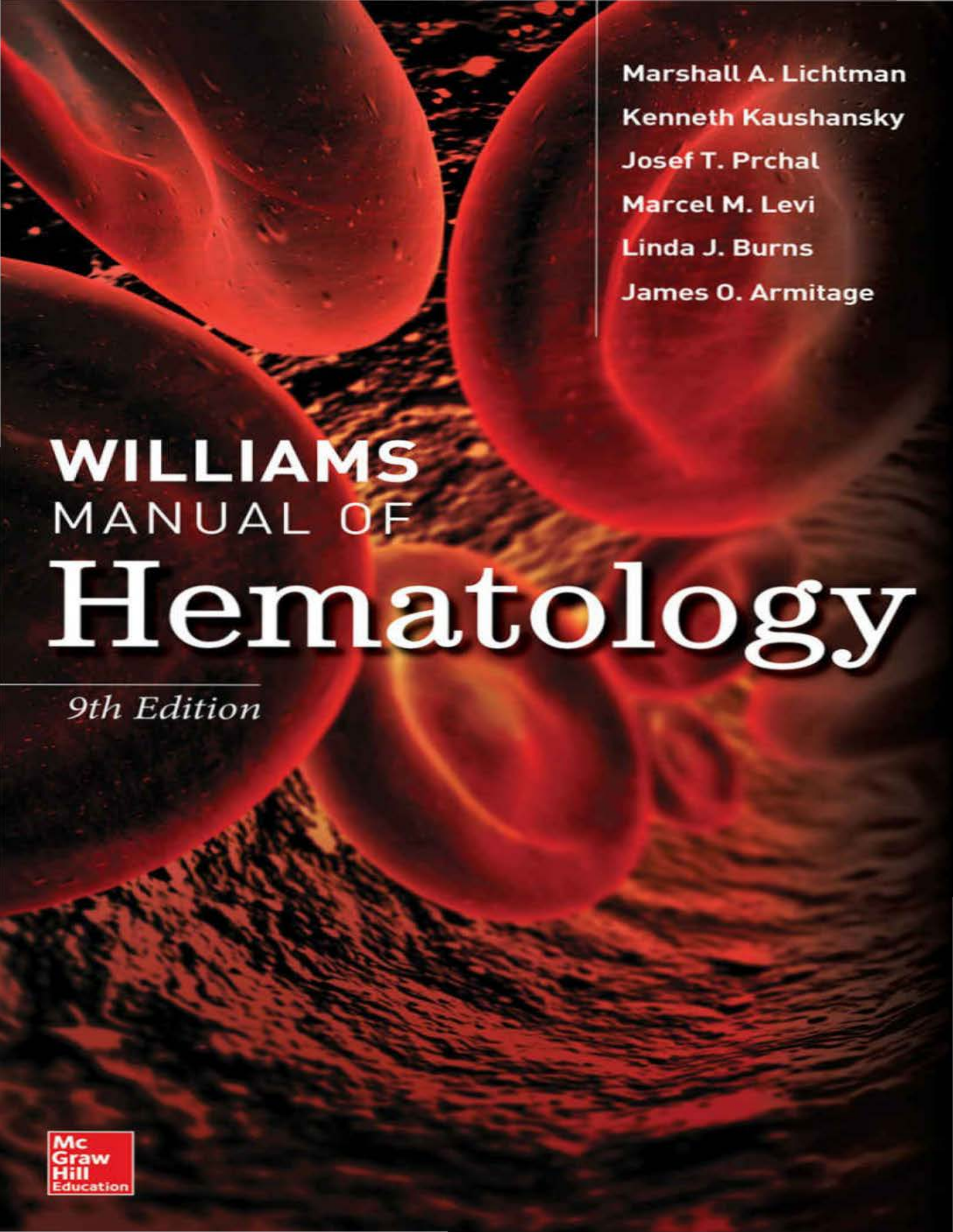
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Williams
Manual of Hematology

Ninth Edition

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CONTENTS

PREFACE

Williams Manual of Hematology provides a convenient and easily navigable précis of the epidemiology, etiology, pathogenesis, diagnostic criteria, differential diagnosis, and therapy of blood cell and coagulation protein disorders. The 93 chapters in the *Manual* are a distillation of the disease- and therapy-focused chapters of the ninth edition of *Williams Hematology*. The *Manual* is a handbook, but it is comprehensive. It is organized into 12 parts, paralleling the ninth edition of *Williams Hematology,* yet of a size that permits it to serve as a companion to the physician in the hospital or clinic. It can be used as a hard copy carried in one's coat pocket or, more deftly, as an app on one's smart phone or tablet.

We have included chapters on the classification of red cell, neutrophil, monocyte, lymphocyte, and platelet disorders and of diseases of coagulation proteins to provide a framework for considering the differential diagnosis of syndromes that are not readily apparent. Also included are numerous tables that contain diagnostic and therapeutic information relevant to the diseases discussed. Detailed chapters describing the features of individual myeloid and lymphoid malignancies provide a guide to diagnosis, staging, and management. Chapters on the manifestations, diagnostic criteria, and therapy of hereditary and acquired thrombophilia consider the role hematologists play in diagnosing and managing this important mechanism of disease. Descriptions of diseases of red cells, neutrophils, monocytes, macrophages, lymphocytes, platelets, and coagulation proteins and their management leave no gaps and meet the needs of the busy hematologist, internist, or pediatrician. In addition, this handbook is very useful for advanced practice professionals, medical and pediatric residents and subspecialty fellows, and medical or nursing students because of its succinct clinical focus on diagnosis and management.

For many tables reproduced in the *Manual*, the reader can find explicit citations documenting those entries in the concordant chapter in the ninth edition of *Williams Hematology.* In addition, where helpful, images of blood or marrow cell abnormalities or external manifestations of disease are included. Each chapter ends with an acknowledgment of the authors of the relevant chapter in the ninth edition of *Williams Hematology,* including the chapter title and number for easy cross-reference to that comprehensive text.

The publisher prints a caution in the *Manual* that admonishes readers to verify drug doses, routes of administration, timing of doses, and duration of administration and to check the contraindications and adverse effects of drugs used to treat the diseases described. We reemphasize that these often complex diseases require direct participation and close supervision of an experienced diagnostician and therapist. This oversight should be provided by a person who is able to individualize therapy depending on the nature of the expression of the primary hematological disease, the patient's physiological age, and the presence of coincidental medical

conditions, among other factors.

The authors acknowledge the valuable assistance of Marie Brito at Stony Brook University, Kim Arnold at the University of Nebraska, and, notably, Susan Daley at the University of Rochester, who entered tables and figures into the chapters, managed the administrative requirements in the preparation of the *Manual*, and coordinated communication among the six of us and McGraw-Hill. We also acknowledge the encouragement and support of Karen Edmonson, Senior Content Acquisitions Editor, and Harriet Lebowitz, Senior Project Development Editor, at the Medical Publishing Division, McGraw-Hill Education.

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PART I

INITIAL CLINICAL EVALUATION

CHAPTER 1
Approach to the Patient

FINDINGS THAT MAY LEAD TO A HEMATOLOGY CONSULTATION

Table 1–1 lists abnormalities that often require an evaluation by a hematologist.

TABLE 1–1 FINDINGS THAT MAY LEAD TO A HEMATOLOGY CONSULTATION

Decreased hemoglobin concentration (anemia)
Increased hemoglobin concentration (polycythemia)
Elevated serum ferritin level
Leukopenia or neutropenia
Immature granulocytes or nucleated red cells in the blood
Pancytopenia
Granulocytosis: neutrophilia, eosinophilia, basophilia, or mastocytosis
Monocytosis
Lymphocytosis
Lymphadenopathy
Splenomegaly
Hypergammaglobulinemia: monoclonal or polyclonal
Purpura
Thrombocytopenia
Thrombocytosis
Exaggerated bleeding: spontaneous or trauma related
Prolonged partial thromboplastin or prothrombin coagulation times
Venous thromboembolism
Thrombophilia
Obstetrical adverse events (eg, recurrent fetal loss, stillbirth, and HELLP* syndrome)

*__H__emolytic anemia, __e__levated __l__iver enzymes, and __l__ow __p__latelet count.
Source: *Williams Hematology*, 9th ed, Chap. 1, Table 1–1.

The care of a patient with a hematologic disorder begins with eliciting a medical history and performing a thorough physical examination. Certain parts of the history and physical examination that are of particular interest to the hematologist are presented here.

HISTORY OF THE PRESENT ILLNESS

- Estimation of the "performance status" helps establish the degree of disability and permits assessment of the effects of therapy (Tables 1–2 and 1–3).
- Drugs and chemicals may induce or aggravate hematologic diseases; drug use or chemical exposure, intentional or inadvertent, should be evaluated. One should inquire about professionally prescribed and self-prescribed drugs, such as herbal remedies. Occupational exposures should be defined.
- Fever may result from hematologic disease or, more often, from an associated infection. Night

sweats suggest the presence of fever. They are especially prevalent in the lymphomas.

- Weight loss may occur in some hematologic diseases.
- Fatigue, malaise, lassitude, and weakness are common but nonspecific symptoms and may be the result of anemia, fever, or muscle wasting associated with hematologic malignancy or neurologic complications of hematologic disease.
- Symptoms or signs related to specific organ systems or regions of the body may arise because of involvement in the basic disease process, such as spinal cord compression from a plasmacytoma, ureteral or intestinal obstruction from abdominal lymphoma, or stupor from exaggerated hyperleukocytosis in chronic myelogenous leukemia.

TABLE 1–2 CRITERIA OF PERFORMANCE STATUS (KARNOFSKY SCALE)

Able to carry on normal activity; no special care is needed.	
100%	Normal; no complaints, no evidence of disease
90%	Able to carry on normal activity; minor signs or symptoms of disease
80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.	
70%	Cares for self; unable to carry on normal activity or to do active work
60%	Requires occasional assistance but is able to care for most personal needs
50%	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	
40%	Disabled; requires special care and assistance
30%	Severely disabled; hospitalization is indicated though death not imminent
20%	Very sick; hospitalization necessary; active supportive treatment necessary
10%	Moribund; fatal processes progressing rapidly
0%	Dead

Source: *Williams Hematology*, 9th ed, Chap. 1, Table 1–2.

TABLE 1–3 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Activity
0	Fully active; able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: *Williams Hematology*, 9th ed, Chap. 1, Table 1–3.

FAMILY HISTORY

- Hematologic disorders may be inherited as autosomal dominant, autosomal recessive, or X chromosome–linked traits (see *Williams Hematology*, 9th ed, Chap. 10). The family history is crucial to provide initial clues to inherited disorders and should include information relevant to the disease in question in grandparents, parents, siblings, children, maternal uncles and aunts, and nephews. Careful and repeated questioning is often necessary because some important details, such as the death of a sibling in infancy, may be forgotten years later.
- Consanguinity should be considered in a patient who belongs to a population group prone to marrying family members.
- Absence of a family history in a dominantly inherited disease may indicate a de novo mutation or nonpaternity.
- Deviations from Mendelian inheritance may result from uniparental disomy (patient receives two copies of a chromosome, or part of a chromosome, containing a mutation from one parent and no copies from the other parent) or genetic imprinting (same abnormal gene inherited from mother has a different phenotype than that inherited from father as a result of silencing or imprinting of one parent's portion of DNA) (see *Williams Hematology*, 9th ed, Chap. 12).

SEXUAL HISTORY

- One should obtain the history of the sexual preferences and practices of the patient.

PHYSICAL EXAMINATION

Special attention should be paid to the following aspects of the physical examination:

- *Skin:* cyanosis, ecchymoses, excoriation, flushing, jaundice, leg ulcers, nail changes, pallor, petechiae, telangiectases, rashes (eg, lupus erythematosus, leukemia cutis, cutaneous T-cell lymphoma)
- *Eyes:* jaundice, pallor, plethora, retinal hemorrhages, exudates, or engorgement and segmentation of retinal veins
- *Mouth:* bleeding, jaundice, mucosal ulceration, pallor, smooth tongue
- *Lymph nodes:* slight enlargement may occur in the inguinal region in healthy adults and in the cervical region in children. Enlargement elsewhere, or moderate to marked enlargement in these regions, should be considered abnormal
- *Chest:* sternal and/or rib tenderness
- *Liver:* enlargement
- *Spleen:* enlargement, splenic rub
- *Joints:* swelling, deformities
- *Neurologic:* abnormal mental state, cranial nerve abnormalities, peripheral nerve abnormalities, spinal cord signs

LABORATORY EVALUATION

The blood should be evaluated, both quantitatively and qualitatively. This is usually achieved

using automated equipment.

- Normal blood cell values are presented in **Table 1–4**. Normal total leukocyte and differential leukocyte counts are presented in **Table 1–5**.
- Hemoglobin concentration and red cell count are measured directly by automated instruments.
- Packed cell volume (*hematocrit*) is derived from the product of erythrocyte count and the mean red cell volume. It may also be measured directly by high-speed centrifugation of anticoagulated blood.
- Both the hemoglobin and the hematocrit are based on whole blood and are, therefore, dependent on plasma volume. If a patient is severely dehydrated, the hemoglobin and hematocrit will appear higher than if the patient were normovolemic; if the patient is fluid overloaded, those values will be lower than their actual level when normovolemic.
- Mean (red) cell volume (MCV), mean (red) cell hemoglobin (MCH), and mean (red) cell hemoglobin concentration (MCHC) are determined directly in automated cell analyzers. They may also be calculated by using the following formulas:

$$\text{MCV} = \frac{\text{hematocrit (mL/dL or \%)}}{\text{erythrocyte count } (\times 10^{12}/\text{L})} \times 10$$

- The units are femtoliters (fL).
- Mean cell hemoglobin (MCH) is calculated as follows:

$$\text{MCH} = \frac{\text{Hb (g/L)}}{\text{erythrocyte count } (\times 10^{12}/\text{L})} \times 10$$

- The units are picograms (pg) per cell.
- Mean corpuscular hemoglobin concentration (MCHC) is calculated as follows:

$$\text{MCHC} = \frac{\text{hemoglobin (g/L)}}{\text{hematocrit (mL/dL or \%)}} \times 10$$

- The units are grams of hemoglobin per deciliter (g/dL) of erythrocytes, or a percentage.
- The MCH may decrease or increase as a reflection of decreases or increases in red cell volume as well as actual increases or decreases in red cell hemoglobin concentration. The MCHC controls for those changes in red cell size, providing a more reliable measurement of hemoglobin concentration of red cells.
- Red cell distribution width (RDW) is calculated by automatic counters and reflects the variability in red cell size. The term “width” in RDW is misleading; it is a measure of the coefficient of variation of the volume of the red cells, and not the diameter. It is expressed as a percent.

$$\text{RDW} = (\text{Standard deviation of MCV} \div \text{mean MCV}) \times 100$$

  — Normal values are 11% to 14% of 1.0.
  — The presence of anisocytosis may be inferred from an elevated RDW value.
- Reticulocyte index. This variable is derived from the reticulocyte count and gives an estimate of the marrow response to anemia reflecting the red cell production rate.
  — The normal marrow with adequate iron availability can increase red cell production two to three times acutely and four to six times over a longer period of time.

— The reticulocyte index is used to determine if anemia is more likely the result of decreased red cell production or accelerated destruction in the circulation (hemolysis).
— By convention, hemolysis should be considered if the reticulocyte index is more than two times the basal value of 1.0.
— This calculation assumes (1) the red cell life span is ~100 days; (2) a normal reticulocyte is identifiable in the blood with supravital staining for 1 day; (3) the red cell life span is finite and the oldest 1% of red cells are removed and replaced each day; and (4) a reticulocyte count of 1% in an individual with a normal red cell count represents the normal red cell production rate per day thus, 1 is the basal reticulocyte index.
— The reticulocyte index provides the incidence of new red cells released per day as an estimate of marrow response to anemia.

- Consider a patient with a red cell count of 2×10^{12}/L and a reticulocyte count of 15%. The reticulocyte index is calculated as follows:
  — Corrected reticulocyte percent = observed reticulocyte percent × observed red cell count/normal red cell count. Calculation for patient values in this example = 15 × 2.0/5.0 = 6. This adjustment corrects the percent of reticulocytes for the decreased red cells in an anemic person. This calculation provides the prevalence of reticulocytes, but we want to know the incidence of reticulocytes (per day).
  — In anemia, under the influence of elevated erythropoietin, reticulocytes do not mature in the marrow for 3 days and then circulate for 1 day before they degrade their ribosomes and cannot be identified as such. Reticulocytes are released prematurely and thus may be identifiable in the circulation for 2 or 3 days and not reflect new red cells delivered that day, as in the normal state.
  — The corrected reticulocyte percent must be adjusted for premature release of reticulocytes. This is done by dividing the corrected reticulocyte percent by a factor related to the severity of anemia from 1.5 to 3. In practice, the value 2 is usually used as an approximation.
  — Thus, the corrected reticulocyte percent of 6 ÷ 2 results in a reticulocyte index of three times the basal value, indicating the anemia is hemolytic.
- Enumeration of erythrocytes, leukocytes, and platelets can be performed by manual methods by using diluting pipettes, a specially designed counting chamber, and a light microscope, but an electronic method provides much more precise data and is now used nearly universally for blood cell counts.
- Leukocyte differential count can be obtained from stained blood films prepared on glass slides. Automated techniques may be used for screening purposes, in which case abnormal cells are called out and examined microscopically by an experienced observer. Normal values for specific leukocyte types in adults are given in **Table 1–5**. The identifying features of the various types of normal leukocytes are shown in **Figure 1–1** and are detailed in *Williams Hematology*, 9th ed, Chap. 2; Chap. 60; Chap. 67; Chap. 73.
- Electronic methods that provide rapid and accurate classification of leukocyte types based largely on the physical properties of the cells have been developed and are in general use as described in *Williams Hematology*, 9th ed, Chap. 2.
- Properly stained blood films also provide important information on the morphology of erythrocytes and platelets as well as leukocytes.

- Examination of the blood film may reflect the presence of a number of diseases of the blood. These are listed in **Table 1–6**.

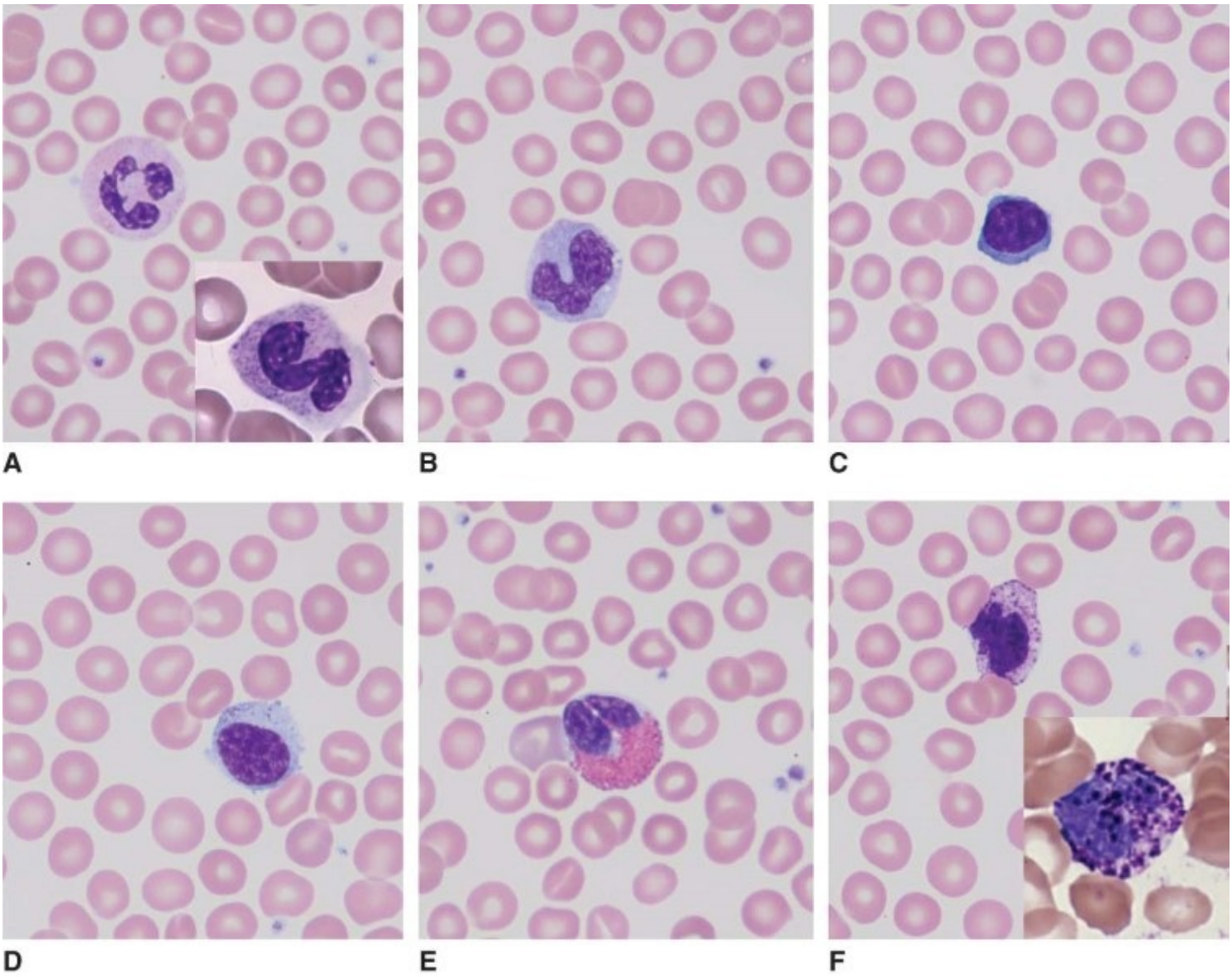


FIGURE 1–1 Images from a normal blood film showing major leukocyte types. The red cells are normocytic (normal size) and normochromic (normal hemoglobin content) with normal shape. The scattered platelets are normal in frequency and morphology. Images are taken from the optimal portion of the blood film for morphologic analysis. **A.** A platelet caught sitting in the biconcavity of the red cell in the preparation of the blood film—a segmented (polymorphonuclear) neutrophil and in the inset, a band neutrophil. This normal finding should not be mistaken for a red cell inclusion. **B.** A monocyte. **C.** A small lymphocyte. **D.** A large granular lymphocyte. Note that it is larger than the lymphocyte in **C** with an increased amount of cytoplasm containing scattered eosinophilic granules. **E.** An eosinophil. Virtually all normal blood eosinophils are bilobed and filled with relatively large (compared to the neutrophil) eosinophilic granules. **F.** Basophil and in inset a basophil that was less degranulated during film preparation, showing relatively large basophilic granules. The eosinophilic and basophilic granules are readily resolvable by light microscopy (×1000), whereas the neutrophilic granules are not resolvable, but in the aggregate impart a faint tan coloration to the neutrophil cytoplasm, quite distinctly different from the blue-gray cytoplasmic coloring of the monocyte and lymphocyte. (Source: *Williams Hematology*, 9th ed, Chap. 2, Figure 2–4.)

TABLE 1–4 BLOOD CELL VALUES IN A NORMAL POPULATION

	Men	Women	Either
White cell count,* × 10^9/L blood			7.8 (4.4–11.3)+
Red cell count, × 10^{12}/L blood	5.21 (4.52–5.90)	4.60 (4.10–5.10)	

Hemoglobin, g/dL blood	15.7 (14.0–17.5)[++]	13.8 (12.3–15.3)[++]	
Hematocrit (Volume of packed red cells as a ratio to a volume of blood)	0.46 (0.42–0.50)	0.40 (0.36–0.45)	
Mean cell volume, fL/red cell			88.0 (80.0–96.1)
Mean cell hemoglobin, pg/red cell			30.4 (27.5–33.2)
Mean cell hemoglobin concentration, g/dL red cell			34.4 (33.4–35.5)
Red cell distribution width, CV (%)			13.1 (11.5–14.5)
Platelet count, $\times 10^9$/L blood			311 (172–450)

*The International Committee for Standardization in Hematology recommends that SI units be used as follows: white cell count, number $\times 10^9$/L; red cell count, number $\times 10^{12}$/L; and hemoglobin, g/dL (dL = deciliter). The hematocrit (packed cell volume) is given as a numerical proportion, for example, 0.41, without designated units. Units of liter (of red cells) per liter (of blood) are implied. Mean cell volume is given as femtoliters (fL), mean cell hemoglobin as picograms (pg), and mean corpuscular hemoglobin concentration as g/dL. Platelets are reported as number $\times 10^9$/L. CV = coefficient of variation.

[+]The mean and reference intervals (normal range) are given. Because the distribution curves may be non-Gaussian, the reference interval is the nonparametric central 95% confidence interval. Results are based on 426 normal adult men and 212 normal adult women, with studies performed on the Coulter Model S-Plus IV. The normal intervals in this table may vary somewhat in different laboratories and in populations with varying ethnic distributions. For example, the mean neutrophil count in persons of African descent is approximately 1.5×10^9/L below that for individuals of European descent of similar sex and age. This difference also decreases the total leukocyte count in Americans of African descent by a similar concentration.

[++]The hemoglobin level of individuals of African descent is approximately 1.0 g/dL below that for individuals of European descent of similar sex and age.

TABLE 1–5 REFERENCE RANGES FOR LEUKOCYTE COUNT, DIFFERENTIAL COUNT, AND HEMOGLOBIN CONCENTRATION IN CHILDREN*

Age	Leukocytes Total ($\times 10^9$/L)	Neutrophils			Eosinophils	Basophils	Lymphocytes	Monocytes	Hemoglobin g/dL Blood
		Total	Band	Segmented					
12 mo	11.4 (6.0–17.5)	3.5 (1.5–8.5)	0.35 (0–1.0)	3.2 (1.0–8.5)	0.30 (0.05–0.70)	0.05 (0–0.20)	7.0 (4.0–10.5)	0.55 (0.05–1.1)	12.6 (11.1–14.1)
		31	*3.1*	*28*	*2.6*	*0.4*	*61*	*4.8*	
4 y	9.1 (5.5–15.5)	3.8 (1.5–8.5)	0.27 (0–1.0)	3.5 (1.5–7.5)	0.25 (0.02–0.65)	0.05 (0–0.2)	4.5 (2.0–8.0)	0.45 (0–0.8)	12.7 (11.2–14.3)
		42	*3.0*	*39*	*2.8*	*0.6*	*50*	*5.0*	
6 y	8.5 (5.0–14.5)	4.3 (1.5–8.0)	0.25 (0–1.0)	4.0 (1.5–7.0)	0.23 (0–0.65)	0.05 (0–0.2)	3.5 (1.5–7.0)	0.40 (0–0.8)	13.0 (11.4–14.5)
		51	*3.0*	*48*	*2.7*	*0.6*	*42*	*4.7*	
10 y	8.1 (4.5–13.5)	4.4 (1.8–8.0)	0.24 (0–1.0)	4.2 (1.8–7.0)	0.20 (0–0.60)	0.04 (0–0.2)	3.1 (1.5–6.5)	0.35 (0–0.8)	13.4 (11.8–15.0)
		54	*3.0*	*51*	*2.4*	*0.5*	*38*	*4.3*	
21 y	7.4 (4.5–11.0)	4.4 (1.8–7.7)	0.22 (0–0.7)	4.2 (1.8–7.0)	0.20 (0–0.45)	0.04 (0–0.2)	2.5 (1.0–4.8)	0.30 (0–0.8)	M: 15.5 (13.5–17.5)
		59	*3.0*	*56*	*2.7*	*0.5*	*34*	*4.0*	F: 13.8 (12.0–15.6)

*The means and ranges are in $\times 10^9$ cells per L. This table is provided as a guide. Normal ranges should be validated by the clinical laboratory for the specific methods in use. The number in *italics* is mean percentage of total leukocytes.
Source: *Williams Hematology*, 8th ed, Chap. 1, Table 1–5.

TABLE 1–6 DISEASES IN WHICH EXAMINATION OF THE BLOOD FILM CAN SUGGEST OR CONFIRM THE DISORDER

Disease	Findings on Blood Film
Immune hemolytic anemia	Spherocytes, polychromatophilia, erythrocyte agglutination, erythrophagocytosis
Hereditary spherocytosis	Spherocytes, polychromatophilia
Hereditary elliptocytosis	Elliptocytes
Hereditary ovalocytosis	Ovalocytes
Hemoglobin C disease	Target cells, spherocytes
Hemoglobin S disease	Sickle cells

Hemoglobin SC	Target cells, sickle cells
Thalassemia minor (alpha or beta)	Microcytosis, target cells, teardrop cells, basophilic stippling, other misshapen cells
Thalassemia major (alpha or beta)	Microcytosis, target cells, basophilic stippling, teardrop cells, other misshapen cells (often more exaggerated than minor form)
Iron deficiency	Microcytosis, hypochromia, absence of basophilic stippling
Lead poisoning	Basophilic stippling
Vitamin B_{12} or folic acid deficiency	Macrocytosis, with oval macrocytes, hypersegmented neutrophils
Myeloma, macroglobulinemia	Pathologic rouleaux formation
Malaria, babesiosis, others	Parasites in the erythrocytes
Consumptive coagulopathy	Fragmented red cells (schistocytes)
Mechanical hemolysis	Fragmented red cells (schistocytes)
Severe infection	Increase in neutrophils; increased band forms, Döhle bodies, neutrophil vacuoles
Infectious mononucleosis	Reactive lymphocytes
Agranulocytosis	Decreased neutrophils
Allergic reactions	Eosinophilia
Chronic lymphocytic leukemia	Absolute small-cell lymphocytosis
Chronic myelogenous leukemia	Promyelocytes, myelocytes, basophils, hypersegmented neutrophils
Oligoblastic myelogenous leukemia (refractory anemia with excess blast cells, myelodysplasia)	Blast forms, acquired Pelger-Huët neutrophil nuclear abnormality, anisocytosis, poikilocytosis, abnormal platelets
Clonal cytopenias (myelodysplasia)	Anisocytosis, anisochromia, poikilocytosis, hypogranular neutrophils, acquired Pelger-Huët neutrophil nuclear abnormality, neutropenia, thrombocytopenia, giant platelets
Acute leukemia	Blast cells
Thrombocytopenia	Decreased platelets
Thrombocytosis or thrombocythemia	Increased platelets

Infancy and Childhood

- Some components of the blood count in infancy and childhood differ significantly from those in adults.
- Hemoglobin levels are high at birth (19.3 ± 2.2 [s.d.] g/dL) but fall over the first 12 weeks of life to reach levels that persist throughout childhood (11.3 ± 0.9 [s.d.] g/dL). Adult levels in males are achieved after puberty. Red cell values for infants during the first 12 weeks of life are given in *Williams Hematology*, 9th ed, Chap. 7, **Table 7–2**.
- The mean leukocyte count is high at birth (mean of 18 × 10^9/L); neutrophils comprise about 60% of the cells. The leukocyte count falls over the next 2 weeks or so, to reach levels that persist throughout childhood. Lymphocytes are the predominant cell type for the remainder of the first 4 years of life (45%–55%). Further details can be found in *Williams Hematology*, 9th ed, Chap. 7, **Table 7–3**.
- Platelet counts are at adult levels throughout childhood.
- Leukocyte function may be depressed in normal infants in the newborn period.
- Reference values for coagulation factors in neonates and infants may be found in *Williams Hematology*, 9th ed, Chap. 7, **Table 7–6**, and for coagulation factor inhibitors in neonates and

infants in **Table 7–7**.

Effects of Aging

- See *Williams Hematology*, 9th ed, Chap. 9.
- Blood count and cell function may also vary with advanced age.
- The hemoglobin level of men older than 65 years of age is statistically lower than that of younger men, even in the absence of a demonstrable cause for anemia, but is not sufficiently lower to warrant use of specific normal values for older men. Anemia in an older person warrants careful evaluation as to its cause before concluding it is the anemia of aging.
- The hemoglobin level in women does not change significantly with advancing age.
- Total and differential leukocyte counts also do not change significantly with advancing age.
- Leukocytosis in response to infection (eg, appendicitis or pneumonia) is the same in older individuals as in people younger than age 60, but special studies indicate that the marrow granulocyte reserve may be reduced in older persons.
- Both cellular and humoral immune responses are reduced in older patients.
- The erythrocyte sedimentation rate increases significantly with age.
- Aging is associated with a net procoagulant propensity and an increased risk of venous thrombosis.

Utility of the Blood Film in Diagnosis

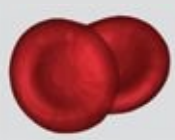
- The blood film is invaluable in developing the differential diagnosis or the specific diagnosis of a blood cell disorder. **Table 1–6** lists several situations in which the blood film can be important or decisive.

The Marrow

- Examination of the marrow is important in the diagnosis and management of a variety of hematologic disorders.
- All bones contain hematopoietic marrow at birth.
- Fat cells begin to replace hematopoietic marrow in the extremities in the fifth to sixth year of life.
- In adults, hematopoietic marrow is principally located in the axial skeleton (ribs, spine, sternum, pelvis, scapula, clavicle, and base of the skull) and the proximal quarter of the humeri and femora.
- Hematopoietic marrow cellularity is reduced in the elderly, falling after age 60 from about 50% to 30%, roughly in inverse proportion to age.
- Marrow is obtained by aspiration and/or needle biopsy. The most frequently utilized site is the iliac crest at the posterior superior iliac spine. Modern biopsy instruments provide excellent material for diagnostic study.
- Aspirated marrow may be evaluated after preparation of films on glass slides and appropriate staining.
- Marrow biopsies are examined after fixation, sectioning, and staining. “Touch” preparations made by holding the biopsy specimen with a forceps and touching the end to one or more clean slides in several places. Imprints of the marrow remain on the slide. The slides are quickly air

dried, fixed with methanol, and stained. Morphologic details of the cells are preserved with this type of preparation and thus provide additional information.

- Interpretation of marrow films and biopsy sections is discussed in *Williams Hematology*, 9th ed, Chap. 3 and in chapters describing specific diseases for which a marrow is usually performed. *Williams Hematology*, 9th ed, **Table 3–1** contains the normal differential count of cells in the marrow.



For a more detailed discussion, see Marshall A. Lichtman and Linda J. Burns: Approach to the Patient, Chap. 1; Daniel H. Ryan: Examination of Blood Cells, Chap. 2; Daniel H. Ryan: Examination of the Marrow, Chap. 3; James Palis and George B. Segel: Hematology of the Fetus and Newborn, Chap. 7; William B. Ershler, Andrew S. Artz, and Bindu Kanapuru: Hematology in Older Persons, Chap. 9; C. Wayne Smith: Morphology of Neutrophils, Eosinophils, and Basophils, Chap. 60; Steven D. Douglas, Ann G. Douglas: Morphology of Monocytes and Macrophages, Chap. 67; Natarajan Muthusamy and Michael A. Caligiuri: Structure of Lymphocytes and Plasma Cells, Chap. 73 in *Williams Hematology*, 9th ed.

PART II

DISORDERS OF RED CELLS

CHAPTER 2
Classification of Anemias and Polycythemias

- Clinically significant red cell disorders can be classified into:
  — Disorders in which the red cell mass is decreased (anemias). The principal effect is decreased oxygen-carrying capacity of the blood. Their severity is best expressed in terms of hemoglobin concentration.
  — Disorders in which the red cell mass is increased (polycythemias also known as erythrocytoses). The principal effect is related to an increased viscosity of the blood (see **Figure 2–1**). In addition to their specific effects, they are best expressed in terms of packed red cell volume (hematocrit).
- The red cell mass is the volume of the mass of red cells in the circulation.
  — The normal red cell mass among women is 23 to 29 mL/kg.
  — The normal red cell mass among men is 26 to 32 mL/kg.
  — More accurate formulas based on body surface have been recommended.
- Because the red cells are measured either as a concentration in the blood as the red cell count, the hemoglobin content of the blood, or the hematocrit (packed red cell volume per 100 mL of blood), rather than the volume of the red cell mass in the total circulation, the anemias and polycythemias can each be subclassified as:
  — Relative, where the red cell mass is normal but the amount of plasma is increased (relative anemia) or decreased (polycythemia)
  — Absolute, where the red cell mass is decreased (true anemia) or increased (true polycythemia)
- The various types of anemia are classified in **Table 2–1**.
- It is essential that the specific cause of anemia be determined. The initial laboratory approach to the diagnosis of anemia follows, and these four studies should be the prelude to guide further specific testing.
  — Hematocrit, hemoglobin, or red cell count to determine degree of anemia. In most cases, these three variables are closely correlated. Hemoglobin concentration is the most direct measure of oxygen-carrying capacity.
  — Red cell indices, such as mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) to determine whether normocytic, macrocytic, or microcytic and normochromic or hypochromic red cells are present on average
  — Measurement of red cell distribution width (RDW) to obtain a measure of anisocytosis
  — Reticulocyte count or index to estimate whether marrow response suggests inadequacy of red cell production or an appropriate erythropoietic response to hemolysis (or acute bleeding). The latter is usually readily apparent clinically.
  — Examination of the blood film to determine red cell size and shape, hemoglobin content,

presence of red cell inclusions, presence of agglutination or rouleaux formation, nonhematopoietic particles such as parasites (ie, *Babesia* and *Plasmodium* species) and helminths (ie, *Wuchereria bancrofti*, nematodes), and accompanying abnormalities of white cells and platelets

- Important caveats:
  - — Red cell size and hemoglobin content are best determined from their indices because the blood film will usually make evident only gross deviations (eg, the need to estimate red cell volume from a two-dimensional area). Moreover, the blood in macrocytic anemia usually contains many microcytic cells and in microcytic anemias, many normocytic cells, which make determination of the average red cell volume from a blood film difficult.
  - — In general, the abnormalities in size, hemoglobin content, and shape are approximately correlated with severity of anemia. If the anemia is slight, the other changes are often subtle.
  - — Anemia classically categorized as macrocytic or microcytic may be present in the face of red cell volumes that are in the normal range. This may be the case because the anemia is so mild that red cell volumes have not yet deviated beyond the normal range, or may be the case with more severe anemias because of confounding effects of two causal factors (eg, iron deficiency and folate deficiency), or well-established megaloblastic anemia may have normocytic index in otherwise asymptomatic individuals such as those being silent carriers or having alpha thalassemia trait (one or two alpha globin deletions) (see Chap. 15).
- A classification of the major causes of polycythemia is shown in **Table 2–2**.
- It is important to search for the specific cause of polycythemia. The diagnosis of polycythemias is discussed in Chaps. 27 (polyclonal polycythemias) and 41 (polycythemia vera).

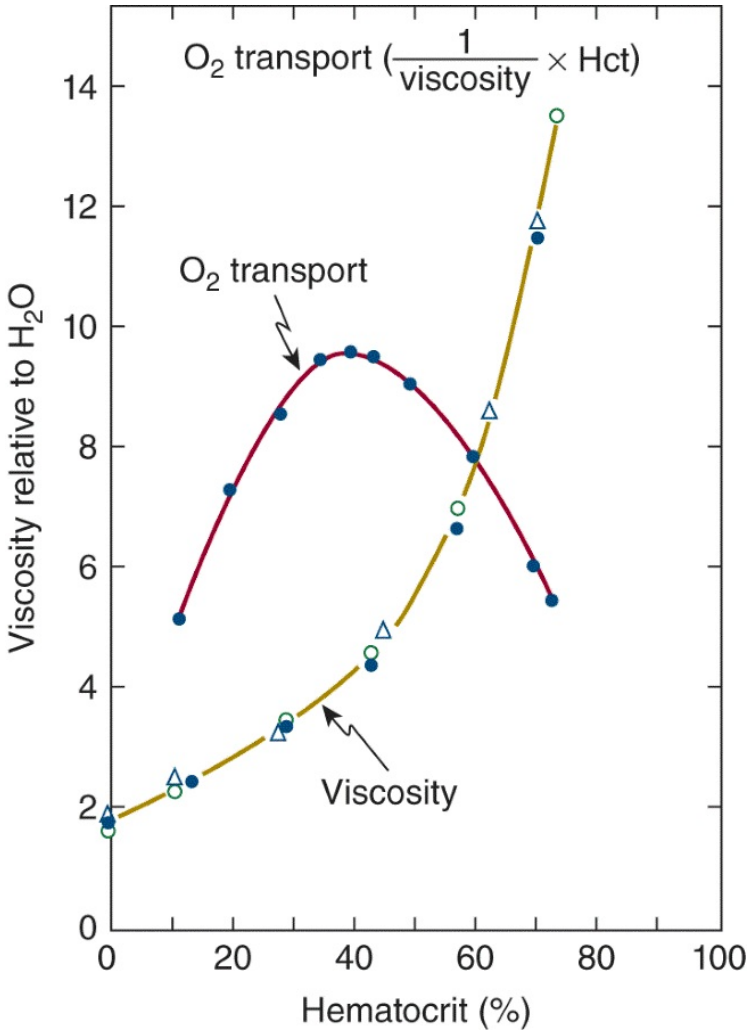


FIGURE 2–1 Viscosity of heparinized normal human blood related to hematocrit (Hct). Viscosity is measured with an Ostwald viscosimeter at 37°C and expressed in relation to viscosity of saline solution. Oxygen transport is computed from Hct and oxygen flow (1/viscosity) and is recorded in arbitrary units. Please note this curve of oxygen transport applies when red cell mass is normal. When red cell mass is increased the curve shifts to the right, when decreased it shifts to the left.

TABLE 2–1 CLASSIFICATION OF ANEMIA

I. Absolute anemia (decreased red cell volume)
- A. Decreased red cell production
  - 1. Acquired
    - a. Pluripotential stem cell failure
      - (1) Autoimmune (aplastic anemia) (see Chap. 3)
        - (a) Radiation induced
        - (b) Drugs and chemicals (chloramphenicol, benzene, etc.)
        - (c) Viruses (non-A-G, H hepatitis, Epstein-Barr virus, etc.)
        - (d) Idiopathic
      - (2) Anemia of leukemia and of myelodysplastic syndromes (see Chaps. 44 and 45)
      - (3) Anemia associated with marrow infiltration (see Chap. 12)
      - (4) Postchemotherapy (see Chap. 38)
    - b. Erythroid progenitor cell failure
      - (1) Pure red cell aplasia (parvovirus B19 infection, drugs, associated with thymoma, autoantibodies, etc. [see Chap. 4])
      - (2) Endocrine disorders (see Chap. 6)
      - (3) Acquired sideroblastic anemia (drugs, copper deficiency, etc. [see Chap. 11])
    - c. Functional impairment of erythroid and other progenitors due to nutritional and other causes
      - (1) Megaloblastic anemias (see Chap. 8)
        - (a) B_{12} deficiency

(b) Folate deficiency
(c) Acute megaloblastic anemia because of nitrous oxide (N_2O)
(d) Drug-induced megaloblastic anemia (pemetrexed, methotrexate, phenytoin toxicity, etc.)
(2) Iron-deficiency anemia (see Chap. 9)
(3) Anemia resulting from other nutritional deficiencies (see Chap. 10)
(4) Anemia of chronic disease and inflammation (see Chap. 5)
(5) Anemia of renal disease (see Chap. 5)
(6) Anemia caused by chemical agents (lead toxicity [see Chap. 20])
(7) Acquired thalassemias (seen in some clonal hematopoietic disorders [see Chaps. 15 and 40])
(8) Erythropoietin antibodies (see Chap. 4)

2. Hereditary
a. Pluripotential hematopoietic stem cell failure (see Chap. 3)
(1) Fanconi anemia
(2) Shwachman syndrome
(3) Dyskeratosis congenita
b. Erythroid progenitor cell failure
(1) Diamond-Blackfan syndrome (see Chap. 3)
(2) Congenital dyserythropoietic syndromes (see Chap. 7)
c. Functional impairment of erythroid and other progenitors from nutritional and other causes
(1) Megaloblastic anemias (see Chap. 8)
(a) Selective malabsorption of vitamin B_{12} (Imerslund-Gräsbeck disease)
(b) Congenital intrinsic factor deficiency
(c) Transcobalamin II deficiency
(d) Inborn errors of cobalamin metabolism (methylmalonic aciduria, homocystinuria, etc.)
(e) Inborn errors of folate metabolism (congenital folate malabsorption, dihydrofolate deficiency, methyltransferase deficiency, etc.)
(2) Inborn purine and pyrimidine metabolism defects (Lesch-Nyhan syndrome, hereditary orotic aciduria, etc.)
(3) Disorders of iron metabolism (see Chap. 9)
(a) Hereditary atransferrinemia
(b) Hypochromic anemia caused by divalent metal transporter (DMT)-1 mutation
(4) Hereditary sideroblastic anemia (see Chap. 11)
(5) Thalassemias (see Chap. 15)

B. Increased red cell destruction
1. Acquired
a. Mechanical
(1) Macroangiopathic (march hemoglobinuria, artificial heart valves [see Chap. 19])
(2) Microangiopathic (disseminated intravascular coagulation [DIC]; thrombotic thrombocytopenic purpura [TTP]; vasculitis [see Chaps. 19, 85, and 90])
(3) Parasites and microorganisms (malaria, bartonellosis, babesiosis, *Clostridium perfringens*, etc. [see Chap. 21])
b. Antibody mediated
(1) Warm-type autoimmune hemolytic anemia (see Chap. 22)
(2) Cryopathic syndromes (cold agglutinin disease, paroxysmal cold hemoglobinuria, cryoglobulinemia [see Chap. 23])
(3) Transfusion reactions (immediate and delayed [see Chap. 91])
c. Hypersplenism (see Chap. 26)
d. Red cell membrane disorders (see Chap. 13)
(1) Spur cell hemolysis
(2) Acquired acanthocytosis and acquired stomatocytosis, etc.
e. Chemical injury and complex chemicals (arsenic, copper, chlorate, spider, scorpion, and snake venoms, etc. [see Chap. 20])
f. Physical injury (heat, oxygen, radiation [see Chap. 20])

2. Hereditary
a. Hemoglobinopathies (see Chap. 16)
(1) Sickle cell disease
(2) Unstable hemoglobins
b. Red cell membrane disorders (see Chap. 13)
(1) Cytoskeletal membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)