HEMATOLOGY

By

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Dedicated

to the late

HENRY A. CHRISTIAN

My chief for the first ten years of my medical experience, who formerly served as Hersey Professor of the Theory and Practice of Physics, Harvard University; Clinical Professor of Medicine, Tufts College Medical School; Physician-in-Chief, Peter Bent Brigham Hospital; Visting Physician, Beth Israel Hospital, Boston

In grateful acknowledgment of my profound indebtedness to him for his example, counsel guidance and the opportunities which he made available to me

PREFACE TO SECOND EDITION

With the revision of the First Edition of this book, an opportunity is afforded to include the significant advances which have been made in hematology in the past five years. Among the more important ones have been the isolation and identification of vitamin B_{12}, now recognized as the extrinsic factor of Castle and the active principle of liver effective in the treatment of pernicious anemia; the introduction of the folic acid antagonists, triethylene melamine and nitrogen mustards, ACTH and cortisone, in the treatment of leukemia and allied conditions; the therapeutic effectiveness of ACTH and cortisone in idiopathic thrombocytopenic purpura and acquired hemolytic anemia; a clarification of the indications for splenectomy; and a widening of our knowledge concerning drugs as etiologic agents in hematologic disorders, especially aplastic anemia and agranulocytosis.

Every page of the book has been carefully scrutinized and many revisions inserted, along with suitable deletions. The space dealing with the historical aspects of hematologic disorders, although extensive, has not been curtailed as comments by reviewers indicate that in general it has received a favorable reception.

The science of hematology is not static but is as fast moving as any other division of medical knowledge. A textbook such as this, therefore, cannot be expected to be entirely complete even if it were revised every few months. An effort has been made, however, to include the important facts concerning each hematologic disorder which appear to have been established beyond the question of a doubt, and to attempt an evaluation of the significant new advances in this field.

To Dr. Frank H. Bethell, Professor of Internal Medicine and Assistant Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, and to Dr. Muriel Meyers, Associate Professor of Internal Medicine and Research Assistant in the Institute, I am especially indebted for their generous aid, counsel and guidance which have been invaluable to me. To Miss Mary A. Kinney, my secretary, I am especially grateful for her constant assistance and valuable direction in the preparation of the revised manuscript.

I am greatly appreciative of the assistance and encouragement given to me in the preparation of this Second Edition by my publisher, Mr. Charles C Thomas and his staff.

Cyrus C. Sturgis

Ann Arbor, Michigan

PREFACE TO FIRST EDITION

One of the most appropriate utterances that has come to my attention concerning the writing of a textbook of medicine is as follows: "Everyone who writes a textbook on any branch of experimental science must set down as many wrong statements as right; he cannot carry out most experiments himself, he must rely on the testimony of others and often take probability for truth. Thus a compendium is a monument of the time when the facts were collected and it must be renewed and rewritten again and again. But while fresh discoveries are accepted and a few chapters improved, others perpetrate misleading experiments and erroneous deductions." (From the *Theory of Colour* by Goethe.)

This remarkably true statement by a master poet and philosopher deserves the careful consideration of all prospective authors of medical texts. This is because the medical sciences are now moving forward so rapidly that the writing of a monograph on any one phase of the practice of medicine necessitates the constant evaluation and sifting of an almost endless amount of material which is appearing at an increasing tempo in the current medical literature. One must apply himself diligently to the task of sorting the good from the bad, differentiating carefully between matters of ephemeral importance and those of permanent value, and of assigning the proper amount of space to the various aspects of different disease syndromes.

The late Harvey Cushing once told me that no one should become the author of a medical book until after he had attained the age of 50 years. This remark has remained in my memory although an appreciation of its significance was not aroused until more recent years. While many admirable medical books have been written by young authors, nevertheless an increasing age has some advantage because it at least provides a longer period of time to accumulate experience and hence formulate more mature and permanent judgments. It is the utilization of the faculty of critical discrimination based upon an extensive well balanced general clinical experience that enables one to avoid to a certain extent the pitfalls described so adequately by Goethe.

It seems appropriate in the preface of a book dealing with this subject to comment briefly upon hematology as a specialty. There has been a regrettable tendency since the rapid development of the laboratory aspect of medicine to place unwarranted reliance upon technical tests and to minimize the importance of the information derived from the history and physical examination of the patient. Some hematologists, for

example, have been too content to limit their examination to a blood film and then attempt to express a definitive opinion in regard to the patient's entire clinical picture. Despite the warnings of experienced clinicians this practice continues and undoubtedly favors error and the improper management of the patient.

Furthermore, in hematology as in cardiology or gastroenterology, or any other branch of medicine, the patient has not infrequently suffered from the narrow efficiency of specialism. This means that a physician may be preeminent in his own chosen field but conspicuously deficient or disinterested or both in the other aspects of medicine. In my opinion the ideal situation in hematology or any other branch of internal medicine, is the practice of a specialty by a physician who has an excellent background and training in internal medicine but a special interest in some one branch of it. Such a physician is not likely to be misled by a laboratory examination, for his clinical balance provides him with a method whereby all which has a bearing on the patient's condition may be properly evaluated. All mature clinicians agree that the information derived from the laboratory should only be employed in a confirmatory manner, for there are few diseases which can be recognized from tests of this nature alone.

On the other hand the availability of laboratory tests which are done accurately by carefully trained individuals, and the correlation of these data with that derived from all other sources constitutes the ideal method of practicing our profession. Often, such a broad method of accumulating diagnostic information is the crux of the difference between the practice of "good" and "bad" medicine.

Perhaps some explanation should be offered for the prominence which has been given in this publication to the historical aspects of hematology. There have been two reasons for this: In the first place this phase of hematology has been largely ignored in many previous monographs and textbooks, and it is my opinion that its inherent interest alone merits more than cursory attention. Second, and probably of greater importance, is my firm conviction that a scholarly knowledge of any branch of medicine can only be based upon a clear understanding of the principal advances and their sequential development which has lead to our present total fund of information in any particular field. While it is possible, of course, to acquire a sufficient number of current facts relating to any disease which will serve for many practical purposes, a true and profound insight into any complex subject can only be based upon a historical study dealing with the evolution of each forward step. Hence it should be emphasized that any scientific matter must be studied historically in order to acquire a proper appreciation of the contemporary knowledge relating to it and about which we may speak so glibly today.

In hematology, as in other branches of medicine, progress was not continuous but halting; that is, with the invention of some instrument

such as the microscope, the hemocytometer, a new method of staining, or under the guiding mind of such a genius as Virchow, Hayem, Ehrlich, or some other equally great hematologist, new and important information was acquired with amazing rapidity. Periodically with the diversion of scientific studies elsewhere, interest in hematology has waned and in some instances it was maintained for a period of years by only a slender thread. Although fragile, it sufficed to sustain the spark of interest until some unpredictable influence fanned the flame anew.

The story of the accumulation of knowledge in any special field of medicine is fascinating, for it is one of persevering interest, false starts with the pursuit of some facts into a cul-de-sac of disappointment which necessitated a retreat and a new beginning. As so frequently happens, the investigator to whom the credit is given may have been preceded by years by some unknown but brilliant scientific semi-recluse who made but did not give the world his discoveries. Many historical surveys show that the path leading to scientific discoveries is not always pleasant, for it may be interwoven with bitter personal and international controversies, false claims and counter claims, and the lack of recognition either with financial reward or scientific acclaim. But finally there is the consoling fact that ultimately justice will always prevail and the proper credit and recognition be given. This is, alas, sometimes delayed for years or even centuries.

Special attention has been given in this publication to the preparation of a carefully selected bibliography. This in my opinion adds greatly to the reference value of any textbook and hence the *extensive list of items has been chosen with great care.* As my colleagues and I at the Simpson Memorial Institute of The University of Michigan for a number of years wrote the review on hematology for the *Archives of Internal Medicine,* an opportunity was afforded to inspect a wide variety of articles, some of which otherwise would have been overlooked. Even with great care, it is always regrettable that a number of important presentations are unintentionally omitted. For such oversights I wish to extend my apologies.

Unusual care has been taken to make the bibliographical references accurate and hence not perpetuate errors which have been known to continue through several generations. In each instance, with exceedingly rare exceptions, the original texts have been consulted, and the reference verified. For this opportunity I wish to extend my warm thanks to Miss Sue Biethan, former Medical Librarian of the University of Michigan, whose assistance and cooperation cannot be over estimated. I desire also to express my appreciation to the Staffs of the Surgeon General's Library, the John Crerar Library, the Library of the American Medical Association and the editors of many medical publications who have given permission to reproduce charts, tables and other material from various

periodicals. Acknowledgment of this in each individual case is made in the text.

It is with pleasure that I acknowledge my indebtedness and gratitude to my secretaries, Mary Kinney and Marguerite Madden Laetz, whose assistance, cooperation and perseverance has been far above that required in the line of duty. Without their constant aid and encouragement this book would never have been completed.

My publisher, Mr. Charles C Thomas and his son, Mr. Payne Thomas, have been most helpful in making many suggestions, and in giving their most careful and meticulous attention to the numerous details concerning the publishing of this book. To them I wish to extend my most sincere expression of gratitude. In conclusion, I wish to state that I am greatly indebted to my friend of many years standing, Dr. Lawrence Reynolds, Editor of *The American Journal of Roentgenology and Radium Therapy,* who was responsible for directing my attention toward the publication of this work on hematology. Had he not made the suggestion at precisely the proper moment it is doubtful that my labors would have ever turned in this direction.

CYRUS C. STURGIS

This Book

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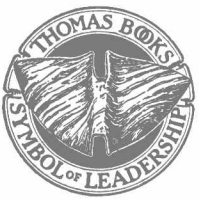

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CHAPTER I

CLASSIFICATION AND GENERAL REMARKS CONCERNING THE ANEMIAS

Definition.—An anemia may be defined as a diminished concentration of hemoglobin or erythrocytes, or both, in the circulating blood below the normal standards for sex and age. The lower limit of normal for adult males is given by Albritton (*1*) as 4.6 million red blood cells per cubic millimeter and a hemoglobin of 14.0 grams per 100 cc. of blood. For adult females, these values are stated as 4.2 million red blood cells per cubic millimeter and a hemoglobin concentration of 11.5 grams per 100 cc. of blood. The standards given by Wintrobe (2) are a red blood cell count of 4.6 millions per cubic millimeter for adult males with a hemoglobin concentration of 14.0 grams per 100 cc. of blood and for adult women a minimum red blood cell count of 4.2 millions per cubic millimeter and a hemoglobin of 12.0 grams per 100 cc. of blood. From my own experience in the northern part of the United States, *I would place the lower limit of normal for hemoglobin at 12.2 grams (78 per cent per 100 cc. of blood) for women, and 13.4 grams (86 per cent) for men; the minimum red blood cell count I have considered to be 4.13 millions per cubic millimeter for women, and 4.7 millions for men.*

Strictly speaking, a true anemia means an actual decrease in the total amount of hemoglobin or number of red blood cells in the entire body, which involves a consideration of the blood volume. For instance, there is the so-called physiological anemia of pregnancy in which the red blood cell count and hemoglobin are decreased as determined by the usual methods. This is not a true anemia, however, but a diminished concentration due to the fact that the plasma volume is increased. Under these circumstances the total number of red blood cells and grams of hemoglobin in the entire body are not less than normal, but are merely present in a decreased concentration. The situation is reversed in acute hemorrhage, for although there may be considerable loss of hemoglobin and erythrocytes, their values in the circulating blood immediately after the bleeding are normal. This is because the blood volume is decreased, and, as a result, there may be no change in the concentration of the erythrocytes in the circulating blood, although their actual total number in the body may be decreased.

Symptoms and Signs of Anemia.—There are certain symptoms common to all anemias regardless of the cause which becomes apparent when the

hemoglobin falls to the level of approximately 11.0 grams per 100 cc. (70 per cent). The main clinical evidences of an anemia are ease of fatigue, weakness, and the cardio-respiratory symptoms and signs which are directly referable to the anoxia of the tissues resulting from the impaired oxygen carrying capacity of the blood due to its decreased hemoglobin content. The manifestations are, for the most part, directly proportional to the level of the hemoglobin.

TABLE I

NORMAL VALUES OF RED BLOOD CELL COUNT, HEMOGLOBIN CONCENTRATIONS, HEMATOCRIT READINGS, AND VARIOUS CORPUSCULAR VALUES FROM BIRTH TO MATURITY

Age	*Red Blood Cell Count (Millions per C.Mm.)*	*Hemoglobin (Gm. per 100 Cc.)*	*Vol. Packed R.B.C. (Cc. per 100 Cc.), Hematocrit*	*Corpuscular Values*		
				M.C.V. (C.μ)	*M.C.H.C (Per Cent)*	*M.C.H.*
At Birth	5.7	21.5	56.6	106	38	38
	Range	Range				
	4.8–7.1	18–27				
End 4th Week	4.7	15.6	44.6	91	35	33
	Range	Range				
	3.9–5.9	12–21.8				
End 12th Mo.	4.6	11.6	35.2	77	33	25
	Range	Range				
	4.0–5.5	9–14.6				
End 12th Year	4.8	13.4	39.6	81	33.8	28
	Range	Range				
	3.8–5.4	11–16.5				
Adult Male	5.4	15.8	47	87	33.5	29
	Range	Range				
	4.6–6.2	14–18				
Adult Female	4.8	13.9	42	87	33.5	29
	Range	Range				
	4.2–5.4	11.5–16.0				

(Based on data presented by Albritton (*1*)).

The *cardio-respiratory* symptoms and signs are usually encountered in patients with an anemia when the hemoglobin level of the circulating blood falls to 11.0 grams per 100 cc. or lower. Comprehensive studies on the cardiovascular system in patients with anemia have been reported by Ellis and Faulkner (*3*), by Wintrobe (*4*), by Hunter (*5*), and by Blumgart and Altschule (*6*). According to Blumgart and Altschule (*6*) when the oxygen carrying capacity of the blood is lowered, as it always is when an anemia is present, an anoxia of the tissues will result unless one or both of two mechanisms are brought into play effectively. One is an increased cardiac output which will augment the blood being delivered to the tissues. If the hemoglobin is reduced one-half but the rate of blood flow is doubled, the amount of oxygen reaching the tissues will