TUMORS OF THE HEMATOPOIETIC SYSTEM

Henry Rappaport, M.D.

TUMORS OF THE HEMATOPOIETIC SYSTEM

Henry Rappaport, M.D.

ARMED FORCES INSTITUTE OF PATHOLOGY

ATLAS OF TUMOR PATHOLOGY

Section III—Fascicle 8

TUMORS OF THE HEMATOPOIETIC SYSTEM

by

Henry Rappaport, M.D.

Professor of Pathology, The University of Chicago, Chicago, Ill.
Consultant
United States Naval Hospital, Great Lakes, Ill.
Veterans Administration Hospital, Hines, Ill.
Walter Reed Army Institute of Research, Washington, D.C.
Former Professor of Oncology, The Chicago Medical School, Chicago, Ill.
Former Registrar, Lymphatic Tumor Registry, American Registry of Pathology
and
Former Chief, Reticuloendothelial and Hematologic Pathology Section
Armed Forces Institute of Pathology, Washington, D.C.

Published by the
ARMED FORCES INSTITUTE OF PATHOLOGY
Under the Auspices of the
SUBCOMMITTEE ON ONCOLOGY
of the
COMMITTEE ON PATHOLOGY
of the
DIVISION OF MEDICAL SCIENCES
of the
NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL

Washington, D.C.
1966

Originally Submitted for Publication November 1959
Accepted for Publication September 1963

For sale by the American Registry of Pathology
Armed Forces Institute of Pathology
Washington, D.C., 20305

ATLAS OF TUMOR PATHOLOGY

Sponsored and Supported
By

AMERICAN CANCER SOCIETY
ANNA FULLER FUND
ARMED FORCES INSTITUTE OF PATHOLOGY
JANE COFFIN CHILDS MEMORIAL FUND FOR MEDICAL RESEARCH
NATIONAL CANCER INSTITUTE, U.S. PUBLIC HEALTH SERVICE
UNITED STATES VETERANS ADMINISTRATION

Supporting Societies

AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS
ARTHUR PURDY STOUT SOCIETY
CALIFORNIA SOCIETY OF PATHOLOGISTS
COLLEGE OF AMERICAN PATHOLOGISTS
CHICAGO PATHOLOGICAL SOCIETY
DELAWARE STATE PATHOLOGY SOCIETY
ILLINOIS SOCIETY OF PATHOLOGISTS
INDIANA ASSOCIATION OF PATHOLOGISTS
KANSAS SOCIETY OF PATHOLOGISTS
KENTUCKY SOCIETY OF PATHOLOGISTS
MAINE SOCIETY OF PATHOLOGISTS
MICHIGAN PATHOLOGICAL SOCIETY
NEW JERSEY SOCIETY OF PATHOLOGISTS
NEW MEXICO ASSOCIATION OF RADIOLOGISTS AND PATHOLOGISTS
NEW YORK PATHOLOGICAL SOCIETY
NEW YORK STATE SOCIETY OF PATHOLOGISTS
OKLAHOMA ASSOCIATION OF PATHOLOGISTS
OREGON PATHOLOGISTS ASSOCIATION
PATHOLOGICAL SOCIETY OF PHILADELPHIA
PENNSYLVANIA ASSOCIATION OF CLINICAL PATHOLOGISTS
SAN ANTONIO SOCIETY OF PATHOLOGISTS
ST. LOUIS PATHOLOGICAL SOCIETY
TEXAS SOCIETY OF PATHOLOGISTS
VERMONT SOCIETY OF PATHOLOGISTS
VIRGINIA SOCIETY OF PATHOLOGY

ACKNOWLEDGMENTS

The author of this fascicle is indebted to members of the Subcommittee on Oncology for their encouragement, comments, and suggestions regarding preparation of the material for publication. As special critics, Dr. W. H. Crosby, Dr. J. W. Rebuck, and Dr. M. N. Richter reviewed the manuscript; their interest and many pertinent recommendations are deeply appreciated. The author wishes to thank Dr. H. J. Zimmerman, Chairman of the Department of Medicine of The Chicago Medical School, and Dr. Paul Heller, Associate Chief of Staff for Research of the Veterans Administration Westside Hospital of Chicago for their constructive criticisms. The author is also indebted to Dr. Philippe Shubik, Professor and Director of the Division of Oncology of The Chicago Medical School, whose encouragement made completion of the fascicle possible. The valuable editorial assistance of Dr. Catherine Blumberg and her staff is gratefully acknowledged. Photomicrographs for the fascicle were made at the Armed Forces Institute of Pathology with the assistance of Mr. Charles Edwards; he deserves much credit for his fine work.

To the following contributors, the author wishes to express gratitude for making available the material and information that was used in preparing the illustrations and legends for the fascicle: Dr. L. V. Ackerman and Dr. S. L. Saltzstein, St. Louis, Mo.; Dr. Herbert Braunstein, Dr. E. A. Gall, Dr. P. N. Jolly, Cincinnati, Ohio; Dr. Hilliard Cohen, Kansas City, Mo.; Dr. T. F. Dutcher, Dallas, Texas; Dr. J. L. Fahey, Dr. G. T. O'Conor, and Dr. J. A. Turner, Bethesda, Md.; Dr. J. B. Frerichs, El Paso, Texas; Dr. I. A. Friedman, Oak Park, Ill.; Dr. R. H. Fuller, Vista, Calif.; Dr. F. J. Glassy, Sacramento, Calif.; Dr. Boris Gueft, New York, N.Y.; Dr. J. A. Harshmann, Kokomo, Ind.; Dr. W. A. Haug, Portland, Oreg.; Dr. W. A. Hentel, Albuquerque, N. Mex.; Dr. A. M. Josephson, Dr. J. B. McCormick, Dr. Otto Saphir, Dr. S. O. Schwartz, Dr. L. S. Tarlow, Chicago, Ill.; Dr. D. S. Kahn, Montreal, Canada; Dr. S. K. Kurland, Denver, Colo.; Dr. E. G. Laforet, Brookline, Mass.; Dr. Leo Lowbeer, Tulsa, Okla.; Dr. J. E. MacIver, Jamaica, British West Indies; Dr. J. J. Marra, Pontiac, Mich.; Dr. Joseph Mendeloff, Atlanta, Ga.; Dr. D. S. Morris, Winston-Salem, N.C.; Dr. Alfred Plaut, Topeka, Kans. (deceased); Dr. J. W. Rebuck, Detroit, Mich.; Dr. M. N. Richter, Phoenix, Ariz.; Dr. M. E. Rubnitz, Hines, Ill.; Dr. J. C. Sieracki, Danville, Pa.; Dr. Henry Ungar, Jerusalem, Israel; Dr. Jonas Valaitis, Parkridge, Ill.; Dr. R. K. Winkelmann, Rochester, Minn.; Dr. D. H. Wright, Kampala, Uganda, East Africa; Dr. J. Ziskind, New Orleans, La.

Permission to use copyrighted illustrations and other material has been granted by:

American Society of Clinical Pathologists:

Proceedings of the Twenty-third Seminar, 1958. For fascicle plates VI A–D and VIII A, B and for figures 10, 12, 13, 18, 19, 52, 56, 101–103, 114, 115, 142, 143, 152, 163, 164, 184, 186, 189, 190, and 283.

C. V. Mosby Co.:

Surgical Pathology, 3d ed., 1964. For fascicle figures 99 and 119.

Grune & Stratton:

Blood, 10: 132–144, 1955. For fascicle figures 160–162.

J. B. Lippincott Co.:

Cancer:

9: 792–821, 1956. For fascicle figures 107, 117, 119, 121, 122, 148, and 167.

12: 164–182, 1959. For fascicle figure 419.

Paul B. Hoeber, Inc.:

Lab. Invest., 6: 383–388, 1957. For fascicle figure 406.

Williams & Wilkins Co.:

Am. J. Clin. Path., 22: 46–55, 1952. For fascicle figures 348 and 349.

All illustrations are the author's unless otherwise acknowledged. The A.F.I.P. accession numbers are for the identification of negatives at the Armed Forces Institute of Pathology.

Henry Rappaport

TUMORS OF THE HEMATOPOIETIC SYSTEM

TABLE OF CONTENTS

MALIGNANT LYMPHOMAS—Continued

TUMORS OF THE HEMATOPOIETIC SYSTEM

INTRODUCTION

The hematopoietic tissues include the bone marrow, lymph nodes, and spleen as the chief centers for blood cell formation and destruction and are parts of a larger system to which the comprehensive term reticular tissue has been applied (Marshall). The reticular tissue derives its name from its undifferentiated, pluripotential components, the primitive reticular cells, which are the cells of origin of both hematopoietic and stromal elements (chart 1). The sinusoidal system of the liver, the thymus, and the aggregates of lymphatic tissue in the mucosa of the respiratory and gastrointestinal tracts are sites of concentration of reticular tissue outside the organs that are primarily concerned with blood cell formation and destruction. In addition, pluripotential primitive reticular cells are widely scattered throughout all tissues; in response to appropriate stimuli, they may give rise to any of the cells found in the hematopoietic organs (Klemperer). This unique anatomic arrangement is responsible not only for many of the clinical and pathologic manifestations of the systemic neoplastic diseases that involve the hematopoietic system, but also for the occurrence of primary tumors of the primitive reticular cells, or their derivatives, in organs that do not normally have well defined lymphopoietic or myelopoietic tissue.

The wide dissemination of neoplastic diseases of the hematopoietic system has been attributed either to multifocal origin of the cellular proliferations or to vascular spread of neoplastic cells from a single focus, with colonization in distant organs. Multifocal origin of the leukemias and other systemic proliferative diseases of the hematopoietic tissues has been assumed, primarily because patients with these disorders usually show clinical evidence of early systemic involvement. However, in the group of neoplasms designated as malignant lymphomas, a single tumor in a lymph node or in an extranodal site is often the only clinical manifestation of the disease. The long remissions that have been observed after excision or roentgen irradiation of clinically localized malignant lymphomas suggest that this type of tumor may develop at a single site and may remain confined to one area for an unpredictable and, often, protracted period.

A distinction between initially localized and primarily systemic neoplastic diseases of the hematopoietic tissues is not always possible. However, therapeutic and prognostic considerations justify an attempt to determine in each case the precise nature of the disease, not only as to its cytologic type but also

its propensity for early generalization. This often requires thorough evaluation of the clinical features and hematologic findings, in addition to accurate interpretation of the microscopic sections of the involved tissues. Even after such complete studies, the disease may not be readily classifiable or may not conform to a single well defined clinical and pathologic entity throughout its course.

The question has often been discussed whether systemic proliferative diseases of the hematopoietic tissues, particularly the leukemias, are neoplasms (Dameshek and Gunz). Since the leukemias are abnormal, progressive, unrestrained, probably autonomous, invasive and disseminated cellular proliferations, most investigators agree that they are neoplastic. Immaturity and imperfect differentiation of the proliferating cells, abnormal nuclear forms, asynchronism of cellular and nuclear maturation, increased numbers of mitoses, and abnormal mitotic figures are often observed in these diseases. However, absence of these cytologic abnormalities in a differentiated form of leukemia, such as chronic lymphocytic leukemia, does not preclude the neoplastic nature of the disease. Whether all of the cytologically differentiated myeloproliferative diseases and histiocytoses are neoplastic disorders is more uncertain; discussions of these diseases are included in this fascicle because, in common with the leukemias, they have abnormal, progressive, unrestrained, and often disseminated cellular proliferations of unknown etiology.

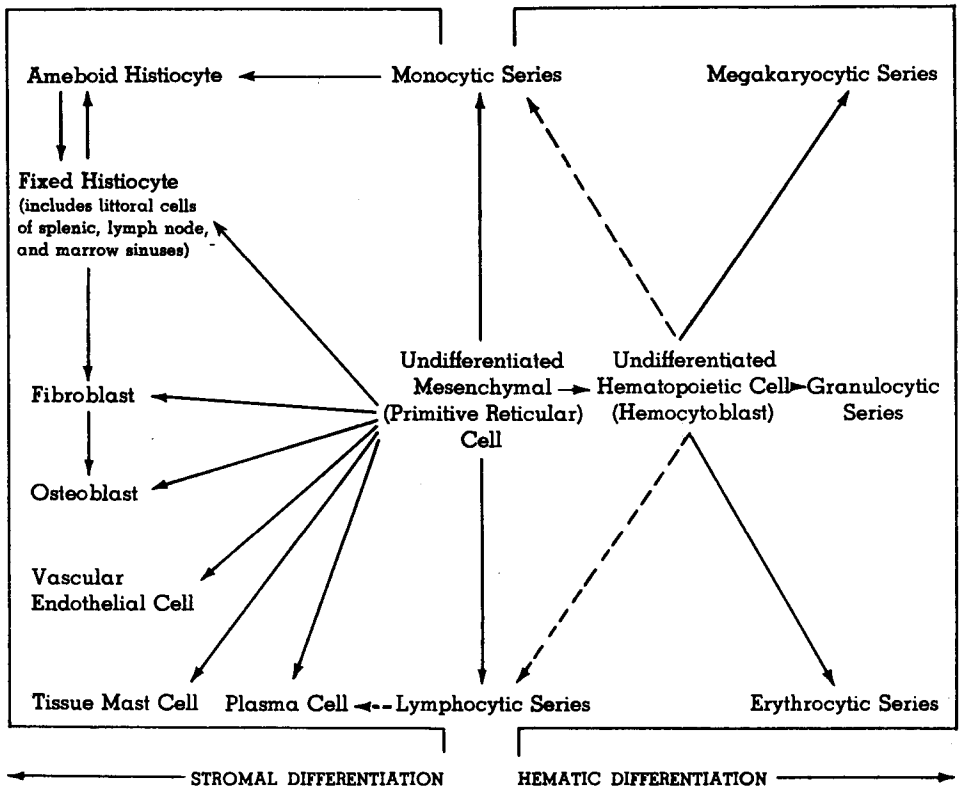
NOMENCLATURE AND CLASSIFICATION

The cytologic nomenclature used in this fascicle and the main pathways of cellular differentiation have been summarized (chart 1). Even though this schema cannot reflect all theoretic and experimental evidence regarding the genesis and interrelationships of the various cell types that originate from the primitive reticular cells, it may assist in understanding the potentialities for abnormal growth that various cell types possess; it may also help to explain the occurrence of mixed cellular proliferations and the changes in cellular composition that are observed during the progression of some of the neoplastic diseases of hematopoietic tissues.

The potential of the embryonal mesenchyme for hematic or stromal differentiation is retained in the adult organism by inconspicuous, fixed cells. These undifferentiated mesenchymal, or primitive reticular, cells are not limited to the blood-forming tissues but are widely distributed throughout the body, with the vascular adventitia as a site of predilection; they are intimately associated with the argyrophilic, fibrillar framework of the blood-forming organs (Bloom and Fawcett). The cells are considered the precursors of all types of blood and connective tissue cells (chart 1). In tissue sections, these cells are characterized by oval pale nuclei that have delicate chromatin structures and small, often indistinct, nucleoli. Their pale-stained cytoplasm forms a syncytium.

Chart 1

SCHEMA OF DERIVATION OF THE CELLS OF THE RETICULAR TISSUE*



*Interrupted lines indicate alternate or uncertain pathways of differentiation.

Small lymphocytes, or the earlier stages of lymphocytic differentiation, have been suggested as the cells of origin of the undifferentiated hematopoietic cells, or hemocytoblasts (Yoffey). These lymphocytes are also believed to serve under certain conditions as free stem cells for granulocytes, monocytes, erythrocytes, and megakaryocytes (Bloom and Fawcett). This concept is based primarily upon experimental observations and certain theoretic considerations; its applicability to the cytologic aspects of primary neoplastic diseases of the hematopoietic system has not been established.

Similarities exist between the primitive reticular cell and one of its derivatives, the histiocyte, notably in their general distribution and in their intimate association with the fibrillar reticulum. However, the histiocyte has a more abundant cytoplasm and is capable of phagocytosis in response to an appropriate challenge; it can also store vital dyes. The primitive reticular cell does not possess these properties to any significant degree. The silver impregnation

method of Weil-Davenport has demonstrated that the histiocyte is a metallophilic cell and that the primitive reticular cell is not (Marshall). Various enzymatic activities have also been demonstrated in the histiocytes but not in the primitive reticular cells (Braunstein et al., 1962). Although the continued use of the term reticulum cell to designate both of these cell types is understandable because of their similarities in routinely stained histologic sections, it has obscured the facts that the primitive reticular cell is a pluripotential stem cell and that the histiocyte is a differentiated cell with specific functions.

In this volume, the term endothelial cell will be used specifically to designate cells that line the blood and lymph vessels; it will not be used for either Kupffer's cells or for the so-called littoral cells that line the sinuses of lymph nodes. These littoral cells are phagocytic and resemble extravascular histiocytes both morphologically and functionally (Braunstein et al., 1958). The cells that line splenic and bone marrow sinuses are probably modified histiocytes, too, even though those of the splenic sinuses were shown by certain enzymatic reactions to differ from histiocytes in other sites (Dorfman).

In selecting terms to designate neoplastic diseases of the hematopoietic tissues, preference was given to those that were most widely used and generally accepted (table I), except where the use of such terms would be inconsistent with more compelling morphologic or histogenetic considerations. The classification of the neoplasms presented in this fascicle is based primarily upon their cellular compositions; however, the systemic proliferative diseases and the initially localized or circumscribed tumors are listed separately (table I) in order to emphasize that one or the other of these clinical and gross morphologic patterns frequently prevails. This arrangement (table I) does not imply that sharp differentiation between the two forms of involvement can always be made. For example, circumscribed tumors and diffuse infiltrations may occur simultaneously or consecutively in one patient. In some instances, also, an initially localized tumor in an area that is not readily accessible to clinical observation, such as the retroperitoneal lymph nodes, may escape detection, and its clinical manifestations may not appear until the disease has assumed the proportions of a systemic disorder.

The terms undifferentiated or stem cell leukemia imply, theoretically, that the proliferating cells are pluripotential hematopoietic cells; actually, the terms mean that, with the methods available, the proliferating or circulating blast cells cannot be classified as either myeloblasts, lymphoblasts, or monoblasts.

The term monocytic leukemia is used to designate a systemic proliferation of abnormal monoblasts, monocytes, or both, and corresponds to the term monocytic leukemia of Schilling; histiomonocytic reticulosis (Cazal) has similarly been used to identify this entity. Monocytic leukemia of Naegeli is an obsolete term, because it denotes a variant of granulocytic leukemia.

The term reticulosis has been applied to such varied and unrelated conditions that its true significance has been obscured; it should only be used to

Table I

CLASSIFICATION OF SYSTEMIC PROLIFERATIVE DISEASES AND TUMORS OF THE HEMATOPOIETIC TISSUES

Predominant component cell(s)	Systemic proliferative diseases (tumor formation may occur)	Initially localized tumors (systemic involvement occurs frequently)
Primitive reticular cell		Malignant lymphoma, undifferentiated*
Undifferentiated hematopoietic cell	Undifferentiated (stem cell) leukemia	
Monocyte	Monocytic leukemia, acute and chronic	
Histiocyte	Malignant histiocytosis	Malignant lymphoma, histiocytic (reticulum cell sarcoma)*
		Hodgkin's disease*
Histiocyte and lymphocyte		Malignant lymphoma, mixed cell (histiocytic-lymphocytic)*
Lymphocytic cells		
Lymphoblast	Acute lymphocytic leukemia	
Poorly differentiated lymphocyte		Malignant lymphoma, poorly differentiated lymphocytic*
Differentiated lymphocyte	Chronic lymphocytic leukemia	Malignant lymphoma, well differentiated lymphocytic*
	Lymphoproliferative disease with dysproteinemia (including primary macroglobulinemia)	
Plasma cell	Myelomatosis (multiple myeloma)	Plasmacytoma
Tissue mast cell	Malignant tissue mast cell disease	Mastocytoma
Myelopoietic cells	Myeloproliferative diseases	
Granulocyte	Granulocytic leukemia, acute and chronic	Granulocytic sarcoma (chloroma)
Erythroblast	Erythremic myelosis	
Erythroblast and granulocyte	Erythroleukemia	
Megakaryocyte	Megakaryocytic myelosis	
	Idiopathic thrombocythemia	
Erythroblast, granulocyte, and megakaryocyte	Polycythemia vera	
	Myelosclerosis with myeloid metaplasia	

*Malignant lymphomas that have follicular (nodular) patterns are designated by addition of "follicular" ("nodular") to the cytologically appropriate terms.

designate a systemic proliferation of primitive reticular cells (Klemperer). When the proliferation is associated with varying degrees of histiocytic differentiation, as it is in most instances, the term reticulohistiocytosis is applicable; this term is preferred to reticuloendotheliosis, since the differentiated cellular elements in the disorder are histiocytes rather than vascular endothelial cells. Histiocytic reticulosis (Cazal) and malignant histiocytosis are terms that have also been applied to the same entity to emphasize the predominantly histiocytic character of the proliferative process.

A more detailed classification of the malignant lymphomas, which comprise the primary malignant neoplasms of primitive reticular cells and their histiocytic and lymphocytic derivatives, is presented elsewhere in this fascicle (chart 2).

The progressive proliferative diseases of myelopoietic cells and their derivatives are considered as a group, regardless of whether the neoplastic character of these disorders has been unequivocally established; this is in accord with the concept that these so-called myeloproliferative diseases have, in common, progressive proliferations of one or more of the cellular constituents of the bone marrow that are derived from a common pluripotential, undifferentiated precursor (chart 1). Although this concept is of some assistance in understanding the simultaneous proliferations of different marrow components in some patients and the transitions from one disease to another in others, it does not permit any conclusions whether the different myeloproliferative disorders are related etiologically or pathogenetically.

In the discussions of the morphologic aspects of diseases of the hematopoietic system, the individual organs will be described in the order of their relative diagnostic importance.

References

Bloom, W., and Fawcett, D. W. Blood Cell Formation and Destruction. In: A Textbook of Histology, 8th ed., pp. 112–143. Philadelphia: W. B. Saunders Co., 1962.

Braunstein, H., Freiman, D. G., and Gall, E. A. A histochemical study of the enzymatic activity of lymph nodes. I. The normal and hyperplastic lymph node. Cancer, 11: 829–837, 1958.

———, Freiman, D. G., Thomas, W., Jr., and Gall, E. A. A histochemical study of the enzymatic activity of lymph nodes. III. Granulomatous and primary neoplastic conditions of lymphoid tissue. Cancer, 15: 139–152, 1962.

Cazal, P. Aspects cliniques et hématologiques de la réticulose maligne. Acta haemat., 7: 65–85, 1952.

Dameshek, W., and Gunz, F. Leukemia. The Etiology of Leukemia, pp. 44–85. New York & London: Grune & Stratton, 1958.

Dorfman, R. F. Nature of the sinus lining cells of the spleen. Nature, London, 190: 1021–1022, 1961.

Klemperer, P. The Relationship of the Reticulum to Diseases of the Hematopoietic System. In: Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by his Pupils, Friends and Colleagues. Vol. 2, pp. 655–671. New York: The International Press, 1932.

Marshall, A. H. An Outline of the Cytology and Pathology of the Reticular Tissue, pp. 1–59. Edinburgh & London: Oliver & Boyd, 1956.

Yoffey, J. M. The present status of the lymphocyte problem. Lancet, 1: 206–211, 1962.

UNDIFFERENTIATED LEUKEMIAS

Stem Cell Leukemia

SYNONYMS AND RELATED TERMS: Acute hemocytoblastosis; acute leukemia, unclassified; acute stem cell leukemia; blast cell leukemia; embryonal cell leukemia; hemoblastic leukemia; hemocytoblastic leukemia; leukemia, unclassified; lymphoidocytic leukemia; Paraleukoblastose; undifferentiated cell leukemia; undifferentiated leukemia.

DEFINITION. A disseminated proliferation of immature hematopoietic cells, or so-called blast cells, without appreciable evidence of granulocytic, lymphocytic, or monocytic differentiation.

INCIDENCE. The incidence of stem cell leukemia varies with the confidence of the investigator in his ability to classify so-called blast cells and to recognize cellular differentiation. For example, Boggs and associates classified 322 cases of acute leukemia as either lymphoblastic or myeloblastic leukemia, basing their diagnoses upon purely morphologic criteria. In contrast, 169 cases of childhood leukemia were diagnosed as acute stem cell leukemias (Zuelzer and Flatz). In another series, comprising 68 cases of acute