Pathophysiology of Blood

Edited by

Archie A. MacKinney, Jr., M.D.

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A.A.M.

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Series Preface

It has come to be generally appreciated that knowledge concerning the pathophysiology of organ dysfunction serves as the basis for our understanding of the underlying mechanisms of disease. The phenomenal growth of pathophysiology as a discipline during the past ten years and its efficacy in medical education have prompted the preparation of the Wiley Pathophysiology Series.

Until recently, the traditional method of instructing first- and second-year medical students has been to teach the basic sciences, including pharmacology and biochemistry, separately. Today, however, an increasing number of medical schools have come to favor a multidisciplinary course of study in which the pathophysiology of each organ system is examined and dealt with in its entirety. It has been found that this provides medical students with a firm basis of knowledge concerning cellular biology and basic science and their relevance to the practice of medicine. The purpose of this series is to offer an accompaniment to such a curriculum that is both thorough and up-to-date.

The first book in the series, *Pathophysiology of Respiration*, dealt with the disordered function of the respiratory system. In *Renal Pathophysiology*, Drs. Harrington and Zimmerman touched on all aspects of the altered performance of the diseased kidney.

This book on the pathophysiology of blood by MacKinney and his colleagues deals in concise fashion with the disordered function of the hemopoietic system. It is hoped that teachers and practitioners of medicine, as well as medical students and house officers, will find it stimulating and useful.

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Preface

In the 1960s, a consortium of medical schools investigated the best methods of teaching hematology. These methods have proven themselves in student teaching, and so we have incorporated them into this book. One conclusion reached by the group was that the erythrocyte is the model cell because it is so well understood, and it followed that a proportionately large share of a hematology text should be devoted to the erythrocyte. A second conclusion was that case development problems are a good way of introducing students to clinical medicine; we also have incorporated this idea into the text. An emphasis on pathophysiology is a third feature of the book. Whereas a textbook of medicine emphasizes the description and treatment of disease, this book links biochemistry, physiology, histology, and genetics to the explanation of disease.

The book begins with an overview of the hemopoietic system. The red cell occupies the next six chapters, beginning with red cell production and moving through iron metabolism, DNA synthesis, and red cell destruction. Each general pathophysiologic process leading to shortened red cell life—abnormal membranes, enzyme defects, and hemoglobin disorders—is given a chapter. Discussions of red cell replacement (blood banking) and the repair of the blood vessels (clotting) follow.

We have concluded with the difficult subject of leukocyte physiology. Our knowledge of the white cells is growing so rapidly that almost constant revision is necessary to keep the material current. Because of this rapid growth, our models still lack the lucidity found in many discussions of red cell physiology. We have outlined the pathophysiology of each of the principal leukocytes and the clinical problems that best illustrate disease mechanisms.

Hematology should be seen as an eclectic discipline, which takes as its province all of the cellular elements of blood as well as the interacting humoral mediators and structural proteins. Hematology constitutes an excellent first step into clinical medicine. The student will find the pathophysiologic principles in this text applicable to many other organ systems.

A.A.M.

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Introduction to Hemopoiesis

Robert D. Woodson
Nasrollah T. Shahidi
Archie A. MacKinney, Jr.
Jonathan L. Finlay

OVERVIEW

Blood is beautiful. It is symbolic of life, courage, and sacrifice. Englishmen swear by it. The Romans loved to shed it in the arena. The ancient Hebrews made it sacred in their sacrifices. Its color fascinates flag makers and artists. Students since Ehrlich have been delighted with the shapes and colors of red cells and leukocytes. The intellectual beauty of blood is apparent to the physiologist and biochemist studying the orchestration of cells, gases, substrates, stimulators, and inhibitors. Three blood cells will be introduced informally. In later discussions they will appear more complicated.

The red cell is a masterpiece of design. Its thin, flexible membrane, in the unusual shape of a biconcave disc, is nearly ideal for gas transport. The red cell is so pliable that it can pass through spaces half its diameter, yet its membrane is rugged enough to remain intact for four months and hundreds of miles; like a good automobile tire, it is self-sealing. It carries no nucleus to impede gas exchange or add a metabolic burden. Only a few nonrenewable enzymes are used to maintain its membrane and respiratory pigment. It carries its respiratory pigment (hemoglobin) at concentrations near saturation. At the end of its life, it is almost completely recycled.

If the red cell is benign and rather passive, the neutrophil is chemically explosive. It is an amebalike phagocyte, loaded with a variety of potent enzymes. After ingesting and digesting bacteria, the neutrophil self-destructs from the effects of its released enzymes and oxidants. The first white cell on the scene of inflammation, it lives a short life of less than 24 hours after leaving the blood. A ready reserve of a cupful of neutrophils is kept in the bone marrow to fight large-scale infections.

The platelet is perhaps the strangest of all the blood cells. It is the smallest, with a diameter that is one-fourth that of the red cell. It is a

fragment of a cell, without a nucleus, containing a complex internal structure that includes neurofilaments and specialized secretory granules. The platelet functions to plug holes in blood vessels. When a vessel wall is injured and its surface endothelium is disturbed, platelets adhere to the injury site and release chemical mediators that attract other platelets to form a gluey mass. This blood vessel "glue" is not tough enough to hold the blood from leaking out indefinitely, but the mass serves as an active site on which long, filamentous fibrin strands form. Fibrin binds the platelets down, much like wire mesh holds the cork in a champagne bottle, until healing of the vessel wound is organized.

HEMOPOIETIC PROGENITOR CELLS

Introduction

Until very recently, knowledge about bone marrow growth was limited to the study of differentiated cells of the bone marrow and their progeny in the peripheral blood. In recent years, however, new culture techniques have provided insight into the growth and development of the stem cell compartment, which feeds the compartment of differentiated cells. One-tenth of 1% of marrow cells are stem cells. They resemble lymphocytes, which are in relative abundance—10% to 20% in adults. Consequently, stem cells cannot be studied by ordinary morphologic techniques.

Uncommitted Stem Cells

The bone marrow is a rapidly dividing tissue with an enormous output: 2×10^{11} red cells are produced daily in a 70-kg man. Under stress such as hemolysis, the hemopoietic system may increase its production of cells by as much as fivefold. Continuous hemopoietic stem cell maturation is necessary to maintain the pools of mature cells, but self-replication of stem cells is also essential; otherwise, the stem cell pool would become depleted. Thus, the fundamental characteristic of primitive uncommitted pluripotent stem cells is that they both self-replicate and differentiate into progenitor cells. The latter, although not morphologically recognizable as erythroid or myeloid precursor cells, are nevertheless committed to one or another pathway. Progenitor cells proliferate and differentiate into morphologically distinct hemopoietic elements (e.g., erythroblasts, myeloblasts, lymphoblasts) (Fig. 1.1).

The hemopoietic stem and progenitor cell pools are not limited to the bone marrow. Small numbers can be grown from the spleen and even from the peripheral blood. Lymphoid cells also can be grown from progenitor cells of the thymus and other lymphoid organs as well as from the bone

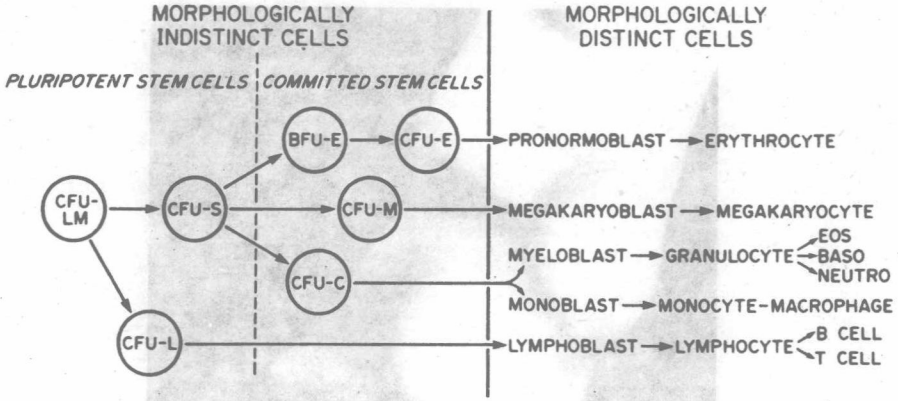

Figure 1.1. Schematic flow of stem cells into differentiated compartments. CFU-LM is a stem cell for lymphoid and myeloid cells. CFU-S is a stem cell for the myeloid series. BFU-E and CFU-E are two successive erythroid stem cells. CFU-M is a megakaryocyte stem cell. CFU-C is the stem cell of granulocytic and monocytic cells.

marrow. The function of stem cells in extramedullary locations is not known, but they may repopulate the bone marrow after portions of it have been injured.

Uncommitted stem cells were first identified in the mouse. When a mouse is exposed to a dose of ionizing radiation sufficient to destroy its hemopoietic cells and then is given by intravenous injection a suspension of normal syngeneic (same-strain) bone marrow, the animal will survive, and its spleen will become a center of donor cell hemopoiesis. After seven to eight days, macroscopic nodules will be found in the spleen (Fig. 1.2). Each nodule arises from a single cell and consists of a recognizable colony of hemopoietic cells. The donor cells taking root in the spleen are called spleen colony-forming units (CFU-S) (Fig. 1.1). The colonies that form may consist purely of cells of one lineage (i.e., erythroid, myeloid, or megakaryocytic), or they may consist of two or even three lineages. Thus, the CFU-S are capable of differentiating into hemopoietic cells of all lineages. Moreover, if these colonies are excised from the mouse's spleen and injected into another syngeneic irradiated mouse, the cells will produce more colonies in the second mouse's spleen. Thus, the CFU-S have also given rise to self-replicating cells, thereby fulfilling both criteria for uncommitted hemopoietic stem cells (self-replication and differentiation).

More recently, the progeny of pluripotent stem cells have been grown from human marrow and peripheral blood in culture. These colonies contain erythroid as well as myeloid, monocytic, and megakaryocytic cells. The methods for growing such colonies are similar to those for committed progenitor cells, but additional growth factors are required

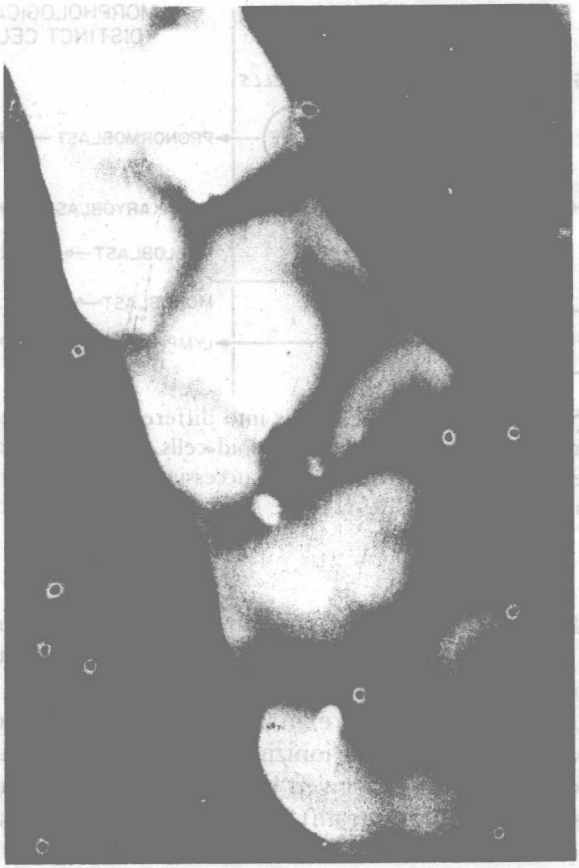

Figure 1.2. Colonies are visible under the spleen capsule after irradiation of the mouse and transplantation with marrow cells from a syngeneic donor. Each colony arises from a single pluripotent stem cell (CFU-S).

Committed Progenitor Cells

Committed progenitor cells may be identified by their ability to form colonies of cells in a variety of in vitro systems; human or mouse hemopoietic cells may be cultured on dishes in semisolid support media (agar for myeloid colonies, plasma clots or methylcellulose for erythroid colonies), along with suitable nutrients for growth and stimulatory factors favoring one or another of the hemopoietic cell lines (e.g., erythropoietin for erythroid colony growth, or colony-stimulating factor—CSF—for myeloid colony growth). Myeloid colonies require 14 days for optimal growth. The cells in these colonies are derived from committed progenitor cells called CFU-C (colony-forming units—culture, because they were first found in tissue culture). They differ from pluripotent stem cells in that all the cells within a colony are of a single type.

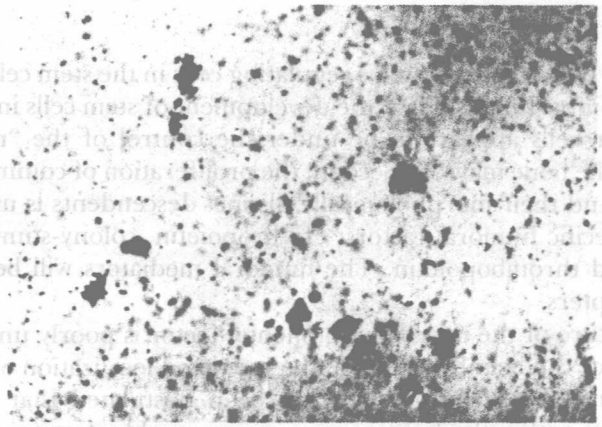

Figure 1.3. Colonies formed from CFU-E.

Two types of committed erythroid progenitor cells now have been described and can be grown in the in vitro colony-forming culture system. The first can be seen optimally after 7 days in culture and is derived from more mature erythroid progenitor cells, the CFU-E (colony-forming units—erythroid) (Fig. 1.3). The second type is called BFU-E (burst-forming units—erythroid) because the colonies look like small explosions (Fig. 1.4). They are seen after 14 days in culture and are derived from more primitive erythroid progenitor cells. While both BFU-E and CFU-E are found in normal bone marrow, only BFU-E can be grown from the peripheral blood (Fig. 1.4). To date, no subtypes of myeloid progenitor cells have been described. Recently, megakaryocyte colonies have been grown in culture. The progenitor cell is termed a colony forming unit–megakaryocytic (CFU-M or CFU-Meg).

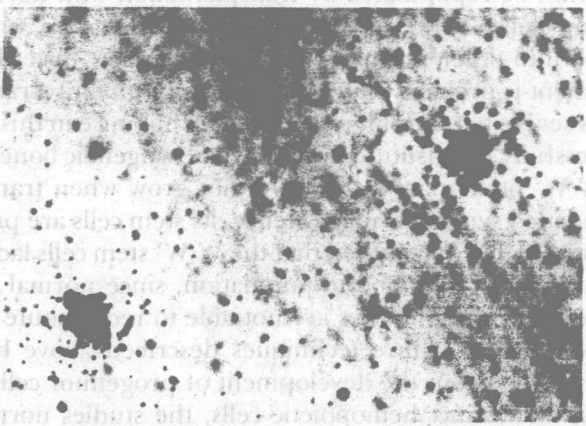

Figure 1.4. Colonies formed from BFU-E.

Control of Hemopoiesis

There are two primary systems regulating cells in the stem cell and progenitor cell compartments. First, the development of stem cells into committed progenitor cells appears to be under the control of the "microenvironment" in the bone marrow. Second, the proliferation of committed progenitor cells and their morphologically distinct descendents is under the control of specific humoral factors: erythropoietin, colony-stimulating factor (CSF), and thrombopoietin. The humoral mediators will be discussed in other chapters.

The nature of the microenvironmental factor is poorly understood, but its existence can be inferred from the restricted localization of hemopoietic tissues throughout the body. It has been postulated that fixed cellular niches exist within the bone marrow—presumably determined by a bone marrow matrix cell. When pluripotent stem cells enter these cellular niches either randomly or through entrapment, they differentiate into committed erythroid or myeloid progenitor cells, depending upon the nature of the niche.

Control of hemopoiesis is further modulated by feedback inhibitors. In the presence of excessive concentrations of CSF, macrophages or monocytes produce prostaglandins that may inhibit myelopoiesis. Lactoferrin secreted by granulocytes also blocks CSF production. T lymphocytes also play an active role in hemopoiesis. They have been shown to be essential for normal erythroid colony growth. T-lymphocyte suppressor cells may inhibit erythropoiesis. Some patients with aplastic anemia, congenital hypoplastic anemia, or neutropenia appear to have immune suppression of hemopoiesis.

The importance of microenvironment and regulatory cells in hemopoiesis can be inferred from current studies of two mouse models. One mutant strain of mice (Sl/Sl^d) has severe hypoproliferative anemia. Its bone marrow cannot be repopulated by transplantation with normal syngeneic bone marrow cells. However, Sl/Sl^d bone marrow cells will grow when transplanted into other normal irradiated syngeneic mice. Hence, its microenvironment is probably defective. A second mutant strain of mice (W/W^v) also has severe hypoproliferative anemia, but mice in this mutant strain can be successfully reconstituted with normal syngeneic bone marrow cells, although W/W^v bone marrow cells will not grow when transplanted into normal irradiated syngeneic mice. Hence, its stem cells are probably defective. Some studies have suggested that the W/W^v stem cells lack the stimulus of a thymus-derived lymphocyte population, since normal bone marrow cells depleted of T lymphocytes are not able to reconstitute W/W^v mice.

While the in vitro culture techniques described above have provided much information about the development of progenitor cells into mature, morphologically distinct hemopoietic cells, the studies normally are performed in isolation from the marrow environment, so that effects

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