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Manual of Clinical Hematology

Third Edition

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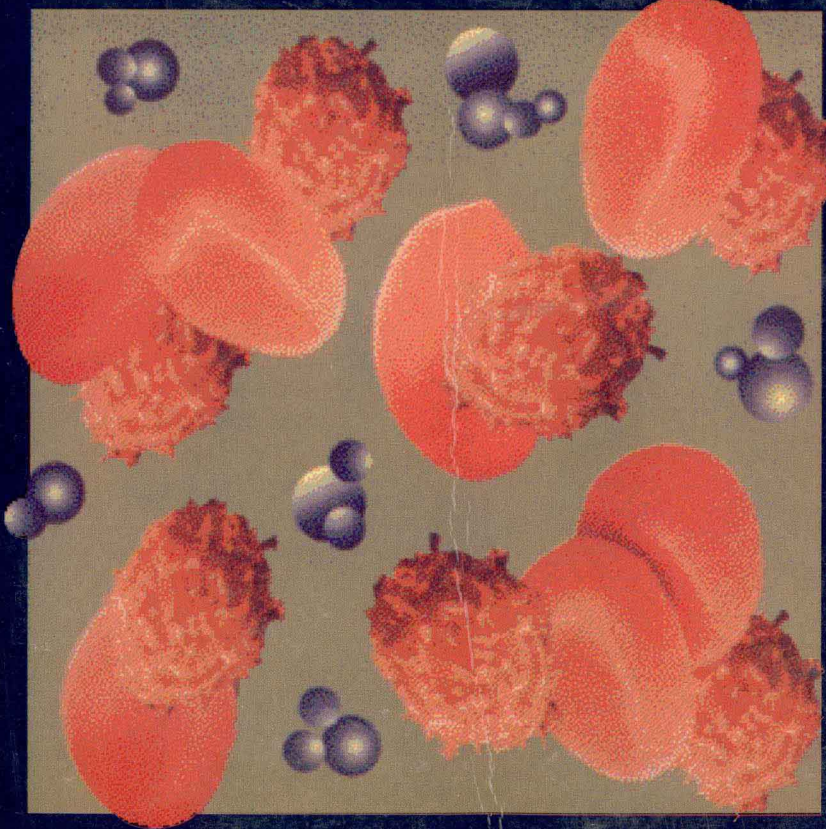
临床血液学手册

Edited by
Joseph J. Mazza



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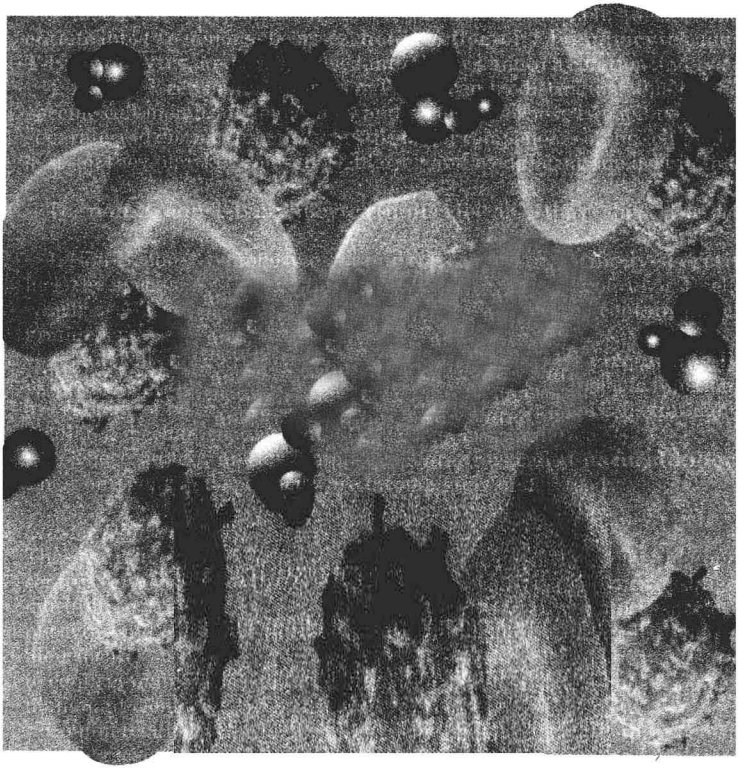

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Third Edition

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This book is dedicated to all medical residents
for their stimulation and their contributions to medical education.
And to their arduous quest, unceasing dedication,
and relentless pursuit of medical knowledge,
which are so seldom recognized and lauded.

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PREFACE

The reward for work well done is the opportunity to do more.
Jonas Salk, M.D.

The incentive to proceed with the third edition of the *Manual of Clinical Hematology* was predicated on the success of the first and second editions. Updating the new edition was a more difficult task, however, given the recent explosion of technology in molecular biology and genetics that has had a direct bearing on the specialties of hematology and immunology, and the importance of maintaining this successful concise format of the text. The update information added to the chapters and the addition of the chapter on transplantation to the text will result in a more comprehensive edition that we hope will be more helpful to the reader in his or her quest to establish a firm foundation in hematology. The added chapter on transplantation procedures in hematologic disorders is in keeping with the current aim of more aggressive approaches to the treatment of hematopoietic malignancies.

We have attempted to retain the intended focus and purpose of the book; that is, to provide a concise clinical text—aimed at students, house staff, and medical practitioners not primarily involved in hematology—that describes common hematologic disorders. This publication is not intended to be an all-inclusive hematology text, but rather an introduction to clinical hematology and a readily available source of information upon which the student and physician can build. It is my fervent wish that the book will provide sufficient motivation and excite the curious student or house staff to seek additional, more detailed information from the more comprehensive reference textbooks of hematology.

Many persons have assisted and contributed to this undertaking. I am first indebted to my colleagues in the field of hematology who have so generously contributed their time and expertise to the contents of the text. I am especially grateful to my colleagues at Marshfield Clinic for allowing me sufficient time away from my practice and supplying me with unlimited library, stenographic, and medical illustration support in reviewing and editing the manuscript. Special acknowledgment is extended to Alice Stargardt for her stenographic expertise and prompt transcription of the many manuscripts prepared for the text; to Julie Seehafer for her help and guidance in preparing the appendices; to Stacey Baze for her editorial assistance; and finally, to my wife, Ginny, for her many years of encouragement and support through all my endeavors.

J.J.M.

Manual of Clinical Hematology

Third Edition

CONTENTS 目 录

1. HEMATOPOIESIS AND HEMATOPOIETIC GROWTH FACTORS

Joseph J. Mazza

Development of the Hematopoietic System

Embryonic Life

1. Clusters of mesenchyme, mesodermal cells, on the yolk sac proliferate and expand during early embryonic life (about 2 weeks), forming the nidus of the embryonic and fetal hematopoietic system.

2. Vascular channels develop, allowing a connection to develop between the yolk sac and embryo, thus increasing the space available for further expansion of the mesodermal cells. In addition, the **primitive embryonic circulatory system** forms, and the endothelial cells derived from the early embryonic hematopoietic precursor cells become the lining cells of these primitive vascular channels.

3. **Proliferation** of the early hematopoietic cells occurs as the embryo grows and becomes a fetus (10–12 weeks). The development of a complex network of vascular channels connects vital organs and tissues, allowing for multiplication of the hematopoietic cells and perfusion by blood and lymph.

4. Differentiation of the hematopoietic precursor cells occurs in the immature reticuloendothelial system, which provides the unique microenvironment for proliferation and differentiation.

Fetal Hematopoiesis

1. During early fetal life, after the tenth week of gestation, and through the entire second trimester of pregnancy, the **liver** and the **spleen** are the major sites for hematopoiesis.

2. As gestation continues into the third trimester, the sites of hematopoiesis gradually shift from the liver and spleen to the **medullary cavities of the bones.**

3. By birth, the medullary cavities of the bones are the major site of hematopoiesis, with virtually every bone contributing in this proliferative process and providing mature functional hematopoietic cells to the peripheral circulation.

4. **Pluripotential cells** remain in the other organs of the reticuloendothelial system as hematopoietic "rest cells." These cells retain the potential to become sites of active hematopoiesis at any time later in life, thus giving rise to extramedullary hematopoiesis.

Hematopoietic Stem Cells

Hematopoietic stem cells make up a unique clone of cells that are capable of differentiating into the multiple cell lines of hematopoietic system. Hematopoietic stem cells are believed to be present in all major organs that make up the reticuloendothelial system, as well as in the peripheral blood.

The stem cell clone must sustain itself by proliferation to continue its differentiation into the specialized hematopoietic cell lines. **Stem cell proliferation** is believed to be under direct influence of hematopoietic growth factors that are present in the local milieu of the reticuloendothelial system:

1. Proliferation and differentiation depend not only on growth factors (glycoprotein) but also on stromal cells and other cells that make up the unique microenvironment of the bone marrow.
2. If and when the uncommitted stem cell compartment has been depleted, hematopoiesis ceases. This may occur following exposure to ionizing radiation or high-dose chemotherapy.

Most **evidence for the existence** of these pluripotential stem cells comes from *in vitro* studies and animal models. Such studies have shown regenerative capabilities of the marrow and hematopoietic system after infusion of certain populations of mononuclear cells following complete hematopoietic ablation (Fig. 1)

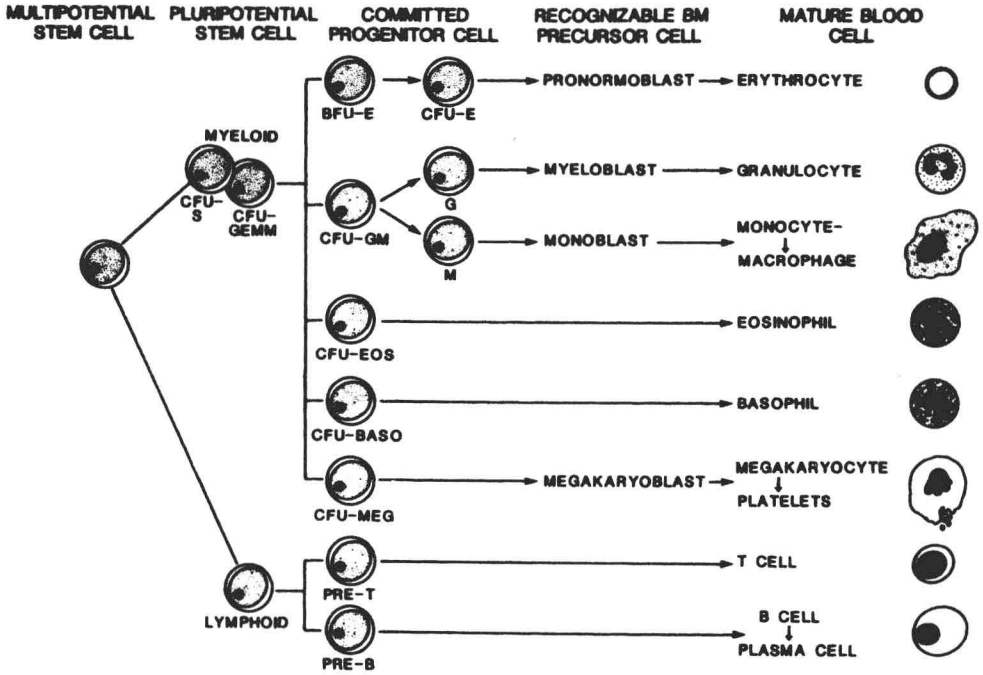

FIG. 1. A model of hematopoietic stem cell differentiation. Illustrated are progenitor cells of increasingly restricted potentiality, which give rise to the maturing cells recognizable in bone marrow preparations as the immediate precursors of peripheral blood elements. BM, bone marrow; CFU, colony-forming unit; S, spleen; GEMM, granulocyte-erythrocyte-monocyte (or macrophage)-megakaryocyte; BFU, burst-forming-unit; EI, erythroid; GM, granulocyte-monocyte (or macrophage); EOS, eosinophil; BASO, basophil; MEG, megakaryocyte. (From Robinson SH. Hematopoiesis. In: Stein JH, ed. *Stein's internal medicine,* 3rd ed. Boston: Little, Brown and Company, 1990, with permission.)

1. Cultured stem cells on agar media grow and differentiate within 5 to 10 days, giving rise to colonies of hematopoietic cells.
2. Given a suspension of mononuclear bone marrow cells, lethally irradiated mice show hematopoietic proliferation in the marrow and spleen.

Only recently have these pluripotential stem cells been identified by surface markers through **cell membrane phenotyping** with monoclonal antibodies (Table 1). Morphologically, they are believed to be similar to large immature lymphocytes and to be diffusely distributed throughout the marrow.

A certain number of the uncommitted pluripotential stem cells will differentiate or become "committed" and give rise to the various myeloid and lymphoid cell lines, thus providing further proliferation and differentiation along the various specific myeloid and lymphoid cell lines.

In early childhood, the medullary cavities of virtually all bones are active sites of hematopoiesis. During adolescence and adulthood, the site of hematopoiesis gradually shifts from the long bones of the skeleton to the more central flat bones (i.e., the skull, vertebrae, ribs, sternum, and pelvis). These flat, more centrally located bones of the skeleton become the major sites of hematopoiesis in the adult.

Kinetics of Hematopoietic Cells

Under normal conditions, all progenitor cells of the various cell lines undergo replication via the cell cycle (i.e., mitosis). Proliferation and differentiation are directly influenced and regulated by low-molecular-weight glycoproteins or hormones that are specific for each lineage of the hematopoietic system (see Appendix Q). These growth factors affect progenitor cells through specific membrane receptors, resulting in activation of the cell and replication and expansion of that precursor cell or lineage (see section entitled **Hematopoietic Growth Factors**). Many factors, in turn, regulate the production and elaboration of the necessary growth factors involved in hematopoiesis. This complex network of various hematopoietic growth factors and hormones, present in the local milieu of the marrow, is currently under careful, extensive investigation and has important therapeutic implications.

Erythropoiesis

Various factors and mechanisms are involved in the regulatory process of production of the new erythrocytes to balance the rate of destruction. In the normal state, the balance of production and destruction is maintained at a remarkably constant rate. Both endocrine and exocrine hormones make important contributions to this dynamic, well-balanced mechanism (Table 2).

The **earliest recognizable erythroid precursor** seen in the bone marrow is a **large basophilic staining cell,** approximately 15 to 20 μm in diameter, which contains a single large, well-defined, round nucleus; ribosomes; mitochondria; and Golgi apparatus (Table 1). As this early precursor cell matures, its nucleus becomes denser and smaller and eventually is extruded into the extracellular matrix of the bone marrow.

As maturation proceeds, the cell becomes progressively smaller and its cytoplasm more eosinophilic, representing increasing amounts of hemoglobin being synthesized from the ribosomes. During **intermediate stages of maturation,** the cytoplasm of the erythroblast is polychromatophilic, indicating the mixture of basophilic cytoplasmic proteins and the eosinophilic hemoglobin. With **further maturation,** hemoglobin synthesis continues, and the cytoplasm becomes entirely eosinophilic. In the **late stages of maturation,** hemoglobin is abundant. Few mitochondria and ribosomes are present in the cytoplasm; a small, dense, well-circumscribed nucleus is apparent.

When the nucleus is extruded, the cell becomes a **reticulocyte,** the last stage of development before it becomes a mature erythrocyte. Shortly thereafter, it acquires a biconcave external contour and specific properties of deformability and pliability. Its diameter is approximately 8 to 9 μm. Most reticulocytes spend 1 to 2 days in the marrow undergoing further maturation before being released into the systemic circulation

Erythrokinetics

The **turnover rate of circulating erythrocytes** can be calculated easily because the number is constant under normal conditions and their circulating life span is

Table 1. Some immune cell antigens detected by monoclonal antibodies

Antigen designation	Comments
Primary T cell associated	
CD1	Expressed on cortical thymocytes and Langerhans histiocytes
CD2	Present on all T cells (thymic and peripheral) and NK cells
CD3	Expressed by thymocytes, peripheral T cells, and NK cells; surface expression requires coexpression of T-cell receptor
CD4	Expressed on the helper subset of peripheral T cells, single positive medullary thymocytes, and CD4/CD8 double positive thymocytes
CD5	Expressed on all T cells and small subset of B cells
CD6	Expressed on all T cells and subset of myeloid cell precursors
CD8	Expressed on the cytotoxic subset of peripheral T cells, single positive medullary thymocytes, double positive cortical thymocytes, and some NK cells
Primary B cell associated	
CD10	Expressed at high levels on marrow pre-B cells and follicular center B cells; also called CALLA
CD19	Present on marrow pre-B cells and mature B cells but not on plasma cells
CD20	Expressed on marrow pre-B cells after CD19 and mature B cells but not on plasma cells
CD21	EBV receptor; present on mature B cells and follicular dendritic cells
CD22	Present on mature B cells
CD23	Present on activated mature B cells
Primarily monocyte or macrophage associated	
CD13	Expressed on immature and mature monocytes and granulocytes
CD14	Expressed on all monocytes
CD15	Expressed on all granulocytes; also expressed by Reed-Sternberg cells and variants in Hodgkin disease
CD33	Expressed on myeloid progenitors and monocytes
CD117	Found on early myeloid precursors and myeloid leukemic clones
Primarily NK cell associated	
CD16	Present on all NK cells and granulocytes
CD56	Present on all NK cells and a subset of T cells
Primarily stem cell and progenitor cell associated	
CD34	Expressed on pluripotent hematopoietic stem cells and progenitor cells of many lineages
Activation markers	
CD30	Present on activated B cells, T cells, and monocytes
Present on all leukocytes	
CD45	Also known as leukocyte common antigen (LCA)
CD45RO	Expressed on activated memory T cells
CD45RA	Expressed on naïve T cells
Miscellaneous	
CD55 CD59	Defective in paroxysmal nocturnal hemoglublinura;
CD58	Present on all hematopoietic cells but not lineage specific;
CD40	Expressed on dendritic (antigen-presenting) cells
CD82	

CALLA, common acute lymphoblastic leukemia antigen; CD, cluster designation; EBV, Epstein-Barr virus; NK, natural killer.

Modified from Cotran RS, et al. *Robbins pathologic basis of disease,* 6th ed. Philadelphia: WB Saunders, 1999:654, with permission.