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WILLIAMS Hematology

9th Edition

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Williams Hematology

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PREFACE

The first edition of *Williams Hematology* (né *Hematology*) was published in 1972. This, our 9th edition, will represent our continued efforts over nearly one-half century to provide the most current concepts of the pathophysiology and treatment of hematologic diseases.

The rate of growth in our understanding of diseases of blood cells and coagulation pathways provides a challenge for editors of a comprehensive textbook of hematology. The sequencing of individual genomes, analysis of the "dark DNA" and noncoding RNAs, advances in knowledge in proteomics, metabolomics, and other "-omics" fields, as applied to hematologic disorders, have accelerated the understanding of the pathogenesis of the diseases of our interest. The rate at which basic knowledge in molecular and cellular biology and immunology has been translated into improved diagnostic and therapeutic methods is equally impressive. Specific molecular targets for therapy in several hematologic disorders have become reality, and it is not hyperbole to state that hematology is the poster child for the rational design of therapeutics applicable to other fields of medicine.

This edition of *Williams Hematology* includes changes designed to facilitate ease of access to information, both within the book and its associated links, and has been modestly reorganized to reflect our greater understanding of the origins of hematologic disorders. Each chapter has been revised or rewritten to provide current information. Four new chapters have been added and other notable changes have been made. Chapter 4 "Consultative Hematology" is new to this edition. The chapter "Epigenetics and Genomics" has been divided into separate chapters to reflect the growth of knowledge in those disciplines. Chapter 14, "Metabolism of Hematologic Neoplastic Cells" is new, as this topic has become the basis of multiple potential drug targets for hematologic disease. A section on "Autophagy" has been added to Chap 15 "Apoptosis Mechanisms: Relevance to the Hematopoietic System," as the topic is becoming increasingly important for understanding of the physiology of blood cell development; and an independent chapter "Heparin-Induced Thrombocytopenia" (Chap 118) has been created to reflect both its pathophysiologic and clinical importance. Recognizing that at the heart of diagnostic hematology is blood and marrow cell morphology, we have continued our incorporation of informative color images of the relevant disease topics in each chapter, allowing easy access to illustrations of cell morphology important to diagnosis.

The 9th edition of *Williams Hematology* is also available online, as part of the excellent www.accessmedicine.com website. With direct links to a comprehensive drug therapy database and to other important medical texts, including *Harrison's Principles of Internal Medicine* and *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, *Williams Hematology Online* is part of a powerful resource covering all disciplines within medical education and practice. The online edition of *Williams Hematology* also includes PubMed links to journal articles cited in the references.

In addition, *Williams Manual of Hematology* will be revised to reflect the diagnostic and therapeutic advances incorporated in the 9th edition of *Williams Hematology*. The convenient *Manual* features the most clinically salient content from the parent text, and is useful in time-restricted clinical situations. The *Manual* will be available for iPhone™ and other mobile formats.

The readers of the 9th edition of *Williams Hematology* will note a "changing of (some of) the guard" of our editorial group; Drs. Marcel Levi (a member of the 8th edition of *Williams Manual of Hematology* editorial group), Oliver Press, Linda Burns, and Michael Caligiuri have joined continuing editors Drs. Kenneth Kaushansky, Marshall Lichtman, and Josef Prchal in the 9th edition.

The production of this book required the timely cooperation of 101 contributors for the production of 139 chapters. We are grateful for their work in providing this comprehensive and up-to-date text. Despite the growth of both basic and clinical knowledge and the passion that each of our contributors brings to the topic of their chapter, we have been able to maintain the text in a single volume through scrupulous attention to chapter length.

Each editor has had expert administrative assistance in the management of the manuscripts for which they were primarily responsible. We thank Susan Madden in Salt Lake City, Utah; Nancy Press and Deborah Lemon in Seattle, Washington; and Annie Thompson, Rebecca Posey, and Kimberly Morley in Columbus, Ohio for their very helpful participation in the production of the book. Special thanks go to Susan Daley in Rochester, New York, and Marie Brito in Stony Brook, New York, who were responsible for coordinating the management of 139 chapters, including many new figures and tables, and managing other administrative matters, a challenging task that Ms. Daley and Ms. Brito performed with skill and good humor. The editors also acknowledge the interest and support of our colleagues at McGraw-Hill, including James F. Shanahan, Publisher, Medical Publishing; Karen Edmonson, Senior Editor for Williams Hematology; and Harriet Lebowitz, Senior Project Development Editor for *Williams Hematology.*

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Part I Clinical Evaluation of the Patient

CHAPTER 1
INITIAL APPROACH TO THE PATIENT: HISTORY AND PHYSICAL EXAMINATION

Marshall A. Lichtman and Linda J. Burns

SUMMARY

The care of a patient with a suspected hematologic abnormality begins with a systematic attempt to determine the nature of the illness by eliciting an in-depth medical history and performing a thorough physical examination. The physician should identify the patient's symptoms systematically and obtain as much relevant information as possible about their origin and evolution and about the general health of the patient by appropriate questions designed to explore the patient's recent and remote experience. Reviewing previous records may add important data for understanding the onset or progression of illness. Hereditary and environmental factors should be carefully sought and evaluated. The use of drugs and medications, nutritional patterns, and sexual behavior should be considered. The physician follows the medical history with a physical examination to obtain evidence for tissue and organ abnormalities that can be assessed through bedside observation to permit a careful search for signs of the illnesses suggested by the history. Skin changes and hepatic, splenic, or lymph nodal enlargement are a few findings that may be of considerable help in pointing toward a diagnosis. Additional history is obtained during the physical examination, as findings suggest an additional or alternative consideration. Thus, the history and physical examination should be considered as a unit, providing the basic information with which further diagnostic information is integrated: blood and marrow studies, imaging studies, and biopsies.

Primary hematologic diseases are common in the aggregate, but hematologic manifestations secondary to other diseases occur even more frequently. For example, the signs and symptoms of anemia and the presence of enlarged lymph nodes are common clinical findings that may be related to a hematologic disease but occur frequently as secondary manifestations of disorders not considered primarily hematologic. A wide variety of diseases may produce signs or symptoms of hematologic illness. Thus, in patients with a connective tissue disease, all the signs and symptoms of anemia may be elicited and lymphadenopathy may be notable, but additional findings are usually present that indicate primary involvement of some system besides the hematopoietic (marrow) or lymphopoietic (lymph nodes or other lymphatic sites). In this discussion, emphasis is placed on the clinical findings resulting from either primary hematologic disease or the complications of hematologic disorders so as to avoid presenting an extensive catalog of signs and symptoms encountered in general clinical medicine.

Acronyms and Abbreviations: Ig, immunoglobulin; IL, interleukin; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; PS, performance status.

In each discussion of specific diseases in subsequent chapters, the signs and symptoms that accompany the particular disorder are presented, and the clinical findings are covered in detail. In this chapter, a more general systematic approach is taken.

THE HEMATOLOGY CONSULTATION

Table 1–1 lists the major abnormalities that result in the evaluation of the patient by the hematologist. The signs indicated in Table 1–1 may reflect a primary or secondary hematologic problem. For example, immature granulocytes in the blood may be signs of myeloid diseases such as myelogenous leukemia, or, depending on the frequency of these cells and the level of immaturity, the dislodgment of cells resulting from marrow metastases of a carcinoma. Nucleated red cells in the blood may reflect the breakdown in the marrow–blood interface seen in primary myelofibrosis or the hypoxia of congestive heart failure. Certain disorders have a propensity for secondary hematologic abnormalities; renal, liver, and connective tissue diseases are prominent among such abnormalities. Chronic alcoholism, nutritional fetishes, and the use of certain medications may be causal factors in blood cell or coagulation protein disorders. Pregnant women and persons of older age are prone to certain hematologic disorders: anemia, thrombocytopenia, or intravascular coagulation in the former case, and hematologic malignancies, pernicious anemia and the anemia of aging in the latter. The history and physical examination can provide vital clues to the possible diagnosis and also to the rationale choice of laboratory tests.

THE HISTORY

In today's technology- and procedure-driven medical environment, the importance of carefully gathering information from patient inquiry and examination is at risk of losing its primacy. The history (and physical examination) remains the vital starting point for the evaluation of any clinical problem.[1–3]

GENERAL SYMPTOMS AND SIGNS

Performance status (PS) is used to establish semiquantitatively the extent of a patient's disability. This status is important in evaluating patient comparability in clinical trials, in determining the likely tolerance to cytotoxic therapy, and in evaluating the effects of therapy. Table 1–2 presents a well-founded set of criteria for measuring PS.[4] An abbreviated version sometimes is used, as proposed by the Eastern Cooperative Oncology Group (Table 1–3).[5]

Weight loss is a frequent accompaniment of many serious diseases, including primary hematologic malignancies, but it is not a prominent accompaniment of most hematologic diseases. Many "wasting" diseases, such as disseminated carcinoma and tuberculosis, cause anemia, and pronounced emaciation should suggest one of these diseases rather than anemia as the primary disorder.

Fever is a common early manifestation of the aggressive lymphomas or acute leukemias as a result of pyrogenic cytokines (e.g., interleukin [IL]-1, IL-6, and IL-8) released as a reflection of the disease itself. After chemotherapy-induced cytopenias or in the face of accompanying immunodeficiency, infection is usually the cause of fever. In patients with "fever of unknown origin," lymphoma, particularly Hodgkin lymphoma, should be considered. Occasionally, primary myelofibrosis, acute leukemia, advanced myelodysplastic syndrome, and other lymphomas may also cause fever. In rare patients with severe pernicious

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 (e.g., recurrent fetal loss, stillbirth, and HELLP syndrome)

HELLP, ***h***emolytic anemia, ***e***levated ***l***iver enzymes, and ***l***ow ***p***latelet count.

TABLE 1–2. Criteria of Performance Status (Karnofsky Scale)[4]

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

Adapted with permission from Mor V, Laliberte L, Morris JN, Wiemann M: The Karnofsky performance status scale: An examination of its reliability and validity in a research setting *Cancer* 1984 May 1; 53(9):2002–2007.

TABLE 1–3. Eastern Cooperative Oncology Group Performance Status[5]

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, e.g., 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

Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*.

anemia or hemolytic anemia, fever may be present. *Chills* may accompany severe hemolytic processes and the bacteremia that may complicate the immunocompromised or neutropenic patient. *Night sweats* suggest the presence of low-grade fever and may occur in patients with lymphoma or leukemia.

Fatigue, malaise, and *lassitude* are such common accompaniments of both physical and emotional disorders that their evaluation is complex and often difficult. In patients with serious disease, these symptoms may be readily explained by fever, muscle wasting, or other associated findings. Patients with moderate or severe anemia frequently complain of fatigue, malaise, or lassitude and these symptoms may accompany the hematologic malignancies. Fatigue or lassitude may occur also with iron deficiency even in the absence of sufficient anemia to account for the symptom. In slowly developing chronic anemias, the patient may not recognize reduced exercise tolerance, or other loss of physical capabilities except in retrospect, after a remission or a cure has been induced by appropriate therapy. Anemia may be responsible for more symptoms than has been traditionally recognized, as suggested by the remarkable improvement in quality of life of most uremic patients treated with erythropoietin.

Weakness may accompany anemia or the wasting of malignant processes, in which cases it is manifest as a general loss of strength or reduced capacity for exercise. The weakness may be localized as a result of neurologic complications of hematologic disease. In vitamin B_{12} deficiency (e.g., pernicious anemia), there may be weakness of the lower extremities, accompanied by numbness, tingling, and unsteadiness of gait. Peripheral neuropathy also occurs with monoclonal immunoglobulinemias. Weakness of one or more extremities in patients with leukemia, myeloma, or lymphoma may signify central or peripheral nervous system invasion or compression as a result of vertebral collapse, a paraneoplastic syndrome (e.g., encephalitis), or brain or meningeal involvement. Myopathy secondary to malignancy occurs with the hematologic malignancies and is usually manifest as weakness of proximal muscle groups. Foot drop or wrist drop may occur in lead poisoning, amyloidosis, systemic autoimmune diseases, or as a complication of vincristine therapy. Paralysis may occur in acute intermittent porphyria.

SPECIFIC SYMPTOMS OR SIGNS

Nervous System

Headache may be the result of a number of causes related to hematologic diseases. Anemia or polycythemia may cause mild to severe headache.

Invasion or compression of the brain by leukemia or lymphoma, or opportunistic infection of the central nervous system by *Cryptococcus* or *Mycobacterium* species, may also cause headache in patients with hematologic malignancies. Hemorrhage into the brain or subarachnoid space in patients with thrombocytopenia or other bleeding disorders may cause sudden, severe headache.

Paresthesias may occur because of peripheral neuropathy in pernicious anemia or secondary to hematologic malignancy or amyloidosis. They may also result from therapy with vincristine.

Confusion may accompany malignant or infectious processes involving the brain, sometimes as a result of the accompanying fever. Confusion may also occur with severe anemia, hypercalcemia (e.g., myeloma), thrombotic thrombocytopenic purpura, or high-dose glucocorticoid therapy. Confusion or apparent senility may be a manifestation of pernicious anemia. Frank psychosis may develop in acute intermittent porphyria or with high-dose glucocorticoid therapy.

Impairment of consciousness may be a result of increased intracranial pressure secondary to hemorrhage or leukemia or lymphoma in the central nervous system. It may also accompany severe anemia, polycythemia, hyperviscosity secondary, usually, to an immunoglobulin (Ig) M monoclonal protein (uncommonly IgA or IgG) in the plasma, or a leukemic hyperleukocytosis syndrome, especially in chronic myelogenous leukemia.

Eyes

Conjunctival plethora is a feature of polycythemia and pallor a result of anemia. Occasionally blindness may result from retinal hemorrhages secondary to severe anemia and thrombocytopenia or blurred vision resulting from severe hyperviscosity resulting from macroglobulinemia or extreme hyperleukocytosis of leukemia. Partial or complete visual loss can stem from retinal vein or artery thrombosis. Diplopia or disturbances of ocular movement may occur with orbital tumors or paralysis of the third, fourth, or sixth cranial nerves because of compression by tumor, especially extranodal lymphoma, extramedullary myeloma, or myeloid (granulocytic) sarcoma.

Ears

Vertigo, tinnitus, and "roaring" in the ears may occur with marked anemia, polycythemia, hyperleukocytic leukemia, or macroglobulinemia-induced hyperviscosity. Ménière disease was first described in a patient with acute leukemia and inner ear hemorrhage.

Nasopharynx, Oropharynx, and Oral Cavity

Epistaxis may occur in patients with thrombocytopenia, acquired or inherited platelet function disorders, and von Willebrand disease. *Anosmia* or *olfactory hallucinations* occur in pernicious anemia. The nasopharynx may be invaded by a granulocytic sarcoma or extranodal lymphoma; the symptoms are dependent on the structures invaded. The paranasal sinuses may be involved by opportunistic organisms, such as fungus in patients with severe, prolonged neutropenia. *Pain or tingling in the tongue* occurs in pernicious anemia and may accompany severe iron deficiency or vitamin deficiencies. *Macroglossia* occurs in amyloidosis. *Bleeding gums* may occur with bleeding disorders. Infiltration of the gingiva with leukemic cells occurs notably in acute monocytic leukemia. *Ulceration* of the tongue or oral mucosa may be severe in the acute leukemias or in patients with severe neutropenia. *Dryness of the mouth* may be caused by hypercalcemia, secondary, for example, to myeloma. *Dysphagia* may be seen in patients with severe mucous membrane atrophy associated with chronic iron-deficiency anemia.

Neck

Painless swelling in the neck is characteristic of lymphoma but may be caused by a number of other diseases as well. Occasionally, the enlarged lymph nodes of lymphomas may be tender or painful because of secondary infection or rapid growth. Painful or tender lymphadenopathy is usually associated with inflammatory reactions, such as infectious mononucleosis or suppurative adenitis. *Diffuse swelling* of the neck and face may occur with obstruction of the superior vena cava due to lymphomatous compression.

Chest and Heart

Both *dyspnea* and *palpitations,* usually on effort but occasionally at rest, may occur because of anemia or pulmonary embolism. *Congestive heart failure* may supervene, and *angina pectoris* may become manifest in anemic patients. The impact of anemia on the circulatory system depends in part on the rapidity with which it develops, and chronic anemia may become severe without producing major symptoms; with severe acute blood loss, the patient may develop shock with a nearly normal hemoglobin level, prior to compensatory hemodilution. *Cough* may result from enlarged mediastinal nodes compressing the trachea or bronchi. *Chest pain* may arise from involvement of the ribs or sternum with lymphoma or multiple myeloma, nerve-root invasion or compression, or herpes zoster; the pain of herpes zoster usually precedes the skin lesions by several days. Chest pain with inspiration suggests a pulmonary infarct, as does *hemoptysis. Tenderness of the sternum* may be quite pronounced in chronic myelogenous or acute leukemia, and occasionally in primary myelofibrosis, or if intramedullary lymphoma or myeloma proliferation is rapidly progressive.

Gastrointestinal System

Dysphagia has already been mentioned under "Nasopharynx, Oropharynx, and Oral Cavity" above. *Anorexia* frequently occurs but usually has no specific diagnostic significance. Hypercalcemia and azotemia cause anorexia, nausea, and vomiting. A variety of ill-defined gastrointestinal complaints grouped under the heading "indigestion" may occur with hematologic diseases. *Abdominal fullness, premature satiety, belching,* or *discomfort* may occur because of a greatly enlarged spleen, but such splenomegaly may also be entirely asymptomatic. *Abdominal pain* may arise from intestinal obstruction by lymphoma, retroperitoneal bleeding, lead poisoning, ileus secondary to therapy with the *vinca* alkaloids, acute hemolysis, allergic purpura, the abdominal crises of sickle cell disease, or acute intermittent porphyria. *Diarrhea* may occur in pernicious anemia. It also may be prominent in the various forms of intestinal malabsorption, although significant malabsorption may occur without diarrhea. In small-bowel malabsorption, steatorrhea may be a notable feature. Malabsorption may be a manifestation of small-bowel lymphoma. *Gastrointestinal bleeding* related to thrombocytopenia or other bleeding disorder may be occult but often is manifest as *hematemesis* or *melena. Hematochezia* can occur if a bleeding disorder is associated with a colonic lesion. *Constipation* may occur in the patient with hypercalcemia or in one receiving treatment with the *vinca* alkaloids.

Genitourinary and Reproductive Systems

Impotence or *bladder dysfunction* may occur with spinal cord or peripheral nerve damage caused by one of the hematologic malignancies or with pernicious anemia. Priapism may occur in hyperleukocytic leukemia, essential thrombocythemia, or sickle cell disease. *Hematuria* may be a manifestation of hemophilia A or B. *Red urine* may also occur with intravascular hemolysis (hemoglobinuria), myoglobinuria, or porphyrinuria. Injection of anthracycline drugs or ingestion of drugs such as phenazopyridine (Pyridium) regularly causes the urine to turn red. The use of deferoxamine mesylate (Desferal) may result in rust colored urine. *Amenorrhea* may also be induced by certain drugs, such as antimetabolites or alkylating agents. *Menorrhagia* is a common cause of iron deficiency, and care must be taken to obtain a history of the

number of prior pregnancies and an accurate assessment of the extent of menstrual blood loss. Semiquantification can be obtained from estimates of the number of days of heavy bleeding (usually <3), the number of days of any bleeding (usually <7), number of tampons or pads used (requirement for double pads suggests excessive bleeding), degree of blood soaking, and clots formed, and inquiries such as, "Have you experienced a gush of blood when a tampon is removed?" However, an objective distinction between menorrhagia (loss of more than 80 mL blood per period) and normal blood loss can best be made by a visual assessment technique using pictorial charts of towels or tampons.[6] Menorrhagia may occur in patients with bleeding disorders.

Back and Extremities

Back pain may accompany acute hemolytic reactions or be a result of involvement of bone or the nervous system in acute leukemia or aggressive lymphoma. It is one of the most common manifestations of myeloma.

Arthritis or *arthralgia* may occur with gout secondary to increased uric acid production in patients with hematologic malignancies, especially acute lymphocytic leukemia in childhood, myelofibrosis, myelodysplastic syndrome, and hemolytic anemia. They also occur in the plasma cell dyscrasias, acute leukemias, and sickle cell disease without evidence of gout, and in allergic purpura. Arthritis may accompany hemochromatosis, although the association has not been carefully established. In the latter case the arthritis starts typically in the small joints of the hand (second and third metacarpal joints), and episodes of acute synovitis may be related to deposition of calcium pyrophosphate dehydrate crystals. Hemarthroses in patients with severe bleeding disorders cause marked joint pain. Autoimmune diseases may present as anemia and/or thrombocytopenia, and arthritis appears as a later manifestation. *Shoulder pain* on the left may be a result of infarction of the spleen and on the right of gall bladder disease associated with chronic hemolytic anemia such as hereditary spherocytosis. *Bone pain* may occur with bone involvement by the hematologic malignancies; it is common in the congenital hemolytic anemias, such as sickle cell anemia, and may occur in myelofibrosis. In patients with Hodgkin lymphoma, ingestion of alcohol may induce pain at the site of any lesion, including those in bone. *Edema* of the lower extremities, sometimes unilateral, may occur because of obstruction to veins or lymphatics by lymphomatous masses or from deep venous thrombosis. The latter can also cause edema of the upper extremities.

Skin

Skin manifestations of hematologic disease may be of great importance; they include changes in texture or color, itching, and the presence of specific or nonspecific lesions. The skin in iron-deficient patients may become dry, the hair dry and fine, and the nails brittle. In hypothyroidism, which may cause anemia, the skin is dry, coarse, and scaly. *Jaundice* may be apparent with pernicious anemia or congenital or acquired hemolytic anemia. The skin of patients with pernicious anemia is said to be "lemon yellow" because of the simultaneous appearance of jaundice and pallor. Jaundice may also occur in patients with hematologic malignancies, especially lymphomas, as a result of liver involvement or biliary tract obstruction. *Pallor* is a common accompaniment of anemia, although some severely anemic patients may not appear pale. Erythromelalgia may be a troublesome complication of polycythemia vera. Patchy plaques or widespread *erythroderma* occur in cutaneous T-cell lymphoma (especially Sézary syndrome) and in some cases of chronic lymphocytic leukemia or lymphocytic lymphoma. The skin is often involved, sometimes severely, in graft-versus-host disease following hematopoietic cell transplantation. Patients with hemochromatosis may have bronze or grayish pigmentation of the skin. *Cyanosis* occurs with methemoglobinemia, either hereditary or acquired; sulfhemoglobinemia; abnormal hemoglobins with low oxygen affinity; and primary and secondary polycythemia. Cyanosis of the ears or the fingertips may occur after exposure to cold in individuals with cryoglobulins or cold agglutinins.

Itching may occur in the absence of any visible skin lesions in Hodgkin lymphoma and may be extreme. Mycosis fungoides or other lymphomas with skin involvement may also present as itching. A significant number of patients with polycythemia vera will complain of itching after bathing.

Petechiae and *ecchymoses* are most often seen in the extremities in patients with thrombocytopenia, nonthrombocytopenic purpura, or acquired or inherited platelet function abnormalities and von Willebrand disease. Unless secondary to trauma, these lesions usually are painless; the lesions of psychogenic purpura and erythema nodosum are painful. *Easy bruising* is a common complaint, especially among women, and when no other hemorrhagic symptoms are present, usually no abnormalities are found after detailed study. This symptom may, however, indicate a mild hereditary bleeding disorder, such as von Willebrand disease or one of the platelet disorders. *Infiltrative lesions* may occur in the leukemias (leukemia cutis) and lymphomas (lymphoma cutis) and are sometimes the presenting complaint. Monocytic leukemia has a higher frequency of skin infiltration than other forms of leukemia. *Necrotic lesions* may occur with intravascular coagulation, purpura fulminans, and warfarin-induced skin necrosis, or rarely with exposure to cold in patients with circulating cryoproteins or cold agglutinins.

Leg ulcers are a common complaint in sickle cell anemia and occur rarely in other hereditary anemias.

DRUGS AND CHEMICALS

Drugs

Drug therapy, either self-prescribed or ordered by a physician, is extremely common in our society. Drugs often induce or aggravate hematologic disease, and it is therefore essential that a careful history of drug ingestion, including beneficial and adverse reactions, should be obtained from all patients. Drugs taken regularly, including nonprescription medications, often become a part of the patient's way of life and are forgotten or are not recognized as "drugs."

Agents such as aspirin, laxatives, tranquilizers, medicinal iron, vitamins, other nutritional supplements, and sedatives belong to this category. Furthermore, drugs may be ingested in unrecognized form, such as antibiotics in food or quinine in tonic water. Specific, persistent questioning, often on several occasions, may be necessary before a complete history of drug use is obtained. It is very important to obtain detailed information on alcohol consumption from every patient. The four "CAGE" questions—about needing to ***c***ut down, being ***a***nnoyed by criticism, having ***g***uilt feelings, and requiring a drink as a morning ***e***ye-opener—provide an effective approach to the history of alcohol use. Patients should also be asked about the use of recreational drugs. The use of "alternative medicines" and herbal medicines is common, and many patients will not consider these medications or may actively withhold information about their use. Nonjudgmental questioning may be successful in identifying agents in this category that the patient is taking. Some patients equate the term "drugs," as opposed to "medicines," with illicit drugs. Establishing that the examiner is interested in all forms of ingestants—prescribed drugs, self-remedies, alternative remedies, etcetera—is important to ensure getting the information required.

Chemicals

In addition to drugs, most people are exposed regularly to a variety of chemicals in the environment, some of which may be potentially harmful

agents and result in a deleterious hematologic effect, such as anemia or leukopenia. An occupational history should explore exposure to potentially harmful chemicals. This information should be supplemented by inquiries about hobbies and other interests that result in work with chemicals, such as glues and solvents. When a toxin is suspected, the patient's daily activities and environment should be carefully reviewed, as significant exposure to toxic chemicals may occur incidentally.

VACCINATION

Vaccinations can be complicated by acute immune thrombocytopenia. In infants, this is most notable after measles, mumps, rubella (MMR) vaccine. This occurrence is approximately 1 in 25,000 children vaccinated, occurs within 6 weeks of vaccination, and in the majority of occurrences is self-limited. There is no evidence that children with antecedent immune thrombocytopenia are at risk of recurrence after MMR vaccination.[7] Analysis, thus far, shows rare cases in following administration of other vaccines (hepatitis A, diphtheria-pertussis-tetanus, or varicella) administered to older children and adolescents and significant risk has not been ascertained.[8]

NUTRITION

Children who are breastfed without iron supplementation may develop iron-deficiency anemia. Nutritional information can be useful in deducing the possible role of dietary deficiency in anemia. The avoidance of certain food groups, as might be the case with vegetarians, or the ingestion of uncooked fish can be clues to the pathogenesis of megaloblastic anemia.

FAMILY HISTORY

A carefully obtained family history may be of great importance in the study of patients with hematologic disease (Chap. 10). In the case of hemolytic disorders, questions should be asked regarding jaundice, anemia, and gallstones in relatives. In patients with disorders of hemostasis or venous thrombosis, particular attention must be given to bleeding manifestations or venous thromboembolism in family members. In the case of autosomal recessive disorders such as pyruvate kinase deficiency, the parents are usually not affected, but a similar clinical syndrome may have occurred in siblings. It is particularly important to inquire about siblings who may have died in infancy, as these may be forgotten, especially by older patients. When sex-linked inheritance is suspected, it is necessary to inquire about symptoms in the maternal grandfather, maternal uncles, male siblings, and nephews. In patients with disorders with dominant inheritance, such as hereditary spherocytosis, one may expect to find that one parent and possibly siblings and children of the patient have stigmata of the disease. Ethnic background may be important in the consideration of certain diseases such as α- and β-thalassemia, sickle cell anemia, glucose-6-phosphate dehydrogenase deficiency, hemoglobin E, and other inherited disorders that are prevalent in specific geographic areas, such as the Mediterranean basin or Southeast Asia.

SEXUAL HISTORY

Because of the frequency of infections with the human immunodeficiency viruses, it is important to ascertain the sexual behavior of the patient, especially risk factors for transmission of HIV.

PREVENTIVE HEMATOLOGY

Ideally, the physician's goal is to prevent illness, and opportunities exist for hematologists to prevent the development of hematologic disorders. These opportunities include identification of individual genetic risk factors and avoidance of situations that may make a latent disorder manifest. Prophylactic therapy, as for example in avoiding venous stasis in patients heterozygous for protein C deficiency or administering prophylactic heparin at the time of major surgery, is a more immediate aspect of prevention because it depends on the physician's intervention. Hematologists may also prevent disease by reinforcing community medicine efforts. Examples include fostering the elimination of sources of environmental lead that may result in childhood anemia. Prenatal diagnosis can provide information to families as to whether a fetus is affected with a hematologic disorder.

PHYSICAL EXAMINATION

A detailed physical examination should be performed on every patient, with sufficient attention paid to all systems so as to obtain a full evaluation of the general health of the individual. The skin, eyes, tongue, lymph nodes, skeleton, spleen and liver, and nervous system are especially pertinent to hematologic disease and therefore deserve special attention.

SKIN

Pallor and Flushing

The color of the skin is a result of the pigment contained therein and to the blood flowing through the skin capillaries. The component of skin color related to the blood may be a useful guide to anemia or polycythemia, as pallor may result when the hemoglobin level is reduced, and redness when the hemoglobin level is increased. The amount of pigment in the skin modifies skin color and can mislead the clinician, as in individuals with pallor resulting from decreased pigment, or make skin color useless as a guide because of the intense pigmentation present.

Alterations in blood flow and in hemoglobin content may change skin color; this, too, can mislead the clinician. Thus emotion may cause either pallor or blushing. Exposure of the skin to cold or heat may similarly cause pallor or blushing. Chronic exposure to wind or sun may lead to permanent redness of the skin, and chronic ingestion of alcohol to a flushed face. The degree of erythema of the skin can be evaluated by pressing the thumb firmly against the skin, as on the forehead, so that the capillaries are emptied, and then comparing the color of the compressed spot with the surrounding skin immediately after the thumb is removed.

The mucous membranes and nail beds are usually more reliable guides to anemia or polycythemia than the skin. The conjunctivae and gums may be inflamed, however, and therefore not reflect the hemoglobin level, or the gums may appear pale because of pressure from the lips. The gums and the nail beds may also be pigmented and the capillaries correspondingly obscured. In some individuals, the color of the capillaries does not become fully visible through the nails unless pressure is applied to the fingertip, either laterally or on the end of the nail.

The palmar creases are useful guides to the hemoglobin level and appear pink in the fully opened hand unless the hemoglobin is 7 g/dL or less. Liver disease may induce flushing of the thenar and hypothenar eminences of the palm, even in patients with anemia.

Cyanosis

The detection of cyanosis, like the detection of pallor, may be made difficult by skin pigmentation. Cyanosis is a function of the total amount of reduced hemoglobin, methemoglobin, or sulfhemoglobin present. The minimum amounts of these pigments that cause detectable cyanosis are approximately 5 g/dL blood of reduced hemoglobin, 1.5 to 2.0 g/dL of methemoglobin, and 0.5 g/dL of sulfhemoglobin.

Jaundice

Jaundice may be observed in the skin of individuals who are not otherwise deeply pigmented or in the sclerae or the mucous membranes.

The patient should be examined in daylight rather than under incandescent or fluorescent light, because the yellow color of the latter masks the yellow color of the patient. Jaundice is a result of actual staining of the skin by bile pigment, and bilirubin glucuronide (direct-reacting or conjugated bilirubin) stains the skin more readily than the unconjugated form. Jaundice of the skin may not be visible if the bilirubin level is below 2 to 3 mg/dL. Yellow pigmentation of the skin may also occur with carotenemia, especially in young children.

Petechiae and Ecchymoses

Petechiae are small (1 to 2 mm), round, red or brown lesions resulting from hemorrhage into the skin and are present primarily in areas with high venous pressure, such as the lower extremities. These lesions do not blanch on pressure, and this can be readily demonstrated by compressing the skin with a glass microscope slide or magnifying lens. Petechiae may occasionally be elevated slightly, that is, palpable; this finding suggests vasculitis. Ecchymoses may be of various sizes and shapes and may be red, purple, blue, or yellowish green, depending on the intensity of the skin hemorrhage and its age. They may be flat or elevated; some are painful and tender. The lesions of hereditary hemorrhagic telangiectasia are small, flat, nonpulsatile, and violaceous. They blanch with pressure.

Excoriation

Itching may be intense in some hematologic disorders, such as Hodgkin lymphoma, even in the absence of skin lesions. Excoriation of the skin from scratching is the only physical manifestation of this severe symptom.

Leg Ulcers

Open ulcers or scars from healed ulcers are often found in the region of the internal or external malleoli in patients with sickle cell anemia, and, rarely, in other hereditary anemias.

Nails

Detection of pallor or rubor by examining the nails was discussed earlier. The fingernails in chronic, severe iron-deficiency anemia may be ridged longitudinally and flattened or concave rather than convex. The latter change is referred to as *koilonychia* and is uncommon in present practice.

Eyes

Jaundice, pallor, or *plethora* may be detected from examination of the eyes. Jaundice is usually more readily detected in the sclerae than in the skin. Ophthalmoscopic examination is also essential in patients with hematologic disease. *Retinal hemorrhages* and *exudates* occur in patients with severe anemia and thrombocytopenia. These hemorrhages are usually the typical "flame-shaped" hemorrhages, but they may be quite large and elevate the retina so that they may appear as a darkly colored tumor. Round hemorrhages with white centers are also often seen. *Dilatation of the veins* may be seen in polycythemia; in patients with macroglobulinemia, the veins are engorged and segmented, resembling link sausages.

Mouth

Pallor of the mucosa has already been discussed (see "Pallor and Flushing" above). *Ulceration* of the oral mucosa occurs commonly in neutropenic patients. In leukemia there may also be infiltration of the gums with swelling, redness, and bleeding. *Bleeding* from the mucosa may occur with a hemorrhagic disease. A dark line of lead sulfide may be deposited in the gums at the base of the teeth in lead poisoning. The *tongue* may be completely smooth in pernicious anemia and iron-deficiency anemia. Patients with an upper dental prosthesis may also have papillary atrophy, presumably on a mechanical basis. The tongue may be smooth and red in patients with nutritional deficiencies. This may be accompanied by fissuring at the corners of the mouth, but fissuring may also be caused by ill-fitting dentures. An enlarged tongue, abnormally firm to palpation, may indicate the presence of primary amyloidosis.

Lymph Nodes

Lymph nodes are widely distributed in the body, and in disease, any node or group of nodes may be involved. The major concern on physical examination is the detection of enlarged or tender nodes in the cervical, supraclavicular, axillary, epitrochlear, inguinal, or iliofemoral regions. Under normal conditions in adults, the only readily palpable lymph nodes are in the inguinal region, where several firm nodes 0.5 to 2.0 cm long are normally attached to the dense fascia below the inguinal ligament and in the femoral triangle. In children, multiple small (0.5 to 1.0 cm) nodes may be palpated in the cervical region as well. Supraclavicular nodes may sometimes be palpable only when the patient performs the Valsalva maneuver.

Enlarged lymph nodes are ordinarily detected in the superficial areas by palpation, although they are sometimes large enough to be seen. Palpation should be gentle and is best performed with a circular motion of the fingertips, using slowly increasing pressure. Tender lymph nodes usually indicate an inflammatory etiology, although rapidly proliferative lymphoma may be tender to palpation.

Nodes too deep to palpate may be detected by specific imaging procedures, including computerized tomography, magnetic resonance imaging, ultrasound studies, gallium scintography, and positron emission tomography.[9,10]

Chest

Increased rib or sternal tenderness is an important physical sign often ignored. Increased bone pain may be generalized, as in leukemia, or spotty, as in plasma cell myeloma or in metastatic tumors. The superficial surfaces of all bones should be examined thoroughly by applying intermittent firm pressure with the fingertips to locate potential areas of disease.

Spleen

The normal adult spleen is usually not palpable on physical examination, but occasionally the tip may be felt.[11] Palpability of the normal spleen may be related to body habitus, but there is disagreement on this point. Percussion, palpation, or a combination of these two methods may detect enlarged spleens.[12] Some enlarged spleens may be visible by protrusion of the abdominal wall.

The normal spleen weighs approximately 150 g and lies in the peritoneal cavity against the diaphragm and the posterolateral abdominal wall at the level of the lower three ribs. As it enlarges it remains close to the abdominal wall, while the lower pole moves downward, anteriorly, and to the right. Spleens enlarged only 40 percent above normal may be palpable, but significant splenic enlargement may occur and the organ still not be felt on physical examination. A good but imperfect correlation has been reported between spleen size estimated from radioisotope scanning or ultrasonography and spleen weight determined after splenectomy or at autopsy.[13] Although it is common to fail to palpate an enlarged spleen on physical examination, palpation of a normal-sized spleen is unusual, and therefore a palpable spleen is usually a significant physical finding.

An enlarged spleen lies just beneath the abdominal wall and can be identified by its movement during respiration. The splenic notch may be evident if the organ is moderately enlarged. During the examination the patient lies in a relaxed, supine position. The examiner, standing on the patient's right, lightly palpates the left upper abdomen with the

right hand while exerting pressure forward with the palm of the left hand placed over the lower ribs posterolaterally. This action permits the spleen to descend and be felt by the examiner's fingers. If nothing is felt, the palpation should be performed repeatedly, moving the examining hand approximately 2 cm toward the inguinal ligament each time. It is often advantageous to carry out the examination initially with the patient lying on the right side with left knee flexed and to repeat it with the patient supine.

It is not always possible to be sure that a left upper quadrant mass is spleen; masses in the stomach, colon, kidney, or pancreas may mimic splenomegaly on physical examination. When there is uncertainty regarding the nature of a mass in the left upper quadrant, imaging procedures will usually permit accurate diagnosis.[13–15]

Liver

Palpation of the edge of the liver in the right upper quadrant of the abdomen is commonly used to detect hepatic enlargement, although the inaccuracies of this method have been demonstrated. It is necessary to determine both the upper and lower borders of the liver by percussion in order to properly assess liver size.[16,17] The normal liver may be palpable as much as 4 to 5 cm below the right costal margin but is usually not palpable in the epigastrium. The height of liver dullness is best measured in a specific line 8, 10, or 12 cm to the right of the midline. Techniques should be standardized so that serial measurements can be made. The vertical span of the normal liver determined in this manner will range approximately 10 cm in an average-size man and approximately 2 cm smaller in a woman. Because of variations introduced by technique, each physician should determine the normal area of liver dullness by the physician's own procedure. Correlation of radioisotope imaging data with results from routine physical examinations indicates that often a liver of normal size is considered enlarged on physical examination and an enlarged liver is considered normal. Ultrasonography and computed tomography measurements are useful in determining size and demonstrating localized infiltrative lesions.[18–20]

Nervous System

A thorough evaluation of neurologic function is necessary in many patients with hematologic disease. Vitamin B_{12} deficiency impairs cerebral, olfactory, spinal cord, and peripheral nerve function, and severe chronic deficiency may lead to irreversible neurologic degeneration. Leukemic meningitis is often manifested by headache, visual impairment, or cranial nerve dysfunction. Tumor growth in the brain or spinal cord compression may be caused by malignant lymphoma or plasma cell myeloma. A variety of neurologic abnormalities may develop in patients with leukemias, lymphomas, and myeloma as a consequence of tumor infiltration, bleeding, infection, or a paraneoplastic syndrome. Essential monoclonal gammopathy is associated with several types of sensory and motor neuropathies. Polyneuropathy is a feature of POEMS, a syndrome marked by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

Joints

Deformities of the knees, elbows, ankles, shoulders, wrists, or hips may be the result of repeated hemorrhage in patients with hemophilia A, hemophilia B, or severe factor VII deficiency. Often, a target joint is prominently affected.

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