HEMATOLOGY

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edited by William S. Beck

fifth edition

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Preface to the Fifth Edition

Since the first edition of this book appeared in 1973, revisions have emerged at four-year intervals—the second edition in 1977, the third in 1983, and the fourth in 1985. A web of circumstance kept this edition, the fifth, from appearing in 1989. But here it is—a year late and all the better.

In previous revisions, the need for renewal was always clear and compelling. This time, it was overwhelming. Among the additions are discussions of the myeloid growth factors, erythropoietin, the red cell cytoskeleton, oncogenes, and newer aspects of immunology, hemato-oncology, and clotting. Indeed, the percentage of text replaced or updated was far higher than in any previous revision—a clear sign of the pace and sweep of contemporary research in hematology and allied fields.

To make the fifth edition something of a special event, we have introduced the following changes and new features:

- Although this syllabus was written orginally for first and second year medical students, it found many readers among house officers and practicing physicians. To better serve them (and medical students in their clinical years), we have included more tables, charts, and text on diagnosis and approach to the patient. It has been said in jest that practicing hematologists face seven major clinical problems: too few and too many red cells; too few and too many white cells; too few and too many platelets; and bleeding. To an extent, it is possible to construct binary logic trees outlining optimal approaches to each of these problems, indicating among other things what tests are to be done when. We urge those confronting such clinical problems to think in large categories before delving into the minutiae of individual diseases. Thus, in the analysis of anemia, one wants to know early whether there is premature red cell destruction (or hemorrhage), or failure of production. The reticulocyte count helps to distinguish these categories and should be considered before other tests—and so on. The flow sheets in this edition suggest rational approaches to several of the hematologist's major problems. They are not written in stone. Other approaches could be described. These are the ones we use and recommend.
- Reference lists and bibliographies are more extensive than in previous editions. As a service to the reader, we have segregated references under the headings Reviews and Original Papers.
- A new lecture has been added on general principles of malignant disease, an acknowledgement that hematology today in many institutions has been converted to hematology-oncology—in practice, if not in course

design and teaching. This lecture covers a number of general points that we felt were not covered elsewhere in the medical curriculum and would provide useful background to the lectures that follow on the aspects of hematologic oncology.

- There is a new appendix containing laboratory methods that should be useful to students in taking hematology or clinical pathology courses as well as to physicians performing such tests in their own laboratories, if such there be.
- The fifth edition is being published in combination with *HEMAVID*, a comprehensive computer program for the teaching of blood and bone marrow morphology. That program, as noted elsewhere, includes an extensive menu that permits users to examine multiple examples of all of the major hematologic disorders discussed in the text. It also includes some hematologic cases in which blood and bone marrow morphology are presented as unknowns as well as a collection of examination questions. The *HEMAVID* program makes extensive references to text in this volume, and we hope our readers will have an opportunity to study both the book and the computer program in tandem.
- The lectures are again in outline form. This seems to help with the organization of ideas and to facilitate note-taking. However, we have tried to make the text even more readable. As before, there is a wide margin and outline headings and their ranks are indicated by labels and font styles. We have made these clearer in this edition and have, in addition, for the first time in the text used bulleted lists, which should add further clarity to the material.
- Finally, to mark this edition I have included on the first page of each lecture brief Editor's Comments, which incorporate remarks of the kind one might offer in the classroom when introducing a new lecturer or topic. These, in effect, set the stage for the material to be covered and in some cases celebrate some of the major advances that have taken place since the first edition of 1973.

The book's general concept remains unchanged. These are lectures—we resolutely call them that rather than chapters—that may be read by students in their own time, both as preparation for and reminder of discussions in lecture hall and laboratory. There is no intention here to preempt lectures and lecturers. Long experience in the hematology courses of Harvard Medical School and the Harvard-MIT Division of Health Sciences and Technology suggests that the lecture hour is now best used for illustration and expansion.

Emphasis remains on physiology and pathophysiology. Discussions of therapy are still framed in terms of principles. We refer readers elsewhere for dosage schedules and other details. Topics are treated in a traditional sequence—red cells, then white cells, then clotting—and we assume that lectures will be read in that sequence. However, cross-references are offered for those who prefer to read the lectures in another sequence.

Reluctantly, we deleted a lecture, which appeared in the first four editions, on histiocytoses and lipidoses. These, of course, have relevance to hematology because the storage cells they display are often found in bone marrow and need to be recognized. Also, these disorders are part of the differential diagnosis of hepatosplenomegaly. However, in the current scheme of things, we felt that if something had to go, it would be a topic that is adequately covered in other courses.

I note again that authors of many of these lectures are indebted to those who lectured in former years and who contributed to earlier editions. Rather than adopt complex rules of authorship, we have chosen to acknowledge these fine predecessors in this preface. I acknowledge with thanks the stimulating past contributions of N. Abramson, A. Aisenberg, C. A. Alper, R. H. Aster, R. W. Colman, R. A. Cooper, A. C. Crocker, D. Deykin, L. K. Diamond, B. G. Forget, B. Glader, H. A. Godwin, R. I. Handin, S. E. Lux, W. C. Moloney, P. R. Reich, G. K. Sherwood, J. T. Truman, and I. Umansky. I also wish to recognize the efforts of Carol Sparling, who assisted in the preparation of the manuscript.

William S. Beck
September 1990

From the Introduction to the First Edition

In the present Harvard Medical School curriculum, hematology is one of a dozen blocks within the large one-year Pathophysiology course, which begins in the middle of the first year. For many years we have furnished our students in this course with syllabus materials and lecture notes. These notes have long been known as "the camel," which, as everyone knows, is an animal that looks as though it had been put together by a committee. When responsibility for the course came to me, the scanty lecture notes took the form of severe and often uninformative outlines. Students complained of the burdens of note taking, and some brought tape recorders. Accordingly lecturers were asked to flesh out their outlines, and our camel grew. It became apparent in time that the value of the syllabus would be enhanced by careful editing. The result is the present volume. The vast expansion of knowledge in the various branches of pathophysiology poses an increasingly difficult problem for those who would define the content of a core curriculum and establish standards and priorities for what is to be taught. It is my view that this difficult cause can be furthered only by the thoughtful preparation of texts such as this, for the very act of editing such a volume necessitates choices and permits correlations and overviews that are never quite possible when many and diverse individuals are responsible for a course of instruction.

The major goal of this endeavor is to improve the quality and usefulness of these notes as teaching instruments. It is our intention to revise this small volume frequently so it will retain the freshness and currency that characterized the informal syllabus materials of previous years.

Some believe it would now be appropriate to abandon formal lectures. I see much merit in that proposal. Surely medical students are capable of handling reading assignments. Surely they deserve exemption from having read to them lectures that they could as well read themselves. Still there is cause for regret about a step that would deny students an hour or two with colleagues who rate high as teachers, scientists, and personalities. How to make the best use of these hours will be the subject of experimentation and innovation in the years ahead.

In a sense, this volume is a successor to Ham's famous *Syllabus* and its revision by Page and Culver. Unlike the present book, however, the earlier syllabuses placed major emphasis on laboratory diagnosis. We hope that this volume will be useful to our students, both in the first- and second-year hematology courses and in later clinical years. We hope too that students

and physicians beyond Harvard Medical School may find this a helpful review of hematology, one that may serve as a compendium and guide to the several large new textbooks of hematology.

William S. Beck
February 1973

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Hematopoiesis

William S. Beck

EDITOR'S COMMENT

Of all the topics in this book, those in this important lecture have required the most revision in successive editions, with some sort of climax occurring in this one. Studies of hematopoiesis have surged in recent years owing to tissue culture techniques for various colony-forming units (CFUs) and progress (much of it in industrial laboratories) in the identification, purification and cloning of the cytokines, lymphokines, and monokines that regulate blood cell production. Knowledge of these factors has both simplified and complicated the field. Certainly, it has opened large new doors in its promise of revolutionary clinical applications. Some have already been realized. The prospect of being able to control cell proliferation and differentiation pushes at the frontiers of clinical hematology: the refractory anemias, bone marrow failure, leukemia, and lymphoma. It is worth noting that these advances were directly attributable to the dogged persistence of some investigators through long years of tedious assays and discouraging results. A case in point: Metcalf's discovery of GM-CSF and related factors. In its auspicious outcome, hematologic research again yielded important insights into basic biologic mechanisms.

I. BIOLOGY OF HEMATOPOIESIS

Hematopoiesis consists in a series of events wherein the hematopoietic stem cells mature into functional blood cells. Its locus changes in the course of development.

A. Ontogeny

In the third week of human embryogenesis, mesenchymal cells in the yolk sac from clusters called **blood islands**. Peripheral cells of the islands join to form a primitive vascular system. Simultaneously central cells of the islands differentiate into elements that become detached and are carried off by the mounting stream of primitive plasma. These are the **yolk sac stem cells**. Some differentiate into **primitive erythroblasts**, the earliest hemoglobin-synthesizing cells. Unlike pronormoblasts of adult bone marrow, they do not mature into erythrocytes.

In the third month of embryonic life, yolk sac stem cells migrate to the liver, which then becomes the chief site of blood cell formation. Additional contributions are then made by the spleen, lympth nodes, and thymus. Hematopoiesis may continue in the liver unitl after birth. However, bone

marrow hematopoiesis begins in the fourth lunar month and by the end of gestation is the major source of blood cells. The terms **medullary** and **extramedullary hematopoiesis** denote blood cell production by bone marrow and by tissues other than bone marrow, respectively.

At birth, medullary hematopoiesis occurs in almost every bone. Flat bones (sternum, ribs, skull, vertebrae, and innominates) retain most of their hematopoietic activity throughout life, but hematopoiesis progessively diminishes within the shafts of long bones. In the adult, it is limited to the ends of these bones. At times of increased demand for blood cells, active marrow reappears in these sites. Hematopoiesis in the adult occurs exclusively in bone marrow. As noted below, even lymphocytes derive from medullary precursors. Some extramedullary hematopoiesis persists at birth, but it rapidly diminishes, to resume only under abnormal circumstances. In such instances, liver and spleen are the major loci of extramedullary hematopoiesis.

B. Phylogeny

Much has been learned of the physiology of blood from studies of the evolution of the hematopoietic system. Amphioxus and other primitive chordates lack blood cells. In some invertebrates, hemoglobin occurs in solution in plasma. The mature red cells of reptiles, birds, and fish contain nuclei, mitochondria, and ribosomes that are actively engaged in hemoglobin synthesis. The locus of adult blood-forming tissue varies in different speices. For example, it is the kidney in amphibia and teleosts; the gonads in some fishes; the liver in turtles; and tissues around the heart in sturgeon and paddlefish.

C. Mammalian bone marrow

Nutrient arteries enter marrow cavities through bone foramina. Arteries branch into distributing arterioles that give rise to an endosteal bed of **sinusoids**. From the bed, sinuses travel in a radial direction toward the central longitudinal veins lying in the long axis of the bone. Hematopoietic tissue lies between the sinuses. **(Erythropoiesis, granulopoiesis** (or **myelopoiesis**), and **thromobopoiesis** take place extravascularly in the marrow **stroma**.

Sinusoidal walls have three layers: **endothelial cells**, **basement membrane**, and **adventitial cells**. Endothelial and adventitial cells are both mononulcear reticulum cells that are capable of phagocytosis (see lecture 2). Blood is present within the sinusoids, but intrasinusoidal materials (both diffusible and particulate) have free access to extrasinusoidal areas through gaps in the walls. Hematopoietic cells, having undergone maturation outside the sinusoids, enter the sinusoid at a critical moment in the maturation sequence. This critical event is termed the **release** of blood cells from marrow into blood. Its mechanism is still poorly understood.