Manual of Clinical Hematology

Edited by
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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

Studies themselves do give forth directions too much at large, except they be bounded in by experience.
Sir Francis Bacon: *Of Studies*

In this day and age of high technology, when sophisticated laboratory studies and computerized programs are a common part of the practice of hematology and textbooks cost in excess of $150, I thought it appropriate to assemble a text consisting of concise clinical descriptions of common hematologic disorders. *Manual of Clinical Hematology* has been written especially for students, house staff, and medical practitioners not primarily involved in hematology. 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 on which the student or physician can build. It is my fervent wish that the book will provide sufficient motivation and titillate the curious student or house staff to seek additional, more detailed information from the more comprehensive, classic textbooks in hematology (e.g., Wintrobe's *Clinical Hematology*, Williams's *Textbook of Hematology*, and Jandl's *Blood: Textbook 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. Not one individual in the group of authors inquired about any monetary remuneration! I am especially grateful to my colleagues at the 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. I would also like to express my gratitude to Dr. George Magnin of the Marshfield Clinic and Dr. Robert Kyle of the Mayo Clinic for encouraging me to undertake this task.

Special acknowledgments are extended to Cheryl Kroening for her stenographic expertise and prompt transcription of the many manuscripts prepared for the text; Julie Seehafer in the Special Hematology Lab for her help and guidance in preparing the appendixes; and finally, my wife, Ginny, for her many years of encouragement and support through all my endeavors.

J. J. M.

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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

1 The Anemias

Iron-Deficiency Anemia

Virgil F. Fairbanks

The term *iron-deficiency anemia* is self-defining: It implies that anemia is due to a less than normal quantity of iron (Fe) in the body. The disorder has a long and interesting history, and many ambiguous terms have formerly been considered synonymous. These include hypochromic microcytic anemia, idiopathic hypochromic anemia, chlorosis, secondary anemia, and milk anemia. All such imprecise terms should be avoided. "Iron-deficient erythropoiesis" is not synonymous with iron-deficiency anemia and should be avoided because it is easily misunderstood. Iron deficiency can often be demonstrated in the absence of anemia, especially in young women. Iron depletion denotes an earlier stage of iron deficiency, when iron stores have vanished but serum iron concentration and blood hemoglobin concentration are normal.

I. Iron metabolism

A. Iron compartments (Table 1-1)

1. **Hemoglobin** is normally the largest iron compartment of the body. Hemoglobin is 0.34% iron by weight. Thus, in an adult, the total iron content of the hemoglobin compartment is about 2 gm, depending in part on sex and body size.
2. **Storage iron** exists in two forms, either as ferritin or as hemosiderin. The storage compartment in men normally contains about 1000 mg of iron. The storage iron is quite variable in women, from 0 to about 500 mg. About one-third of healthy young women have no significant amount of iron in the storage compartment. Most of the storage iron is in cells of the reticuloendothelial system of the liver, spleen, lymph nodes, and bone marrow, but nearly all nucleated cells of the body contain some storage iron.
   a. **Ferritin** is a water-soluble iron storage protein. It consists of a spherical, hollow protein called **apoferritin** and a crystalline core that occupies the hollow interior of apoferritin. The crystal is a lattice of hundreds or thousands of ferric oxyhydroxide (FeOOH) molecules. The average ferritin molecule normally contains about 2500 iron atoms in its interior crystal. Within the cytosol, ferritin acts as an iron buffer. When the cell has a surfeit of iron, Fe^{2+} readily enters pores in the apoferritin shell, is oxidized to FeOOH, and is added to the interior FeOOH crystal. Conversely, when the cell lacks sufficient iron for its metabolic needs, iron is readily released from the FeOOH crystal and passes out through apoferritin pores into the cytosol.
   b. **Hemosiderin** is a water-insoluble derivative of ferritin. It is aggregated ferritin, partially stripped of the apoferritin component. Hemosiderin iron turnover is presumed to be less rapid than that of ferritin.
3. **Transport iron** is the iron bound to transferrin in plasma. This is the

Table 1-1. Iron compartments in normal man*

Compartment	Iron Content (mg)	Total Body Iron (%)
Hemoglobin iron	2000	67
Storage iron (ferritin, hemosiderin)	1000	27
Myoglobin iron	130	3.5
Labile pool	80	2.2
Other tissue iron	8	0.2
Transport iron	3	0.08

*These values represent estimates for an "average" person, that is, 70 kg, 177 cm (70 in.) in height. They are derived from data in several sources.
Source: V. F. Fairbanks and E. Beutler, Iron Metabolism. In W. J. Williams et al. (eds.), *Hematology* (3rd ed.) New York: McGraw-Hill, 1983. Pp. 300–310.

mechanism of iron exchange between storage iron or iron absorbed from the gastrointestinal tract and the blood-forming bone marrow. **Transferrin** is a protein of approximately 80,000 daltons. Each molecule of apotransferrin can bind two atoms of trivalent iron. Normally, approximately one-third of these Fe^{3+}-binding sites are occupied at any time. Apotransferrin is also formed in cells of the intestinal mucosa and may play a role in iron absorption. Other cells of the body, including erythrocyte precursors, take up iron from extracellular fluid by internalizing the entire Fe^{3+}-transferrin–membrane receptor complex. Thus, transferrin is a normal cytoplasmic protein of most cells. The transport iron compartment is estimated by measurement of the serum iron concentration. The transferrin concentration in plasma is usually estimated by measurement of the total iron-binding capacity (TIBC). It can also be measured immunologically. Normally, the transport iron compartment contains approximately 3 mg of iron.

4. **Myoglobin iron.** Skeletal and cardiac muscle cells contain myoglobin, and the iron in this compartment normally amounts to about 130 mg.
5. **Other tissue iron** denotes iron that is part of enzymes, cytochromes, and myoglobin. Normally there are a few milligrams of iron bound to various enzymes and cytochromes. Approximately one-half of the enzymes of the Krebs cycle contain iron or require it as a cofactor. Many of these enzymes become iron depleted quite readily, and some of the clinical effects of iron deficiency are due to reduction in function of iron enzymes rather than to reduction in oxygen transport consequent to anemia.
6. **Labile pool.** The labile iron pool is not defined anatomically or functionally, but by analysis of data obtained in plasma iron clearance studies. The labile pool may represent either iron in the extravascular component of the intercellular fluid such as lymph or iron that rapidly exchanges between plasma and cytosol or both. Normally, there is approximately 80 mg of iron in the labile iron pool.

B. **Absorption.** Limited absorption of iron occurs at all levels of the intestinal tract, but absorption is most efficient in the duodenum. Inorganic iron must be in the divalent state for absorption to occur, although heme is absorbed together with its ferric component. The **amount** of iron absorbed increases with the dose of iron ingested, although the **percent** absorbed declines as the dose increases. Large doses of iron do not "block" iron absorption. In healthy persons, approximately 10% of the dietary iron is absorbed. In men, this amounts to about 1 mg daily. Poorly defined substances in gastric and intestinal secretions facilitate iron absorption. The proportion of iron absorbed is increased when there is anemia or accelerated erythropoiesis and decreased when there is bone marrow hypoplasia. The effect of alcohol ingestion on iron

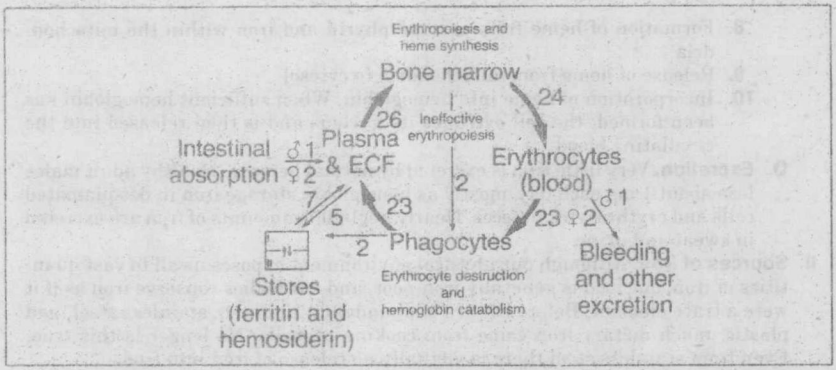

Fig. 1-1. The major pathways of iron metabolism. Numerals indicate milligrams of iron that normally enter or leave each compartment daily. Differences are also shown for males (♂) and females (♀). The milligrams of iron shown are only approximate, as normal persons differ according to body size, sex and other variables. Iron stores are represented as consisting of two distinct pools, designated I and II. The iron in pool I exchanges readily with plasma iron, but that of pool II exchanges very slowly. (ECF = extracellular fluid.)

absorption is controversial; studies have yielded conflicted results. The physiologic mechanisms that regulate iron absorption are poorly understood.

C. **Utilization and catabolism** (Major pathways of iron metabolism are shown in Fig. 1-1.). Normal erythrocytes remain in circulation for about 4 months. By the end of that time they are old and worn-out (senescent) and must be removed, destroyed, and replaced. This signal for their removal and destruction is the appearance on the erythrocyte membrane of a protein called **erythrocyte senescent antigen.** Normally, about 25 ml of senescent erythrocytes are destroyed daily by phagocytic macrophages of the reticuloendothelial system. In these cells, hemoglobin is digested. The globin is digested, and the amino acids are reutilized. The heme is further degraded to bilirubin and excreted by the liver, but the iron is salvaged and recycled. Since 25 ml of erythrocytes contains approximately 25 mg of iron, the destruction of senescent erythrocytes releases about 25 mg of iron daily. About 80% of the iron released each day by hemoglobin catabolism is promptly reincorporated into newly formed hemoglobin. A portion of the rest is incorporated into other iron compounds in other tissues, but most is retained in the reticuloendothelial system as storage iron. To make up for the daily loss of about 25 ml of erythrocytes, approximately 25 mg of iron must be incorporated into newly synthesized hemoglobin and 25 ml of newly formed erythrocytes must be released each day from the bone marrow into the circulating blood. About 20 mg of the needed iron comes from hemoglobin catabolism. The rest comes from iron stores or iron absorption.

Effective utilization of iron requires

1. Iron transport by transferrin.
2. Binding of the transferrin-Fe^{3+} complex by receptors on the cell membrane of erythrocyte precursors in bone marrow.
3. Internalization of the transferrin-Fe^{3+}–membrane receptor complex into the cytosol.
4. Release of Fe^{3+} from transferrin, within the cytosol.
5. Reduction of Fe^{3+}.
6. Intracellular transport of Fe^{2+} to mitochondrial membranes.
7. Internalization of iron by mitochondria.

8. Formation of heme from protoporphyrin and iron within the mitochondria.
9. Release of heme from mitochondria to cytosol.
10. Incorporation of heme into hemoglobin. When sufficient hemoglobin has been formed, the cell extrudes its nucleus and is then released into the circulating blood.

D. **Excretion.** Very little iron is excreted by normal persons. Healthy adult males lose about 1 mg each day, mostly as hemoglobin storage iron in desquamated cells and erythrocytes in feces. Nearly negligible amounts of iron are excreted in sweat and urine.

II. **Sources of iron.** Although our physical environment exposes us all to vast quantities of iron, our food is generally iron-poor, and our bodies conserve iron as if it were a trace element. Before the era of abundant aluminum, stainless steel, and plastic, much dietary iron came from cooking utensils. No longer is this true. Even from stainless steel there is virtually no release of iron into food.

Foods that are relatively rich in iron include liver, oysters, and legumes. Beef, lamb, pork, poultry, and fish are all mediocre sources of iron. Cereals, even though iron-fortified, provide little absorbable iron (most is chelated by phytates in the cereal), and fruits essentially none. Contrary to folk wisdom, spinach and raisins are poor sources of iron. As an approximation, a typical American diet contains about 6 mg of iron for each 1600 calories.

III. **Prevalence of iron deficiency.** Iron deficiency is among the most common of organic disorders of humans and is unquestionably the most frequent hematologic disorder. It occurs most commonly in children, poor people, and women of all ages.

A. **Children.** Iron deficiency is common in children because their iron needs often exceed the amount of iron they can absorb from food during their rapid growth. This is particularly true of children who remain on a diet entirely of milk beyond the first few months of age.

B. **Women.** Iron deficiency is common in young women because many lose iron at twice the rate or more than do men, as a consequence of menstruation and loss of blood at childbirth, yet their iron intake is less than that of men. Among healthy young white women, at least one-third have no demonstrable iron stores. Iron deficiency is common in older women who may not have compensated for the loss of iron earlier in life.

C. **Poor people.** Iron deficiency is common among poor people because their dietary sources of iron are poor (carbohydrates compose most of their diets). Furthermore, a large proportion of the world's poor people live in tropical areas, where hookworm infestation is common. In many areas of Latin America, Africa, and India, iron-deficiency anemia is nearly universal.

D. **Blacks.** Until a decade ago, iron deficiency was thought to be very prevalent among black Americans because of the many black people who have blood hemoglobin concentrates below the normal range and because erythrocyte microcytosis is common in black people. This view needs revision for three reasons: (1) The median value of blood hemoglobin concentration is about 1 gm/dl lower in black people who are not iron deficient than it is in whites. (2) Twenty-eight percent of black Americans have a mild form of α-thalassemia that is not associated with microcytosis, but about 3% of black Americans are homozygous for this α-thalassemia and have microcytosis that is due not to iron deficiency but to thalassemia. (3) Furthermore, about 1% of black Americans have β-thalassemia trait and microcytosis due to this condition. If only because of the prevalence of thalassemias among black Americans, 1 out of every 25 may be expected to have microcytosis. Thus, in nutritional surveys of black Americans, blood hemoglobin concentration and mean corpuscular volume (MCV) cannot be relied on as indices of the prevalence of iron-deficiency anemia.

E. **Southeast Asians.** Because nearly half of Southeast Asians have either α- or β-thalassemia or hemoglobin E in various combinations and these conditions cause microcytosis, MCV also cannot be used as an index of iron deficiency in Southeast Asians.