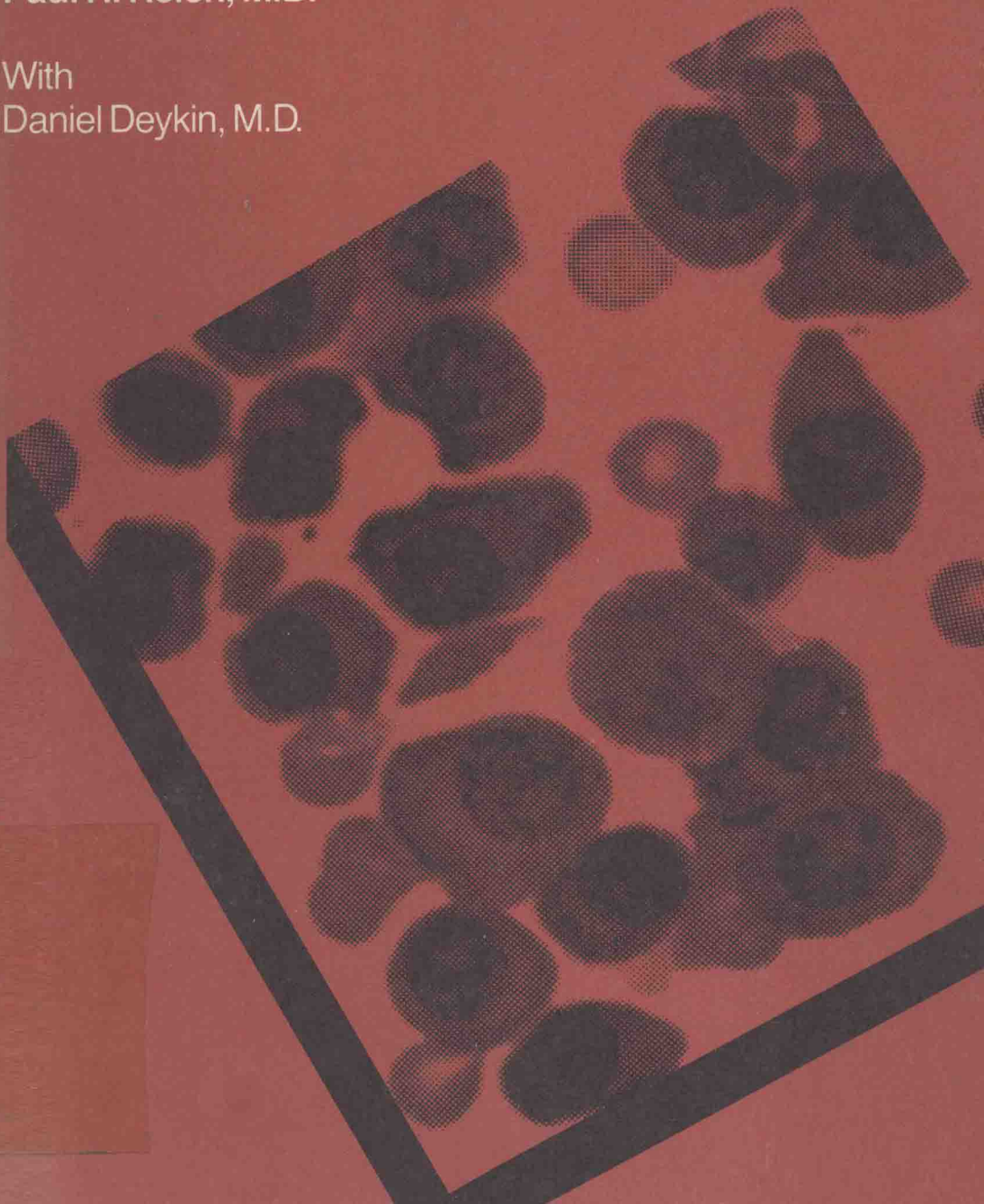
Hematology

Physiopathologic Basis for Clinical Practice

Paul R. Reich, M.D.

With
Daniel Deykin, M.D.



Hematology:
Physiopathologic Basis for Clinical Practice

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with a chapter on blood coagulation
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To my wife, Dianne

Foreword from the Series Editor

The goal of the Little, Brown Physiopathology Series is to provide textbooks that describe and illustrate the scientific foundations underlying the current practice of clinical medicine. The concept of this series developed from curricular changes that occurred in many medical schools during the early 1970s. These changes resulted in increased emphasis in the teaching of normal and abnormal human biology, usually to second-year medical students, as the bridge between the traditional basic science courses and the clinical clerkships. A need exists for textbooks in this "bridge" area.

Each book in this series will deal with a different medical subspecialty. Each book will aim to provide a clear and solid discussion of the basic scientific concepts and principles on which the clinical subspecialty is built. This discussion will include selected aspects of normal and abnormal physiology, biochemistry, morphology, cell biology, and so on, as appropriate. The discussion of the basic science material will usually be presented in the context of the approach to the study of clinical material. Major clinical phenomena and disease processes will, in turn, be analyzed in terms of normal and abnormal human biology. Thus, the books will try to show how the art of modern clinical medicine involves firm scientific knowledge and the scientific approach in order to be effective.

Although designed for second-year medical students, this series will, we hope, be useful as well to more advanced students and practitioners as a readable and up-to-date review of the scientific basis for clinical practice in a given area.

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Preface

This textbook is designed for use by students in an introductory hematology course. Each chapter serves as a unit of study. First, basic physiology and pathology are reviewed with particular attention to defining a vocabulary of hematologic terms, understanding diagnostic tests, and learning normal and abnormal cellular morphology. Stained slides illustrating blood cell morphology should be studied along with the color illustrations bound into this book. Once basic physiopathology and morphology have been mastered, attention should be directed to the approaches outlined for the important problems encountered in medical practice. The case development problems at the end of each chapter serve as a final review that measures the student's fundamental knowledge of the concepts discussed in each chapter. Clinical material chosen to pique student interest is stressed in these problems. The chapter bibliographies are not annotated or complete, but rather direct students who desire to read more about a topic to readily available textbooks and review articles containing detailed discussions and references to original articles. Original articles are cited in areas of ongoing research or where controversies exist. A list of topics for theses, term papers, and seminars is supplied for each chapter. In many cases, particular topics have been selected because knowledge in these areas is growing, changing, and sometimes controversial.

Although primarily intended for medical students enrolled in a hematology course, this textbook should also be suitable for use by nursing and paramedical students, and by house officers and physicians who desire a concise, easily readable overview of common hematologic problems. It could not have been written without my ten-year exposure to students in the Harvard Medical School course in hematology. Nor would it have seen the light of day without the encouragement and patience of Dianne, my wife, and the expertise of Ms. Lin Richter and Ms. Jacqueline Cohen, my editors at Little, Brown.

P. R. R.

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NOTICE

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contents

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Symptoms of anemia (roughly in order of appearance in an increasingly anemic patient)
Pallor Fatigue Rapid pulse Shortness of breath Irritability, difficulty in concentrating Headache Dizziness Nausea and decreased appetite Menstrual irregularities Loss of libido or potency Heart murmurs Angina pectoris (chest pain with exertion) Heart failure Coma

kidney is the chief site of its production or activation, erythropoietin has been difficult to extract from renal tissues. Two explanations have been proposed to explain this discrepancy. One suggests that a material called *renal erythropoietic factor* (REF) or *erythrogenin* is produced in the kidney and that this material acts on a substance manufactured by the liver to yield active erythropoietin. As REF is chemically and immunologically different from erythropoietin, it would not be detected by techniques aimed at extracting erythropoietin. An alternative hypothesis has been advanced by those who believe the kidney contains a lipid inhibitor of erythropoietin. Experimental addition of serum to an erythropoietin-lipid complex releases erythropoietin from the complex. Thus, the release or activation of renal lipid-bound erythropoietin may be moderated by a circulating serum factor. It is possible that both mechanisms are operative in controlling erythropoietin production.

Development of primitive cells into cells recognizable as belonging to the red cell or erythroid series is stimulated by erythropoietin. Cell physiologists found that marrow cells injected into lethally irradiated mice gave rise to homogenous colonies in the spleens of these mice. Using chromosomal markers, they showed that each colony was derived from a single hematopoietic colony-forming cell (CFC, also called colony-forming unit spleen, CFU_s). The CFC was thought to have the potential to develop into either an erythroid, a granulocytic, or a megakaryocytic cell precursor. The pluripotential cell (the CFUs) was called a *stem* cell; and the primitive but committed erythroid cell, which responded to erythropoietin by forming erythrocyte precursors, was designated an *erythropoietin-responsive* cell (ERC). Erythropoietin can act on the ERC to stimulate proliferation of more ERC and to develop ERC into recognizable early erythroid cells.

The effect of erythropoietin stimulation is recognizable in bone marrow and peripheral blood. Before discussing these changes we must review the normal maturation of red cell precursors in the bone marrow. The pluripotential stem cell and the committed erythropoietin-responsive cell have not been definitely identified, although some investigators believe they resemble lymphocytes.

With Wright stain the earliest recognizable erythroid cell is the *erythroblast* or *pronormoblast* (Plate 1), a large cell with blue cytoplasm. It contains a finely reticular and multinucleolated nucleus. When the nuclear chromatin becomes more clumped and nucleoli are lost, the cell is called a *basophilic normoblast* (Plate 2). Hemoglobin is first seen in the *polychromatic normoblast* (Plate 3) as pink material mixed with the blue cytoplasm.

Its nucleus is smaller and contains more clumped chromatin than the basophilic normoblast. This cell represents the last stage in which DNA synthesis and cell division can occur. The *orthochromatic normoblast* (Plate 4) has a pink or gray cytoplasm and a small pyknotic nucleus. With further maturation the nucleus is extruded, but some ribonuclear protein remains; with Wright stain the cytoplasm has a diffuse basophilic appearance. The overall cell size remains larger than the normal mature erythrocyte. This cell is called a *reticulocyte* (Plate 5), since the ribonuclear protein appears as a blue reticular network when stained supravitally with new methylene blue. The reticulocyte normally remains in the marrow for one day and then circulates in the bloodstream for another day before it becomes a normal adult red cell. If a nucleated erythroid precursor escapes into the peripheral blood, it is called a *nucleated red cell.* Ordinarily the complete maturation sequence from erythroblast to adult red cell takes 4 to 6 days. The normal life span of the adult erythrocyte is 120 days.

The erythropoietin-stimulated marrow has a greater than normal number of nucleated red cells. The peripheral blood contains macrocytic polychromatophils derived from early denucleation of basophilic and polychromatic normoblasts. These *stress reticulocytes* contain increased amounts of cytoplasmic ribonuclear proteins, which when stained supravitally show the blue reticular network characteristic of reticulocytes. Since they have been released early from the bone marrow, their maturation into normal erythrocytes takes approximately two days rather than one.

Biochemical studies have shown that erythropoietin acts first to increase production of several species of RNA and then to increase DNA and protein synthesis. New erythroid cell components are produced, and finally hemoglobin synthesis begins. It is not clear what is the primary biochemical event triggered by erythropoietin, nor how many of the effects attributed to erythropoietin are direct rather than a consequence of the initial inductive steps in the differentiation of the ERC.

Red Cell 2,3-Diphosphoglycerate (2,3-DPG)

Erythropoietin, by increasing the number of hemoglobin-containing erythrocytes in the peripheral blood, enhances blood oxygen-carrying capacity and thereby tissue oxygenation. Another mechanism by which tissue oxygenation is enhanced in the face of anemia involves the affinity of oxygen for hemoglobin. If oxygen is more easily released from hemoglobin, then less hemoglobin is required to maintain normal tissue oxygen supply. This is illustrated in Figure 1. In both normal and anemic individuals there is a blood oxygen dissociation curve, sigmoid in shape,

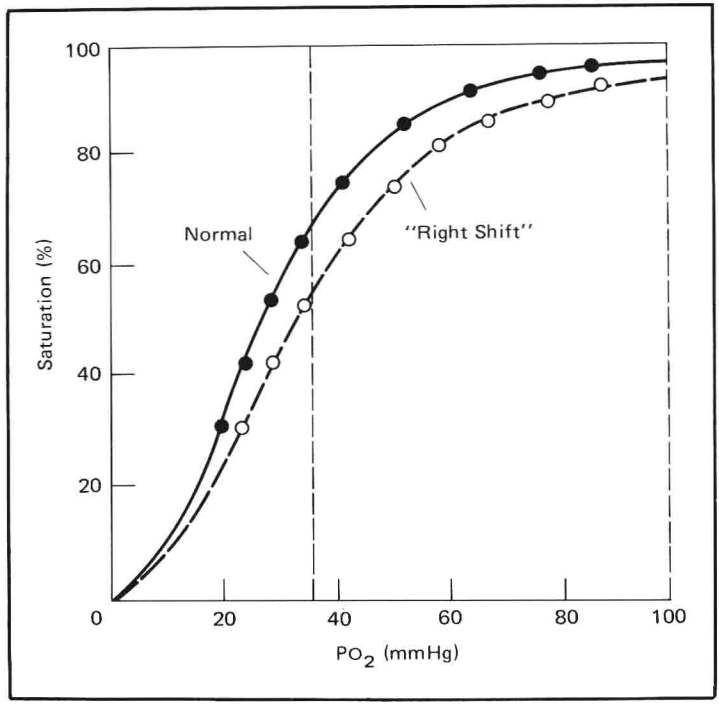

Fig. 1 : Oxygen dissociation curve of hemoglobin

which describes the relationship between oxygen content (percentage of saturation), determined colorimetrically, and partial pressure of oxygen (PO_2), determined by special electrodes. At arterial PO_2 of 100 mm Hg a normal subject (upper curve in Figure 1) carries approximately 20 ml of oxygen per deciliter of whole blood, while at venous PO_2 of 40 mm Hg, the oxygen content is approximately 15 ml of oxygen per deciliter of whole blood. The 5.0 ml/dl of blood difference represents oxygen released to tissues. The sigmoid curve can be shifted to the right (decreased oxygen affinity) by a decrease in pH (Bohr effect), an increase in temperature, or hypoxic conditions such as altitude adaption or anemia. In an anemic patient, if arterial PO_2 is maintained, this rightward shift, or decrease in oxygen affinity, will lead to greater release of oxygen to hypoxic tissue.

The shift of the oxygen dissociation curve in anemic individuals is mediated by the phosphate ester 2,3,-diphosphoglycerate (2,3-DPG). It is produced from 1,3-diphosphoglycerate by the action of a mutase enzyme (Fig. 2). This enzyme is inhibited by free 2,3-DPG. Since 2,3-DPG binds readily with deoxygenated hemoglobin, hypoxia will release this product inhibition. Deoxygenated hemoglobin is more alkaline than oxygenated, and alkaline pH stimulates glycolysis, thereby increasing 2,3-DPG

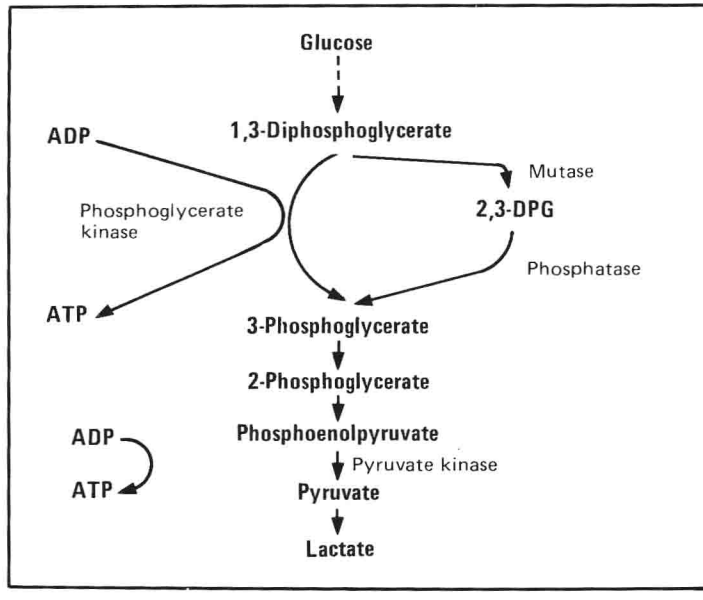

Fig. 2 : The Rapoport-Luebering shuttle of the Embden Meyerhof glycolytic pathway. (From Grimes, A. J., Red cell 2,3-diphosphoglycerate. Br. J. Haematol. 25:555, 1973. Reproduced by permission.)

production. Other effects of hypoxia and pH on 2,3-DPG metabolism are also known but will not be discussed here.

The manner by which 2,3-DPG binding to deoxyhemoglobin affects oxygen affinity is complex. Basically the binding of the 2,3-DPG molecule to the central cavity between the β-chains of deoxyhemoglobin increases the affinity of the oxygen-binding site located near the heme irons, a so-called *heterotropic interaction.* These binding sites are also affected by their state of oxygenation, that is, oxygenation of one site on a hemoglobin molecule enhances affinity for oxygen at a different but chemically identical site. This *heme-heme* or *homotropic interaction* is expressed in the sigmoid shape of the hemoglobin oxygen dissociation curve. Certain characteristics of this curve — for example, P_{50}, the partial pressure at which 50 percent of hemoglobin is saturated — are used clinically to measure changes in hemoglobin oxygen affinity.

Quantitation and Characterization of Anemia

Hemoglobin concentration is determined by converting hemoglobin to methemoglobin (converting the elemental iron in heme from the ferrous to the ferric state) and then to cyanmethemoglobin. Cyanmethemoglobin absorbs light at 540 nanometers, and the concentration of hemoglobin varies logarithmically as a function of its light absorption at 540 nm. Sources of error include variations in patients' plasma volume and the relative insolubility of certain abnormal hemoglobins such as sickle cell hemoglobin, which clouds the solution and thereby falsely

Table 1-1 : Blood Counts in Normal Adults

Measurement	Males		Females	
	Mean	95% Range	Mean	95% Range
Hemoglobin (gm/dl)	16.0	14.0–18.0	14.0	12.0–16.0
Packed cell volume (PCV, L/L)	0.46	0.41–0.51	0.42	0.37–0.47
Erythrocyte ($\times 10^{12}$/L)	5.2	4.4–6.0	4.8	4.2–5.5

Adapted from Wintrobe, M. M., et al, *Clinical Hematology,* 7th ed., p. 1791. Philadelphia: Lea & Febiger, 1974.

elevates the hemoglobin concentration. All forms of hemoglobin (oxyhemoglobin and deoxyhemoglobin, carboxyhemoglobin, and methemoglobin) except sulfhemoglobin are converted to cyanmethemoglobin. Normal values for hemoglobin, packed cell volume (PCV), and erythrocyte number are shown in Table 1-1.

The packed cell volume (PCV) or *hematocrit* is determined by centrifugation of blood in a heparinized capillary tube. The volume of packed red cells relative to the total volume of blood, expressed as a decimal, is the PCV. Sources of error include changes in patient's plasma volume, inadequate mixing or centrifugation, and expression of relatively larger amounts of plasma than red cells when obtaining blood by fingerstick. This measurement is most frequently used in clinical practice, because it can be done quickly and accurately with minimal equipment.

The red cell count (RBC or RCC) was in the past performed with a hemocytometer or counting chamber. A suitably diluted specimen of blood was placed in a chamber of known volume and the red cells enumerated with the use of a microscope. This method was notoriously inaccurate because of a large dilution factor and the difficulty of evenly distributing the red cells in the counting chamber. The development of electronic particle counting meant a vast improvement in the accuracy of red cell counting and also allowed automated determination of the hematocrit.

The Coulter principle for cell counting is most widely used. A known volume of blood is mixed with a measured amount of isotonic electrolyte solution, and the mixture is passed through a small orifice between two electrodes. An electric current is applied to the electrodes. Since a red cell is a relative nonconductor and displaces a volume of conducting electrolyte solution it induces a change in the current flowing between the electrodes. This results in electric pulses whose number, when appropriately corrected for coincidence, represents the red cell count. By averaging the pulse heights and with proper standardization

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