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Atlas of Clinical Hematology

6th Edition

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Initiated by L. Heilmeyer
and H. Begemann

Sixth Revised Edition

With 199 Figures, in 1056 separate Illustrations,
Mostly in Color, and 17 Tables

Springer

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Preface to the Sixth Edition

Soon after the 5th edition of this volume appeared, the WHO published details on the pathology and genetics of the hematopoietic and lymphatic tissues. Work in progress found in short journal articles had already been integrated into the last edition. Now it was possible to incorporate the new proposals for classification and diagnosis and to include figures of new types of leukemia and lymphoma. These include leukemias of dendritic cells, intravascular large B-cell lymphoma, the liver-spleen T-cell lymphoma as well as persistent polyclonal B-cell lymphocytosis, which is placed between benign and malignant.

The present volume completes and extends the cytogenetic and molecular-genetic characterization of the different diseases and incorporates new figures. At this point we would like to thank PD Dr. Claudia Schoch, Munich, for her valuable help and for graciously providing new zytogenetic and FISH figures. In addition, several figures and tables were replaced, and a schematic drawing of the topography of lymphoma infiltration in bone marrow (courtesy of Prof. Dr. H.E. Schaefer, Freiburg) was added to the lymphoma chapter.

Even in 2004, diagnosis in hematology and lymphomas starts, as a rule, with the morphological examination of blood, bone marrow or lymphatic tissues. It can direct the subsequent use of immunophenotyping, cytogenetics and molecular genetics, in this way demonstrating ways of saving money and avoiding unnecessary investigations.

Gene expression profiling and, in the future, proteomics still represent very expensive methods that must find their place in diagnosis and prognostic evaluation. Gene profiling studies have already confirmed morphological subtypes in AML, e.g., M3 and M3V, which cannot be distinguished into strictly separate groups by cytogenetic and molecular-genetic methods. New therapeutic measures (especially immunotherapy) have brought interesting progress into the MDS group. For example, the biological entity 5q minus syndrome, which is well defined by morphology and cytogenetics, responds very well to treatment with the thalidomide derivative CC 5013. The fusion gene BCR-ABL, which was originally detected by cytogenesis and is today routinely detected by FISH or PCR in CML, was the first example of a specifically tailored molecular therapy in a tumor; certainly other examples will follow. Cases of ALL involving t(9;22), t(4;11) and t(8;14) have also been established as separate prognostic groups with special therapeutic problems.

All of these examples demonstrate that a comprehensive arsenal of diagnostic methods has to be used today for diagnostic and prognostic decisions and individualized therapeutic planning.

We are again grateful to Prof. Dr. R. Disko of Munich who agreed to revise and update the chapter on the principal causative agents of tropical diseases. Finally we wish to thank Mrs. Stephanie Benko and the entire staff of Springer-Verlag in Heidelberg as well as Ms. Marina Litterer at ProEdit GmbH for their thoughtful and effective support.

Preface to the Fifth Edition

The first edition of the Atlas of Clinical Hematology was published over 40 years ago. The first four editions were coauthored by Herbert Begemann, who died unexpectedly in April of 1994. We wish to dedicate the fifth edition as a memorial to this dedicated physician and hematologist.

Since the fourth edition was published in 1987, hematology has undergone profound changes. New methods such as cytochemistry and immunophenotyping have been joined by cytogenetics and, more recently, molecular genetic techniques, which have assumed a major role in routine diagnostic procedures. This has been due in part to significant advances in methodology and new tools in molecular biology. When used in standardized protocols, these tools can furnish swift results that are relevant to patient care. Since the advent of cytogenetics and molecular genetics, we have formulated new definitions for clinical and biological entities. An example is promyelocytic leukemia with its two variants (M3 and M3v), the (15;17) translocation, and the PML/RARA fusion gene, which has been successfully treated for the first time with differentiation therapy. Another example is acute myelomonocytic leukemia with abnormal eosinophiles (M4Eo), inversion 16, and the MYH/11/CBFB fusion gene, which has a very good prognosis. The transmission of morphologic findings by electronic data transfer is also gaining importance in hematology, as it permits the immediate review of difficult findings by specialists. Several colleagues seated at their own desks and microscopes can communicate with one another instantaneously by computer monitor. These advances do not alter the fact that hematologists must still have a sound grasp of morphologic principles. Diagnostic problems often arise when modern counting devices and cell sorters, with their impressive capabilities, are used without regard for cellular morphology. There is no question that classical morphology has gained much from its competition and comparison with the new techniques, leading to significant diagnostic and prognostic advances.

While retaining the basic concept of the previous editions, we found it necessary to eliminate several chapters. Now that many hematologic centers and laboratories are equipped with fluorescence-activated cell sorters (FACS) for immunotyping, and given the availability of reliable commercial kits and precise staining instructions for immunocytochemistry, the chapter by B. R. Kranz has been omitted from the present edition. We have also dropped the methodology section and most of the electron micrographs supplied by Prof. D. Huhn. Both colleagues merit our sincere thanks. Ever since the first edition, Prof. W. Mohr of Hamburg has authored the chapter on blood parasites as the principal causative agents of tropical diseases, and we gratefully acknowledge his contribution. Following the death of Prof. Mohr, we have chosen to include this chapter owing to the special importance of tropical diseases in the modern world. We are grateful to Prof. R. Disko of Munich, who agreed to revise and update the chapter.

The chapters on chronic myeloproliferative diseases, and especially those dealing with myelodysplasias, acute leukemias, malignant lymphomas, and malignant mastocytoses, had to be extensively revised or rewritten. We have added new sections and illustrations on therapy-induced bone marrow changes, cytologic changes in the cerebrospinal fluid due to leukemic or lym-

phomatous meningeal involvement, and NK cell neoplasias. We have also endeavored to give due attention to issues in pediatric hematology.

In compiling this revised fifth edition, in which over 90 % of the illustrations are new, we benefited greatly from our two decades of central morphological diagnostics for the ALL and AML studies in adults and the morphological consulting of the BFM treatment study on AML in children (H. L.). We thank the directors of these studies, Professors D. Hoelzer, T. Büchner, U. Creutzig, and J. Ritter, for their consistently fine cooperation. We also thank the Institute of Pathology of the University of Kiel, headed by Prof. Karl Lennert, and the current head of the Department of Hematologic Pathology, Prof. Reza Parwaresch, for preparing histologic sections of the tissue cores that we submitted.

Acknowledgements

We are indebted to Prof. Brigitte Schlegelberger, Prof. Werner Grote (director of the Institute of Human Genetics, University of Kiel), Dr. Harder, and Mr. Blohm for providing the cytogenetic findings and schematic drawings. We limited our attention to important findings that have bearing on the diagnosis or confirmation of a particular entity.

A work of this magnitude cannot be completed without assistance. My secretary of many years, Mrs. Ute Rosburg, often freed me from distracting tasks so that I could gain essential time. Mrs. Margot Ulrich efficiently organized the processing of the photographic materials, while Mrs. Ramm-Petersen, Mrs. Meder, and Mrs. Tetzlaff were meticulous in their performance of cytologic, cytochemical, and immunocytochemical methodologies. My senior staff members in Kiel, Prof. Winfried Gassmann and Dr. Torsten Haferlach, helped with the examination and evaluation of many of the specimens pictured in the Atlas. My colleague Dr. Haferlach collaborated with the study group of Prof. Schlegelberger to introduce the FISH technique into routine clinical use. Finally, we thank Mrs. Monika Schrimpf and the entire staff at Springer-Verlag in Heidelberg as well as Ms. Judith Diemer at PRO EDIT GmbH for their thoughtful and effective support.

St. Peter and Munich
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Helmut Löffler · Johann Rastetter

Preface to the First Edition

So far the diagnostic advances of smear cytology have found only limited applications in medical practice. This is due largely to the fact that available illustrative materials have been too stylized to give the novice a realistic introduction to the field. In the present atlas we attempt to correct this situation by portraying the great morphologic variety that can exist in individual cells and in pathologic conditions. In so doing, we rely mainly on artist's depictions rather than photographs. On the one hand the "objectivity" of color photos, though much praised, is inherently questionable and is further degraded by the process of chemographic reproduction. An even greater drawback of photomicrographs is their inability to depict more than one plane of section in sharp detail. By contrast, a person looking through a microscope will tend to make continual fine adjustments to focus through multiple planes and thus gain an impression of depth. A drawing can recreate this impression much better than a photograph and so more closely approximates the subjective observation. We have avoided depicting cells in black and white; while there is merit in the recommendation of histologists that students' attention be directed toward structure rather than color, this is rarely practicable in the cytologic examination of smears. The staining methods adopted from hematology still form the basis for staining in smear cytology. For this reason most of the preparations shown in this atlas were stained with Pappenheim's panoptic stain. Where necessary, various special stains were additionally used. For clarity we have placed positional drawings alongside plates that illustrate many different cell types, and we have used arrows to point out particular cells in films that are more cytologically uniform.

We were most fortunate to have our color plates drawn by an artist, Hans Dettelbacher, in whom the faculties of scientific observation, technical precision, and artistic grasp are combined in brilliant fashion. We express our thanks to him and to his equally talented daughter Thea, who assisted her father in his work. Without their contribution it is doubtful that the atlas could have been created.

We are also grateful to a number of researchers for providing scientific help and specimens, especially Prof. Dr. Henning and Dr. Witte of Erlangen, Dr. Langreder of Mainz, Prof. Dr. Mohr of the Tropical Institute of Hamburg, Dr. Moeschlin of Zurich, Dr. Undritz of Basel, and Dr. Kuhn of our Freiburg Clinic. We also thank our translators, specifically Dr. Henry Wilde of our Freiburg Clinic for the English text, Dr. Rene Prevot of Mulhouse for the French text, and Dr. Eva Felner-Kraus of Santiago de Chile for the Spanish text. We must not fail to acknowledge the help provided by the scientific and technical colleagues at our hematology laboratory, especially Mrs. Hildegard Trappe and Mrs. Waltraud Wolf-Loffler. Finally, we express our appreciation to Springer Verlag, who first proposed that this atlas be created and took the steps necessary to ensure its technical excellence.

Freiburg, Spring 1955 Ludwig Heilmayer · Herbert Begemann

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Methodology

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Blood Smear

Differentiation of the peripheral blood is still an important procedure in the diagnosis of hematologic disorders. The requisite blood smears are usually prepared from venous blood anticoagulated with EDTA (several brands of collecting tube containing EDTA are available commercially). However, many special tests require that the blood be drawn from the fingertip or earlobe and smeared directly onto a glass slide with no chemicals added. The slide must be absolutely clean to avoid introducing artifacts. Slides are cleaned most effectively by degreasing in alcohol for 24 h, drying with a lint-free cloth, and final wiping with a chamois cloth (as a shortcut, the slide may be scrubbed with 96 % alcohol and wiped dry).

Preparation of the Smear. The first drop of blood is wiped away, and the next drop is picked up on one end of a clean glass slide, which is held by the edges. (When EDTA-anticoagulated venous blood is used, a drop of the specimen is transferred to the slide with a small glass rod.) Next the slide is placed on a flat surface, and a clean coverslip with smooth edges held at about a 45 tilt is used to spread out the drop to create a uniform film. We do this by drawing the coverslip slowly to the right to make contact with the blood drop and allowing the blood to spread along the edge of the coverslip. Then the spreader, held at the same angle, is moved over the specimen slide from right to left (or from left to right if the operator is left-handed), taking care that no portion of the smear touches the edge of the slide. The larger the angle between the coverslip and slide, the thicker the smear; a smaller angle results in a thinner smear.

Once prepared, the blood smear should be dried as quickly as possible. This is done most simply by waving the slide briefly in the air (holding it by the edges and avoiding artificial warming). The predried slide may be set down in a slanted position on its narrow edge with the film side down. For storage, we slant the slide with the film side up, placing it inside a drawer to protect it from dust and insects.

The best staining results are achieved when the smear is completely air-dried before the stain is applied (usually 4 – 5 h or preferably 12 – 24 h after preparation of the smear). In urgent cases the smear may be stained immediately after air drying.

Bone Marrow

Percutaneous aspiration of the posterior iliac spine is the current method of choice for obtaining a bone marrow sample. It is a relatively safe procedure, and with some practice it can be done more easily and with less pain than sternal aspiration. Marrow aspirate and a core sample can be obtained in one sitting with a single biopsy needle (e.g., a Yamshidi needle). When proper technique is used, the procedure is not contraindicated by weakened host defenses or thrombocytopenia. However, there is a significant risk of postprocedural hemorrhage in patients with severe plasmatic coagulation disorders (e.g., hemophilia), in patients on platelet aggregation inhibitors, and in some pronounced cases of thrombocytosis. In all cases the biopsy site should be compressed immediately after the needle is withdrawn, and the patient should be observed. The procedure should be taught by hands-on training in the clinical setting.

Aspiration is usually performed after a core biopsy has been obtained. The needle is introduced through the same skin incision and should enter the bone approximately 1 cm from the biopsy site. A sternal aspiration needle may be used with the guard removed, or a Yamshidi needle can be used after removal of the stylet.

The operator rechecks the position of the spine and positions the middle and index fingers of the left hand on either side of the spine. The sternal aspiration needle, with adjustable guard removed, is then inserted until bony resistance is felt and the needle tip has entered the periosteum. This is confirmed by noting that the tip can no longer be moved from side to side. The needle should be positioned at the center of the spine and should be perpendicular to the plane of the bone surface. At this point a steady, gradually increasing pressure is applied to the needle, perhaps combined with a slight rotary motion, to advance the needle through the bone cortex. This may require considerable pressure in some patients. A definite give will be felt as the needle penetrates the cortex and enters the marrow cavity. The needle is attached to a 20-mL glass syringe, the aspiration is performed, and specimens are prepared from the aspirated material.

After the needle is withdrawn, the site is covered with an adhesive bandage and the patient instructed to avoid tub bathing for 24 h.

The usual practice in infants is to aspirate bone marrow from the *tibia*, which is still active hematopoietically.

We prefer to use the needle described by Klima and Rosegger, although various other designs are suitable (Rohr, Henning, Korte, etc.). Basically it