main type. There are reasons for looking on all eosinophiles as variants.

The Leucoblastic Line of Development.—Starting with the primoroial cell, the changes which take place in it may be described according to the same plan already adopted for the other series. The primordial cell is multivalent. This strongly basophile cell, with a large rounded nucleus, whose markings are characteristic, and may or may not present azur granules, undergoes a nuclear change which impresses on it the characters of the leucoblast. Here the markings of the nucleus are those peculiar to the myelocyte: transverse shadowing becoming more and more intense until the shades appear as deeply-staining streaks or lines. This cell divides and gives rise to the promyelocyte, where a commencing acidophilia of the cell-body becomes discernible, and a few scattered neutrophile granules begin to appear side by side with the azur granules (when such are present).

The promyelocyte may differentiate with or without division. The succeeding stage is a myelocyte which either divides or merely differentiates into the metamyelocyte and then into the familar neutrophile leucocyte.

Blumenthal[24] believes that most of the phenomena noticeable within the myelocyte nucleus during its evolution into polynuclears are explicable as the result of: (1) Osmotic influences; (2) Increasing deposition of granules within the cell-body. The more granules, the more incurved does the nucleus become, until, little by little, the polynuclearity is assumed. Once the leucocyte reaches the blood, the difference of osmotic pressure in the serum from that in the marrow-tissue allows some plasmolysis to occur, and deformity of the nucleus results. This would *explain the paucity with which polynuclears are met with in the marrow-tissue itself.* The very means of entry of the myelocytar cell into the blood-channel is

explained on physical principles by Errera[25] as a surface-tension phenomenon; the change of chemical structure acting on one part of the leucocyte causes it to throw out a pseudopodium through the demarcating membrane, and so attracts it into the correct direction.

The natural line of development, then, is along the successive stages dealt with in this section. We find, however, that differentiation may become inhibited at any time, so that leucocytoid forms of any type may come to be an end-point of development. Pathological polymorphosis of the nucleus without other signs of maturity manifests the existence of influences adverse to normal differentiation, and gives rise to a bizarre picture of the tissue under consideration.

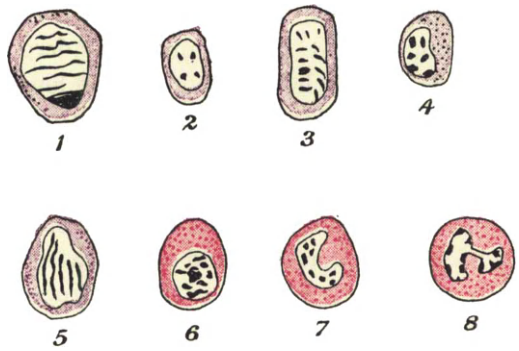
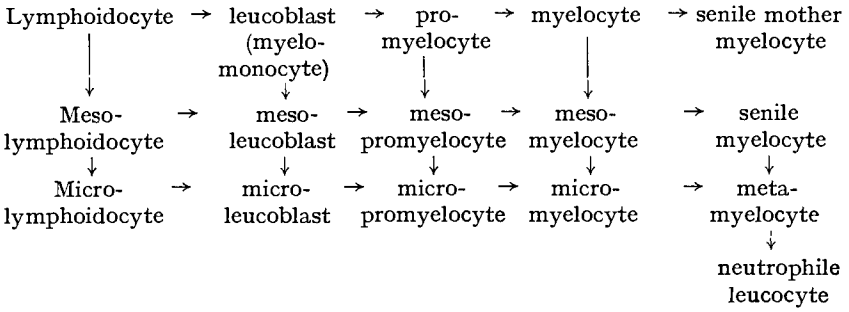
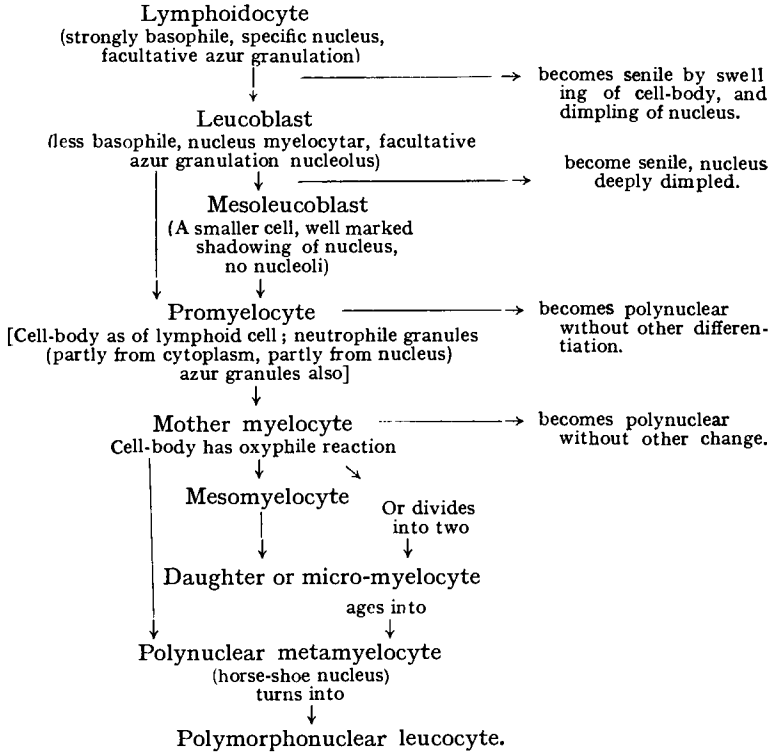


Fig. 54.—DIAGRAM REPRESENTING SOME OF THE CELLS OF THE MYELOIC SERIES. (*1*) Myeloblast; (*2*) Micromyeloblast; (*3*) Mesoleucoblast; (*4*) Microleucoblast; (*5*) Myelomonocyte; (*6*) Micromyelocyte; (*7*) Metamyelocyte; (*8*) Polynuclear leucocyte. The purple stippling indicates basophilia of cell-body, the pink stippling indicates definite oxyphilia of cell-body. The varying nuclear markings show certain types encountered; they are purposely drawn distinctly, whereas in the actual nuclei they appear as shadowings. The black dots represent azur granules, the red ones neutrophile granules.

Pappenheim's Scheme of the Development of the Neutrophile Leucocyte is as follows :—



Or, demonstrating the metamorphoses taking place at the same time:—



At this stage it will be convenient to tabulate the cells which are normal, and those which are only found pathologically, in the circulating blood.

Cells Strictly Normal to the Blood.—

Neutrophile polynuclears.
Eosinophile polynuclears (different forms).

Facultatively Normal.—

Neutrophile metamyelocytes.

Cells Pathological to the Blood.—

A. VARIANTS OF THE MATURE CELL—

Degenerative forms:—

Fatty neutrophiles.*
Caryorrhectic forms (with 5 or more segments).
Vacuolated forms.

---

* Detected with Sudan III. Seen in septic inflammations.

Neutrophiles with altered staining reaction of the granules or nuclei.
Unduly fragile neutrophiles (easily damaged in making films).

Atypical forms:—
Polynuclear cells with granules but basophile cell-body.
Non-granular polynuclears with oxyphile cell-body.*
Dwarf forms.
Giant forms (seen in inflammatory leucocytosis).†

B. CELLS NORMAL TO THE LEUCOPOIETIC TISSUE, BUT NOT DESTINED TO ENTER THE BLOOD-STREAM.—

Lymphoidocyte.
Leucoblast.
Neutrophile promyelocyte.
Eosinophile promyelocyte.
Neutrophile (mother) myelocyte.
Eosinophile (mother) myelocyte.
Neutrophile metamyelocyte.
Eosinophile metamyelocyte.
Giant neutrophile polynuclear (10–12 μ in diameter).
Giant eosinophile cell with active amœboid and phagocytic properties.

C. CELLS USUALLY CONFINED TO THE LEUCOBLASTIC TISSUE, BUT ENTIRELY ATYPICAL.—

Lymphoidocyte with Rieder nucleus.
Polynuclear leucoblast (basophile, non-granular, polynuclear).
Non-granular myelocytes with oxyphile cell-body.
Dwarf myelocytes.
Metamyelocytes with basophile cytoplasm.
Polynuclear macromyelocytes: cells like the lymphoidocyte, but having a definitely polymorphous nucleus, and containing specific granules.
Hybrid cells: with both eosinophile and mast-cell granules:‡
(*a*). Mast cells with eosinophile granulation as well.
(*b*). Eosinophile cells with mast granulation as well.
(*c*). True bastards.

The Birth of the Neutrophile Leucocyte into the Blood-stream.—Reference has already been made to the suggestions of Blumenthal and Errera, to the effect that the mechanism of the liberation of these cells into the blood-stream is largely physical in nature. On the other hand, the known migratory power renders the phenomenon less difficult to understand. The actual factors which bring about the migration at this stage, and not earlier in the prenatal life-history, are, however, completely unknown to us.

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* Seen in myeloid chloroleukæmia (Helly).

† These are presumably derived from pro- or myelocyte forms by nuclear differentiation, and not from the micro-promyelocyte forms.

‡ Seen in myeloleukæmic blood-cells. See also under eosinophile cells.

III.—THE LIFE-CYCLE OF THE BLOOD-MATURE LEUCOCYTE.

THE morphological characters of the cell—Arneth's system; Schilling's modification—The functions of the cell—Chemical characters: the granules: neutrophilic, iodophilic, sudanophilic, phenolphilic, oxydase, myeloic azur—Theories relating to the nature of these granules: ferments; extractives—The death of the leucocyte—Phenomena in the cytoplasm, and in the nucleus—The comparative cytology of the neutrophile leucocyte.

The Morphological Characters of the Neutrophile Leucocyte are as follows :—

Size.—10–12 μ.

Shape.—Spherical when at rest, polymorphous when in motion.

Cell-body.—Strikingly oxyphile in reaction. Relatively abundant, but spongioplasm not conspicuous. A centrosome is present. Heidenhain[26] believed that the centrosome was formed of the radii of force tending to bring the astrosphere into the centre of the cell.

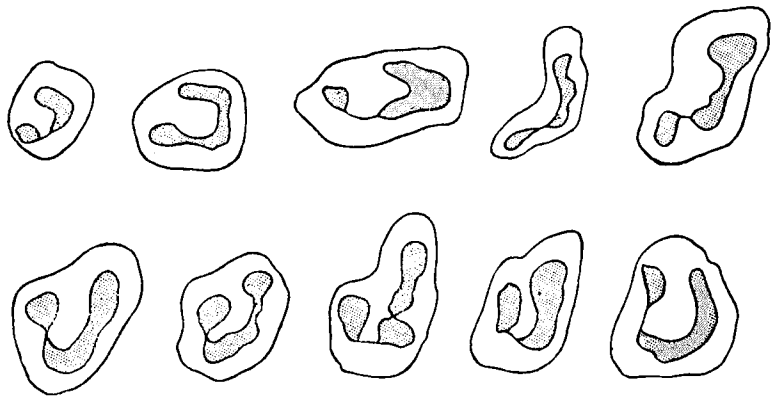


Fig. 55.—LEUCOCYTES SHOWING AMŒBOID MOVEMENT (after Brugsch and Schilling).

Granules.—The cell-body is loaded with the specific granules, which are chiefly congregated towards the periphery of the cell, and are scanty in the perinuclear zone. They are more clearly demonstrated by triacid than by Giemsa. Azur granules are absent.

Nucleus.—The shape of the nucleus is polymorphous. It is

rich in chromatin, and poor in parachromatin, following the usua rule of condensation with progressive maturation.

Nucleolus.—Absent.

The characters of the nucleus are not necessarily fixed ; they may even vary from hour to hour. Neumann[27] considered that abnormal stimuli might cause a restriction of movement of the leucocyte with resultant retraction to a spherical or lymphocyte form, just as the latter does not exhibit amœboid properties while circulating, but appears to do so under certain other conditions. On the other hand, the functional as well as the nuclear differences between the lymphocyte and the polynuclear, render this idea of changing morphology rather unlikely. Researches by Brugsch and Schilling[28] on the nuclear changes in this cell as seen by dark-ground illumination show that the lobation does not alter fundamentally whatever be the change of shape of the cell-body in the course of the amœboid movements. More precisely, the *type* of the lobation does not change (*Fig.* 55) ; segments do not turn into bridges, or vice versa. However attenuated the nucleus may become, it will not show such slender bridges as to simulate the filamentous interlobar connections characteristic of bi-, tri-, quadri-, and multi-partite nuclei. The writers quoted are inclined to believe the contrary to what has been stated above, but their drawings do not entirely bear them out.

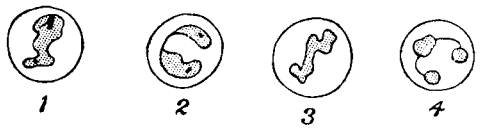


Fig. 56.—NEUTROPHILES FROM A CASE OF ACUTE PNEUMONIA (after Brugsch and Schilling). Diagrammatic drawing to show the varying nuclear form. (*1*) Neutrophile with rod-shaped thick nucleus (acute pneumonia) ; (*2*) Neutrophile with bisegmented thick nucleus ; (*3*) Neutrophile with rod-shaped slender nucleus ; (*4*) Neutrophile with tri-segmented slender nucleus. The first two are young cells, the last two old.

The filamentous change with the polynuclear leucocyte has been regarded by Deetjen[29] as evidence of amitosis, though this view is not accepted by Brugsch and Schilling, because they aver that such appearances can be induced at will by over-heating the preparation. In that event, the number of segments in the nucleus does not *per se* decide the age of the cell ; they only indicate the effect of opportunities of more or less vigorous amœboid activity. The age of the cell may, however, be deduced by noticing the actual bulk of the nuclear matter. In the accompanying figure (*Fig.* 56), for instance, the younger cells show thick nuclei, while the older ones have small lobes and long filamentous interconnections, or are more slender than the first-named.

The polymorphonuclear leucocytes were subjected to elaborate classification by Arneth,[30] under the idea that a careful study of the segment-nuclear forms might afford data valuable to the clinician. *Fig.* 57 forms a convenient graphic representation of the scheme.

Class I. M —

W
·2 per cent

T
5 per cent.

Percentage in normal blood.
5

Class II. 2K
·27 per cent

2S
23·46 per cent

IKIS
11·69 per cent

35

Class III. 3K
2·27 per cent

3S
5·6 per cent

2K1S
16·66 per cent

1K2S
16·4 per cent

41

Class IV. 4K
3·8 per cent

4S
·07 per cent

3K1S
6·4 per cent

3S1K
1·6 per cent

2K2S
4·73 per cent

17

Class V. 5K
1 per cent

4K1S
0·4 per cent

3K2S
0·4 per cent

4K2S
·07 per cent

3K3S
·07 per cent

2

100

Fig. 57.—Graphic Representation of Arneth's System.

There are several objections to the theory: (1) Brugsch and Schilling's view that degree of segmentation of nucleus has no relation to age of cell; (2) Reniform nucleate myelocytes are thrown into the same category as metamyelocytes, and yet one has an amblychromatic nucleus, and the other a trachychromatic nucleus. These differences are not brought out by triacid staining (the method utilized by Arneth); (3) A polynuclear leucocyte, according to Neumann, becomes simpler in form when it ceases amœboid movement; (4) Heat fixation accounts for the deep nuclear indentations.

Weidenreich, using Deetjen's agar method, considered that the polymorphism of the leucocyte nucleus was a sign of morphological, but not of

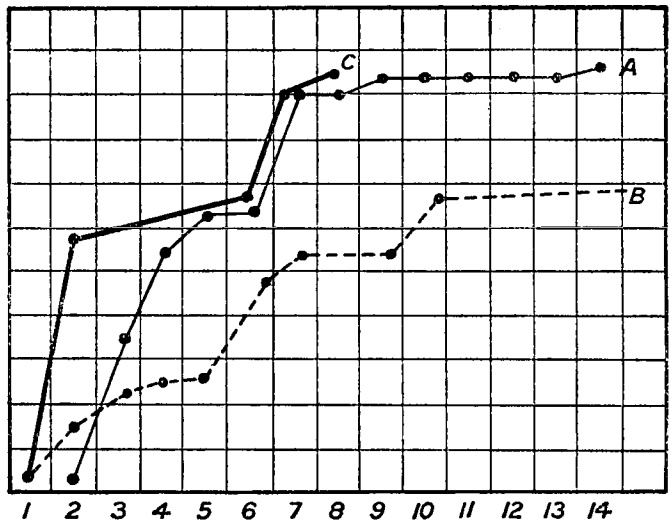
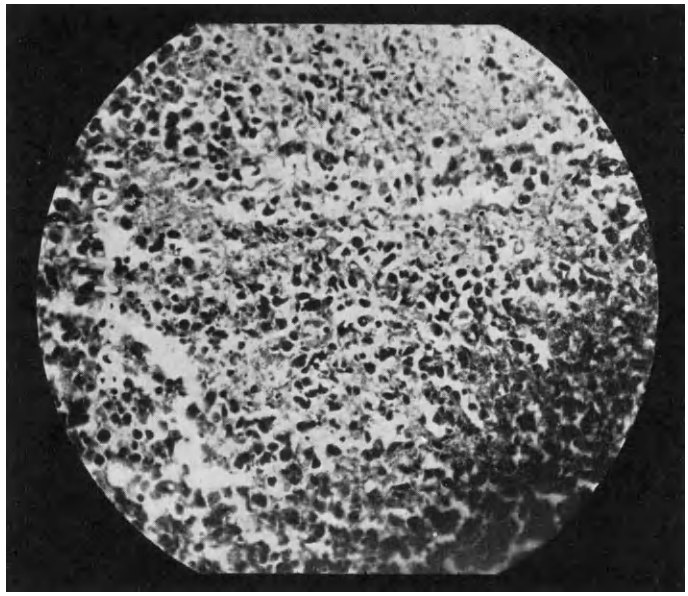


Fig. 59.—CURVES SHOWING EFFECT OF CERTAIN ORGANISMS ON THE CHARACTER OF THE CELLS OF THE EXUDATE. (*A*) pus from empyema due to streptococcus pyogenes. Good reaction, moderate destruction of neutrophiles. (*B*) Mastoid pus in a case of streptococcic infection showing scanty proportions of healthy and abundance of necrotic neutrophiles. (*C*) Peritoneal exudate in a case of gonorrhœal salpingitis, showing well-marked output of young leucocytes, scanty destruction of same, and mononuclear richness. The curves are constructed on the same lines as the marrow charts. Each square represents a 10 per cent increase. The figures below indicate the variety of cell referred to. (*1*) Young neutrophile leucocyte; (*2*) Normal adult ditto; (*3*) Bifid nucleate ditto; (*4*) Trifid nucleate ditto; (*5*) Fragment-nucleate ditto; (*6*) Dead ditto; (*7*) Trachychromatic lymphocytes; (*8*) Amblychromatic ditto; (*9*) Leucocytoid ditto; (*10*) Large mononuclears; (*11*) Transitional cells; (*12*) Endothelial cells; (*13*) Mast cells; (*14*) Eosinophile cells. *(From the Author's collection.)*

physiological, degeneration, and was a definite sign of progressive development, although he was disposed to view the partition as a sign of amitosis. The band and filament forms are not seen to be interchangeable by this method, or, at least, they are not interchanged during the progress of amœboid motion, but rather by intracellular functional changes.

Used in a purely empirical manner, the Arneth system, modified in some such way as that of Schilling,[31] serves exceedingly useful purposes, indicating as it does what manner of reaction to infection is being exhibited by a patient



" In acute infections, polymorphism of the nucleus " (of the neutrophile leucocyte) " tends to be extreme " (p. 217).

Fig. 58.—CARYORRHECTIC LEUCOCYTES IN AN INFLAMMATORY AREA. The photograph shows a number of dark bodies of irregular shape and size. These are the fragmented nuclei of polynuclear leucocytes seen in section. The darker portion of the field in the right lower corner is the edge of the inflamed area where cell-destruction is not so extreme.

(Oc. 2, Zeiss apochrom, 4 mm.).

Face p. 217

In the acute infections, polymorphism of the nucleus tends to be extreme (*Fig.* 58). The same holds good in the case of the cells of purulent exudates, since personal observations on material from abscesses have shown a relation between the character of the organism and degree of change in the leucocytes (*Fig.* 59). Whether a trifid nucleus is or is not as old as a quinquefid nucleus may then be looked on as a matter of indifference. Possibly the multipartite nuclei are the result of severe toxic influences on the cell.

Schilling's modification may be here referred to, because of its clinical importance.

In the first place, the *technique* consists in staining the blood films with Pappenheim's method of combined May-Grünwald and Giemsa. Fix the air-dried film with May-Grünwald solution; three minutes. Pour on an equal quantity of water (distilled). Leave one minute. Rinse briefly. Pour on diluted Giemsa (10 drops of stock Giemsa to 10 c.c. distilled water) and leave 15 minutes or more. Carefully rinse in distilled water. Blot with fluffless blotting-paper, and dry. The film is now studied, and the various cells are marked off as they are passed before the eye (oil-immersion lens essential), using the following classification: (1) Segmented-nucleate polynuclears; (2) Rod-nucleate polynuclears; (3) Juvenile polynuclears; (4) Myelocytes; (5) Large mononuclears; (6) Lymphocytes; (7) Basophile cells (mast cells); (8) Eosinophile cells.

In the differentiation of the last four there is no difficulty. The so-called transitional cells and the " hyaline " cells are grouped as large mononuclears. It is only necessary to define the first four. The *segmented-nucleate* polynuclears are those which have two, three, four or more separate clumps of nuclear matter, united or not by threads; in other words, they are the polynuclears which are known as such by the non-specializing clinician. The *rod-nucleate* forms are those which possess a ribbon-like nucleus, without any special nodosities. The *juvenile* forms possess an S-shaped nucleus which has the ends of the S thickened; some forms possess a reniform nucleus, the indentation being conspicuously deep. The *myelocytes* are similar cells to the latter, though a little larger, have a slightly indented nucleus, and at first sight appear like the mononuclear leucocyte. The differences lie in the presence of granules in the myelocyte plasma, and the presence of a nucleolus (sometimes more than one). With these few headings a careful differential count becomes easy, and according to the author quoted serves all the purposes for which Arneth's classification was intended. That is to say, the classification given is less complicated than that of Arneth, but gives as good results in practice.

The deductions to be made are that if the " picture " is displaced to the left, there is regeneration of leucocytes (neutrophiles); if to the right, the neutrophiles are degenerating. Extreme displacement to the left indicates hyperplasia in the bone-marrow. We have the following groups: (1) No change in blood-picture: aplastic anæmia, chlorosis, pernicious anæmia (occasionally), pseudoleukæmia (usually), splenic new growths, ordinary tumours, chronic protozoal disease. (2) To the right: most acute infectious diseases, especially typhoid, pure tuberculosis, lues. (3) To the left: septic diseases (puerperal fever, appendicitis, peritonitis, septicæmias,

mixed infections in tuberculosis), scarlet fever, diphtheria, new growths, pneumonia, acute protozoal diseases. (4) Extreme displacement to left: agonal septicæmia, leukæmias.

Schilling points out further that the method serves as a good indicator for therapeutic measures such as operations, use of serum treatment, use of *x*-rays; that it serves for warning against relapses or against retrogression in the condition of the patient; or, finally, for controlling the use of such an agent as tuberculin. In other words, "a neglect of Arneth's method, on the lines indicated, in the investigation of the leucocytes clinically, is a technical error."

To present a more concrete impression of the applicability of the method, the following records may be appended, selected from the contribution already discussed.

Disease	No. of white cells per c.mm (in thousands)	Basophiles	Eosinophiles	Neutrophiles				Lymphocytes	Large Mononuclears
				Myelocytes	Juvenile	Rod-nucleate	Segment'd nucleate		
Normal	6	1	3	—	—	4	63	23	6
Typhoid fever	3	—	—	—	—	**30**	19	**36**	15
Severe sepsis	7	—	—	**1**	**12**	**49**	25	**9**	**4**
Liver abscess	6	1	2	—	—	**27**	42	20	8
Ankylostomiasis	6·5	2	**32**	—	—	4	32	22	8
Leukæmia	50	**3**	**6**	**14**	13	**20**	36	**3**	**5**
Lymphatic leukæmia ..	120	—	1	—	—	2	1	**55**	**41**
Aplastic anæmia	3	1	2	—	—	**5**	62	23	6
Hodgkin's disease ..	5·7	1	1	—	—	7	40	**45**	8

The figures in thick type indicate how the "picture" is deviated in one direction or the other.

Thus, the youngest type of polynuclear leucocyte in normal blood is the rod-nucleate form. In typhoid fever the picture is deviated to the left (great increase in rod-nucleate forms, diminished segmented nucleate forms). In severe sepsis there is marked deviation to the left (black figures in first two columns of neutrophiles, with still higher percentage of rod-nucleates). Similarly with leukæmia. On the other hand, in lymphatic leukæmia the picture is deviated to the right, the chief figures being in the lymphocyte and large mononuclear columns. The aplastic anæmia shows no deviation. Note the high and low values marked in thick type in the other cell-columns, which draw attention to lymphocytosis, lymphopenia, eosinophilia, large mononucleosis in the different diseases.

Some work on this subject carried on by Minor and Ringer furnishes interesting results which, though not giving exactly the same figures as those of Arneth, nevertheless point in a similar direction. A good idea of the real usefulness of this method of study is shown by the chart given (*Fig.* 60),

where the cases are divided into normal, good, medium, bad, and very bad (from the prognostic standpoint). The figure (I) indicates cells with only one nucleus or two lobes joined by an isthmus; (II) Double nuclei connected by only a thread; (III) Three segments; (IV) Four segments; (V) More than four segments. The increase of Class I cells in the very

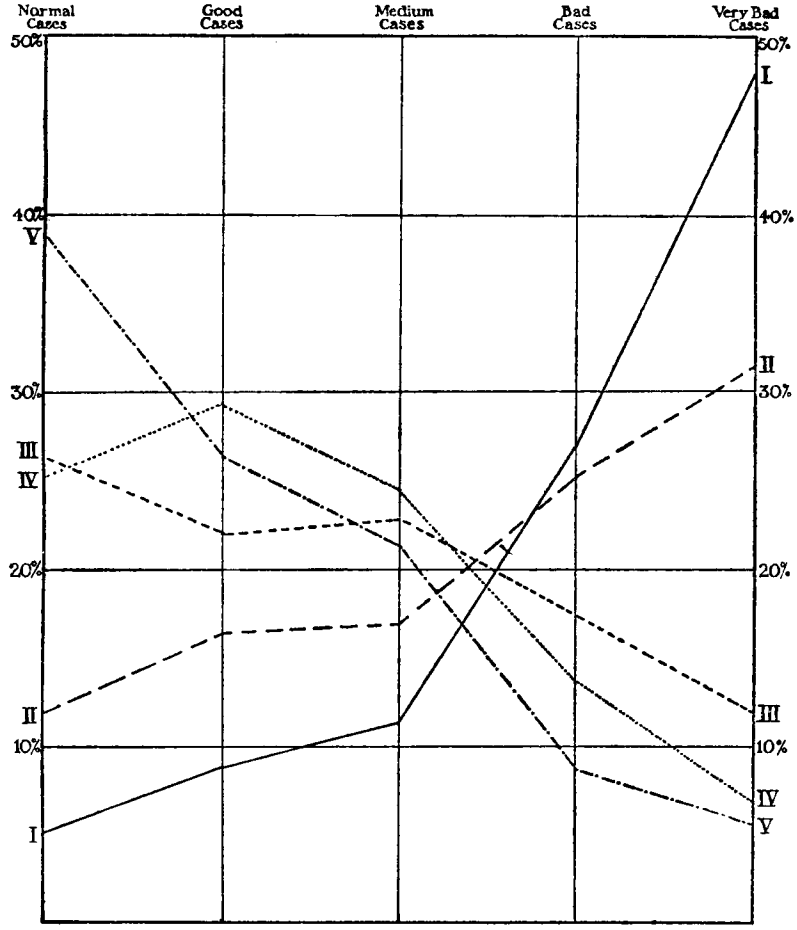


Fig. 60.—CHART ILLUSTRATING ARNETH'S METHOD.
(After Minor and Ringer.)

bad cases is shown in a striking way. An example is given in which a patient suffering from tuberculosis seemed to be doing well, but showed a count of 20–45–30–5–0. This count could not be explained until, a few days afterwards, the illness relapsed, spread rapidly, and ended fatally.

Characters of the Leucocyte as seen with the Ultramicroscope.—The cell-body shows three zones: an outer narrow zone in which there are silvery motile granules of large size, a middle zone of large granules where motility is very active, and an inner zone of rapidly-moving or dancing particles.[32] Some of these were thought by Pappenheim to be lipoid.[33]

It is from the middle zone that the pseudopodia arise, and when vacuoles appear in the cell they are found to be situated here.

The inner perinuclear zone is clear and devoid of granules. The nucleus itself is opalescent and shows a finely granular structure, the granules being arranged in filamentous fashion. There are some larger non-motile granules within the nucleus. A centrosome can be seen in its vicinity (Schilling[34]).

The Leucocyte as seen by Vital Staining.—Brilliant cresyl-blue or neutral-red does not stain the nucleus unless the cell is dead. Numerous dancing particles of brilliant colour are seen in the cell-substance by this means.

The Leucocyte as seen with Ultra-violet Light.—Grawitz found that the granules come out most distinctly. They are seen to vary much in size, even in the same cell. The variable opacity of the granules shows that they are not all of the same nature. The nucleus is much more transparent than in the case of the lymphocyte —a fact which points to differences in chemical constitution; further, the bridges between the segments are found to be replaced by broad bands.

Mitosis.—Does the circulating leucocyte undergo mitosis? According to Schäfer, mitosis occasionally takes place.[35] Pollitzer[36] described the following changes in the nucleus during circulation. Curving of the arms of the nucleus round the centrosome, almost, if not quite, up to ring formation; clumping of the chromatin to one side till an equatorial band is formed, such as is found in the neutrophiles in cases of infective disease. This again divides into a double row of nuclei, which pass to the opposite poles of the cell. Looked at in this way, the partition of the nucleus into fragments (caryorrhexis) is really an incomplete mitosis. In support of it is the statement that constrictions of the cytoplasm may be observed round these nodal masses, with accumulation of granoplasm around each

nuclear fragment. Weidenreich[37] believes that the phenomenon is not proliferative, but, as described previously, degenerative in character.

Differential Diagnosis.—It is hardly possible to mistake a polynuclear leucocyte in a blood smear, but under certain circumstances there may be temporary doubt about some of the variant forms. The distinction from a metamyelocyte, or from an aberrant parent cell with polymorphous nucleus and no neutrophilic granules may be difficult at times, but will be based on the nuclear characters detailed on preceding pages. The distinction between the neutrophile and a large mononuclear leucocyte with a polymorphous nucleus is made out by noting the presence of delicate bridges between the nuclear segments in the one with trachychromatism of the nucleus in the one, as contrasted with the findings in the other. (*Fig.* 61). The tendency to loss of typical characters under the influence of degenerative changes may also cause difficulty. These degenerative changes are referred to below.

Fig. 61.—The neutrophile leucocyte (*a*) and large mononuclear cell (*b*) contrasted.

The Functions of the Neutrophile Leucocyte.—The relation of this cell to *phagocytosis* and immunity is best dealt with in treatises on that subject. Of interest in connection with the biology of the cell, however, is the problem concerning the purpose of the granules present in its cytoplasm.

The influence of surface-tension phenomena upon the power of *amœboid movement* has been considered by Loeb and Michaelis.[38] The superficial saponification of the lipoid envelope by lipoid soluble substances in the blood in such bacterial infections as cause destruction of red cells would form an instance in point. The action of saponin and hydroxylamine on the blood-forming organs[39] has furnished parallel evidence. Massart and Bordet[40] found that the addition of a drop of oil to frog-lymph in a moist chamber would suffice to inhibit the output of pseudopodia.

Chemotaxic influences on amœboid movement have been widely studied, and Metchnikoff has regarded the process of anti-

bacterial immunity as nothing more than a conversion of negative into positive chemotaxic influence on the leucocytes.

The influence of such simple agents as sodium chloride, calcium chloride, alkalies, potassium chloride, adrenalin, calcium[41] on phagocytosis is of much interest, but will be passed over.

Chemical Characters.—

THE GRANULES OF POLYMORPHONUCLEAR LEUCOCYTES.—The granules which may be detected in these cells vary in size. They show active Brownian movement, dependent on purely physical circumstances, since changes in the molecular concentration of the medium influences them (Achard and Ramond[42]). They are visible with dark-ground illumination as well as by vital staining.

The following varieties may be distinguished :—

Neutrophilic and variants (basophilic, oxyphilic)
Iodophilic
Sudanophilic
Phenolphilic
Oxydase
Myeloic azur granules (in parental cells).

THE NEUTROPHILIC GRANULE AND ITS VARIANTS.—The problems relating to the origin and purpose of these various granules are as complicated and difficult of solution as are those relating to secretory granules in general. The leucocyte granules are variously interpreted as secretory, as precipitation-effects, as metabolic products, as zymogen, as nodal intersections of the spongioplasmic network, or as degeneration products.

1. *That they are Precipitation Effects.*

Pro.—(*a*) Analogy with the deposition of starch grains in a vegetable cell (Ehrlich).

(*b*) The granules increase in number in the presence of pyocyanase, which contains ammonium carbonate.[43]

(*c*) The addition of saline to an emulsion of leucocytes is found to increase the number of granules. These new granules are very minute and are soluble in 10 per cent saline, indicating that they are globulin precipitations.

(*d*) Loeb[44] found that osmotic influences may cause the disappearance of granules from the cell, hypertonic solutions withdrawing

water and rendering the granules indistinct, whereas hypotonic solutions cause swelling and vacuolation of the cell-body. Acid reaction may cause them to disappear. The Brownian movement depends on the texture of the intergranular cytoplasm under varying conditions of tonicity.

(*e*) Dark brown or black granules of varying size are found round and on the nucleus when the triacid stain is used. These are the effect of heat fixation or the artificial effects of the dye (Neusser's perinuclear granules).

Con.—The granules stain vitally and give the indophenyl-blue reaction.

2. *That they are Nodal Intersections of the Spongioplasmic Network* (Gulland[45]).

Pro.—Pollitzer's views[36] about granoplasm, as a third constituent of cell substance. This is so dense in mature cells that the true hyaline cytoplasm can only be seen in specimens which have been crushed. It may simulate chromatin structures in the nucleus, in that optical projection causes the granoplasm to appear to be within the nucleus as a nuclear network. This would explain the view expressed by Decastello and Krjukoff[46] that the granules are segments of caryogenic protoplasmic fibrils.

Con.—(*a*) The granules have no relation to spongioplasmic structure (Ehrlich).

(*b*) They disappear during starvation without a disappearance of the other (Kollmann).

(*c*) The fact of active Brownian movement while within the living cell, especially under certain conditions (Mühlmann[47]).

3. *That they are of Secretory Character.*—They may act the part of an internal secretion. Downey[48] points out that certain leucocytes of the fish may have such a function, the cells being looked on as unicellular glands with the power of phagocytosis added. Bound up with this question is that of their specificity.

Pro.—(*a*) The peptic action of the cells.

(*b*) They are absent from the starving cell.

(*c*) Their staining reactions are specific.

(*d*) The reaction with indophenyl blue.

(*e*) Loew and Bokorny[49] showed that the addition of such weak

bases as very dilute ammonia and ammonium carbonate to a preparation of living spirogyra would cause granules to appear within the cytoplasm. These were called proteosomes, because they were derived from labile protein, and had the property of reducing very dilute alkaline silver solutions (i.e., aldehyde protein). Similarly a $\frac{1}{2}$ per cent solution of caffeine produced a similar phenomenon on these vegetable cells, the granules disappearing again when the filaments were placed in pure water. The granules stained with neutral red were actively Brownian, and soluble in Lugol's solution (cf. glycogen granule).

(*f*) Schneider's study of the relation between complement and bactericidal substances.[50] The so-called leukine is of complement character. The whole subject of the relation of leucocytes to complement and amboceptor is paramount evidence in favour of the view in question; Metchnikoff has strongly advocated that the specific secretion of these leucocytes is complement.

Con.—(*a*) Oxner[51] showed that when nemertines are stained vitally by methylene blue and neutral red, the mucus which they secrete is colourless, although the mucin cells contain many vitally-stained granules. This indicates that the granules are not necessarily secretory.

(*b*) Eosinophile granules are not specific, therefore neutrophile granules are not necessarily so.*

4. *That they are Zymogen.*—In favour of this view is the analogy to the granules in the cells of secretory glands. They give a proteolytic reaction. Microchemical reactions show the presence of marked acidity in the vicinity of ingested particles. Drzewina[53] found that acidophile leucocytes were very common in the hepato-pancreas of fish, and concluded that the granules were thrombogen. Fry[54] suggested that the large granules of fish leucocytes were "kinases" concerned in coagulation. Against the view is the fact that some are lipoid (Ciaccio[55]), and that they are genetically related to the plasmosomes.

5. *That they are Metabolic Products.*

Pro.—(*a*) They are absent from the starving cell.

* Kollmann found that the granular cells in the tortoise contain amphophile granules at first, and acidophile granules later, with associated changes of solubility.

(*b*) Some of them are lipoid.[55]

(*c*) Different kinds of granule can appear in the same cell.

(*d*) Neutrophile granules can be made to stain acidophile or basophile at will (Marino[56]).

(*e*) They are normally present in the rabbit bone-marrow (Löwit[52]).

(*f*) The view that they come from the nucleolus (Bogdanoff[57]), or from the nucleus (Sabrazès and Muratet[58]) in scyllium, is in support of this interpretation.

Con.—(*a*) Their specific staining reaction.

(*b*) Their genetic relation to the plasmosomes (Arnold[59]).

(*c*) Their reaction with indophenyl blue.

(*d*) The arguments in favour of their secretory nature.

(*e*) The fact that stimulation of the bone-marrow in rabbits is never associated with a failure to breed true neutrophile granular cells (Schwarz[60]).

(*f*) The triacid stain shows the presence of green granules around the nucleus (Neusser's perinuclear basophilia), which, in spite of the staining reaction, are not made of nucleo-albumin.

(*g*) They are not affected in number by the uric-acid diathesis.

6. *That they are Degeneration Products.*—Against this view is all the evidence for their secretory nature, and the fact that they are present in mitosing cells.

The Basophilic Granule.—Extremely fine granules can be seen, especially when methylene blue is used alone. Pappenheim considers them to be spongioplastic, but Schur and Grawitz seem disposed to regard them as precursory granules.

The Oxyphilic Granule.—It is well known that some of the very fine (so-called) neutrophile granules stain as brilliant a red as do the coarse eosinophile granules. It must be admitted as possible for a neutrophilic granule to become oxyphilic. The neutrophile myelocyte is the only cell which shows genuine neutrophilic granules. On the other hand, the view that α, β, γ, δ, and ε granules are successive phases of the same granulation has been done away with by Pappenheim.[61]

The Iodophilic Granule.—Normal leucocytes do not stain with iodine. Abnormal ones may show the following three grades

of iodophilia (stainability with iodine) : (*a*) With rod-like granules ; (*b*) Diffuse colouring without granules ; (*c*) Brown-red inclusions. In the last two cases, the iodine reaction is a sign of degeneration (Commessatti[62]). In the first case the granules may form clumps within the cell-body.

Conditions in which the iodine reaction (glycogen) is met with : spreading suppurative processes, general sepsis (if not too virulent), at the acme of appendicitis, pneumonia, pyæmia, diabetes, pernicious anæmia, leukæmia. In such cases 90 per cent of the polynuclears may show the change.

Significance.—The presence of glycogen granules in the leucocyte may be taken to mean increased functional activity (W. H. Brown[63]), or it may be a degenerative process (Da Costa[64]), since myelocytes do not show it. Pappenheim[65] regarded it as a product of the interspongioplastic paraplasm.

Abetti[66] used it as a sign of inflammation somewhere in the body. Woskressenski[67] considered that it means a severe infection.

Neukerich[68] divides the bodies staining with iodine thus :—

1. True glycogen—stainable with iodine and Best's carmine, soluble in saliva.
2. Iodophile substance stainable by Best's method, but not soluble in saliva.
3. Granules in leucocytes and myelocytes which cannot stain with iodine, not soluble in saliva, but stainable by Best's method.
4. Iodophile substance only partly stainable with Best.
5. Iodophile substance in a diffuse form, not stainable with Best.

This author believes that the bodies staining with Best's method are preglycogen, which break up with necrobiotic processes into not readily soluble glycogen-like substances ; with less severe processes, bodies appear which are readily soluble.

THE SUDANOPHILIC GRANULE.—Leucocytes containing granules staining with Sudan III were called lipoferous leucocytes by Ciaccio.[69] The granules vary in size up to 1 μ. In severe suppurative processes, 90 per cent of the neutrophiles contain this form of granule, 35 per cent show it in suppurative processes with much anæmia, and 15 to 20 per cent in rheumatism, tubercle, and chronic infections (Quarelli and Bottino). They are met with in

puerperal blood.[70] They do not vary with digestion (Ciaccio, Tousset et Troisier[71]).

According to some authorities, the phenomenon is degenerative, and concomitant with the similar change seen in any cell; according to others, the granules are the result of absorption by phagocytosis of fatty matter in the blood-stream (Martelli[72]).

THE PHENOLPHILIC GRANULE.—The occurrence of phenolphilic substance in neutrophile leucocytes was observed by Loele, as mentioned when discussing metabolic changes in the spleen. It is related to the oxydase granule.

THE OXYDASE GRANULE.—This form of granule is not peculiar to the neutrophile leucocyte, and will be discussed in connection with the eosinophile cell. Some forms are stainable with cresyl, neutral, or Nile blue. The Winkler-Schultze indophenyl reaction is the usual method of detection. Sapegno considered the number of oxydase granules a criterion of the age of a cell.

Jochmann[78] thought the granules might play some part in inhibiting the coagulation of the serum in an exudate.

Other Ferments in Leucocytes.—Leber's finding[73] that aseptic pus has the power of digesting proteid matter was an early observation on the subject of leucocyte ferments. Erben[74] studied the ferment action of leukæmic leucocytes, and Müller and Jochmann[75] studied the question very thoroughly. More recently a full review of the subject was given by Wiens,[76] to whose work reference should be made. The existence of proteolytic ferment in such cells is of interest in connection with the question of the meaning of pus or suppurative processes generally. The digestive action is necessary for the liquefaction of the tissue, although conditions occur in which this result is undesirable, because of consequent rapid absorption of poisonous metabolic products. Antiferments play an important part in rectifying such error.

Extractives in Leucocytes.—Both living and shed leucocytes, when extracted with saline, can be shown to contain bodies which possess bactericidal activity, varying in amount with different organisms. The bactericidal substance was shown by Meisner[77] to withstand 60° C.

THE MYELOIC FORM OF AZUR GRANULATION.—This is present

only in the immature members of the blood-cell series. There has been much discussion regarding the relation between this and the neutrophile granulation of the mature cell. Pappenheim's[79] view is that its basis lies in some derivative from the nuclear matter, remaining temporarily there as a granule, but able to unite with azur-eosinate through the aid of an amboceptor *basic* group. The prevailing tint is then that of the polybasic salt of the colour acid (cyanophile component). The subsequent redistribution of the chemical structure of the granule enables it to unite with the dye through the aid of an amboceptor *acid* group. The chief colouring is then that of the polyacid salt of the colour base (erythrophile component).

Granule	Amboceptor	Component of Azur-eosinate
Azur ..	Basic group ..	Polybasic salt of colour base
	Neutrobasic group ..	Monobasic ,, ,, ,,
Neutrophile	Neutroacid group ..	Monacid ,, ,, ,,
	Acid group ..	Polyacid ,, ,, ,,

The reversal of affinity towards the different sides of the colour base must mean a loss of identity of the azur granule in the juvenile cell. It is evident, too, that there can be an intermediate stage between relative immaturity (primitive granule) and maturity (specific granule), the intermediate stage passing continuously from neutrobasophilia to complete neutrophilia, while the passage from the primitive granule to the intermediate stage is interrupted. In physical parlance, the curve is interrupted, and is mathematically expressed as a discontinuous function.

Such speculations as these are not purely academic. They illustrate the mechanism of metaplasia in the individual cell, and afford an explanation, for instance, of why large lymphocytic leukæmia may be really myeloid.

The Death of the Leucocyte.—The phenomena which have been described as occurring within the myelocyte during the process of its decay are also met with in the case of the mature leucocyte, although they are best observed outside the circulation, on the surfaces of mucosæ, in the connective tissue spaces, etc. They are

most commonly observed in smears of inflammatory exudates. While the changes are tabulated according to their position in the cytoplasm and in the nucleus, it will be borne in mind that the nuclear changes usually precede the cytoplasmic.

CHANGES IN THE CYTOPLASM.—Vacuolation of the cytoplasm; fragibility; coagulation necrosis; albuminoid degeneration; swelling to giant size (especially in inflammatory exudates).*

Changes in the granules: fusion to larger masses;[80] partial up to complete disappearance; altered staining (metachromatism) of some, prior to their fusion; basophile change in the granules;[81] unequal decolorization.

Appearance of new bodies: fat globules; glycogen granules; mast granules (perhaps).

CHANGES IN THE NUCLEUS.—Swelling, with separation of the chromatin markings; fragmentation into portions without filamentous interconnections (*see Fig.* 58).†

Alteration of staining reaction (metachromatism).

Formation of uninucleate forms by nuclear agglutination.[81]

Fragibility of the nucleus demonstrated in the film preparation.[83]

When a polynuclear cell is engulfed by a macrophage, the changes noticed during the death of this cell are characteristic. They were first studied by Cesaris-Demel[84] in inflammatory exudates induced by inoculations of diplococci. The nucleus first acquires a strong blue colour‡ in place of the normal violet, then the nuclear membrane becomes lost, and the outlines of the nucleus become indistinct, while the chromatin network disappears. The diffusely-staining body breaks up into several fragments, which appear as formless masses, the whole structure being finally lost.

Ciaccio[85] found that lipoid substances accumulate in the cell-body during the death of a leucocyte; sudanophile granules become numerous in the course of pneumococcic infection. Such granules are especially noted in the pus cells of fluid exudates.[86]

The average *duration of the life* of a polynuclear leucocyte has not been determined with any pretension to probability,

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* This leads to the production of a giant leucocyte. It may be the effect of osmotic action, or signify an origin from a myelocyte or myeloblast.

† The so-called amitosis is regarded by Weidenreich[82] as a degenerative phenomenon.

‡ Nuclein, nucleic acid + nuclease = purin (Ciaccio, quoted by Zoja, F. H. x. 1. p. 239).

though some authorities consider that it never lives more than a few days.*

The Comparative Cytology of the Neutrophile Leucocyte.—True neutrophile leucocytes are not found far back in the vertebrate scale, and it is doubtful whether the phagocytic cells of the invertebrates should be included among them merely because their functional properties are similar. Hardy's explosive cells[87] of crustacea are hardly exact analogies. They are concerned in the process of clotting in these animals.

In the *tunicates* (*Ciona intestinalis*), the white cells are mononuclear, of short round form, with scanty cytoplasm, which is very rich in fine granules.[88]

In the *scorpion*, Kollmann[89] found: (*a*) Large round cells crowded with granules of spherical shape, and specially densely arranged at the periphery; (*b*) Smaller oval cells full of rod-like granules. The granules stain violet with triacid; they are amphophile, with a marked tendency towards basophilia. The fine granules are acidophile. Amphophile granules were only found in one species of tegenaria.

In the *king-crab*, the white cells are similar to those of the scorpion both in form and in granulation. (The serum contains hæmocyanin.) Bruntz[90] found that the amœbocytes of arthrostracea multiply by amitosis during circulation.

The leucocytes of *fishes* are of two kinds—spindle-shaped and round. Both are covered with small fine granules which stain bright red with Giemsa. The nucleus is elongated in the spindle-shaped forms; in the round forms it is sometimes round, and sometimes horseshoe-shaped. These round forms are divisible into two groups according to their size. In each case, bright red granules are present, those in the larger cells being angular and less numerous; in the smaller cells they are smaller and thickly distributed through the cell (Fry[91]). The granules of these spindle cells are directly concerned in coagulation.

The observations of Sabrazès and Muratet[92] on the blood of the torpedo, have shown that acidophile cells stand in place of neutrophile leucocytes of other animals. They occur in two forms: (*a*) Small cells with ovoid or lanceolate granules; (*b*) Larger cells with strongly acidophile granules. In each case the nucleus is rounded. Amœboid movements are active. The number of white cells is about 18,000 per c.mm.

The blood of the cartilaginous *fishes* is rich in granular leucocytes, but not that of teleostean fish. The granules in the leucocytes of the ganoid fish polyodon were especially well studied by Downey.[93] This author found that there are at least three types of secretory leucocyte, which are not interchangeable: (*a*) The most numerous forms are nearly round, with large round granules of equal size, filling up the cell to such an extent as to crowd the nucleus to one side. The nucleus is reniform, and contains a moderate amount of chromatin. The granules in the cell are amphophile. They

* Horbaczewski attempted to deduce it from a ratio between excreted urea and purin bases, as evidence of leucocytolysis, but there is the obvious fallacy that nucleic acid comes from other places as well.

develop in vacuoles within the cell-body, and as the granules form, the nucleus diminishes in size. Later on, the granules come to vary in size, and ultimately dissolve away, leaving vacuoles once more. (*b*) A cell with small granules which are not so closely packed together as the preceding, but occur all round the nucleus, leaving it central in position. The nucleus does not change in size with the appearance of the granules, but undergoes certain degenerative changes (loss of network, breaking up of the chromatin ; ultimate pycnosis ; final dissolution). (*c*) A cell with granules which stain brilliantly with safranin. They vary considerably in shape, size, and distribution ; are large, round, or spindle-shaped. When these cells degenerate, they show a polymorphous nucleus and homogeneous coloration of the cytoplasm. The whole cell shrinks, and may finally undergo vacuolation.

Interesting observations on the formative tissue of the mudfish protopterus were made by Stephan.[94] The lymphoid tissue occurs in the substance of the kidney and round the digestive tube. It is made up of polyhedral cells, some of which are crowded with granules, staining with eosin, orange, safranin, and fuchsin. Parker thought they were alimentary reserve for the period of torpor, but others are indisposed to consider them as such. At the time of full activity, the lymphoid tissue is full of these acidophile cells, but they disappear during the torpid period, and are almost absent in the awakening animal. The first granules appear in the neighbourhood of the nucleus where the cytoplasm is more dense. The granules are at first extremely small, and then enlarge. When the cell is full, the granules lose their affinity for staining, the nucleus takes some share in the liberation of the granules, which appear to arise by pulverization of the fragmenting nucleus.

In the *amphibia*, the granular cells are chiefly mast-cell in type, but uninucleate eosinophiles of characteristic form are prominent. The acidophile leucocytes of the tortoise arise by the production of granules in large mononuclear leucocytes, not only in the bone-marrow but also in the loose connective tissue. There are no true neutrophile leucocytes in the reptiles ; eosinophiles are the characteristic granular cell.

In triton, the cytoplasm of the neutrophile leucocyte is feebly oxyphile, and contains a scanty basophile network without granules. An amphophile effect is thus produced. The nucleus is deeply coiled, and forms nodes connected by filamentous connections. These are sometimes so indistinct as to give rise to a multinucleate appearance (Grüneberg)[95] The leucocyte of siredon has a rose-coloured cell-body, with a scarcely visible basophile network. The nucleus has an S or U-shape. In the frog, the cell-body is amphophile, and shows no granules. The nucleus is markedly polymorphous. In gongylus, the cells rather resemble the myelocyte form of human hæmatology.

Metchnikoff's observations on the functions of cold-blooded leucocytes show that the granular leucocytes are able to take up such organisms as cholera, streptococcus, *B. tetani*, *B. coli*, *B. typhi*, *B. pyocyaneus*, as long as they are not too virulent. In the pigeon they take up avian tubercle bacilli, but are destroyed in the process. They are negatively chemotactic

to tetanotoxin. In the frog and other reptiles the part of the human polynuclear leucocyte is played solely by the macrophage.

From these considerations it will become evident that there is no such thing as a true specific neutrophilic-granular leucocyte in the cold-blooded vertebrates.

In the *birds*, the leucocytes include mast-cells, eosinophile cells with rod-like granules (the most numerous), and cells of a similar size to the preceding, but with a bifid nucleus, whose chromatin structure is radial and myelocytoid. The cell-body is feebly oxyphile and full of minute oxyphile granulations. Such cells are very scanty. Kasarinoff,[98] Niegolewski, and others have found these varieties in the fowl, pigeon, and Senegal finch. A few myelocytes are normal to goose blood.[99]

Among the *mammals*, the leucocytes of the ape, pig, goat, cow, dog, and mouse[96] have neutrophile granules, while those of the rabbit show amphophile granules, and those of the guinea-pig acidophile granules. The granules of the horse leucocyte are extremely fine.[97] A few neutrophile myelocytes are normal for this animal. The leucocytes of the goat are small, and the granules stain violet with triacid stain. Furno's observations on the granules in the leucocytes of the domestic animals have shown that in man, the horse, and the dog, the neutrophile granules appear violet with triacid, while the colour is red in the case of the sheep, goat, cow, and pig. Neutrophile granules are not found in the white mouse, rabbit, guinea-pig, cat, or rat—these animals showing only oxyphile granules in their polynuclear cells.[100]

IV.—THE CYTOPLASIAS OF THE LEUCOPOIETIC TISSUES.

LEUCOCYTOSIS: principles in white-cell counting; causes of leucocytosis; the phases of leucocytosis—Leucopenia—The hyperplastic and metaplastic processes of leucopoietic tissues: contrast between leukæmia and leucocytosis; auxetic processes.

IT is of interest to reflect that we never make a differential blood-count without at the same time involuntarily obtaining data for a study of cytoplastic processes in the patient's blood-formative tissues. The better we find ourselves able to make deductions about these tissues by the method of clinical examination in question, the more stimulated do we find ourselves towards pursuing the investigation of the correlations between histological changes and hæmocytological formulæ. Common as are the evidences of damage to red cells, or even of the erythropoietic properties of the bone-marrow, the most familiar changes observed in blood-counting are doubtless those classed as examples of leucocytosis.

1. **Leucocytosis.**—Strictly speaking, the word *leucocytosis* should mean the occurrence of an increase in the white cells of the blood as a whole, but common usage limits it to express an increase in the polynuclear leucocytes alone. However interpreted, a case of leucocytosis requires investigation along the following lines:* A microscopic study of the blood-film informs us (*a*) Whether there is any increase of any one cell-form at all; (*b*) Which of the cell-forms exhibit the increase; (*c*) Whether the cells present are all mature, or are admixed with immature, juvenile, or prematurely liberated cells. Secondly, an examination of the blood by means of the counting pipettes shows us (*d*) How much increase of the white cells there is. These various data enable us to speculate as to the character of the agent which is setting up the change called leucocytosis.

It is well known, that while the total cell-count may reveal no change in the white cells, the differential count may show the existence of what is called relative leucocytosis, but it is far from

* Ably laid down by Pappenheim[109]

customary for clinicians to extend the study of the blood to this point.* Still less is it customary to report upon the white cells of the blood in a manner which shall show the ratio between mature and immature forms circulating in the peripheral blood at the given time of examination. The changes to be looked for may be tabulated as follows :—

Quantitative Changes :—

1. Total number of white cells increased—Absolute leucocytosis.

2. One type of cell alone increased—Relative leucocytosis.

3. Total number of white cells diminished—Absolute leucopenia.

Qualitative Changes :—

4. Normal types of cell alone present.

5. Ontogenetic forms

(*a*). Present.

(*b*). Preponderant.

6. Phylogenetic forms present (ancestral cells, up to leucoblast).

Combining these according to the most practical requirements, we have the following, arranged in symbolic form :—

Class A. 2 + 5*a* + 1	*Class D*. 2 + 4 alone
„ *B*. 2 + 5*b* alone	„ *E*. 2 + 5 + 3
„ *C*. 2 + 4 + 1	„ *F*. 3 + 5*b* (possibly 1 also).

In each of these cases we are dealing with an effect produced by some noxious agent which acts either on the blood or upon the tissues forming the cells. The character of this agent is either inflammatory, infective, or non-infective. Two or more may be acting at one and the same time. The mode of action may be in the direction of stimulating or paralyzing the bone-marrow, and finally of producing or inhibiting regenerative processes. In that the phenomenon of leucocytosis is to be interpreted as evidence of a reaction towards an organism or substance, for the purpose of

* Thus, in a case of lymphocytosis of 35 per cent (quoted by Pappenheim), with eosinophiles 12 per cent, the lymphocytes are increased 10 per cent, and the eosinophiles 8 per cent ; and yet the *percentage increase* of the lymphocytes is 40, while that of the eosinophiles reaches 200 !

protecting the body as a whole, we may speak of a reactive leucocytosis—a process demonstrating to us that there is a need for the prevalence of a particular cell, associated as a rule with effective powers of mobilizing the supplies. As soon as there is a failure to carry out the latter, leucopenia results, or immature cells appear in the blood.

Leucocytosis, then, is a symptom, the result of various circumstances conveniently codified by the phrase "infective process." Just as a number of conditions must be fulfilled before infection can take place at all, so the reaction of the bone-marrow depends on the nature and mode of action of the exciting agents,* on the individual peculiarities of the organism at work, on time-intervals (stage of disease), and the character of the viscus or tissue which first bore the brunt of the attack. Leucocytosis is a "function" of all these factors. A noxious agent may be chemotaxic purely for the particular leucocyte, and draw out a certain number of the reserve cells already present in the bone. Another noxious agent may do more than this: it may stimulate the cell to a certain degree of activity, so that new ones are being made in larger numbers. The degree of activity may be just sufficient to satisfy the demands of the moment, may be in excess of demands, or may result in the discharge of immature forms into the blood-stream. Under ordinary circumstances the youngest cell to appear in the blood is the metamyelocyte, but in some cases myelocytes appear to the extent of 1 or 2 per cent. Finally, cases may occur in which paralysis of white-cell formation sets in, the demand being beyond the powers of the tissue—or inhibition of cell-multiplication has ensued—so that leucopenia results. In other words, diminution of total numbers of white cells, or of neutrophile leucocytes, may be regarded as an extreme stage of leucocytosis.

As has been stated, all manner of noxæ may set up leucocytosis, even substances arising in the course of physiological metabolism being able to excite it (*e.g.*, digestion leucocytosis), so that every noxa must not be regarded as necessarily pathological. Such bodies as nuclein, nucleic acid, adrenalin, lactic acid—formed during

* Benneckε, F. H. ix. 2, p. 154.

normal metabolism—will account for the ever-varying numbers of these cells in the same individual's blood. It will be evident that the difference between physiology and pathology here lies in the curious circumstance that in the former, supply exactly meets demand (which is only of temporary character), while in the latter the demand is in excess of the normal, and may or may not be temporary.

Study of the blood of infants by Wernstedt[101] has shown a remarkably rapid variation of the leucocyte content. Thus, the waking infant readily shows leucocytosis, while during sleep there is a marked fall in the white-cell content of the blood. Active muscular movements appear to account for the increase occurring during waking hours, a point of interest in reference to the subject of myogenic leucocytosis already referred to (*Chapter III.*).

Drugs Causing Neutrophile Leucocytosis.—Arranged alphabetically, the following may be mentioned: Anæsthetics (ether, rarely chloroform); blood-poisons, such as met-hæmoglobin formers (potassium chlorate, pyrogallol, phenylhydrazin, pyrodin, salicylates, antipyrin, antifebrin, phenacetin); camphor; cinnamate of soda, cinnamic acid; collargol; [102] digitalis, digitoxin;* ethereal oils (Meyer); fats,[104] gelatin;† irritants such as turpentine, croton oil, copper sulphate; nuclein, nucleinic acid;[105]‡ organ extracts; ozonized turpentine intravenously in animals;[107] antitoxic sera; tinct. amara and quinine (Hirt); *x*-rays act in ten minutes (Krause).[108]

Other Agents.—Pregnancy, hæmorrhage, cancer, septic and inflammatory conditions; such diseases as rickets, gout, acute yellow atrophy, cirrhosis of the liver.

The above list does not exhaust the possible causes of the condition. It will be evident that the ordinary physiological phenomenon of leucocytosis will itself react upon the formative organs, and excite a compensatory proliferative activity,§ whose result is an automatic replacement of cells into the blood. Should the products of white-cell destruction become abnormal, they would excite an abnormal reaction and tend to bring about the entry of abnormal cells into the blood. Further, it is evident that

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* Acts in seven to eight hours, and increases steadily after, by actual stimulation (Mirano[103])

† 40 c.c. of 10 per cent solution, subcutaneously, causes a leucocytosis up to 40,000.

‡ But Löwit states that this destroys white cells, and that it is the break-down products that stimulate hyperleucocytosis.[106]

§ Zoja[115] found that leucolytic substances have a definite specific action on the bone-marrow.

many circumstances might work together to overturn the equilibrium between leucocytolysis and leucopoiesis. An inability or a defective action of the leucocytophages in certain regions may have far-reaching effects. According to Zoja,[115] the balance of the processes has something to do with production of leukæmia on the one hand, and pseudoleukæmia on the other. However, the rarity with which such loss of equilibrium is met with, itself speaks against such a view being of fundamental importance, and necessitates still deeper researches into the mechanism of metabolism in the leucopoietic system.

Turning back to consider the possible variations in the white-cell formula in relation to the clinical deductions desired, we find that increase in the polynuclear leucocytes in the blood may take on one of the following forms :—

Polynuclear neutrophilia plus (*a*) absolute hyperleucocytosis : *
Class *C*,† or hyperorthocytosis.

Polynuclear neutrophilia plus (*b*) only relative leucocytosis.
Class *D*, or normo-orthocytosis.

Neutrophilia with appearance of metamyelocytes and occasional myelocytes :

(*a*). With absolute hyperleucocytosis
Class *A*, hyperneocytosis

(*b*). Without absolute hyperleucocytosis
Class *B*, normoneocytosis.

(*c*). With absolute leucopenia
Class *E*, hyponeocytosis.

Leucocytosis occurs in two degrees: the first degree is usually called *absolute* leucocytosis, and the second *relative*. Each is conveniently subdivided into two phases: the first, that in which only mature or blood-normal cells are present, while the second phase is indicated by the presence of immature cells as well. If these are only scanty, we deal with a second-phase first-degree leucocytosis; if they are prevalent, we deal with a second-

* Hyperleucocytosis means a " good reaction," and does *not run parallel with severity of infection.*

† *See List* on p. 234.

phase second-degree leucocytosis. If the phenomenon belongs to the first phase, the blood-forming organs are "sufficient," while the second-phase second-degree implies "marrow incompetence," or commencing exhaustion of the marrow. The degree of the latter is estimated by noting whether there is or is not leucopenia supervening.

The first phase includes :—

Cases showing the formula of 2 (*see Table* on p. 234) without 5.

Cases showing 1 and 2 without 5 (implies a simple leucocytotic irritant).

Cases showing 2 + 3. Here the appearance of 5 might be expected to follow very shortly.

The second phase includes :—

Cases showing a formula with 2 + 5*a* and no total cell-increase.

Cases with 2 + 5*a* + 1 (reserves being used up).

Cases with 2 + 5*b* + 1

Cases with 2 + 5*a* + 3 (toxic action on factories, and a *sub finem vitæ* stage, if 5*b* appears).

Cases with 2 + 5*b* (or 6) + 3 (complete exhaustion).

The regenerative phase of functional leucocytosis is expressed by Class *B*, irritative leucocytosis by class *A*, a vigorous first stage of leucocytosis by Class *C*, a commencing or fading reaction by Class *D*, over-irritation by Class *E*, and exhaustion by Class *F*.

This mode of presentation gives the necessary changes that may be found in practice, without the redundance of verbiage which would be inevitable were a description of the varieties attempted. It is evident that there is extensive scope for permutations and combinations, but the essential points to notice in white-cell-counting (in non-leukæmic conditions) are the existence or not of neutrophilia, lymphophilia, eosinophilia, monocytosis, and *whether juvenile forms are present at all.* In the latter event we ask ourselves, Do they go back as far as, or further than, the leucoblast stage ? The existence of juvenile forms is conveniently expressed as a "*deviation to the left.*"

2. **Leucopenia.**—The opposite condition to leucocytosis is a diminution of the numbers of the white cells of the blood. This may involve all the cells of the white-cell-formula. or it may involve

only one group. We should then speak of a neutropenia, a lymphopenia, an eosinopenia, a monopenia, etc. In a sense, this disappearance of large numbers of a given leucocyte from the stream may be expressed as the extreme stage of leucocytosis. It may also be the result of dissolution of the white cells—so-called leucocytolysis—in excess of the normal. Manuchin[110] found that the injection of peptone, diplococcotoxin, staphylotoxin, or typhoid toxin would produce this effect, and that the heated toxins failed to do so. Such bodies would be called leucocytolysins.

The following *drugs* will *cause leucopenia*: Large doses of quinine, atropine, benzol dissolved in olive oil (Selling[111]), thorium X (Falte, Kriser, Zehner[112]), horse serum. Trypsin produces this effect within three or four hours after injection (Magi[113]). *Other causes* are: Malnutrition, pernicious anæmia, traumatic conditions (shock), protozoan infections (malaria, kala-azar, trypanosomiasis); fevers, such as typhoid, measles, Malta, influenza, tuberculosis; severe toxæmias of any kind.

The pathology of leucopenia may be one of the following: Over-irritation by chemotaxic agencies; exhaustion of the regenerative power of the marrow; direct paralytic action on the mobilizing powers of the marrow; direct paralysis of cell-formation (typhoid).

3. **The Hyperplastic and Metaplastic Processes of Leucopoietic Tissues.**—So far we have only considered the effects of irritants upon the marrow, acting either at a distance, or becoming concentrated in the tissue itself. We have not referred to the outpouring of leucocytes into the site of invasion of the body by an infective agent, where the chemotaxic force collects all the circulating white cells to the spot, and only secondarily acts on the marrow by placing it in a position that demands increased activity on its own part. This is a local leucocytosis. It is easy to imagine that the effect of such a lesion would produce secondary substances that might in their turn set up a blood-leucocytosis, and finally proliferative processes in the formative organs.

In Leukæmia we have to deal with a different process altogether. In leucocytosis the agent at work lies in the blood-stream or, as

just indicated, at a distance from the bone-marrow, whereas in leukæmia the agent is situated in the tissue itself. Leucocytosis will cease as soon as the stimulus is removed, but the leukæmic process knows no ending, cannot at the present day be certainly or permanently arrested, and certainly exhibits no spontaneous tendencies towards subsidence, any more than does a sarcoma. We deal here with a hyperplastic or a metahyperplastic process that can never undergo retrogression in the ordinary course of events. The cells liberated into the blood present a moderate degree of mobility and phagocytic power, and retain the power of mitosis, which is not seen in leucocytosis.

This is perhaps the really fundamental feature of the disease called leukæmia,* about which so much has been written and so much theorized. A table of contrasts will bring out the important features of the two processes and render detailed discussion unnecessary :—

Leukæmia	Leucocytosis
Cause unknown	Easily discerned
The tissue change is plastic	Is functional
The process is unlimited	Depends strictly on the persistence of a metaplastic reaction or regenerative stimulus
Cell-increase is constant	Proliferation declines as soon as immature forms appear
The stimulus to hyperplasia is in the tissue	In the blood-stream
Ancestral cells are characteristic	Do not occur, only ontogenetically immature forms
The increased formation of these cells is the primary change	Immature cells appear only as a secondary process
The proliferation is purposeless	Is purposive, and of advantage to the body
The cell-division is homoplastic	Is heteroplastic, i.e., differentiated cell-types are produced
There may be no more cells in the blood than usual (aleukæmia)	The *total* count may be normal, but there is always " osis "
The cells enter the blood by *pressio a tergo.*	The cell-increase is due to *tractio a fronte.*

* See also Chapter I, Section III, and Chapter VII, Section III.

There is a certain analogy between the leukæmic proliferation and the formation of merozoites in a sarcomatous tumour without discernible immigration of the cells into the blood-stream. On the other hand, to speak of leukæmia as a form of sarcoma is to confuse the significance of sarcoma itself. There is no analogy between a spindle-celled sarcoma of a bone, and a leukæmic bone, and since the published accounts of round-celled sarcomas do not include studies along modern histological lines, they furnish no satisfactory evidence in the direction of the comparison so frequently instituted. (*See also p.* 42.) It is more satisfactory to regard the two diseases as having causative agencies that possess certain features in common. The liberation or not of the homoplastically proliferated cells into the blood-stream depends on the position of the cells with respect to the vascular walls in the marrow, and it is far from certain that sarcomatous cells do not circulate in the blood in large numbers in cases of so-called " round-celled sarcoma " or of lymphosarcoma. Observations by the writer in this direction have suggested that more care and more detail in differential counting would lead to the certain clinical diagnosis of at any rate some cases.

Auxetic Processes.—Certain interesting researches by H. C. Ross[114] deserve mention in connection with the cytoplasias of leucopoietic tissue. This observer, working by a special technique, which is equivalent to the much-talked of " in vitro " growth of cells, finds that certain substances can influence the mobility of leucocytes, while others excite their proliferation. Such substances were named " auxetic." Common to all these bodies is the amidine grouping : $N-C=N$. Leucocytes exposed to reagents containing this group would undergo division ; ulcerated areas exposed to such reagents would heal more rapidly than before. " Proud flesh " would be the result of the amidine bodies liberated in the course of decomposition of the exuded matter. Certain of .the auxetic substances (amines and aminoacids) were found to require the presence of certain alkaloids (e.g., atropine) before they were activated. Such observations will stimulate further research in the direction of correlating changes in blood-cell formulæ with changes in composition of the blood or tissues. Just as it should

be ultimately possible to subdivide micro-organisms according to the atom-groups which their toxins contain, rather than according to their cultural characters, so we should be able to detect the character of the toxin by observing the type of leucocytic or red-cell formula exhibited by the patient's blood or tissues. In other words, the clinical examination of the blood would aim at the detection of certain atom-groups at work in the course of the various infections. This conception finds greater prospect of corroboration by studies of cytoplastic phenomena in the tissues, as will be shown in Chapter VII.; but the diagnosis of the fundamental character of morbid conditions in the hæmopoietic tissues may be aimed at, even if knowledge is never to be actually reached at in full. Furthermore, the study of toxic substances able to inhibit or accelerate cell-differentiation, or to turn the developmental sequence along unnatural, lines cannot fail to throw desirable light upon the obscurities of cytometaplastic and allied processes.

CHAPTER VI.

ON CERTAIN PHLOGOCYTES.

Section I.—ABERRANT ABORTIVE HÆMOPOIESIS: The small round-celled infiltration of tissues—The meaning of the term " phlogocyte."

Section II.—THE EOSINOPHILE CELL: Varieties—Morphology—The granules, and their properties—Source—Functions—Eosinophilia and eosinopenia of the blood and tissues—Source of the cell—Comparative cytology.

Section III.—THE MAST CELL: Varieties—Morphology of the mast cell of the blood; of the tissue—Occurrence—Function—Chemistry of the granules—Views as to nature—Source—Comparative cytology.

Section IV.—THE PLASMA CELL: Varieties—Morphology of the plasma cell of the blood—Occurrence in the blood—Table of blood-plasma cells—Occurrence in the tissue—The lymphoblastic plasma cell—The granules—Ancestry—Theories—Effect of plastic irritation of the adventitial cells—Fate of the plasma cell—Functions—Comparative cytology.

Section V.—THE CLASMATOCYTE and other purely connective-tissue cells—The giant cell.

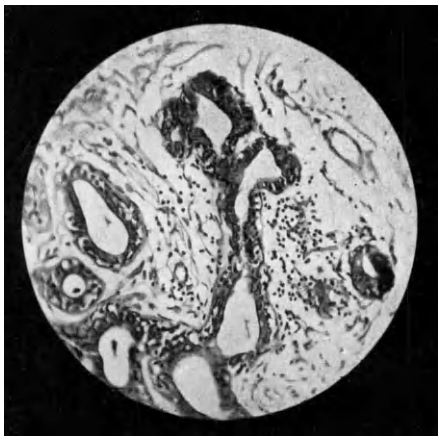
Section VI.—THE CYTOPLASTIC INTER-RELATIONS BETWEEN THE VARIOUS PHLOGOCYTES.

I.—ABERRANT ABORTIVE HÆMOPOIESIS.

THE small round-celled infiltration of tissues—The meaning of the term "phlogocyte."

WHEN discussing the lymphocyte, it was pointed out that morphologically similar cells occur in many tissues, both normal and pathological, under the guise of "small round-celled infiltration." That is to say, there is evidence for the belief that some of the circulating lymphocytes may make their way into the tissue spaces. *Fig.* 62 shows lymphocytes scattered in the vicinity of a small duct in the breast, without any definite suggestion that their presence is in any way abnormal—since the capillaries show no changes, and there is no undue deposition of fibrous tissue. The presence of these cells must nevertheless signify the existence of an attracting agent, and from what has been said about the function of lymphocytes, we should assume that some abnormal kinds, or an excess of normal fatty acids, diffusing through the walls of the duct, are being dealt with by the cell-accumulations, in some mysterious way. A similar explanation affords a satisfactory clue to the meaning of the varying forms of infiltration met with in the interglandular tissue of the small intestinal tract.

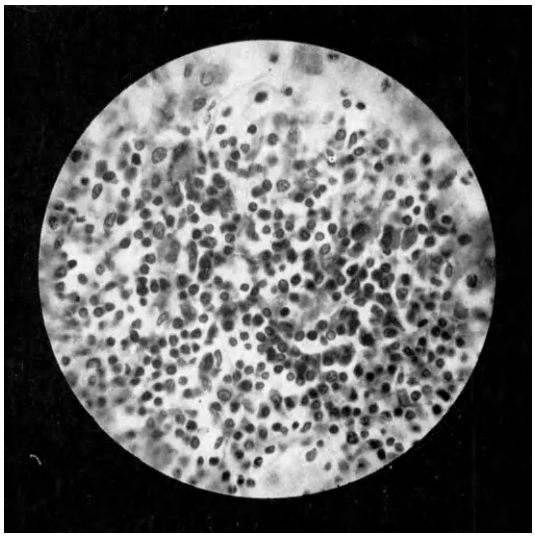
A slightly different form of round-celled accumulation is shown in *Fig.* 63, taken from the medullary region of the adrenal, where such cell-aggregations are not infrequently found. The cells are not all of the same type, but vary considerably in size, while some have pale and others dark nuclei. There is no obvious relation between these cells and a blood-vascular channel, so that the meaning of the process must be slightly different from that quoted for the breast. On the other hand, the adrenal cortex is rich in lipoids, and it is easily understood that the lymphocytoid cells may play some part in relation to them. There is here no evidence of chronic inflammation, so that the cell-aggregation would not be



" . . . lymphocytes scattered in the vicinity of a small duct in the breast " (p. 244).

Fig. 62.—The trifid duct is noticed in the centre, while a few small round cells occur here and there in the loose tissue around.

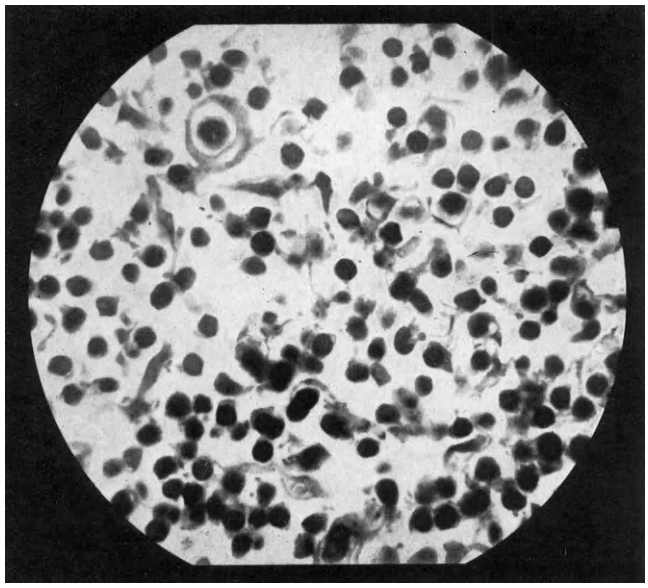
(Oc. 2, Zeiss Obj. A)



" The cells are not all of the same type, but vary considerably in size, while some have pale and others dark nuclei " (p. 244).

Fig. 63.—ADRENAL MEDULLA, SHOWING SMALL-ROUND-CELLED INFILTRATION. The large, pale, ill-defined cells at the upper and lower portions of the photograph are the adrenal cortical cells. The small round cells filling up the remainder of the field are those referred to in the above quotation from the text.

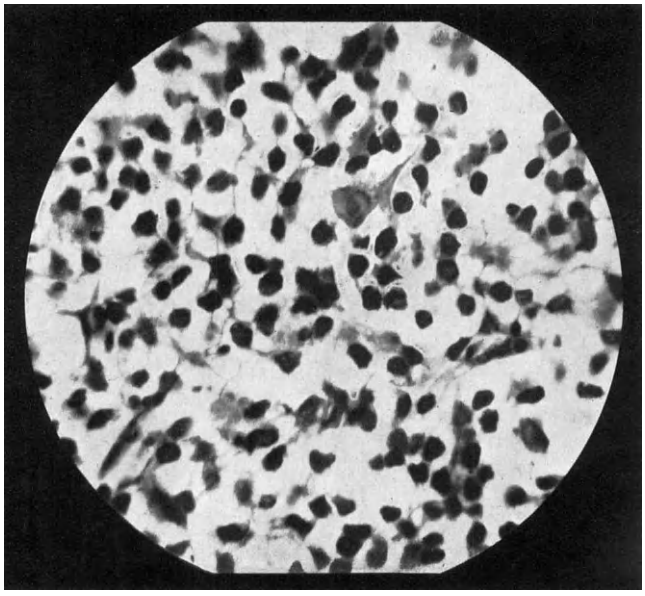
(Oc. 2, Zeiss Oil-immersion.)



" . . . the scattered round cells are separated by a fluid containing granular matter (coagulable proteid), and are admixed with . . . elongated spindle-shaped cells " (p. 245).

Fig. 64.—VIEW IN A ZONE OF CHRONIC INFLAMMATORY CELL INFILTRATION. Most of the cells in this figure are small round histiogenic lymphoctyes.

(Oc. 4, Zeiss Apochrom. 4 mm.).



" . . . a large polygonal cell is noticed, which has a granular cytoplasm and a relatively large rounded nucleus " (p. 245).

Fig. 65.—Another view in the same zone as the preceding. This photograph shows the uniformity of morphology of the lymphocytes, the presence of an endothelioid cell, a fibroblast, and the existence of astral processes from lymphocyte to lymphocyte, as if they organize by joining hands. Above the large cell referred to in the text quotation is a dividing macroplasma cell. (*These two photographs are from a specimen of chronic syphilitic orchitis.*)

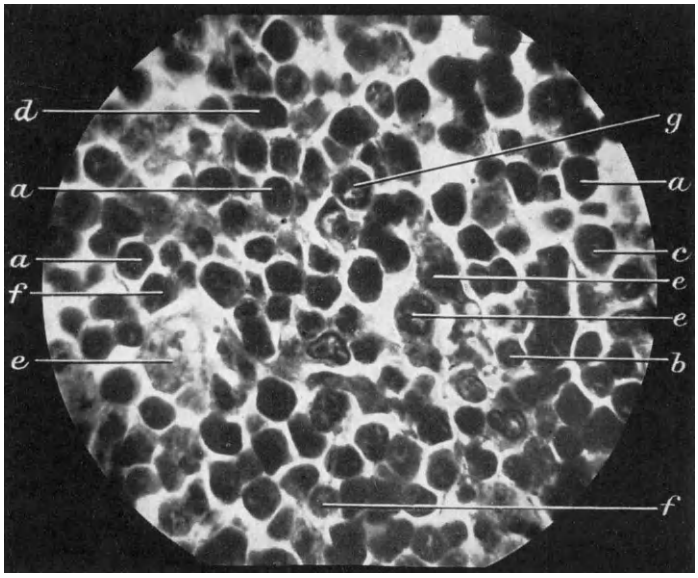
(Oc. 2, Zeiss Oil-immersion).

correctly placed in the same category as the small round-celled infiltration of chronic inflammation. Further, a comparison of such cells with those seen in a lymphoid follicle reveals the fact that in each case we have large, medium, and small lymphoid-cell forms, each being a successive generation. It may be assumed, then, that there is some resemblance between the two cell aggregations, and we might speak of the adrenal collection as a Ribbert lymphoma, which, it was pointed out, is an accessory factory of lymphocytes.

When we compare these forms of infiltration with a definite inflammatory mass (*Fig.* 64), we find a certain degree of resemblance between the cell-constituents in each case, but here the scattered round cells are separated by a fluid containing granular matter (coagulable proteid), and are admixed with a variable number of elongated spindle-shaped cells (young fibroblasts), and not infrequently the lymphoid cells may be seen to throw out slender processes which interlace with those of adjoining cells. In this way a variably dense meshwork is produced. A large polygonal cell is also noticed (*Fig.* 65) which has a granular cytoplasm and a relatively large rounded nucleus. Such a cell bears a resemblance to the primordial cell of the tissues, and its presence must bear some relation to the other cells already referred to. The multitudinous types of cell which are described in inflammatory tissues, or tissues recovering from some injury (repair) form a striking feature of the process, and it is well known that every case of small round-celled accumulation does not go on to the formation of a dense spindle-celled tissue. For some unknown reason, some of these cases remain lymphoid, others become, and remain, plasmoid, others eosinoid, and a few become fibroid. Under the influence of exceptional stimuli (e.g., *x*-rays) fibroblasts may alter their characters, undergo true anaplasia (in chemical parlance, we have a reversible reaction), and deviate along any other line of development. This interpretation cannot be proved beyond cavil, because it is impossible actually to trace one individual cell-form into any other. The fibroblast, for instance, may really have undergone necrosis and solution, while new lymphocytes enter the scene of action. On the other hand, the plasmoid change is traceable

through various stages from a lymphocytic outpouring to an extent sufficient to make it very suggestive that fibroid and eosinoid changes may actually take place also. It must be pointed out, further, that the only difference between a tissue made of fibroblasts and true fibrous tissue lies in the amount of dead inert material (Gewebsschlacken) containing something akin to chondroitin-sulphuric acid, which has been sweated out or deposited around the formative cells that have lost the power of movement; they lie inert among their excreta until in process of time they suffer asphyxia, or starvation, owing to the inability of the necessary food materials to penetrate or osmose through this new colloidal material. In those cases where the cells do not succumb, the removal of the excreted matter by ferment action would once more liberate the cells, and render them amenable to some auxetic or kinetic stimulus, convert them into free-floating cells, and rejuvenate them sufficiently to despatch them once more along the original cycle of changes familiar to them at an earlier period of their life-history, when the original stimulus or irritant had set the so-called inflammatory process in motion.

From these considerations it is seen that one can trace a definite series of changes in the cells scattered through the tissue spaces which is quite analogous to that already described in the case of the well-known blood-cells. If the parent of a blood-cell is at one time an adventitial cell, there is no reason for excluding the tissue-cells of the types mentioned from origin in a similar parent. The invention of the term "phlogocyte" by Türk, emphasizes the family resemblance between the two main groups of migratory cells, and a description of the biology of the blood-cells would be incomplete without a consideration of the changes which may take place in some of them after they have left the circulating blood. The association of plasma cells, eosinophile cells, and mast cells with the ordinary pulpar cell of the lymph-node and spleen is sufficient to show that there must be some very close relation between the hæmopoietic and the phlogocyte series (phlogopoiesis), which is probably correctly expressed by saying that certain of the lymphoid-ocytar cells may at one time give rise to circulating cells and at another to local tissue inhabitants. The latter may occasionally



" . . . the difficulty of certainly distinguishing daughter-plasma-cells from a lymphocyte " (p. 273).

Fig. 66.—CHRONIC INFLAMMATORY CELL INFILTRATION IN A CASE OF GONORRHŒAL SALPINGITIS (*a*, *a*), daughter plasma cells; (*b*), lymphocyte, with nucleolus; (*c*), lymphoblastic cell; (*d*), large or mother plasma cell; (*e*, *e*), adventitial cell; (*f*, *f*), polynuclear leucocytes; (*g*), eosinophile cell.
(Oc. 12, Zeiss Oil-immersion).

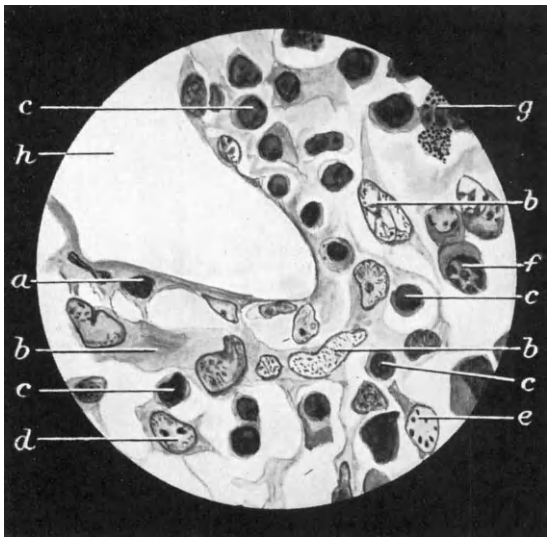


Fig. 67.—PORTION OF A CAPILLARY WALL IN AN INFLAMMATORY AREA IN A CASE OF CHRONIC INTERSTITIAL APPENDICITIS. (*a*), endothelial cell lining (*h*), the vascular channel; (*b*, *b*), adventitial connective tissue cells; (*c*, *c*), lymphocytes; (*d*), mesenchymal connective tissue cell; (*e*), wandering cell; (*f*), plasma cell; (*g*), eosinophile cell.
(Oc. 12, Zeiss Oil-immersion. *Camera Lucida Drawing*)

Face p. 247]

ooze into the blood-stream and appear there as eosinophile leucocytes, irritation cells, and mast leucocytes.*

In tracing out this analogy between two broad cytoplastic processes, we need to draw a sharp distinction between the acute suppurative processes and non-suppurative conditions. The former are associated with an outpouring of fibrin, and show very few mononuclear cells. With the subsidence of the acute change, however, factors arise which allow of a phlogoblastic development in some cases. Lymphoblastic cells then arise, such as are seen typically in the subacute or chronic gonorrhœal cases of salpingitis (*Fig.* 66). These lymphoblasts are as truly parental here as in the bone-marrow or lymphatic tissues, but the sequence of development is patently different. We have before us an *aberrant hæmopoiesis*, shown by the tendency to produce plasma cells, eosinophiles, and no fibroblasts; at other times, fibroblasts are also produced. The main significance of these cell-forms lies in the fact that future research should tell us exactly what atom-groups are responsible for their appearance in the tissue.

The perivascular cellular tissue would then be described, after Pappenheim,[1] as a slumbering blood-cell-forming tissue (*Fig* 67), and the *fundamental principle common to hæmopoiesis and inflammatory cell formation* would be emphasized. The scheme :—

lymphoidocyte → eosinophile myelocyte
↓
daughter eosinophile myelocyte → eosinophile leucocyte

finds its analogue in

lymphoidocyte
↓
daughter lymphoidocyte → eosinophile myelocyte → eosinophile leucocyte of tissue space
(small round cell of inflammatory tissue)
(histiogenic lymphocyte)
(tissue lymphocyte)

The daughter lymphoidocyte is like a tissue-lymphocyte; further than this it is not possible to go—we cannot say exactly what may have been the source of any given individual lymphoid

* Naegeli, Marchand, and Pappenheim believe in the local origin of inflammatory cells, while Ziegler, Schridde, and Maximow consider them as emigrants, attracted by chemotaxis.

cell that we see through the microscope in this situation. The correct attitude to adopt in respect to the study of chronic inflammatory cytology is that of deciding the cytoplastic stage which has been reached by any given cell, using the nuclear characters as a criterion of development along the phlogoblastic line. More briefly, the nuclear structure affords a clue to the direction along which the given cell is trending at the moment of fixation of the tissue, and not to the road along which it has previously travelled.

II.—THE EOSINOPHILE CELL.

VARIETIES—Morphology—The granules, and their properties—Source—Functions —Eosinophilia and eosinopenia of the blood and tissues—Source of the cell— —Comparative cytology.

IN every hundred leucocytes that pass by any given point of the circulation, we may expect *one* to contain granules intensely stainable with eosin. In some physiological states they may not be as numerous as this, and in others they are more frequent. A large number of morbid states are associated with increase or decrease of their numbers. As with all the other blood-cells, our curiosity is aroused as to whence these cells are derived, and while history tells us that they are supposed to come from a mother cell in the bone-marrow, it is only necessary to study microscopic sections of many tissues to convince ourselves that such supposition is extremely one-sided. Just as the lymphocyte of the blood-stream bears some relation to the lymphocyte of the tissue, and is yet not always the same, so the eosinophile cell of the blood-stream is sometimes similar to the eosinophile of the tissue, but not in every instance exactly the same. In other words, the neutrophile leucocyte always comes from one series of cells, viâ the neutrophile myelocyte, but the eosinophile leucocyte has a variable ancestry, and is rather to be looked on as representing a functional stage of more widespread cells.

Varieties of Eosinophile Cell :—

The eosinophile "myelocyte."

The eosinophile leucocyte.

The eosinophile cell of the intestinal mucosa.

The eosinophile cell of chronic inflammatory tissue, including the eosinophile clasmatocyte.

The eosinophile corpuscle of ocular tissues.

The eosinophile cell of Hodgkin's disease.

Morphology.—In each of these cells the all-important feature*

* Arneth's method applied to the eosinophile cell[2] has proved to be of no service.[3]

EXPLANATION OF PLATE VII.

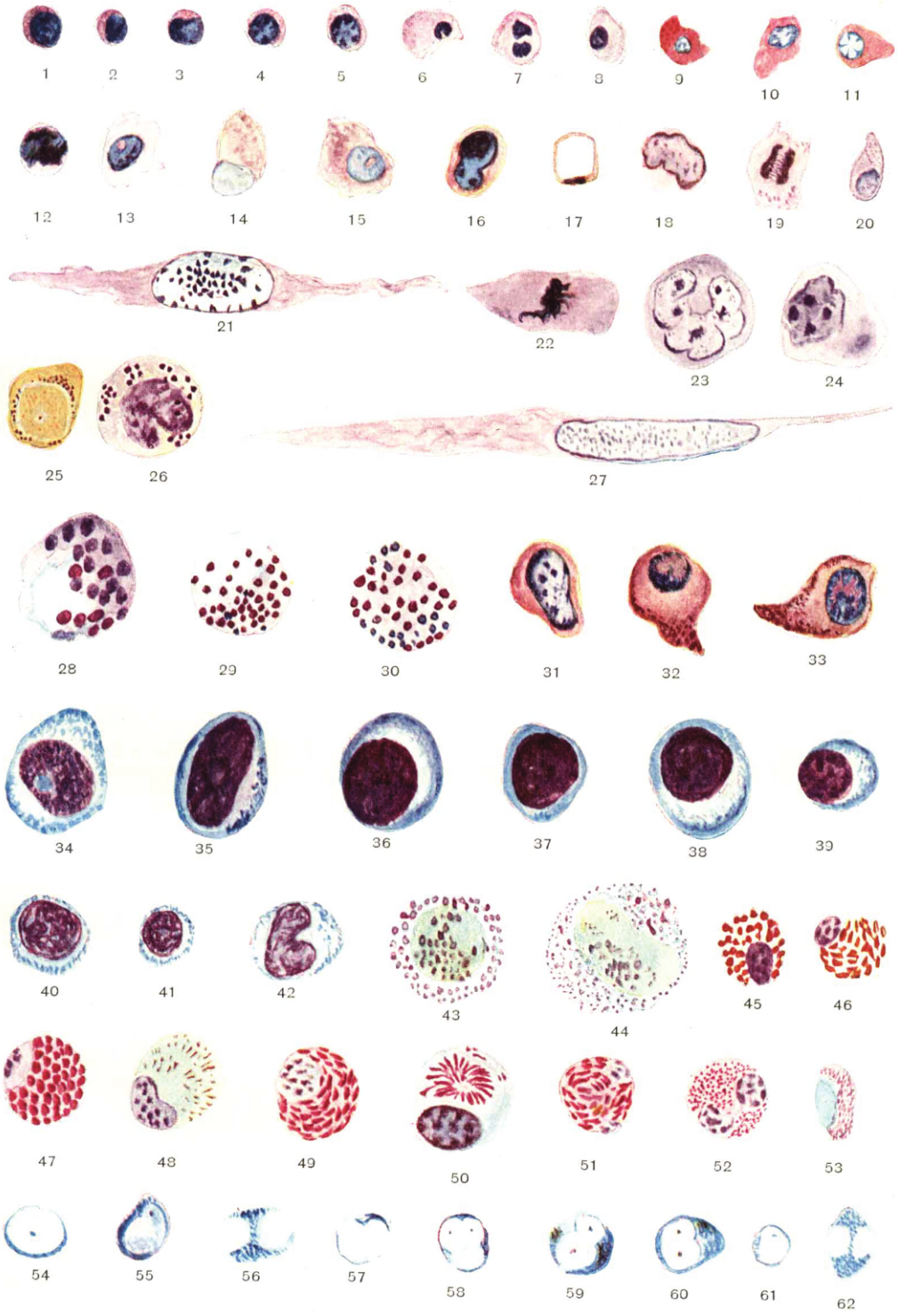
1-3.—Tissue lymphocytes. 4.—Ditto, showing wheel markings. 5.—Ditto, showing p asmoid change, while the external contour is unaltered. 6-8.—Plasma cells with swollen body; 7 is dividing; the cell-body is dusky but the nucleus is hyperchromic. 9.—Tissue eosinophile. 10.—Eosinoid lymphocyte. 11.—Eosinoid plasma cell, with wheel marking. 12.—Lymphoblastic cell, with hyperchromic nucleus. 13.—Swollen connective-tissue cell, showing lymphoblastic nucleus and nucleolus. 14. 15.—Adventitial cells, rich in granoplasm. 16.—Marchand wandering cell, with rather oxyphilic cell-body and undergoing division. 17.—Degenerated vacuolated lymphocyte. 18.—Leucoblastic adventitial cells, having analogies with the pulpar cell. 19.—Giant cell undergoing division. 20.—Young fibroblastic lymphoid cell. 21.—Giant endothelioid cell or mesenchymal cell. 22.—Smaller form with caryolytic nucleus; the cytoplasm is more basophile. 23.—Megakaryocyte, showing the characteristic nuclear form, from a case of Hodgkin's disease. 24.—Another form, showing exudation of nuclear material into the cell-body. 25.—Lymphatic leukæmic leucocyte, stained to show Altmann granules and perinuclear halo (after St. Klein, Fol-hæm. Bd. x, *Plate XIII*). 26.—Leukæmic mast cell (after Pappenheim, Grundriss). 27.—Giant fibroblast. 28-30.—Hybrid mast-eosinophile cells (after Benacchio, Fol. hæm. Bd. xi, *Plate V*). 31.—Hodara plasma cell. 32, 33.—Marschalko plasma cells (31-33 after Hertz. Fol. hæm. Bd. xiii, *Plate V*). 34-42.—Various forms of plasma cell (after Pappenheim, Atlas): 34.—Lymphoidocytar form, with characteristic nucleus, nucleolus, and basophilic cell-body. 35, 36.—Macrolymphocytar form, with astrosphere. 37.—Young mesolymphocytar form, showing intense nuclear staining, deep basophilia of the periphery of the narrow cell-body. 38.—Mesolymphocytar form, with slight oxyphilia in the astrospheric region. 39.—Microlymphocytar form, with wheel-marking in the nucleus. 40.—Macroleucoblastic form, showing the shadowing of the nucleus and deep blue cell-body. 41.—Microleucoblastic form. 42.—Leucomonocytar form, with characteristic nuclear outline, deeply basophile cell-body. 43-53.—Various forms, as seen in the lower animals (43-53 after Werzberg, Fol. hæm., Bd. xi.; 51, 52, after Kasarinoff, Fol. hæm. Bd. x): 43.—Mast cell, siredon pisciformis. 44.—Mast cell, second type. 45.—Eosinophile of emys lutaria, with round granules. 46.—With spindle-shaped granules. 47.—Eosinophile myelocyte with halo round nucleus and inter-granular oxyphile cytoplasm, ophiosaurus pseudopus. 48.—Eosinophile cell with sparse spindle-shaped granules and tigroid nucleus from lacerta viridis. 49.—Eosinophile cell with dense rod-like granulation. 50.—Large myelocyte, with rosette of needle-like granules round the astrosphere, from hemidactylus. 51.—Pseudo-eosinophile cell of fowl-blood, showing a trace of polynuclearity; the granules are spindle-shaped. 52.—True eosinophile leucocytes of fowl-blood. 53.—Eosinophile cell from beetle. 54-62.—Normal marrow cells (rat) stained by the vital brilliant cresyl-blue method, showing granules in the cell-body, dividing forms, etc.

Magnification: 1-24, 27, 53, Zeiss oil-immersion lens, Oc. 12; 54-62, oil-immersion lens, Oc. 4; the remainder are more magnified than the first series.

Stains: 1-24, 27, hæmatoxylin and eosin, cells drawn from sections; 25, Altmann's method; 26, 28-30, 34-52, Panoptic stain; 53, triacid stain; 54-62, vital stain.

PLATE VII.

PHLOGOCYTES



Biology of Blood-cells *O. C. Gruner*

is the character of the granules* which serve to render their detection in the blood-film or tissue extremely easy. The morphological characters need not be detailed. Suffice it to say, in the myelocyte form, the nucleus is " myelocytoid " in being single, reniform, oval, or slightly indented. If the indentation be deep, we could speak of a metamyelocytoid form. These nuclei stain feebly. The leucocyte form, on the other hand, has a bi-lobed nucleus which stains very intensely. Schridde considered that these varying appearances might be explained as the effect of obliquity of section, one lobe only being caught in some, while both are caught in the others; on the other hand, the difference in the degree of chromatism could not be accounted for in this way.

The granules stain an intense glistening vermilion red with eosin. With dark-ground illumination they take on a golden-yellow sheen and are very conspicuous. The speculations regarding their nature are intimately bound up with the question of the meaning of the eosinophile at all.

Properties of the Eosinophile Granule.—(1) They possess an oxydase (Loele[5]) but no protease (Wiens-Schlecht[6]), and contain a haptophore group whose chemical structure is — NH_2.† This is shown by the intense phenolphilic reaction obtainable with these cells, which indicates that the granules must constitute oxygen-centres from which the oxidation of leuco-bases can proceed. (2) They contain an aldehyde group (Weiss[7]), shown by the fact that they give the furfurol reaction of Molisch-Udransky, or the Reichel-Mikosch aldehyde reaction (violettblau). This indicates the presence of protein in the granule, and of a skatol grouping. (3) They give the pyrrhol reaction with paraminobenzaldehyde and HCl;[8] so they must contain a protein akin to melanin or keratin (Petry, Schlecht, and Ziegler). (4) They contain 11 per cent of iron, according to an analysis by Petry.[9] (5) Gollasch found that the granules might give rise to Charcot-Leyden crystals in cases of asthma, and pointed out that the latter are identical with the

* Arnold's plasmosomes.[4]

† The detection of an — NH_2 group is of importance in connection with the relationship of eosinophile to mast cell granules (*see* " Hybrid Cells "). It seems possible for the one to be converted into the other. Mast-cell granules need diamidobenzol or α-naphtylamine (benzol radicle) for their demonstration, but the staining is not specific (Loele).

seminal crystals of Böttcher, which are composed of ethylene-imine, C_2H_4NH. (5) Ciaccio claimed to have demonstrated the presence of lipoid substance within the granules. (6) An extract of eosinophile cells will give a marked oxydase reaction as long as it is not boiled.[10] (7) They contain no phosphorus (Petry), and are very resistant to solvents and ferments. (8) They react with adrenalin.[11]

Other Granules within the Eosinophile Cell.—Arnold[12] found glycogen granules in the tissue-eosinophile of the frog, rabbit, and child, and demonstrated that they were more abundant after a starch diet. He noticed that the character of the nucleus altered with the numbers of the granules.

Mast granules are noticed in the circulating eosinophiles in leukæmic blood, and in the bone-marrow eosinophiles in certain animals. Such " hybrid mast cells " are referred to later.

Source of the Eosinophile Granule.—There are two possibilities to consider. Either the material may be derived from within the cell, or it may be taken in from without. In other words, it is the manifestation of purely catabolic processes, or it may represent anabolic or anabolic-plus-catabolic changes. These may be tabulated as follows :—

Formed from within —

(*a*). From the *cytoplasm.* Benacchio has referred to a prodromal[13] granulation occurring diffusely through the cell. Schwarz[14] and Hirschfeld have considered that the neutrophile granule may become eosinophilic.

(*b*). From the *nucleus.* Stephan[15] described this mode of derivation in the case of Protopterus. Reicher,[16] in an elaborate study of asthma cases, found that the basic derivatives of cell nuclei (purin bases, or pyrimidin, pyrazin, pyrrhol, pyridin, etc.) might give rise to eosinophilic substance.

Derived from without—

(i). From the *proteins of food.* Rous[17] found this to hold good in the intestinal mucosa.[18]

(ii). From *red cells.* The hæmoglobin of dissolved red cells was supposed to convert a neutrophile into an eosinophile granule (St. Klein, Fuchs). Weidenreich thought that the hæmoglobin of dissolved red cells converted a lymphocyte into an eosinophile cell.[19] Sacharoff believed that it was the paranuclein of the red cell which converted the neutrophile into the eosinophile. The arguments *in favour* of an origin from red cells are : (1) That the eosinophile is more commonly met with now that formalin fixation is common ; (2) That the granules contain iron ; (3) That the ionized iron in the cell may be derived from the bone-marrow ; (4) That the chemical characters of the iron-protein compound (resistance to solvents and ferments, elastin-like reactions,

etc.) are opposed to relation to the hæmatin group (Petry)[9]. *Against* the view are (1) The fact that the glycogen granule is related in some manner to the eosinophile ; and (2) The facts of phenolphilia (*q.v.*).

(iii). From *injurious substances in the tissues* (Kämmerer[20]). On this view the neutrophiles in an inflammatory zone take up specific bodies, convert them into eosinophile substance, and lose their phagocytic activity. Similarly in infection by worms, the toxic substances are carried away by these cells.

(iv). From the *chromatin of degenerated spermatozoa* (Tettenhamer's explanation of eosinophilia in the testis).

The Functions of the Eosinophile Cell.—This subject is almost as obscure as that relating to the lymphocyte. Speculations are rife, but facts are few. The first question of interest, and the most simple to decide upon, is that of the factors which bring about eosinophilia or eosinopenia in the blood-stream.

CAUSES OF INCREASE IN THE BLOOD (greater than 3 per cent of the white cells).

Physiological States.—After food ; during childhood ; in 15 per cent of the healthy natives of Southern China.

Pathological States.—Presence of macroscopic parasites (trichina, hydatid, oxyuris, ascaris, ankylostomum, tænia mediocannelata).

Skin Affections.—Urticaria, zoster, pemphigus, psoriasis, eczema, etc.

Nervous Affections.—Graves' disease, puerperal mania, acute mania, melancholia, epilepsy, tetany, hemicrania, asthma (9–22 per cent).

Drugs.—Tuberculin, pilocarpine (Neusser, Falta, Eppinger : denied by Aschenheim and Tomono), secretin, fluid of hydatid cyst.

The following miscellaneous conditions have also been mentioned by different observers : tuberculosis of lung associated with emphysema, subacute or chronic tuberculous lesions, leprosy, scarlet fever up to the third week, congenital syphilis, uræmia, cirrhosis of liver, chlorosis, myeloleukæmia (up to 7 per cent), carcinoma with metastasis in the bone-marrow.

CAUSES OF DIMINUTION (less than ·5 per cent).—Pulmonary tuberculosis (unless irregular suppuration is also present) ; in lymphatic leukæmia, in measles, in starvation (Opie) ; wherever there is neutrophilia.

Eosinophilia as a *diagnostic aid*: Its presence may be used to distinguish between gout and tubercle of joints, between active malaria and typhoid, between scarlet fever and measles, between trichinosis and acute rheumatism.

As a *prognostic aid*: The reappearance of these cells after a suppurative process indicates approaching convalescence. In osteomalacia it signifies that the case has a good prognosis (eosinopenia indicates the reverse).

Eosinophile cells are *met with in the following tissues* :—

In the wall of the intestine, especially after intake of food.* They are found round the bases of the Lieberkühn follicles, are scanty in the villi and over the Peyer's patches. They ooze out into the mucus poured out into the lumen of the intestine. The cells are much more common in intestinal catarrh, appendical catarrh, and the "lower" grades of appendicitis. Between the epithelial cells of the bronchial mucosa. The periphery of the follicles of lymph-nodes; sometimes they occur within the peripheral sinuses; also in the connective tissue round the nodes (Opie). The periphery of the Malpighian bodies, especially if there is blood eosinophilia. The bone-marrow. The thymus (apparently the secretion attracts them). The hæmolymph nodes. Woltmann[23] believed that they develop here during the disintegration of red cells, whose products are absorbed by the large mononuclears. In the interstitial tissue of the kidney, of the fœtal thymus, of active guinea-pig breasts (Berka[24]). Here the clasmatocyte forms, mononuclear spindle cells, are to be seen.[25] Wherever there is breakdown of epithelium and cells. The nucleins and purin bases may play a part.

Causes of Increase in the Tissues.—Skin diseases show very well-marked local eosinophilia; chronic tuberculous lesions; the growing edge of cancerous growths. In tissues undergoing repair. Specially numerous in certain forms of appendicitis. After parenteral administration of protein.† After immunizing to anaphylaxis. After injection of tæniotoxin (Pröscher).

Organisms causing tissue eosinophilia of the conjunctiva: spring catarrh, diphtheria, staph. p. aureus, gonorrhœa, sporotrichosis. Cysticercus. *Tumours causing:* epithelioma and rodent

* Rous[17] thought these were the direct source of the eosinophiles of the lymph.

† See also Schlicht, M. 1013, p. 800.

ulcer. Lymphogranuloma. Acute myeloic leukæmia. Nasal polypus. [Local eosinophilia does not arise in follicular conjunctivitis (B. ichtimanicus), trachoma, molluscum contagiosum (Pascheff[22]).]

Organisms causing disappearance of eosinophiles from a tissue: typhoid toxin, streptococci, anthrax bacilli (C. P. Howard[26]).

Drugs failing to induce local eosinophilia: leucin, alanin, phenylalanin, asparagin, glycocoll.

From all these observations it may be concluded that the eosinophile cell is amœboid (Sansonow[27]), (Stöhr's phenomenon), is subject to chemotaxic influences, and may take up diphtheria bacilli (G. B. Foster[28]), or staphylococci (Pascheff[29]). Further, that it plays some part in the digestion of proteid, that it may make antibodies to certain organisms (diphtheria, tubercle), that it may furnish a body like enterokinase, and activate the glandular secretion of the intestinal wall (Simon, Pirone,[18] Schwarz[14]).

While much more definite information is needed on these points, it is advantageous to look upon a tissue-eosinophilia as meaning the presence of a definite protein substance whose nature requires elucidation. The excessive numbers found at the periphery of the follicle remnants in a Hodgkin's gland, for instance, must mean the accumulation of noxious bodies in that situation, bodies which are probably of the protein-group, perhaps polypeptids, perhaps more complex than these. On the other hand, bodies belonging to the fats may possibly have some relation to them, eosinophiles being observable in diseased mammary tissue. In the latter, the preponderance of lymphocytes, meaning as it does the presence of abnormal fats, would indicate that a protein constituent may have become liberated as well, and is being dealt with by the eosinophiles.

Source of Eosinophile of the Tissue.—As with other tissue cells, the presence of eosinophiles may be explained in two ways. Either they have wandered thither, or they have been formed *in situ*. A third possibility, that some have wandered, and others have developed locally, is probably the correct explanation of most of these cell-aggregations.

The arguments in favour of the eosinophiles being of *histiogenic* and not hæmopoietic origin are as follows :—

1. Eosinophilia in the bone-marrow bears no constant relation to the tissue changes at the site of infection (Campbell Howard[30]) ; similarly, the bone-marrow is not eosinophilic in cases of blood eosinophilia ; and *vice versa* (Leighton[31]).

2. Amitosis can be observed in the tissue (cells with dumb-bell nuclei ; observations on osmic fixed material*). *Plate VII* shows some observations made on inflammatory tissue, exemplifying the gradual transition between lymphocytiform through leucocytoid to eosinoid forms. In some instances the cell-body takes on a diffuse eosinophilia, in others definite granules can be detected. The amœboid nature of these cells is also well shown by the elongated processes. The mitotic forms are shown by hyperchromia of the nucleus and even the presence of diasters. Conversion of lymphoid cells into eosinophiles has also been described by others in non-inflammatory tissues, and in the bone-marrow. The mononuclear forms are called α-(micro)myelocytes.

3. The occurrence of eosinophile corpuscles in tissues indicates the possibility of local formation.

4. The blood is full of lymphocytes in lymphatic leukæmia, but the exudate of an inflammation arising during the course of that disease fails to show lymphocytes. Neutrophiles occur instead. Tissue eosinophilia therefore does not necessarily demand blood eosinophilia as well.

The arguments raised against the view are :—

1. The cell-increase in the blood in cases of asthma, e.g., is quite enough to account for the tissue increase.

2. There are quite enough eosinophiles in the blood at any time to account for local emigration.

3. Opie[32] claimed to have observed their diapedesis.

4. There is marked eosinopenia of the blood after an asthma attack (Heinecke, Deutschmann).

5. Naegeli denied the possibility of their arising from endothelial cells.

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* Denied by Schridde.

In relation to the third, intermediate view, it may be pointed out :—

1. That there is no reason why local or tissue eosinophilia and blood eosinophilia should not both be produced by the same cause.

2. The evidence offered by a study of cytometaplastic processes in the tissues makes it perfectly obvious that certain tissue cells might just as easily make eosinophiles under the influence of a phlogoblastic stimulus as the hæmopoietic cells of the bone-marrow make them in the ordinary processes of life. The tissue lymphocyte, which partakes of the characters of a microleucoblast, or micromyeloblast, may readily undergo metamorphosis into an α-micromyelocyte, and finally appear as a tissue-eosinophile. Whether the chromatin of the nucleus remains the same or not is unessential; the myelocytic chromatin has a different composition and a different morphological arrangement, but may acquire its new characters by a perfectly continuous series of metabolic processes which are not necessarily either advance or regress, although some might take the view that an anaplastic phase is the first, and the metaplastic change the second stage in the process.

Further, it must be added that the tissue eosinophile is not for ever debarred from entry into the blood, and that some of the uninucleate eosinophiles of the normal blood* may have been derived from the tissues and would be distinguished from the bone-marrow myelocyte chiefly by reason of the large size of the latter.

Comparative Morphology of the Eosinophile Cell.—The eosinophile cells met with in the blood of the lower vertebrates are of considerable interest by reason of the bizarre forms which the granules assume. In the fish, eosinophiles are seldom seen, and do not present the vivid features noticed in the mammal. Carassius auratus, as described by Werzberg,[34] shows cells of moderately large size, with a relatively very small nucleus (almost myelocytoid in structure), varying in form from short to long oval, and slightly indent forms. The granules are more numerous toward the centre of the cell, are of uniform size, moderately numerous, and stain rather feebly. They are, however, much larger than the neutrophile granule and are somewhat highly refractile.

Reptile blood is characterized above all things by the absolute predominance of eosinophilic cells, which vary greatly in form and size in the different species. They are usually mononuclear, but in the tortoise and lizard also include polymorphonuclear forms. The following classification

* Described by Weidenreich.[33]

given by Werzberg is of interest:—(*A*) Very large cells whose cytoplasm is quite filled with short polygonal granules. This group includes (*a*) Cells with a small round or oval definitely excentric nucleus, which stains deeply (grass-snake, emys, anguis fragilis, lacerta); (*b*) Cells with a larger, often indent or even polynuclear central nucleus (tortoise, lizard, newt). Some few animals have blood which contains both these varieties. The density of granulation is variable. (*B*) Still larger cells, whose nucleus is always large, vesicular, amblychromatic, while the cytoplasm is characterized by the presence of but few granules, which are often arranged in a stellate fashion, are elongated or fusiform, and sometimes clubbed (*see Plate VII*). The nucleus is (*a*) Rounded or slightly indent, (*b*) Polymorphous (skink, chameleon, iguana). Lacerta viridis is the only reptile which contains cells of both *A* and *B* varieties.

The relations between these forms is assumed by the author quoted as: *Ba* ages into *Bb*, gives rise to *Aa* by mitosis, and the latter to *Ab* by ageing. It seems doubtful, however, whether these eosinophiles are truly analogous to the human form, and the peculiar stellate structures appear to be of very peculiar nature, and must subserve an entirely different purpose from that of the eosinophile of the mammal.

The blood of AMPHIBIA contains eosinophile cells which are more closely allied to the mammalian cells. In the salamander, they are usually polymorphonuclear; in proteus, mononuclear forms are also found. Astrospheres and centrosomes are sometimes very clearly demonstrable. Spelerpes, the tree-frog hyla, and the triton have no eosinophiles. In the frog, the granules appear to be intranuclear, but they really lie in little vacuoles in the cytoplasm. The polynuclear forms are prevalent in the old animal, the uninucleate forms are prevalent in the young. The granules are of regular size, round, rather pale, and variably dense. They are quite numerous in the adult. Arnold[35] described occasional forms with rod-shaped granules, but as a rule, the regular spherical shape is a characteristic difference from the reptile eosinophile. It is possible that some of these eosinophiles are derived from the lympholeucocytes.

The eosinophile of the BIRDS differs little from that of the mammals, and hardly requires special description. The nucleus is frequently bi-lobed, the two lobes being connected by a slender thread. Each portion exhibits markings which correspond to those of the mammalian myelocyte. The cell-body is oxyphile, and completely filled with very fine, intensely oxyphile granules. They occur in very small numbers.

The existence of a cell in birds resembling the reptilian cell, but called *pseudo-eosinophile* by Kasarinoff,[36] must be called attention to, as it would naturally be classed as a true eosinophile from analogy with the forms described above. These cells are crowded with rod-shaped, brightly eosinophile "granules" arranged in all directions, like iron-filings before a magnet is placed against them. The nucleus of such cells is double, or even treble, and has a structure like that of the mammalian neutrophile leucocyte. The fact that they preponderate in the avian blood, and that they are subject to the same chemotaxic influences as in the neutrophile of mammals, justifies the decision of the author quoted, which relegates these cells to the polymorphonuclear series of the mammalian leucocyte.

III.—THE MAST CELL.

VARIETIES—Morphology of the mast cell of the blood; of the tissue—Occurrence—Function—Chemistry of the granules—Views as to nature—Source—Comparative cytology.

JUST as the blood contains only a small number of eosinophile cells, so it contains very few mast cells (about the same percentage), while the tissues show them much more frequently. There is this difference, that the content of the tissues in mast cells is considerably less than holds for eosinophiles, and the tissues in which they occur are themselves largely morbid.

The Varieties of Mast Cells—

1. IN THE BLOOD.

(i). Polynuclear mast-leucocyte (guinea-pig type).

(*a*). α- and β-pseudo-mast-leucocytes.

(*b*). Mast-myelocytes.

These are cells with broad cytoplasm, suboxyphile reaction, and immature granules. Some of them are immature leucocytes (with specific granules).

(ii). Mononuclear mast-lymphocytes (rabbit type).

(*a*). True blood mast cells; γ-mast-leucocytes.

These are cells with narrow cytoplasm. The granules vary in size; these are lymphocytes which have undergone mucoid degeneration, and are not specific (include mononuclear and polynuclear micromyeloblasts). The granules are sparse.

(*b*). Pathological blood mast cells, or myeloleukæmic mast cells.

The granule here is of the nature of an altered primitive azur-granulation.

2. In the Tissue.
   (i). Amœboid polyblastic mononuclear forms.
      (*a*). Of spindle shape, rich in cytoplasm and granules.
      (*b*). Of lymphocytoid character, rounded forms with narrow and medium amounts of cell-body. This group includes the plasma mast cell of Krompecher (the lymphocytoid mast cell of Ehrlich).
   (ii). Fixed "sessile" clasmatocyte forms of spindle or plate-like form.

Morphology of the Mast Cell of the Blood.—

Outer form.—The size is variable, usually from 9–12 μ. The shape is rounded.

Cell body.—The spongioplasm is foamy or vacuolated, but is very scanty in amount. The granules are intervacuolar, and average about a micron in diameter. They possess the chemical characters detailed below. There is no visible *astrosphere.*

Nucleus.—Central in position, variable in shape. Typically, it is like a clover leaf, being deeply indent, almost polynuclear. Less indented forms occur, as also forms with a rounded nucleus (lymphoidocytoid form). With the usual stains, the nucleus has only a feeble affinity for dyes.

Nucleolus absent.

This cell occurs to the extent of ·47 per cent of the white cells in 60 per cent of people. It is said to vary inversely with the eosinophiles. It is frequent in *leukæmic* blood,[37] but here the type of cell is pathological, the granules being extremely soluble in water. It is increased in number in cases of staphylococcic infection (Levaditi), after the injection of pyrodin, hemialbumose (Levaditi), colchicine, tuberculin, phrynolysin, milk, cancer extracts; in cases of moribund cholera, severe malaria, acromegaly.

The *mast cell myelocyte* is probably a degenerate form, and not a parent of the mast cell of the blood. It is really a dead or dying cell,[38] because (1) There are no transitions from a coarsely granular pseudo-mast cell myelocyte to a polynuclear cell; (2) Basophile ancestors of the pseudo-eosinophile cell exist, but the granules are

fine; (3) The colour reactions are different; metachromatin is basophile; the granules do not stain with methyl green; retain alcohol but not water or glycerin; stain with rhodamin-S.

The *hybrid mast cell* has been referred to in connection with the eosinophile.

Morphology of the Mast Cell of the Tissue.—

Size: Variable; up to 22 μ.

Shape: Polymorphous. Sometimes spherical, sometimes ovoid, sometimes club-like, or spindle-shaped, with long pseudopodia. The older forms tend to be angular.

Contour: Clearly defined.

Cell body: Abundant, with a foamy or vacuolated structure. Contains metachromatically-staining granules which are more soluble in water than in the case of the blood mast cell.

Astrosphere: Present; two centrioles have been described as present in it.

Nucleus: The position varies according to the shape of the cell as a whole. The shape is ovoid. The nucleus does not stain metachromatically. Chromatin, abundant, deeply staining. It is arranged in clumps, amongst which vacuoles may be seen (Weidenreich).

Nucleolus: Absent.

Mitosis: This was described as occurring in the guinea-pig cell by Jolly; in the rabbit, hedgehog, and dog bone-marrow by Maximow.

The variants of this cell are numerous. They have been described according to their position, though it does not follow that they are really of various distinct orders. Thus, in the muscle, the cell has the form and diameter of the muscle fibres amongst which it lies. In the cellular tissues, the cell takes on the form of the clasmatocyte or adventitial cell with which it is identical, according to Weidenreich.[38]

The tissue mast cell is *met with* in the subcutaneous cellular tissue, especially in urticaria pigmentosa (Unna), miliary vesicle (Unna, Michaelis), vesicle of erythema multiforme, lupus, epithelioma, rhinoscleroma, rhinophyma, and many other skin conditions; near the blood-vessels of tumours of cerebral cortex; in cases of general

paralysis of the insane; in the connective-tissue septa of organs, in the bone-marrow,[39] in the testis of the horse, rat, pig; in the spleen of lower vertebrates; in the muscular tissues of the root of the tongue of the bat. It is met with in chronic inflammatory exudates in many situations, e.g., at the edge of the infiltrated tissue in many forms of appendicitis. In colostrum[40] and other exudates.[37]

The Function of the Mast Cell.—The polymorphous shape of the cell body, the manner in which its processes are observed to probe into the interstices of the tissue in which it lies, strongly suggest an amœboid property on the part of this cell; its accumulation in certain tissues (urticaria pigmentosa) suggests that it is amenable to chemotaxic influences; while the wide distribution of the type through the animal world suggests its possessing some definite importance. Fahr considered that the mucinous granule exerted bactericidal properties.

Unna[41] believes that the tissue mast cells form centres of storage of oxygen, especially in the vicinity of the blood-vessels, somewhat as the eosinophile cell behaves in the blood. It is possible that the oxygen of the oxyhæmoglobin in the circulating corpuscles may be stored up by means of the mast or other granules in its passage through the tissue spaces. The mast granule itself is devoid of catalase, but contains peroxydase, so that a catalyser is necessary in such tissue spaces as those in which the mast cell occurs. The oxygen is given up to the plasma as the corpuscles pass through the capillaries, and is re-activated by the mast granule preparatory to its distribution to the cell-protoplasm.

This theory may hold good to the extent of an accidental occurrence; the paucity of mast cells in any given tissue indicates that these granules cannot be the main agent in the oxygenation of the tissue cells.

The Mast Granule.—The granules of the mast cell are of large size, spherical, and stain metachromatically with certain dyes. With toluidine blue they appear dark red. They are much more basophile than the nucleus.

The solubility of this substance in various agents has been much studied. Thus, they are unaffected by alcohol, are soluble in glycerin, salt solution, alkalies, and very soluble in water. Acids,

such as osmic and chromic acid, destroy the staining power without dissolving the granules. Oxidizing agents diminish, and reducing agents increase, the metachromatic staining power. They contain no fat (Ciaccio),[42] and no iron.

SOURCE OF THE MATERIAL.—The mast granule may be derived from the cell body, or from the nucleus or the nucleolus. If from the former, it would be regarded as *evidence of cell degeneration.*

In favour of this are the following points: (1) The existence of the granules in lymphocytes which have turned plasmoid (Krompecher); (2) The staining reactions are those of mucin (stain with Mayer's mucicarmine, muchæmatin, Bizzozero's gentian violet (Randnitz, Hoyer); (3) They lie in vacuoles.

Against this view are the following considerations: (1) The granules are more resistant to water than mucin; Schwenter-Trechsler considered them to be some other substance than mucin, but secretory in nature; (2) Mitoses have been observed in them (Dantschakoff, Meirowsky[43]); (3) The appearance of vacuoles is artefact, dependent on the solubility of the material in water.

View that they are of Nuclear Origin.—Pappenheim[44] considers that the granules are formed from the lipoid of the spongioplasm by combination with the basophile metachromatin from the nucleus. This is a (mucoid) metaplastic process resulting in the formation and deposition of mucolecithid.[45] In favour of this view are the dye-reactions exhibited by the material.[46] The granules are not grouped specially round the astrosphere. Considerations relating to the phenolphilic substance of Loele show that the nuclear excretion may discharge a basophile substance which interacts with the phenol-group to form a precipitate of phenolphilic granules, but on the other hand there must be some other factors at work to account for the difference from eosinophile granules (which are brought out by the same method of staining). Weidenreich believed them to arise by pigmentation of the nucleus. But they are not of the nature of chromatic substance.

Meirowsky believes that they were derived from nucleolin, and might form precursors of melanin. On this view the mast cell would be a pre-chromatophore cell.

PURPOSE OF THE GRANULES.—As already stated, they have been

regarded as centres of oxygen-storage. Schneider thought they might constitute reserve substance. Ehrlich believed them to be the expression of over-nutrition of certain of the connective-tissue cells from exposure to much fluid. Harris[47] called the cell a mucinoblast because they could be traced to the hyaline cells, and might exhibit a crystalline appearance in their cell bodies.

These various points require to be disposed of before the nature of the mast cell can be determined. Ehrlich and Schridde believe the cell to be specific, arising by differentiation from a specific cell called a mast myelocyte. The chief evidence in favour of this view lies in the existence of mast myelocytes in the guinea-pig. Weidenreich classified blood mast cells into those of "rabbit type" and those of "guinea-pig type."

On the other hand, there are definite objections to the idea of a myelocyte form; among them are the following:—

1. Histiogenic and blood mast cells only resemble each other in the staining reaction of the granules.

2. There are no promyelocyte and metamyelocyte forms of mast cell (Bennachio[48]).

3. The leukæmic mast cell is probably of a different nature altogether.

4. The mast cells of one animal are practically indistinguishable from those of any other (save regarding the point raised by Weidenreich). Mast cells are only absent in fish.

5. Some plasma cells may contain mast granules.

6. Eosinophiles occur which contain mast granules ("hybrid mast cells").

It is more than probable that the mast cell is not an entity, but that these granules may appear in any connective-tissue cell,* clasmatocyte,[49] plasma cell, monocyte, or wandering cells of any kind. For this reason, the cell is regarded as merely a phase in the life-history of certain blood cells. The lymphocyte of the blood-stream, for instance, may undergo mucoid degeneration of this kind under the influence of certain toxins (staphylotoxin, phrynolysin),

* *Cf.* Audry's "isoplastic cells."

and constitute a mast cell of the blood-stream (Pröscher[50]). In favour of this view is the fall in the percentage of mast cells with rise in eosinophile content of the blood. The leukæmic mast cell may be derived by a similar change in the lymphoidocyte, or may pass on towards an eosinophile cell, and finish as an eosinophile myelocyte.

Staffel and Rheindorf believed that the mast cell of the tissue might turn into a pigment cell.

Comparative Cytology.—The characters of this form of cell present remarkable uniformity through the animal series. Beginning with the amphibia (fish do not contain such cells), two forms occur: (1) A histioid form with fine granules of irregular size, and staining red-violet with Giemsa. The cytoplasm is broad. (2) A lymphocytiform type whose granules are scanty, coarse, and whose cytoplasm is narrow.

These two main types are found throughout the vertebrate series. They are well seen in the horse.[51] In the chick, they appear as early as the ninth day of incubation. Kasarinoff described exactly isomorphous forms for the fowl, pigeon, Senegal finch.

IV.—THE PLASMA CELL.

VARIETIES—Morphology of the plasma cell of the blood—Occurrence in the blood—Table of blood-plasma cells—Occurrence in the tissue—The lymphoblastic plasma cell—The granules—Ancestry—Theories—Effect of plastic irritation of the adventitial cells—Fate of the plasma cell—Functions—Comparative cytology.

THE time-honoured view that the eosinophile and mast cell of the blood represent specific orders of cells, each with its own ancestry distinct from that of the neutrophile leucocyte and lymphocyte, has been considered incorrect enough to justify their being classed as "phlogocytes." In other words, we would prefer to regard them as the manifestation of certain phases of life of other body cells, and not distinct species. In a sense, they are accidental contaminations of the circulating blood, but this would be ignoring the possibility that their presence may actually be required here, although not possessing the same importance as when located in the tissue spaces.

In classing the plasma cell with these others, we find it possible to demonstrate the logic of the above conception, in adducing evidence to show the narrowness of the view that this cell is a purely tissue cell, and itself specific. The plasma cell is found in certain tissues, represents a phase of development or metabolism of other cells, already known as "small round cells," "lymphocytoid cells," lymphoid cells," etc., and may pass on to other phases. It is unusual for it to make its way into the blood-stream, but under some circumstances does appear there, and is then called a Türk or irritation cell. Under abnormal circumstances, too, any of the existing orders of non-granular blood cells may undergo a plasmoid change, and lead to the appearance of cell-forms which must be specified by as many corresponding names. In this way we come to consider lymphocytoid, macrolymphocytar, microlymphocytar, lymphoidocytar, macroleucoblastic, microleucoblastic, leucomonocytoid, and lymphomonocytar forms. Any of these may undergo amitotic division, and give rise to a corresponding daughter cell.

The plasma cells of the tissue are of two orders: those of

hæmopoietic tissue, and those of inflammatory tissue. Following Pappenheim, who has done so much to unravel the intricacies and confusion arising from applying the same word to many forms of cell in hæmatology, we should classify these thus :—

1. PLASMA CELLS OF HÆMOPOIETIC TISSUE.—These signify "irritation." Occurrence: normal mucosa of alimentary tract, especially during digestion. In the spleen, especially during digestion (Hertz[52]); also in old age, and in cases of intestinal cancer (Brötz[53]). According to Pappenheim they may enter the blood as Türk cells.*

(i). Lymphatic cells.

(*a*). Lymphoblastic. Here come the so-called Schridde-Hodara cells found in the Malpighian follicles, in the intestinal lymphoid follicles, and in the conjunctiva, and tonsil. They are mobile.

(*b*). Lymphocytar. Such cells enter the blood in any case of splenic enlargement.

(ii). Myeloic cells.

(*a*). Lymphoidocytar.

(*b*). Leucoblastic.

2. PLASMA CELLS OF INFLAMMATORY TISSUE, and perivascular tissue.

(i). Fibroblastic Unna plasma cells.

(ii). Unna's daughter plasma cells.

(iii). True plasma cells, or Marschalko plasma cells (polyblastic). These arise from clasmatocytes *via* lymphocyte of the tissue; are small, large, or Saxer in type. They give rise to

(*a*). Large plasma mother cell with broad cell-body.

(*b*). Small plasma daughter cells.

3. PATHOLOGICAL PLASMA CELLS include those of myelomas composed of plasma cells; those of leukæmia† of plasma cell type.

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* But these are not the same as the plasma cells of the tissue, for they do not possess a "wheel" nucleus. Pappenheim's Atlas, however, shows that this objection is not always true.

† Gluzinski, Reichenstein, Foa and Michaeli, Lucksch.

Pappenheim[54] gives a useful table gathering together all the types :—

WALDEYER'S PLASMA CELL.

Ehrlich mast cell	Basophile wandering cell	Unna's strongly basophile plasma cells (collective)		
		Schridde plasma cell	Marschalko TRUE PLASMA CELL	Fibroblastic plasma cell Unna's histioid plasma cell (limited term)

The true plasma cell comes from a microleucoblast or micromyeloblast. The fibroblastic cell comes from a fixed connective-tissue cell.

Morphology of the Plasma Cell of the Blood.—

Size.—Variable ; between 5 and 14 μ (average 8·5).

Shape.—Rounded or oval.

Cell-body.—Extremely basophile, staining a deep blue with the panoptic stain. The spongioplasm is very clearly seen, largely because of the vacuolation present. But the granoplasm is more abundant. With triacid, the cell-body stains a dull brown.

Granules.—Azur granules are rare,[55] but have been described.

Nucleus.—This stains very deeply. It is excentric, oval or rounded, and varies in structure according to the type of cell.* (*See Table opposite*).

Nucleolus.—Occasionally seen.

Astrosphere.—Conspicuous.

Degeneration Forms.—(*a*) With fat vacuoles; (*b*) Vacuolar generation, producing a " foam " cell with vesicular nucleus. The granoplasm has altered. (*c*) Appearance of hyaline spherules; (*d*) Appearance of phagocytic inclusions (red cells, e.g.); (*e*) Cytolytic forms, or Klein-Gumprecht shadows.

Mitosis.—Mitotic division is not observed. but amitotic changes

* Schridde[56] only recognizes lymphoblastic and lymphocytar forms.

Table of Blood-Plasma Cells.

	Lymphoido-cytoid	Macrolympho-cytoid	Mesolympho-cytoid	Lymphocytoid	Lymphomono-cytoid	Macroleuco-blastic	Leucoblastic	Microleuco-blastic
Size	> 12 μ	> 15 μ	> 12 μ	> 10 μ	> 15 μ	> 10 μ	> 10 μ	> 7 μ
Shape	ovoid	ovoid	rounded	rounded	ovoid	rounded	round	round
Cytoplasm	intense blue abundant	strongly basophile, moderate in amount	rim deeply basophile scanty	dark blue, no markings, scanty perinuclear halo	deep blue, abundant	deep blue, scanty	deeply basophile, scanty vacuolated	strongly basophile, narrow rim, perinuclear halo
Azur granules	o	o	o	o	o	o	o	o
Paranuclear spherule or astrosphere	+	+	occasional	o	+	o	+	o
Nucleus: size	medium	large	large	large	medium	large	large	large
shape	oval	oval	rounded	rounded	oval	round	indent	ovoid
position	slightly excentric	central or excentric	central	central or excentric	excentric	central	central	central
chromatin	lepto-chromatic	pachy-	pachy-trachy-	intensely pachy-	intense	myelocytar	leucoblastic	lepto-chromatic
affinity for dyes	moderate	marked	marked	marked	considerable	slight	moderate	moderate
wheel-markings	o	+	occ	occ	trace	o	o	o
Nucleolus	+	o	o	o	o	+	occasional	o

can be encountered. The cell-body then appears narrow, and stains deeply. The cycle of division must be a long one, as otherwise it would escape notice during fixation. The result of division is a plasma daughter cell.

Occurrence in the Blood.—They have been found in the capillaries of the liver (Wallgren[57]), in the vena cava of rabbits (Carletti); in man suffering from malaria, scarlet fever (11 per cent in one case of Hertz's[52]), and whenever the spleen is enlarged. They may also appear in the blood in association with inflammatory or infective leucocytosis.

Morphology of the Plasma Cell of the Tissue.—

Outer Form.—The absolute *size* is variable. The *shape* is oval or round, cuboidal, or regularly polygonal, or elongated. *Contour* rather ill-defined.

Cell-body.—Is abundant on one side, relatively abundant in any case, and exhibits a foamy structure. It is extremely rich in amorphogranular granoplasm, and stains strongly basophile* with polychroma methylene blue, thionin or toluidin blue. It is specially dense towards the periphery. The paraplasm is abundant, chromophobic, and most abundant in the region of the astrosphere.

Granules.—These are irregular clumps of cytoplasm. They stain blue with toluidine blue. Schridde or Altmann granules occur towards the periphery. Gentianophile granules are present.

Perinuclear Zone.—Well-marked. It is formed of minute fluid drops which increase in size towards the periphery. The intermediate material is basophile.† According to Wallgren, this zone can be subdivided into a dark inner and a slightly pale outer layer.

Astrosphere.—Well marked. Wallgren[57] observed in it three centrioles connected by filaments.

Nucleus.—Position, excentric, "tucked away in a corner." *Outer form:* rounded or oval in shape, relatively small in size. *Chromatin,* abundant, darkly staining, but showing a characteristic wheel-structure.

Nucleolus.—May be one, or two. If one, it is central.

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* Because young. Compare with the basophile myeloblast, larger lymphocytes, and sarcoma cells.

† Hofmann.[58]

Mode of Division.—By amitosis. Pappenheim,[59] Unna, and Schridde record occasional mitotic division. The basophile granoplasm disappears during the amitotic stage.

The above description applies to the true plasma cell, type Marschalko. The following forms of tissue plasma cell may be also described :—

Morphology of the Schridde-Hodara* Plasma Cell: better named the lymphoblastic plasma cell.

Outer Form.—The cell is very large, and rather polymorphous in shape. May tend to a spindle form (amœboid movement ?).

Cell-body.—Cytoplasm narrow, but sometimes abundant, especially in senile forms. Stains dark blue with methylene blue, bright red with pyronin. An astrosphere is present in some instances.

Nucleus.—Relatively large, central in position, sometimes almost structureless, at other times showing coarse nodal markings. Amblychromatic. No wheel structure. Nearly fills the cell.

Perinuclear Halo present.

Nucleolus present.

The *plasma mast cell of Krompecher* is a lymphoid cell that has undergone mast and plasmoid change simultaneously. It may be compared with the pigment mast cell of Staffel, and the hybrid mast cell of leukæmia.

THE UNNA DAUGHTER PLASMA CELL is intermediate between the lymphocyte and the large plasma cell. The *Enderlen-Justi plasmoid connective-tissue cell* is a fibroblast with a strongly basophile cell-body.

The Granules of the Plasma Cell.—It is hardly correct to speak of granules in this form of cell, because they are not comparable with those of other blood-cells. The cytoplasm has a granular appearance without an ability to define discrete bodies in it. They are certainly not artefact, because they are visible in frozen sections of absolutely fresh tissue (Schridde).[62] The substance

* If there be any difference between the Schridde and the Hodara cell, it is that the former is derived from the lymphoblast, the latter from the pulp cell of the spleen (splenocyte) but perhaps these forms are really functional stages of the same kind of cell (Hertz[53]). Pappenheim treats them as identical.

which imparts this appearance to the cell-body is found to be iron-containing (Harris[60]), just as holds in the case of the osteoblast at the time that it is about to secrete bone. The iron in the plasma cell may therefore bear some relation to the formation of fibrous tissue secretion. Pappenheim believes the granoplasm to consist of paranucleoproteid. It is strongly acid, and readily soluble in saline. It may arise after the manner of a " sclerosis of the spongioplasm."

Supposedly lipoid granules were found by Proell[61] in the astrospheric region. The observation that these bodies were similar to those in the cytoplasm of macrophages led to the conclusion that the plasma cell is related to the tissue lymphocyte on chemical as well as on morphological grounds.

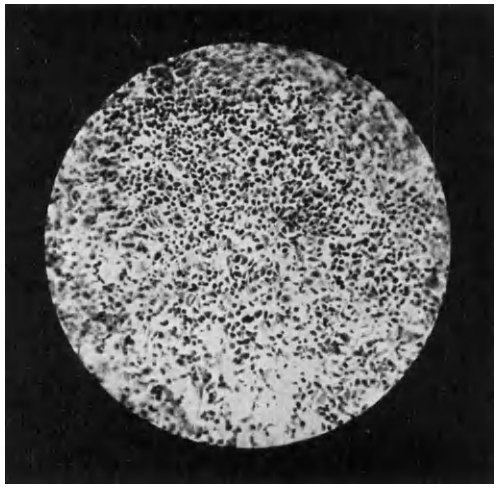
Gentianophile granules and basophile (mast cell granules) have been found in these cells. Loele found much phenolphilic substance in the vicinity of the nucleus.

The Ancestry of the Plasma Cell.—This has been the theme of an incredible amount of literature. Were it not for the impossibility of directly observing the processes of metaplasia, the divergence of opinions would have been obviated; and although one can appeal to the appearances in various tissues to advocate the view that any tissue cell may undergo a plasmoid change under suitable circumstances, the difficulty remains that every observer of such phenomena would not interpret them alike. The following are the views which have been put forward from time to time :—

1. That it is a *connective-tissue cell,* or *fibroblast.**—*Pro* : The finding of all transitions in the tissue of a soft sore, hard chancre, acne, rhinoscleroma,† rhinophyma. *Con.* : The following contrast :

Plasma Cell	Connective Tissue Cell
Granoplasm very abundant	Spongioplasm very abundant
No relation to fibrous tissue formation	Immediate relation to fibrous tissue formation
Morphology characteristic	Morphology unlike the plasma cell
Chief constituent of granuloma	Chief constituent of fibrosing tissue

* Unna, Leo, Ehrlich, Jannovics (partly), Enderlen and Justi (partly).
† Sherrington and Balance.



"The finding of all gradations between follicle lymphocytes and plasma cells" (p. 273).

Fig. 68.—PORTION OF AN INTESTINAL LYMPHOID FOLLICLE, FROM A CASE OF TYPHOID FEVER. Notice the variability of these mononuclear cells: many are elongated and are grey in colour, while others are definitely round and come out intense black in the photograph.

(Oc. 2, Obj. A).

Face p. 273

It will be evident that these distinctions cannot be emphasized too strongly.

2. That it is a *lymphocyte*.* If so, there are the following possible ultimate sources :—

(*a*). Emigration from the blood.†

(i). Blood-lymphocyte.

(ii). Large mononuclear leucocyte.‡

Against this view is Pappenheim's observation that plasma cells do not occur within the follicles of the spleen, but in the pulp and at the periphery of the follicle. This indicates that they have some closer relation to the pulp tissue. The lymphocytes of the follicle are permanently agranulopotential. This is a striking fact in the case of the follicles of the appendix.

(*b*). Local formation from the *endothelium* or *perithelium* (lymphoid or lymphocytoid polyblasts), whether blood or lymphatic,§ or from wandering lymphocytes, or from the lymphocytes of a Ribbert lymphoma. ||

Pro.—The finding of all gradations between follicle lymphocytes and plasma cells in such a lesion as the inflamed follicle of the intestine in typhoid fever. (*See Fig.* 68.) Further, the inconstancy of the characters, and the difficulty of certainly distinguishing the (e.g., daughter-) plasma cells from a lymphocyte. Schridde has suggested that the origin from this source must be pathological, because of the occurrence of forms with two, three, four, or even six nuclei.

Con.—The formation from a lymphocyte has never been observed. The Malpighian follicle should be studded with plasma cells, and it is not.

On the other hand, knowing as we do that the tissue lymphocyte is not always a member of the lymphatic series, but should be called a micromyeloblast, there are found certain arguments for believing that the tissue plasma cell is myeloblastic in origin :

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* Baumgarten, Marschalko, Deganello, Benda, Dominici, Helly, K. Ziegler, Neisser.

† Marschalko, Maximow, Schridde.

‡ Krompecher, Schottländer, Schlesinger.

§ I.e., adventitial cell.

|| Jadassohn, Enderlen and Justi.

(i) Its absence from the lymphoid follicles of the spleen, intestine, conjunctiva; (ii) The existence of plasma-cell myelomas (myeloplasmocytosis) in the bone marrow; (iii) The association of Marschalko cells with chronic inflammatory cell infiltration; (iv) Altmann granules occur equally in lymphocytoid and myeloblastoid cells (Wallgren, Butterfield, Klein); (v) Preformed lymphocytomas never give rise to plasma-cell tumours.

(*c*). Both by emigration and by local formation (Maciesco-Jalenska[63]). They are very numerous in the lung in cases of caseous tuberculous pneumonia, but absent in fibrinous pneumonia. In this tissue they are perivascular, peribronchial, interalveolar, and subpleural. They occur anywhere where regeneration is proceeding.

3. That it is an *altered adventitial cell* (Marchand's clasmatocyte). This view is really covered by the preceding, for it must be supposed that the tissue lymphocyte is so derived.

4. That it is an *altered endothelial cell* (Rheindorf). This view depends on the close morphological resemblance between the cells as seen by sublimate fixation (Enderlen and Justi[64]).

5. That it is a mere functional state of *any kind of lymphoid cell*, and merely means that basophile material has been taken up or formed in excess. This is indicated by their reversion, for instance, to lymphocytes after the inflammatory stimulus is over (Grimani). We should thus picture to ourselves a periodic flooding of the cell-body with nuclear acids, leading to the obscuration of the cytoplasmic structure.

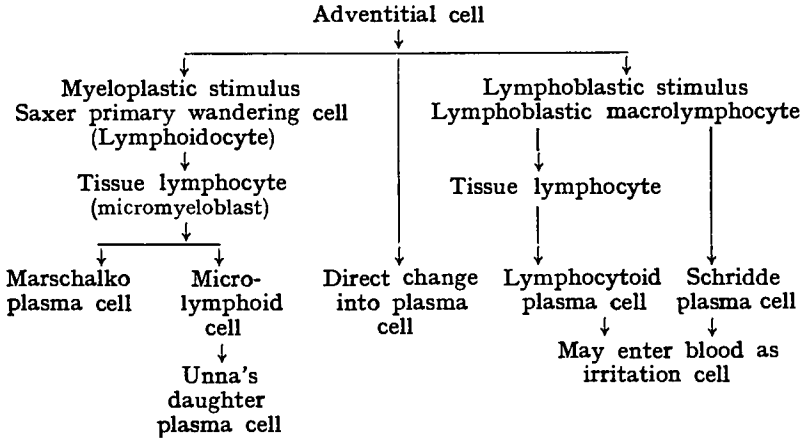
Against this theory are the facts that :—

(*a*). Basophilia is not due to functional irritation, but to the absorption of the substrate (Enderlen and Justi).

(*b*). The cell may be in a pathological state—sclerosis of the spongioplasm.

Expressed in a nutshell, the Schridde cell is the plasmoid large lymphocyte, while the Marschalko cell is the plasmoid microleucoblast, arising in the spleen, e.g., from the granulopotential lymphoid cells of the pulpar tissue.[65]

The following chart may express the possible effect of a plastic irritation of the cells covering in the walls of the capillaries :—



Functions of the Plasma Cell.—The main purpose of the plasma cell appears to be connected with the deposition of fibrous tissue in the affected area. Whether it has anything to do with the formation of antitoxic substances (Maciesco-Jalenska[63]), or not (Wolf[66]), whether it serves to transport substances away from the zone of inflammation or not (Wolf), is difficult to establish. The analogous appearance to that of the pancreatic or other secretory gland cell during the resting stage may be drawn attention to as indicating that the granular appearance is due to the storage of substances within it which are of use when discharged into the surrounding medium. That these cells possess migratory powers (Alegno[68]) is easily shown by the observation of the epithelium of the tonsil or intestinal villus (Joannovics and Pirone[69]).

The *duration of life* is variable. Schridde believed them to be very long-lived, and certainly from one's observations of inflammatory infiltrations of surgical tissues, and especially such a condition as linitis plastica, one would be prepared to believe that they remain apparently stationary for months.

Fate of the Plasma Cell.—The cells may enter the blood as Türk irritation cells, as already mentioned. They may become fixed connective-tissue cells, for they disappear from an inflammatory

focus as scar formation takes place. They may undergo regression to lymphocyte-like cells after the plastic stimulus has passed off. Or they may undergo the following degenerative changes :—

1. Cells with feebly staining cytoplasm, of any grade up to complete loss of basophile property. Nucleus remains clearly defined.

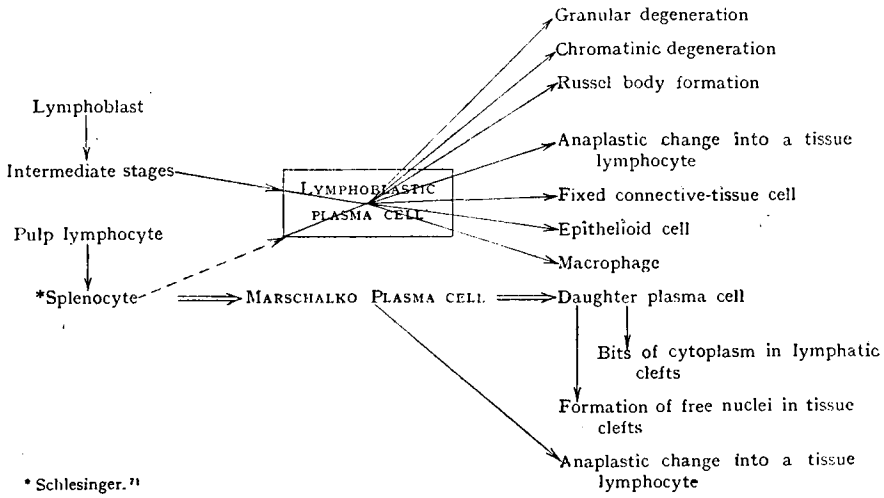
2. Cells with normal cytoplasm, but a large nucleus which has lost its wheel structure and chromatin network.

3. Cells with vacuoles (Wolf[66]).

4. Cells with hyaline, granular or chromatic degeneration. The intracellular Russell bodies are considered the result of myelin degeneration of the cell-substance (Miller[67]).

5. Fragmentation of the cell-body with the appearance of free nuclei in the tissue.

SCHEME SHOWING THE FATE OF THE PLASMA CELL.



* Schlesinger.[71]

Comparative Cytology.—The most valuable contribution on this subject is that by Downey,[70] who investigated the ganoid fish polyodon, amblystoma, frogs, the garter snake, various mammals, and man, using specimens which were to all intents and purposes

quite healthy. This author found that plasma cells are abundant in certain definite regions of cold-blooded animals: thus, in the lympho-renal tissue of polyodon, in the mesentery of the frog, in the lung of the garter snake. In all cases they were formed from the clasmatocytes. He concludes that the various types are merely functional conditions of the same species of cell, and that a description of their cytology is no more than one of the cytology of other hæmopoietic cells with the characteristic plasmoid change superadded.

V.—THE CLASMATOCYTE.

THE CLASMATOCYTE and other purely connective tissue cells*—The giant cell.

THE clasmatocyte, mesenchymal or adventitial cell appears in many forms. As shown by the method of vital staining first described by Goldmann,[72] the same cell comes to notice as a "pyrrhol cell," which is not only found in chronic inflammatory tissues, but also in the intestinal wall, and interstitial tissues of glandular organs. This cell has a variable shape, being sometimes elongated into a spindle form, at other times exhibiting a branching form as if it were amœboid. The cell-body is rich in granoplasm, and dark or dusky in appearance. Its contour is clearly defined. There is never any metachromatic staining. The nucleus is rather large, dark, irregular, and usually shows dense chromatic structure, though leptochromatic forms occasionally occur. Transition forms between this and a fibroblast may be observed by the method of vital staining.

Strictly speaking, this cell would be classed as a primordial cell, and the remarks made in Chapter I. would become applicable to it. (*See Plate I*, 1; *Plate VII*, 6 *and* 58.)

The Giant Cell appears in various forms. The most important in connection with the hæmopoietic tissues is the megakaryocyte already described. This occurs typically in the bone-marrow, but is also found in the spleen under certain conditions, and appears in the lymph-nodes in cases of Hodgkin's disease. The multiple nuclei may be the result of pluripolar mitosis. or of fragmentation.

The so-called *foreign-body giant cell* appears to be the result of fusion of endothelioid cells or monocytic forms, but even the megakaryocyte may be, in some cases at any rate, a derivative of the primary wandering cell of Saxer.†

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* "Stroma," "stromatic" cells.

† See also Gruner, "Diagnosis of Morbid Tissues," *Medical Annual*, 1911, p. 116.

VI.—THE CYTOPLASTIC INTER-RELATIONS BETWEEN THE VARIOUS PHLOGOCYTES.

THE mechanism of inflammatory cell infiltration may be better understood by a consideration of the processes which occur in the interstitial tissue of any vertebrate (or even of an invertebrate). Following the plan of describing microscopic fields of action of the various processes which go to make up what is termed hæmopoiesis, we may describe the appearances seen in the vicinity of any capillary blood-channel, whether it be in the cellular tissue or in granulation-tissue (*Fig.* 67). We have the lining cells of the capillary wall, which may be the only structure separating the circulating cells from the tissue elements. As a rule, we may regard the presence of an outer layer of cells as essential. These are the perithelial or adventitial cells, characterized by a relatively large oval vesicular nucleus, whose chromatin is in the form of punctate markings near the nuclear membrane, and an elongated cell-body. They are usually in a resting state, but may be roused into activity by certain chemical plastic stimuli. It is feasible, for instance, that an excess of a body with an amidine grouping oozing through the vascular wall, disturbs the equilibrium of the perivascular cells, and makes them first motile (now dignified by the name of primary wandering cell of Saxer), and then acquire or manifest other potentialities. The facts shown by the histological study of any chronic inflammatory mass reveal that this potentiality is dual. In other words, the slumbering perivascular cell acquires hæmopoietic tendencies, and is either lymphoblastic or myeloblastic.

The exact effect depends rather on the character of the stimulus at work or on the degree with which the exit of lymph (and with it, the deleterious substance) is interfered with, and the consequent degree of concentration of the noxa—whether or not it is sufficient to set the cytometaplastic changes in motion.

In a field such as is being considered, then, we notice the proportions of the different cells present, the endothelioid cells, the lymphocytes, the micromyeloblasts, the leucocytoid cells, the lymphoblasts, the plasma, mast, and eosinophile cells, etc. In this way we can draw up a *cell formula for the tissue*, and seek for a relation between noxious agent and certain types of cell-formula.

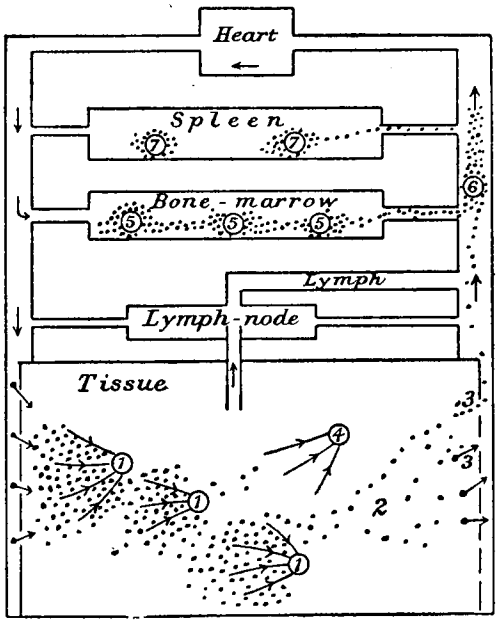

Fig. 69A.—Diagram to show the Double Action of Noxious Agents on Tissues and Blood-forming Organs.

Eosinophilia. ... eosinophile cells ; 1, 1, 1, eosinotaxic centres (e.g., in the appendix wall, Hodgkin's node). These centres are shown the seat of aggregations of locally-formed eosinophiles, with blood-eosinophiles intermingled. *2*, eosinophile cells distal to *1, 1, 1,* passing at *3* into the circulation (tissue-eosinophiles in the blood). → circulating eosinotaxic substance. *4*, fibroblastic centre, excited by the preceding; *5*, centres of eosinophile proliferation in the bone-marrow, produced by the action of the circulating eosinotaxic substance. *6*, blood-eosinophilia (some admixture with tissue-eosinophiles). *7*, centres of possible simultaneous eosinophile proliferation in the spleen.

The processes taking place in the zone of inflammation are not completely considered as long as that particular region alone is being studied, because there is really a circle of vicious action. Thus, a noxious agent may not only excite eosinophilia of the tissue in which it lies, but it may also exert an action on the bone-marrow in the direction of causing an increased production of eosinophiles there

also. These new cells are then attracted back to the area affected, and constitute blood-eosinophiles as opposed to the local histiogenic cells. The latter are the result of the powerful attractive power of the noxa for the eosinophiles anywhere in the vicinity of the diseased area, and their very presence may be the means of flooding the

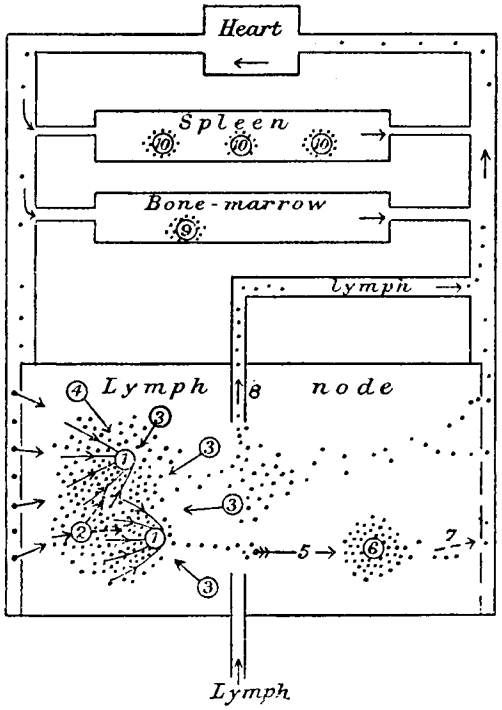

Fig. 69B.—Diagram to show the Double Action of Noxious Agents on Tissues and Blood-forming Organs.

Lymphomatosis. ... lymphocytes and other lymphoid cells. 1, 1, lymphotaxic centres. *2,* lymphocyte that has wandered to that point, entering the attractive force of more than one lymphotaxic centre at once. *3,* wandering cells being drawn towards *1, 1. 4,* tissue eosinophile also attracted to the same focus. The drawing shows a small lymphoma formed round *1, 1. 5,* excreta of the proliferated cells, exciting. *6,* more lymphomatous proliferation. → circulating lymphotaxic substance. *7,* possible course of lymphotaxic substances. *8,* exit of the same, with lymphocytes, to next node or to blood tissue is not necessarily acted on. *10,* enlarged Malpighian follicles. *9* and *10* would not occur if the lymphotaxic material did not pass *7* or *8.* In the aleukæmic proliferation there is no passage of cells at *7,* but the noxious material may excite *9* or *10,* or both.

tissue with metabolic products which themselves act in a baneful manner by exciting further cell-proliferation locally or at a distance. The cell-proliferation is peculiar to this extent, that the initial stages of the process are very vigorous, and promise to end in the

same way as in any blood-forming organ. Yet they fail to do so, and deviate along lines ordinarily quite unknown in the last-named type of tissue. *Cytometaplasia* has taken place, and a neoplastic transformation has been the result, the "neoplasm" tending to pass into a mass of fibrous tissue in some cases, into a mass of inert structureless material in others, and so on.

If the field of battle could be mentally limited to two adjacent capillary channels with a viscid interstitial substance, we should picture the stream in each side of the field as consisting of blood-cells and plasma—containing lymphoblastic, eosinoblastic, and other plastic substances. The intervening material contains the attractive force for all these substances, and the surplus, having diffused through the area in question, passes out of sight, but ultimately comes in contact with blood-formative cells, and excites eosinophilia, lymphocytosis, etc., as the case may be. Migratotaxic substances would account for the mobilization of potentially wandering cells to this field of activity. Meanwhile, the adventitial cells have succumbed to the influence of the stimuli in their vicinity, and have undergone active proliferation, and their excreta may contain auxetic substances which incite local cell-metaplasia.

Some of the cells so formed may turn into fibroblasts of different kinds, and ultimately produce a scar, or they may escape from the scene of action, or they may undergo degeneration, or pass along other lines of development (plasmoid, eosinoid, etc.). The diagrams on pages 280, 281 may make this clearer.

It may be noted that there is no finality about the metaplastic changes. It does not follow, because fibroblastic tendencies have appeared, and a quantity of fibrous tissue has been formed, that therefore there is no escape from the fibrosis or cheloid formation. It is well known that agents such as *x*-rays, and certain bacterial toxins, may lead to the disappearance of scar tissue. Consequently we are faced with the fact that a chronically inflamed area, no matter how long a time has elapsed since its first inception, no matter how indolent it may have been, may be excited to resolve so soon as adequate lymph-flow from the affected area is assured, phlogoblastic substances have been removed, and anaplastic stimuli are brought to bear.

The following scheme more clearly indicates the inter-relations between the cells :—

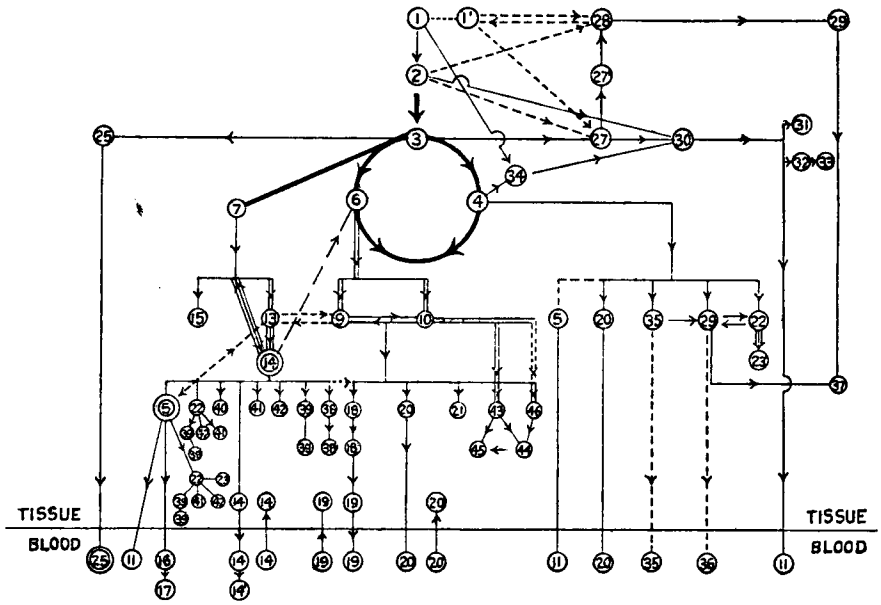

Fig. 70.—CHART REPRESENTING THE INTER-RELATIONS BETWEEN THE PHLOGOCYTES.

1.—Resting perithelial cell ; 1′, Endothelial cell. 2.—Wandering cell of Saxer (pyrrhol cell). 3.—Lymphoidocyte. 4.—Lymphoprimitive cell. 5. Monocyte (is double-ringed to show its subjection to inflammatory stimuli). 6.—Polyblast of Maximow, Schridde, and Neumann. 7.—Lymphoblastic macrolymphocyte. 9.—Microlymphoidocyte. 10.—Microleucoblast. 11.—Monocytoid macrophage. 13.—Mesolymphocyte. 14.—Tissue lymphocyte (one of these is doubled-ringed to emphasize its subjection to unusual conditions). 14′, Leucocytoid microlymphocyte. 15.—Schridde-Hodara plasma cell. 16.—Large mononuclear leucocyte. 17.—Transitional cell. 18.—Promyelocytar eosinophile cell ; 18′, α-micromyelocyte. 19.—Eosinophile cell. 20.—Mast cell. 21.—Senile leucoblast. 22.—Plasma cell. 23.—Older plasma cell. 25.—Rieder cell (double-ringed to show that it is abnormal to blood). 27.—Megakaryocyte ; 27′, Marchand wandering cell. 28.—Mesenchymal cell. 29.—Fibroblast. 30.—Foreign body giant cell. 31.—Giant cell with hollow nucleus. 32.—Caryolytic giant cell. 33.—Cytolytic giant cell. 34.—Epithelioid cell of Marschalko, Krompecher, Schottländer. 35.—Mast cell with plasma nucleus, Krompecher plasma-mast cell. 36.—Martinotti's desmoid pseudoplasma cell. 37.—Fibroblastic plasma cell. 38.—Unna daughter plasma cell ; 38′, Plasma cell containing Russell (myelin) body. 39.—Atrophic plasma cell (granoplasm breaks up into dots) ; 39′, Ditto, but naked nucleus. 40.—Large lymphocyte of Botkin, Deganello. 41. Cell in state of hyaline degeneration ; found in chronic inflammatory processes. The spongioplasm and nucleus remain intact. 42.—Foam cell of œdematous granulation tissue. 43.—Polynuclear cell of inflammatory cell infiltration. 44. Michaelis' spherinucleate cell (undergoing pycnosis). 45.—Pseudolymphocyte of Ehrlich, which has lost its granules. Produced from 43, or 44, by cytorrhexis. 46.—Daughter myelocyte of Türk and Pappenheim.

The connection from ringed 14 to 6 is due to Lindberg (Upsala Läkareförenings Fürhandlingar, vol. xvi., No. 3).

The connection from 3 to 11 is by vacuolation.

The connection from ringed 14 to 18 is based on Pascheff.

The connection from ringed 14 to ringed 5 is based on Weidenreich, Maximow, Schridde, Patella.

CHAPTER VII.

THE CYTOPLASTIC PHENOMENA OF BLOOD-FORMING TISSUES.

Section I.—(1) ON METAPLASIA IN GENERAL—Meaning of the term metaplasia—Metaplastic changes in epithelium and skeletal tissues—Evidences of metaplasia in hæmopoietic tissues—Errors to be avoided in studying these tissues—Anaplasia—Transportation *versus* local manufacture—Metahyperplasia—The question of inventing artificial means of influencing the process—The study of cytoplasia is essential to a comprehension of tissue-metaplasia—(2) THE MECHANISM OF METAPLASIA—(3) THE EXCITING AGENTS OF METAPLASIA.

Section II.—SPECIAL EXAMPLES OF METAPLASIA IN HÆMOPOIETIC TISSUES—(*A*) Myeloid—(*B*) Lymphoid—(*C*) Megakaryocytomatotic—(*D*) Mast cell—(*E*) Plasma cell—(*F*) Splenoid—(*G*) Sarcoid—(*H*) Erythroblastic.

Section III.—SURVEY OF THE HYPERPLASTIC, METAPLASTIC, METAHYPERPLASTIC, AND ALLIED PROCESSES IN THE PULPAR AND FOLLICULAR TISSUES.—The play between parenchyma and stromatic elements in different diseases—Schemata illustrating the causes of enlargement of (*a*) lymphatic glands, (*b*) spleen.

I.—METAPLASIA IN GENERAL.

(1). On Metaplasia in General—Meaning of the term metaplasia—Metaplastic changes in epithelium and skeletal tissues—Evidences of metaplasia in hæmopoietic tissues—Errors to be avoided in studying these tissues—Anaplasia—Transportation *versus* local manufacture—Metahyperplasia—The question of inventing artificial means of influencing the process—The study of cytoplasia is essential to a comprehension of tissue-metaplasia—(2). The Mechanism of Metaplasia—(3). The Exciting Agents of Metaplasia.

1.—On Metaplasia in General.

BY the term "metaplasia" is generally understood the process by which a fully differentiated tissue becomes converted into another allied and equally differentiated tissue-form, without the agency of an intermediate stage of cell-interpolation.* While this process is usually studied by observing the tissue as a whole, it is an advantage to replace the word "tissue" in the definition by "cell," and consider the individual cells as isolated units; for it is in this way that the phenomena of metaplasia in the pulpar tissue (lymph-node or spleen) become much more intelligible, and the word "cytoplasia" appropriate, inasmuch as it emphasises the importance of studying cell metabolism before theorizing upon such diseases as pseudo-leukæmia, splenomegaly, or hyperplastic tuberculosis of lymph-nodes.

The literature[1] confines itself almost exclusively to those instances of metaplasia that are exhibited by epithelial tissues under certain conditions, and those occurring in skeletal tissues undergoing regenerative repair after injury.† Much attention has been paid to the former, because it was hoped that herein would lie some explanation of the development of carcinoma in epithelium. The further question arose, as to whether epithelium can undergo metaplasia into connective tissue and thus account for the occurrence

* The transformation of one definite tissue into another which is functionally different from the first (Orth[1]).

† Thus, Borst, Schridde, and many others, have written upon metaplasia in epithelium. In a recent article (March, 1913) by G. M. Smith, references to this subject are made, as if epithelium were the only tissue to consider in such connection.

of a sarcomatous tumour in tissues apparently epithelial. This question has always been answered by a definite negative in the halls of orthodox pathology, and yet anyone who examines a microscopic section of a tonsil cannot fail to notice that there is so intimate an association between the so-called epithelium of the crypt and the primordial adventitial cell of the follicles, that a denial of an inter-relation between epi- and meso-thelium cannot be dismissed lightly.

Analysis of the apparently similar metaplastic processes in epithelium and bone, reveals the existence of subtle differences between them, and the invention of terms to express these has become necessary. Thus we have the term "allomorphism" or "dysmorphism" applied to such a process as the conversion of a columnar into a squamous epithelium by mechanical agencies; "prosoplasia," where there is a pathological differentiation of one form of epithelium into another of higher type than that exhibited under normal conditions; "heteroplasia" where epithelium is deposited in sub-epithelial tissues during either embryonic or later life. "Normoplasia" is the usual physiological differentiation of a cell.*

Ribbert objects to the word metaplasia on the ground that the so-called examples are really not distinct from any of the known processes met with in general pathology. The objection cannot be entertained by those who see in metaplasia and its allies the only true explanation of the multiform protean metamorphoses met with in the tissues we are considering. Indeed, it may be truly said that the seats of hæmogenesis constitute the most accurate examples of the processes of cytoplasia, so that it is easier to discuss them in connection with hæmogenesis than with any other tissue-changes. The familiarity of the reader with the changes set up in the course of repair to a bone after injury, or in response to inflammatory or neoplastic activity, nevertheless affords a convenient starting-point for a discussion of the hæmopoietic cytoplasias.

The periosteum, for instance, is usually fibrillar, but has a natural tendency to form osseous tissue by passing through a phase

* Thus, if œsophageal epithelium becomes keratohyalin, this is normoplasia. If vesical or vaginal epithelium does so, this is prosoplasia.

in which the fibrillæ are embedded in hyaline material, whose constituent particles (colloidal) become more and more dense by successive aggregation until the staining properties become similar to, and ultimately identical with, those exhibited by osteoid bone. The deposition of lime salts through this material may be described as completing the change of the osteoid tissue into bone, but in truth the salt deposition and the aggregation of the colloidal particles are really one and the same process, so closely are they interdependent. The mutations which may arise are the following : Firstly, the dense hyaline tissue may lose its lime salts, and simultaneously lose the power of staining to such an extent that the product is colourable by acid dyes even less than is the original hyaline matrix. The constituent cells lose their shape, become ovoid, larger, paler, and are enclosed in fluid lymph, and the material is now recognizable as ordinary cartilage. Secondly, after the osseous tissue has lost its lime salts, it may undergo liquefaction to a greater extent, and reveal the presence of fibrillations through it, the fibrillar form having been reassumed by its constituent cells. Thirdly, the metaplastic process may be complicated by the concurrent existence of proliferation and of inflammation, as is well seen in such bone-diseases as syphilis, rickets, Paget's disease, chronic deforming arthritis.

In each of these cases the complexity of the changes may be interpreted to be the result of the excreta, as it were, of the new cells themselves, modifying, as they might, the processes of regeneration in the original tissue elements. The dawning light upon colloidal changes in the human organism shows us with no uncertain signs that the appearance in a tissue of such bodies as amidine compounds, imido compounds, and even diazo-groupings, may bring about a long chain of sequent reactions which result in colloidal interchanges between cytoplasm and intercellular material, and are of the most profound significance in the problems of lymphopoietic cytoplasias.

Turning now to the bone-marrow, we find this tissue to be the subject of a constant and definite sequence of metabolic changes (*p.* 199). The transformation of adipose into mucoid tissue, or *vice versa*, brings about the appearance and disappearance of " gelatinous

degeneration" of the marrow. More constant than this is the process of atrophy of the fat cells with hypertrophy of the hæmopoietic cells, and *vice versa*. The phenomena which take place within the cells themselves are genuinely metaplastic in character, and, as we have seen in the successive chapters of this book, are liable to manifest variations of detail according to the changes in the stimuli which may reach the hæmatic parenchymal cells in these regions, endowed as they are with "multivalent" or multiple potentialities. In this way we find a ready explanation for the varying appearances set forth in the literature as characteristic of the various diseases of the bone-marrow as a blood-forming organ.

If such interpretation be allowable for the changes in the bone-marrow, it is equally legitimate for the other centres of blood-formation. As a consequence, we shall seek for strictly metaplastic changes in such tissues as the lymph-nodes, the lymphoid follicles disseminated through the body, and in the spleen. Seeking for such cytoplasias, we find them indeed. For, just as the last decade has performed the great service of throwing light upon the meaning and nature of the "small round cells" characteristic of the interstitial tissues, so we are able to understand those in the lymph-nodes and spleen more clearly now than a few years ago. The modern literature replaces the words "small round cell" with others that more definitely express their significance and purpose in the tissue, although it is one thing to pass over the short stage from the phrase quoted to "lymphoid cells," and quite another to pass the long educational journey which would enable us to pick out the cells, classify them into microlymphocytes, microlymphoidocytes, macrolymphocytes, macrolymphoidocytes, splenoblastic lymphocytes, monocytoid cells, pseudoplasma cells, eosinoid cells, etc., and then *count them out and write out the cell-formula that expresses the tissue-reaction to one or other toxin, or toxoid.** That is one lesson which has to be mastered before we can intelligently produce artificial anaplasia in these cell-clusters, and finally bring about the cure (by fibrosis) of any lesion that we desire. The other lesson is easy to learn, because it is only one of recognition of a fundamental truth,

* Benda suggested that granulosarcoma was produced by a toxoid.

that all the cells of the blood-forming organs are neither similar, nor constantly or persistently the same in function, destiny, or origin. On this view the influence of new stimuli may lead a blood-cell parent to pass along a collateral line of development, and its progeny may acquire the habit of passing along this line, so that ultimately a tissue is produced whose cells are all different in type from the original.

While the basis of such a conception is afforded by careful preparations of ANY lymph-node (oil-immersion lens!), the interpretation of the histological appearances is always difficult, and liable to vary with different observers. It is not easy to decide whether the cells present are really the result of cytoplasia of hæmopoietic cells, and are not produced by *multiplication of indifferent* or non-hæmopoietic *tissue-elements* (i.e., a productive "inflammatory" process, with subsequent pressure atrophy of the specific parenchymal cells). The classical references to metaplasias of the pulp tissues in the spleen or lymph-node nevertheless show that there is a consensus of opinion among those who know best, to the effect that cytoplastic changes may actually take place, and that an interpretation in a phlogoblastic direction is not always justified. We should therefore conclude that in some of the so-called blood diseases, the tissue-changes partake of the character of local intracellular metamorphoses.

In the second place, it is necessary to distinguish between metaplasias and *degenerative processes*. It is evident that a preponderance of plasma cells in a lymphadenoid tissue, e.g., must be the result either of infiltration by extraneous cells, or of degeneration of existing cells, or, lastly, of a tendency, abnormal it is true, to develop along that line. If the change into a plasma cell is to be looked on as a degeneration, then the whole process must be described as degenerative and not metaplastic. But we have already seen that the conversion of lymphoid into plasma cells is not the whole story, because these in their turn are apt to become fibroblastic in certain cases, a fact which stamps the process as not itself degenerative.

In the third place, a metaplastic process may be simulated by a *hyperplastic one*. In the example just referred to, one might

interpret a change of type from lymphocytoid to plasmoid as the effect of hyperplasia of plasma cells. On the other hand, this would imply that the mass of the plasma cells was not advancing in differentiation, and would always remain in the same phase of development. Secondly, it would imply that the plasma cell was a physiological inhabitant of the given tissue. The term hyperplasia may, however, be applied correctly, if we interpret the process as one of excessive multiplication along accustomed lines, peopling the tissue with cell-units which are usually only present at all, as a response to substances whose character are at present unknown, sometimes found in apparently healthy tissues (normal catabolic processes), but usually abundant in certain pathological lesions.

In the same way, the question of anaplastic versus metaplastic or phlogoblastic changes largely depends on the view-point adopted about the individual cells. Those who see a retrograde process in the formation of plasma-cell accumulations would call the tissue change anaplastic, but the almost regular presence of amitosis in such inflammatory areas as are in mind, seem to contraindicate the theory of retrogression.

There remains only one other possibility, that the cells present in the tissue are *merely transported cells*. Are plasma cells and eosinophiles carried thither, or are they formed on the spot ? This has been the burning question, especially in the case of the so-called myeloid metaplasia. There can be little doubt that both events take place in the latter instance. The blood of such cases may contain isolated myelocytes which possess the power of locomotion, and may easily congregate in the special regions where myeloid metaplasia is met with. On the other hand, there is definite evidence in favour of the view that many myelocytic cells actually form from parental parenchymal cells pre-existent in the tissues.

We have discussed these points seriatim, as the whole argument would necessarily be obscured in an attempt to show that there is no hard-and-fast line of distinction between any of the processes named, and that we may easily encounter combinations between them. If metaplasia be associated with hyperplasia we should speak of a metahyperplastic process without attempting to define

where the one ends and the other begins. There is no reason why a cell may not undergo anaplasia (descent in the scale of phylogenetic differentiation, at the same time as the cell ages*) and then re-awaken and pursue another path of phylogenetic development.

The most ardent and thorough exposition of the principles laid down above we owe to the labours of Pappenheim[2] in the first instance, and the intricacies of his arguments dependent on cytological dye-reactions and other considerations afford a very convincing proof of his thesis, although the complexity of the terminology adopted by him renders the study of his contributions in the "Folia Hæmatologica" rather toilsome. Other workers, well-known in the field of hæmatology, have joined in the demonstration of the labile and protean character of the cell-constituents, principally of the pulpar tissues; of the changes in type of development arising under noxious bacterial influences. We may further instance the observations of Tomaszewski,[3] Müller,[4] Marchand,[5] Lüdke,[6] Voswinckel and Dunzelt,[7] in reference to the production of hyperplastic processes in special cell-groups in the different forms of leukæmia; the work of Kelling[8] and Litten[9] on the inter-relation between leukæmic changes and the myelotoxicoses of clinically pernicious anæmia; the investigation of Arnsperger[10] on endemic leukæmic manifestations. Pappenheim[11] has pointed out the difference between the action of a phanerogenetic infection on the blood-forming tissues, and that of a cryptogenetic infection. The former sets up a pure metaplasia, the latter sets up hyperplasia in addition. The importance of this distinction lies in the fact that specific cell proliferation may be set up *regardless of inborn tendencies* on the part of the cells affected, because it leads to the conclusion that cytoplastic processes may be artificially induced. The converse may be reasonably expected, and curative treatment hoped for. The pure hyperplasia may be an inevitable result of the obscure infections, but the metaplastic change (as in leukæmic diseases, and in malignant granulomatosis)† depend entirely upon an exogenic agent, whether that be organismal or of the nature of an intoxication.

* The question of time complicates the description of these phenomena. It is more convenient to ignore it as a merely relative idea.

† One of the forms of Hodgkin's disease.

Duval demonstrated an ability to produce a lesion analogous to the crytogenetic granulomatosis of Hodgkin's disease by the exhibition to a guinea-pig of an attenuated mallein. Podwyssozki[12] showed that talc injected intraperitoneally, produces nodules in the mesentery and peritoneum, rich in giant cells derived from the perithelial and adventitial cells, and forms a granuloma. He argued that here a substance acting mechanically (because it could not be digested), and not toxically, would produce a strong formative stimulus on the cell nuclei and set up nuclear proliferation.

Expressed in symbolic form, these different morbid lesions may be gathered together by taking cognizance of: *A*, the predisposition to develop neoplasms; *B*, the predisposition to autonomous and unlimited proliferation common to all cells; *C*, *C'*, *C''*, *C'''*, different stimuli to hyperplasia.

In the case of malignant granuloma,* the addition of *A* and *C* leads to *B*.

In the case of leukæmia, the addition of *A* and *C'* leads to *B*.

In the case of pseudoleukæmias, the addition of *A* and *C''* produces *B*.

Chronic inflammatory processes, again, under the influence of *A* and *C'''*, will sometimes end in *B*, manifested in the formation of some neoplasm.

The various processes designated by the letter *B* are also labelled variants or types of lymphosarcoma by the clinical or the surgical pathologist. One single noxa, one form of atom-group, or, as we shall see presently, some stereochemical position,* may be the ultimate reason for the different manifestations, working as it would upon a variable material.

At first sight it appears impossible that so many diverse tissue masses should be produced in a seemingly simple group of lymphoid cells. A little reflection will, however, show that in the hæmopoietic tissue, as in the solid portions of bone, we are dealing with a connective-tissue cell with multiple potentialities. If one such cell can secrete bone at one time, cartilage at another, fibrous tissue at another, there is no reason why the mesenchymal cell should not

* Cf. "conditions" of an experiment.

at one time develop myelo- at another lympho-potentialities. Once accept the view that the adventitial cell can withdraw its hold from a capillary, acquire powers of locomotion, and appear as a Saxer wandering cell, and there is no difficulty in believing that different extraneous influences, different pabulum, and so forth, may lead to varying products of proliferation. In a sense this would be described as endowment of the mesenchymal cell with embryonic characters, but the word embryonic is apt to be misleading. The formation of a polyblast (Maximow), of the parent of small-round-celled infiltration, of mast cells, of plasma cells of various forms (Krompecher[13]), of fibroblasts (Borst), or of epithelioid cells (Marschalko, Krompecher, Schottländer), and so on, is only on a par with the ability of indifferent connective-tissue cells taking on mucoid, chondroid, osseous, or any other allied character.*

In the lymphadenoid tissue we have indifferent cells which usually run along a definite line of development, culminating in cells habitual to the blood-stream. Under abnormal stimuli they may be expected to enter on unusual lines of development, and even exhibit some of the metaplastoid or neoplastoid tendencies associated with subacute and chronic inflammatory processes elsewhere in the body.

The key-note for the study of these changes, then, remains this: that the cell-individual itself must be investigated. When the mechanism and causes of metaplasia in a cell are understood, the gross effect of the tissue mass as a whole is readily understood, being, as it is, the outcome of cytoplastic change occurring simultaneously in a number of cell-individuals of the same order. More than this, a given agent may set up changes, not merely in one order of cells, but may act on several varieties simultaneously. It may, for instance, act not only on the parenchymal cells, but also on the stromatic cells of the pulpar tissue.†

2.—The Mechanism of Metaplasia.

When referring to the chemical questions arising in connection

* It will be remembered that the indifferent connective-tissue cells of bone are *stromatic*, and not *parenchymal*.

† Refer also to Section III. of Chapter I.

with cell metabolism, the interaction between nuclear matter and spongio- or hyaloplasm was discussed. The most striking example of the kind was exhibited by the red cell during its conversion from a nucleated hæmoblast to a non-nucleated hæmoglobin-rich erythrocyte. The steady oozing of the parachromatin (probably in an altered form) into the paraplasm, brings it in contact with amino-groups and leads to the synthesis of hæmoglobin. Speaking in general terms, the chemical basis of metaplasia might be regarded as a conversion of paraplasm and parachromatin from basophilia to oxyphilia, *plus* loss of spongioplasm.[14] The nuclear precedes the cytoplasmic differentiation in point of time.[15]

If we deal with cells as if they were organic chemical compounds, we find ourselves able to draw some analogies between metaplastic processes as discussed above, and certain interactions met with in organic chemistry. Before doing so, however, it must be pointed out that the analogies are merely suggested, are not capable of logical proof, and must be associated with other factors (surface tension, etc.); for this reason they will only be given briefly.

Certain substances endowed with stereochemical attributes are comparable with cells in process of metaplasia, because each may possess a given outward form (molecular formula: special morphology) under which are variants differing from one another in internal structural arrangements (structural or spacial formula: morphology of variants). Simple chemical agencies may bring about rearrangement of the atom-groups in one direction, or back to the original position (reversible reaction). We might label such processes as metaplastic, or anaplastic. Thus, the following simple example will suffice to indicate what is meant: Starting with ethyl nitrate and hydroxylamine, an interaction is possible with benz-aldehyde. The product is benzaldoxime, a body which exists in three stereo-isomeric forms. The γ-compound passes into the α-compound under the influence of an ethereal solution of hydrochloric acid. The second isomer is convertible by the action of heat into the β-oxime. The structural formula is the same in each, but the spacial one is different, as the atom-groups occupy different positions with respect to each other. This is an extreme example of a metaplastic process, in which the final product is only differen-

tiable by very subtle methods, just as the change from an indifferent pulpar cell into a leucoblastic cell is at first sight hypothetical. Each of the oximes may undergo a further and still more definitely metaplastic change by a process called Beckmann's substitution. The γ-compound furnishes benzoyl phenyl urea, the α-compound becomes dibenzenylazoxime, and the β-compound gives rise to oxanilid. This series of metamorphoses is very striking, because

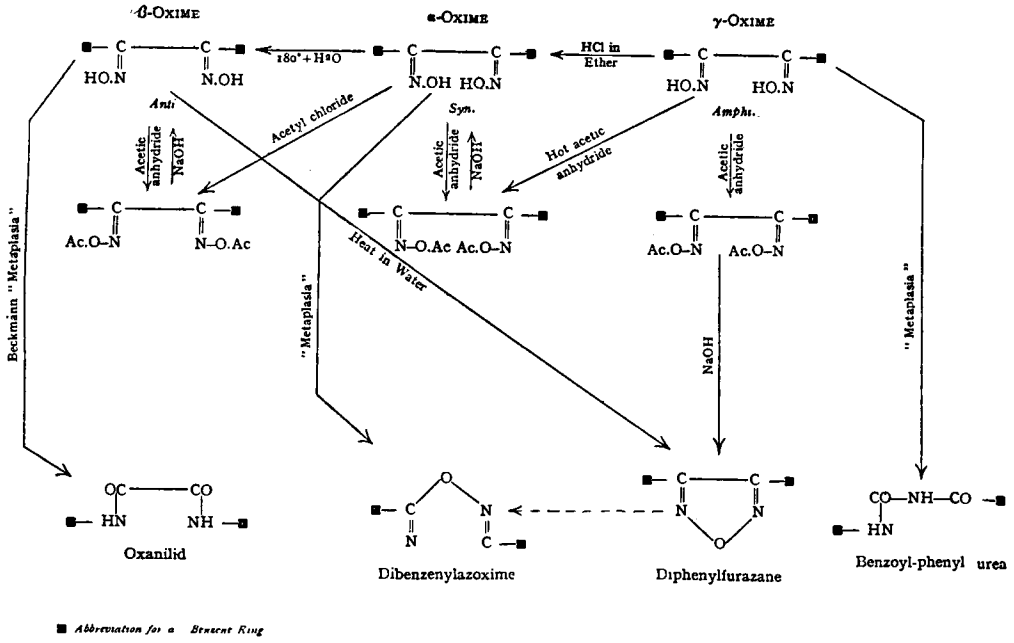

Fig. 71.—Steric Chemical Interchanges.*

the structural formula now differs both spacially and when drawn on plane paper. More than this, while two of the reactions produce bodies which are still more or less chain compounds, the third one (the α-derivative) is a ring compound like that characteristic of nucleoproteid catabolism. In drawing the latter comparison, however, there is no suggestion that there is any similarity between the cell-process and that cited from steric chemistry; the point is only

* Adapted from Werner's text-book of Stereochemistry.

that similar examples might well exist within the cell-body-nucleus complex. Moreover, the fact that this complex is somewhat of the nature of a galvanic pile (acid-base association) furnishes a possible explanation for, and a simple means of accomplishing, chemical inter-actions between nucleus and cell-body. Alter the sequences, introduce new agencies from without, which shall sterically or otherwise hinder some phases and accelerate others, and we have all the desiderata for the production of a cytometaplastic phenomenon within a cell. The same process, repeated in thousands of juxtaposed cells of like order (all exposed to the same noxa) affords us the metaplastic tissue change under consideration.

There is one other sequence of reactions exemplified by our oxime example to which reference may be made. The simple reagents, sodium hydrate (base), acetyl chloride (acid), acetic anhydride, produce slightly different effects on the different stereoisomers. The anhydride produces an acetyl compound in each case, but the γ-oxime, subjected to hot anhydride, will give the same derivative as the α-compound does in the cold. The acetyl compounds from the α and β-oximes can be reversed into the original bodies by the action of soda, but the γ-compound, under the same conditions, undergoes further molecular interchange into diphenylfurazane, which body is also produced directly from the β-compound under the influence of steam (heat in water). This diphenylfurazane is isomeric with the dibenzenylazoxime produced from α-oxime by the Beckmann substitution method. Acetyl chloride, acting on the α-oxime, converts it into the β-derivative; the anhydride is alone sufficient to produce this substance when acting on the β-compound.

These examples will suffice to show that there are other possible lines upon which to pursue the investigation of the changes in the blood-forming organs. The reader will remember that even these would be insufficient, because the purely physical and physicochemical properties of the bodies have also to be taken into consideration.

3. **The Exciting Agents of Metaplasia.**

As already mentioned, there are two possible sources of excitation of metaplastic processes: the inherent properties of the indifferent mesenchymal cell, and the superaddition of an extraneous factor. We have seen that an extracellular agent may be assumed to excite the metaplastic processes characteristic of the leukæmias and of the malignant lymphogranulomatoses, while the change into lymphosarcoma is dependent on the associated action of an intracellular complex of factors. On Pappenheim's view, the proliferating tumour cell is the anaplased tissue cell itself, which, after undergoing retrograde differentiation into the primeval type of germ-cell, is itself the parasite and at the same time the cause of the disease. The origin of the proliferation without further differentiation lies essentially in the disposition of the cell in that direction, although the writer would agree with Ribbert in assuming that there must be loss of inhibition of multiplication as well, before this indefinite growth can be accomplished. As was pointed out in connection with Paget's disease of bones,[16] it appears likely that alteration of pituitary secretion, for instance, may have more to do with the production of unlimited unrestrained sarcomatous proliferation than has usually been taken into consideration. Possibly some such influence, or the absence of it, may be of importance in connection with some of the hæmopoietic tissue-lesions that give rise to the so-called "diseases of the blood." As regards the character of the original stimulus itself there is little to be said. We find that any non-specific inflammatory, or infective or leukæmic noxa may come into prominence in this direction. Pappenheim and Hirschfeld, in discussing two cases of acute macrolymphocytar leukæmia,[17] showed that the same external stimulus might set up any grade of productive regenerative inflammatory process up to a lesion which would be classed as neoplastic.

II.—SPECIAL EXAMPLES OF METAPLASIA IN HÆMOPOIETIC TISSUES.

MYELOID—Lymphoid—Megakaryocytomatotic—Mast cell—Plasma cell—Splenoid—Sarcoid—Erythroblastic.

THE foregoing general account of cytoplasias is conveniently supplemented by a short description of certain special forms. At first sight, there are as many varieties of metaplasia possible as there are of cell-forms met with in hæmopoietic tissues. Close analysis, however, reveals the fact that the more subdivision of plastic processes is attempted, the more difficult it is to draw the line of distinction between them, and the greater liability there is to fall into the error of regarding every tissue change as a metaplasia, without first critically investigating its claims to that distinction. Even the most conspicuous example—the so-called myeloid metaplasia or transformation—is not looked on by all observers alike, some holding that it is strictly metaplastic in nature, others that the elementary constituents are descendants of local cells, or are mere accumulations of others swept to the part from the bone-marrow.

The two opposite views—local formation* versus metastatic transference—can be held with respect to each and every instance of metaplasia so far adduced, and the arguments *pro* and *con* are so applicable to each that it suffices to present the arguments relating to the first-named alone.†

The forms of metaplasia which call for consideration here are: (1) *Myeloid*; (2) *Lymphoid, including* (*a*) *macro-*, (*b*) *micro-lymphocytar forms*; (3) *Megakaryocytomatotic*; (4) *Mast cell*; (5) *Plasma cell*; (6) *Splenoid*; (7) *Sarcoid*; (8) *Erythroblastic.*

1. **Myeloid Metaplasia.**—The term myeloid metaplasia is

* This, again, may be regarded as a meta- or a hyper-plasia, or both.

† The literature on the subject is so extensive and technical that a monograph devoted solely to it would be appropriate. The writer's findings in experimental animals and at autopsy afford abundant interesting evidence bearing on the subject. It is felt inadvisable to introduce details on the subject into the present work.

applied to the condition in which granular cells (myelocytes) accumulate in a tissue normally free from them.

The tissues in which this change may be met with are few: the spleen, the pulp tissue of the lymph nodes,[18] and the liver.[19] In the latter region the foci are perivascular in situation; in the lymph-nodes the change occurs close to dilated vessels and not in the follicles—these last-named being compressed by the myeloid tissue.*

The change has been described in connection with the thymus, in congenital syphilis (Schridde, Ghika); with the kidney in the same disease (Schridde, Swart); with the diaphragm; with the omentum of newly-born animals (Schwarz); or even in association with any of the perivascular formations of the embryo.

Diseases Associated with Myeloid Metaplasia.—In the *liver*—Congenital syphilis, bone-cancer, osteosclerosis, myeloid leukæmia,[20] diseases of children (Swart, Nattan-Larier); experimental anæmias (Meyer and Heinecke) and infections (Nattan-Larier). In the *spleen*—in congenital syphilis (Naegeli, Hecker, Erdmann, Kimla);† in acquired syphilis (Schridde), in scarlet fever (Klein, Hirschfeld), diphtheria (Simon, Hirschfeld), erysipelas (Wolff, Hirschfeld), lymphomatosis of bone (Hirschfeld[21]). In the spleen and lymph-nodes—in fatal pneumonia (Uskoff, Hirschfeld[22]), small-pox (Weil), typhoid fever, septicæmia and peritonitis (Dominici, Hirschfeld); severe anæmias in man (Wolff, Hirschfeld, Naegeli, etc.); pernicious anæmia (Schatiloff[23]), plumbism also if experimentally induced (Ribadeau, Dumas), carcinoma of bone (Kurpjuweit), osteosclerosis (Askanazy, Nauwerk and Moritz, Naegeli). It is also met with in plethora vera (Hirschfeld), and in the lymph-nodes in experimental infections (Dominici).

Experimental Production of Myeloid Metaplasia.—The induction of microbic infections in animals already rendered anæmic (Dominici, Bésançon et Labbé, Nattan-Larier). Inoculation of anthrax, pyocyaneus, and bacillus mucosus capsulatus leads to

* The myeloid form of hæmolymph-node is indistinguishable from a condition of myeloid metaplasia in an ordinary lymph-node.

† Here it is due to the persistence of the embryonic perivascular formations which should otherwise disappear.

appearance of eosinophile myelocytes in the spleen within four hours (Opie, 1904).* Dominici found it in a guinea-pig inoculated with tubercle eighteen weeks previously; in this case eosinophile and megakaryocytes were present also. Werzberg's[24] experiments with myelotoxins have been referred to at length, and may be recalled in the present connection (*p.* 35). Collargol injections were found to produce myeloid reactions (Achard and Weil).[25]†

THE TISSUE CHANGES IN MYELOID METAPLASIA.—There are two main varieties of the condition: one where both granular and non-granular cells are found, the other where the elements are entirely non-granular. In the second case the tissue simulates a lymphatic interfollicular hyperplasia.[29] The non-granular cells are myeloic lymphoid cells, or may be classifiable as lymphoidocytar myeloblastic or as microlymphocytar micromyeloblastic cells, according to their varying morphology.‡

The histological details are exactly similar to those seen in cellular bone-marrows. There is an aggregation of discrete cells of hæmopoietic character around the capillaries of the organ concerned. If it be the lymph-node or splenic pulp, the original elements are replaced and the ordinary myeloid cells of the bone-marrow appear in their stead. In *Fig.* 72 is shown a characteristic field of splenic pulp which is the subject of the myeloid metamorphosis. There are seen the various discretely placed specific hæmopoietic cells, mostly of myeloblastic type, large pale-staining cells with oval or slightly indent nuclei in which chromatin markings are clearly visible, smaller cells with round nuclei and narrow cell-body, intermingled with modified pulpar cells. Neutrophile granules occur in the myelocytes. Myelocytes, mast cells, bone-marrow giant cells, normoblasts, megaloblasts—all familiar inhabitants of the bone-marrow—are all met with in the spleen.

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* The fact that they had disappeared again four hours later led him to believe them to be bone-marrow in origin, and only temporarily lodged in the spleen.

† Other workers are Jarotzky,[26] Selling,[27] Sternberg,[28] etc.

‡ Myeloid metaplasia cannot well be studied by film preparations alone (from organ scrapings *in vivo*, as was done by Japha and Fränkel[30]), because the blood itself may contain myelocytes in large numbers. On the other hand, it is very helpful to combine a study of a film preparation with the investigation of the histological preparation *lege artis*.

THE NATURE OF MYELOID METAPLASIA.—This subject has come in for a storm of discussion, which is most conveniently summarized in the following form. The main theories are : (1) That the myeloid cells are metastatic ; (2) That they are formed locally (autochthonous origin). The latter theory is subdivisible into the variants : (*a*) True autochthonous formation, by metaplasia of a pulp-cell, (*b*) Hyperplasia of preformed lienal myelocytes, (*c*) Origin in Saxer and Marchand cells, (*d*) Origin in local myelopotential cells.

Theory A.—That the myeloid change is due to *metastasis of cells from the bone-marrow.*[31] Arguments *in favour* : (1) Colonization of wandering cells occurs in the foci of development found in 11 mm. human embryos (Askanazy).[32] (2) The analogy to sarcomatous or pyæmic emboli. (3) The superabundance of myeloid cells in the blood in these cases. (4) Opie's experiments with anthrax, pyocyaneus, etc., in guinea-pigs.* (5) The fact that giant cells can form emboli (Schwarz and Michaelis[33]). (6) Inability to see cancer cells in the blood is no argument against metastatic deposition of cancer, so why should the paucity or absence of myelocytes in the blood be considered to contraindicate metastasis of foci of myeloid metaplasia ?

Arguments *against* this idea : (1) The structure of the focus in the liver or spleen is not like that of a tumour metastasis. (2) The new facts about the histology of the spleen and lymph-nodes (Neumann[34]). (3) If blood cells are specific, how could one of them settle down and make neutrophile, eosinophile, and all other elements ? They would have to undergo anaplasia first, and that is impossible for the finally differentiated cell-elements. (4) Often there are no myelocytes in the blood in these cases (cf. argument 6 in favour). (5) Werzberg's experiments[40] with myelotoxic sera, which set up myeloid metaplasia in the spleen. (6) M. B. Schmidt (1892) proved that in the liver the myeloid change starts in the vessel wall, as in the fœtus. (7) Atrophy of the follicle would mean excessive proliferation of the other part of the tissue (myelogenic leukæmia would thus, according to Banti,[35] be a "systematic myelogenic

* Not a satisfactory argument, because a few myelocytes in a tissue do not make myeloid metaplasia.

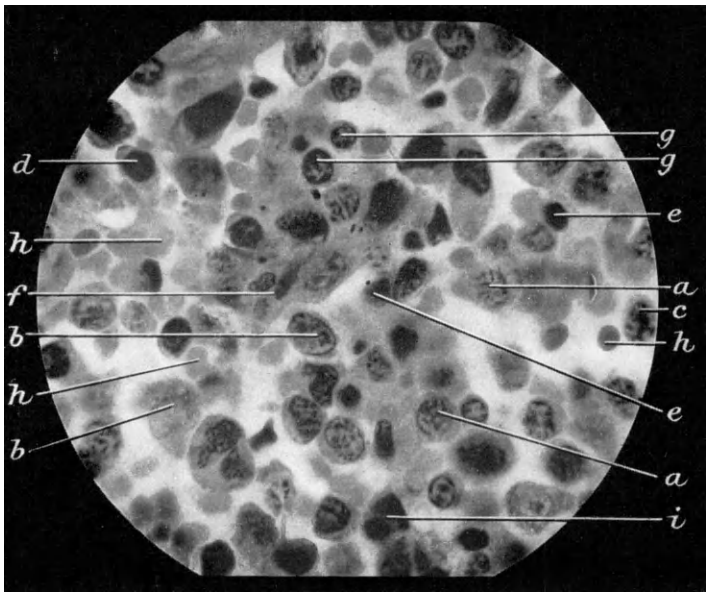
sarcomatosis of the hæmo- and lympho-poietic apparatus"). (8) When cancer cells metastase they are accompanied by cachectic symptoms: if the blood mother-cells are metastasing, should not they also set up deleterious effects? (9) The following considerations: If the cells in subacute inflammatory exudates are to be looked on as, at any rate in part, a local production, why should not metaplasia be local? Some authors agree that some of the small round cells are formed *in situ* as a result of microbic irritation of the adventitial cells of the vessels of the affected area, and that the same irritant may lead the altered cells to prosecute unusual lines of progressive development or degenerative change. There is therefore no *a priori* reason against the supposition that similar irritants should excite the interfollicular parenchymal cells to pursue a leucoblastic method of growth ordinarily not habitual to them in the locality to which they are accustomed. To take on such a changed mode of growth would be to undergo a strictly metaplastic metamorphosis, and it would not be unnatural to find such a phenomenon limited to a solitary lymph-node or group of nodes, whereas there can be no satisfactory explanation for a limited distribution of myeloid transformation if the "abnormal" cells have been carried from the bone-marrow all round the circulation to settle in the places in question and in those only.

Theory B.—That the myeloid change is due to *local production of the unusual cells.* The variants of this view have already been quoted. The arguments against the view (taken collectively) are the same as those in favour of the metastatic origin; in favour of the view (taken collectively) are the same as those against the first-named theory. Taken seriatim, we find the following arguments employed *in favour* of each successive variant:—

(1). That there is a true autochthonous formation by *metaplasia of a pulp cell* (Meyer, Heinecke, Mareiwitz, Hirschfeld).

Assuming that the spleen pulp-cell has myeloid "ancestral memories" (O. C. G.), it is easy to see that any damage or interference with the activity of the bone-marrow might be responded to by a compensatory myeloid change in the splenic tissue. The myelopathic condition is usually microbic.

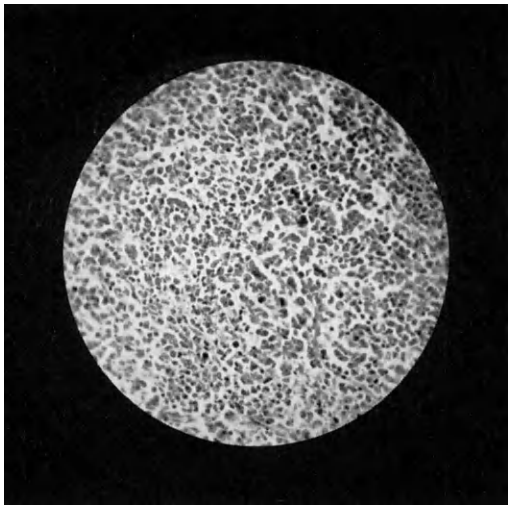
(2). That there is *a hyperplasia of preformed lienal myelocytes*



". . . a characteristic field of splenic pulp, which is the subject of the myeloid metamorphosis" (p. 300).

Fig. 72.—SPLENIC PULP IN A STATE OF MYELOID METAPLASIA. (*a*) myelocyte; (*b*) metamyelocyte; (*c*) lymphoblastic cell; (*d*) mesolymphocyte; (*e*) microlymphocyte; (*f*) polynuclear leucocyte; (*g*) normoblast; (*h*) red cell; (*i*) dividing plasmoid cell.

(Oc. 12, Zeiss Oil-immersion).



". . . a metaplastic process in the parental cells" (p. 304).

Fig. 73.—SPLENIC TISSUE IN A CASE OF ACUTE LYMPHATIC LEUKÆMIA, SHOWING COMPLETE LOSS OF DIFFERENTIATION INTO FOLLICLES AND PULP. The cells vary little in character, being all of lymphoid type.

(Oc. 6, Obj. A (Zeiss)).

Face p. 302]

(Sternberg). But myeloid tissue is only pre-existent in the marrow. The cells must be more than merely latent (Dominici, Hirschfeld, Walz): they must be simply indifferent and myelopotential cells. In favour of the theory: (*a*) myeloid relics do occur*; (*b*) indifferent primordial cells occur; (*c*) normal spleen contains myelocytes in man,† in the mouse,‡ kangaroo (Pappenheim), new-born guinea-pig (Dominici), rabbit (Dominici, Naegeli, Scott); especially after repeated bleeding (Dominici[36]).

(3). Origin in Saxer and Marchand cells by *re-awakening of their leucogranuloplastic and lymphoblastic powers.* An unknown stimulus must be assumed, similar to that which excites undue activity on the part of the bone-marrow (Pappenheim). In favour are these three facts: indifferent primordial cells are found in each tissue. Marchand showed that adventitial cells (clasmatocytes can differentiate in post-embryonic life). Neumann showed that there is an analogy with formation of lymphoid nodules all over the body in lymphatic leukæmia.

(4). Origin in *local myelopotential cells* (Hertz).[37] This writer believes that *follicles* can make promyelocytes. Fundamentally this variant is the same as (1). The pulp cell is myelopotential. Hertz based his conclusion on the effects shown by the use of pyrogallic acid in rabbits. Local activity of the myelopotential cells is then observed.

2. **Lymphoid Metaplasia.**—It has been said that lymphatic metaplasia is an impossibility, because the tissue in question is so widely disseminated, and is so constantly active, that the existence of lymphoid masses in any region would belong to the category of hypertrophies or hyperplasias. On the other hand, Pappenheim[38] has spoken at length about the change of macrolymphocytes into lymphocytes in the bone-marrow of chronic microlymphocytar leukæmia; this change being the explanation of the lymphadenoid small-celled lymphocytar metaplasia of the marrow ("auto-parenchymal metaplasia") met with in this form of leukæmia. This view is believed by him to be a more satisfactory explanation

* Not proved yet.
† Flemming, Weidenreich, Dominici, Hirschfeld, v. Ebner, Sternberg, Kurpjuweit.
‡ Ashheim, Wolff.

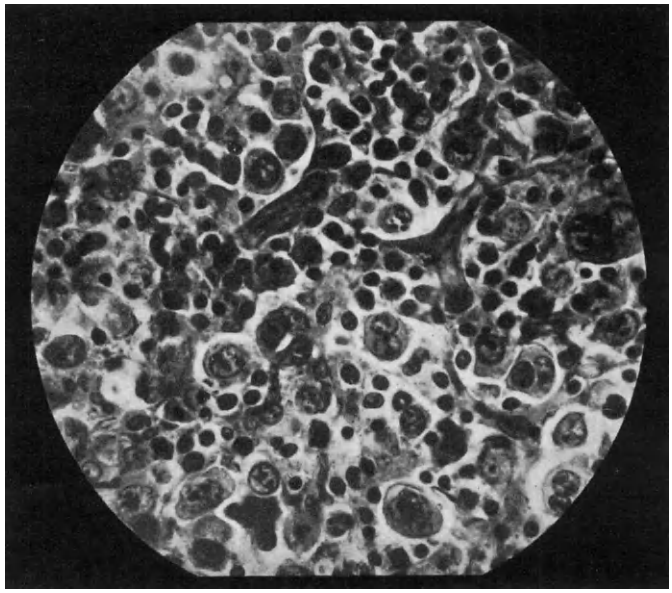
of the phenomenon than the assumption of a substitution of the marrow tissue by foreign perivascular lymphoma formation. Just as in the spleen the follicles are composed of heterogeneous descendants of perithelial cells that do not turn into pulp cells, while the pulp cells are also of perithelial origin—so in the bone-marrow the parent cells of the myeloid tissue may become true lymphomas (in rickets, e.g.). This is to be looked on as a functional aberration of the myeloid parental cells, with consequent formation of lymphocytes which have been produced by a metaplastic process in the parental cells and are not the result of proliferation of the so-called paramyeloid lymphomas.

Similarly, Neumann[34] regards the so-called lymphadenoid hyperplasia met with in all parts of the body under pathological conditions as analogous to myeloid metaplasia, so that whatever view may be taken of the latter process, the same would be justifiable for the former.

Two forms of lymphoid metaplasia may be mentioned: macro- and micro-lymphocytar forms.

Macrolymphocytar metaplasia has been discussed, for instance, by Hertz[39] and Werzberg,[40] as occurring in splenic pulp by means of a prosoplastic change in the macrolymphocytes of the follicles (*Fig.* 73). The isomorphism between the lymphoblast and the lymphoidocytar pulp cell being admitted, the basis of a metaplastic change in either becomes intelligible. Paremusoff,[41] working in Kraus' laboratory in Berlin, refers to Pappenheim's views about the mutability of splenocytic cells into microlymphocytes, and to the belief that the pulpar splenocytes are the resting forms, while the germ-centre cells are the same in a state of lymphoblastic irritative mitotic activity. This conception explains how it is that a macrolymphocytar proliferation is always located in the pulp[42] or "interfollicular ground tissue," and is associated with atrophy of the follicular tissue.

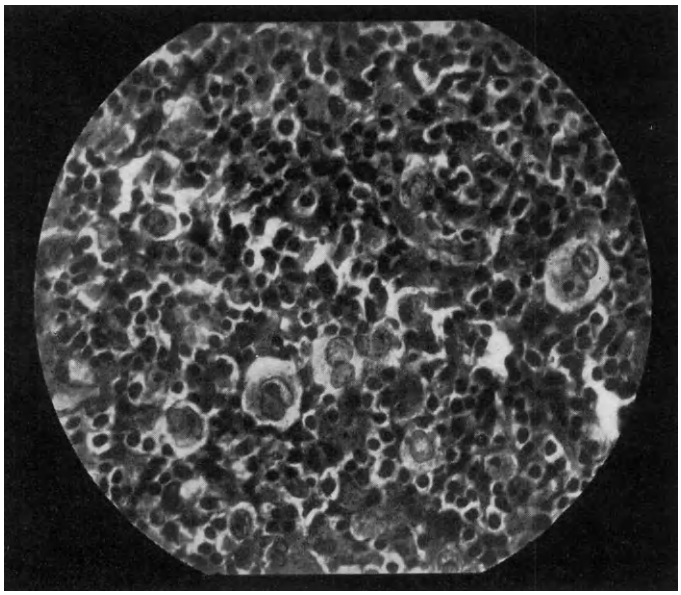
When this phenomenon is seen in the bone-marrow, the hyperplasia of large lymphoid cells is diffuse, and is associated with defective formation of erythroblasts and myelocytes, while lymphocytes appear in abundance—not that they are paramyeloid, but that they are potential progenies of the first-named. Rubinstein[43] reported a case of this kind, in which there was also an osteosclerosis.



" The picture shows numbers of very large mononucleate and binucleate forms with clear nuclei whose chromatic markings are very distinct " (p. 305).

Fig. 74.—FROM THE PULP TISSUE OF THE SPLEEN IN A CASE OF CHRONIC LYMPHATIC LEUKÆMIA. So-called transition to lymphosarcoma.

(Oc. 6, Zeiss Oil-immersion).



" Germ-centres with well-marked endothelioid cells . . . have frequently been observed " (p. 306).

Fig. 75.—LARGE NUMBERS OF LYMPHOID CELLS, with well-defined clear ovoid spaces amongst them; in each space lies a large vesicular mono- or bi-nucleate cell, the adventitial cell. Contrast with the preceding photograph.

Oc. 6, Zeiss Oil-immersion).

Face p. 305]

Hirschfeld, criticising this case report,[44] referred to a similar one published by Senator. The condition may be classed as a lymph-adenoid myelogenic pseudoleukæmia.[45]

Microlymphocytar metaplasia has been described as occurring in chronic myeloid leukæmia. Thus, Frank and Isaak[46] observed this to follow prolonged treatment with *x*-rays. Marked swelling ultimately appeared in the lymph-nodes, without any abnormality in the blood. The lymphatic tissue had become entirely micro-lymphocytic, save for the co-existence of a few myelocytar elements. Further, von Decastello,[47] reporting a similar case, was led to decide that the microlymphocytar change was truly metaplastic in type—not a sudden reversal from granuloblastic to lymphoblastic properties, but a gradual inhibition of differentiation till the bone-marrow alone contained the lymphocytoid descendants (normal in lymph-nodes, but pathological in the marrow) of the original parental cells. In such cases, anaplasia and disturbance of proliferation would not always run parallel, so that the appearance of intermediate forms of all kinds would excite no surprise. This change was also the effect of *x*-rays. A number of similar cases have been recorded by other observers.

3. **Megakaryocytomatotic Metaplasia.**—This is always a mixed process, for we do not meet with tissues entirely made up of megakaryocytes. The other stromatic elements are usually involved, partly by hyperplasia, and partly by other cytoplastic changes. The condition is perhaps best exemplified by the lesions of Hodgkin's disease of the Dorothy Reed type, about which so much has been written. The close relation of the process to that called lympho-sarcoma is also noteworthy.

The appearance of fibrosis, with clusters of "giant cells," some of which conform to the classical megakaryocyte type, while others are large uninucleate cells, of giant size; the appearance of large numbers of eosinophile cells, are all well-known features. An interesting example of the metaplastic change is afforded by *Fig.* 74, which shows a high-power view of the splenic tissue in a case of chronic lymphatic leukæmia.* The picture shows numbers of very

* Studied at the Leeds General Infirmary.

large mononucleate and binucleate forms with clear nuclei, whose chromatic markings are very distinct, while the cytoplasm stains rather feebly and is polymorphous in outline. Scattered amongst these are some small lymphoid elements which at the same time serve to show the great size of the first-named cells. A few bands of fibrous trabeculæ are also noticeable. This change is of interest as showing what is usually spoken of as a transition from leukæmia to sarcoma. The existence of numbers of these large cells is usually looked on as evidence of lymphosarcoma,* although every lymphosarcoma does not present them. It may be said that the more numerous these cells are, the more malignant (clinically)—i.e., the nearer death—is the subject of Hodgkin's disease.

It is likely that these cells are derived by intracellular metaplasia from the adventitial cells of the original tissue, because similar bodies are frequently met with in the lymphoid follicles (in the appendix, *par excellence*) as manifestations of a particular phase of activity of the cells. Germ-centres with well-marked endothelioid cells as centres of clusters of macrolymphocytes have been frequently observed by the writer in such tissues (*Fig.* 75).

The association of such findings, as depicted in the figure, with stromatic hyperplasias is most commonly seen in the so-called lymphogranuloma. Fabian[48] has collected all the literature on this subject and given an excellent summary of our knowledge of the condition, both pathological and with correlation of the clinical manifestations. Kundrat,[49] Yamasaki,[50] Hirschfeld,[51] B. Fischer,[52] Meyer,[53] Dietrich,[54] and others [55]† have discussed the subject from different aspects. Inasmuch as the transformation is associated with the production of tumour masses of variable size, and inasmuch as the larger masses come to simulate sarcomatous growths clinically, the diagnosis of the condition has come to be expressed by a very

* Ribbert, in his *Allgemeine Pathologie*, 1909, however, describes as lymphosarcoma what others name lymphocytoma, a tumour composed of small lymphocyte-like cells lying in a loose reticulum. Ziegler, in his text-book, figures a lymphosarcoma bearing characters described in the above text.

† The bone-marrow was remarkably changed in one case of megakaryocytomatosis in the literature.[56] The cells in question were greatly increased in number, showed mitosis in many instances, while degenerative processes of various kinds were noticed in others (chromatolysis, pycnosis, loss of protoplasm, appearance of "giant nuclei.") The eosinophiles were greatly increased, and foci of anæmic degeneration occurred. The lungs and liver showed infiltration by similar cells.

varied terminology. In more recent times the tendency has been to recognize an infective basis in all cases, thus bringing together the cases of "pure" Hodgkin's disease, pseudoleukæmia, and allied clinical forms, and yet furnishing satisfactory means of differentiation between them anatomically.* Without entering into the question of etiology, the problem is conveniently regarded from the standpoint of the possibility or otherwise of production of metaplastic tendencies of certain cells in these regions under the influence, sometimes of phanerogenetic, but usually of cryptogenetic, infective or toxic agents.

Allied to this condition† is the phenomenon observed in the Gaucher splenomegaly, where clusters of large endothelial cells are found, like nodules of tumours, scattered through the splenic substance. The condition is associated with a long history, and mitoses are not observed.[57] Chemically, the enormous accumulation of iron in lipoid form is a striking and significant feature.

4. **Mast-cell Metaplasia.**—Aggregations of mast cells might be referred to as examples of metaplasia, when met with under certain circumstances.[59] Since the phenomenon of mast granule formation has been described already as evidence of a cytoplastic phenomenon, possibly anaplastic, possibly metaplastic, it is not necessary to do more than mention the occurrence in the present list. Appearance of dense clusters of these cells is striking, but unless met with in association with evidences of neoplasia, there is nothing to be gained by further discussion of the condition.

5. **Plasma-cell Metaplasia.**—The same remarks would apply to the accumulation of plasma cells in a tissue. Since the formation of plasma cells is to a certain extent the normal fate of the lymphoid cells met with not only in the spleen and nodes but also in the centres of microbic irritation, their appearance in any tissue does not introduce any novelty. The definition of metaplasia originally

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* It is evident that all varieties of Hodgkin's disease might be produced by varying (*a*) The proportion of the different stromatic elements participating in the hyperplasia; (*b*) The degree of hyperplasia in each group.

† Endothelial hyperplasia has been described as a special condition by some writers in the literature, when it is nothing more than a part of the phenomena associated with lymphogranuloma. Thus, a case of multiple enlargement of the lymph-nodes of acute onset and course, was referred to by Milligan.[58] This would probably be an example occurring in the course of an acute sublymphæmia.

given does not hold good in either of these cases, even though the plasmoid or mast-cell change is strictly a metaplastic process. However, it is noteworthy how frequent this cell-aggregation is noticed in lymph-nodes abutting on the line of irritation of a cancerous tumour. Similar phenomena have been noticed in the axillary glands, where the breast is the subject of chronic interstitial mastitis, with abundant cell-infiltration round the gland acini. It must, however, be pointed out that the lymphoid follicles never become the subject of a plasmoid stimulus, because true plasma cells are never observed in the Malpighian bodies.[60]

The condition described as plasmocytoma would come under this heading. At first sight, such a tumour (case of Hedinger[61]) appears like a large round-celled sarcoma with transitional tendencies towards granulation tissue. In the case referred to, the basis of the tumour was an inflammatory process, a chronic suppurative ulceration. In other cases, the inflammatory cause has not been so evident. Klose[62] collected three cases from the literature and added one of his own. The tumour in his case was composed of closely-packed polymorphous amitosing cells of the type of plasma cells. There was infiltrating growth in some areas. The cell aggregations were closely related to blood-vessels.

6. **Splenoid Metaplasia.**—It will be evident from the mode of dealing with the subject of lymphopoiesis that the above term is misleading, even though it is convenient. The lymph-node may acquire characters which closely resemble those of the splenic pulp (*see Fig.* 34), merely because the pulpar cell is in each case isomorphous, and may exhibit similar hyperplastic and other tendencies, sometimes towards successively differentiating cells, either along purely lymphoid or along monocytar lines, and sometimes tending to undergo granulocytar metaplasia. The appearance of numerous irregularly placed fibroblasts, with the formation of an extremely ill-defined labyrinthine meshwork in which the pulp-cords of the lymph-node become completely obscured, is characteristically like the familiar histological aspect presented by the spleen under many seemingly physiological circumstances.

7. **Sarcoid Metaplasia.**—This condition has been discussed by numerous writers under different names (sarcomatosis, sarco-

leukæmia, leucosarcomatosis, myelosarcomatosis, etc),* although it has usually been considered rather in relation to leukæmia. In a sense, the leucosarcomatosis of Sternberg is a sarcoid metaplasia of the blood-forming organs,[63] in that it may be regarded as a sarcoid variant of a large or small-celled myeloblastic leukæmia, or as a sarcoid large or small-celled lymphæmia. The sarcoid character is indicated by the tendency to infiltrative growth and metastasis (cf. Buschke-Hirschfeld's case[64]). Myeloid micro-leucosarcoma cells have also been described as associated with simple hyperplastic proliferation.[65] The writer studied a case of sarco-leukæmia which could be classed with the foregoing.[66] In these cases it is of special interest that the blood-films may show tumour cells, quite distinctly identifiable by the clinical pathologist, although usually passed over trivially as large mononuclears.

There is a close relation between the myelomatous, leukæmic, acute leukæmic, and infective granulomata on the one hand, and sarcoid lymphosarcomatous and leucosarcomatous processes on the other. The latter are infiltrative, and produce metastases, but differ from true sarcoma in their morphology. The sarcoid tumours lie between inflammatory leukæmic proliferation and true tumours. One may pass from lymphosarcoma to true sarcoid proliferation, and thence to true sarcoma. There are only slight histological gradations between the various conditions, which accounts for the tendency nowadays to place the leukæmias with the sarcoid blastomatoses of the hæmopoietic apparatus. Perhaps the most thorough, elaborate and finished discussion of the whole subject—of which the above is a mere fragment—is that in Pappenheim's numerous Prolegomena.[67]

Yamasaki and Dietrich showed the transition between infective processes and sarcoid growth, while tuberculoid rods were found by Coley, Ewing, Arnot, Fränkel-Much in the acute lymphatic leukæmias. It is a question of whether there is resistance on the part of the body or not, that decides whether a chronic inflammatory stimulus is likely to produce a purely parenchymal proliferation or a simultaneous connective-tissue granuloma (lymphocytoma or reactive granuloma, in other words). Moreover, the noxa at work may act on the stromatic tissue cells as well as on the

* Palma, Strauz·Virchow, Israel-Lazarus, Drozsda, Warthin, P. Grawitz.

parenchymal elements. The co-existence of a disposition to tumour formation may lead to the production of an infiltrating granuloma or sarcogranuloma (Pappenheim).

The existence of such a condition as eosinophile lymphosarcoma (Kanter and Goldmann[68]) is of great interest in this connection, for it will be borne in mind that the Hodgkin's lesion is typically eosinophilic.

Lymphosarcoma has been thus classified by Lewin[69]:—

1. Solitary primary sarcoma of round-celled type. This is lymphadenoid in structure. Ziegler's true lymphosarcoma tends to burst through the capsule of the node.

2. Kundrat's generalized lymphosarcomatosis (Billroth's malignant lymphoma, Orth's aleukæmic lymphadenoma, Ribbert's lymphocytoma). This is transmitted along the lymph-channels.

3. Generalized aleukæmic pseudoleukæmic tumours—malignant lymphadenoma.

4. Leukæmic lymphosarcoma. Also called sarcoleukæmia. Is sarcoid metaplasia.

8. **Erythroblastic Metaplasia.**—This phenomenon was encountered in the spleen in a case of fulminating acute leukæmia which was brought to the writer's notice. The picture observed in the spleen was characteristic, the pulp being rich in normoblastic cells. The follicles were much diminished in size. This may be classed as an "embryonization," and therefore as really anaplastic in nature.

Anaplastic Phenomena need not be entered into beyond a mere mention. It is evident that many of the metaplastic processes could not come into effect were it not that an anaplastic change had taken place in some of the tissue constituents. On the other hand, it is not easy to be dogmatic in an assertion that this is always essential, and examples of anaplasia in lymph-nodes or macrolymphoid anaplasia of the bone-marrow[70] are liable to criticism as purely theoretical in basis.

III.—SURVEY OF THE HYPERPLASTIC, METAPLASTIC, META-HYPERPLASTIC, AND ALLIED PROCESSES IN THE PULPAR AND FOLLICULAR TISSUES.

THE play between parenchymal and stromatic elements in different diseases —Schemata illustrating the causes of enlargement of (*a*) lymphatic glands (*b*) spleen.

THE principles which have been laid down in discussing the life-history of the various cellular elements that go by the name of "blood-cells" enable us to bind together the whole structure as observed under the influence of pathological and other stimuli. We have come to see that the biology of blood-cells is intimately dependent upon the character of three main groups of formative tissue, the erythropoietic, the lymphopoietic, and the leucopoietic, and we have seen that the adult depends almost, if not entirely, on the bone-marrow for the former, while he makes use of very widely-spread tissues in order to provide himself with an adequate supply of the other types. We have also seen that the incidence of various forms of irritant may excite hæmopoiesis (in its wide sense) at any part of the hæmo- or lymph-vascular system, owing to the peculiarity that the adventitial cell maintains primitive faculties or potentialities throughout the life of the individual. What we speak of as round-celled infiltration is nothing more than an abortive hæmopoiesis, the proliferating tendencies of the adventitial cells being brought out, but unable to follow out the ordinary genealogical chart, owing to the fact that the (stereo- or other) chemical characters of the irritant are not exactly the same as those which induce normal blood-formation. The preponderant tendency to plasmoid, or eosinoid, or microlymphocytoid or other metamorphoses, with subsequent fibrosis, are peculiarities which even occur in such a tissue as the marrow with the progress of senile "decay."

In order to understand the histological lesions encountered in any of the blood-forming tissues, but especially those in the lymph-nodes and spleen, we find that the classification into three

main types of parenchyma is of inestimable assistance. We find that the last two tissues manifest changes according to the avidity with which the follicular or the pulpar cells take up the insults to which they are exposed. The changes, too, as we have seen, are of metaplastic (or, generally, cytoplastic) character, so that there is less difficulty in understanding the preponderance of one or other cell-type in a given lesion. The decision has therefore been reached, that the phenomena of tissue-substitution in these organs is largely —not entirely—the result of autochthonous and not of heterotopic processes ; otherwise it would not be true to say that the histological lesions in these organs are fairly easily comprehended.

Analysing the lymph-nodes and spleen into their elements, we have the main subdivision into follicular and pulpar " histological organs." In each case we have parenchymal and stromatic elements —the former being the immediate relations of the blood cells proper, while the part played by the latter is less evident and has not been fully dealt with in the preceding chapters, save to indicate that some of them—the adventitial or endothelial cells—constitute cells of the order of primordial, mother, or parental structures. Without enumerating again the various names given to the successive generations and life-phases of the parenchymal cells, it will suffice to emphasize the main differences between them as being that the follicular cells belong to a non-granular series, while the pulpar cells have granular (granule-forming) potentialities—the word granule being understood, as usual, to mean " specific " granule.

As regards these particular groups, we have seen that the non-granular cells are related either to arterial blood or to the special vicinity of lymph, while the granular series are related rather to venous blood. These details are of importance in connection with the fact of their disposition to branch along divergent lines of intra-cellular metabolism.

The stromatic elements include the ordinary elements of connective tissue ; these vary in age and form ; we have to deal with fibroblasts, or young connective-tissue cells, older fibre cells commonly glossed over as " fixed connective-tissue cells," epithelioid, adventitial connective-tissue, plasma, leucocytoid, endothelioid, megakaryocytar, pyrrhol, floating mesenchymal cells, etc. Some

of these have already been referred to as belonging to one or other phase of the life-history of certain blood cells, and the others may be conveniently brought together as representing different phases of one and the same connective-tissue cell. As Adami[71] has pointed out, the "fibrous connective-tissue cell is actually lining a potential lymph-space; and the cells that we recognize as lining lymph-channels and lymph-sinuses are the same kind of cell. . . . . It matters not whether the progeny of these cells be set free in the blood-stream, the lymph-stream, the tissue spaces, or the serous cavities, for they, the progeny, are like cells."

These words, used in reference to the pathology of inflammation, if applied to the pulpar tissue, for instance, come to have a still deeper significance, because they go to prepare the way for the fundamental truth, that the diseases of spleen and lymph-nodes are nothing more than an expression of reaction towards noxious agents, acting on parenchymal cells on the one hand and on stromatic cells on the other, or on both equally, at one time producing lymphomatosis, at another lymphogranulomatosis of different forms, at another lymphosarcomatosis. The stromatic cell may at one time act as a parental cell for free-floating cells familarly known as "normal," at other times differentiate along other lines which bring before us the picture of purely stromatic hyperplasias, fibroses, and a multitude of other unnamed or unspecified histological lesions.*

We can then translate the processes of disease in these organs into phenomena of cytoplasia of different forms, hyperplastic, metaplastic, metahyperplastic or hypermetaplastic, anaplastic,

* Proliferative changes within the stroma may be set up by long-continued venous stasis, or by obscure and long-continued toxic influences. Whether the stroma and pulp cell are interchangeable is uncertain, because it is not feasible to eliminate readily the possibility of pressure atrophy of the latter, following upon hypertrophy of the former. The enterogenic theory which has been offered to explain the fibro-adenia of Banti's disease affords an example of the cytometaplastic processes in which the stroma cells themselves may be concerned. In syphilis, Hodgkin's disease, kala-azar, malaria, and a number of other conditions, we find that changes occur in the stromatic elements, with or without simultaneous meta- or hyper-plastic manifestations in the parenchymal cells. The inter-relations between them, however, are capable of further investigation. The fact that a change of picture may take place from leukæmia to "sarcoma," and from non-leukæmic to leukæmic conditions, suggests that the whole story of the pulpar cell cannot yet be written. We can only say that the correct interpretation of the pathology of certain diseases where anæmic manifestations are superadded to enlargement of the spleen will not be possible until the inter-relation between stromatic and pulpar elements is understood.

fibroblastic, and so on, and fit in the cases reported in the literature into one or other of these.* Further, we come to understand how it is that the blood-picture of these so-called " blood-diseases " may be quite equivocal, and even disappointing. Whether the processes set going in follicle or pulp are to be associated with an overflow of the proliferated elements into the blood-stream, whether the overflowing elements are parental in type, or intermediate, or quite mature, is relatively of secondary importance. Whether, for instance, the blood-picture is or is not leukæmic, is not of so much interest as the character of the change in the tissue. Why leukæmic cells should appear at one time and not at another, is a problem whose solution may prove to be of significance, but as everyone knows, the disappearance of myelocytes from the blood-stream after using x-rays upon a leukæmia is not synonymous with a cure of the disease. Where the tissue change is " leukæmic," and the blood-picture is apparently normal, we speak of aleukæmia as a means of distinguishing the cases from one another more precisely than might otherwise be possible, but the first lesson to be learnt in connection with the tissue lesions of the organs in question is, that there are two main groups of systematic (system-) disease, otherwise similar, viz., those with leukæmic blood, and those without. The aleukæmic disease may pass over into a leukæmic form at a subsequent date, not because the change in the tissue is any different, but merely because the abnormal cells are finding their way into the blood-current. Similarly, a leukæmic process may become aleukæmic under the influence of therapeutic measures, or even in the course of apparently spontaneous metamorphosis. The explanation of supervention of leukæmic change in a hyperplastic organ such as the lymph-node cannot be other than that the products of proliferation secrete substances which ultimately set up leukæmic hyperplasia in the bone-marrow.[36 72]

The different lesions of the lieno-lymphatic system depend on the play upon the different cell-elements present in them ; increase

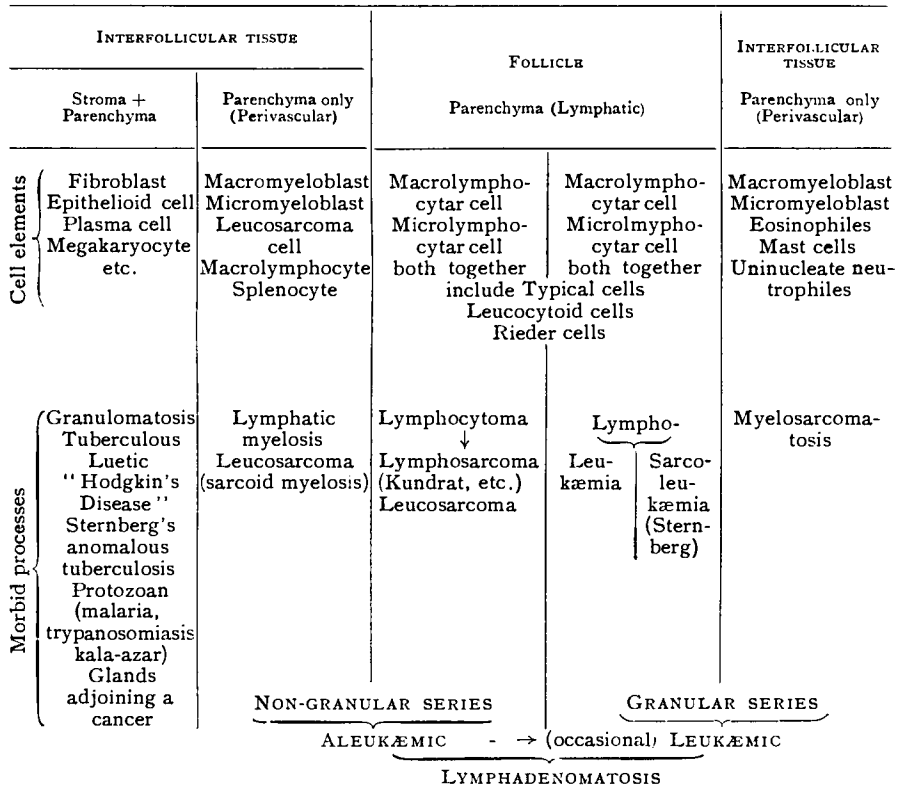
* It is not the aim of this book to do more than merely indicate the broad outlines of the subject, reserving for some favourable occasion the full discussion of the subject as based on the study of several hundred autopsies in which the tissue-lesions bore on the subject of cellular metaplasia.

one variety, and the others diminish; increase one, and another begins to increase; increase one, and all others increase; and so on. In one case the macrolymphocytes preponderate and produce a lymphoblastoma. In another, the fibroblasts are preponderant as a result of certain protozoan infections (malaria, trypanosomiasis, kala-azar), in another the fibroblasts; epithelioid cells, megakaryocytes, and plasma cells also appear and produce some forms of granulomatosis. There is no phase of the life-history of the parenchymal cells, finally, which may not form the key-note of the cytoplastic change in a lymph-node, for instance, owing to almost unlimited tendency of the proper cells to go so far along the road of differentiation, and settle down at that phase without ever passing on to further development. In this way we may have a lymphomatosis before us, all the cells remaining microlymphocytic or some isomorphous type, or we may have a leucosarcomatous change, or a micromyeloblastic change, and so on. If the blood-stream remains unoccupied by such differentially abortive and inordinately proliferating forms, we call it an aleukæmic lymphocytomatosis, or an aleukæmic leucosarcomatosis, or broadly an aleukæmic lymphadenomatosis; whereas as soon as such cells appear in the blood the processes become leukæmic: subleukæmic if only a few appear, true leukæmic if they are preponderant.

The remarks which have been made may be materialized in the form of the tables overleaf.

The schemes here submitted are intended rather to bring out the cytoplastic relationships between the various morbid processes to which special names have been assigned than to present a classification of the generalized or system-diseases of the hæmopoietic organs. In the latter connection it will suffice to say that a division of such diseases into (*a*) hyperplastic and (*b*) lymphosarcomatous appears to meet requirements. Each of these has been subdivided by Pappenheim[75] into lymphadenoid and myeloid, and each of these again into colourless and coloured (chloromatous) varieties. Each of the latter, finally, can be grouped according as they are or are not associated with leukæmic manifestations in the blood.

Enlargement of Lymphatic Glands.



ENLARGEMENT OF THE SPLEEN.

	FOLLICLE	PULPAR TISSUE		FOLLICLE
	Parenchyma	Stroma + Parenchyma	Parenchyma only	Parenchyma
Cell elements	Macrolymphocyte 1. Typical 2. Leucocytoid 3. Rieder Mesolymphocyte Microlymphocyte	1. Fibroblast 2. Epithelioid cell 3. Megakaryocyte 4. Adventitial cell 5. Myeloblastic types 6. Eosinophiles 7. Plasma cell etc.	Macromyeloblast 1. Narrow body 2. Leucocytoid form 3. Rieder form Micromyeloblast Eosinoid cell Plasmoid cell Mast cell Uninucleate neutrophile	Macrolymphocyte Microlymphocyte
Morbid processes	Lymphocytoma Lymphosarcoma Typhoid Hæmolytic splenomegaly[72]	Granulomatosis Tuberculous Luetic[g.a.] Hodgkin's disease[c.f.] Banti's disease[a] Protozoan (malaria[a], trypanosomiasis, kala-azar) Gaucher splenomegaly[d] Primary granulomatous splenomegaly (Pauliczek) Jaksch anæmia	Myelosarcomatosis Lienal leukæmia Myeloid metaplasia Rachitic splenomegaly[73] Experimentally by Splenotoxins[74]	Lymphosarcoma Lymphocytoma
	NON-GRANULAR ↓ ALEUKÆMIC		GRANULAR LEUKÆMIC	

a. Preponderant cell is 1.
b „ „ 2.
c. Preponderant cell is 3.
d. „ „ 4.
e. „ „ 5.
f. Preponderant cell is 6.
g. „ „ 7.

Under the colourless lymphadenoid hyperplastic diseases are (1) Aleukæmic pseudoleukæmia; including (*a*) aleukæmic lymphadeny and aleukæmic splenomegaly—so-called lymphatic or lienal pseudo-leukæmia; (*b*) medullary pseudoleukæmia—a diffuse myeladeny which may also be associated with involvementof other extra-medullary lymphadenoid tissue; (2) Lymphadenoid leukæmia; (*c*) multiple myelomatosis.

Under the coloured lymphadenoid hyperplastic diseases are (1) Aleukæmic chlorolymphoma; including forms in which the glands, spleen, or bone-marrow respectively are involved; (2) Leukæmic chloroma.

Under the colourless myeloid hyperplastic diseases are the myeloid pseudoleukæmias, including forms in which the glands, spleen, or bone-marrow respectively are involved; and the myeloid myeloma. The second group is the myeloid myelæmia.

Under the coloured myeloid hyperplastic diseases are (1) The pseudoleukæmic myeloid chloroma; (2) The leukæmic myeloid chloroma.

Under the colourless lymphocytar lymphosarcomatoses are (1) Aleukæmic forms, including lymphatic and lienal lymphosarcomatosis, Nothnagel's lymphadenia ossium, and multiple sarcomyeloma; (2) Leukæmic lymphosarcomatosis, or Sternberg's leucosarcomatosis.

Under the coloured lymphocytar lymphosarcomatoses are (1) Aleukæmic chlorolymphosarcoma; (2) Leukæmic chlorolymphosarcoma.

Under the colourless myeloid lymphosarcomatoses (Sternberg's myelosarcomatosis) are (1) Aleukæmic forms, including lienal, lymphatic, and myeloid forms, and myeloid myelosarcoma of the bone-marrow; (2) Sternberg's myeloleucosarcomatosis.

Under the coloured myeloid lymphosarcomatoses are (1) Pseudoleukæmic chloromyelosarcomatosis; (2) Sternberg's chloromyeloleucosarcomatosis.

The range of thought must also be considerably widened by reflecting that the changes in pulpar and follicular tissues are not confined to "blood diseases" for their manifestation. That they are produced by every agent that excites disease, is shown by studying these tissues in the most varied pathological conditions; we find changes in the ordinary acute infections: we find special lesions associated with such chronic infective processes as typhoid and rheumatism (chronic in the sense of lasting more than a week); we find them associated with various intoxications exemplified by eclampsia, puerperal toxæmia, pernicious vomiting of pregnancy, chronic interstitial fibrosis of the kidney, of the liver, and so on.

Viewed in this way, then, our study of diseases of the blood is not limited to the leukæmias, the splenomegalies, the lymphadenopathies, and the various types of anæmia; but we find material

for study in a vast number of morbid conditions whose primary seat is in non-hæmatopoietic viscera : material, too, which throws a flood of light upon the obscurity of the processes usually associated with the more special hæmopoietic tissues. The first suggestion that comes from a pursuit of investigation along these lines is that which has already been expressed, that *our cell-formula for the tissue is an expression of certain fundamental* (chemical, structurally specific) *agencies* being at work in the body. The richness of the spleen in extractives (i.e., bodies belonging to the xanthin group) suggests to us the extreme affinity which the pulpar cells have for such bodies, and renders the supposition reasonable that herein lies the secret of some of the cytometaplastic phenomena of which we have endeavoured to draw a picture.

APPENDIX.

ABBREVIATIONS EMPLOYED.

A. de B.	Archiv de Biologie.
A. de Med.	Archiv de Méd. exp. et d'anatomie pathologique.
A. f. e. P.	Archiv für experimentelle Pathologie u. Pharmakologie.
A. f. m. A.	Archiv für mik. Anat. u. Entwickelungsgeschichte.
A. I. M.	Archives of Internal Medicine.
A. J. Am. J. M. S.	American Journal of Medical Sciences.
Ann. Pasteur	Annales de l'Institut Pasteur, Paris.
A. p. Sc. M.	Archives per le Scienze Mediche
B.	Berliner klinische Wochenschrift.
B. H. G.	Berliner Haematologische Gesellschaft.
B. M. J.	British Medical Journal.
B. z. k. Ch.	Beiträge zur klinische Chirurgie.
B. z. P. A.	Beiträge zur pathologische Anatomie.
B. Z.	Biochemische Zeitschrift.
C.	Centralbatt f. allgem. Path. u. patholog. Anatomie.
C. f. Bakt.	Centralblatt f. Bakteriologie, Parasitenkunde, u. Infek.
C. Grenz.	Centralblatt f. d. Grenzgebiete der Med. u. Chir.
C. M.	Centralblatt f. d. medizinischen Wissenschaften.
C. R.	Comptes Rendus de la Société de Biologie.
D.	Deutsche medizinische Wochenschrift.
D. A.	Deutsches Archiv f. klinische Medizin.
D. Z.	Deutsche Zeitschrift f. Chirurgie.
E.	Lubarsch und Ostertag, Ergebnisse.
F. H.	Folia Hæmatologica, herausgegeben von Dr. A. Pappenheim.
F. Z.	Frankfurter Zeitschrift f. Pathologie.
G. de H.	Gazette des hôpitaux, Paris.
I. D.	Inaugural Dissertation.
J. A. M. A.	Journal of American Medical Association.
J. A. P.	Journal of Anatomy and Physiology.
J. C. M. A.	Journal of Canadian Medical Association.
J. E. M.	Journal of Experimental Medicine.
J. H. H. B.	Johns Hopkins Hospital Bulletin, Baltimore.
J. Inf. Dis.	Journal of Infectious Diseases.
J. M. R.	Journal of Medical Research, Boston.
J. P. B.	Journal of Pathology and Bacteriology.
M.	Münchener medizinische Wochenschrift.
V. A.	Virchow's Archiv.
V. P. G. V. d. D. P. G.	Verhandlungen der deutsch. path. Gesellschaft.
W.	Wiener medizinische Wochenschrift.
W. K. W.	Wiener klinische Wochenschrift.
Z. B.	Beiträge zur path. Anat. u. z. allg. Pathologie, Ziegler.
Z. e. P.	Zeitschrift f. exp. Path. u. Therapie.
Z. f. H.	Zeitschrift fur Heilkunde.
Z. f. Hyg.	Zeitschrift f. Hygiene u. Infektionskrankheiten.
Z. f. a. P.	Zeitschrift f. allg. Path. u. Path. Anat.
Z. f. kl. M.	Zeitschrift f. klinische Medizin.

REFERENCES TO THE LITERATURE.

The references in the following list are purposely abbreviated, because those who are specially desirous of referring to original articles will find the quotations in full in the various Sammelreferate that have appeared from time to time. The references marked with an asterisk may be looked upon as being not only valuable, but associated with a good literature list of their own. Numbers not preceded by a page marking refer to the week of the year in which the journal was issued, or to the volume number of the volume which that journal has reached. In the case of F. H., the roman number shows the volume-number, and the succeeding arabic figure " 1 " indicates the " archiv," figure " 2 " refers to " referate." Thus, F. H. ix. 2 means the ninth volume, second part designated " referate."

N.B.—Where References to authors quoted in the text are omitted from the following list, they may be found in the "Index of Authors," or in the modern fountain of hæmatology—Pappenheim's Folia.

Without having specially investigated the point, the writer believes that there is no hæmatological paper of any value that is not in some part of F.H., literary references in the original articles going back to 1870.

CHAPTER I.

[1] FERRATA. Arch. de Fisiol, 1908, Fasc. iii. H. 2.
[2] PAPPENHEIM. F. H. v. p. 366.
[3] AUER. A. J. 1906, p. 1002.
[4] DUTTON, TODD, AND TOBEY. Ann. Trop. Med., i. 3 (1907).
[5] LÖWIT. C. f. Bakt. 1905, Bd. 39. H. 3; and V. d. D. P. G. 1905. Bericht, 1906. p. 40.
[6] HYNEK. Bull. Internation. de l'Acad. d. Sci. de Bohême, 1910.
[7] WERZBERG. F. H. xi. 1, p. 17.
[8] PAPPENHEIM. F. H. ix. 1, p. 555.
[9] KNOLL. D. A. f. Klin. Md. Bd. 102, H. 5, 6.
[10] KANITZ. Oppenheimer's Hdbch.d. Biochemie, Gustav Fischer, Jena, 1910, p. 213.
[11] NEUMANN. V. A. 207, Heft 3.
[12] PAPPENHEIM. Atlas d. menschlichen Blutzellen, Gustav Fischer, Jena, 1905, 1909, 1911. Erste Lieferung, 1905, p. 59.
[13] PAPPENHEIM. F. H. ix. 1, p. 574.
[14] ZOJA. F. H. x., i. p. 230.
[15] PAPPENHEIM. Cited by Hirschfeld, Ergebn. der Wissenschaft. Med 1911, Bd. ii. H. 6. p. 237.
[16] AUER, PAPPENHEIM, HIRSCHFELD, WEICHSELBAUM.
[17] JOCHMANN AND BLÜHDORN. F. H. xii. 1, p. 192.
[18] MORSE. Berl. Med. Gesellsch. June 21, 1901.
[19] PAPPENHEIM. Atlas (see ref. 12 above), Prototyp 56, nos. 33-36.
[20] NAEGELI. Quoted by Pappenheim, F. H. vi. p. 247 sqq.
[21] GRUNER. Autopsy case No. 100—1912 series, R. Vict. Hosp. Montreal.
[22] See ref. 12.
[23] GRUNER. Dominion Medical Monthly, 1912, Sept.
[24] LEO LOEB. J. M. R. 1902 (vii. 1).
[25] Unpublished Observations (O. C. G.)
[26] STERNBERG. In Krehl and Marchand, Handbuch d. Allgemeinen Pathologie, Leipzig, 1912. Bd. ii, p. 163.

[27] GRÜNEBERG, Medizinisch-Naturwissenschaftliches Archiv 1908, Bd. L. Nr. 3.
[28] NAEGELI, Blutkrankheiten und Blutdiagnostik, Leipzig, 1908 p. 126 sqq.
[29] BROWNING. J. P. B. 1905, Vol. x.
[30] MAXIMOW. A. f. m. A. 1909, No. 73, 1910; No. 76, p. i.; A. f. m. A. 1910, B.d. 76, p. i.
[31] DANTSCHAKOFF. A. f. m. A. 1909, No. 74.
[32] NEUMANN, V. A. 207, Heft 3.
[33] BERGEL. M., 1912, p. 636.
[34] ST. KLEIN. F. H. x. i. p. 475.
[35] SCHRIDDE. Studien und Fragen zur Entzündungslehre, Gustav Fischer, Jena, 1910.
[36] CIACCIO. F. H. vii. p. 321 (1909).
[37] LINDBERG. Upsala Läkareförenings Fürhandlinger, Vol. xvi., No. 3.
[38] HAL DOWNEY. F. H. xi. Plate VI., fig. 27.
[39] DANTSCHAKOFF. Verhandlungen der anatom. Gesellschaft, Berlin, April 22-25, 1908, Ref. F.H. vi. p. 472.
[40] DRZEWINA. Arch. d. Zool. Exp. 1905.
[41] HAL DOWNEY. F. H. viii. p. 415 (429).
[42] NEUMANN. V. A. 207, Heft 3.
[43] ELLERMANN. Deut. Path. Gesellschaft, Kiel, 1908, ref. F. H. vii. p. 261.
[44] WERZBERG. V. A. 204, Heft 2, 3.
[45] DIXON AND MALDEN. J. Phys, 1908, p. 50.
[46] LÜDKE. D. A. 100, Heft 5, 8.
[47] LEVY, MARGARETHE. F. H. ix. 1 p. 58 (1910).
[48] ZOJA. F. H. x. i. p. 237 (1910).
[49] WEIDENREICH. F. H. v. p. 135, 150; 1908.
[50] BLUMENTHAL. Bull. de Soc. royale d. sciences méd. et nat. de Bruxelles, 1908, No. 1.
[51] KASARINOFF. F. H. x. i. p. 391. (1910).
[52] V. DOMARUS. F. H. xiii. 1, p. 384 (1912). Good reference also F. H. vi. p. 337–382 (1908).
[53] VIRCHOW. Charité-Annalen, 1898. PALMA: W. 1903, No. 9, referate.
[54] DROZSDA. D. 1892.
[55] LEHNDORFF. E. d. inn. Med. 1910, vi.
[56] FABIAN. Z. B. 1908.
[57] SCHMIDT. Dissertation Göttingen, 1895.

CHAPTER II.

[1] NEUMANN. C. M. 1868.
[2] RINDFLEISCH. A. f. m. A. xvii. 1880.
[3] LEIGHTON. J. P. B. 1911. p. 465.
[4] TOMMASSI. Lo Sperimentale, 1906, fasc. 4. BLUMENTHAL. See ref. 10 under Chap. iv. DUESBERG. A. de B. 1906.
[5] SCHRIDDE. Anat. Hefte, xxxiii. 1.
[6] WRIGHT. Boston M. and S. Journal, 1906, p. 643.
[7] VERSON. Bollettino della Societa Medico-Chirurgica di Pavia, 1906. 1.
[8] PERLMESCHKO. See ref. 3, Chap. iv.
[9] PUGLIESE. Fortschritte d. Med. 1897, p. 729.
[10] WALKER. Proc. Roy. Soc. B. lxxviii. 1906.
[11] BUNTING. J. H. H. B., 1910.
[12] GRUNER. J. C. M. A. 1912, July.
[13] KÖLLIKER. Hdbch. d. Gewebelehre, Leipzig, 1889, vol. 1.
[14] SANFELICE. Quoted by ref. 15.
[15] HEIDENHAIN. Plasma u. Zelle, II, Jena, 1911.
[16] EBNER. Quoted by ref. 15.
[17] PAPPENHEIM. V. A. 1898, Bd. 151, p. 89.
[18] FOA. Z. B. 1899. p. 376.
[19] WERIGO AND JAGUINOW. Pflüg. Arch. 1901, p. 457.

[20] LIFSCHITZ. I. D. Zürich, 1906.
[21] WRIGHT. Boston M. & S. Journal, 1906, p. 643.
[22] BUNTING. J. E. M. 1909; J. H. H. B. 1911, pp. 114, 369; OGATA. Z. B. 52. H. 1. (1912).
[23] STERNBERG. In Krehl and Marchand (ref. 7, Chapter i).
[24] CIACCIO. Quoted by Downey, F. H. ix. 1. 81.
[25] BIZZOZERO AND TORRO. Moleschott's Untersuchungen, xi. 1881.
[26] DENYS. La Cellule, t. iv. 1888; ISAAC and MÖCKEL. Z. f. kl. M. 72, p. 314.
[27] MAXIMOW. A. f. m. A. lxxxiii., 1909.
[28] SCHÄFER. In Quain's Anatomy, Vol. II, Part i. 1912.
[29] HIS. Untersuch, 1868.
[30] MAXIMOW. A. f. m. A. 76, H. 1.
[31] ENGEL. D. 1906. 29; SAXER, Anat. Hefte, 1896, vi; MOLLIER, A. f. m. A. 74; ASKANAZY, V.A. 205, 3; LOBENHOFFER, Z. B. 1908, Bd. 43; KOSTANECHI, Anat. Hefte, 1891. i; GOODALL, J. P. B. 1903, p. 191; T. H. BRYCE, Quain's Anatomy, Vol. ii, Part i. p. 237; PAPPENHEIM, quoted by Hirschfeld, F. H. vi. p. 388.
[32] GRAWITZ. Klin. Path. des Blutes, Thieme, Leipzig, 1911. Taf. iii.
[33] GRAWITZ. Ibid. p. 160.
[34] THAYER. A. I. M. 1911, p. 223.
[35] SAPEGNO. Pathologica, 1910, No. 33.
[36] SCHILLING. M. 1911, p. 447.
[37] DIETRICH. B. H. G. Jan. 1910, ref. F. H. ix. 2, p. 170.
[38] LOELE. M. 1910, no. 46.
*[39] SCHILLING. Ref. 36; *The latest and most fundamental article* is F. H. xiv. 1, pp. 96-244 (1912), *with full literature* upon the red blood cell.
[40] PAPPENHEIM. Atlas, Supplbd. p. 221; see ref. 37, Chapter 1.
[40a] FREYTAG. Z. f. a. Phys. Bd. vii. H. 1; Pappenheim's comment. F. H. vii., p. 51.
[40b] PAPPENHEIM. B. H. G. Nov. 1909, ref. F. H. ix. 2 p. 91.
[41] PAPPENHEIM. Atlas, Supplbd. p. 218.
[42] WEIDENREICH. Ergeb, d. Anat. 1903, 4, 1909; A. f. m. A. lx. 1. 1903; lxix. 1906.
[43] LEWIS. J. M. R. x. 1904.
[44] RADASCH. Anat. Anz. xxviii. 1906.
[45] SCHÄFER. Ibid. xxv. 1905.
[46] DAVID. A. f. m. A. lxxi. 1907.
[47] JORDAN. Anat. Anz. xxxiv. 1909.
[48] JOLLY. C. R. lviiii. 1905; Arch. d'anat. mic. xi. 1909.
[49] ORSÓS. F. H. vii. p. 1 (1909).
[50] LÖHNER. Pflüg. Arch. cxl. 1911.
[51] ROSCOE KING. J. M. R. 1911. p. 91; KRONBERGER, F. H. xii. 1, p. 302.
[52] SCHILLING. M. 1911, p. 445, 2803; Verhdl. d. anatom. Gesellsch., 1911. p. 188, and ref. 39 (above).
[53] ROBERTS. Quart. Jour. Med. Sci. 1873.
[53a] DIETRICH. B. H. G. Feb. 1911, ref. F. H. xi. 2, p. 105.
[54] LIEBERKÜHN. Ueber Bewegungserscheinungen der Zellen, Schriften der Gesellsch. zur Beförd. der Naturw. Marburg. 1872.
[55] JORDAN. Anat. Anz. 1909, xxxiv.
[56] ROLLETT. Stricker's histology, 1870.
[57] SCHÄFER. Quain's Anatomy, Vol. ii, Part i. 1912.
[58] WALKER, ROSS AND MOORE. Tr. Path. Soc. Lond. 1907.
[59] LÖHNER. A. f. m. A. Bd. 71, 1.
[60] SCHÄFER. Ref. no 57. p. 373.
[61] G. N. STEWART. Am. Jour. Phys. viii. 1902.
[62] DIETRICH. Deutsch. Path. Gesellschaft, Kiel, 1908, ref. F. H. v. p. 781.
[63] NORRIS. Am. Jour. Phys. vii. 1903.
[64] GRAWITZ, loc. cit. p. 164.
[65] BUNGE. Lehrbuch d. Phys. d. Mensch. 1905, Vol. ii.

[66] Rona and Takhaschi. B. Z. 30, p. 99; Sattler, F. H. ix. 1, p. 216; Ferrata, F. H. ix. 1, p. 253 (1910); Rosenthal, F. H. x. 1, p. 253 (1910).
[67] Zoja. F. H. x. 1, p. 232; Il Morgagni, 1911. L. fasc. 16, 31.
[68] Blumenthal. F. H. ix. 1, p. 199 (1910).
[69] Riva and Zoja. Fol. clin. chim. e. microscopica, 1909. p. 320
[70] Dietrich. See ref. 62 and 90a.
[71] Cesaris-Demel. F. H. iv. Supplbd. p. 1, (1907).
[72] Ferrata. F. H. ix. 1, p. 253.
[73] Pappenheim. F. H. iv. Supplbd. p. 46.
[74] Biondi. F. H. vi. p, 205.
[75] Chauffard and Fiessinger, Bull. Soc. méd. des. Hôpitaux de Paris, 1907, no. 31.
[76] Widal et Abrami. Ibid. Nov. 1907.
[77] Schilling. F. H. xi. 1, p. 351 (327).
[78] Schüffner. D. A. Bd. 64.
[79] Maurer. Z. f. Bakt. 1900, xxviii.
[80] Pappenheim. F. H. iv. Supplbd. p. 46.
[81] Ferrata and Viglioli. Fol. clin. chim. et microscopica, Vol. iii. fasc. 8.
[82] Pappenheim. F. H. iv. Supplbd. p. 320.
[83] Ferrata and Viglioli. F. H. ix. 1, p. 315. and Taf. vii.
[84] Ferrata. B. H. G.. 1909. Nov. 2; ref. F. H. ix. 2, p. 94.
[85] Pappenheim. F. H. ix. 2, p. 311 (1909); Böllke, V. A. 176, 1904.
[86] Schilling. F. H. xi. 1, p. 327, 370.
[87] H. C. Ross. Further Researches on Induced Cell-Proliferation, London, 1912.
[88] Hertz. F. H. x. 1, p. 419 (1910).
[89] Pappenhein. Atlas, Supllbd. p. 226. Prototyp. 75.
[90] Pappenheim. F. H. iv. supplbd. p. 46, and B. H. G. Nov. 2. 1909, ref. F. H. ix. 2. p. 93; Dietrich, F. H. ix. i. p. 297.
[91] Cesare Biondi. F. H. vi. p. 205.
[92] Kasomoto. B. Z. 1908. xiii. p. 354.
[93] Rosenthal. F. H. x. 1, p. 253 (1910).
[94] Heinz. Z. B. 1901, xxix; Hartwich, F. H. xiii. 1, p. 257 (1912).
[95] Schwalbe and Solley. V. A. Bd. 168 (1902).
[96] Friedstein (Dora). F. H. xii. 1, p. 265.
[97] Herzog. A. f. m. A. lxxi. 3.
[98] Dietrich. Deut. Path. Gesellschaft. Kiel, 1908, ref. F. H. v. p. 781.
[99] Cabot. J. M. R. 1903.
[100] Schleip. D. A., Bd. 91. H. 5, 6.
[101] Gabriel. Ibid. Bd. 92.
[102] Sluka. W. K. W. 1908, p. 243.
[103] Ferrata and Viglioli, see ref. 83.
[104] Pappenheim. Prolegomena, F. H. ix. 2, p. 317.
[105] Walker, Ross and Moore. Tr. Path. Soc. Lond. Jan. 1907.
[106] Giglio-Tos. Z. f. Wissensch. Mikroskopie Bd. xvi., p. 167.
[107] Israel and Pappenheim. V. A. 143, p. 427.
[108] Swingle. J. Inf. Dis. 1908, p. 46.
[109] Brodie and Russell. J. Phys. xxi. 1897, p. 390.
[110] Reid. Edin. Med. Jour. 1912, p. 432.
[111] Morse. Boston M. & S. Journ. 1912, p. 448.
[112] Pratt. J. A. M. A., 1905.
[113] Wright. Ibid. 1911; J. Morph. July, 1910; V. A. 1861 (1906).
[114] Muir. J. A. and P., xxv., p. 259.
[115] Affanassiew. D. A. 1884, xxxv., p. 217.
[116] Kemp. Am. J. Phys., 1902.
[117] Deetjen. Arch. f. Path. Anat., 1898; Spodara, Il Tommasi, 1907, No. 12.
[118] Bizzozero. V. A., 90, 1882.
[119] Schäfer. Proc. Roy. Soc., xxxiv. 1882.
[120] Eminet. Arch. f. Kinderheilk., 1912, No. 57.
[121] Aynaud. Ann. Pasteur, 1911.

[122] Brockbank. Lancet., 1911, p. 1526; Med. Chron. 1908.
[123] Hirschfeld. V. A. Bd. 160.
[124] Preisch and Heim. V. A. 178.
[125] Roscoe King. J. M. R. 1911, p. 91.
[126] Eisen. Jour. Morph., xv., 1899.
[127] Dantschakoff. A. f. m. A. Bd. 74 (1909).
[128] Morse (Mary). Boston M. & S. Jour., 1912, p. 448.
[129] Bunting. J. E. M., 1909, p. 541.
[130] Weidenreich. Verhandl. d. anat. Gesell. 20th Versamml. Rostock, 1906.
[131] Sternberg. In Krehl and Marchand, see ref. 7, Chapter i.
[132] Buckmaster. Morphology of Normal and Pathological Blood, London, 1906.
[133] Hayem. Arch. de physiol., 1878; Leçons sur les maladies du sang, Paris, 1900.
[134] Schilling. Notizen aus der Tropenpraxis d. Archiv. f. Schiff. und Tropenhyg. 1911, p. 364.
[135] Sergent. C. R., 1905, Jan. 14; Ann. Pasteur, 1905, p. 138: 1906, p. 245.
[136] Brumpt. Soc. de path. exotique, 1908; t. L. p., 201.
[137] Müller. Z. f. allg. Path. 1895, Bd. vii, p. 13.
[138] Porter. B. M. J., 1907, Dec. 21.
[139] Reicher. Verein, f. inn. Med. Berlin, July 6, 1908.
[140] Rosenthal. Beobachtungen an Hühnerblut mit dem ultramikroscop. Thieme, Leipzig, 1907.
[141] Pappenheim. Comment to above, in F. H. iv. Supplbd., p. 314.
[142] Neumann. W. K. W., 1907, 28; 1908, 27.
[143] Wiener. Ibid. 1908, 29.
[144] Dehler. A. f. m. A. Bd. 46, 1895; M. Heidenhain, Nicholas, quoted by Schäfer, ref. 28.
[145] Meves. Anat. Anz. Bd. 23, 25, 26, 28 (1903, 1904, 1905, and 1906 respectively); A. f. m. A., 1911, Bd. 77; A. Smirnow, Anat. Anz. Bd. 29 (1906).
*[146] Werzberg. F. H. x. 1, p. 301; Fry, F. H., viii., p. 467.
[147] Sabrazès et Muratet. F. H. vi., p. 167.
[148] Recklinghausen. A. f. m. A., 1866.
[149] Meves. A. f. m. A., 1906, Bd. 68, p. 311.
[150] Mondino and Sala. Arch. ital. de Biologie, 1889, t. xii.
[151] Wright. V. A., 1906, Bd. 186.
[152] Rawitz. A. f. m. A., 1899, Bd. 54; 1900, Bd. 56.
[153] Eberth and Schimmelbusch. V.A., 1887, Bd. 108.
[154] Dekhuyzen. Verhdl. d. anat. Gesell. in Wien., 1892.
[155] Luzet. Arch. d. Phys. ,1891, t. iii., p. 5.
[156] Müller. Sitzungsber. d. Ak. zu. Wien, 1889, Bd. 98, Abt. iii.
[157] Heinz. Z. B., 1901, Bd. 29.
[158] Freidsohn. A. f. m. A. 75, p. 435.
[159] Eberhardt. Dissertation St. Petersburg, 1907-8.
[160] Wenzlaff. A. f. m. A., 1911, Bd. 77.
[161] Kasarinoff. F. H. xi. 1, p. 391.
[162] Cottin. Arch. de mal. du cœur, des vaiss. et du sang., 1911, p. 755.
[163] Trincas. Boll. Soc. tra Calt. Science med. e. nat. 1906.
[164] Pappenheim. B. 1911, p. 1375.
[165] Widal et Abrami. Tribune medic., nov. 9 1907, No. 45; Bull. et mém. d. l. Soc. méd. des hôpitaux de Paris, 1907, p. 1127.
[166] Ciccaterri-Bono. Il Policlinico, 190, Sez. medica, fasc. 10.
[167] Hirschfeld. D. A. 102, H. 5. 6.
[168] Donzello. Lo Sperimentale, 1906, 15.
[169] Pappenheim. Comment on Krehl, Pathologische Physiologie, F. H. x. 2, p. 60 (1911).
[170] Krehl. Pathologische Physiologie. F. C. W. Vogel, Leipzig, 1910.
[171] Grawitz. Med. Record, 1910, Oct. 29.
[172] Hirschfeld. B. H. G., Oct. 10, 1911, ref. F. H., xii. 2, p. 235.
[173] Gibelli. Arch. f. exp. P. Bd. 65, 3 4.
[174] Kapinow. B. Z. 30, p. 160.

[175] KRÄMER. W. K. W. 1908, 34.
[176] SENATOR. Polyzythæmie v. Plethora, Hirschwald, Berlin, 1911.
[177] PAPPENHEIM. Footnote commenting on Rubinstein (Russki Wratsch, 1908, 7, 8, in F. H. x. 2., p. 205.)
LUCE. Med. Klinik., 1909, 4, 5.
[178] RUBINSTEIN. Russki Wratsch 1908, 7, 8, 9.
Good résumés on Pernicious Anæmia: Friedstein, xii. 1, p. 239: Pappenheim Prolegomena, F. H. x. 2, p. 217; * B. H. G., 1911 (4 sessions), ref. F. H. xi. 2, p. 311, sqq.

CHAPTER III.

[1] WEIDENREICH. Verhdl. d. anat. Gesell. Würzburg, 1907 (ref. F. H. v. 34); Verhdl. d. Berl. Hæmatol. Gesellschaft, March 5, 1911 (ref. F. H. xi. 2. p. 22).
[2] RIBBERT. V. A. 150 (1897).
[3] HEDINGER. F. Z. Bd. I., Nr. 3, 4.
[4] OEHME. M. 1909, p. 446.
[5] PAPPENHEIM. F. H. iv. Suppltbd. p. 297.
[6] FLEMMING. A. f. m. A. xxiv., 1885.
[7] BUNTING. J. Anat. and Phys. xxxix., 1904–5.
[8] BAUM AND HALLE. Anat. Anz. xxxii., 1908.
[9] NAEGELI. Blutkrankheiten und Blutdiagnostik, Leipzig, 1908.
[10] PIRONE. Lo Sperimentale, jeuillet, 1907.
[11] KEUTHE. D., 1907, 15.
[12] SCHMIDT, M. B. Z. f. allg. Path (Path.) 1907, xviii. 15.
[13] CIACCIO. F. H. viii. p. 135 (p. 151), 1909; CIACCIO ET PIZZINI. A. de Méd., Tome xvii. mars, 1905, p. 129.
[14] STHEEMANN. Z. B. xlviii. 1.
[15] RUBENS-DUVAL ET FAGE. Société de Biologie, 1909, t. lxviii, 39, p. 696.
[16] METCHNIKOFF AND TARASSEVITSCH. Ann. de l'Inst. Past. 1902, xvi. p. 127.
[17] MACLACHLAN. Tonsillitis, a Histopathological Study, Publications from the University of Pittsburg, 1912.
[18] HERTZ. F. H. xiii. 1, Tafel V. (1912).
[19] ANDREWS, F. W. Tr. Path. Soc. Lond., 1902, p. 305.
[20] LOELE. C. xxii. 10, 1911.
[21] PASCHEFF. M., 1911, p. 1937.
[22] MARCUSE. V. A. 160 (1900).
[23] v. WENDT. F. Z. viii. 3, 1911.
[24] HESSE THAYSEN. Z. B. 50, 3.
[25] SCHRIDDE. In Lubarsch and Ostertag, Ergebnisse, ix. 2, p. 313 seq.
[26] BORKA. V. A. 205, 1–3; See Quain's Anatomy, Vol. i., Embryology.
[27] MAXIMOW. V. d. anatom. Gesell. Brussels, 1910, p. 64.
[28] GRUNER. Studies in Puncture Fluids, H. K. Lewis, London, 1908.
[29] GRAWITZ. Klin. Pathologie des Blutes, Georg Thieme, Leipzig, 1911, p. 201; *see also* RASKIN, MARIE, F. H. ix. 1, p. 123 (1910), and BERGEL, M. 1912, p. 634.
[30] KÄLLMARK. F. H. xi. 1, p. 411.
[31] CARO. B. 1908, p. 1755.
[32] GALAMBOS. F. H. xiii. 1, 152 (*with full literature*).
[33] ROUS. J. Exp. M., 1908, x., p. 329.
[34] HARVEY. J. Phys. Dec., 1906.
[35] BERGEL. M. 1912, p. 636.
[36] LOEB AND MICHAUD. B. Z., iii., p. 31, 317; LOEB, A. f. e. P. 1907. 56, p. 320.
[37] BALDONI. Arch. di farmac. sperim. e scienze affini. 1905, p. 93; OPPENHEIMER, Handbuch der Biochemie, Bd. ii. 2, p. 171.
[38] ERDELY, quoted in Grawitz[29], p. 271.
[39] GOODALL, GULLAND AND PATON. J. Phys. xxx., 1903.
[40] CRESCENZI. Lo Sperimentale, 1904; [40a] BURIAN AND SCHUR., W. K. W. 1897, 6.
[41] PAPPENHEIM. F. H. vii. p. 167, footnote (1909).
[42] TSCHISTOWITSCH. D., 1907, 13.

[43] GERHARTZ, in Oppenheimer, Handbuch,[37] p. 116.
[44] COHNHEIM, in Nagel, Handbuch der Physiologie, Bd. ii., p. 598, F. Vieweg und Sohn, Braunschweig, 1907.
[45] FISCHEL. M., 1910, p. 1203.
[46] BERGEL. M., 1902, 2; 1910, 32.
[47] MICHAELIS UND WOLFF-EISNER. V. A. 167, 1902.
[47a] CIACCIO, Fol. Clin. Chim. Microscop., Bd. ii., p. 224.
[48] PAPPENHEIM. F. H. ix. 1, p. 321 (1910).
[49] JAGIC. B. 1909, 26.
[50] PAPPENHEIM UND FERRATA. Ueber die verschiedenen lymphoiden Zellformen, etc., F. H. x. 1, p. 78 (1910), published as a monograph in 1911, p. 76.
[51] KLEIN. C., 1910, Bd. xxi., p. 677; Berl. Hæmat. Gesell., May 3, 1910 (ref. F. H. ix. 2, p. 407).
[52] MEVES. A. f. m. A., lxxv. p. 642 (1910); FREIDSOHN. A. f. m. A., lxxv., 1910.
[53] SABRAZÈS ET MURATET. F. H. vi. p. 167 (1908).
[54] DOWNEY. F. H., viii. p. 415 (1909).
[55] FRY. F. H. viii. p. 467 (1909).
[56] DRZEWINA. A. d'anat. mic. 1910, xii. 1, 1.
[57] WERZBERG. F. H. xi. i. p. 17.
[58] KASARINOFF. F. H. x. 1, p. 391 (1910).
[59] DAVIS AND CARLSSON. Am. J. Phys., 1909, xxv.
[60] ROSENTHAL. F. H., x. 1, p. 278 (1910).
[61] SELLING. Z. B., 51, 3.
[62] HOFMEISTER A. f. e. P. 1887, xxii.
[63] HAMMAR. Anat. Anz. 1905, Bd. xxvii.
[64] PENNY. B. M. J., 1909, June 12.
[65] PRÖSCHER. F. H., vii. p. 107 (1909).
[66] BARTEL. Vers. deut. Naturforscher u. Artze, Salzburg, 1907; ref. F. H. x. 2, p. 109.
[67] KÖRMÖCZI. Krankenvorstellung im Verein der Spitalärzte zu Budapest, May 4, 1910, ref. F. H. xi. 2, p. 297.
POHL. Arch. f. e. P. 1889, xxv. p. 51.
JOLLY. C. R. de l'assoc. des anatomistes, 13 reunion, Paris, 1911, p. 164.
LABBÉ. La Presse Médicale, 1908, No. 97, p. 786.

CHAPTER IV.

The following references may be quoted as supplying very full information about the subject of this chapter:—

PAPPENHEIM, xii. 2, p. 382–411; B. H. G. xi. 2, p. 224.
Monograph, ref. 50. Chapter iii.

[1] MANGUBI-KUDRJAVTZEWA, ANNA. Inaug.-Dissert. Giessen, 1909; Anat. Hefte, 1900, p. 699.
[2] MOLLIER. A. f. m. A., Bd. lxxvi.
[3] PERLMESCHKO. Quoted by Pappenheim, editorial note to ref. No. 43, F. H. vii. p. 68.
[4] KALATSCHNIKOFF. Russki Wratsch, 1907, 27.
ASAI. Tokio Igakkai, 1908, 16.
[5] CIACCIO AND PIZZINI. A. de Méd., Tome xvii., mars, 1905, p. 129.
[6] PIRONE. Lo Sperimentale, jeuillet, 1907.
[7] CIACCIO. V. A. Bd. 199, H. 2, 3.
[8] LOELE. F. H. xiv. 1, 38; F. H. xiii., p. 331 and references; C. B. 1911, xxii. 10; F. Z. ix. 3, p. 436; F. H. xi. 2, pp. 45–48.
[9] SIEGFRIED. E. d. Phys. 1910, ix. p. 334.
[10] BLUMENTHAL. Bull. Acad. méd. Belgique, 1904; Bull. de Soc. royale des sc. méd. et nat. de Bruxelles, 1908, 1.
[11] GROSS. Quoted by Kohlenberger, M. 1911, p. 2013.
[12] HERZEN. Quoted by Ciaccio, A. de Méd. 1905, p. 129.

[13] PAULICZEK. F. H. ix.. 1, p. 475 (1910).
AZZURINI. Lo Sperimentale, 1906, vol. iv. fasc. 4.
[14] ASHER. D. 1011, p. 1310.
[15] GROSSENBACHER AND ZIMMERMANN. B. Z. xvii., pp. 78, 297.
[16] SZOKALSKI. Medycyne, 1908, No. 16.
[17] JUNGANO. Il Tommasi, 1906, No. 16.
[18] AZZURINI. Lo Sperimentale, 1906, vol. iv., fasc. 4; JAROTZKY, V. A. (1908), 191.
[19] SCOTTI. Gazz. Internazionale, 1910, p. 51.
[20] BERGEL. M. 1912, p. 635.
[21] BRAUNSTEIN. B. 1911, No. 45; M. 1911, p. 2465; [21a] OSER AND PRIBRAM, Z. e. P. 12, 2, ref. M., 1913, p. 770.
[22] POPIELSKI. M. 1912, p. 554.
[23] DINKLER. M. 1911, p. 1331.
[24] WINKLER. Charkowski Medizinski, 1907.
[25] FALTIN. D. Z. Chir. 1911, No. 1–3.
[26] LITTEN. Nothnagel's Handbuch, Krankheiten der Milz, 1898, p. 16.
[27] TIZZONI, MOSLER. Quoted by Paremusoff, F. H. xii. 1, p. 234.
[28] FALTIN. M. 1911, p. 1738 (D. Z. Chir. 110, 1–3).
[29] RADFORD. J. Anat. and Phys. 1908, p. 288.
[30] FOURGEOT. C. R. de l'Assoc. des anatomistes, 11e reunion, Nancy, 1909, p. 133.
[31] VINCENT AND HARRISON. Quoted in Quain's Anatomy, Vol. ii., Part i., 1912.
[32] QUAIN'S Anatomy, Vol. ii., Part i, 1912.
[33] WARTHIN. Meeting of Am. Assoc. Path. and Bacteriologists, Chicago, 1911.
[34] LEWIS. Proc. Physiol. Soc., March, 1912.
[35] WOLTMANN. J. E. M., 1905.
[36] HOUSTON. B. M. J., 1904, Sept. 10.
[37] COIE. Thèse de Lyon, 1911.
[38] SAPEGUS. Pathologica, 1910, No. 33.
[39] SPADARO. Mononukleosi, endoteliosi, linfocitosi, Verlag Fronusco Vallardi, Milano, 1908; ref. F. H. v. p. 454 (out of print, 1912).
[40] GRAWITZ. Klin. Pathologie des Blutes, Thieme. Leipzig, 1911, p. 206.
[41] KURLOFF. Ehrlich, Anämie, Bd. i. p. 57.
[42] PAPPENHEIM. F. H. v. p. 347 (364), 1908.
[43] PATELLA. F. H. v. p. 195 (1908).
[44] PATELLA. La genêse endothéliale des leucocytes mononucléaires du sang. Siena, 1910.
[45] PATELLA. Riforma Medica, 1907, No. 8–9.
[46] CESARIS DEMEL. Lo Sperimentale, 1905, vol. 59.
[47] CICACIO. *See* ref. 7.
[48] GRÜNEBERG. Medizinisch-Naturwissenschaftliches Archiv, 1908, vol. i., No. 3.
[49] GRAWITZ. *See* ref. 40.
[50] PAPPENHEIM AND FERRATA. *See* ref. 50, Chapter III.
[51] SPADARO. *See* ref. 39.
[52] PAREMUSOFF. F. H. xii. 1, p. 236, and Taf. xi, Nos. 1–8.
[53] JAGIC. B., 1909, No. 26.
[54] PATELLA. D. 1910, 32; F. H. vii. p. 218 (full details); full discussion, Frumkin, F. H. xii., 1, 50 (1911).
[55] PATELLA. La genesi endotheliale dei leucociti mononucleati, etc., edit. S. Bernardino; ref. F. H. v. 786.
[56] PATELLA. F. H. vii. p. 219.
[57] PATELLA. Gaz. degl. Osped., 1911, p. 94.
[58] FERRATA. Arch. per le scienze mediche, 1906, t. xxx.
[59] CARPI. Auto-riassunti, vol. v. No. 5.
[60] FRUMKIN. F. H. xii. 1, p. 50 (1911).
[61] METCHNIKOFF. L'Immunité dans les maladies infectieuses. Paris, 1901.
[62] BERGEL. M., 1912, p. 635.
*[63] RIEUX. F. H. x., 1, p. 209.
[64] PENNY. B. M. J. June 12, 1909.
[65] SCHIFONE. Prima contribuzione alla genesi dei mononucleari del sangue. Napoli, 1907; ref. F. H. ix. 2, p. 17.

[65a] PAPPENHEIM. F. H. ix., 1, p. 560.
[66] HYNEK. Berl. Hæm. Gesell. March 5, 1911, ref. F. H. xi. 2, p. 224.
[67] CIACCIO. *See* ref. 47[a], Chapter III.
[68] BRUNTZ. C. R. de la Soc. de Biol. t. lx. p. 831.
[69] POLICARD ET MAWAS. C. R. de l'Assoc. des Anat., 9e réunion, Lille, 1907, p. 25.
[70] MESTRAL. Trav. Instit. path. de Lausanne, 1907, vol. iv.
[71] MAXIMOW. Ref. 27, Chapter III.
[72] JOLLY. Soc. de Biol. 1911, p. 259.
[73] WERZBERG. F. H. xi. 1, p. 17.
[74] HIRSCHFELD-KOSSMANN. Beitrag z. vergleich. Morphol. d. weissen Blutkörperchen, Inaug. Dissert, Berlin, 1908.
[75] KASARINOFF. F. H. x. 1, p. 391.
[76] PAREMUSOFF. F. H. xii. 1, p. 195.
[77] LIFSCHITZ. I. D. Zürich, 1906.

CHAPTER V.

[1] Quoted by MAXIMOW. Z. B., 1907, Bd. xli. H. 1.
* [2] CARNEGIE DICKSON. The Bone-Marrow, A Cytological Study. Longmans, Green & Co., London, 1908.
[3] WALKER, C. E. Proc. Roy. Soc. lxxix. 1907 (Observations on the Life History of Leucocytes, iii.).
[4] CIACCIO. F. H. vii. p. 321 (1909).
[5] CRUIKSHANK. J. P. B., 1911, p. 167.
[6] GRUNER. J. C. M. A. July, 1912.
[7] LUCIBELLI. Riforma Medica, 1909, 2.
[8] LONGCOPE. Bull. Ayer Clin. Lab., 1907, No. 4, p. 6.
[9] CIACCIO. Same as ref. 4.
[10] MINKOWSKI. E. Bd. vii. p. 39.
[11] PIRONE. Lo Sperimentale, 1907, Fasc. 1, 2, p. 83; and refs. in F. H. vii. pp. 67-71.
[12] AUBERTIN AND BEAUJARD. F. H. vi., p. 31 (1908). BILAMIONI. Lo Sperimentale, 1906.
[13] PAPPENHEIM. F. H. v. p. 341, 1908.
[14] HELLY. Verh. d. deutsch. Path. Gesell. 1910, p. 198.
[15] CIACCIO. F. H. vii. p. 321 (1909), and *see* Schridde, M., 1906, p. 1885.
[16] TSUNOTA. V. A. 202, H. 1.
[17] LOSSEN. M., 1907, 39.
[18] DANTSCHAKOFF, WERA. Verhandl. d. anat. Gesell. April, 1908.
[19] HELLY. Z. B., 1905, 2.
[20] SCHRIDDE. *See* ref. 35, to Chapter I.
[21] RIBBERT, MUIR, DOMINICI.
[22] BLUMENTHAL. Bull. de Soc. royale d. Sciences méd. et nat. de Bruxelles, 1908, No. 1.
[23] JAGIC. B. 1909, 26.
[24] BLUMENTHAL. F. H. vii. p. 297 (1909).
[25] ERRERA. Recueil de l'Institut botanique, 1908, Bruxelles, t. vii.
[26] HEIDENHAIN. A. f. m. A. xliii. 1894.
[27] NEUMANN. V. A. 143, 174, p. 41.
[28] BRUGSCH AND SCHILLING. F. H. vi., p. 322 (1908).
[29] DEETJEN. Quoted by ref. 28.
[30] ARNETH. D., 1904, 2, 3, and a number of papers *given in extenso* by Schilling-Torgau, F. H. xii. 1, pp. 130 sqq.
*[31] SCHILLING. F. H. xii. 1, 130 (1911).
[32] RUSSO. Soc. Méd. des hôp. de Lyon, 31 mai, 1910.
[33] PAPPENHEIM. B. H. G. Jan. 11, 1910, ref. F. H. ix. 2, p. 172.
[34] SCHILLING. F. H. vi., p. 429 (1908).
[35] SCHÄFER. Quain's Anatomy, ref. 32 to Chapter IV.

[36] Pollitzer. Z. f. H., 1907, Bd. 28, H. 10.
[37] Weidenreich. A. f. m. A., lxxii, p. 209.
[38] Michaelis. Berl. Hæm. Gesell., 1909, ref. F. H. vii. p. 81.
[39] Pappenheim and others, same ref. as 38.
[40] Massart et Bordet. Soc. royale des Sciences méd. et nat. de Bruxelles, Feb. 1890.
[41] Milkowitsch. Russki Wratsch, 1911, 22.
[42] Achard and Ramond. C. R. t. lxxi., No. 27, p. 260.
[43] Winkler. F. H. ix. 1, p. 94 (1910).
[44] Loeb. Same ref. as 38.
[45] Gulland. J. Phys., xix.
[46] Decastello and Krjukoff. Untersuchungen über die Struktur der Blutzellen. Urban and Schwarzenberg, 1911.
[47] Mühlmann. B. 1907, No. 8.
[48] Downey. F. H., vii., p. 415 (1909).
[49] Loew and Bokorny. Die chemische Energie der lebenden Zellen. Stuttgart, 1906.
[50] Schneider. M., 1908, p. 499.
[51] Oxner. Bull. de l'Inst. Ocaenograph. Monaco, 1908; Kollmann, C. R. t. lxxi., No. 27, p. 262.
[52] Löwit. E. 1900, p. 36.
[53] Drzewina. Soc. de Biol. 1908, t. lxiv. p. 1039.
[54] Fry. F. H. viii., p. 499.
[55] Ciaccio. *See* ref. 47[a] to Chapter III.
[56] Marino. Ann. Past. 1903, p. 357.
[57] Bogdanoff. B. Z., 1898, H. viii.
[58] Sabrazès et Muratet. F. H. vii. p. 171, 1908.
[59] Arnold. V. A., 159, p. 101.
[60] Schwarz. W. K. W. 1901, 42.
[61] Pappenheim. V. A. 151, 1898, p. 134, and criticism of Lefas, ref. F. H., vi. p. 70.
[62] Commessatti. Rivist. critic. di clinica med. 1907, No. 47, 48.
[63] Brown, W. H. Practitioner, Jan., 1910; *see also* refs. F. H. ix. 2, pp. 131–135, on iodophilia.
[64] Da Costa. Therapeutic Gazette, Oct. 5, 1906.
[65] Pappenheim. F. H. ix. 1, p. 321 (370).
[66] Abetti. Il Policlinico, 1910, No. 8.
[67] Woskressenski. Russ. med. Rundschau, 1907, No. 12.
[68] Neukerich. Z. f. kl. Med. Bd. lxx. 3, 4.
[69] Ciaccio. *See* ref. 55, and Fol. clin. chim. e microscop. 1910, p. 224.
[70] Gardella. La Ginecologia, 1909.
[71] Tousset et Troisier. Soc. de Biol., 1907, p. 104.
[72] Martelli. Pathologica, 1909, No. 23.
[73] Leber. Die Enstehung der Entzündung, Leipzig, 1891.
[74] Erben. Z. f. H. 24; Z. f. kl. Med. 40; Hofmann's Beitr. 5.
[75] Müller and Jochmann. M. 1906, Nos. 29, 31, 41, 43.
[76] Wiens. E., 1911, 15te Jahrgang, 1 abt.
[77] Meisner. Z. f. H., vol. 72, 1912; *see also* Proc. Roy. Soc. Med., Dec. 1912, on anti-diphtheritic serum and iodine.
[78] Jochmann. V. A., 194, p. 342.
[79] Pappenheim. Atlas (ref. 12, Chapter I.), Suppltbd. p. 84.
[80] Cesaris-Demel. R. Academia di Med. di Torino, 1906; Arch. per la scienze mediche, 1905, t. xxix.
[81] Kaplan. F. H., vii., p. 97 (1909).
[82] Weidenreich. A. f. m. A. Bd. lxxii. p. 209.
[83] Helly. Z. B., 1905, xxxvii, 2.
[84] Cesaris-Demel. V. A., 1909, 195, 1; *see also* F. H. viii., p. 155 (1909).
[85] Ciaccio. Same ref. as 47[a], Chapter III.
[86] Quarelli and Bottino. Giorno dell. R. Acad. d. Med. d. Torino, 1907.
[87] Hardy. J. Phys., 1892.

[88] FRY. F. H. viii., Plate 8, Fig. 2.
[89] KOLLMANN. Soc. de Biol. 1907, p. 226; Ann. de Sci. Nat. Zool. 1908, t. viii, 1, 4.
[90] BRUNTZ. C. R. de la Soc. de Biol. vol. lx. p. 835.
[91] FRY. F. H. viii., p. 472 (1909).
[92] SABRAZÈS ET MURATET. F. H. vii. p. 171, 1908.
[93] DOWNEY. F. H. viii., p. 432.
[94] STEPHAN. C. R., t. lxi., p. 501.
[95] GRÜNEBERG. V. A., 1901, Bd. 163.
[96] HIRSCHFELD. B. H. G. Jan. 11, 1910; ref. F. H, ix. 2, p. 171.
[97] SABRAZES, MURATET ET DURROUZ. Gaz. hebd. des Soc. méd. de Bordeaux, 1908, p. 325 sqq.
[98] KASARINOFF. F. H. x. 1, p. 391–1910.
[99] SCHIFONE. Contributo alla morfologia comparata dei leucociti nei vertebrati. I. Mammiferi et Uccelli; Napoli, Michele d'Auria, Tribunali 386, 1907; and PAPPENHEIM, Z. f. klin. Med. 43, and V. A. 1899, Bd. 157, p. 74.
[100] FURNO. F. H. xi. 1, p. 219, 1911.
[101] WERNSTEDT. Nordisch. med. Archiv f. inn. Med. 1910, Abt. ii., H. 3.
[102] DUNGER. D. A. xci., 3, 4.
[103] MIRANO. La riforma medica, 1907, 23.
[104] KEUTHE. D. 1907, 15.
[105] LEPINE AND POPOFF. Soc. de Biol., 1907, t. lxiii., p. 364.
[106] MILKOWITSCH. Russki Wratsch, 1911, No. 22.
[107] GAUTIER. Soc. de Biol., 1907, t. lxii. p. 88.
[108] KRAUSE. 3 Kongress der Deutsch. Röntgengesellschaft, 1907, ref. F. H. v. 450.
[109] PAPPENHEIM. Grundriss d. hæmatolog. diagnostik u. praktischen Blutuntersuchung, Werner Kinkhardt, Leipzig, 1911.
[110] MANUCHIN. Russki Wratsch, 1910, Bd. ix. H. 11.
[111] SELLING. Z. B., 51, 3.
[112] FALTE, KRISER, ZEHNER. M., 1912, p. 734.
[113] MAGI. Arch. di Farmacol., 1908, 3.
[114] ROSS. Further Researches on Induced Cell Proliferation London, 1912; see also B. M. J. Jan. 23, 1909, p. 33, Lancet 1909, Jan. 30; Literature given here.
[115] ZOJA. F. H., x. 1, p. 239 (1910).

CHAPTER VI.

[1] PAPPENHEIM. F. H. xi. 2, p. 129.
[2] ARNETH. D. A., Bd. xcix.
[3] ROTH. D. A., cii., H. 5, 6.
[4] ARNOLD. V. A. 1907, cxc. 1; M. 1907, p. 2441; PIRONE, Lo Sperimentale, 1907, Fasc v.
[5] LOELE. C. Path., 1911.
[6] WIENS-SCHLECHT. Quoted by Pappenheim, remarks to ref. Kreibich, F. H. ix. 2, p. 390.
[7] WEISS. Hæmatologische Untersuchungen, 1896. Wien and Leipzig, Carl Prohaska.
[8] NICKEL. Die Farbenreaktionen der Kohlenstoffverbindungen, 1890, Berlin, H. Peters; *see also* Pappenheim, F. H. iv. p. 328 (1907).
[9] PETRY. M. 1912, p. 1092; B. Z. 38, p. 92.
[10] MARWEDEL. Beit. z. Path. Anat., 22, 507.
[11] KREIBICH. W. K. W., 1910, 19.
[12] ARNOLD. Z. f. a. P., xxi. 1, and M. 1907, p. 2441; *see also* BERKA, Z. f. a. P. xxi. 8.
[13] BENNACHIO. F. H. xi. 1, p. 253.
[14] SCHWARZ. W. K. W. 1901, 42.
[15] STEPHAN. C. R. 1906, t. lxi. No. 34.
[16] REICHER. B. H. G. Ap. 12, 1910; ref. in F. H. ix. 2, p. 397.
[17] ROUS. J. E. M. 1908, x. p. 537.
[18] PIRONE. Lo Sperimentale, 1907, fasc. v.
[19] WEIDENREICH. V. d. D. P. G., 1903.

[20] KÄMMERER. M., 1907, 29.
[21] ASCHENHEIM UND TOMONO.
[22] PASCHEFF. F. H. xi. 1, p. 430.
[23] WOLTMANN. J. E. M. 1905, pp. 119, 162.
[24] BERKA. Z. f. a. P. xxi. 8.
[25] PAPPENHEIM. Quoted by Pröscher, F. H. ii. p. 547 (1905).
[26] HOWARD, C. P. J. M. R. 1907, p. 237.
[27] SANSONOW. Dissert. St. Petersburg, 1908.
[28] FOSTER. J. M. R., 1908, p. 837.
[29] PASCHEFF. F. H. xi. 1, 460, and Plate X.
[30] HOWARD, C. J. M. R., 1907 (Dec.).
[31] LEIGHTON. J. P. B. 1911, p. 463.
[32] OPIE. Am. J. M. S. 1904, Feb.
[33] WEIDENREICH. A. f. m. A., 1908, 72.
[34] WERZBERG. F. H. xi. 1, p. 17 (1911).
[35] ARNOLD. V. A. 1899, Bd. 150.
[36] KASARINOFF. F. H. x. 1, p. 391 (1910).
Literature on Mast Cells, *see* F. H. xi. 1, pp. 252 and 269; SABRAZÈS ET LAFON, F. H. vi. p. 3 (1908).
[37] MICHAELIS AND WOLFF. M., 1902, p. 227.
[38] WEIDENREICH. F. H. v. p. 135 sqq. Gives list of literature.
[39] EHRLICH. Verhdl. d. Physiol. Gesell. Berlin, 1878-9.
[40] BERKA. V. A., 205, 1-3.
[41] UNNA. A. f. m. A. 1911, Bd. 78 (Waldeyer Festschrift).
[42] CIACCIO. Fol. Clin. Chim. Microscop. Bd. II. p. 224.
[43] MEIROWSKY. F. H. vi. p. 42 (1908).
[44] PAPPENHEIM. On methyl-green pyronin reaction, F. H. vi. p. 51 (6).
[45] PAPPENHEIM. F. H. ix. 1, p. 576, 1910.
[46] PAPPENHEIM. F. H. ix. 1, p. 596.
[47] HARRIS. Phil. Med. Journal, April, 1910.
[48] BENNACHIO. F. H. xi. 1, p. 253 (1911).
[49] SCHREIBER. M. 1902, p. 2075.
[50] PRÖSCHER. F. H. vii. p. 107 (1909).
[51] SABRAZÈS ET LAFON. F. H. vi. p. 3 (1908), and Plate II., and ARNOLD, M. 1906, 13. Good on Mast Cells: Pappenheim and Szécsi, F. H. xiii. 1, p. 34.
*[52] HERTZ. F. H. xiii. 1, p. 177 (1912).
[53] BRÖTZ. Z. f. a. P., 1910, No. 14.
[54] PAPPENHEIM. F. H. xiii. 2, p. 334 (Prolegomena) (1912).
[55] PAPPENHEIM. F. H. ix. 1, p. 569 (footnote) (1910).
[56] SCHRIDDE. Z. B., 1907, Bd. 41; consult also "Die eitrigen Entzündungen des Eileiters," Gustav Fischer, Jena, 1910.
GOOD on Plasma Cells: PAPPENHEIM, F. H. xiii. 2, pp. 1-6, p. 334, and F. H. xi. 2, pp. 170-178, xl. 1, p. 310.
[57] WALLGREN. Z. B., Bd. 51, H. 2.
[58] HOFMANN. M., 1904, No. 47.
[59] PAPPENHEIM on Schridde in F. H. iv., Suppltbd. p. 283 (p. 295, foot), (1907).
[60] HARRIS. *See* ref. 47.
[61] PROELL. Z. f. a. P. xxii. 9.
[62] SCHRIDDE. C. xvi., 11, 1905.
[63] MACIESKO-JALENSKA. M., 1907, p. 1790.
[64] ENDERLEN AND JUSTI. D. Z. Bd. 62.
[65] PAPPENHEIM. F. H. xii. 2, Prolegomena, p. 4.
[66] WOLF. F. Z. v. H. 2.
[67] MILLER. V. A. cxc. p. 482 (1910).
[68] ALEGNO. V. A. 204, 2.
[69] JOANNOVICS. C., 1909, Bd. xx.; and Z. f. H. 1899, Bd. xx.
[70] DOWNEY. F. H. xi. 1, p. 275 (1911).
[71] SCHLESINGER. V. A. 169, p. 428.
[72] GOLDMANN. B. z. k. Ch. 1989, No. 64, p. 192.

CHAPTER VII.

[1] ORTH. Ueber Metaplasie, xvi. Congrés I. M. 4 section.
M. BORST. Metaplasie, Aschoff's Path. Anatomie, 1911, I, p. 599.
SCHRIDDE. Die ortsfremden Epithelgewebe des Menschen. Untersuchungen und Betrachtungen. Samml. Anat. u. phys. Vortrage u. Aufsätze. Gaupp u. Nagel. Jena, 1909, Heft 6.
G. M. SMITH. J. M. R. 1913, p. 147; BENDA, B. H. G., Nov. 7, 1911, ref. F. H. xii., 2, p. 249; also PAPPENHEIM, F. H. iv. pp. 150–160, 350–360, 539–542.
[2] PAPPENHEIM. F. H. vii. Prolegomena; ix. 1, p. 572; and innumerable other works.
[3] TOMASZEWSKI. F. H. xii. 1, p. 115.
[4] MÜLLER. M. 1911, p. 713.
[5] MARCHAND. M. 1911, p. 924.
[6] LÜDKE. D. A. Bd. c. 5, 8.
[7] VOSWINCKEL U. DUNZELT. D. A. Bd. c. 5.
[8] KELLING. M. 1906, p. 1901.
[9] LITTEN. B. 1877.
[10] ARNSPERGER. M. 1905.
[11] PAPPENHEIM UND HIRSCHFELD. F. H. v. p. 347 (1908) (especially pp. 371, 390).
[12] PODWYSSOZKI. B. z. P. A. Bd. 47, H. 2.
[13] KROMPECHER. Z. B. 1898.
[14] PAPPENHEIM. F. H. ix, p. 574.
[15] PAPPENHEIM. F. H. ix. 1, p. 346.
[16] GRUNER, SCRIMGER, AND FOSTER. A. I. M., 1912, p. 641.
[17] *See* ref. 11.
[18] PALTAUF. M. 1912, p. 214.
[19] ASKANAZY. V. A. 205, p. 3.
[20] NEUMANN. V. A. 207, H. 3 (1910), p. 379.
[21] HIRSCHFELD. B. 1906, No. 32.
[22] HIRSCHFELD. B. 1902, p. 701.
[23] SCHATILOFF. Charkowskij Medizinsky, 1908, T. v. No. 3.
[24] WERZBERG. V. A. 204, H. 2, 3.
[25] ACHARD ET WEIL. Arch. de méd. exp. et d'anat. path. 1907, p. 319.
[26] JAROTSKY. Vortrag d. Dorpater Naturforschergesellschaft, May, 1911, ref. F. H. xii. 2, p. 327.
[27] SELLING. Z. B. Bd. 51, H. 3.
[28] STERNBERG. W. K. W. 1911, p. 1623 (also literature in this paper).
[29] PAPPENHEIM. Prolegomena, F. H. xii. 2, p. 285.
[30] FRÄNKEL in EHRLICH, Anæmia, Bd. I.
[31] EHRLICH AND LAZARUS, EHRLICH AND PINCUS, SCHRIDDE, ZIEGLER, HELLY, LÖWIT.
[32] ASKANAZY. V. A. 205, H. 3; M. 1912, p. 38.
[33] SCHWARZ AND MICHAELIS. Z. f. H. Bd. 32, p. 294; Verhdl. d. Kongress f. inn. Med. 19th Congress, 1901, p. 273.
[34] NEUMANN. V. A. 207, H. 3.
[35] BANTI. Z. f. path. Anat. 1904, H. 1.
[36] DOMINICI. A. d. Méd., 1901, 1.
[37] HERTZ. F. H. xii. 1, p. 40.
[38] PAPPENHEIM. Ref. No. 15 (p. 352 sqq.).
[39] HERTZ. Z. f. kl. M. lxxi.
[40] WERZBERG. Same as ref. 24.
[41] PAREMUSOFF. F. H. xii. 1, p. 195 (1911).
On Myeloid Metaplasia. FISCHER. Julius Springer, Berlin, 1909. For Theories on Myeloid Metaplasia, PAPPENHEIM, F. H. iv. Suppltd., p. 336.
[42] PAPPENHEIM. F. H. v. p. 396 (1908).
[43] RUBINSTEIN. Z. f. kl. M. Bd. 61, H. 5, 6.
[44] HIRSCHFELD. F. H. vii., p. 144, 1909.
[45] PAPPENHEIM. Same ref. as preceding, footnote.

[46] FRANK AND ISAAK. M. 1912, p. 491; Z. f. kl. Med., Bd. 74, H. 1, 2.
[47] v. DECASTELLO. F. H. xiii. 1, p. 471 (1912).
[*48] FABIAN. C. 1911, with full literature.
[49] KUNDRAT. W. K. W. 1893.
[50] YAMASAKI. Z. f. H., 1904.
[51] HIRSCHFELD. Ergeb. d. inn. Med. u. Kinderheilk. 1911.
[52] B. FISCHER. M. 1911, p. 220.
[53] MEYER. F. Z. 1911, viii.
[54] DIETRICH. D. 1908, 27.
[55] PAPPENHEIM. F. H. xii. 1, p. 26 (1911).
[56] HELLY. Naturforscherversammlung, 1908, ref. F. H. x. 2, p. 60.
[57] MABEE. Meeting of American Assoc. of Path. and Bact. at Chicago, 1911.
[58] MILLIGAN. Manch. Path. Soc., March 10, 1909.
[59] *See* ref. 50, Chapter III., refer to Plate IV., Fig. 193 in that ref.
[60] HERTZ. F. H. xiii. 1, p. 177.
[61] HEDINGER. F. Z. vii. No. 3.
[62] KLOSE. B. z. k. Ch. Bd. 74, p. 20.
[63] PAPPENHEIM'S Comment on Paltauf. W. K. W. 1912, No. 1 (F. H. xii. 2, p. 272).
[64] BUSCHKE UND HIRSCHFELD. F. H. xii. Plate v.
[65] PAPPENHEIM. F. H. xii. 1, Plate I. sub Ib.; Atlas, Supplbd. Taf. 36.
[66] GRUNER. Bull. Roy. Vict. Hospital, No. 2, 1912, p. 59.
[67] PAPPENHEIM. Prolegomena, F. H. xii. 2, p. 257, and others.
[68] KANTER, GOLDMANN. F. H. vii. p. 46 (quoted by Pappenheim).
[69] LEWIN. F. H. viii. p. 21, 1909. Also, K. ZIEGLER, Die Hodgkinsche Krankheit, Gustav Fischer, Jena, 1911 (with full literature). Other references in F. H. vii. pp. 177–192 (on Lymphosarcoma), pp. 153 sqq. (on Pseudoleukæmia).
[70] *See* ref. 29, and 2.
[71] M. B. SCHMIDT. Z. f. a. P. 1907, xviii. 15.
[72] LA ROY. Ann. de Soc. de Méd. de Gand 89, p. 209
PAPPENHEIM, Prolegomena, F. H. x. 2, p. 3.
MICHELI. Hæmolytic Splenomegaly, W. K. W. 1911, p. 1269.
[73] ASCHENHEIM AND BENJAMIN. D. A. Bd. 97, H. 5, 6.
[74] FOA. Pathologica, 1910 (Note di ematologia).
[75] PAPPENHEIM. *See* ref. 109, Chapter v.
Recent good text-book should be consulted: GULLAND AND GOODALL, The Blood, H. K. Lewis, London.

GLOSSARY OF HÆMATOLOGICAL TERMS.

Adventitial Cell. *Syn.*: clasmatocyte, perithelial cell. The cell lying immediately external to the capillary wall. *See* Marchand's wandering cell.

Agranuloplastic. Formation of non-granular cells. Inability to form granular cells.

Aleukæmia. *Syn.*: lymphadenia ossium (Nothnagel). *See* Myeloma.
A disease in which the organs show the histological changes of leukæmia, but the blood does not. It is a lymphadenoid metaplasia of the bone-marrow, displacing the erythroblastic tissue and so causing "anæmia." No outpour of abnormal cells, but cell-production increased.

Aleukæmic Diffuse Marrow Hyperplasia. *See* Latent leukæmia.

Aleukæmic Lymphosarcomatosis. *See* Lymphosarcoma.

Aleukæmic Malignant Lymphadenoid Lymphadenoma. *See* Pseudo-leukæmia.

Alibert's Granulosarcoid. An anomalous form of sarcoma.

α-Granule. Eosinophile granule.

α-Prothrombin. *See* Prothrombin.

α-Substance. *Syn.*: reticular substance of Cesaris-Demel (q.v.). Substantia reticulo-filamentosa.

Alymphopotent. Devoid of the power of giving rise to lymphoid cells.

Amammalian Blood-cell. Such as occurs in animals other than mammals.

Amblychromasia, Amblychromatic. Having a scanty amount of chromatin. The nucleus therefore stains faintly.

Ametachromophile. *See* Orthochromophile.

Ametaneutrophile. *See* Orthoneutrophile.

Amæboididity. Having the power of locomotion.

Amœbocyte. A cell having the power of amœboid movement, e.g. neutrophile leucocyte.

Amorphous Hæmoglobin. *See* Schistocyte.

Amphiblast. A term invented and solely used by Fr. Freytag to describe a cell which he believes generates red cells from the stromata of old erythrocytes. Habitat: bone-marrow. Amphiblast = mitosis = free nucleus = red cell (!)

Amphileukæmic. A leukæmic state in which the outpouring of cells corresponds to the degree of cell production. Correlated terms: sub-leukæmic, aleukæmic (q.v.).

Amphipyrenin. A constituent of the nucleolus.

Amphochromophilia. A dusky heliotrope colour due to the admixture within a cell of two colour constituents. Same as

Amphophile. The colour effect produced by the same cell substance having material in it which can take up acid dyes, and also material which can take up basic dyes.

Amphophile-basophile. The same as preceding, but with the basophile constituents in excess.

Amphophile-oxyphile. The same as "Amphophile," but with the oxyphile constituents preponderating.

Amyeloic. *Syn.*: lymphatic.

Anæmic Degeneration of Red Cells. (Ehrlich.) *Syn.*: polychromasia.

Anæmia Pseudoleukæmia Infantum. *Syn.*: rachitic megalospleny.

Analogues. The following examples may be instructive:—

Caryogenic	*versus*	plasmatic
Diffuse hæmoglobin	,,	leucocyte granule
Erythrocyte	,,	polynuclear leucocyte
Jolly-body stage	,,	metamyelocyte stage
Megaloblast	,,	large myelocyte
Lymphoid erythroblast	,,	leucoblast with myelocyte nucleus
Normoblast	,,	myelocyte daughter cell
Orthochromatic erythroblast	,,	myelocyte with oxyphile plasma
Ontogenetic	,,	phylogenetic
Polychromoblast	,,	promyelocyte
Protohæmoblast	,,	myeloblast
Pycnosis	,,	segmentation of nucleus
Substitutive metaplasia	,,	autoparenchymatous metaplasia

See also "Correlated Terms."

Anaplasia. *Syn.*: reversionary atrophy, prosoplasia, reverse differentiation, embryonization, atavism.

Anerythrocyte. *Syn.*: lympherythrocyte, lymphoid erythrocyte.

Anerythroplastic. Absence of formation of red cells.

Anerythroregenerative. Absence of regeneration of red cells.

Angioblast. Primitive formative vascular cell.

Anisohypercytosis. The total white-cell count is increased, but abnormal neutrophile leucocytes are present.

Anisohypocytosis. *Syn.*: leucolysis. The total white-cell count is diminished, and abnormal neutrophile leucocytes are present.

Anisonormocytosis. The total white cell-count is normal, but abnormal neutrophile leucocytes are present.

Aplastic. *Syn.*: aregenerative; passive.

Aplastic Leukæmia. (Wolff-Eisner.) *See* Pseudoleukæmia.

Archoplasm. *Syn.*: paranuclear spherule.

Archosoma. *See* Somosphere.

Aregenerative. Absence of regeneration of blood-cells. *See* Aplastic.

Astrosphere. *Syn.*: centrosome, attraction-sphere. A small area from which lines radiate to the neighbouring part of the protoplasm. In its centre is the centriole.

Attraction Particle. *See* Centriole.

Attraction Sphere. *See* Astrosphere.

Atypical Myelomonocyte. This cell has a dusky amphophile protoplasm. The nucleus has a structure like that of a lymphatic large mononuclear leucocyte. There are no nucleoli.

Auer's Bodies. Rod-like structures met with in acute leukæmic blood-cells.

Augmentor (Ross). A substance which aids action of an auxetic or kinetic.

Aurantiophile. Affinity for aurantia.

Autochthonous. Derived from the body itself.

Autonomous. Rampant, uncontrolled, independent, unbridled, and spontaneous.

Autoparenchymatous Metaplasia. Metaplasia occurring in the parenchymal cells proper to the tissues. *See* Analogues.

Autotoxin. Toxin derived from the body tissues of the individual himself.

Auxetic (Ross). A substance which excites cell proliferation.

Basichromioles. The granules which enter into the composition of the caryomitom.

Basicytoparaplastin. That form of basiparaplastin which occurs in the protoplasm.

Basicaryoplastin. That form of basiparaplastin which occurs in the parachromatin. Includes: basiparachromatin: basophile nucleolus.

Basiparachromatin. *Syn.*: basicaryoplastin (q.v.)

Basiparaplastin. That form of paraplastin which occurs partly in the nucleus and partly in the cytoplasm. It includes: (*a*) Basicaryoplastin (parachromatin) and (*b*) Basicytoparaplastin (in the protoplasm).

Basometachromophile. Staining another (metachromatic) colour with basic dyes.

Basophile. Having an affinity for the basophile component of a neutral dye mixture.

Basophile Bodies in Red Cells. Granules assigned the following names—Foa and Mondino's, Zenoni, Plehn's, Beck's, Heidenhain's central, Celli and Guarneri bodies, Schüffner-Maurer-Ruze stippling, Horseley's spherules, Heinz bodies, Bloch bodies, Jolly body, Lavdowsky's nucleoids, Arnold's, Pappenheim's, Engel's nucleoids, Nissl's centrosome, C-bodies of Cesaris-Demel, Schur's basophile inclusions of Graves' disease. Weidenreich's chromatin dust, the endoglobar bodies named after Wlassow, Maximow, Bremer, Hirschfeld, Schultze, Schmauch, Maragliano-Castellino, Arnold-Schwalbe.

Basophile Myelocyte (Dominici.) *See* Large lymphocyte.

Basophile Nucleolus. *See* Basicaryoplastin.

Basoplasm. The part of the cytoplasm having affinity for basic dyes.

Benda Chondrosome. *See* Chondrosome.

β-Substance. *Syn.*: Heinz bodies, substantia metachromatico-granularis.

β-Granule. An amphophile granule.

Bioblast (Altmann). Cell granule (q.v.).

Blood Crisis. (*a*) Sudden appearance of large numbers of "blast" forms of red cells; (*b*) Sudden appearance of leucocytes during the course of pernicious anæmia (v. Noorden).

Blood-disc. *See* Erythrocyte.
Blood-dust. *Syn.*: Hæmoconia.
Blood-pathological Monocyte *See* Leucoblast.
Blood-plasma Cell. *Syn.*: Türk cell, phlogocyte, lymphoid marrow cell, irritation cell, stimulation cell, large mononuclear cell, hæmatic plasma cell, plasma cell.
Blood-plastid (Minot). A red cell altered by concentrated salt solution.
Blood-platelet (Bizzozzero). *Syn.*: elementary bodies (Zimmermann), globulins (Robin), hæmatoblasts (Hayem), soterocyte.
Bone-marrow Monocyte. *See* Myelolymphocyte.
Bremer's Endoglobar Body. *See* Paranuclear spherule.
Broad-bodied Endothelioid Small Lymphocyte. *See* leucocytoid lymphocyte.
Brood Cell. Mother cell.

Cabot Ring. Chromatin rest.
Caryogenic. *Syn.*: parachromatic. *See* Analogues.
Caryolobic. Having a lobe-shaped nucleus.
Caryolysis. The process of solution of nuclear matter.
Caryomicrosome. *See* Cell granule.
Caryomitom. The formed material of the nucleus, consisting of: (*a*) threads disposed in a network; (*b*) nuclear membrane. Includes basichromatin, basichromioles, etc., nuclear network.
Caryophilia. Affinity for thiazin ammonium dyes.
Caryoplasm. *Syn.*: oxychromatin, achromatin. The formless substance in the nucleus occupying the meshes of the caryomitom.
Caryoplastin. *Syn.*: parachromatin, caryogenic plastin, nuclear plastin body. The plastin substances within the nucleus. Some are ampho-basophile, some are ampho-oxyphile.
Caryorrhexis. The process of fragmentation of nuclear matter.
Caryosome. *Syn.*: nucleolus, plasmosome.
Caryospherical. Having a globular nucleus.
Cell Granule. *Syn.*: ozonophore (Altmann); cytomicrosome, caryomicrosome; bioblast (Altmann), plasmome (Wiesner); plasmosome (Arnold); microsome (Hanstein), protomere (Heidenhain).
Cellule Medullaire Incolore. *See* Large Lymphocyte.
Cellule Rhagiocrine. *See* Marchand's wandering cell.
Central Particle. *See* Centriole.
Centriole. *Syn.*: central particle, attraction-particle; centrosome (incorrect). The particle occupying the centre of the attraction-sphere (it is frequently double).
Centrosome. *Syn.*: attraction-sphere (*see* centriole); astrosphere. The clear halo immediately round the centriole.
Chloranæmia. Diminution of hæmoglobin content.
Chloroanæmia. A myelopathic chlorosis with secondary degeneration of red cells (anisocytosis, poikilocytosis), and occasionally with regenerative phenomena (basophilia, polychromasia).

Chloroblast. *Syn.*: lymphoid erythroblast, q.v.

Chlorolymphosarcoma. A sarcomatous variant of chloroma.

Chloroma. A disease characterized by: (1) Presence of lymphoid deposits in the orbits, temporal fossæ, and periosteum of the bones of the skull, and the symptoms and signs arising therefrom; (2) Green colour of the lesions; (3) Profound blood change; enormous numbers of lymphocytes; (4) Affection of the bone-marrow, spleen, lymph-glands, and organs throughout the body (infiltration with lymphoid deposits) as in lymphatic leukæmia.

Chloromyeloma. }
Chloromyelosis. } Multiple tumours in bone, of green colour.

Chlorosarcolymphadeny. *See* Chlorolymphosarcoma.

Chlorosarcomyelosis. A sarcomatous variant of chloromyeloma.

Chlorosis. A disease in which there is enfeebled power of assimilation of iron; "hypoplasia of hæmoglobin."

Chondroconta. *Syn.*: mitochondria (q.v.), Schridde granule. A red-coloured granule (Altmann-Schridde) met with in a myeloblast. Said by Schridde to be different from the lymphocyte granule and from the large mononuclear leucocyte granule.

Chondromitom. *Syn.*: paranucleus (q.v.).

Chondrosome (Benda). Altmann - Schridde granule of lymphocyte, according to Meves. *See* Mitochondria.

Chromatinic Nodal Points. *Syn.*: pseudonucleolus.

Chromatinolysis. The process of solution of chromatin.

Chromatinorrhexis. The process of fragmentation of the chromatin.

Chromatokinesis. Rearrangement of the chromatin by metakinesis into wheel forms, etc.

Chromatolysis. *Syn.*: chromatinolysis. The process of solution of chromatin.

Chromidium. The central chromatic structure of the blood-platelet.

Chromidia. *Syn.*: mitochondria, chondroconta, Schridde granule (but incorrect).

Chromidial. Derived from chromatin.

Chromiole. The constituent particles of the chromosomes.

Chromoblast. *See* Lymphoid erythroblast.

Chromocyte. *See* Erythrocyte.

Chromomere. A group of two or three chromioles bound together by linin.

Chromophobic. Inability to take up a given dye.

Chromoplast. A small mass of resting chromatic substance from which the chromosomes arise during division.

Chromosome. The separate portions of the nuclear chromatin which appear when the nucleus is in process of division, though also present at other times.

Chromotoxic Hyperchromæmia. Anæmia, associated with hyperchromia, due to toxic action on the hæmoglobin.

Clasmatoblast. *Syn.*: mast cell.

Clasmatocyte. *See* Marchand's wandering cell.

Clasmatosis. The formation of pseudopodia-like processes by plasmolysis and not by true pseudopodia formation ; bud-like constrictions.
Coctostable. *Syn.* : thermostable (not absolute syn.). Withstanding the temperature of boiling water without decomposition.
Condensateur. *See* Plasmosome, cell granule.
Cornil Lymphoid Marrow Cell. *See* Large Lymphocyte.
Corps en demi-lune. *See* Fig. 27. *Syn.* : demi-lune body.
Correlated Terms. The following are of interest : chromotoxic *v.* hæmotoxic ; chromotoxanæmia *v.* hæmotoxanæmia ; pernicious anæmia *v.* simple anæmia ; hæmotoxicosis *v.* myelotoxicosis. *See* Analogues.
Cryptogenetic. Of obscure origin. Correlated term : phanerogenetic.
Cyanophile. Having an affinity for the blue-staining component of a neutral mixture.
Cytochylem. Interspongioplastic substance.
Cytode. The simplest form of cell.
Cytogenesis. Cell formation.
Cytokerastic. The process of " moulding " of a cell into a higher type.
Cytomicrosome. *Syn.* : caryomicrosome ; bioblast. *See* Cell granule.
Cytomitome. *Syn.* : spongioplasm. A bundle of fine fibrils traversing the cytoplasm (in a ciliated cell for instance).
Cytophage. Examples are : erythrophage, leucophage, pigmentophage, protozoophage.
Cytophyletic. Pertaining to the genealogy of a cell.
Cytoplastin. The plastin bodies of the cytoplasm. They consist of spongioplastin and paraplastin (q.v.).
Cytostromatic. Referring to the stroma of a cell.
Cytozyme. *Syn.* : thrombokinase.

Darier's Polyeidocyte. Large mononuclear leucocyte of normal spleen.
δ-Granule. A small mast granule.
Demi-lune Body. *Syn.* : hæmodemilune. *See* Corps en demi-lune.
Deviation to the left . . . . right. Applied to white-cell formulæ to indicate prevalence (or absence) of immature forms.
Deuteropathic. (*a*) Producing pathological effects along two directions ; (*b*) A secondary action of a toxic agent.
Deuteroplasm. *Syn.* : paraplasm. The non-protoplasmic matter within a cell-body.
Dihypercytosis. *Syn.* : hyperhypercytosis (q.v.).
Dinormocytosis. *Syn.* : normonormocytosis ; isonormocytosis.
Dipotent. Having a potentiality for development along two directions.
Discoplasm (Ehrlich). A part of the cytoplasm which possesses vital properties.
Discostroma. The stroma of the red cell.
Dwarf Leucocytes. Miniature forms.

Elementary Bodies (Zimmermann). *See* Blood-platelet.
Embryonic Erythroblast. *Syn.* : primary erythroblast (Schridde), megaloblast (Ehrlich).

Embryonization. Reversion of a cell or tissue into an embryonic form. *See* Anaplasia.

Enchylema (Carnoy). *See* Hyaloplasm.

Endoglobar Body (of red cell). *See* Nucleoid.

Endointoxication. Intoxication of the tissue by an endogenous toxin.

Endosoma. (Weidenreich). A hypothetical solution of hæmoglobin occupying the red cell.

Endothelial Cell (fixed). *Syn.*: lymphatic clasmatocyte, mesenchymal cell.

Endothelial Lymphocyte (Patella). *Syn.*: leucocytoid lymphocyte, Schleip's hypertrophic lymphocyte; Pappenheim's indent-nucleated leucocytoid lymphocyte; senile lymphocyte; hyaline lymphocyte; hyaline leucocyte;* large mononuclear leucocyte (q.v.).

Endothelial Micromonocyte. *See* Lymphocyte.

Endothelioid Habit. A condition in which the nucleus is relatively small in volume compared with the cytoplasm (broad cell-body).

Endothelioid Leucocyte. *Syn.*: leucocytoid leucocyte.

Endothelioid Lympholeucocyte. *Syn.*: Schridde's lymphoblast.

Endothelioid Pseudolymphocytar Micromonocyte (Patella)) is a large mononuclear leucocyte.

Endothelio-vascular Cell. *See* Large mononuclear leucocyte.

Endotoxicosis. Disease due to poisoning by endotoxin.

Endotoxinæmia. The presence of endotoxin in the circulating blood.

Engel's Fuchsinophile Cell is a polychromatic erythroblast, which takes on a pink colour with the fuchsin of triacid.

Eosinoblast. *Syn.*: microleucoblast; micromyeloblast. Fate—becomes a micropromyelocyte with alpha granules.

Eosinopenia. A condition in which the number of eosinophiles in the circulating blood (or in a tissue) is diminished.

Eosinophile Leucocyte. *See* text.

Eosinophile Promyelocyte. An eosinophile cell whose nuclear characters are those of a promyelocyte.

Eosinotactic. Having an attractive or repulsive action on eosinophile cells.

Epigenetic. Pertaining to the growth and differentiation of a single egg-cell.

ε-Leucocyte. *See* Neutrophile Leucocyte.

ε-Myelocyte. *See* Neutrophile Myelocyte.

Ergastoplasm (Ciaccio). The prezymogenic substance of basophile reaction which appears in glandular cells before the formation of vacuoles or secondary granules within them.

Erythræmia (Löwit, v.d. Stricht). *Syn.*: polycythæmia (q.v.).

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* It will be evident that each of this list of synonyms is not synonymous with every other

Erythroblast. *Syn.*: lymphoid erythroblast; chloroblast; chromoblast: protohæmatoblast (Malassez); hématie secondaire (Jolly); hæmoblast (Pappenheim); erythroblastic erythrogonia (Helly); lymphocyte (Weidenreich); large lymphocyte (Maximow); lympherythroblast; proerythroblast (Zoja, Ferrata, Dantschakoff); hæmonormoblast; hæmerythroblast; lymphoid hæmoblast; normoblast.

Erythrocyte. *Syn.*: erythrocytode; mononuclear mammalian red blood-corpuscle: blood-disc; chromocyte; red cell. *See* Analogues.

Erythrocytoblast (Zoja). *Syn.*: lymphoid hæmoblast.

Erythrocytode. *See* Erythrocyte.

Erythrocytosis. *Syn.*: polycythæmia (q.v.).

Erythrodysplasia (of bone-marrow). A state in which there is interference with the process of differentiation of the erythropoietic cells, due to: (1) Primary leukæmic change; (2) Secondary to regenerative changes. Variant: aplastic anæmia (aregenerative anæmia).

Erythrogonia (Helly). *See* Erythroblast.

Erythrolysis. Solution of red cells; globulicidy; effect of an erythrolytic agent.

Erythroneocytosis. Appearance of regenerative immature forms of red cells in the blood.

Erythrophile. Having an affinity for the fuchsin component of triacid.

Erythrorrhectic. The fragmented condition of an erythrocyte discharged into the circulating blood, or taking place as a result of noxæ.

Eumorphism. A pathological change, but without disturbance of the natural form or shape of the cell.

Exotoxic. A toxic process introduced from without the body.

Extramedullary (Heterotopic) Myeloid Tissue Formation. *See* Myeloid transformation.

False Anæmia. Where the patient looks anæmic, but the blood-count is normal.

Filar Mass. *Syn.*: *See* Reticular substance.

Filar Structure. The reticular matter of young erythrocytes which stains by vital staining. *See* Reticular Substance.

Fuchsinophile. *Syn.*: Erythrophile (Engel). Having affinity for the fuchsin of triacid. It is not the same as polychromatophil, and cannot be detected by Romanowsky stains.

γ-Granule. A large mast-cell granule.

Germ-centre Cell. *Syn.*: lymphogonia (Benda), lymphoidocyte, interfollicular germ-centre cell, intrafollicular germ-centre cell, monocyte, large lymphocyte.

Ghost Corpuscle. A shadow form of blood-cell (whether red or white).

Giant Leucocyte. A very large form of polynuclear leucocyte, occasionally encountered in blood smears.

Gigantoblast. Possible *Syn.*: megaloblast.

Gigantochromoblast. *Syn.*: gigantoblast. A large nucleated red cell.

Gigantocyte. A very large red cell.
Gigantolymphocyte. Applied to Naegeli's lymphoblast, and to the meso-lymphocyte.
Glass-body. *See* text and Fig. 23.
Globulicidy. *Syn.*: erythrolysis.
Globulin of Robin. *See* Blood-platelet.
Granoplasm. The portion of the cell-substance which has a granular appearance, but is not possessed of true granules in the Ehrlich sense.
Granular Pseudolymphocyte. *Syn.*: promyelocyte.
Granuloblast. *Syn.*: large lymphocyte. The mother cell of a granulocyte.
Granulocyte. A white cell of the blood which contains specific granules.
Granuloplastic. *Syn.*: granulopotent. Having the potentiality of forming granules.
Granulopotent. *See* Granuloplastic.
Granulopotent Leucoblast. *See* Leucoblast.
Granulosarcoid. A form of sarcoma.
Guaiac Reaction of the Blood. The blue colour obtained by addition of tincture of guaiac alone, found in chronic mixed leukæmia.

Hæmatoblasts (Hayem). *See* Blood-platelets.
Hæmatogonia. *See* Hæmogonia.
Hæmobasocyte. Basophile (immature) red cell devoid of nucleus.
Hæmoblast, Lymphoid. *See* Lymphoid Erythrocyte, Erythroblast.
Hæmoconia. *See* Blood-dust.
Hæmogonia. *See* Large lymphocyte.
Hæmonormoblast. *See* Erythroblast.
Hæmosemeiological. Pertaining to the symptoms of blood-disease.
Heinz Body. *See* text. *Syn.*: β-substance, reticular substance (q.v.): Howell nuclear rest; Schmauch's endoglobar body.
Hématie Granuleuse. *See* Reticular Substance.
Hématie Secondaire (Jolly). *See* Erythroblast.
Hepatothrombin. A substance antagonistic to fibrinolysis. The action of leucothrombin derived from the liver.
Heterometaplasia, Heterometaplastic. A metaplastic process resulting in the production of an apparently foreign tissue.
Heteroplasia, Heteroplastic. A specific differentiation in another direction than physiological. This may be indicated by the admixture in the cell-body of lymphospongioplasm and oxyparaplasm.
Heterotopia. The appearance in the blood of immature ancestors of the leucocytes. Also applied to the appearance of any cell in a region in which it is normally absent. *Adj.*: Heterotopic.
Heterotopic Myeloid Tissue Formation. *See* Myeloid transformation.
Histiogenic. *Syn.*: histioid. Arising in tissues, as opposed to the blood.
Histiogenic Lymphocyte. *Syn.*: lymphocytiform microleucoblast; myeloic lymphocyte, myelolymphocyte, pseudolymphocyte, microlymphoidocyte; small lymphocytoid cell, micromyeloblast, eosinoblast. *See* also under Permanent Lymphocyte. Properties: possession of granuloplastic power. Fate = histiogenic eosinophile.

Histioid. *Syn.*: histiogenic, histogenic.
Histio-irritative. Tending to irritate or excite the connective tissues.
Histiometaplastic. Having the power to give rise to metaplasia of tissue.
Histothrombin. A thrombin derived from the connective-tissue cells.
Holozyme (Fuld). *Syn.*: thrombin.
Homogeny. Identical structure inherited from an ancestor common to two cells or organisms being compared.
Homohyperplastic. Excessive overgrowth with production of similar cells.
Homoioplastic (Pappenheim). Where the daughter cells are exactly like the mother cell.
Homophane. Without optical differentiation.
Homoplastic. Formation of a highly-developed tissue from an apparently undifferentiated cell.
Homoplasy. Independent development of like structure along two different lines of descent.
Hyaline Leucocyte. *See* under "Endothelial Lymphocyte."
Hyaloplasm (Leydig). *Syn.*: enchylema. The clear substance which occupies the meshes of the spongioplasm.
Hyperchromatic Macrocytosis. *Syn.*: macrocytar hyperchromia.
Hyperchromia. *Syn.*: pleiochromia.
Hyperchromic Anæmia. When the colour index is greater than unity.
Hyperchromophile Chromotoxic Anæmia. *See* Chromotoxic hyperchromanæmia.
Hypercytochromia. A sign of degeneration of the blood.
Hypercytosis. *Syn.*: leucocytosis; neutrophilia; hyperorthocytosis. An increase in the number of leucocytes.
Hypereosinophile Granulation (Müller and Rieder). Granules that stain unduly brilliantly with eosin, but occur in cells otherwise classifiable as neutrophile leucocytes.
Hyperglobulism. *Syn.*: polycythæmia (q.v.).
Hyperhypercytosis. *Syn.*: di-hypercytosis. The total white count is increased, the neutrophile percentage is excessive.
Hyperhypocytosis. The total white count is diminished, the neutrophile percentage is increased.
Hyperleucocytosis. *See* Leucocytosis.
Hyperneocytosis. *Syn.*: hyperskæcytosis. The total white count is increased. Along with this is deviation to the left.
Hypernomic. Pertaining to unduly vigorous independent and uncontrolled proliferation.
Hypernormocytosis. The total white-cell count is normal. The neutrophiles are relatively increased.
Hyperplasmia. An increase in the size of the red cell from imbibition. *Alt.*: an aleukæmic excessive proliferation of the normal cells prevalent in the organ concerned.
Hyperorthocytosis. *See* Hypercytosis.

Hyperplasia. The over-proliferation of normal cells, which are in any case predominant in the given tissue or organ.

Hyperplastic Aleukæmia. *Syn.*: aleukæmic lymphocytomatosis; aleukæmic leucocytomatosis; malignant hyperplastic aleukæmic lymphoma; lymphomatosis (Trousseau); lymphadenomatosis; lymphadeny; malignant lymphona (Orth). Generalized hyperplasia of the lymphadenoid tissue, or myeloid tissue.

Hyperskæocytosis. *See* Hyperneocytosis.

Hypertrophic Lymphocyte (Schleip). *See* Endothelial lymphocyte.

Hyperchromatin. The azurophile portion of chromatin.

Hypochromic Anæmia. Where the colour index is less than unity.

Hypochronological. Shifting back of the development of a blood-cell to an earlier period of time.

Hypocytosis. The total white count is diminished. *See* Leucopenia.

Hyponeocytosis. *Syn.*: hyposkæocytosis. The total white count is diminished, and there is deviation to the left.

Hyponeutrophile. Immature neutrophile granules.

Hypo-orthocytosis. *Syn.*: hypocytosis, leucopenia. The total white count is diminished, but only mature cells are present.

Hypoplastic Monster (Pappenheim). Applied to the lympherythrocyte.

Hyposkæocytosis. *See* Hyponeocytosis.

Idiozome. A body occurring within red cells, leucocytes, and epithelial cells.

Immature Cells (Grawitz). *See* Large lymphocyte.

Immature Leucoblastic Parenchymal Cell. *See* Marchand's wandering cell.

Immature Lymphoblastic Parenchymal Cell. *See* Marchand's wandering cell.

Immature Monocyte. A transitional form of monocyte.

Immature Myelocyte. *Syn.*: leucoblast.

Inclusion Body. *See* Nucleoid.

Indenization. *See* Inniadation.

Indifferent Cell. A cell capable of metaplasia. *See* Lymphoidocyte.

Indifferent Lymphomyeloblast. *See* Large lymphocyte.

Indifferent Marrow Cell. A cell occurring in the marrow, having potentiality for development along different directions. It has a narrow reticular basophile protoplasm, and a large simple badly staining nucleus. *See* Large lymphocyte.

Indifferent Mesenchymal Primordial Cell. *See* Large lymphocyte.

Inniadation. *Syn.*: indenization, colonization, metastasis. Applied to cells which, carried from one part of the body to another, settle in the new situation, and multiply there.

Interfollicular Germ-centre Cell. A cell in the resting stage, and yet capable of developing a new germ centre, on occasion.

Interfollicular Tissue. *Syn.*: non-specific lymphadenoid tissue, circumvenous perivascular tissue; extra-parenchymatous tissue.

Interphyletic. Morphological transitions between two kinds of cells during the course of metaplastic differentiation.

Interspongioplastic Substance. *Syn.*: cytochylem.

Intrafollicular Germ-centre Cell is one in a state of lymphoblastic metamorphosis (actively proliferating and differentiating).

Intraphyletic. Morphological transitions of development during the course of life of one and the same kind of cell.

Irritation Cell. *See* Blood-plasma cell.

Irritation Cell Leucocytosis. *Syn.*: phlogocytosis, plasmacytosis, plasma-cell leucocytosis.

Irritation Myelocytosis. An increase of the myelocytes with plasmoid change.

Isochromatophile. Having the same affinity for a given dye.

Isogenesis. Identity of morphological development.

Isohypercytosis. The total white-cell count is increased, but the neutrophile percentage is normal. Correlated term: aniso-hypercytosis.

Isohypocytosis. *Syn.*: leucopenia. The total white-cell count is diminished; the neutrophile percentage is normal. Correlated term: anisohypocytosis.

Isomorphous. Having the same morphological characters.

Isomorphous Cells.

Large mononuclear leucocyte	with	leucoblast.
Leucocytoid large lymphocyte of normal blood	"	leucocytoid myeloblast of pathological blood.
Leucocytoid lymphocyte ..	"	leucocytoid macrolymphocyte of lymphæmic blood; leucosarcoma cell of Sternberg.
Lymphoblast	"	lymphoidocyte
Lymphocyte	"	lymphæmic microlymphocyte microlymphoidocyte myelæmic microlymphoidocyte
Microlymphoidocyte ..	"	small lymphocyte
Monocyte (broad-bodied large lymphocyte)	"	broad-bodied leucocytoid leucoblast
Lymphoidocyte	"	macrolymphocytar lymphæmic lymphadenoid leucosarcoma cell
Transition cell	"	leucocytoid leucoblast

Isonormocytosis. *Syn.*: normonormocytosis; di-normocytosis. The total count is normal, and neutrophile percentage is normal. Correlated term: anisonormocytosis.

Isotypical. Belonging to the same type.

Jolly Body. *See* text. *Syn.*: nuclear spherule, chromatin rest. *See* Analogues.

κ-Granule. The azur-granule.

Karyogenic
Karyogenic Plastin
Karyolysis
Karyomicrosome
Karyomitom
Karyophilia
Karyoplasm
Karyoplastin
Karyorrhexis
Karyosome
} See under letter **C** in each case.

Kinetic (Ross). A substance which excites amœboid movement.

Kinoplastic. Pertaining to the process of laying down the " anlage " for a locomotor tissue.

Krompecher's Fibroblast. A form of plasma cell.

Krompecher Mast Cell. A plasma cell with coarse basophile granules.

Large Leucocytoid Lymphocyte (Helly). *Syn.*: Pappenheim's lymphoid leucocyte.

Large Lymphocyte. For the most part the synonyms of this term are identical with those for the term Lymphoidocyte, and are entered under that heading.

Large Mast-cell Lymphocyte. *Syn.*: lymphoidocytar mast cell.

Large Monocyte. *Syn.*: monocytoid large lymphocyte.

Large Mononuclear Leucocytes include (*a*) irritation forms; (*b*) Naegeli's myeloblasts (Türk's lymphoid marrow cells); (*c*) neutrophile myelocytes; (*d*) true large mononuclears.

Other Syn.: leucomonocyte, pathological monocyte, lympholeucocyte (q.v.), monocyte, large lymphocyte, leucocytoid lymphocyte (Schridde, Helly), leucocytoid large lymphocyte, hyaline leucocyte, lymphoid leucocyte, macrocyte (Schäfer), maker of macrocytase, splenocyte (Türk), splenoblast, transitional cell, Patella's desquamated endothelial cell, endotheliovascular cell, protozoophage, cytophage, lymphomonocyte, normal monocyte, splenomonocyte.

Large Myelocyte. *See* Analogues.

Large Myelolymphocyte. *See* Lymphoidocyte.

Latent Leukæmia. *Syn.*: medullary pseudoleukæmia, aleukæmic diffuse bone-marrow hyperplasia, subleukæmic diffuse bone-marrow hyperplasia.

Lavdowsky's Nucleoid. *Syn.*: paranuclear body, Bremer's endoglobar-body, centrosome.

Leptochromatic. Having a delicate chromatin network.

Leucæmia. *See* Leukæmia.

Leucoblastic Lymphocyte. *See* Myelolymphocyte.

Leucoblastic Monocyte. *See* Monocyte, myelolymphocyte.

Leucoblastic Plasma-cell. A leucoblast which has changed into a plasma-cell.

Leucoblast with Myelocyte Nucleus. *Syn.*: lymphoid myelocyte.

Leucoblast. *Syn.*: blood-pathological monocyte, bone-marrow monocyte, granulopotential leucoblast, histiogenic lymphocyte, leucoblastic lymphocyte, leucoblastic monocyte, leucoblastic myelomonocyte, lymphoid ancestor of granulocyte, lymphoid bone-marrow cell, lymphoid myelocyte, lymphoidocyte undergoing granuloplasia, microleucoblast, micromyeloblast, micromyelolymphocyte, monocyte of pathological blood, myeloic leucoblast, myeloic monocyte, myeloic splenocytoid cell, myelolymphocyte, myelomonocyte, eosinoblast, pathological leucocytoid (Marchand) monocyte, pathological monocytoid lympholeucocyte, myelogonium (Benda, Aubertin). *See* Lymphoidocyte, Histiogenic lymphocyte, Analogues.

Leucocyte. *See* Neutrophile leucocyte; large mononuclear leucocyte.

Leucocytoblast (Zoja). Parent cell of leucocytes.

Leucocytoblastoma. *See* Lymphosarcoma.

Leucocytoid Habit. Where the ratio between nucleus and plasma is small owing to the enlargement of the cytoplasm.

Leucocytoid Leucocyte. *Syn.*: endothelioid leucocyte.

Leucocytoid Lymphocyte. *Syn.*: leucocytoid microlymphocyte. A senile lymphocyte.

Leucocytoid Microlymphocyte. A senile lymphocyte.

Leucocytoid Mesolymphocyte. A senile mesolymphocyte.

Leucocytoid Wandering Cell (Marchand). *Syn.*: Metchnikoff's endothelioid macrophage. *See* Marchand's wandering cell.

Leucocytoid Wandering Cell (Sternberg). *See* Myeloblast.

Leucocytosarcoma. *See* lymphosarcoma.

Leucocytosis. *Syn.*: neutrophilia, hypercytosis, hyperleucocytosis polynucleosis, hyperorthocytosis. *Variants*: hypernormocytosis, hyperhypocytosis, hyperhypercytosis, dihypercytosis, isohypercytosis. Conditions in which the total white-cell count is increased.

Leucolysis. *Syn.*: anisohypocytosis.

Leucoma. Correlated term: lymphoma. A tumour made up of cells belonging to the leucocyte series.

Leucomonocytar Plasma-cell. A plasma-cell with nuclear characters as of a lympholeucocyte.

Leucomonocyte. *Syn.*: lympholeucocyte, large mononuclear leucocyte (q.v.), pathological monocyte.

Leucopenia. *Syn.*: hypocytosis, isohypocytosis. *Variants*: hyponeocytosis, hyposkæocytosis, hypo-orthocytosis, anisohypocytosis. Condition in which the total white-cell count is diminished.

Leucopoietic Tissues. Tissues concerned in the formation of white cells in general.

Leucosarcoma Cell. Leucosarcoma cell of Sternberg. *Syn.*: Rieder cell.

Leucosarcoma. *Syn.*: leukæmia sarcomatosa, sarcoleukæmia, Helly's leucocytoid lymphosarcoma.

Leucosarcomatosis. An acute disease which is histologically sarcoma, cytologically a proliferation of large lymphoid leucocytes (lymphoidocytes) (Sternberg).

Leucothrombin. A substance derived from the leucocytes, which unites with thrombokinase.

Leukæmia. A malignant primary hyperplasia of the hæmopoietic tissues clinically associated with blood changes of specific type. *Syn.*: status leukæminicus.

Leukæmic Lymphosarcomatosis. *See* Lymphosarcoma.

Leukæmia Carcinomatosa. *See* Leucosarcoma.

Leukæmia Correlations.

Myelogenic leukæmia, myelæmia (Ehrlich)	lymphatic leukæmia, lymphæmia
Myelocyte leukæmia (Walz) ..	lymphocyte leukæmia
Mixed-cell leukæmia (Pappenheim, Grawitz)	lymphoid leukæmia
Poikilocyte leukæmia (Löwit) ..	homoiocyte leukæmia
Bone-marrow leukæmia (Lazarus) ..	lymphatic leukæmia
Lieno-medullary leukæmia of older authors	lymphatic leukæmia of older authors

Intermediate form = lymphoid-cell leukæmia of Wolff.

Leukanæmia. A variant of the leukæmic process wherein the virus causes cytoplastic action + hæmotoxic hæmorrhagic change; or, it may be described as a hæmotoxic process in which the hæmotoxic virus causes lymphoblastic or leucoblastic reaction just as with other infections and intoxications, but passes on to hyperplasia. Hypermetaplastic anæmia; hæmointoxication; metahyperplastic infection + anæmia; myeloleukæmia associated with pernicious anæmia.

Leukine (Schneider). *Syn.*: endolysin (Petterson). A moderately thermostable bactericidal substance present in leucocyte extract.

Linin. An oxyphilic material of thread-like form which joins the nodes of the nuclear network.

Lipoferous Granules. (Ciaccio). *Syn.*: sudanophile granules.

Lipoferous Leucocyte. (Ciaccio). Leucocyte containing granules stainable with Sudan.

Lymphadenoid Aleukæmia. *See* Pseudoleukæmia.

Lymphadenoid Cell. A cell derived from a lymphocyte-forming tissue.

Lymphadenoid Leucocyte. A leucocyte derived from a lymphocyte-forming tissue.

Lymphadenoid Tissue-cell. *See* Lymphocyte.

Lymphadenomatosis is aleukæmic or leukæmic. *Syn.*: lymphadeny, lymphadenosis (Schridde); lymphocytomatosis (micro-, macro-), each of the latter is follicular or diffuse.

Lymphatic. *Syn.*: amyeloic. Pertaining to the lymphocyte series of cells.

Lymphatic Clasmatocyte. *Syn.*: fixed endothelial cell. *See* endothelial cell.

Lymphatic Lymphocyte. *See* Lymphocyte.

Lymphatic Monocyte. *Syn.*: agranuloplastic monocyte of normal blood. A cell derived from the interfollicular tissue of glands, and lying in normal pulpar tissue.

Lymphatomyelogenic Lymphocyte. *See* Plasma-cell.
Lympherythroblast. *See* Erythroblast.
Lympherythrocyte. *Syn.*: lymphoid erythrocyte; anerythrocyte; "hypoplastic monster." A red cell without hæmoglobin or nucleus.
Lymphoblast. *See* Myeloblast.
Lymphoblast (Naegeli). *Syn.*: gigantolymphocyte, mesolymphocyte.
Lymphoblastic Macrolymphocyte. *See* Lymphoidocyte.
Lymphocerastism. The process of formation of lymphoid cells.
Lymphocyte. *Syn.*: blood-mature lymphocyte, endothelial micromonocyte (Patella), leucocytoid lymphocyte, lymphadenoid-tissue cell, lymphatic lymphocyte, mature lymphocyte, merozooiform reversible product of proliferation (Pappenheim), microcyte (Schäfer), microlymphocyte, micromyeloblast of Naegeli, permanent lymphocyte, sessile cell of lymphadenoid tissue, small lymphocyte. *See* also Histiogenic lymphocyte.
Lymphocyte (Weidenreich). *Syn.*: erythroblastic erythrogonia of Weidenreich, large lymphocyte of Maximow.
Lymphocyte of Myeloid Tissue. *Syn.*: pseudolymphocytoid myeloblast of dualists.
Lymphocytiform Microleucoblast. *See* Histiogenic lymphocyte.
Lymphocytoblast (Zoja). The parent cell of lymphocytes.
Lymphocytoid Cell. A lymphocyte-like cell with round nucleus, nucleoli, and strongly basophile cytoplasm.
Lymphocytoid Lymphoidocyte. *Syn.*: pseudolymphocyte, myeloblast, myelolymphocyte, lymphoidocyte.
Lymphocytoid Monocyte. *See* Monocyte.
Lymphocytoid Plasma Cell. A lymphocytoid cell which has become plasmoid.
Lymphocytomatosis. *Syn.*: lymphadenomatosis.
Lymphoid. *Syn.*: lymphocytar myeloblastic cell. *See* Lymphoid cell.
Lymphoid Ancestor of Granulocyte. *See* Lymphoidocyte.
Lymphoid Bone-marrow Cell. *See* Myelolymphocyte.
Lymphoid Cell. Any non-granular basophile cell. Includes the following: lymphoidocyte (q.v.), large lymphocyte of Ehrlich, myeloblast and lymphoblast of Naegeli and Schridde, Pappenheim's indifferent lymphomyeloblast, Troje's lymphoid marrow-cell, true lymphocyte, large mononuclear leucocytes, etc.
Lymphoid Erythroblast. *See* Erythroblast; Analogues.
Lymphoid Erythrocyte. *See* Lympherythrocyte.
Lymphoid Gigantohæmoblast. A giant megaloblast without hæmoglobin. Its cytoplasm is absolutely basophile.
Lymphoid Hæmoblast. *See* Erythroblast.
Lymphoididity. Having a lymphoid character.
Lymphoid Leucoblast. *Syn.*: myeloblast, partly differentiated lymphoidocyte.
Lymphoid Leucocyte (Ehrlich). *Syn.*: monocyte, large leucocytoid lymphocyte. (Helly). A trachychromatic lymphocyte.
Lymphoid Leucocyte. (Sternberg). *See* Myeloblast.

Lymphoid Marrow-cell. *Syn.*: blood-plasma cell, irritation cell, large mononuclear cell, phlogocyte, stimulation cell, Türk cell. *See also* Leucoblast.

Lymphoid Myelocyte. *Syn.*: lymphomyelocyte; leucoblast with myelocyte nucleus.

Lymphoidocytar(-oid) Plasma-cell. A plasma-cell possessing the nuclear characters of a lymphoidocyte.

Lymphoidocyte. The following synonyms are to be found in the literature :—

Autoparenchymatous proliferating myeloid parent cell.
Basophile mononuclear.
Basophile myelocyte (Dominici).
Benda's lymphogonia.
Cellule médullaire of Cornil.
Cellule médullaire incolore of Engel.
Cornil-Müller non-granular marrow-cell.
Endothelioid lymphocyte (Patella).
Endothelioid macrophage (Metchnikoff).
Erythroblastic erythrogonia.
Fleming's germ-centre cell.
Germ-centre cell of Flemming.
Giant lymphocyte.
Gonocyte (Pappenheim).
Granuloblast.
Grawitz immature cell.
Hæmatogonia.
Hæmogonocyte.
Hæmocytoblast (Zoja).
Hæmomacrophage (Metchnikoff).
Homogeneous uninucleate cell (Schleip).
Hyperplastic lymphocyte.
Hypertrophic lymphocyte.
Immature cell of Grawitz.
Indifferent cell.
Indifferent lymphoid cell (Michaelis).
Indifferent lymphoid primitive cell (Wolff).
Indifferent lymphomyeloblast (Pappenheim).
Indifferent marrow-cell of Troje.
Indifferent mesenchymatic parent cell.
Indifferent parent cell.
Large myelolymphocyte.
Leucoblast.
Leucocyte mother cell.
Leucosarcoma cell (Sternberg).
Lymphadenoid spleen pulp cell.
Lymphoblast (Naegeli).
Lymphoblastic macrolymphocyte.

Lymphoidocyte. Synonyms (*continued.*) :—

Lymphocyte of Weidenreich.
Lymphocytogonia.
Lymphogonia (Benda, K. Ziegler).
Lymphoid ancestor of granulocyte.
Lymphoid cell (Türk).
Lymphoid marrow-cell (Troje).
Lymphoid primitive cell (Wolff).
Lympholeucoblast.
Lymphomacrophage (Metchnikoff).
Lymphomyeloblast.
Macrolymphocyte.
Marchand's leucocytoid wandering cell.
Marrow-cell (Troje).
Megakaryocyte (Maximow).
Megalymphocyte.
Metchnikoff macrophage.
Mother cell.
Myeloblast (Schridde, Naegeli).
Myelogonia (Benda, Aubertin).
Myeloid large lymphocyte.
Myelo-macrolymphocyte.
Multivalent lymphomyeloblastic parent cell.
Naegeli's lymphoblast ; myeloblast.
Non-granular marrow-cell.
Parenchymal cell of hæmopoietic tissue.
Parent cell.
Patella's endothelioid lymphocyte.
Perivenous endothelial cell.
Perivenous perithelial cell.
Polyeidocyte (Darier).
Primary wandering cell of Saxer.
Primeval cell.
Primitive cell.
Primitive lymphocyte.
Primitive lymphoid cell.
Primordial cell.
Proliferating germ-centre cell.
Proliferating lymphoblast.
Pseudo-eosinophile myelocyte (Maximow).
Schleip's homogeneous uninucleate cell.
Splenoblastic macrolymphocyte.
Splenocytar monocyte.
Sternberg's leucosarcoma cell.
Troje's marrow-cell.
True eosinophile myelocyte.
True parenchymal cell.

Türk lymphoid cell.
Wolff's lymphoid primitive cell.

Lymphoidoma (la Roy). A tumour resulting from the proliferation of lymphoid elements. Clinically like sarcoma.

Lympholeukæmia. A disease in which there is marked leucocytosis, the lymphocytes being increased; atypical or ancestral forms occur as well.

Lympholeucoblast. *Syn.*: immature differentiated lympholeucoblastic large primitive cell; partly differentiated large lymphocytic myeloblast; and all the terms given under lymphoidocyte.

Lympholeucocytar(-oid) Monocyte. *See* Monocyte.

Lympholeucocyte (Coie). Analogues: myelomonocyte, monocytoid leucoblast, pathological monocyte, K. Ziegler's myeloblast. *See* Large mononuclear leucocyte.

Lymphomonocytar Plasma-cell. A plasma-cell originating in a large mononuclear leucocyte.

Lymphomegaloblast. A megaloblast whose cell-body is devoid of hæmoglobin.

Lymphomonocyte. *See* Monocyte, splenocyte, large mononuclear leucocyte.

Lymphomyelocyte. *Syn.*: lymphoid myelocyte, leucoblast with myelocyte nucleus.

Lymphopathy. (1) Disease of the lymphopoietic tissues. (2) Having a morbid action on the lymphatic tissues.

Lymphoplasmia. Applied to red cells to express total absence of hæmoglobin.

Lymphoplasm. *Syn.*: spongioplasm.

Lymphopotential. Propensity for developing along lymphoid lines. Correlated terms: myelopotential, leucopotential, hæmopotential.

Lymphosarcoma. *Syn.*: leucocytosarcoma; leucocytoblastoma; leukæmic lymphosarcomatosis; leukæmia on a sarcomatous basis; generalized aleukæmic Kundrat's lymphosarcomatosis; sarcoleukæmia, sarcoid variant of parenchymatous lymphocytoma formation; aleukæmic lymphosarcomatosis.

Lymphotaxis. Having the power of attracting or repelling lymphocytes.

Macrocyte. *See* Large mononuclear leucocyte. Also, more familiarly, applied to a large specimen of a red cell.

Macrocytar Hyperchromia. *Syn.*: hyperchromatic macrocytosis. A state in which the blood contains unduly large red cells with relative abundance of hæmoglobin.

Macroerythroblast. *See* Macronormoblast.

Macroleucoblast. A leucoblast of unduly large size.

Macroleucoblastic Plasma-cell. A plasma-cell derived from a macroleucoblast.

Macrolymphocytar(-oid) Lymphoblastic Plasma-cell. A plasma-cell derived from a macrolymphoblast.

Macrolymphocyte. *See* Lymphoidocyte.

Macrolymphocytogenic. Giving rise to a macrolymphocyte.
Macrolymphoid. *Syn.*: macrolymphocytar myeloblastic.
Macromegaloblast. A megaloblast of unduly large size.
Macromonocyte. A monocyte of unduly large size.
Macronormoblast, Macronormochromoblast. *Syn.*: Maximow's megaloblast; macroerythroblast. A cell derived by mitosis from a mesolymphoidocyte.
Macropromyelocyte. A promyelocyte derived from a macro- instead of a micro-lymphoidocyte.
Malignant Lymphogranulomatosis. *Syn.*: multiple granulolymphadenomatosis. Hodgkin's disease.
Marchand's Wandering Cell. *Syn.*: adventitial cell, cellule rhagiocrine, clasmatocyte, immature lymphoblastic parenchymal cell, immature leucoblastic parenchymal cell, mast cell, primary wandering cell of Saxer, primitive leucocytoid wandering cell of Marchand, pyrrhol cell.
Marrow Lymph Gland. Myeloid type of hæmolymphgland.
Marschalko's Lymphocytoid Cell. *See* Plasma-cell.
Marschalko's Plasma-cell. *See* Plasma-cell.
Mast Cell. *Syn.*: clasmatocyte (Schridde).
Mast Lymphocyte
Mast Lymphoidocyte } Cells containing mast-cell granules.
Mast Myelocyte
Maturatio Antecedens Nuclei. Where maturation is relatively far advanced along ontogenetic lines; the cell as a whole remains phylogenetically immature.
Maturatio Præcox Nuclei. Undue ontogenetic maturation.
Mature Erythroblast. A non-mammalian erythrocyte with a permanent rod-like nucleus. Also inadvisedly applied to the mammalian non-nucleate erythrocyte.
Mature Lymphocyte. *See* Leucocytoid lymphocyte, lymphocyte.
Mature Monocyte. Adult form of large mononuclear leucocyte present in the blood-stream.
Maximow's Megaloblast. *Syn.*: macronormoblast; mesoerythroblast.
Medullary Pseudoleukæmia. *Syn.*: latent leukæmia, pseudoleukæmia.
Megaloblast. *Syn.*: hématie primordiale (Jolly), primary erythroblast, metrocyte of first generation (Engel). *See* Analogues.
Megakaryocyte. *Syn.*: myeloplax (Robin).
Megalopathy. A morbid state of the bone-marrow in which megaloblasts appear in the blood.
Merozoitiform Reversible Product of Proliferation. *See* Lymphocyte.
Mesenchyme Cell. *See* Angioblast.
Mesocyte. *Syn.*: mesolymphocyte.
Mesoerythroblast. *Syn.*: macronormoblast; Maximow's megaloblast.
Mesoleucoblast. A leucoblast of middle size.
Mesolymphocytoid Plasma-cell. *Syn.*: mesolymphocytar irritation cell.
Mesolymphocytoid Irritation-cell. *See* preceding.
Mesolymphocyte. *Syn.*: lymphoblast (Naegeli); gigantolymphocyte.

Mesolymphoidocyte. A lymphoidocyte of middle size.

Mesomicromyelolymphocyte. A redundance of terms, to express a secondary generation of myelolymphocyte.

Mesonormoblast. A normoblast of middle size.

Metabasophile Granules. Granules which stain violet with eosin-orange-toluidine blue.

Metachromatin. The general basophile constituent of nuclear chromatin which has an affinity for methyl green (Pappenheim).

Metahyperplasia. Hyperplasia complicated by simultaneous metaplasia.

Metakinesis. The process of separation of chromosomes at the height of mitosis.

Metamyelocyte. *See* Analogues.

Metamyelocytoid. A cell like a metamyelocyte.

Metaphase. The stage in division of the nucleus at the moment of division of the chromosomes.

Metaplasia. Excessive proliferation of cells which normally do not play the chief part in the histology and function of the corresponding organ. Correlated term: metahyperplasia. *See* substitutive metaplasia.

Metathrombin. *Syn.*: metazyme (Fuld), β-prothrombin (Morawitz). A substance resulting from fibrin ferment during the process of contraction of blood-clot. It is inactive.

Metazyme. *See* preceding.

Methylgreenophobic. Inability to stain with methyl green.

Metrocyte of First Generation. *Syn.*: primordial erythroblast. *See* Megaloblast in text.

Metrocyte of Second Generation. *Syn.*: secondary erythroblast. *See* Megaloblast in text.

Metrocyte. *Syn.*: premegaloblast (C. P. Jones), orthochromatic megaloblast of embryonic blood-formation.

Metchnikoff's Endothelial Macrophage. *Syn.*: first generation of lymphoidocyte. *See* Marchand's wandering cell.

Metchnikoff's Microphage. Polynuclear leucocyte, pulpar cell.

Microcyte. (*a*) A small red cell; (*b*) A lymphocyte (Schäfer).

Microleucoblast. *See* Histiogenic lymphocyte, myelolymphocyte, eosinoblast, micromyeloblast.

Microleucoblastic Plasma-cell. A plasma cell having the fundamental characters of a microleucoblast.

Microlymphocyte. A more precise description of the true lymphocyte (q.v.).

Microlymphoidocytar Myelolymphocytic Leukæmia. A redundance of terms. Leukæmia with preponderance of microlymphoidocytes in the blood.

Microlymphoidocyte. *Syn.*: micromyeloblast, myelolymphocyte (q.v.). A daughter lymphoidocyte.

Micromegaloblast. A daughter megaloblast.

Micromyeloblast. *See* Histiogenic lymphocyte, myelolymphocyte.

Micromyelocyte. A myelocyte daughter cell.

Micromyelolymphocyte. *See* leukoblast.

Microphage. (Metchnikoff). *See under* Metchnikoff.

Micropoikilocyte. A small poikilocyte. A good sign in pernicious anæmia.

Micropromyelocyte. A daughter cell of a promyelocyte.

Microsomes. (Hanstein). *See* Cell granule.

Microsplenocyte. *Syn.*: leucocytoid lymphocyte.

Mitochondria. *Syn.*: chrondrosome, chondroconta, Schridde granule, chromidia (according to some). Cell granules which tend to form fibrillæ, and are stainable with ease.

Mitochrome. A longitudinal fold observed in the nucleus of spindle cells.

Monochromatophile. *Syn.*: orthochromatic. Opposite of metachromatism.

Monocyte. A dual term to describe certain cell-forms: a senile form of large lymphoblastic lymphocyte (Weidenreich, Helly), a senile form of myeloblast or leucoblast (Ziegler), a senile splenocyte. It is representative of a third branch of differentiation of the lymphoidocytar parent cell (the other two being the lymphocyte and the neutrophile lines of development). Normal monocytes are: lymphatic monocyte (*Syn.*: large mononuclear of normal blood; splenocyte), lymphocytar monocyte, lymphomonocyte, splenocytar monocyte or germ-centre cell, splenomonocyte. Pathological monocytes are: (*a*) Senile lymphoblastic macrolymphocyte; (*b*) The myeloic leucoblast (*see* Leucoblast). *Syn.*: leucoblastic monocyte, myelomonocyte, lympholeucocytar monocyte, ancestor of polynuclear leucocyte, progeny of lymphoidocyte; resting interfollicular cell; spleen-pulp cell.

Monocytoid Large Lymphocyte. *Syn.*: large mononuclear leucocyte of Ehrlich.

Monocytopenia. Diminution of the number of monocytes in the blood.

Monocytosis. *Possible syn.*: myeloblastic leukæmia. Preponderance of monocytes in the blood.

Mononuclear Mammalian Red Blood Corpuscle. *Syn.*: Erythrocyte.

Monophyletism. The doctrine which derives all blood-cells from one ancestor. The two following schemes may be quoted:

Old view (Maximow, Erik Meyer, v. Domarus, Hirschfeld):

Large lymphocyte (= myeloblast + lymphoblast) ⟶ myelocyte
↓ ↓
lymphocyte leucocyte

More modern view:

Lymphoblast or lymphoid cell (not in normal blood).
↙ | ↘
all blood cells

Mother Cell. *Syn.*: brood cell, primordial cell.

Müller's Lymphoid Marrow Cell. *See* Lymphoidocyte.

Multiple Granulolymphadenomatosis. The same as malignant lymphogranulomatosis, which is the most accurate designation for Hodgkin's disease of the Dorothy Reed type.

Myelæmia. *Syn.*: myeloid leukæmia, myeloleukæmia.

Myeloblast. *Closest syn.*: leucoblast. *See also* Lymphoidocyte. The wealth of synonyms is accounted for by the vagueness of the morphology of the cell form originally described, as well as by the fact that the cell is variable in appearance during the course of its normal life. *See* Analogues.

Myeloblast of K. Ziegler is synonymous with Coie's lympholeucocyte, leucomonocyte, or pathological monocyte.

Myelocyte. *Syn.*: mother myelocyte, myeloleucocyte, polymorphocyte (Schäfer), polynuclear leucocyte (some authors, incorrect).

Myelocyte Daughter Cell. *See* Analogues.

Myelocytoblast (Zoja). The parent cell of the myelocyte.

Myelocytosis. The presence of myelocytes in the blood.

Myelogenic. Arising in the bone marrow; giving rise to the myeloid series of cells.

Myelogonia. *Syn.*: orthobasophile mononuclear, basophile myelocyte, leucoblast (q.v.).

Myeloic. Belonging to that series of cells which normally terminates in a neutrophile leucocyte.

Myeloic Granulation (Azur). *Syn.*: pseudo-azur granulation.

Myeloic Leucoblast. *Syn.*: pathological monocyte. A redundance of terms, leucoblast being necessarily myeloic. *See* Leucoblast.

Myeloic Lymphocyte. *See* Histiogenic lymphocyte.

Myeloic Monocyte. *See* Leucoblast.

Myeloic Small Lymphoid Cell. A small lymphoid cell having myeloic potentiality.

Myeloic Splenocytoid Cell. *See* Leucoblast.

Myeloid. Having myelocytar myeloblastic characters or potentialities, and not necessarily situated in the bone marrow (not necessarily " medullary ").

Myeloid Aleukæmia. *See* Pseudoleukæmia.

Myeloid Leukæmia. *See* Myelæmia.

Myeloid Metaplasia. *See* Myeloid transformation.

Myeloid Multiple Myeloma. A form of pseudoleukæmia.

Myeloidocyte. A term applied to the lymphoblast to indicate its morphological resemblance to a myeloblast.

Myeloid Splenocytoid Cell. *See* Leucoblast.

Myeloid Transformation. *Syn.*: extramedullary myeloid tissue formation; heterotopic myeloid tissue formation; extramedullary heterotopic myeloid tissue formation; myeloid metaplasia; myelokinesis. The formation in a non-myeloid tissue of cell-aggregations which tend along the neutrophile line of development.

Myeloleukæmia. A form of leukæmia in which ancestral cells of the myeloid series occur in the blood.

Myelolymphoblast. *See* Lymphoidocyte.

Myelolymphocyte. *Syn.*: lymphocytoid lymphoidocyte, microlymphoidocyte. *See under* Leucoblast.

Myelomacrolymphocyte. *See* Lymphoidocyte.

Myeloma. *Syn.*: lymphadenia ossium (Nothnagel), malignant plasmoma; mollities ossium (Macintyre and Down), multiple primary sarcomatosis of the bone-marrow (Buch), multiple sarcoma of ribs (Spiegelberg), myelogenous pseudoleukæmia (Zahn), primary multiple myelogenic sarcoma (Wieland), sarcomata cranii et medullæ (Grawitz), sarcomatous ostitis (Hammer), senile osteomalacia (Marchand).

Myelometaplastic Stimulus. An agent which excites metaplasia along myeloid lines.

Myelomonocyte. *See* Leucoblast.

Myelopathy. (1) Disease of the myeloid tissue. (2) Having a morbid action on myeloid tissue.

Myelophthisic. Atrophic process in the bone-marrow whereby defective formation of red cells results.

Myeloplastic. Producing myeloid tissue.

Myeloplax (Robin). *See* Megakaryocyte.

Myelopotent, Myelopotential. Having the power of giving rise to cells of the myeloid series.

Myelopotentiality. *See* Myelopotential.

Myelosarcoma. (Sternberg). *Syn.*: sarcomyelomatosis.

Myelosis. *Syn.*: leukæmic myelosis, myeloic leukæmia, leukæmic lymphadenosis.

Myelotorpidity. Sluggish activity of multiplication on the part of the bone-marrow cells.

Myelotoxic Polynuclear. In cases in which the monocytes in the blood are leucoblastic, the polynuclear leucocyte is found to have much darker, denser, and flaky neutrophile granulation.

Myelotoxicosis. A morbid condition caused by the action of a virus on myeloid tissue.

Naegeli's Myeloblast. *Syn.*: Goodall's primitive leucocyte; large lymphoid cell. *See* Leucoblast.

Negative Anæmia. An anæmia shown by the presence of erythroblasts but without diminution of the red cells per cmm. (may even be increased). Probably due to functional derangement of the spleen.

Neocytosis. *Syn.*: skæocytosis, normoneocytosis. Deviation to the left. Appearance of juvenile forms in the blood-stream. *Variants*: hyperneocytosis, normoneocytosis, hyponeocytosis.

Neodualist View.

Parent cell, existing only in embryo

wall of lymphatic vessel	wall of blood-vessel	→ myeloblast
↓	↓	↓
lymphoblast	basophile erythroblast	myelocyte
↓	↓	(true dualism, Helly, sole representative)
lymphocyte	erythrocyte	
↓		
large lymphocyte (Schridde, Ziegler)		

Neometaplasia. A metaplastic process in a tissue culminating in a "neoplasm."

Neoplasia. The process of formation of new growth.

Neoskæocytosis. Deviation to the left. Redundance of terms; neo and skæo are co-equivalent.

Neozyme. Activated metathrombin (by the transient action of decinormal alkali followed by neutralization with acid).

Neutroleukæmia. Leukæmia in which cells with neutrophile granules are conspicuous.

Neutrometachromatophile. Ability to stain another colour with a neutral dye.

Neutrophile Leucocyte. *Syn.*: polynuclear leucocyte, polymorphonuclear leucocyte; polymorphocyte; Neumann's myelocyte.

Neutrophile Promyelocyte. *See* text.

Neutrophilia. Hypercytosis, leucocytosis, polynucleosis.

Neutrotaxic. Having an attractive or repellant action on neutrophile leucocytes.

Normal Large Lymphocyte. *Syn.*: large mononuclear leucocyte.

Normal Monocyte. *See* Monocyte.

Normoblast. *See* text. *Syn.*: hæmonormoblast, hæmoblast, erythroblast, erythrogonia (Helly), lymphoid hæmoblast, proerythroblast. *See* Analogues.

Normocytosis. *Syn.*: normo-orthocytosis. The condition in which the number of white cells in the blood is normal.

Normocyte. A normal red cell.

Normoneocytosis. *Syn.*: neocytosis, skæocytosis. The total white count is normal, but there is deviation to the left.

Normonormocytosis. *See* Iso-normocytosis.

Normomorphism. Having a normal shape of form.

Normo-orthocytosis. Total white count increased, cell formula normal. *See* Normocytosis.

Normoplasia. A specific differentiation characteristic of a cell, not exceeding the typical limits of differentiation under physiological conditions (Schridde).

Normoskaeocytosis. Total count normal, immature cells present.

Noxotropic. Having an affinity for a particular noxious agent.

Nuclear Network. *Syn.*: caryomitom.

Nuclear Plastin Body. *Syn.*: caryoplastin, caryogenic plastin.

Nuclear Spherule. *Syn.*: Jolly body.

Nucleoid. *Syn.*: nuclear rests, inclusion-body. (*a*) A precipitation effect of hæmoglobin; (*b*) If basic, a special appearance of the basophile cell membrane. *See* Ladovsky's Nucleoid.

Nucleolin. *Syn.*: pyrenin, plastin. The constituent of nucleoli.

Nucleolus. *See* Plasmosome, caryosome.

-Oid. Suffix to imply similarity of morphology to the cell-type used as prefix.

Oikoid. (Brücke). The supporting substance of red cells.
Oligochromæmia. Diminished content in hæmoglobin.
Ontogenetic. Pertaining to the development of an individual cell. Depends on the formation of paraplasm. *Analogue*: phylogenetic.
Orthobasophile Granule. (Ciaccio). Granules which stain blue-black with eosin-orange-toluidin.
Orthobasophile Mononuclear Cell. *See* Leucoblast.
Orthochromasia. Total loss of basoplasm.
Orthochromatic Erythroblast. *See* Analogues.
Orthochromophile. *Syn.*: ametachromophile. Staining true with a neutral dye.
Orthocytosis. The condition in which only mature cells are present. Variants: normo-, hyper-, hypo-.
Orthoneutrophile. *Syn.*: ametaneutrophile. Staining true with a neutral dye.
Oxycaryoplastin. Oxyphilic plastin substances in the nucleus.
Oxychromatin. *Syn.*: oxyphile oxycaryoplastin. *Example*: oxyphile nucleolus. A substance arising from the basophile parachromatin.
Oxychromiole. Oxyphile granules which enter into the composition of the caryoplasm.
Oxyparaplastin is that form of paraplastin which occurs in the nucleus and in the cytoplasm. It includes (*a*) oxyphile oxychromatin (that part which is in the nucleus), and (*b*) oxyphile oxyplastin (that part in the protoplasm).
Oxyphile. Having affinity for the acid component of a neutral dye mixture.
Oxyphile Intestinal Epithelial Cell. *Syn.*: Paneth cell.
Oxyphile Nucleolus. *Syn.*: oxyphile oxycaryoplastin; oxychromatin.
Oxyphile Oxycaryoplastin. *See* preceding.
Oxyphilia. Signifies replacement of basophile COOH groups in the amphophile plasma-molecule by oxyphile NH_2 side-chains (chromo-receptors).
Oxyplastin. Arises from basophile paraplastin.
Ozonophore (Altmann). Cell granule.

Pachychromatic. Having very coarse chromatin network.
Pachydermia. Applied to a red cell, this term expresses increased resistance of the red cells in anæmia.
Pander's Islands. *Syn.*: Wolff's islands. The primitive formative centres in the embryo for red cells.
Paneth Cell. Oxyphile intestinal epithelial cell.
Parablast (His). *Syn.*: mesenchyme cell, angioblast.
Parachromatic. *Syn.*: caryogenic. *See* Parachromatin.
Parachromatin. *Syn.*: basicaryoplastin, interchromatinic substance, caryoplastin. *Adj.*: Parachromatic.
Parachromatinorrhexis. *Syn.*: basophile punctation (one view). Separation of the parachromatin into fragments.

Parafunctional. Perversion of function.

Paramyeloic, Paramyeloid. A tissue which, usually developing myeloid cells, now develops lymphoid cells.

Paranuclear Body. *See* Lavdovsky's Nucleoid.

Paranuclear Spherule. *Syn.*: archoplasm. In its centre is the centrosome.

Paranucleolus. A small basophile particle attached to the nuclear envelope. Its significance is unknown.

Paranucleus. *Syn.*: chondromitom. A spherical mass formed by the conglomerated fibrillæ derived from mitochondria.

Paraplasia. The analogue of aplasia (*cf.* aplastic anæmia *versus* pernicious anæmia).

Paraplasm. *Syn.*: deuteroplasm. Is the functionating part of the cell-body. *Ex.*: the substance which makes hæmoglobin, the substance which makes granules (oxyphile, neutrophile). Also defined as the non-protoplasmic matter within a cell-body.

Paraplastin. A substance related to parachromatin. It includes the basoparaplastin and the oxyparaplastin. It is sometimes amphobasophile, and sometimes ampho-oxyphile. This and spongioplastin constitute cytoplastin.

Paraplastinoid. Having resemblance to paraplastin.

Parasplenoid. *Cf.* accessory splenic tissue.

Passive. When applied to anæmia is synonymous with aplastic.

Patella's Endothelial Lymphocyte. *See* Endothelial Lymphocyte.

Pathological Leucocytoid Monocyte (Marchand). *See* Leucoblast.

Pathological Monocyte. *See* Lymphoblastic macrolymphocyte, myeloic leucoblast.

Pathological Monocytoid Lympholeucocyte. *See* Leucoblast.

Pathomonocyte. *Syn.*: myelomonocyte, leucoblastic monocyte.

Pathomorphic, Pathomorphism. Abnormal morphology.

Perinuclear Granulation. (Neusser). Dark blue-black granules seen in the nuclear matter of the polynuclear leucocyte with triacid staining. It is regarded as a dye precipitation, because the granules only appear when unfiltered dye solution is used.

Perithelial Cell. *See* Adventitial Cell.

Permanent Lymphocyte. *See* Lymphocyte.

Phanerogenetic. Applied to diseases whose etiology is known.

Phlogocyte. *See* Blood-plasma Cell.

Phlogocytosis. *Syn.*: plasma-cell leucocytosis. A condition in which the blood is rich in Türk irritation cells.

Phyletic. *Syn.*: phylogenetic, phylogenic, pertaining to a sub-kingdom (a phylarch was the chief of a tribe). Genealogical history; evolution of a race or tribe of cells.

Phylogeny. *See* the preceding. The process depends on conversion of paraplasm (which increases also) into oxyplasm. *Analogue*: ontogeny.

Plasma-cells may be classified according to form and according to site. *Syn.*: Hodara-Schridde cell, Krompecher's fibroblast, Marschalko's large lymphocytiform plasma-cell (lymphocytoid cell); Unna's histioid fibroblastic plasma-cell. Any blood-cell may pass into a plasma-cell *See* text.

Plasmacytosis. *Syn.*: plasma-cell leucocytosis. *See* Phlogocytosis.

Plasma Daughter Cell. *Syn.*: lymphocyte (incorrect).

Plasmatic. *See* Analogues.

Plasmatropinogenic. Producing effects on the plasma.

Plasmobasophilia. Basophilia of the cytoplasm.

Plasmodiblast. One of the constituents of the spindle cell according to Eisen. *See* Somosphere.

Plasmolysis. Solution of cytoplasm.

Plasmome (Weisner). Cell granule (q.v.)

Plasmorrhexis. Fragmentation of the cytoplasm. Applied also to macrocytes when they break up into microcytes.

Plasmosome (Arnold). *See* cell-granule. *Syn.*: condensateur (Gurwitch), vacuoles rhagiocrines de Renaut.

Plasmotropic. The action of a poison on the blood by altering the hæmoglobin (into methæmogoblin).

Plasmozyme. *Syn.*: thrombogen.

Plastin. *See* Pyrenin, Nucleolin.

Plastin Bodies, -Substances. All bodies which have no ability to take up methyl green. They contain phosphorus or protein-lecithids. They include (1) spongioplastin, which is only in the cytoplasm; (2) paraplastin, which is found both in the nucleus and in the cytoplasm: (*a*) basiparaplastin (q.v.), (*b*) oxyparaplastin (q.v.); (3) basiparachromatin, oxychromatin, oxyplastin, nucleolin are present in the nucleolus and not in the cytoplasm.

Polychromasia. *Syn.*: anæmic degeneration of red cell (Ehrlich). A condition in which oxyphile hæmoglobin and basoplasm exist side by side.

Polychromatic Erythroblast. *Syn.*: Polychromoblast.

Polychromatic Erythrocyte. *Syn.*: polychromocyte. A red cell staining polychromatically.

Polychromoblast. *See* Polychromatic Erythroblast, Analogues.

Polychromocyte. *See* Polychromatic erythrocyte.

Polycythaemia. *Syn.*: erythræmia; erythrocytosis; hyperglobulism; polycythæmia rubra megalosplenica; polyglobulism; Vaquez' disease (1892).

Polyeidocyte (Darier). Large mononucleate cell in normal spleen.

Polyglobulism. *See* Polycythæmia.

Polymorphocyte (Schäfer). *Syn.*: polynuclear leucocyte (q.v.)

Polymorphonuclear Leucocyte. *Syn.*: ε-polynuclear.

Polynuclear(ity). *Syn.*: polysegmented, hyperpolymorphous, polymerization.

Polynuclear Leucocyte. *See* text; Neutrophile leucocyte; Analogues.

Polynucleosis. *See* Leucocytosis.

Polyphyletic. Relating to several orders of cells.

Polyphyletic Unitarianism. A doctrine accepting the existence of more or less indirect relationships and genetic interconnections between various orders of blood-cells. The transitions so resulting are gradual.

Polyplasmia. An increase of plasma in the blood, such as occurs in chlorosis.

Postpycnotic. Disappearance of the nucleus subsequently to the stage of pycnosis in the red cell (chromatolysis).

Postpycnotic Chromatolysis. *Ex.*: Jolly body.

Pre-agonic Staining. *Syn.*: vital staining.

Premegaloblast. *See* Metrocyte.

Primary Saxer Wandering Cell. *See* Lymphoidocyte.

Primary Erythroblast. (Schridde). *Syn.*: Ehrlich's megaloblast.

Primary Wandering Cell of Saxer. *See* Marchand's Wandering Cell.

Primitive Leucocytoid Wandering Cell of Marchand. *See* preceding.

Primordial Erythroblast. *Syn.*: (Ehrlich's) megaloblast.

Primordial Red Cell. *See* preceding.

Prochromatin. The special azurophile constituent of nuclear chromatin met with in protista.

Proeosinophile Myeloblast (Zoja). The parent cell of the eosinophile before α-granules have appeared.

Proerythroblast. (Ferrata, Zoja, Dantschakoff). *Syn.*: hæmoblast. *See* Erythroblast .

Proleukæmia. *Syn.*: leukanæmia.

Prolymphocyte.* A cell between a lymphoidocyte and the mature lymphocyte.

Promast Cell.* The predecessor of the mast cell.

Promegaloblast.* The intermediate stage between lymphoidocyte and megaloblast. Its nucleus contains nucleoli and has a radial structure. *Analogue*: myeloblast.

Promyelocyte.* A granular leucoblast. *Syn.*: granular pseudolymphocyte. *See* Analogues.

Proneutrophile Myeloblast (Zoja).* The parent cell of the neutrophile before its granules have appeared.

Prosoplasia. A differentiation exceeding beyond the phase of differentiation normal for physiological conditions. *See* Anaplasia. *Adj.* prosoplastic.

Prothrombin. (Peckelharing). *Syn.*: α-proferment (Morawitz), α-prothrombin. Consists of thrombogen plus thrombokinase.

Protoerythrocyte. *See* Protometrocyte.

Protohæmoblast. (Malassez). The next generation to the primordial cell (Jolly). *See* Erythroblast, Analogues.

Protoleucocyte. *See* Protometrocyte.

Protomeres (Heidenhain). A term applied to certain cell granules.

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* The prefix *pre* may be used, if preferred to *pro*.

Protometrocyte (Ciaccio). The parent of the hæmoglobin and of the leucocyte series. It gives rise to (*a*) protoleucocyte with amblychromatic nucleus, (*b*) protoerythrocyte with trachychromatic nucleus.

Protozoophage. A cell which ingests protozoa.

Pseudo-azur Granulation. *Syn.*: myeloic granulation.

Pseudo-leukæmia. *Syn.*: 1, aleukæmic hyperplasia in the medullary tissue, 2, aleukæmic malignant lymphadenoid lymphadenoma; 3, aplastic leukæmia; 4, latent leukæmia; 5, lymphadenoid aleukæmia; 6, medullary hyperplastic pseudoleukæmia; 7, myeloid aleukæmia; 8, myeloid multiple myeloma: numbers 2, 5, 6, 7, 8 are synonymous with Cohnheim's pseudoleukæmia.

Pseudolymphocyte. *See* Histiogenic Lymphocyte.

Pseudolymphocyte (Patella). *Syn.*: small leucocytoid lymphocyte (Pappenheim); broad-bodied endothelioid small lymphocyte.

Pseudolymphocytoid Myeloblast of dualists = lymphocyte of myeloid tissue.

Pseudo-nucleolus. *Syn.*: chromatin nodal points; chromatin intersections.

Pseudo-oxyplasmatic. The oxyplasmic effect produced by over-staining with acid dyes.

Pseudo-structure. A term applied to the filar mass.

Pulpar Cell. *Syn.*: Metchnikoff's macrophage. The specific cell constituent of the spleen pulp.

Punctate Basophilia. *Syn.*: parachromatin rest; basophile punctation.

Pycnotic. The clumping of the nucleus associated with increased intensity of staining. *See* Analogues.

Pyrenin. Another name for plasmosome. Nucleolar matter. *Syn.*: pyrenoid substance.

Pyrenoid. *Syn.*: Meirowsky's pyrenin-plastin. Bodies having the same chemical and physical features as pyrenin. *See* Plastin bodies.

Pyrrhol Cell. *See* Marchand's Wandering Cell.

Rachitic Splenomegaly. *Syn.*: anæmia pseudoleukæmica infantum.

Red Cell. *Syn.*: erythrocyte (q.v.).

Resting Interfollicular Cell. *Syn.*: splenocyte, spleen pulp cell; normal monocyte; lymphomonocyte; splenoid cell.

Reticular Substance (of Cesaris-Demel). *Syn.*: α-substance; filar mass; Rosin-Demel reticular substance; substantia reticulofilamentosa; vital stainable reticular substance; hématies granuleuses; pseudo-structure; vital punctation.

Retroplasia. The conversion of a tissue into one further back in the stage of development.

Reversionary Atrophy. The same as anaplasia.

Rhagiocrine. A clasmatocyte; a "resting" wandering cell (Maximow).

Rieder Cell. The same as leucosarcoma cell.

Rieder Lymphoidocyte. One having a deeply lobed trachychromatic nucleus.

Sarcoid Variant of Parenchymatous Lymphocytoma Formation. *See* Lymphosarcoma.

Sarcoleukæmia. *Syn.*: lymphosarcoma, leucosarcoma, leukæmia sarcomatosa.

Sarcolymphadenia. Enlargement of the lymphatic glands, of sarcomatous character.

Sarcomyelomatosis. Myelosarcoma of Sternberg.

Sarcomyelosis. Multiple myeloma associated with sarcomatous change.

Schistocyte. A fragmented erythrocyte. A burst cell whose granules are scattered some distance away. Amorphous hæmoglobin.

Schizocytosis. The formation of microcytes out of macrocytes or megalocytes or gigantocytes. Fragments of red cells met with in the blood-film.

Schleip's Hypertrophic Lymphocyte. *See* Endothelial lymphocyte (Patella).

Schmauch's Endoglobar Body. *See* Heinz Body (sometimes synonymous).

Schridde-Hodara Plasma-cell. *Syn.*: pseudoplasma cell, hæmatogenic plasma-cell. *See* text.

Schridde Granules. *See* Mitochondria.

Schridde's Lymphoblast. *Syn.*: endothelioid lympholeucocyte. A large mononuclear cell with vesicular nucleus rich in chromatin.

Schridde's Myeloblast. Differs from the preceding in the structure of the nucleus, the network being delicate.

Schüffner Punctation. Seen in red cells in cases of tertian malaria.

Secondary Erythroblast. Occurs in two forms: (*a*) of small size, (*b*) of large size. The latter is regarded by French writers as identical with the primitive erythroblast.

Senile Lymphocyte. *Syn.*: hyaline leucocyte; leucocytoid lymphocyte; indent-nucleate leucocytoid lymphocyte; Patella's endothelial lymphocyte; Schleip's hypertrophic lymphocyte.

Sessile Cell of Lymphadenoid Tissue. *See* Histiogenic lymphocyte; lymphocyte.

Shadow Corpuscle. *Syn.*: Ghost corpuscle. Applied to dying red cells, lymphocytes and other leucocytes.

Skæocytosis. *Syn.*: neocytosis. The same as deviation to the left.

Small Leucocytoid Lymphocyte. *Syn.*: Patella's pseudo-lymphocyte. *See also* Senile Lymphocyte.

Small Lymphocyte. *Syn.*: microlymphocyte. *See also* Lymphocyte.

Small Lymphocytoid Cell. A cell having morphological characters resembling those of a small lymphocyte, but not necessarily identical. *See* Histiogenic Lymphocyte.

Somosphere (Eisen). One of the three constituents of the archosoma which enters into the structure of a spindle cell. The other two constituents are the centrosphere and the centrosome.

Soterocyte. *See* Blood-platelet.

Spermagonia. The parent cell of the spermatozoon.

Spilling's Transitional Cell. A form of transitional cell.

Spirem. The threads of chromatin which appear during anaphase.
Spleen-Pulp Cell. *See* Resting interfollicular cell.
Splenoblast. The mother cell of the large mononuclear leucocyte.
Splenoblastic Microlymphocyte. *See* Lymphoidocyte.
Splenocleisis. Exciting the formation of fibrous tissue round the spleen by wrapping it in iodoform gauze.
Splenocyte. *See* Resting Interfollicular Cell.
Splenoid Cell. *See* preceding.
Splenoidocyte. *Syn.*: normal monocyte; splenomonocyte; splenoid monocyte.
Splenomonocyte. *See* preceding, and Monocyte.
Splenopathy,-ic, having a morbid action on the spleen: diseased condition of the spleen.
Spongioplasm. *Syn.*: cytomitom, lymphoplasm. The supporting part of the cytoplasm. It consists of a globulin lecithid.
Spongioplastin. *See* Cytoplastin.
Status Leukæminicus. *See* Leukæmia.
Stimulation Cell. *See* Blood-plasma Cell.
Stromatocrater (Dekhuyzen). The concavity of the red cell, on the view that it has an inverted bell-form.
Subleukæmic. *Syn.*: aplastic leukæmia, subleukæmic diffuse bone-marrow hyperplasia. A leukæmic state in which the outpour of abnormal cells is less than their production. A disease in which the blood-forming organs show leukæmic changes, the blood-film contains ancestral cell types, and yet the number of leucocytes is not increased.
Subleukæmic Diffuse Bone-marrow Hyperplasia. *Syn.*: latent leukæmia.
Sublymphæmia. A condition in which the total number of white cells is not increased, but there is an enormous increase in the number of lymphocytes, and the blood-forming tissues show leukæmic change.
Submyelæmic. Analogous to the preceding. The cell increase lies with the myelocytes.
Substantia Metachromatico-granularis. *Syn.*: Heinz body.
Substantia Reticulo-filamentosa. *See* Reticular substance.
Substitutive Metaplasia. *Analogue*: autoparenchymatous metaplasia (q.v.). *Syn.*: false metaplasia, pseudometaplasia.
Sudanophile Granule. Ciaccio's lipoferous granule of the leucocyte.
Sympathicotropic. Having special affinity for the sympathetic nerve substance.
Sympexis. The deposition of red cells according to the laws of surface tension (M. Heidenhain).

Thrombin. *Syn.*: Fuld's holozyme. The material which turns fibrinogen into fibrin.
Thromboblast (Dantschakoff). A small basophile cell very similar to a small lymphocyte, with round nucleus. Differentiates into a thrombocyte with assumption of an oval shape by the nucleus.

Thrombocyte. (Dekhuyzen). *Syn.*: spindle cell, hæmatoblast (Hayem).

Thromogen. *Syn.*: Plasmozyme. A substance present in the circulating plasma which, with thrombokinase and lime salts, forms thrombin.

Thrombokinase. *Syn.*: cytozyme. Activator of thrombogen, supplied by the platelets and leucocytes.

Thymocyte. A term introduced to indicate that the lymphocytoid cell of the thymus gland is not a true lymphocyte in function.

Tigroid. A substance met with in nerve-cell cytoplasm.

Trachychromatic. Applied to nuclei whose chromatin has the property of staining very deeply with nuclear dyes.

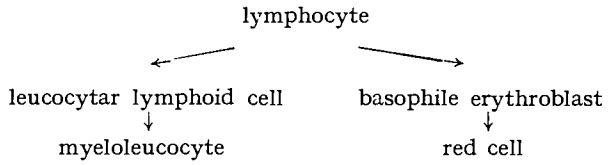
Transitional Cell. A cell so named because it was once believed to be a transition form between the large mononuclear and the polynuclear leucocyte. *See* Monocyte.

Troje Lymphoid Marrow-cell. *See* Lymphoidocyte.

Trophospongium. Canaliculi traversing the cell body in some cells, and communicating with the lymph-canaliculi all round. Sometimes they are occupied by processes of connective-tissue cells.

Türk Cell. *See* Blood-plasma cell.

Unitarian View of Hæmogenesis.



According to this, the blood is full of immature cells.

Unna's Plasma-atrophic Lymphocytoid Daughter Plasma Cell. A form of plasma-cell.

Unna's Plasma Cell. Any cell in an inflammatory cell infiltration which has a strongly basophile cytoplasm. It is strictly histioid. *Syn.*: young fibroblast, basoplasmatic fibroblast.

Vacuolar Degeneration of Lymphocytes. The appearance of vacuoles in the cell-body, other than from the occurrence of plasma-cell change.

Vacuoles Rhagiocrines (Renaut). *See* Cell granule.

Vagotropic. Having special action or affinity for the vagus nerve substance.

Vasothrombin. Thrombin derived from the endothelial cells lining the vessels.

Vital Punctation. *Syn.*: filar mass.

Wandering Cell. *See* Marchand's wandering cell.

Weidenreich's Cromatin Dust. A minute Howell-Jolly body.

Winkler-Schultze Oxydase Reaction. The blue colour produced within cells containing oxydase ferment, depending on a synthesis of indophenyl-blue out of the following reagents: (1) 1 per cent α-naphthol containing 1 per cent Na_2CO_3; (2) 1 per cent aqueous dimethylparaphenylenediamine.

$$C_6H_4\begin{cases}NH_2\\N(CH_3)_2\end{cases} + C_{10}H_7OH + O_2 = C_6H_4\begin{cases}(1)N(CH_3)_2\\(4)N=C_{10}H_5OH\end{cases} + 2H_2O.$$

It was regarded at one time as a specific means of differentiating lymphoblasts from myeloblasts.

Wolff's Islands. *Syn.*: Pander's islands.

Wolff's Pseudomast Cell. Leucocyte containing spermatozoon heads, which stain metachromatically.

Xanthophile. Having affinity for the orange component of triacid.

Zoja's Hæmocytoblast. *See* Lymphoidocyte.

Zooid (Brücke). Hæmoglobin, which is supposed to have vital properties.

GENERAL INDEX.

Figures in thick type indicate main references.

N.B.—Consult also "GLOSSARY," "INDEX OF DISEASES," "INDEX OF ANIMALS," *and* "INDEX OF AUTHORS" *referred to in this Volume.*

ABERRANT abortive hæmopoiesis, 244, 247
— cells, 136
Absolute leucocytosis, 237
Accessory factories, leucopoiesis, 282
— — lymphopoiesis, 122
— — pulp cell, 168
— spleen, 168
Achroglobins, 92
Acid granules in red cell, 84
Adipose tissue in bone, 197, 198
Adrenal cortex, 244
Adsorptoid function of lymphocytes, 141
Adventitial cell, 250, 273, 274, 279, 306, 317
Age, changes with, in blood cells, 148, 151, 174, 191, 205
Agglutinins in bone-marrow, 52
Aldehyde reaction, 251
Allomorphism, 286
Alterations of resistance, 75
— of shape, 91
— of size, 91 (red cells)
Altmann-Schridde granules, 32, 49, 125, 274
Amidine grouping, 241, 279
Amitosis in blood cells, 128, 136, 151, 177, 181, 214, 229, 256, 268, 271
Amœboid movement of blood cells, 141, 183, 213
— — of megakaryocytes, 49
— — nature of, 221
Amphochromophile myeloblasts in reptiles, 11
Amphochromophilic change, 174
Anaplasia, 14, 245, 257, 310
— discussion of, 17, 38
— expressed graphically, 39
— versus metaplasia, 290
Ancestral memories of cell, 302
Ancestry of plasma cell, 272
Angioblast, 53, 57
Anisocytosis, 92
Anisotonia of serum, 66
Anthrax, eosinophiles in, 255
— spleen in, 299
Anti-auxetics, 192
Anti-bodies, formation of, 86
— in spleen, 192
Antitoxic function of lymphocytes, 154
Aplasia, 100, 104
Area vasculosa, 54
Arginase in lymphoctyes, 142
Arguments relating to dualism, 30
— — existence of primordial cell, 25–29
— — infective theory of leukæmia, 41
— — leukæmia and sarcoma, 42
— — lipoid film over red cell, 72
— — myeloid metaplasia, 301
— — neutrophile granule, 221
— — primordial cell, 27
— — source of eosinophiles, 256
— — unitarianism, 33
(*See also under* THEORIES.)
Artificial production of aplasia in bone-marrow, 107
Astrosphere in blood-cells, 133, 151, 176, 187, 204, 260, 268, 270, 271
Atrophic plasma cell, 283
Atrophy of spleen-follicle, 301
Attraction-sphere in primordial cell, 8
Atypical bone-marrow cells, 212
— forms of blood cells, 20, 131, 209, 212
— — eosinophiles, 209
— — metamyelocytes, 209
— — mother cells, 20
Auer bodies, 9
Autocytolysins, 74
Auto-isolytic substances in blood, 107
Autolytic changes in bone-marrow, 198, 199
— — monocytes, 182
(*See* DEGENERATIVE CHANGES.)
— ferments, 142
— substances, 107
Autoparenchymal metaplasia, 303
Auxetic processes, 241
Azur granules, 32, 143, 176, 178, 181, 185, 204, 206
— — myeloic, 143, 227
— — origin of, 185, 204
Azurophile polychromatophilia, 78
Azurophilia, 186

BACTERIAL action and cytoplasia 291
— substances and neutrophiles, 224
Basement membrane, 25
Basichromatin, 13
Basophile substances in cells, 14
Basophilia, cause of, 274
Basophilic granules in neutrophile, 225
Bastard cells, 212
Beckton granules, 133
Bedside study of anæmia, 106

Bilinogen in urine, 75
Billroth's malignant lymphoma, 310
Birth of large mononuclear leucocyte, 183
— of neutrophile, 208, 212
— of red cell, 65
Blood cell, formula, 4
— — factories, 2, 45, 111, 156, 195
— dust, 98
— in newly born, 109
— in infants, 236
— in various diseases, *see* INDEX TO DISEASES
— platelets, 70, 85
— supply, of bone, 195
— — lymph-node, 113
— — spleen, 119
— tumour cells in, 309
Bone marrow, 105, 254, 278
— — anaplasia, 310
— — as red-cell factory, 45
— — as source of lymphocytes, 112 (footnote), 121
— — — white cells, 195
— — eosinophilia of, 252, 256
— — giant cells, 300
— — hyperplasia, 314
— — in megakaryocytomatosis, 306
— — in erythræmia, 109
— — lymphoid cells of, 112
— — metaplasia, 304, 287
— — of fowls during hunger, 34
— — primitive, 56
— — structure of, 2, 45, 195
Böttcher crystals, 252

CABOT ring bodies, 76, 79, 83
— membranes, 66
Cancer extract and mast cells, 260
— juice, effect on lymphocytes, 153
Capsule body, 70, 85
Carcinoma cells, 145, 186
Caryolysis, 229
Caryorrhexis, 217, 220, 229
Cause of high colour index, 89
Cell constituents of splenic pulp, 161
— counts, anæmia, 92
— — bone marrow, 51
— couples, 137
— formula of tissues, 280, 288, 319
— — abnormal, in birds, 11
— inclusions in primordial cell, 9
— proliferation in testis, 25
Central sinus of lymph gland, 130
Centriole of blood cells, 49, 70, 85, 88, 261
Centrosome, 97, 213, 220
Change in hæmoglobin content, 89
— in staining reaction, 13
Charcot-Leyden crystals, 251
Chart of anæmias, 104
— Arneth's method, 219
— exudate cells, 216
— interrelations between follicle and pulp, 193
— (*See also* SCHEME.)
Chemical characters of blood-platelets, 85
— — cells, 11
— — neutrophiles, 222
— composition of lymph-node, 142
Chemistry of eosinophile granule, 251
— erythroblast, 62
— lymphocyte, 141
— phenolphilic substance, 166
— large mononuclear leucocyte, 184
— normoblast, 64
— red cell, 72
Chemotaxis, 31, 221
Chondriosome, 145
Chromatin, metaplasia of, 153
Chromatolysis, 65
Chromidial bodies, 9
— fragments, 79
Chromidium, 85
Chromolinin granules, 83
Chromosomes, 13
Ciliated cells in spleen, 161
Clasmatocyte, 261, 264, 267, 274, 277, 278, 303
Classification of anæmias, 101, 105
— blood-cells, 5
— large mononuclear cells, 179
— lymphoid elements of blood-stream, 131
— lymphosarcoma, 310
— myeloic cells, 132
— neutrophiles, 217
— plasma cells, 267
— system diseases of blood-forming organs, 318
— (*See also* TABLE.)
Clinical diagnosis from study of blood-films, 233, 309
— evidences of regeneration, 106
— significance of punctate basophilia, 81
— study of anæmia, 106
Colloidal action in metaplasia, 287
— character of red cell, 72
— — hyperchromia, 89
Colloids in spleen, 160
Comparative cytology, 9, 92, 94, 145, 186, 257, 265, 276
(*See also* SPECIAL INDEX OF REFERENCES TO ANIMALS, or under appropriate blood-cell.)

Comparison of Schridde with azur granule, 144
Connective-tissue spaces, 150
Contour of cell (*see* MORPHOLOGY)
Contrast between leukæmia and leucocytosis 240
— (*See also* TABLE)

Couples of cells, 137
Cryptogenetic agents, 307
— infections, 291
Curvilinear character of cytoplasia, 153
Cyclical character of progress of hæmopoiesis 14
— change in lymph follicle, 115
Cytology, laws of, 18
Cytolysis, 132
Cytolytic forms, 24
Cytometaplasia, 37, 148, 152, 282
Cytometaplastic processes, 30
Cytoplasias, 30, 37, 148, 152, 153, 188, 191, 233, 278, 284
— curvilinear character of, 153

DARK-GROUND illumination, eosinophile, 251
— — neutrophile, 214
— — red cell, 72, 82, 145
Date of formation of blood cells, 55, 59
— — bone-marrow, 56 (footnote)
Daughter myelocyte, 283
— plasma cell, 267
Death of leucocyte, 228, 229
— of primordial cell, 23
Defects of ordinary cell-count, 5
Degenerate spermatozoa, 253
Degenerative changes in lymphocyte, 264
— — bone-marrow, 199
— — myelocyte, 208
— — plasma cell, 276
— — red cell, 73
— — spleen, 103
— character of sudanophile leucocyte, 227
— — neutrophile granule, 225
— forms of large mononuclear leucocyte, 179
— — lymphocyte, 137
— — plasma cell, 268
— — pulpar cell, 190
Demilune body, 88
Development of lymph nodes, 130
Deviation to the left, 106, 197, 217, 218, 238
Diazin green, 70
Difference between hæmopoietic tissue and organ, 6 (footnote)
Differential diagnosis of leucoblast, 205
— — lymphocyte, 135–137
— — lymphoidocyte, 20
— — megakaryocyte, 49
— — monocyte, 175, 176, 178, **179**
— — neutrophile, 229
— — normoblast, 64
— — plasma cell, 272, 269
— — polychromatophilia, 78
— — transitional cell, 178
Differentiation, discussion of, 16
— signs of, 18
Digestion lymphocytosis, 142
— lymph follicle during, 115
— Malpighian body during, 120
— spleen during, 161
— sudanophile leucocyte in, 227
— leucocytosis, 140, 235
Diplococci, action on leucocytes, 229
Discoplasm, 82
Discussion of cell-descent, 38
Drugs, effects, 78, 79, 109, 147, 169, 236
— — anæsthetics, 236
— — antitoxic sera, 236
— — atropine, 239
— — auxetics, 241
— — benzol, 149, 239
— — blood poisons, 207
— — camphor, 236
— — cinnamate of soda, 236
— — colchicin, 38, 260
— — collargol, 236
— — digitalis, 236
— — digitoxin, 237
— — ethereal oils, 236
— — hydatid fluid, 253
— — hydroxylamine, 221
— — mesothorium, 104
— — nitrobenzol, 38
Drugs, effects, nucleinic acid, 236
— — organ extracts, 236
— — peptone, 239
— — pilocarpine, 253
— — potassium chlorate, 236
— — pyrodin, 260
— — pyrogallol, 236
— — quinine, 236, 239
— — phenylhydrazin, 82
— — radium, 99
— — saponin, 82, 221
— — — on bone marrow, 52
— — thorium X, 239
— — toxins, 36, 239
— — turpentine, 236
— — trypsin, 239
— — tuberculin, 253, 260
— — *x*-rays (*q.v.*)
— — on large mononuclears, 184
— — on lymphocyte, 139
— — on myelocytes, 207
— — on spleen, 300
— — on tissue eosinophiles, 255
— leucoblastic action of 147, 169
Dualism, 29, 30
Duration of life of leucocyte, 229
— — of lymphocyte, 148
— — of plasma cell, 275
— — of primordial cell, 20
Dwarf cells, 20, 134, 136, 212
— lymphocyte, 134, 136
— lymphoidocyte, 20, 136
— myelocyte, 134
— promyelocyte, 134
Dysmorphism, 286

EFFECT of hunger on bone-marrow, 34
— short-circuiting thoracic duct, 33
Elastic fibrils in spleen, 161
Embryology, bearing on existence of primordial cell, 28
— of myeloid and lymphatic elements, 31
Embryonization, 63, 81, 310
Endothelial cell, 56, 115, 161, 173, 274, 283
— — isomorphism of, 56
— hyperplasia, 307
— theory of large mononuclear cell, 181
Endothelioid cells, 173, 191, 278
— — in germ centre, 306
Enterokinase, source of, 167
Eosinoid cell, 250, 317
— change, 154, 282
Eosinopenia, 239, 256
Eosinophile cell, 193, 209, 247, **249**, 64, 283, 305, 316, 317
— — functions, 253
— — granules of, 14, 251
— — in bone marrow, 202
— — in hæmolymph gland, 170
— — in spleen, 121, 160
— — morphology, 249
— — normal percentage, 4
— — source, theories, 252
— — varieties, 249
— lymphosarcoma, 310
Eosinophilia, 218, 238, 280
— causes, 253
— scheme, 280

Epithelioid cells, 283, 293, 315, 316, 317
Epithelium, metaplasia in, 285
Erythroblastic metaplasia, 310
Erythroblasts, 56
— chemistry of, 62
— discharge of nucleus, 56
Erythrolysis, 170
Erythrophages, 74, 162, 190
Erythropoiesis in chick, 57
— in spleen, 92, 167
Estimate of life of red cell, 73
Evidence of destruction of red cell, 74
Experimental alteration of blood-cell formula in birds, 11
— lymphocytosis, 139
Experiments by Werzberg, 35
Extractives of leucocytes, 227
Extrusion of nucleus of red cell, 55 (*Fig.*)

FABRICIUS, pouch of, 147
Factories of blood cells, 2, 4, 45, 111, 156, 195
Fallopian tube, lymphocytes in, 152
Fasting, effect on tissues, 115, 120, 184, 201
— (*See* HUNGER, STARVATION.)
Fat, absorption of, 118
— in lymph nodes, 116, 118, 184
Fate of leucoblast, 205
— lymphocyte, 148, 154
— myelocyte, 207
— plasma cell, 275
— primordial cell, 15
— red cell, 73
Ferments in leucocytes, 223, 227
— lymphocytes, 144
Fibrinogen, seat of formation, 52
Fibroblastic plasma cell, 267, 283
Fibroblasts, 193, 245, 247, 283, 293, 308, 315, 316, 317
Fixed connective tissue cell, developmental sequence, 30
Flemming bodies, 132
Foam cell, 283
Follicle, Malpighian, 120, 174
— of intestine, 274
— of spleen, 274
— plasma cells round, 273
Foreign body giant cell, 278, 283
Formation of bone-marrow in embryo, 55
— in lymph-node, 50
— of hæmoglobin, 58
— of red cells in spleen, 59
Formative marrow, 45
Formula, blood-cell, 4
— cell, of tissues, 280, 288, 319
Fraenkel-Much granules, 309
Fuchsinophile granules, 206
Functions of bone-marrow, 52
— eosinophile, 253
— large mononuclear leucocyte, 183
— leucocyte, 238
— lymphocyte, 137
— lymph-nodes, 118
— myelocyte, 207
— neutrophiles, 221
— oxydase granules in neutrophiles, 227
— plasma cell, 275
— spleen, 167

GANGLION cells in spleen, 161
Gelatinous degeneration of bone-marrow, 199, 288
Genealogy of erythrocyte, 97 (birds)
Gentianophile granules, 270, 272
Germ-centre cells, 124, **127**, 115
— — endothelioid cells in, 306
— — locular arrangement in, 129
Giant cells, 46, 48, 59, 161, 250, 278, 283, 292
— — in bone-marrow, 48
— — in spleen, 59, 161
— leucocyte, 134, 212, 229
— large mononuclear cell, 178
— nuclei, 306
Gigantocyte, 91
Glass body, 70, 88
Glossary, reference to, 5
Glycogen granules in eosinophile, 252
— reaction, 226
Goblet cell, 152
Granoplasm, 223, 272
Granular cell of marrow, 46
Granules, 229, 270, 312
— acid, in red cell, 84
— Altmann, 274
— azur, 144, 185
— basophilic in neutrophile, 225
— Beckton, 133
— fuchsinophile, 206, 309
— gentianophile, 270, 272
— glycogen, 252
— mast, **263**
— monocyte, 144, 185
— neutrophilic, 185, 213, 221
— phenolphilic, 166
— of leucocytes, 213, 232
— of plasma cell, 271
— of red cell, 84
Granulomatosis, 315
Granulosarcoma, 288
Graphic record of bone-marrow cytology, 196
— representation of Arneth's system, 215

HÆMAL lymph glands, 170
Hæmoblast, 54, 58
— metaplasia in, 294
Hæmoglobin, formation of, 65
— mechanism of formation, 62
— percentage of, 4
— synthesis, 294
Hæmokonia, 85, 98
Hæmolymph glands (nodes) 102, 168, 170, 254
— — types, 169
— — functions, 170
Hæmolysis in spleen, 162
Hæmo- versus spermogenesis, 27
Head kidney, 169
Heinz bodies, 82
Heteroplasia, 286
Histology of bone-marrow, 46
Histolysis of red cells in spleen, 74
Hodara plasma cell, 250
Hormone for bone-marrow, 201
Horse serum, 239
Hourly rate of cell multiplication, 51
Hunger, effect of on bone-marrow of fowls, 34

Hunger, lymph-node in, 117
— (*See* FASTING, STARVATION.)
Hyaline cell, 5, 137, 174
— leucocyte, 5
Hybrid cell, 134, 212, 251, 250
— mast cell, 252, 261, 264
Hyperchromia, 89
Hyperhypolymphocytosis, 138
Hyperleucocytosis, 236, 237
Hypermetaplasia, 154
Hypernomic secretion, 142
Hyperplasia, discussion of, 39, 289
— versus metaplasia, 289
Hyperplastic bone-marrow, 109
— processes in leucopoietic tissue, 239

INDETERMINATE cells, 45
Indifferent cells, 45
— marrow cells, 205
Infant, blood in, 236
Infective character of leukæmia, 41
— granuloma, 309
Immunization, effect on bone-marrow, 52
Immunity, relation of spleen to, 167
Inanition (*see* STARVATION)
Innenkörper, 82
Inner structure of cells (*see* MORPHOLOGY)
Internal secretions and bone-marrow, 52
Interfollicular cell, 193
— ground tissue, 304
— sinus of lymph gland, 113
— tissue, 316, 317
Intestinal mucosa, eosinophiles in, 252
— epithelial cell of salamander, 13
Intestine a source of lymphocytes, 140
Ionic concentration, 160
Iodophilia, 226
Iodophilic granule, 225
Iron in plasma cell, 272
Irritation cells, 24, 179, 188, 247, 266
— — (*See* PLASMA CELLS.)

JOLLY body, 66, 79, 82, 83, 84, 107
Juvenile large mononuclear cell, 190
— lymphocyte, 136

KARYOLYSIS, 65
Klein-Gumprecht shadows, 24, 132, 148, 268
Krompecher plasma mast cell, 271, 283
Kundrat's lymphosarcomatosis, 312
Kurloff bodies, 144, 176, 177, 181, 182

LARGE lymphocyte, meaning of term, 5, 127, 283
— mononuclear leucocyte, 134, 153, 171
— — — drawing of, 190, 193
— — — fate, 188
— — — functions, 183
— — — increase of in blood, 218
— — — normal percentage, 4
— mononucleosis (*see* MONOCYTOSIS), 218
Laws of cytology, 18
Leucoblast, 20, 21, 48, 112, 132, 134, 178, 179, 193, 203
Leucoblastic cells, 250
— line of development, 209
Leucocyte (*see* NEUTROPHILE)
— death of, 228
Leucocyte, duration of life, 229
Leucolytic substances, 236
Leucocytoid cell, 132, 134, 135, 179, 193, 316, 317
— lymphocyte, 20
— macrolymphocyte, 20
— microlymphocyte, 283
Leucocytolysis, 230, 239
— determination of, 230
Leucocytophages, 237
Leucocytosis, 14, 52, 233–238
— phases of, 237, 238
— significance of, 235
Leucomonocyte, 250
Leucopenia, 14, 235, 238
— drugs causing (*see* DRUGS)
Leucosarcoma cell, 20, 22, 23, 134, 316
Leukæmia (*see* INDEX OF DISEASES)
Leukæmic mast cell, 264, 265
— monocytoid leucoblast, 193
Leukæmoid effects of colchicin, 38
Lienolymphatic system, 314
Life history of red cell, 69
Linin, 19
Lipase in large mononuclear leucocyte, 185
— in lymphocyte, 142
Lipoid granules in large mononuclear leucocyte, 186
Lipoids in eosinophile granule, 252
— plasma cell, 272
Lipolysis, 167
Lipolytic ferments in blood cells, 81, 164
— toxins on red cells, 81
Lipoferous leucocytes, 226
Liver, erythropoiesis, 55
— red cell formation in, 56
Local eosinophilia, theories, 256 (*see under* EOSINOPHILE)
Locular arrangement of germ-centres, 129
Loss of nucleus of erythroblasts, 56
Löwit's bodies, 9
Lymphadenoid cell, 111
— hyperplasia, 304
— marrow, 102
— tissue, 293
Lymphæmic lymphocyte, 193
— microlymphocyte, 20
Lymphatic plasma cell, 267
— system, structure of, 3
Lympherythroblast, 30
Lymph follicle, cyclical changes in, 115
— nodes, 60, 278, 301
— — blood supply, 113
— — development from adipose tissue, 118, 130
— — effect of toxins, 118
— — functions, 118
— — in hunger, 117
— — purins in, 117
— — red cell formation in, 60
— — regressive changes in, 118, 130
— — structure, 311
Lymphoblast, 32, 57, 125, 132, 164, 191, 271
— differential diagnosis, 32, 178, 191
— function, 164
— morphology, 125
— versus myeloblast, 32
Lymphoblastic cells, 247, 250

Lymphoblastic cells, line of development, 124, 126
— — macrolymphocyte, 20, **21**, 124, 179, 191, 193
— — monocyte, formation of, 162
Lymphocyte, 56, 57
— chemistry, 141
— definition, 111
— differential diagnosis, 135
— functions, 137
— in intestinal wall, 140
— in puncture fluid, 139
— in spleen pulp, 160
— in starvation, 140
— made in bone-marrow, 112 (footnote)
— morphology, 132
— normal percentage, 4
— nutrioid function, 139
— of blood-stream, 131, 134
— of chronic lymphatic leukæmia, 133
— of follicle, 190
— of tissue, 131, **150**
— relation to thrombocyte, 153
— with reniform nucleus, 135
Lymphocytoid cell, 111
— large mononuclear cell, 178
Lymphocytoma, 274
Lymphocytosis, 33, 138, 153, 218, 235
— causes, 138
— varieties, 138, 153
Lymphogenesis, scheme, 126
Lymphogranulomatosis, 302
Lymphoid elements of blood stream, classification of, 131
— erythroblast, 46, 55
— — (*Fig.*), 60
— — morphology, 60
— follicle, 114
— hæmoblast, 20, 76, 134, 136, 195
— metaplasia, 303
Lymphoidocyte, 8, 11, 15, 47, 112, 134, 190, 193, 203, 247, 283
— azur granules, 32
— chemical characters, 11
— comparative cytology, fate, 15
— morphology, 8
— phases in life of, 15
Lympholeucocyte, 174, 187, 190
— comparative cytology, 187
Lymphoma, 273
Lymphoma cell, 193
— paramyeloid, 304
— perivascular, 122, 123, 154
— — function of, 123
Lymphomatosis, scheme, 281
Lymphopenia, 138, 139, 218, 239
— causes, 139
Lymphophilia, 238
Lymphopoiesis, accessory factories, 122
Lymphoprimitive cell, 192, 283

MACROCYTASE, 162, 183, 184
Macrocyte, 76, 91
Macroleucoblast, 250
Macrolymphocytar metaplasia, 304
Macrolymphocyte, 30, 117, 125, 132, 134, 137, 179, 283, 316, 317
— developmental sequence, 30
Macrolymphoidocyte, 203
Macromyeloblast, 316, 317
Macronormoblast, 76
Macrophage, 66, 119, 120, 171, 190, 229
— in bone-marrow, 66
Macroplasma cell, 160
Malachite green on lymphocyte, 142.
Malarial red cell, 70
Malpighian body, 3, 120, 161, 308
— follicle, 3, 120, 161, 308
Marchand cell, 171, 173, 250, 283
Marrow leucocyte, 45
Marrow lymph gland, 169
Marchalko cell, 250, 267, 274
Martinotti's pseudoplasma cell, 283
Massage, effect on lymphoctyes, 152
Mast cell, 4, 14, 19, 57, 153, 160, 193, 229, 247, 250, 251, 259, 260, 261, 262, 264, 283, 293, 307, 316
— — change, 19, 153, 307
— — chemistry, 251
— — function, 262
— — granules, 14, 229, 251, 262
— — metaplasia, 19, 153, 307
— — morphology, 260, 261
— — myelocyte, 260
— — normal percentage, 4
— — table, 259
— — transformation (*see* METAPLASIA)
— — varieties, 259, 264
Maurer-Schüffner punctation, 84
May-Giemsa stain, 62
Meaning of "diseases of blood," 6
Mechanism of extrusion of red cell nucleus, 65
— formation of hæmoglobin, 62
— metaplasia, 293
Megakaryocytes, 45, **48**, 49, 50, 87, 98, 161, 162, 193, 192, 201, 215, 250, 278, 283, 300, 305, 306, 312, 316, 317
— differential diagnosis, 49
— during digestion, 162
— functions, 49
— in bone-marrow, 201
— in liver, 58
— in spleen, 192
— in lymph nodes, 305
— occurrence, 49
— relation to hæmogenesis, 49
— significance, 49
— theories concerning, 50
Megakaryocytomatotic metaplasia, 305
Megaloblast, 46, 55, 62, 63, 76
— differential diagnosis, 63
— figure, 55
— forms, 62
— views as to nature, 63
Megaloblastic degeneration, 63
Meristem formation of red cells, 52
Meristematic proliferation, 15
Merozoites, 15
Mesenteric lymph nodes, 184
Mesolymphocyte, **128**, 134, 135, 147, 193, 250, 283, 317
Mesoleucoblast, 204
Mesenchymal cells, 130, 283, 312
— tissue, 130, 186
— — in invertebrates, 186

Metabolic changes in blood cells, 13
— — bone-marrow, 198
— — lymph nodes, 117
Metabolism in bone-marrow cells, 199
— spleen, 162
Metachromatin, 13, 263
— of granules, 229
Metahyperplasia, 100, 108
Metahyperplastic character of leukæmia, 41
Metamyelocyte, 134, 178, 190, **208**, 209
— typical forms, 209
Metaplasia, 23, 39, 52, 64, 100, 104, 108, 153, 169, 173, 201, 228, 239, 285, 289, 290, 293, 297, 298, 302, 303, 304, 305, 307, 308, 310, 311
— curvilinear character, 153
— definition, 285
— discussion, 285, 311
— erythroblastic, 310
— exciting agents, 297
— expressed graphically, 39
— in bone-marrow, 52
— lymphoid, 303
— macrolymphycotar, 304
— mast cell, 307
— mechanism, 293
— megakaryocytomatotic, 305
— microlymphocytar, 304
— of cells, 228
— of plasma cell, 307
— sarcoid, 23, 308
— special examples, list of, 298
— splenoid, 109, 308
— versus anaplasia, 290
— — degeneration, 289
— — hyperplasia, 289
Metaplastic processes in leucopoietic tissue, 239
Metastatic nature of myeloid transformation, 302
Methylene blue-picric acid stain, 66, 70, 76
Methyl-green-pyronin, 32, 79, 84
Methyl-green-Giemsa-aurangeate, 13
Metrocyte, 61
Michaelis' spherinucleate cell, 283
Microcyte, 76, 82, 91
Microleucoblast, 250
Microlymphocytar metaplasia, 304, 305
Microlymphocyte, 135, 193, 250, 316, 317 (*See also* LYMPHOCYTE)
Microlymphoidocyte, 9, 20, 193, 203, 283
Micromyeloblast, 105, 132, 273, 280, 316, 317
Micromyelocyte, 193, **208**
Micropromyelocyte, 206
Middle zone of lymphocyte, 133
Migratotaxic substances, 282
Miniature large mononuclear, 178
Mitochromes, 97
Mitosis of mast cell, 261
— of neutrophiles, 220
Monocyte, 5, 131, 132, 134, 144, 172, 173, 185, 187
— granulation, 144, 185
— in animals, 187
Monocytoid macrophage, 193, 253
Monocytopoiesis, 167
Monocytosis, 182, 184, 238
Monopenia, 139, 184
Monophyletism, 29, **30**
Morphology of blood platelets, 85
— endothelial cell, 181
— eosinophile cell, 249
— large lymphocyte, 127
— large mononuclear leucocyte, 176
— leucoblast, 21, 203
— lymphoblast, 32, 125
— lymphoblastic macrolymphocyte, 21
— lymphocyte, 132
— lymphoid erythroblast, 60
— lymphoidocyte, 8, 21
— mast cell, 251, 260
— megakaryocyte, 48
— megaloblast, 61
— mesolymphocyte, 128
— monocyte, 174
— myeloblast, 32, 205
— myelocyte, 207
— myeloic cell, 203
— neutrophile leucocyte, 213
— normoblast, 64
— plasma cell, 267
— primordial cell, 8
— pulpar cell, 189
— red cell, 69, 74
— Rieder cell, 22
— Schridde-Hodara cell, 271
— spindle cell, 97
— tissue lymphoctye, 127, 150
Mother cell, 175, 189
Multipotentiality of cells, 191, 288
— of pulpar cell, 191
Muscular exertion, effect of, on lymphocytes, 149
Myelæmic microlymphoidoctye, 20
Myeloblast, 205, 317
Myelocyte, 56, 134, 207, 300
Myeloic azur granulation, 143, 151, 206, 227
Myeloic cells, 132, 154
— — list of, 132
— plasma cell, 267
— pseudolymphocyte, 179

Myeloid metaplasia, 33, 36, 41, 52, 167, 169, **173**, 186, 192, 201, **298**, 300
— — nature of, 300
— — in pernicious anæmia, 41 (and *see under names of diseases*)
— — in birds, 186
— tissue, 31, 33
— — action of infective fevers on, 33
— transformation (*see* MYELOID METAPLASIA)
Myeloleucocyte, 57
Myelolymphocyte, 21
Myelolymphoidocyte, 125, 134, 136, 179
Myelopathy, 101
Myelopotential cell, 303
Myelotoxic sera, 301
Myelotoxins, 35
Myogenic leucocytosis, 152, 236

NERVE fibrils in spleen, 161
Neutropenia, 239
Neutrophile leucocyte, chemical characters, 222
— — death of, 228

Neutrophile leucocyte, differential diagnosis, 221
— — duration of life, 229
— — function, 221
— — granules, 222, 145
— — morphology, 213
— — uninucleate, 316
— pseudolymphocyte, 136
Neutrophilia, table of, 237
Nile blue, 71, 75, 82, 85
Nomenclature, variation of, 5 (*and see* Glossary)
Nongranular cells of marrow, 47
Normal process of extrusion of normoblast nucleus, 66
Normoblast, 161
— figure, 55
— chemistry, 64
— differential diagnosis, 64
— morphology, 64
— nucleolus, 64
Normoplasia, 286
Nuclear origin of mast granule, 263
Nucleases, 142
Nucleinic degeneration, 163
Nucleoid, 386
Nucleolus (*see* Morphology of Respective Cells)
— fate, 60
— in megaloblasts, 61
Nucleophage, 190
Nucleus (*see under* Morphology of Respective Cells)

Objections to Arneth's theory, 216 (*see also* Theories)
Old age of cell, 15
— — signs of, in cell, 18, 144, 151
Ontogenetic development, signs of (*see* Old Age)
Origin of tissue-eosinophiles, 256
Orthochromatic megaloblast, 61, 62
Orth's leukæmic lymphadenoma, 310
Osmotic action, 67, 73, 91, 210, 222, 229
— — in extrusion of nucleus, 67
— — on myelocyte, 229
— — on neutrophile, 222
— — of phagocytosis, 210
— — in red cell, 73
Osteoclast, 48, 56
Outer form of cell (*see* Morphology)
Oxydase, 32, 73, 163, 164, 185, 200, 227, 251
— granules, 125, 163, 174, 185, 227
— in bone marrow, 251
— in red cell, 31
— in eosinophile, 251
Oxydase reaction, 31, 35, 61, 176, 185
Oxyphilic granules in neutrophiles, 225

Pachydermia of red cell, 89
Pander's islands, 53
Panoptic stain, 135
— — method, 135
Parablast, 53
Paramyeloid lymphoma, 304
Paranuclear attraction-sphere (*see* Morphology of the Various Cells)
Paraplasm (*see* Morphology)
Parenchymal cells, 293
— tissue, 316, 317
Parent cell, 203
Paroxydase, 142
Pathological plasma cell, 267
— process of extrusion of normoblast nucleus, 66
Pathology of leucopenia, 239
Percentage composition of red cell, 73
Perichondrium and hæmogenesis, 55
Perifollicular lymph-sinus, 113, 130
Perinuclear zone (*see* Morphology), 270
— — of lymphocyte, 151
Periosteum, 286
Perithelial cell, 193, 279, 283
Perithelium, 273
Perivascular lymphoma, 3, 122
— tissue, 247
Phagocytes, 115, 141, 161, 167, 170, 183
Phagocytic properties of marrow cells, 47
Phagocytosis and drugs, 222
Phanerogenetic agents, 307
— infection, 291
Phases of leucocytosis, 237, 238
— in life of primordial cell, 15
Phenolase, 164
Phenolphilia, 163, 253
— of eosinophiles, 251
— of mast granules, 263
Phenolphilic cells, 121
— granule, action of, 166
— — of leucocyte, 227
— — in plasma cell, 272
— substance, 163
Phlogocyte, 243, 246, 266
Phlogocytosis, 243
Phlogopoiesis, 246
Phylogenetic development, signs of, 18
Physiological leucocytosis, 236
Pigment cell, 265
Pigmentophages, 47, 179, 183
Plasma cell, 57, 120, 134, 136, 153, 162, 186, 193, 247, 250, 264, **266**, 283, 289, 290, 293, 315, 316, 317
— — change, 20
— — comparative cytology, 276
— — degenerative change, 276
— — duration of life, 275
— — fate, 275
— — functions, 275
— — granules, 271
— — metaplasia, 307
— — myeloma, 274
Plasmocytoma, 308
Plasmoid cell, 146, 160, 190, 271, 274, 317
— change, 154, 245, 277, 282
— stimulus, 308
Plasmolysis, 24
Plasmosomes, 144, 176, 224, 225
Plastin matter, 84
Platelets, 132
— in anæmia, 86
Play between parenchymal and stromatic elements, 311
Plumbism, 80
Pneumotoxin, action on myeloid tissue, 36
Poikilocyte, 76
Poikilocytosis, 91

Poisons on blood (*see* DRUGS), 109, 147, 169
Polyblast, 154, 273, 283, 293
Polychromatophilia, 77, 78, 204
— differential diagnosis, 78
— erythroblast, 57
Polychromatic gigantocyte, 76
— megaloblast, 61, 62
Polymorphonuclear leucocyte, normal percentage, 4 (*see* NEUTROPHILE)
Polynucleosis in intestinal wall, 141
Pouch of Fabricius, 147
Prechromatophore cell, 263
Prespermatogonium, 27
Primitive bone-marrow, 56
— erythroblasts, 54
Primordial blood cell, 5, 7, 8, 15, 23, 131, 175, 179, 189, 201, 278
— — — list of, 132
— — — morphology, 8
— — — fate, 15
— — — death of, 23
— — — phases in life of, 15
Prochromatin, 13
Progress only cyclical, 14
Proliferation, meristematic, 15
— of cells in bone-marrow, 51
Promegaloblast, 60
Promyelocyte, 134, 137, 175, 179, 206, 209
Prosoplasia, 286
Protometrocyte of selacia, 33
Proteosomes, 224
Pseudo-eosinophile cell, 250
Pseudolymphocyte, 136, 283
Pseudoplasma cell, 121
Pulp cord, 114, **157**
— tissue (*see* PULPAR TISSUE)
Pulpar cell, 158, 188, **189**, 190, 193
— tissue, 4, 113, 114, 156, 157, 158, 186, 274, 300, 312
— — in myeloid metaplasia, 300
— — in teleostean fish, 186
— — relation to venous channels, 158
Pulpocyte, 172
Punctate basophilia, 67, 71, 76, 77, **78**, 79, 84, 107
Puncture fluid, lymphocytes in, 139
Purinic degeneration, 163
Purins, 117, 229
Pus cells, 229
Pycnosis of nucleus, 64, 200
Pycnotic megaloblast, 63
— nucleus, 200
Pyrrhol cell, 283
— — reaction, 251

RADIUM therapy, 99
Red blood-cell, **44**
— — — acid granules in, 84
— — — alterations of shape, 91
— — — — of size, 91
— — — — of resistance, 75
— — — birth of, 65
— — — chemistry, 72
— — — counts in animals, 96
— — — fate, 73
— — — formation in liver, 56
— — — — in lymph-node, 60
— — — — in spleen, 59
Red blood-cell, life history, 69
— — — lipoids in, 62
— — — number per c.mm., 4
— cell shadows, 82
Regenerative phase, 238
Regressive changes in lymph node, 118
Relative leucocytosis, 237
Reserve factories of blood-cells, 3
Resistance of red cells, 73
Reticular substance of red cell, 75, 177
Reticulum of lymph-node, 115
Reversible reaction, 16
Ribbert's lymphocytoma, 310
— lymphoma, 112, 122, 168, 273
Rieder cell, 20, **22**, 132, 134, 136, 179, 193, 203, 283, 316
Rules for studying anæmia, 106
— — — leucocytosis, 234–238
Russell bodies, 276

SARCOID blastomatosis, 309
— metaplasia, 23, 308
Sarcoma cell, 113, 145, 167, 270
— injection of, 167
Sarcomatosis, 308
Scene of action in blood-forming tissues, 159, 196, 279
Scheme of development of neutrophile, 210, 211
— effect of plastic irritation, 275
— embryonic erythropoiesis, 57
— enlargement of lymph-glands, 316
— — of spleen, 317
— eosinophilia, 280
— erythropoiesis, 68
— inter-relations between phlogocytes, 283
— lymphogenesis, 126
— fate of lymphocyte, 154
— — of plasma cell, 276
— lymphomatosis, 281
— monocytes, 174
Schridde granule, 133, 144, **145**
— — comparison with azur granule, 144
Schridde-Hodara plasma cell, 193, 267, 271, 274, 283
Schizocyte, 89
Sclerosis of spongioplasm, 274
Seasonal periodicity of red cell formation, 94
Secondary erythroblasts, 62
Secretory character of neutrophile granule, 223
— vacuoles, 177
Senile change of myelocyte, 207
— leucoblast, 193, 283
— lymphoidocyte, 20
Sera, myelotoxic, 301
Sertoli cell, 15, 26, 51
Shape of cells (*see* MORPHOLOGY)
Significance of basophilia, 81
— blood film, 90
— iodophilia, 226
— leucocytosis, 235
— macrocytes, 92
— mast cell granules, 14
— polychromatophilia, 78
— small round-celled infiltration, 288
— tissue eosinophile, 255
Signs of death of leucocyte, 229

Signs of ontogenetic development,' 18 (*see also under* FATE, DEGENERATIVE CHANGES)
Sinus, central, 118
Sinuses in lymph glands, 113
Sinusoids in liver, 58
Small-round-celled infiltration, 151, 244, 288
— — significance of, 288
Soterocyte, 86
Source of eosinophile granule, 252
— — of tissue, 255
— — of mast granule, 263
Spaces, connective tissue, 150
Specific granules, 32
Spermacytoma versus myeloblastoma, etc., 28
Spermatids, 26
Spermatocytes, 26
Spermatogenesis, 25, 37
Spermatogonia, 25, 27
Spindle cell, 96
Spirochæte and Kurloff bodies, 177
Spleen, 119, 267, 278, 301
— blood supply, 119
— date of erythropoiesis, 55
— effect of severe injury, 138
— follicle, 274
— histolysis of red cells in, 74
— lymphoid cells, 112
— myeloid metaplasia, 299
— plasma cells in, 273
— pulp in myeloid metaplasia, 300
— red cell formation in, 59
— structure of, 3, 119, 157, 311
— syncytial formation in, 157
Splenocyte, 172, 189, 271, 304, 316
Splenoid metaplasia, 169, 308
Splenomonocyte, 173
Splenotoxins, 35
Spongioplasm (*see* MORPHOLOGY)
Spongioplasmatic cells, 112
Staining by thiazin, 147
— method, for Schilling's modification of Arneth, 217
— — Pappenheim, 135
— reaction of tingible bodies, 117
Starvation, blood in, 150, 184, 253
— bone-marrow in, 199
Stereochemistry and metaplasia, 291
Sternberg leucosarcoma cell, 22
Streptococci and cell-count, 38
— and eosinophiles, 255
Stroma of red cells, 71
Stromatic cells, 48, 161, 193, 278, 293, 305, 309, 312, 316, 317
— — of bone marrow, 48
— — reaction by, 309
— tissue, 316, 317
Substantia granulo-filamentosa, 71, 84
— reticulosa, 62
Sudanophilic granule of neutrophile, 226
Surface tension and leucocyte, 209, 221
Syncytial character of marrow cells, 26
— — of testicular cells, 27
— formation, 158
System, lieno-lymphatic, 314
System-diseases of blood, table of, 319
TABLE of Arneth's system, 215
— blood cells, 211
— — plasma cells, 269
— changes in white cell count, 234
— cells pathological to blood, 211
— comparison of vital stainable substance and basophilia, 81
— contrast between genetic relations of monocyte, 180
— — — granules in lymphoid cells, 175
— — — large mononuclear leucocyte and lymphocyte, 180
— — — lymphoidocyte and leucoblast, 21
— — — leucocytosis and leukæmia, 240
— — — monocytes, 175
— — — myeloic mother cells and lymphatic mother cells, 21
— — — myeloid and lymphatic cells, 31
— genetic relations between monocytes, 180
— granules in lymphoid cells, 175
— enlargement of lymph-glands, 316
— — of spleen, 317
— forms of neutrophilia, 237
— granular structures in red cells, 83
— granules in lymphoid cells, 175
— mast cells, 259
— of theories of origin of large mononuclear cells, 179
— plasma cell versus connective tissue cell, 272
— — — 267, 268
— showing modes of extrusion of normoblast nucleus, 81
— — views about extrusion of normoblast nucleus, 67
Testis, cell-proliferation in, 25
Theatre of action, 157, 196
Theories about nature of azur granulation, 144, 180, 185
— — — germ-centre cell, 124
— — — Kurloff bodies, 177
— — — large mononuclear leucocyte, 180
— — — megaloblast, 67
— — — megakaryocyte, 50
— — — myeloid metaplasia, 301
— — — neutrophile granulation, 222
— — — pernicious anæmia, 103
— — origin of blood-platelets, 86
— — — eosinophile, 252
— — — large mononuclear leucocyte, 179
— — — mast granule, 263
— — — megakaryocyte, 50
— — — plasma cell, 272
— — — spindle cell, 98
— — — tissue eosinophile, 256
— — significance of polychromatophilia, 78
Thiazin, 147
Thoracic duct a source of lymphocytes, 140
Thrombocytes, 57
— relation to lymphocyte, 153 (footnote)
Thymic state, 154
Thymocyte, 112
Thymus, 112, 254
— myeloid metaplasia in, 299
Tigroid patches in megakaryocytes, 49
— — eosinophile, 250
Tingible bodies, 117, 148
Tissue, cell-formula, 280, 288, 319

Tissue change in myeloid metaplasia, 300
— eosinophilia, 254
— — meaning of, 255
— eosinophile, source of, 255
— lymphocyte, 247, 250, 283
— mast cell, 260
— plasma cell, morphology, 270
Tonsil, 112, 152, 267, 286
— plasma cells in, 275
Toxins and leucocytosis, 239
— effect on bone-marrow, 52, 102, 108
— — lymph nodes, 118
— — lymphocytes, 153
— long continued, effect on bone-marrow, 52
Toxoids, action on blood-forming tissues, 43, 288
Transitional cell, 131, 171, 174, 178, 188, 190, 193, 283
Transition from leukæmia to sarcoma, 306
— forms, discussion of, 18
Transplantable leukæmia of hens, 35
Triacid stain, discussion of, 18
Trypsinogenic function of spleen, 167
Trypanosomes and Kurloff bodies, 177
Tryptic systems in spleen, 165
Tumour cells in blood, 309
— — differential diagnosis, 137
Türk cell, 63, 266
Typhoid toxin and eosinophiles, 255

ULTRAMICROSCOPE, blood-cells in, 133, 145, 220
Ultraviolet light on blood-cells, 61, 71, 133, 144, 145, 177, 178, 220
Uninucleate neutrophile, 316
Unitarian view, 180
Unitarianism, 29
— graphic account of, 30
Unna daughter plasma cell, 283
— plasma cell, 267

VACCINE, small-pox, effect on lymphocytes, 154
Vacuolar structures in primordial cell, 9
Vacuoles in primordial cell, 24
Value of blood film, 233
Variants of large mononuclear cell, 178 (*see also* ATYPICAL CELLS)
Venous channels, relation to pulpar tissue, 158
Villus, plasma cells in, 275
Vital staining, 62, 72, 75, 144, 207, 220, 223, 278
— — of azur granules, 144
— — neutrophile, 220
— — myelocyte, 207
— — red cell, 62, 72, 75

WANDERING cells, 130, 171, 191, 192, 278, 283, 293
Wheel structure of nucleus, 62
— — chemistry of, 62
White cells, number in normal blood, 4
White thrombi, 86
Winkler-Schultze granules, 61, 176, 185
— — — in blood-platelets, 85
— — — in red cell, 69
X-rays action, 104, 236, 245, 282, 314, 305
— on bone-marrow, 201

YOLK-SAC, hæmogenesis in, 53

ZINOWSKI's equation, 74

INDEX OF DISEASES REFERRED TO IN THIS VOLUME.

[Figures in thick type indicate main references. Figures marked with a (*) indicate a reference to blood-cells; those marked with a (†) refer to tissue-cells, and those not marked at all are references to histopathology.]

Abscess, hepatic, 184*
Acromegaly, 260*
Acute hæmorrhagic macrolymphocytar leukæmia, 60
— infections, 138, 163, 169, 184, 208, 217
— — action on spleen, 163
— — hæmolymph glands in, 169
— — large mononuclears in, 184
— leukæmia, 24, 35, 38
— sublymphæmia, 307 (*see also under* Leukæmia)
— yellow atrophy, 236*
Addison's disease, anæmia in, 109
Agonic conditions, 218*
Aleukæmia, discussion of, 41, 107, 108, 281, 314–318
Aleukæmic lymphadenomatosis, discussion of, 23
Anæmia, 41, 64, 76*, 78*, 79*, 83*, 86*, 90, 92, **100**, **101**, 102, 103, **104**, 105, 106, 184*, 199 (spleen), 208* (*see also* Pernicious Anæmia)
— experimental, myeloid metaplasia in, 299
— pseudoleukæmica infantum, 83*
Aneurysm, bone-marrow in, 50
Ankylostomiasis, 218*
Aplastic anæmia, 79, 101, 102, 103, 105, 217, 218
Appendicitis, bone-marrow in, 50, 122*, 217*, 226,† 254†, 262†
Asphyxia, 208*
Asthma, 253*, 256†
Atheroma, spleen in, 119

Bacillus aerogenes capsulatus infection, spleen in, 192
Banti's disease, histopathology, 41, 90, 108, 167, 313, 317
— — large mononuclear leucocytes in, 184
Blood diseases, 6, 104, 105

Cancer, 41, 78*, 90, 105, 184*, 236*, 253*, 317
— bone-marrow in, 50, 199
— tissues in, 254, 267
— of bone, myeloid metaplasia in, 299
Cardio-vascular disease, 184*
Chloroleucosarcoma, 42
Chloroma, 28, 42, 318
Chloromyeloleucosarcomatosis, 318
Chlorosarcomatosis, 22
Chlorosis, 79*, 106, 138, 217, 253*
Cholera, 260
Chorea, 109
Chronic deforming arthritis, 287
— diseases, 184*
— nephritis, 109, 318
— — bone-marrow in, 50
— — spleen in, 163
Cirrhosis of liver, 109, 164†, 236*, 253*
Cryptogenetic anæmia, 103

Diabetes, 226*
— spleen in, 164
Diarrhœa, bone-marrow in, 199
Diphtheria, 86*, 218*, 254*
— spleen in, 299

Eclampsia, 318
Eczema, 253*
Epilepsy, 253*
Epithelioma, 184*, 255†, 261
Erysipelas, spleen in, 299
Erythema multiforme, 261†
Erythræmia, bone-marrow in, 109

Gaucher splenomegaly, 41, 307, 317
General paralysis of insane, 262†
German measles, 184*
Gonorrhœa, 254*
Gout, 236*, 254*
Granulomatosis, 316, 317
Graves' disease, 122, 138*, 253*

Hæmatic anæmia, 101
Hæmolytic anæmia, 101
— splenomegaly, 317
Hæmophilia, 138*
Hæmophthisic anæmia, 105
Hæmorrhage, 236 *
Hæmorrhagic diseases, hæmolymph glands in, 170
Hæmotoxic anæmia, 105
Hemicrania, 253*
Hepatic abscess, 184*
Hodgkin's disease, 41, 142*, 218*, 250, 278†, 291, 292, 305, 306, 307, 310, 313, 316, 317
Hydatid disease, 255*
Hyperchromic anæmia, 105

Infant, 207*, 236*
Infantile splenic anæmia, 108

Infections, acute, 33, 102, 138*, 208*, 217*, 260*, 270*, 318
— — bone-marrow in, 50
— chronic, 138*, 226*
— experimental tissues in, 299
— mixed, 218*
Infective granuloma, 309
Inflammatory conditions, 236*
Influenza, 239*

v. JAKSCH anæmia, 41, 184*, 208,* 317

KAHLER's disease, 105
Kala-azar, 41, 239*, 313, 315, 316, 317
Kundrat's lymphosarcoma, 316, 317

LEPROSY, 184*, 253*
Leucanæmia, 105, 107
Leucosarcoma versus chloroma, 42
— versus myeloma, 42
Leucosarcomatosis, 22, 40, 309, 316, 317, 318
Leukæmia, 22, 35, 107, 108, 184*, 185*, 218*, 226*, 237*, 239*, 241, 252, 260, 267†, 291, 292, 316, 317
— acute, 24, 35
— — discussion of, 38
— — lymphatic, 309
— — macrolymphocytar, 63, 297
— — myeloic, 255†
— chronic, 305
— — lymphatic, 23, 117, 133*, 139*, 154, 167, 253
— discussion of, 39
— due to nitrobenzol, 38
— of hen, 35
— hyperplastic character of, 23
— infective character, 41
— lymphatic, 256†
— metahyperplastic character of, 41
— modern view of, 41
— myeloid metaplasia, 299
— nature of, 301
— theory of, 313, 314
— versus chloroma and sarcoma, 42
Leukæmic lymphomatosis, 123, 310
Linitis plastica, 275†
Liver abscess, 218*
Lues (*see* SYPHILIS)
Lupus, 261†
Lymphadenomatosis, 316, 317
Lymphæmia, 184*
— acute, 309
Lymphoblastoma, 28, 315
Lymphocytoma, 306, 317
Lymphogranuloma, 255
Lymphomatosis, 281
— blood-forming organs in, 299
— leukæmic, 123, 310
Lymphosarcoma, 42, 123, 292, 306, 317
— eosinophile, 310

MALARIA, 88, 105, 184*, 239*, 254†, 260*, 270*, 313, 316, 317
Malignant granuloma, 291, 292
Malnutrition, 239*
Malta fever, 239*
Mania, 208*, 253*
Measles, 239*, 253*
Melancholia, 253*
Menstruation, 86*
Miculicz's disease, 122
Molluscum contagiosum, 255†
Morbus maculosus, 105
Myeloblastoma, 28
Myeloid chloroleukæmia, 212*
Myeloleukæmia, 212*, 253*
Myeloma, 28, 105, 274†
Myelopathic anæmia, 105
Myelophthisic anæmia, 101
Myelosarcomatosis, 309, 316, 317
Myelotoxic anæmia, 102
Myelotoxicosis, 291

NEPHRITIS, chronic, spleen in, 163
Neurasthenia, 109

OLD age, 182*, 267†
Osteomalacia, 254*
Osteosclerosis, 106
— bone-marrow in, 304
— myeloid metaplasia in, 299

PAGET's disease, 287
Parasites, animal, 253*
Paroxysmal hæmoglobinuria, 109
Pemphigus, 253*
Peritonitis, 217*
— spleen in, 299
Pernicious anæmia, 33, 41, 63, 83*, 89*, 104, 105, 107, 138*, 184*, 208*, 217*, 226*, 239*, 291
Phanerogenetic anæmia, 105
Plasmogenic anæmia, 105
Plethora vera, spleen in, 299
Plumbism, 83*, 107
— spleen in, 299
Pneumonia, 218*, 226*, 274†
— bone-marrow in, 50
— spleen in, 299
Polycythæmia, 109
— after splenectomy, 168
Polypus of nose, 255†
Post-hæmorrhagic anæmia, 105
Pregnancy, 208*, 236*, 318
Primary splenomegaly, 317
Protozoan disease, 217*, 218*, 239*, 316, 317
Pseudoleukæmia, 22, 124, 167, 217*, 237*, 292, 305, 307, 318
Psoriasis, 253*
Puerperal fever, anæmia of, 105, 217*, 226*, 318
— mania, 253*
Pyæmia, 226*

RACHITIC splenomegaly, 317
Rheumatism, 226*, 254†, 318
Rhinophyma, 261†
Rhinoscleroma, 261†
Rickets, 138*, 140*, 184*, 208*, 236*
— metaplasia in, 287
Rodent ulcer, 255†
Rubeola, 184*

SALPINGITIS, 247†
Sarcoleukæmia, 308, 310, 316, 317
Sarcoma, 241
— theory of, 313
Sarcomyeloma, 42
Scarlet fever, 28, 86*, 184*, 253*, 270*
— — myeloid metaplasia in, 299
— — relation to leukæmia, 41
Scurvy, 109, 138*
Septic infections, 164, 211, 217, 218*, 226*, 236*
Septicæmia, 217*, 218*
— bone-marrow in, 50
— spleen in, 299
Shock, 237*
Skin diseases, 254†
Small-pox, 184*
— spleen in, 299
Splenectomy, 109, 138*, 140*, 157, 167, 168, 172
Splenic anæmia, 105
— — infantile, 108
— new growth, 217
Splenomegaly, 184*, 318
Sporotrichosis, 254*
Spring catarrh, 254†
Status lymphaticus, 122*
Sternberg's anomalous tuberculosis, 316, 317
Subleukæmia, 108
Suppurative processes, 226*, 254*
Syphilis, 79, 90, 138*, 208*, 217*, 313, 316, 317
— congenital, 253*, 299
— metaplasia in, 287
— spleen in, 163, 299
— thymus in congenital, 299

TETANY, 253*
Texas fever, hæmolymph glands in, 169
Thyroid enlargement, 122
Toxæmias, 239*
Toxic anæmia, 64
Trachoma, 255†
Trichinosis, 254†
Trypanosomiasis, 239*, 315, 316, 317
Tuberculosis, 109, 139*, 184*, 217*, 219*, 226*, 239*, 253*, 254*, 274†, 316, 317
— bone-marrow in, 50
— pleural exudate in, 152
Tumours, 217*, 218*
Typhoid fever, 88, 184*, 217*, 218*, 254†, 273†, 318
— — bone-marrow in, 199
— — spleen in, 192, 299

URÆMIA, 208*, 253*
Urticaria, 253*, 261†

ZOSTER, 253*

INDEX OF ANIMALS REFERRED TO IN THIS VOLUME.

ACANTHODACTYLUS, 147, 187
Actinia, 186
Agama lymphoidocyte, 11, 147, 187
Algiroides nigropunctatus, 11, 147
Amblystoma, 34, 276
Amphibia, 11, 33, 93, 146, 185, 186, 187, 231, 258, 265
Anguilla, 11, 146, 187, 190
Anguis, 147, 258
Anolis, 147, 187
Ape, 144, 232
Arthrostracea, 230
Axolotl, 11, 94, 198

BAT, 262
Beetle, 168, 250
Bird, 11, 51, 73, 78, 95, 97, 147, 169, 186, 187, 251, 252, 258

CAMEL, 96
Carassius, 187, 257
Carp, 186
Cat, 77, 83, 168, 232
Caterpillar, 28
Chameleon, 11, 95, 147, 187, 258
Chick, 57, 265
Child, 252, 253
Ciona intestinalis, 230
Cobitis, 11, 146
Cod, 187, 190
Cow, 232
Crustacea, 92, 186, 230

DOG, 77, 83, 168, 232, 261
Dogfish, 146
Duck, 147

ECHINODERMS, 86, 92
Emys lutaria, 76, 190, 250, 258

FINCH, 187, 232, 265
Fish, 9, 93, 146, 187, 224, 225, 230, 265
Fowl, 11, 34, 76, 147, 190, 232, 250, 265
Frog, 76, 139, 147, 187, 190, 231, 232, 252, 258, 276, 277

GADUS lota, 187, 190
Garter snake, 276, 277
General, 10, 11, 92
Goat, 232
Gongylus, 231
Goose, 147, 232
Grass snake, 187, 258
Guinea-pig, 77, 78, 83, 89, 143, 144, 177, 232, 254, 261, 264, 300, 301, 303

HEDGEHOG, 261
Hemidactylus, 250
Hen, 35
Horse, 77, 168, 232, 262, 265
Hyla, 258

IGUANA, 258
Infant, 207, 236
Invertebrates, 9, 92, 186

KANGAROO, 303
Kingcrab, 28, 230

LACERTA, 11, 187, 190, 250, 258
Leuciscus, 187
Limulus, 28, 230
Lizard, 11, 95, 187, 257, 258

MAMMALS, 232, 258, 276
Mexican axolotl, 11
Molluscs, 92
Mouse, 77, 78, 83, 232, 303
Mudfish, 231

NEMERTINES, 224
Newly born, 109
Newt, 11, 147, 186, 258

OPHIOSAURUS acanthodactylus, 11, 187, 250
Ox, 77.

PERCH, 146, 187
Petromyzon, 76, 93, 146
Pig, 232, 262
Pigeon, 77, 96, 231, 232, 265
Platydactylus, 11
Polyodon, 34, 146, 230, 276, 277
Proteus, 258
Protopterus, 252
Puppy, 161

RABBIT, 78, 83, 102, 199, 225, 232, 252, 261, 264, 270, 303
Rana (*see* FROG)
Rat, 88, 120, 167, 168, 181, 232, 250, 262
Reptiles, 11, 94, 146, 187, 231, 232, 257
Ruminants, 169

SALAMANDER, 11, 13, 97, 147, 190, 258
Scincoid lizard, 11

Scorpion, 230
Scyllium, 76, 93, 225
Selacia, 33
Senegal finch, 232
Shark, 186
Sheep, 59, 168, 232
Siredon, 11, 147, 231, 250
Skink, 258
Sparrow, 76
Spelerpes, 258
Swan, 147
Swine, 169
Teal, 147
Tegenaria, 230
Teleosteans, 186, 230
Tinca, 11, 187
Torpedo, 93, 146, 230
Tortoise, 11, 147, 187, 224, 257, 258
Triton, 11, 76, 97, 147, 186, 231, 258
Tunicate, 230
Vertebrates, 143
White mouse, 232
Worms, 92

INDEX OF AUTHORS REFERRED TO IN THIS VOLUME.

Abetti, 226, 331
Abrami, 75, 77, 325
Achard and Ramond, 222, 331
— and Weil, 300, 334
Adami, 313, 335
Affanassiew, 85, 325
Alagna, 275, 334
Albrecht, 168
Alibert, 337
Altmann, 145, 339, 340, 362
Andrewes, 121, 327
Arneth, 78, 197, 214-217, 249, 330, 332
Arnold, 33, 225, 251, 252, 258, 331, 332, 333, 339, 340
Arnot, 309
Arnsperger, 291, 334
Asai, 161, 328
Ashenheim and Benjamin, 317, 335
— and Tomono, 253
Asher, 118, 141, 167, 329
Ashheim, 303
Askanazy, 55, 58, 78, 79, 80, 299, 301, 324, 334
Aubertin, 350, 354
— and Beaujard, 202, 330
Audry, 264
Auer, 9, 24, 323
Aynaud, 86, 326
Azzurini, 52, 167, 429

Baes and Lustig, 49
Baldoni, 139, 327
Banti, 40, 41, 301, 334
Bartel, 118, 141, 154, 328
Baum and Halle, 115, 130, 327
Baumgarten, 273
Beck, 339
Beckton, 145
Benacchio, 250, 252, 264, 332, 333
Benda, 70, 273, 288, 334, 341, 344, 350, 354
Bennecke, 235
Bergel, 31, 139, 142, 167, 184, 322, 327, 328, 329, 330
Berka, 254, 262, 333
Besredka, 184
Besançon et Labbé, 299
Bezançon, 118
Biebergeil, 75
Biedl and Decastello, 121
Biernacki, 91
Bilamioni, 202, 330
Bill, 184
Biondi, 77, 82, 325
Bizzozzero, 86, 326, 340
— and Salvioli, 55
— and Torro, 51, 324
Block, 63, 78
Blumenthal, 30, 40, 49, 67, 74, 93, 144, 167, 180, 208, 212, 323, 325, 329
Bogdanoff, 225, 331
Böllke, 79, 325
Bönniger, 63
Borka, 327
Borst, 285, 293, 334
Botkin, 283
Bottino, 226, 229, 331, 332
Braunstein, 167, 329
Bremer, 339, 349
Brockbank, 86, 87, 326
Brodie and Russell, 85, 87, 325
Brötz, 267, 333
Brown, 226, 331
Browning, 28, 322
Brücke, 362, 370
Brugsch and Schilling, 213, 214, 216, 330
Brumpt, 88, 326
Bruntz, 186, 230, 330, 332
Bryce, 324
Buch, 360
Buckmaster, 88, 326
Bunge, 73, 325
Bunting, 50, 86, 87, 323, 324, 326, 327
Burian and Schur, 140
Buschke-Hirschfeld, 309, 335
Butterfield, 32, 274

Cabot, 83, 325, 340
Carletti, 270
Carnegie Dickson, 45, 195, 330
Carnoy, 343
Caro, 327
Carpi, 182, 329
Castellino, 78, 339
Celli, 339
Centanni, 74
Cesare Biondi, 82, 325
Cesaris Demel, 75, 144, 229, 325, 331, 332, 366
Chauffard, 77
— and Fiessinger, 75, 325
Ciaccio, 51, 117, 120, 130, 142, 167, 177, 186, 198, 200, 205, 224, 225, 226, 227, 322, 324, 327—333, 343 351, 362, 365, 368
— and Pizzini, 161, 328
Cicaterri-Bono, 102, 326
Cohnheim, 142, 328, 366
Coie, 174, 329, 355
Coley, 309
Commessatti, 226, 331
Cornil, 353
Cottini, 98, 326
Creszenzi, 140, 167, 328
Cruikshank, 198, 330

Da Costa, 226, 331
Dantschakoff, 29, 34, 53, 57, 86, 206, 263, 322, 326, 330, 344, 365, 368
Danzelt, 35
Darier, 354, 361
David, 69, 324
Davis and Carlsson, 148, 328
v. Decastello, 305, 335
Decastello and Krjukoff, 87, 223, 331
Deetjen, 85, 214, 325, 330
Deganello, 273, 283
Dehler, 92, 144
Dekhuyzen, 326, 368
Demel (*see* Cesaris Demel)
Denys, 51, 118, 324
Deutschmann, 256
Dickson, Carnegie, 45, 195, 330
Dietrich, 62, 70, 72, 75, 80, 82, 306, 309, 324, 325, 335
Dinkler, 168, 329
Dixon and Malden, 38, 323
v. Domarus, 41, 42, 323, 358
Dominici, 33, 55, 273, 299, 303, 314, 330, 339, 353
Donzello, 101, 326
Downey, 34, 146, 223, 230, 276, 322, 323, 328, 331, 332, 334
Drozsda, 42, 309, 323
Drzewina, 34, 146, 224, 322, 328, 331
Duesberg, 49, 323
Dumas, 299
Dunger, 236, 332
Dutton, 9, 323
Duval, 292

Eberhardt, 95, 147, 326
Eberth, 86, 326
Ebner, 50, 303, 324
Ehrlich, 18, 19, 30, 41, 63, 66, 67, 71, 78, 79, 82, 91, 103, 136, 144, 171, 180, 222, 262, 264, 271, 333, 338, 342, 351, 352, 364, 365
Ehrlich-Lazarus, 103, 301, 334
Ehrlich-Pincus, 334
Eisen, 86, 326, 364, 367
Ellermann, 35, 41, 323
Eminet, 86, 326
Enderlen and Justi, 272, 273, 274, 333
Engel, 55, 56, 63, 66, 67, 78, 79, 87, 94, 103, 324, 344, 353, 356
Engel and Grüneberg, 28, 322
Eppinger, 253
Erben, 227, 331
Erdely, 140, 327
Erdmann, 299
Errera, 210, 212, 330
Ewing, 309

Fabian, 42, 306, 323, 335
Fahr, 262
Falte, 239, 253, 332
Faltin, 168, 329
Ferrata, 73, 75, 79, 90, 108, 144, 145, 176, 182, 325, 328, 329, 344, 365
— and Pappenheim, 178, 328, 329
— and Viglioli, 76, 78, 83, 325
Fiessinger, 77, 325
Fischel, 142, 328
Fischer, 71, 306, 335
Fleischmann, 35
Flemming, 114, 117, 303, 327, 353
Foa, 50, 75, 107, 199, 267, 317, 324, 335, 338
Foster, G., 255
— L., 297, 334
Fourgeot, 168, 329
Frank and Isaac, 305, 335
Fränkel-Much, 309
Freidsohn, 94, 146, 326, 328
Freytag, 65, 324, 337
Friedstein, 63, 82, 325, 327
Frumkin, 182, 329
Fry, 93, 146, 224, 230, 326, 328, 331, 332
Fuchs, 252
Fuld, 346, 357, 368
Furno, 232, 332

Gabriel, 83, 101
Gabritschewsky, 78
Galambos, 139, 327
Gardella, 227, 331
Gautier, 236, 332
Gerhartz, 142, 328
Ghedini, 197
Ghika, 299
Gibelli, 107, 327
Giglio Tos, 75, 84, 325
Gluzinski, 267
Goldmann, 278, 333
Gollasch, 251
Goodall, 59, 324, 335, 360
— and Gulland, 121
— — and Paton, 140, 328
Grawitz, 32, 33, 61, 63, 71, 72, 77–80, 103, 104, 112, 133, 140, 144, 145, 146, 177, 178, 180, 220, 309, 324, 325, 327, 347, 351, 353, 360
— and Rosenthal, 148
Griesbach, 71
Grimani, 274
Gross, 138, 167, 329
Grossenbacher, 167, 329
Grüneberg, 28, 78, 80, 178, 184, 231, 322, 332
Gruner, 50, 132, 199, 278, 298, 309, 322, 323, 327, 330, 334, 335
Grünsky, 184
Guarneri, 339
Gulland, 130, 144, 223, 331, 335

Hamel, 79
Hamer, 150, 328, 360
Hanstein, 340, 358
Hardy, 230, 332
Harris, 264, 272, 333
Hartwich, 82, 325
Harvey, 139, 327
Hayem, 88, 97, 326, 340, 345, 368
Hecker, 299
Hedinger, 112, 308, 327, 335
Heidenhaim, 13, 18, 50, 92, 213, 324, 326, 330, 339, 340, 365, 368
Heinecke, 32, 256, 299, 302
Heinz, 82, 325, 326, 367, 368
Helly, 30, 42, 111, 180, 205, 208, 212, 229, 273, 306, 330, 332, 334, 335, 344 349, 350, 352, 358, 360, 361

Hertz, 80, 250, 267, 270, 271, 303, 304, 307, 308, 325, 327, 333, 334, 335
Herzog, 82, 325
Hesse Thaysen, 123, 327
Hirschfeld, 24, 33, 41, 55, 62, 86, 102, 105, 232, 252, 297–299, 302, 303, 305, 306, 309, 323, 326, 327, 332, 334, 335, 339, 358
Hirschfeld Kossmann, 147, 187, 330
Hirt, 236
His, 53, 324, 362
Hofmann, 270, 333
Hofmeister, 150, 328
Horbaczewski, 230
Houston, 329
Howard, 255, 256, 333
Howell, 50, 83
Hoyer, 263
Huxley, 1
Hynek, 9, 114, 185, 323, 330

Isaac and Möckel, 52, 63, 103, 324
Israel, 141
Israel and Lazarus, 309
— and Pappenheim, 84, 325

Jadassohn, 273
Jagic, 133, 144, 181, 208, 328, 329, 330
Japha and Frankel, 300, 334
Jarotzky, 300, 334
Jawein, 79
Joannovics, 272, 275, 334
Jochmann, 227, 331
— and Blühdorn, 24, 323
— and Schumm, 42
Jolly, 66, 69, 83, 147, 180, 186, 261, 324, 328, 344, 345, 356, 361, 365
Jones, 357
Jordan, 69, 70, 324
Jungano, 167, 329

Källmark, 150, 327
Kämmerer, 253, 333
Kanitz, 323
Kanter and Goldmann, 310, 335
Kapinow, 107, 327
Kaplan, 229, 331
Kasarinoff, 10, 76, 96, 147, 187, 232, 250, 258, 265, 323, 326, 328, 330, 332, 333
Kasomoto, 82, 325
Kastanuchi, 50
Kalatschnikoff, 161, 328
Kelling, 291, 334
Kemp, 85, 325
Ketterer, 130
Keuthe, 116, 138, 139, 236, 327, 332
Kimla, 299
Klein, 32, 125, 134, 145, 250, 252, 274, 299, 322, 328
Kling, 130
Klose, 308, 335
Knoll, 13, 323
Koeppe, 71
Kölliker, 50, 67, 323
Kollmann, 224, 230, 332
König, 78
Körmöczi, 154, 328
Kostanecki, 59, 324
Krämer, 109, 327
Krause, 236, 332
Krehl, 103, 326
Kreibich, 252, 332
Kriser, 239, 332
Krompecher, 260, 263, 273, 283, 293, 334, 364
Kronberger, 70, 142, 324
Kundrat, 41, 306, 335, 355
Kurloff, 329
Kurpjuweit, 299, 303

Labbe, 118, 328
Langaron, 89
La Roy, 314, 335, 355
Lavdovsky, 361, 363
Lazarus, 79, 351
Leber, 227, 331
Lehndorff, 30, 41, 42, 323
Leighton, 256, 323, 333
Leo, 272
Lepine and Popoff, 236, 332
Levaditi, 141, 144, 260
Levy, 38, 323
Lewin, 310, 335
Lewis, 169, 324, 329
Leydig, 346
Lieberkühn, 70, 169, 324
Lifschitz, 50, 192, 324, 330
Lindberg, 34, 283, 322
Litten, 91, 168, 291, 329, 334
Liubomadrow, 150
Lobenhoffer, 59, 324
Loeb, 28, 221, 222, 322, 331
Loebe and Michaud, 139, 327
Loele, 62, 121, 163, 227, 251, 263, 324, 327, 328, 332
Loew and Bokorny, 223, 331
Löhner, 69, 71, 324
Longcope, 199, 330
Lortol-Jacob, 184
Lossen, 207, 330
Löwit, 9, 33, 88, 112, 225, 236, 323, 331, 334, 343, 351
Luce, 109, 327
Lucibelli, 199, 330
Lüdke, 38, 291, 323, 334
Luksch, 267
Luzet, 88, 326

Mabee, 307, 335
MacCallum, 141
McDonagh, 177
Maciesco-Jalenska, 274, 275, 333
Macintyre and Down, 360
Maclachlan, 118, 327
Magi, 223, 239
Malassez, 344, 365
Mangubi-Kudrjavtzewa, 158, 328
Manuchin, 239, 332
Maragliano, 78, 339
Marchand, 247, 291, 303, 334, 350, 356, 357, 360, 364, 366
Marchiafava, 182
Marcuse, 122, 327
Mareiwitz, 302

Marino, 225, 331
Marlin, 5
Marschalko, 268, 273, 283, 293, 356, 364
Martelli, 227, 331
Martinotti, 283
Marwedel, 252, 332
Massart and Bordet, 221, 331
Maurer, 77, 325
Maximow, 29, 32, 33, 52, 53, 55, 57, 59, 66, 80, 87, 111, 180, 186, 198, 247, 261, 273, 283, 293, 322, 327, 330, 339, 344, 354, 356, 358, 366
Meirowsky, 263, 333, 366
Meisner, 227, 331
Mestral, 186, 330
Metchnikoff, 162, 171, 183, 186, 221, 231, 329, 353, 354, 357, 366
— and Tarassewitch, 118, 327
Meves, 92, 97, 145, 326, 328
Meyer, Erik, 32, 33, 41, 63, 92, 236, 299, 302, 306, 335, 358
Michæli, 267, 314, 335
Michælis, 221, 261, 267, 283, 331, 353
— and Wolff, 260, 333
— and Wolff Eisner, 143, 328
Milkowitsch, 222, 236, 331, 332
Miller, 276, 333
Milligan, 307, 335
Minkowski, 200, 330
Minor and Ringer, 218
Minot, 340
Mirano, 236, 332
Mollier, 58, 158, 324, 328
Mondino, 97, 339
Morawitz, 30, 357, 365
Morris, 83
Morse, 24, 85, 323, 325
Mosler, 168, 329
Mosse, 41, 86, 326
Mühlman, 98, 223, 331
Muir, 85, 325, 330
Müller, 52, 98, 99, 291, 326, 334
Müller and Jochmann, 227, 331
Müller and Rieder, 346
Mya, 63

Naegeli, 24, 28, 30, 31, 41, 63, 79, 92, 111, 115, 144, 171, 205, 247, 256, 299, 303, 322, 323, 352, 353, 354, 356
Nattan-Larier, 299
Nauwerk and Moritz, 299
Negri, 75
Neisser, 273
Neukerich, 226, 331
Neumann, 29, 33, 41, 46, 67, 97, 98, 214, 216, 299, 301, 303, 304, 322, 323, 326, 327, 330, 334, 361
Neusser, 253, 363
Nicholas, 326
Nickel, 251, 332
Niegolewski, 147, 232
v. Noorden, 72, 325
Norris, 72, 325
Nothnagel, 42, 337, 360

Oehme, 112, 327
Ogata, 50, 324
Opie, 253, 254, 256, 300, 333
Orsós, 69, 324
Orth, 285, 334, 347
Oser and Pribram, 167
Overton, 72
Oxner, 33, 224

Pachon and Gachet, 167
Palma, 42, 309, 323
Paltauf, 41, 299, 334
Pander, 362, 370
Paneth, 362
Pappenheim, 5, 9, 10, 12, 13, 18, 19, 23, 24, 28, 30, 33, 35, 41, 50, 54, 60, 62, 63, 66, 67, 75–78, 82–84, 89, 92, 94, 97, 98, 100, 101, 103, 104, 109, 111, 114, 116, 130, 142, 143, 144, 145, 153, 172, 174, 177, 180, 186, 205, 210, 220, 221, 225, 226, 228, 232, 233, 234, 247, 250, 263, 267, 268, 271, 274, 283, 291, 294, 297, 300, 303, 304, 305, 306, 309, 310, 314, 315, 322-335, 344, 346, 347-351, 353, 357, 366
— and Ferrata, 328, 329
Paremusoff, 179, 190, 191, 304, 329, 330, 335
Pascheff, 122, 255, 283, 327, 333
Patella, 171, 177, 181, 182, 283, 329, 343, 352–354, 363, 367
Pauliczek, 167, 317, 329
Pavy, 139
Pawlow, 167
Peckelharing, 365
Penny, 150, 184, 328, 330
Perlmeschko, 49, 161, 323, 328
Petry, 251, 252, 253, 332
Petterson, 351
Pfeiffer and Wassermann, 141
Pincus, 30, 41
Pirone, 115, 162, 201, 252, 255, 275, 327, 328, 330, 332, 333, 334
Plehn, 91, 339
Podwyssozki, 292, 334
Poggi, 75
Pohl, 139, 328
Pol, 83
Poletaew, 150
Policard and Mawas, 186, 330
Pollitzer, 220, 223, 331
Popielski, 167, 329
Porter, 98, 326
Pratt, 85, 325
Preisisch and Heim, 86, 326
Proell, 272, 333
Pröscher, 141, 153, 254, 265, 328, 333
Pugliese, 49, 323

Quain, 169, 329
Quarelli and Bottino, 226, 229, 331, 332

Radasch, 324
Radford, 168, 329
Randnitz, 263
Rawitz, 98, 326
Rechzeh, 78
Recklinghausen, 96, 326
Reed, 358
Reichenstein, 267

Reicher, 98, 252, 326, 333
Reid, 85, 325
Renaud, 369
Rheindorf, 265, 274
Ribadeau, 299
Ribbert, 42, 286, 297, 306, 327, 330
Rieder, 350, 366
Rieux, 184, 330
Rindfleisch, 66, 323
Ringer, 218
Riva and Zoja, 75, 325
Roberts, 70, 324
Robertson, 170
Rollett, 71, 324
Romanowsky, 143
Rona and Takhaschi, 73, 325
Roscoe King, 69, 86, 324, 326
Rosenthal, 73, 82, 98, 132, 149, 325, 326, 328
Rosin, 75, 340, 345, 356, 360
Rosin Demel, 366
Ross, 65, 80, 132, 137, 241, 325, 332, 339, 349
Roth, 249, 332
Rous, 139, 252, 254, 327, 333
Roux and Driesch, 74
Rubens, Duval et Fage, 118, 327
Rubinstein, 109, 304, 327, 335
Runeberg, 42
Russo, 220, 331

Saar, 80
Sabin, 130
Sabrazes, 79, 94, 96, 326
— et Lafon, 265, 333
— et Muratet, 93, 96, 146, 225, 230, 231, 232, 326, 328, 332
— — et Durroux, 232, 332
Sacharoff, 252
Sala, 97, 326
Sanfelice, 50, 323
Sansanow, 255, 333
Sapegno, 61, 69, 85, 176, 227, 324, 329
Sattler, 73, 325
Saxer, 58, 130, 324, 354, 356
Schäfer, 53, 69, 71, 85, 86, 220, 324, 326, 331, 349, 352, 357, 359, 364
Schatiloff, 299, 334
Schaumann, 79, 92
Schifone, 184, 232, 330, 332
Schilling, 61, 64, 65, 69, 70, 77, 80, 87, 88, 89, 213, 214, 216, 218, 220, 324, 325, 326, 331
Schimmelbusch, 86, 326
Schleip, 33, 83, 325, 347, 353, 354
Schlesinger, 273, 276, 334
Schlicht, 254
Schmauch, 339
Schmidt, 12, 42, 78, 80, 83, 117, 123, 301, 323, 327, 335
Schmorl, 112
Schneider, 224, 264, 331, 351
Schottländer, 273, 283, 293
Schreiber, 264
Schridde, 19, 30, 32, 41, 49, 50, 87, 111, 122, 123, 150, 180, 206, 207, 247, 251, 256, 264, 268, 271, 273, 283, 285, 299, 322, 323, 327, 330, 334, 341, 342, 349, 351, 354, 356, 360, 361, 365
Schwalbe, 339
— and Solley, 82, 325
Schwenter-Trechler, 263
Schüffner, 77, 325
Schuhmacher, 122
Schultz, 71
Schultze, 35, 89, 339
Schumberg, 148
Schur and Grawitz, 225
Schwarz, 225, 252, 255, 331, 332, 333
— and Michælis, 301, 334
Scott, 303
Scotti, 167, 329
Scrimger, 297, 334
Selling, 149, 239, 300, 328, 332, 334
Senator, 109, 327
Sergent, 88, 326
Sherrington and Balance, 272
Siegfried, 164, 328
Simon, 255, 299
Sirensky, 141
Sluka, 83, 325
Smith, 285, 333
Spadaro, 179, 329
Spiegelberg, 360
Spilling, 367
Spodara, 85, 325
Staffel, 271
— and Rheindorf, 265

Stephan, 231, 252, 332, 333
Sternberg, 28, 30, 33, 41, 42, 50, 87, 134, 300, 303, 322, 326, 334, 350, 353, 354, 360, 367
Stewart, 72, 324
Stheemann, 118, 327
Stöhr, 112, 255
Strausz, 42, 309, 323
v. d. Stricht, 50, 343
Swart, 299
Swingle, 85, 325
Szokalski, 167, 329

Tettenhamer, 253
Thayer, 61, 324
Thoma, 119
Thomson, 5
Timofijwsky, 51 (footnote)
Tomaszewski, 291, 334
Tommassi, 49, 50, 323
Torday and Schwartz, 141
Tos, 75, 84, 325
Tousset and Troisier, 227, 331
Trincas, 100, 326
Troje, 352–354
Trousseau, 347
Tschistowitsch, 142, 328
Tsunota, 330
Türk, 33, 41, 63, 78, 111, 114, 171, 246, 283, 349, 353, 354, 355, 363

Unna, 261, 262, 268, 271, 272, 333, 364, 369
Uskoff, 299

Vaquez, 364
Vassale, 75
Verson, 49, 323

Vincent and Harrison, 160, 329
Virchow, 42, 195, 309, 323
Voswinckel, 35
— and Dunzelt, 291, 334

WALDEYER, 268
Walker, 49, 77, 198, 323, 330
— Ross and Moore, 70, 84, 324, 325
Wallgren, 32, 270, 274, 333
Walz, 303, 351
Wanters, 141
Warthin, 169, 309, 329
Washburn, 91
Wassermann, 118
Weichselbaum, 24, 323
Weidenreich, 33, 38, 67, 69, 71, 75, 78, 87, 111, 114, 146, 180, 216, 221, 229, 252, 257, 261, 263, 264, 283, 303, 323, 324, 327, 343, 344, 352, 354, 358, 369
Weil, 299
Weiss, 251, 332
v. Wendt, 123, 327
Wenzlaff, 96, 326
Werigo and Jaguinow, 50, 324
Werner, 295
Wernstedt, 236, 332
Werzberg, 9, 10, 35, 76, 88, 92, 97, 98, 145, 147, 187, 190, 250, 257, 300, 301, 304, 323, 326, 328, 330, 333, 334
Widal, 75, 77
— et Abrami. 75, 77, 101, 325, 326
Wieland, 360
Wiener, 98, 326
Wiens, 227, 331
Wiens-Schlecht, 251, 332
Wiesner, 340
Winkler, 168, 222, 329, 331
Wlassow, 339
Wolf, 275, 276, 333
Wolff, 180, 299, 303, 351, 353, 354, 355, 362, 370
Wolff and Arpad, 141
Wolff-Eisner, 338
Woltmann, 170, 254, 329, 333
Wooldridge, 88
Woskressenski, 226, 331
Wright, 50, 85, 87, 98, 323, 324, 325, 326

YAMASAKI, 306, 309, 335

ZAHN, 360
Zehner, 239, 332
Zenoni, 339
Ziegler, 30, 35, 41, 42, 63, 103, 111, 180, 247, 273, 334, 335, 354, 355, 358, 359, 360
Zimmermann, 167, 329, 340, 342
Zoja, 22, 29, 38, 51, 73, 74, 107, 229, 236, 237, 322, 323, 325, 332, 344, 350, 352, 353, 359, 365, 370
Zuntz, 148

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