HEMATOLOGY FOR INTERNISTS

Edited by

Robert I. Weed, M. D.

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PREFACE

SEVERAL ELEMENTARY HEMATOLOGY TEXTS are currently available, as are recent revisions of inclusive advanced texts and new comprehensive works of value to those with an extensive background in hematology. This book has been written for practicing physicians with a special interest in hematology; the complexity and coverage of individual topics are oriented toward a general medical audience. Like the American College of Physicians Course on Hematology for Internists, with Emphasis on Recent Advances, given at The University of Rochester, the book is intended for practicing internists as well as residents and fellows in training; but it is hoped that much of the content will be of interest also to pediatricians, general practitioners, and clinical pathologists.

Selection of topics for the book was based in large part on the interests of the various chapters were all members of the faculty of The University given in Rochester, although much of the material has been updated and several new subjects have been added. With the important exceptions of Dr. Clement A. Finch, a guest lecturer, and Dr. Robert Hillman, the authors of the various chapters were all members of the faculty of The University of Rochester School of Medicine and Dentistry at the time that the course was presented.

Three important assumptions underlie the format and content of the book. The assumptions are that the reader (1) has a basic background and continuing interest in hematology, (2) is significantly interested in important recent advances that have been made in our understanding of the pathologic biochemistry and pathophysiology of major hematologic disorders, and, most importantly, (3) wishes to be informed about current therapy for the various disorders, particularly in the light of newer insights into pathophysiology.

Hematology for Internists is divided into parts dealing with anemia, problems of hemostasis, and myeloproliferative and lymphoproliferative disorders. Each part contains at least one chapter reviewing basic science and research contributions, to provide the clinician the understanding essen-

tial for rational diagnosis and treatment. The length of the chapters and the balance of emphasis within each chapter on diagnostic procedures versus therapeutic recommendations relate more to the extent of our current knowledge than to the statistical frequency of the disorders themselves.

This book emphasizes recent advances in the important areas of hematology rather than attempting to cover *all* topics or *all* advances. For this reason and because much of the material has been organized to emphasize pathophysiology, certain very important subjects such as iron deficiency and thalassemia do not appear as separate chapters. However, clues to the recognition of iron deficiency and the interaction of iron with erythropoietin are discussed in the chapter on clinical approaches to anemia, while thalassemia is discussed under the more general heading of Heinz body disorders. When diagnosis or therapy, or both, warrant, major disorders are grouped together; for example, chronic lymphocytic leukemia is discussed along with the management of lymphomas.

In addition to being selective about inclusion of topics in the interest of reasonable brevity, authors have been encouraged to express and amplify their own opinions regarding specifics of clinical management. By such selection and by avoiding presentation of all views on controversial subjects, the book admittedly has something of a Rochester flavor except for Chapter 1. Certainly we have passed over many who have made major contributions. However, it is hoped that the resultant relatively short text may thus be more readable and of more practical value to its intended audience—particularly if it is recognized that whenever opinion supplements facts in the text, the opinion is that of the particular author.

In order to save space and to avoid interrupting the text, most reference citations have been eliminated. The selected references found at the end of each chapter represent either pertinent general review articles or new contributions to the understanding and management of the disease under discussion. Certain key references are indicated in the text by author's name and date of publication, however. The appendix, a current bibliography of methodology in various areas of hematology, is included for readers who wish up-to-date references on various techniques important in the hematology laboratory.

The assistance of Carol B. Weed, my wife and secretary, is hereby gratefully acknowledged. Her hard work, sense of organization, and assistance in providing firm encouragement to the authors to complete their manuscripts have been invaluable.

R. I. W.

CONTRIBUTING AUTHORS

Except as otherwise noted, all authors are at The University of Rochester School of Medicine and Dentistry, Rochester

RICHARD F. BAKEMEIER, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

ARTHUR W. BAUMAN, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

JOHN M. BENNETT, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

ROBERT T. BRECKENRIDGE, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

LAWRENCE N. CHESSIN, M.D.
CLINICAL ASSISTANT PROFESSOR OF MEDICINE

CLEMENT A. FINCH, M.D.
PROFESSOR OF MEDICINE, THE UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE, SEATTLE

KONG-OO GOH, M.D.
ASSOCIATE PROFESSOR OF MEDICINE AND OF ANATOMY

WILLIAM A. GREENE, M.D.
PROFESSOR OF MEDICINE AND OF PSYCHIATRY

PAUL F. GRINER, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

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THOMAS C. HALL, M.D.
PROFESSOR OF MEDICINE AND OF PHARMACOLOGY AND TOXICOLOGY

ROBERT S. HEUSINKVELD, M.D.
SENIOR INSTRUCTOR IN MEDICINE

ROGER S. HILL, M.D.
RESEARCH FELLOW, DEPARTMENT OF HAEMATOLOGY, ROYAL POSTGRADUATE MEDICAL SCHOOL, LONDON

ROBERT S. HILLMAN, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, THE UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE, SEATTLE

LEON W. HOYER, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF CONNECTICUT SCHOOL OF MEDICINE, HARTFORD

FREDERICK A. KLIPSTEIN, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY, ROCHESTER, AND THE UNIVERSITY OF PUERTO RICO, SAN JUAN

PAUL L. LACELLE, M.D.
ASSOCIATE PROFESSOR OF MEDICINE AND OF RADIATION BIOLOGY AND BIOPHYSICS

JOHN P. LEDDY, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

MARSHALL A. LICHTMAN, M.D.
ASSOCIATE PROFESSOR OF MEDICINE AND OF RADIATION BIOLOGY AND BIOPHYSICS

ARNOLD I. MEISLER, M.D.
ASSISTANT PROFESSOR OF MEDICINE

DENIS R. MILLER, M.D.
ASSOCIATE PROFESSOR OF PEDIATRICS, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK

GEORGE E. MILLER

CHIEF LABORATORY TECHNICIAN, HEMOPHILIA CENTER OF ROCHESTER AND MONROE COUNTY, ROCHESTER GENERAL HOSPITAL, ROCHESTER

SEYMOUR I. SCHWARTZ, M.D.

PROFESSOR OF SURGERY

DAVID A. SEARS, M.D.

ASSOCIATE PROFESSOR OF MEDICINE AND OF PHYSIOLOGY, THE UNIVERSITY OF TEXAS MEDICAL SCHOOL AT SAN ANTONIO, SAN ANTONIO

STANLEY B. TROUP, M.D.

PROFESSOR OF MEDICINE

ROBERT I. WEED, M.D.

PROFESSOR OF MEDICINE AND OF RADIATION BIOLOGY AND BIOPHYSICS

LAWRENCE E. YOUNG, M.D.

DEWEY PROFESSOR OF MEDICINE AND CHAIRMAN, DEPARTMENT OF MEDICINE

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ANEMIAS

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1. A CLINICAL APPROACH TO ANEMIA

Clement A. Finch
Robert S. Hillman

THIS PRESENTATION is a brief summary of a problem-solving approach to anemia adapted from the University of Washington Red Cell and Hematology laboratory manuals. Its purpose is to provide the physician with a pathophysiologic classification of anemia in which the functional disturbance of the erythron is emphasized. In this approach it is necessary to begin with a few general statements about the behavior of the erythron.

The normal *erythron* is composed of a generating tissue in the medullary cavities of the axial skeleton and a mass of circulating red cells. The relationship between the erythroid marrow and circulating red cells is shown in Table 1-1. Approximately 4 days are required for the immature red cell to undergo some four mitotic divisions and extrude its nucleus; additional time is spent as a maturing *reticulocyte* within the marrow. Finally, after entering the circulating blood, the reticulocyte requires 1 day or more to lose its reticulum. The mature red cell lives 120 days in the circulation, after which time it is destroyed by the reticuloendothelial cell.

Marrow activity is regulated by *erythropoietin*. This hormone determines the degree of proliferation of the marrow and also affects the rate of maturation. Under increased erythropoietin stimulus, immature erythroid cells increase in number within 2 or 3 days and the reticulocyte output from the marrow increases over the following 3 or 4 days. Total production will be 3 to 5 times base level within a week, provided adequate iron is available. In addition to the increased proliferation, *shift cells* (basophilic macroreticulocytes) appear in the circulation.

Iron supply for erythropoiesis normally is derived almost completely from broken-down erythrocytes. When increased amounts of iron are required for erythropoiesis beyond that available from red cell breakdown, iron must be mobilized from stores. Rates of erythropoiesis in man follow-

Table 1-1. Relationship Between Erythroid Marrow and Circulating Red Cells

Cell Type	Time Span (Days)	Relative Number
Nucleated RBC	5	1.5
Marrow reticulocytes	1.5	1.5
Blood reticulocytes	1	1
Adult RBC	120	100
Cell Type	**Circulating Mass**	**Daily Turnover**
Red cells	2000 ml	17 ml
Hemoglobin	660 gm	5.7 gm
Porphyrin pigment	23 gm	190 mg
Iron	2.2 gm	18 mg

Conversion constants: body hematocrit = 0.90 × venous hematocrit; iron per gram hemoglobin = 3.38 mg; daily red cell breakdown = 1/120 (or 0.83%); hemoglobin molecular weight = 66,000; protoporphyrin molecular weight = 566; urobilinogen molecular weight = 580; iron atomic weight = 56.

ing blood loss do not usually increase above 2 times normal because of the limitations of iron mobilization from stores. Higher rates of erythropoiesis are found in hemolytic states because of the ease with which the reticuloendothelial cell can catabolize iron from nonviable red cells.

The normality of the erythron is usually judged by the concentration of red cells in the circulation. Usual values for normal subjects are shown in Table 1-2. *Anemia* is defined as a significant decrease in circulating hemoglobin, usually more than 10% of the accepted mean. Thus anemia is a

Table 1-2. Concentration of Red Cells in Circulation in Normal Subjects

Age	Hemoglobin (gm/100 ml)	Hematocrit (%)
Birth	17.0	50
1 to 3 months	14.0	42
3 months to 5 years	12.0	36
6 to 10 years	12.0	37
11 to 15 years	13.0	39
Adult male	15.5	47
Menstruating female	13.5	41
Pregnancy (last trimester)	12.0	37

laboratory diagnosis related to a population norm rather than to the physiology of the individual.

LABORATORY TESTS

The nature of anemia is determined both from qualitative abnormalities in individual cells as revealed by examination of the aspirated marrow, the blood film, and red cell indices and from those parameters that characterize the rate of blood production and destruction, the reticulocyte index, marrow E:G ratio (ratio of erythroid to granulocytic cells in the aspirated marrow), and bilirubin.

BLOOD SMEAR

An estimation should be made of the red cell size, and shape abnormalities should be identified. The following cell forms have particular significance: *shift cells,* which indicate increased erythropoietin stimulus; *true macrocytes,* which indicate a nuclear maturation defect (and, when accompanied by a hypersegmentation of granulocytes, indicate megaloblastic anemia); *hypochromic microcytes,* which indicate a block in hemoglobin synthesis; *spherocytes,* which indicate a hemolytic process. Other cell forms that suggest hemolysis are fragmentation, sickle cell, ovalocytes, and acanthrocyte and stomatocyte deformities. *Poikilocytosis* is significant as an indication of defective maturation process. A *myelophthisic blood picture,* including immature cells of all series, indicates disease within the marrow.

RED CELL INDICES

Measurements of hemoglobin, hematocrit, and red cell number permit calculations of cell size, hemoglobin concentration, and content. Basal values are shown in Table 1-3. These "normal" values are modified by erythropoietin and iron supply. Increased erythropoietin produces an increase in the MCV and decreases in the MCHC. For the increase in volume to occur, however, the plasma iron must be above 100 μg per 100 ml.

Table 1-3. Basal Adult Values (Coulter Counter)

MCV	(mean cell volume in μ^3)	$\frac{\text{Hct}}{\text{RBC}}$	90 ± 8
MCH	(mean cell hemoglobin in $\mu\mu$g)	$\frac{\text{Hgb}}{\text{RBC}}$	30 ± 3
MCHC	(mean cell hemoglobin concentration in gm/100 ml)	$\frac{\text{Hgb}}{\text{Hct}}$	33 ± 2

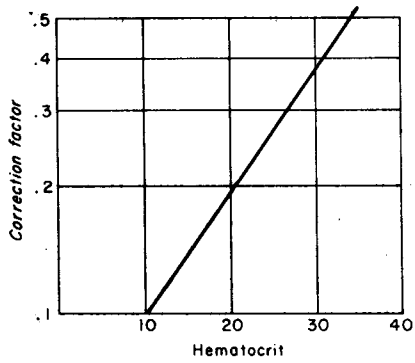

Figure 1-1. Chart for calculation of reticulocyte index. The reticulocyte index may be obtained by multiplying the patient's reticulocyte count by a correction factor derived from the patient's hematocrit.

RETICULOCYTE INDEX

The number of circulating cells containing reticulum provides a measure of red cell production. In order for this to be meaningful from a quantitative standpoint, the reticulocyte count must be corrected for the number of cells in circulation and for the maturation time of the reticulocyte in the peripheral blood. Increased erythropoietin produces a shift of reticulocytes from marrow to blood and prolongs the maturation time. Combined correction factors for various degrees of anemia are shown in Figure 1-1. In making the correction for shift, a predictable relationship between erythropoietin level and the degree of anemia is assumed. It is well to check the blood film to determine whether or not the expected degree of shift is present. Normal reticulocyte count is 1% or about 60,000 reticulocytes per cubic millimeter. The corrected reticulocyte count or reticulocyte index should be compared to the normal value of 1. This index indicates the number of reticulocytes entering the blood stream per day (effective erythropoiesis).

PLASMA IRON AND IRON-BINDING CAPACITY

Plasma iron level and the ratio of plasma iron to iron-binding capacity of the plasma indicate the adequacy of the iron supplied to marrow. Normal plasma iron fluctuates from 50 to 150 μg per 100 ml, and usually shows a diurnal fluctuation from 110 in the morning to 70 μg per 100 ml in the evening. Iron-binding capacity is usually stable at about 330 $\pm$ 50 μg per 100 ml. A plasma iron of less than 30 μg per 100 ml and a percent satura-

tion of 15 or less indicate a deficient iron supply if erythropoiesis is at a basal level.

ICTERUS INDEX OR BILIRUBIN

The amount of pyrrole pigment in the plasma is normally between 4 and 8 units of icterus index or 0.4 to 0.8 mg of bilirubin. Values below this are useful in indicating decreased red cell breakdown.

BONE MARROW EXAMINATION

An approximation of the number of nucleated red cells may be obtained from the E:G ratio. Such a ratio is meaningful only if granulocyte production is normal as reflected by a normal circulating granulocyte count. The normal E:G ratio in marrow smears is 1 to 3. This indicates the degree of proliferation of erythroid cells within the marrow (total erythropoiesis). Qualitative changes in the red cell series which are important to recognize are megaloblastic alterations and sideroblastic changes (iron accumulations within the cytoplasm as determined by a Prussian blue iron stain). Reticuloendothelial iron stores should also be examined in marrow aspirate.

RED CELL LIFE-SPAN AND SPLENIC LOCALIZATION

^{51}Cr tagging of erythrocytes is useful for measuring both shortening of red cell life-span and, by in vivo counting, excessive accumulation of radioactivity in the splenic area. Normal ^{51}Cr life-span is 29 ± 3 days.

CLINICAL MANIFESTATIONS

With mild degrees of anemia (hemoglobin 10 to 14 gm per 100 ml) symptoms are usually not detected. If present, they are more often attributable to underlying disease than to anemia per se. At most, symptoms appear only on heavy exercise and reflect the compensatory overactivity of heart and lungs. They consist of palpitation, dyspnea, and sometimes excessive sweating. With moderate anemia there is increase of these symptoms and fatigue. In severe anemia tachycardia, wide pulse pressure and hyperpnea, sensitivity to cold, loss of appetite, weakness, and occasional syncope may be seen. In elderly people local vascular disease may sensitize certain tissues to the effect of anemic hypoxia and result in such manifestations as intermittent claudication and angina.

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