
MANUAL OF HEMATOLOGY

CLAUDE SULTAN, M.D.
MICHÈLE GOUAULT-HEILMANN, M.D.
MICHÈLE IMBERT, M.D.

Translated by
ROBERT V. PIERRE, M.D.

MANUAL OF HEMATOLOGY

CLAUDE SULTAN, M.D.
MICHÈLE GOUAULT-HEILMANN, M.D.
MICHÈLE IMBERT, M.D.

Service Central d'Hématologie-Immunologie
Hôpital Henri Mondor
Département d'Hématologie Biologique
Faculté de Médecine de Créteil
Paris, France

Translated by

ROBERT V. PIERRE, M.D.
Department of Laboratory Medicine
Mayo Clinic
Rochester, Minnesota

A WILEY MEDICAL PUBLICATION
JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto • Singapore

Cover and interior design by Wanda Lubelska

Translated and modified from the original Second French Edition published in 1982 by Flammarion under the title *Aide-mémoire d'hématologie*, ISBN 2-257-12402-2.

Copyright © 1985 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Sections 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

Sultan, Claude.

Manual of hematology.

(A Wiley medical publication)

"Translated and modified from the original second French edition published in 1982 by Flammarion under the title: *Aide-mémoire d'hématologie*"—T.p. verso.

Includes index.

1. Hematology—Handbooks, manuals, etc. I. Gouault-Heilmann, M. II. Imbert, M. III. Title. IV. Series.

[DNLM: 1. Hematology—Outlines. WH 18 S954a]

RB145.S88713 1985 616.1'5'00202 83-26071

ISBN 0-471-06002-X

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

PREFACE

Manual of Hematology is designed in outline form to provide a concise and clear overview of the subject of hematology. Both laboratory and clinical aspects of hematologic disorders are covered, but the primary emphasis is on the pathophysiology of hematologic disorders. The book is aimed at the medical student and resident in medicine, pathology, or other discipline who wishes a concise review of the subject. It should also be a helpful quick reference source for the general pathologist.

The book is divided into six sections. Part 1 provides a concise review of the structure and function of the normal cell components of the hemic system as well as the major plasma components, such as iron, vitamin B₁₂, and folate, that are of special interest in hematologic disease. The methods of study of these components are also reviewed. Part 2 deals with the major disease groups and presents the important basic features of the disorders, such as frequency, genetic factors, symptomatology, diagnostic features, appropriate laboratory studies, course, and treatment. Part 3 deals with hemostasis and coagulation. The components of the hemostatic mechanisms are described, and the normal and abnormal physiology of these factors is emphasized. The pathophysiology, clinical and laboratory features, and diagnostic approach to both the hereditary and acquired coagulation disorders are discussed. The use of anticoagulants in management of thrombotic disorders is summarized. Part 4 covers immunohematology, with special attention to the blood group antigens, HLA antigens, use of blood components in therapy, and transfusion reactions. Various morphologic terms are described and the classification systems of the acute and chronic leukemias and the lymphomas are presented in the Appendix.

The last section of the book is unique; it consists of a series of diagnostic problems in which pertinent clinical and laboratory data are provided. These cases are selected to teach interpretation of laboratory data in a logical manner and should prove a valuable and interesting aspect of the book.

The contents of this book are based on teaching material and principles developed by Professor Sultan and his colleagues at the Henri Mondor Hospital and Créteil University in Paris. This program has demonstrated its excellence for many years.

When I encountered the first edition of this textbook in French, I was greatly impressed by its succinct but lucid style. The illustrations, tables, and flow charts were well thought out and effective teaching devices. I told Professor Sultan that I was not aware of a comparable book in English and that I had frequently recommended it to students, residents, and pathologists who were seeking a concise, up-to-date text for review of hematology, but always had to point out that, unfortunately, it was only available in French. Professor Sultan

suggested that I translate the text into English. I accepted this task since I believed that the book would be a valuable addition to the English language hematology literature.

French hematologists of the past several decades have made major contributions to the field of hematology, such as describing clinical and laboratory entities, in providing an understanding of basic pathogenetic mechanisms of disease, and in classifying leukemias, but many of these significant achievements are not well known or recognized in the United States because of the language barrier. We have also frequently misunderstood some differences in basic concepts that exist between French and other European hematologists and ourselves because of the difficulty in communication. I hope that the readers of this book will gain a new respect for the knowledge and excellence of our European colleagues in the field of hematology.

Robert V. Pierre

CONTENTS

PART 1

GENERAL HEMATOLOGY: PHYSIOLOGY AND METHODS OF STUDY

1. Myelopoiesis 3
2. Erythropoiesis 4
3. Erythropoietin 7
4. Iron 9
5. Vitamin B₁₂ and Folic Acid 13
6. The Red Cell 16
7. Granulopoiesis 29
8. Polymorphonuclear Neutrophils 33
9. Eosinophils and Basophils 36
10. Monocyte-Macrophage (Histiocytes) 37
11. Thrombopoiesis 42
12. Platelets 44
13. Lymphocytes 47
14. Plasmacytes 54
15. Structure and Function of the Immunoglobulins 57
16. Blood Viscosity 62
17. Complement 63

PART 2

GENERAL HEMATOLOGIC PATHOLOGY

18. Anemias: General Principles 69
19. Interpretation of Morphologic Abnormalities of Red Blood Cells 72
20. Dysmyelopoiesis: Description and Analysis 74
21. Diagnostic Evaluation of Hypochromia 79

22. Hypochromic Anemia Due to Iron Deficiency 80
23. Anemia of Chronic Inflammatory Disease 82
24. Sideroblastic Anemias 84
25. Causes of Normochromic Normocytic Anemias 86
26. Causes of Normochromic Macrocytic Anemias 87
27. Etiology of Megaloblastic Anemias 89
28. Macrocytic Anemias Due to Vitamin Deficiency 89
29. Diagnosis of Hemolytic Anemias 92
30. Thalassemic Syndromes 95
31. Acquired Anomalies of Hemoglobin Synthesis 99
32. Hemoglobinopathies 99
33. Causes of Sulfhemoglobinemia 102
34. Causes of Methemoglobin 103
35. Hereditary Spherocytosis 104
36. Enzymatic Defects of Aerobic Glycolysis 105
37. Enzymatic Defects of Anaerobic Glycolysis 108
38. Paroxysmal Nocturnal Hemoglobinuria (PNH) 109
39. Hemolytic Anemias Secondary to Autoantibodies 111
40. Different Types of Anemia Associated with Cirrhosis 114
41. Different Types of Anemia Associated with Cancer 115
42. Different Types of Anemias Seen in Pregnancy 116
43. Causes of Polycythemia (Erythrocytosis) 117
44. Causes of Neutropenia 119
45. Drug-Induced Cytopenias 121
46. Acute Drug-Induced Agranulocytosis 123
47. Anomalies of Neutrophils 125
48. Causes of Neutrophilic Leukocytosis 126
49. Causes of Hypereosinophilia 127
50. Leukoerythroblastic Blood Picture 128
51. Thrombocytopenias 129
52. Purpura 132

-
53. Idiopathic Thrombocytopenic Purpura (ITP) 133
 54. Causes of Thrombocytosis 135
 55. Myeloid Stem Cell Disorders 136
 56. Aplastic Anemia 137
 57. Classification of Myelodysplastic Syndromes 140
 58. Acquired Idiopathic Sideroblastic Anemia (AISA) 140
 59. Refractory Anemia with Excess of Blasts (RAEB) 142
 60. Refractory Cytopenias with Cellular Marrow 144
 61. Secondary Myelodysplasia 145
 62. Acute Myelodysplasia with Myelofibrosis 146
 63. Chronic Myelomonocytic Syndrome 147
 64. Polycythemia Rubra Vera—Vaquez's Disease 149
 65. Chronic Granulocytic Leukemia (CGL) 151
 66. Essential Thrombocythemia 153
 67. Agnogenic Myeloid Metaplasia or Myeloid Metaplasia with Myelofibrosis 154
 68. Myelomonocytic Syndrome of the Infant 156
 69. Acute Leukemia 157
 70. Erythroleukemia 161
 71. Lymphocytosis 163
 72. Infectious Mononucleosis 164
 73. Chronic Lymphocytic Leukemia (CLL) 165
 74. Plasmacytic or Multiple Myeloma 168
 75. Primary Macroglobulinemia (Waldenström's Macroglobulinemia) 172
 76. Diagnosis of Monoclonal Gammopathy 174
 77. Diagnosis of Cryoglobulinemia 177
 78. Sézary Syndrome 179
 79. Hairy Cell Leukemia 180
 80. Malignant Lymphomas 181
 81. Malignant Histiocytosis 188
 82. Angioimmunoblastic Lymphadenopathy (AILD) 189

- 83. Immune Deficiencies 191
- 84. Causes of Lymphadenopathies 192
- 85. Histologic Patterns of the Benign Adenopathies 195
- 86. Causes of Splenomegaly 196
- 87. Histopathology of the Spleen (After J. Burke) 198
- 88. Causes of Bone Marrow Failure 199
- 89. The Etiology of Pancytopenias 201
- 90. Myelofibrosis 202
- 91. Acute Myelofibrosis 205
- 92. Mechanism of Action of Cytotoxic Agents 206

PART 3

HEMOSTASIS: PHYSIOLOGY AND METHODS OF STUDY

- 93. Introduction 213
- 94. Physiology of Hemostasis 214
- 95. Physiology of Primary Hemostasis 215
- 96. Nomenclature and Biologic Characteristics of the Coagulation Proteins in Humans 217
- 97. Physiology of Coagulation 218
- 98. In Vivo Hemostasis 222
- 99. Fibrinolysis 223
- 100. Methods of Study of Primary Hemostasis 225
- 101. Studies of Coagulation 226
- 102. Methods of Study of the Fibrinolytic System 231

PART 4

HEMOSTASIS: PATHOLOGY

- 103. Disorders of Primary Hemostasis 235
- 104. Constitutional and Acquired Thrombopathies 238
- 105. Von Willebrand's Disease 239
- 106. Disorders of Coagulation 240
- 107. The Hemophilias 242
- 108. Constitutional Deficiencies of Factors V, II, VII, and X 245

109. Constitutional Deficiencies of Contact Factors 246
110. Constitutional Deficiencies of Factors Involved with Fibrin Formation 247
111. Hemostasis and Hepatocellular Failure 249
112. Defibrination Syndromes 250
113. Disseminated Intravascular Coagulation (DIC) Syndromes 251
114. Primary Fibrinogenolysis 253
115. Acquired Inhibitors of Coagulation 254
116. Thrombosis 255
117. Antiaggregating Treatment 257
118. The Vitamin K Antagonists 257
119. Heparin 260
120. Thrombolysis 261
121. Diagnosis of a Prolonged Prothrombin Time (PT) 264
122. Diagnosis of a Prolonged Activated Partial Thromboplastin Time (APTT) 265
123. Diagnosis of a Prolonged Thrombin Time 266
124. Diagnosis of a Prolonged Bleeding Time 267

PART 5

IMMUNOHEMATOLOGY

125. Erythrocyte Blood Group Antigens 271
126. HLA Complex in Humans 278
127. Principles of Utilization of **Blood** Components 282
128. Immunologic Reactions to **Transfusions** 284

APPENDIXES

- A. Morphologic Abnormalities of Red Cells 289
- B. Sideroblasts-Siderocytes 290
- C. Congenital Dyserythropoietic Anemias (CDA) 290
- D. Classification of the Acute Leukemias 291
- E. Lymphoid Malignancies (CLL, Primary Macroglobulinemia, Myeloma) 298

- F. Sézary Cells 301
- G. Hairy Cell Leukemia 302
- H. Mononucleosis Syndromes 302
 - I. Hodgkin's Disease 303
 - J. Non-Hodgkin's Malignant Lymphomas 305
- K. Drugs or Other Substances that may Precipitate Hemolysis in Patients with G6PD Deficiency 307
- L. Drugs that Induce Cytopenias 308
- M. Primary Immune Defects 309
- N. Normal Values 312

RECOMMENDED READINGS 319

EXERCISES IN HEMATOLOGY AND HEMOSTASIS 321

INDEX 375

PART 1

GENERAL HEMATOLOGY: PHYSIOLOGY AND METHODS OF STUDY



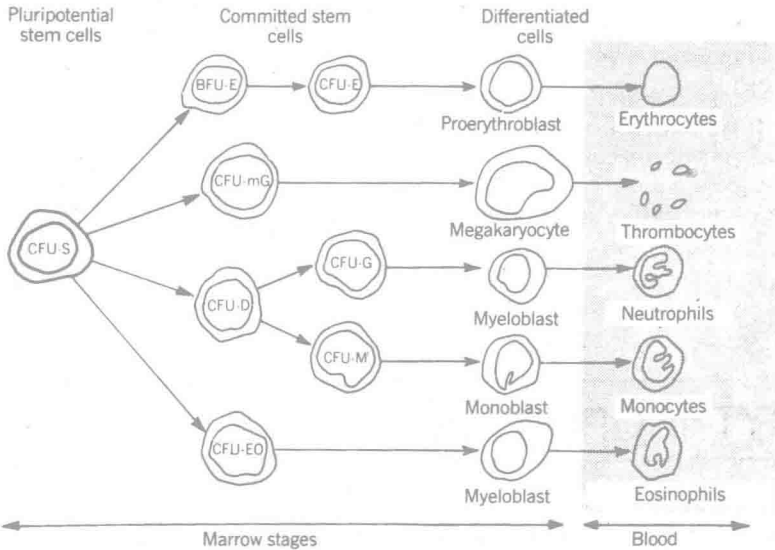
1

MYELOPOIESIS

Myelopoiesis is the production and release into the circulation of red blood cells, granulocytes, monocytes, and platelets. The precursors of these cells are found in the bone marrow.

STAGES OF MYELOPOIESIS

In vitro cell culture studies have defined the interrelations of the marrow precursor cells.



Pluripotential Myeloid Stem Cell

The pluripotential stem cell of the marrow is called CFU-S (colony forming unit—spleen). The bone marrow function of lethally irradiated animals may be restored by transfusion of blood or bone marrow of an isologous animal containing CFU-S. The different myeloid cell lines form colonies in the spleen of the irradiated mouse in a few days. The pool of CFU-S remains constant and is self-renewing.

Committed Stem Cells

Cells at this stage are committed to differentiation along a particular cell lineage under the influence of humoral control factors.

Erythropoiesis (Red Cell Line)

Two types of committed stem cells are recognized: the BFU-E (burst forming unit), which appear first in culture and show little response to erythropoietin stimulation, and the CFU-E, which appear later in culture and are very sensitive to the action of erythropoietin.

Granulopoiesis (Granulocyte and Monocyte Cell Lines)

A committed stem cell called CFU-D appears to be common to neutrophil and monocyte production. It gives rise to two cells: the CFU-G and the CFU-M. A precursor cell for the eosinophil cell line must exist; therefore, the term CFU-EO is proposed for the eosinophil precursor. The humoral factor "granulopoietin" has not been fully characterized. It appears to be a glycoprotein substance secreted partly by monocytes, and has been called "colony stimulating factor," or CSF. It is thought to play an essential role in the regulation of granulocyte and monocyte differentiation.

Thrombocytopoiesis (Megakaryocyte Cell Line)

The committed stem cell is called the CFU-MG. This cell differentiates to megakaryocytic precursors under the influence of a humoral factor called thrombopoietin.

The mature, differentiated cells are described in the following chapters.

2

ERYTHROPOIESIS

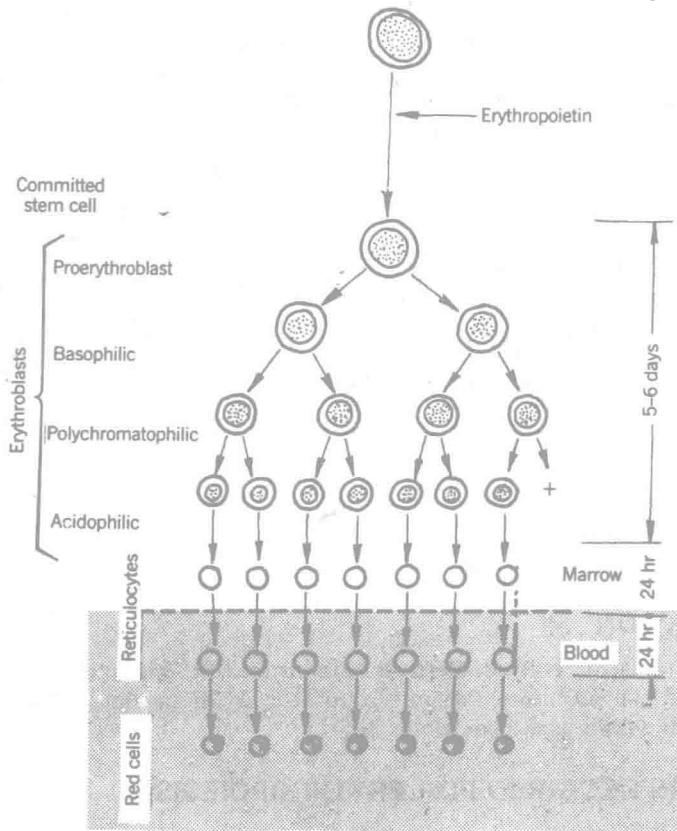
Erythropoiesis consists of a well-regulated mechanism that maintains the number of red blood cells and the level of hemoglobin within narrow physiologic limits.

The life span of the normal red blood cell is 120 days; 1/120th (0.83%) of the red cell mass is destroyed each day. The bone marrow production compensates for this loss of red cells and hemoglobin by production of the same quantities.

Normal erythropoiesis consists of







- Progressive decrease in size of erythroblasts
- Reduction in nuclear/cytoplasmic ratio
- Progressive increase in hemoglobin content
- Expulsion of the nucleus

- Intramedullary death of 5 to 10% of erythrocytic precursors (i.e., ineffective physiologic erythropoiesis)



STAGES OF ERYTHROPOIESIS

ERYTHROPOIESIS (MORPHOLOGIC CHARACTERISTICS OF CELL STAGES)

Cell Type (Size in μm)	Nucleus		Cytoplasm	
	Chromatin	Nucleolus	Color	
Proerythroblast (15 to 20)	Very fine	Visible	Basophilic	
Basophilic erythroblast (12 to 18)	Fine	Absent	Basophilic	
Polychromatophilic erythroblast (12 to 15)	Clumped	Absent	Polychromatophilic	
Acidophilic erythroblast (8 to 12)	Very dense	Absent	Red to purple	
Reticulocyte (8 to 10)	No nucleus		Red, + reticulin	
Erythrocyte (7 to 8)			Red	

REGULATION

The humoral factor, **erythropoietin**, transforms the CFU-E into the first recognizable red cell precursor, the proerythroblast. Erythropoietin also partially controls the synthesis of hemoglobin.

FACTORS REQUIRED FOR ERYTHROPOIESIS

- Metals: iron, copper, and cobalt primarily
- Vitamins:
 - Folic acid and vitamin B₁₂ are required for normal cell division (DNA synthesis)
 - Vitamins E, B₆, B₁, C
- Amino acids: Required for globin chain synthesis
- Hormones: **Erythropoietin**, androgens, thyroxine

LABORATORY ASSESSMENT OF ERYTHROPOIESIS

Initial studies:

- Hemoglobin value
- Absolute reticulocyte value