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Color Atlas of Hematology

Practical Microscopic and Clinical Diagnosis

血液学彩色图谱

2nd revised edition

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Color Atlas of Hematology

Practical Microscopic and Clinical Diagnosis

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Preface

Our Current Edition

Although this is the second English edition of our hematology atlas, this edition is *completely new*. As an immediate sign of this change, there are now three authors. The completely updated visual presentation uses digital images, and the content is organized according to the most up-to-date morphological classification criteria.

In this new edition, our newly formed team of authors from Munich (the "Munich Group") has successfully shared their knowledge with you. Heinz Diem and Torsten Haferlach are nationally recognized as lecturers of the diagnostics curriculum of the German Association for Hematology and Oncology.

Goals

Most physicians are fundamentally "visually oriented." Apart from immediate patient care, the microscopic analysis of blood plays to this preference. This explains the delight and level of involvement on the part of practitioners in the pursuit of morphological analyses.

Specialization notwithstanding, the hematologist wants to preserve the opportunity to perform groundbreaking diagnostics in hematology for the general practitioner, surgeon, pediatrician, the MTA technician, and all medical support personnel. New colleagues must also be won to the cause. Utmost attention to the analysis of hematological changes is essential for a timely diagnosis.

Even before bone marrow cytology, cytochemistry, or immunocytochemistry, information based on the analysis of blood is of immediate relevance in the doctor's office. It is central to the diagnosis of the diseases of the blood cell systems themselves, which make their presence known through changes in blood components.

The exhaustive quantitative and qualitative use of hematological diagnostics is crucial. Discussions with colleagues from all specialties and teaching experience with advanced medical students confirm its importance. In cases where a diagnosis remains elusive, the awareness of the next diagnostic step becomes relevant. Then, further investigation through bone marrow, lymph node, or organ tissue cytology can yield firm results. This pocket atlas offers the basic knowledge for the use of these techniques as well.

Organization

Reflecting our goals, the inductive organization proceeds from simple to specialized diagnostics. By design, we subordinated the description of the bone marrow cytology to the diagnostic blood analysis (CBC). However, we have responded to feedback from readers of the previous editions and have included the principles of bone marrow diagnostics and non-ambiguous clinical bone marrow findings so that frequent and relevant diagnoses can be quickly made, understood, or replicated.

The nosology and differential diagnosis of hematological diseases are presented to you in a tabular form. We wanted to offer you a pocketbook for everyday work, not a reference book. Therefore, morphological curiosities, or anomalies, are absent in favor of a practical approach to morphology. The cellular components of organ biopsies and exudates are briefly discussed, mostly as a reminder of the importance of these tests.

The images are consistently photographed as they normally appear in microscopy (magnification 100 or 63 with oil immersion lens, occasionally master-detail magnification objective 10 or 20). Even though surprising perspectives sometimes result from viewing cells at a higher magnification, the downside is that this by no means facilitates the recognition of cells using your own microscope.

Instructions for the Use of this Atlas

The organization of this atlas supports a systematic approach to the study of hematology (see Table of Contents). The index offers ways to answer detailed questions and access the hematological terminology with references to the main description and further citations.

The best way to become familiar with your pocket atlas is to first have a cursory look through its entire content. The images are accompanied by short legends. On the pages opposite the images you will find corresponding short descriptive texts and tables. This text portion describes cell phenomena and discusses in more detail further diagnostic steps as well as the diagnostic approach to disease manifestations.

Acknowledgments

Twenty years ago, Professor Herbert Begemann dedicated the foreword to the first edition of this hematology atlas. He acknowledged that—beyond cell morphology—this atlas aims at the clinical picture of patients. We are grateful for being able to continue this tradition, and for the impulses from our teachers and companions that make this possible.

We thank our colleagues: J. Rastetter, W. Kaboth, K. Lennert, H. Löffler, H. Heimpel, P.M. Reisert, H. Brücher, W. Enne, T. Binder, H.D. Schick, W. Hiddemann, D. Seidel.

Munich, January 2004 Harald Theml, Heinz Diem, Torsten Haferlach

Contents

Physiology and Pathophysiology of Blood Cells: Methods and Test Procedures

Introduction to the Physiology and Pathophysiology of the Hematopoietic System

The reason why quantitative and qualitative diagnosis based on the cellular components of the blood is so important is that blood cells are easily accessible indicators of disturbances in their organs of origin or degradation—which are much less easily accessible. Thus, disturbances in the erythrocyte, granulocyte, and thrombocyte series allow important conclusions to be drawn about bone marrow function, just as disturbances of the lymphatic cells indicate reactions or disease states of the specialized lymphopoietic organs (basically, the lymph nodes, spleen, and the diffuse lymphatic intestinal organ).

Cell Systems

All blood cells derive from a common stem cell. Under the influences of local and humoral factors, stem cells differentiate into different

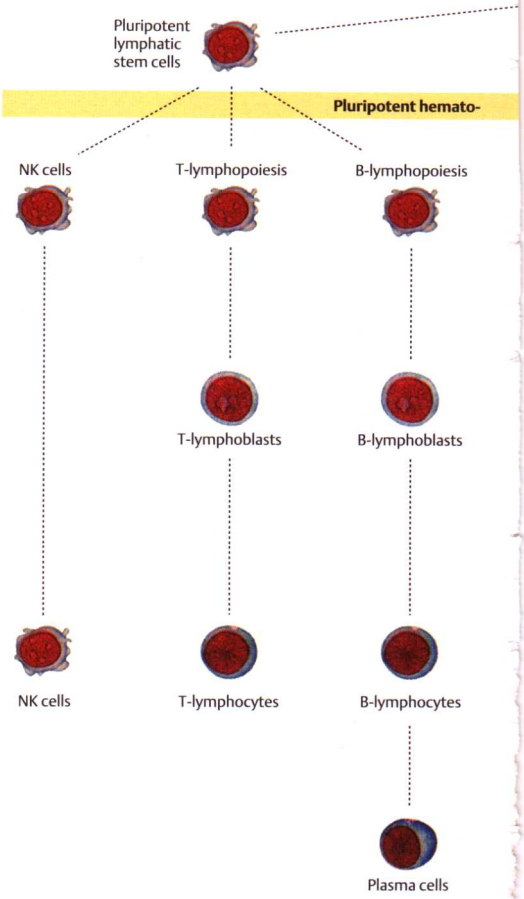
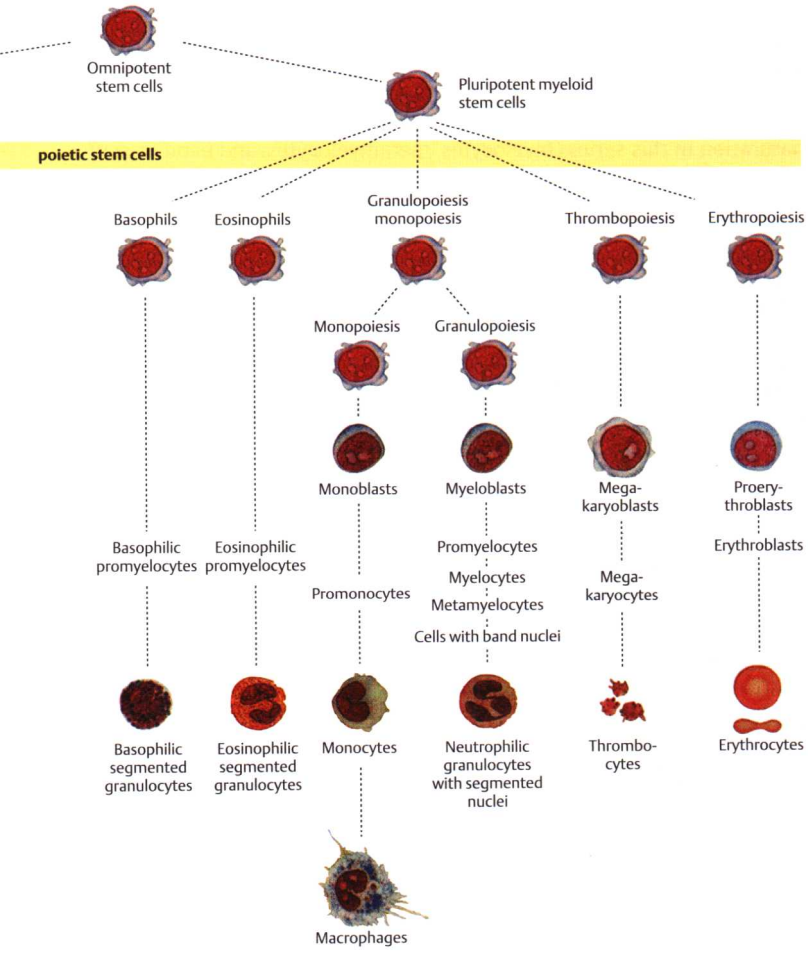


Fig. 1 Model of cell lineages ▶ in hematopoiesis

cell lines (Fig. **1**). Erythropoiesis and thrombopoiesis proceed independently once the stem cell stage has been passed, whereas monocytopoiesis and granulocytopoiesis are quite closely "related." Lymphocytopoiesis is the most independent among the remaining cell series. Granulocytes, monocytes, and lymphocytes are collectively called leukocytes (white blood cells), a term that has been retained since the days before staining



methods were available, when the only distinction that could be made was between erythrocytes (red blood cells) and the rest.

All these cells are eukaryotic, that is, they are made up of a nucleus, sometimes with visible nucleoli, surrounded by cytoplasm, which may include various kinds of organelles, granulations, and vacuoles.

Despite the common origin of all the cells, ordinary light microscopy reveals fundamental and characteristic differences in the nuclear chromatin structure in the different cell series and their various stages of maturation (Fig. **2**).

The developing cells in the granulocyte series (myeloblasts and promyelocytes), for example, show a delicate, fine "net-like" (reticular) structure. Careful microscopic examination (using fine focus adjustment to view different depth levels) reveals a detailed nuclear structure that resembles fine or coarse gravel (Fig. **2a**). With progressive stages of nuclear maturation in this series (myelocytes, metamyelocytes, and band or staff cells), the chromatin condenses into bands or streaks, giving the nucleus—which at the same time is adopting a characteristic curved shape—a spotted and striped pattern (Fig. **2b**).

Lymphocytes, on the other hand—particularly in their circulating forms—always have large, solid-looking nuclei. Like cross-sections through geological slate, homogeneous, dense chromatin bands alternate with lighter interruptions and fissures (Fig. **2c**).

Each of these cell series contains precursors that can divide (blast precursors) and mature or almost mature forms that can no longer divide; the morphological differences between these correspond not to steps in mito-

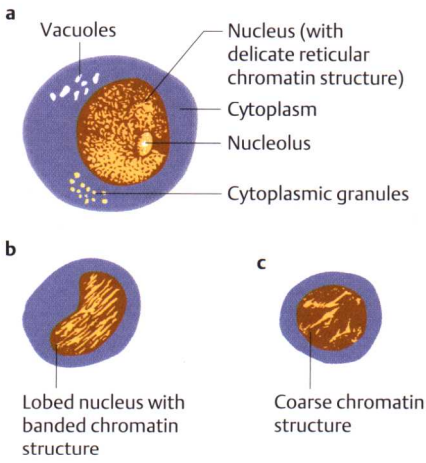


Fig. **2** Principles of cell structure with examples of different nuclear chromatin structure. **a** Cell of the myeloblast to promyelocyte type. **b** Cell of the myelocyte to staff or band cell type. **c** Cell of the lymphocyte type with coarsely structured chromatin

sis, but result from continuous "maturation processes" of the cell nucleus and cytoplasm. Once this is understood, it becomes easier not to be too rigid about morphological distinctions between certain cell stages. The blastic precursors usually reside in the hematopoietic organs (bone marrow and lymph nodes). Since, however, a strict blood–bone marrow barrier does not exist (blasts are kept out of the bloodstream essentially only by their limited plasticity, i.e., their inability to cross the diffusion barrier into the bloodstream), it is in principle possible for any cell type to be found in peripheral blood, and when cell production is increased, the statistical frequency with which they cross into the bloodstream will naturally rise as well. Conventionally, cells are sorted left to right from immature to mature, so an increased level of immature cells in the bloodstream causes a "left shift" in the composition of a cell series—although it must be said that only in the precursor stages of granulopoiesis are the cell morphologies sufficiently distinct for this left shift to show up clearly.

The distribution of white blood cells outside their places of origin cannot be inferred simply from a drop of capillary blood. This is because the majority of white cells remain out of circulation, "marginated" in the epithelial lining of vessel walls or in extravascular spaces, from where they may be quickly recruited back to the bloodstream. This phenomenon explains why white cell counts can vary rapidly without or before any change has taken place in the rate of their production.

Cell functions. A brief indication of the functions of the various cell groups follows (see Table **1**).

Neutrophil granulocytes with segmented nuclei serve mostly *to defend against bacteria.* Predominantly outside the vascular system, in "inflamed" tissue, they phagocytose and lyse bacteria. The blood merely transports the granulocytes to their site of action.

The function of **eosinophilic granulocytes** is *defense against parasites*; they have a direct cytotoxic action on parasites and their eggs and larvae. They also play a role in the *down-regulation of anaphylactic shock reactions* and autoimmune responses, thus controlling the influence of basophilic cells.

The main function of **basophilic granulocytes** and their tissue-bound equivalents (tissue mast cells) is to regulate circulation through the release of substances such as histamine, serotonin, and heparin. These tissue hormones *increase vascular permeability* at the site of various local antigen activity and thus regulate the influx of the other inflammatory cells.

The main function of **monocytes** is the defense against *bacteria, fungi, viruses,* and *foreign bodies.* Defensive activities take place mostly outside the vessels by phagocytosis. Monocytes also break down endogenous cells (e.g., erythrocytes) at the end of their life cycles, and they are assumed to perform a similar function in defense against tumors. Outside the bloodstream, monocytes develop into histiocytes; macrophages in the

endothelium of the body cavities; epithelioid cells; foreign body macrophages (including Langhans' giant cells); and many other cells.

Lymphocytes are divided into two major basic groups according to function.

Thymus-dependent T-lymphocytes, which make up about 70% of lymphocytes, provide *local defense against antigens* from organic and inorganic foreign bodies in the form of delayed-type hypersensitivity, as classically exemplified by the tuberculin reaction. T-lymphocytes are divided into helper cells and suppressor cells. The small group of NK (natural killer) cells, which have a direct cytotoxic function, is closely related to the T-cell group.

The other group is the bone-marrow-dependent B-lymphocytes or B-cells, which make up about 20% of lymphocytes. Through their development into immunoglobulin-secreting plasma cells, B-lymphocytes are responsible for the entire *humoral side of defense* against viruses, bacteria, and allergens.

Table **1** Cells in a normal peripheral blood smear and their physiological roles

Cell type	Function	Count (% of leukocytes)
Neutrophilic band granulocytes (band neutrophil)	Precursors of segmented cells that provide antibacterial immune response	0–4%
Neutrophilic segmented granulocyte (segmented neutrophil)	Phagocytosis of bacteria; migrate into tissue for this purpose	50–70%
Lymphocytes (B- and T-lymphocytes, morphologically indistinguishable)	B-lymphocytes (20% of lymphocytes) mature and form plasma cells → antibody production. T-lymphocytes (70%): cytotoxic defense against viruses, foreign antigens, and tumors.	20–50%
Monocytes	Phagocytosis of bacteria, protozoa, fungi, foreign bodies. Transformation in target tissue	2–8%
Eosinophilic granulocytes	Immune defense against parasites, immune regulation	1–4%
Basophilic granulocytes	Regulation of the response to local inflammatory processes	0–1%

Erythrocytes are the oxygen carriers for all oxygen-dependent metabolic reactions in the organism. They are the only blood cells without nuclei, since this allows them to bind and exchange the greatest number of O_2 molecules. Their physiological biconcave disk shape with a thick rim provides optimal plasticity.

Thrombocytes form the aggregates that, along with humoral coagulation factors, close up vascular lesions. During the aggregation process, in addition to the mechanical function, thrombocytic granules also release factors that promote coagulation.

Thrombocytes develop from polyploid megakaryocytes in the bone marrow. They are the enucleated, fragmented cytoplasmic portions of these progenitor cells.

Principles of Regulation and Dysregulation in the Blood Cell Series and their Diagnostic Implications

Quantitative and qualitative equilibrium between all blood cells is maintained under normal conditions through regulation by humoral factors, which ensure a balance between cell production (mostly in the bone marrow) and cell degradation (mostly in the spleen, liver, bone marrow, and the diffuse reticular tissue).

Compensatory increases in cell production are induced by cell loss or increased cell demand. This compensatory process can lead to qualitative changes in the composition of the blood, e.g., the occurrence of nucleated red cell precursors compensating for blood loss or increased oxygen requirement, or following deficiency of certain metabolites (in the restitution phase, e.g., during iron or vitamin supplementation). Similarly, during acute immune reactions, which lead to an increased demand for cells, immature leukocyte forms may appear ("left shift").

Increased cell counts in one series can lead to *suppression* of cell production in *another series*. The classic example is the suppression of erythrocyte production (the pathomechanical details of which are incompletely understood) during infectious/toxic reactions, which affect the white cells ("infectious anemia").

Metabolite deficiency as a pathogenic stimulus affects the *erythrocyte series* first and most frequently. Although other cell series are also affected, this series, with its high turnover, is the one most vulnerable to metabolite deficiencies. Iron deficiency, for example, rapidly leads to reduced hemoglobin in the erythrocytes, while vitamin B_{12} and/or folic acid deficiency will result in complex disturbances in cell formation. Eventually, these disturbances will start to show effects in the other cell series as well.

Toxic influences on cell production usually affect *all cell series*. The effects of toxic chemicals (including alcohol), irradiation, chronic infections, or tumor load, for example, usually lead to a greater or lesser degree of suppression in all the blood cell series, lymphocytes and thrombocytes being the most resistant. The most extreme result of toxic effects is panmyelophthisis (the synonym "aplastic anemia" ignores the fact that the leukocyte and thrombocyte series are usually also affected).

Autoimmune and allergic processes may *selectively affect* a *single cell series*. Results of this include "allergic" agranulocytosis, immunohemolytic anemia, and thrombocytopenia triggered by either infection or medication. Autoimmune suppression of the pluripotent stem cells can also occur, causing panmyelophthisis.

Malignant dedifferentiation can basically occur in *cells of any lineage at any stage where the cells are able to divide*, causing chronic or acute clinical manifestations. These deviations from normal differentiation occur most frequently in the white cell series, causing "leukemias." Recent data indicate that in fact in these cases the remaining cell series also become distorted, perhaps via generalized atypical stem cell formation. Erythroblastosis, polycythemia, and essential thrombocythemia are examples showing that malignant processes can also manifest themselves primarily in the erythrocyte or thrombocyte series.

Malignant "transformations" always affect blood cell precursors that are still capable of dividing, and the result is an accumulation of identical, constantly self-reproducing blastocytes. These are not necessarily always observed in the bloodstream, but can remain in the bone marrow. That is why, in "leukemia," it is often not the number of cells, but the increasing lack of normal cells that is the indicative hematological finding.

All disturbances of bone marrow function are accompanied by quantitative and/or qualitative changes in the composition of *blood cells* or *blood proteins*. Consequently, in most disorders, careful analysis of changes in the blood together with clinical findings and other laboratory data produces the same information as bone marrow cytology. The relationship between the production site (bone marrow) and the destination (the blood) is rarely so fundamentally disturbed that hematological analysis and humoral parameters will not suffice for a diagnosis. This is virtually always true for *hypoplastic–anaplastic* processes in one or all cell series with resulting cytopenia but without hematological signs of malignant cell proliferation.