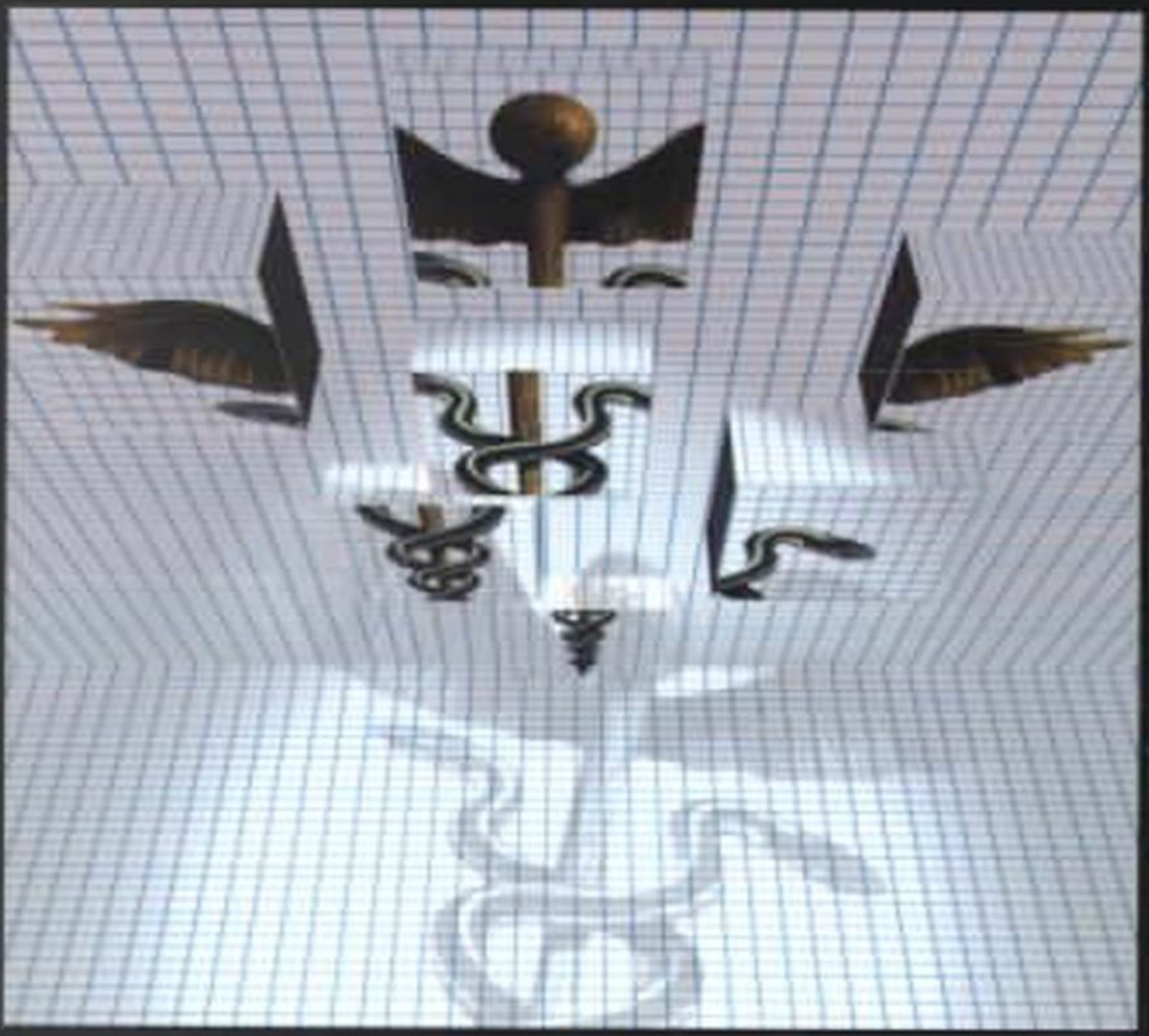
LIPPINCOTT WILLIAMS & WILKINS

SPIRAL® MANUAL

Problem-Oriented Medical Diagnosis

Seventh Edition

Edited by
H. Harold Friedman



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Vũ Minh Hồng

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SEVENTH EDITION

Editor

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PREFACE

The objective of this seventh edition of *Problem-Oriented Medical Diagnosis* is unchanged from that of the first edition. Briefly, it is to provide a concise but comprehensive, logical, stepwise approach to the diagnosis of medical problems encountered in the everyday practice of adult medicine. Problem identification begins with a complete history and physical examination. From the information thus obtained, it is possible to select appropriate laboratory procedures that may assist in establishing a diagnosis. Many physicians also order routinely a battery of laboratory tests for screening purposes. The findings of the history, physical examination, and laboratory investigations provide the essential data on which the diagnosis, prognosis, and management of the patient are based.

The problem-oriented medical record devised by Weed has largely supplanted the traditional methods for medical record-keeping. Although the merits of the problem-oriented system may be debated by some, it is hardly disputable that, regardless of the method of record-keeping employed, one of the physician's major responsibilities is to discover all the patient's problems. Such problems may present themselves as symptoms, physical signs, laboratory or radiologic abnormalities, symptom complexes or syndromes, and clinical diagnoses. The subjects selected for discussion in this manual were chosen because they occur frequently or because they are clinically important. In a field as vast as internal medicine, a great deal of selectivity must be exercised to keep the book within reasonable limits.

The problems chosen for consideration are listed as sections within the chapters. To explain these problems, I have chosen academically oriented physicians who are engaged primarily in the care of patients. It is hoped that the work of these authors will give this manual the imprimatur of both authenticity and practicality.

This book is intended for the medical student, the intern, the family practice or internal medicine resident, and the private practitioner, whether a family physician or an internist. It should also be useful to the nurse practitioner and the physician's assistant.

Most textbooks of medicine are organized in terms of diseases rather than patients, and properly so. Such books, however, do not provide the methodology for proceeding from symptoms, signs, or abnormal laboratory findings to the diagnosis of disease. This text, which gives the diagnostic approach to the problems presented, should help to bridge the gap. It is intended to supplement, not to replace, conventional textbooks of medicine.

The book is written primarily in outline form for clarity and conciseness while maintaining a reasonable degree of comprehensiveness. Because individual contributors were permitted some latitude in dealing with the topics assigned to them, the presentations of the various problems are not uniform throughout the book. Most of the authors, however, have used the following format: definition of the entity, consideration of its etiology and significant clinical features, and presentation of a practical diagnostic approach to the problem. Brief interpretations of the relevant laboratory tests also are given. Discussions of pathophysiology, prognosis, and treatment have been omitted, however, not only because they are outside the scope of the book but also because this information is readily available from other sources. For similar reasons, a bibliography is not included.

In this edition, the entire text has been updated and much of it has been revised.

H.H.F.

thrombophlebitis:

1. GENERAL PROBLEMS

Edema

H. Harold Friedman

Definition

Edema is an increase in the volume of interstitial fluid (i.e., the extravascular portion of the extracellular compartment). The plasma volume may or may not be increased.

Diagnosis

Interstitial fluid volume may increase considerably before it is clinically appreciated. The symptoms and signs of edema are unexplained weight gain, tightness of a ring or shoe, puffiness of the face, swollen extremities, enlarged abdominal girth, and persistence of indentation of the skin following pressure.

Etiology

1 *Localized Edema*

This term usually refers to edema produced by regional obstruction to venous or lymphatic flow, or both. It is usually limited to one or two limbs. Examples include unilateral lower extremity edema caused by deep venous thrombosis or thrombophlebitis, venous insufficiency, popliteal (Baker's) cysts, cellulitis, and trauma. The term is sometimes used to refer to patches of "vascular" edema seen in allergic states.

Hydrothorax and ascites may be localized phenomena or may occur in any generalized edematous state. When such an association is not evident, or if the effusions do not respond to treatment, the involved serous cavity should be tapped and the fluid examined by appropriate means (Chapter 4, Differential Diagnosis of Pleural Effusion; Chapter 5, Abdominal Distention and Ascites). Unilateral leg edema may be produced by increased hydrostatic pressure caused by deep vein thrombophlebitis, venous insufficiency, or popliteal (Baker's) cysts. It also can be the result of increased capillary permeability from cellulitis or trauma. Local lymphatic obstruction or pelvic neoplasm sometimes is causative.

Bilateral leg edema is usually a manifestation of generalized edema. It is the result of bilateral venous insufficiency in some instances, however.

2 *Generalized Edema*

The more common causes of generalized edema are listed in the following: (5)

I. Congestive heart failure
   A. *Symptoms.* A history of heart disease usually can be obtained. Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, weakness, and swelling of the lower extremities are common.
   B. *Signs.* Physical examination usually reveals distended jugular veins, cardiomegaly, bibasilar rales, hepatomegaly, and dependent edema.
   C. *Laboratory findings.* The hemogram usually is normal. Urinalysis may disclose proteinuria (trace to 2+). Mild azotemia caused by renal hypoperfusion is not unusual.

II. Pericardial disease
   A. Chronic constrictive pericarditis
      1. *Symptoms.* The major symptoms are dyspnea, fatigue, weakness, abdominal distention, and edema.
      2. *Signs.* The classic findings are markedly elevated venous pressure, often with a deep Y trough and Kussmaul's sign; pulsus paradoxus; a quiet precordium; slight to moderate cardiac enlargement; and absence of significant murmurs.

B. Pericarditis with effusion
   1. *Symptoms.* Chest pain is common but may not be present. Dyspnea, orthopnea, and cough are frequent complaints.
   2. *Signs.* The area of cardiac dullness is increased. The apical impulse may be impalpable or, if present, may be located well within the lateral border of cardiac dullness. A pericardial friction rub is often but not always present. When cardiac tamponade occurs, there may be elevated venous pressure, decreased blood pressure with a narrow pulse pressure, pulsus paradoxus, ascites, and edema.

C. *Laboratory findings.* Chest films and an electrocardiogram are helpful in the diagnosis of pericardial disease. Echocardiography and other procedures may be useful in the diagnosis of pericardial effusion. Hemodynamic studies are important in the evaluation of chronic constrictive pericarditis.

III. Liver disease
   A. *Symptoms.* A history of alcoholism and jaundice may be obtained. Weakness, fatigability, anorexia, and weight loss are common.
   B. *Signs.* Physical examination usually reveals evidence of liver disease: jaundice, spider nevi, palmar erythema, hepatomegaly, sometimes splenomegaly, parotid swelling, gynecomastia, testicular atrophy, and clubbing. Although lower extremity edema is not uncommon, the edema may be limited to the peritoneal cavity (ascites).
   C. *Laboratory findings.* An elevated serum bilirubin level, abnormal liver function tests, and reduced serum albumin level are typical. Urinalysis may reveal proteinuria (0 to 1+).

IV. Hypoalbuminemic states
   A. Nephrotic syndrome
      1. *Symptoms.* The history may or may not reveal evidence of renal disease or a systemic illness that can produce the nephrotic syndrome (e.g., diabetes mellitus, systemic lupus erythematosus [SLE]). Constitutional symptoms may be present but are nonspecific.
      2. *Laboratory findings.* Urinalysis shows marked proteinuria (>3.5 g in 24 h) and lipiduria. Hypoalbuminemia, hyperlipemia, and hypercholesterolemia typically are present.
   B. Protein-losing enteropathy
      1. *Symptoms.* This is a rare disorder that may occur in association with disorders such as chronic inflammatory enterocolonopathies, Ménétrier's disease, and gastric carcinoma. The symptoms are those of the underlying disease.
      2. *Signs.* There are no specific signs.
      3. *Laboratory findings.* Decreased serum albumin level and a normal urinalysis are typical.
   C. Malnutrition associated with severe protein deficiency may result in edema.

V. Miscellaneous causes
   A. Acute nephritic syndrome. This disorder is characterized by oliguria, proteinuria, hematuria, red blood cell casts, hypertension, and edema. Acute poststreptococcal glomerulonephritis is the most common cause of the acute nephritic syndrome.
   B. Idiopathic edema. This condition occurs almost exclusively in premenopausal women. Its etiology is unknown. The characteristic feature of the disorder is excessive weight gain (usually 4 to 12 pounds) from morning to evening when the patient is up and about. Purely cyclic edema is rare, but it is sometimes superimposed on the aforementioned pattern.
   C. Myxedema. Patients with hypothyroidism often have puffiness below the eyes and in the pretibial region. It may be firm and nonpitting at the latter site.
   D. Trichinosis. This disease, commonly associated with the ingestion of raw or improperly cooked pork, has muscle aches, fever, periorbital edema, and eosinophilia as symptoms and signs.
   E. Hemiplegia. Unilateral edema in the paralyzed extremity or extremities is a common finding in stroke victims.

   F. Lymphedema
   G. Filariasis

Diagnostic Approach

I. As a first step, it is essential to determine whether the edema is localized or generalized. This usually can be accomplished by careful attention to the history and physical examination. Once localized edema and its causes have been excluded, it can be assumed that the edema is generalized.

II. The three most common causes of generalized edema are congestive heart failure, liver disease, and the nephrotic syndrome. The diagnosis is usually apparent on clinical grounds in the first two conditions, whereas heavy proteinuria suggests the third.
   A. Congestive heart failure and cardiac tamponade sometimes present a problem in differential diagnosis. The presence of an apical impulse that is displaced downward and to the left and a gallop rhythm are strong evidence in favor of congestive heart failure rather than cardiac tamponade. It is also worth noting that congestive heart failure is so frequently associated with cardiomegaly that a normal cardiac silhouette almost excludes the diagnosis.
   B. Liver disease as the cause of edema is usually evident from the physical examination. Abnormal liver function tests support the diagnosis.

III. When generalized edema is found not to be owing to cardiovascular or hepatic disease or the nephrotic syndrome, consideration must be given to other, less frequent causes.

IV. Routine studies in patients with edema should include the following:
   A. CBC
   B. Urinalysis
   C. Biochemical screening, including T_4 and T_3 resin uptake, serum albumin and total protein, serum cholesterol, and liver function tests
   D. Chest films
   E. Electrocardiogram

V. Urinary findings of heavy proteinuria, hematuria, cylindruria, and formed elements in the sediment are generally indicative of renal parenchymal disease (Chapter 7, Renal and Urinary Tract Disorders).

VI. Moderate to heavy proteinuria, with or without hypoalbuminemia, suggests the nephrotic syndrome. Additional studies are necessary to determine its etiology.

VII. Hypoalbuminemia without proteinuria requires investigation for malnutrition or protein-losing enteropathy, provided liver disease is excluded.

VIII. The diagnosis of idiopathic cyclic edema is based on an appropriate clinical setting, the exclusion of other causes, and a positive water-loading test.

Fatigue

H. Harold Friedman

Fatigue is one of the most common symptoms for which patients seek medical attention.

Definition

Fatigue is a sense of weariness, described by patients variously as exhaustion, tiredness, lack of pep and energy, loss of ambition or interest, low vitality, or a feeling of being "all in." It is often accompanied by a subjective sensation of weakness and a strong desire to rest or sleep.

Etiology

Fatigue is normal when it is the result of a full day's work or sustained physical activity. It may also be a consequence of a period of prolonged emotional stress or mental strain. In these circumstances, the cause of the fatigue is usually evident to the patient, and he or she rarely seeks advice because of it. Chronic fatigue, however, is not a normal state. Although chronic fatigue may be caused by a physical ailment, it is most often psychogenic in origin. Table 1-1 lists the more common causes of chronic fatigue.

Table 1-1. Causes of chronic fatigue

I. Fatigue of psychogenic origin (80% of cases)
  A. Anxiety states
  B. Depression
II. Fatigue of physical origin (20% of cases)
  A. Infectious disease
    1. Febrile states
    2. Tuberculosis
    3. AIDS or AIDS-related complex
  B. Metabolic disorders
    1. Diabetes mellitus
    2. Hypothyroidism
    3. Hyperparathyroidism
    4. Hypopituitarism
    5. Addison's disease
  C. Blood dyscrasias
    1. Anemia
    2. Lymphoma and leukemia
  D. Renal diseases
    1. Acute renal failure
    2. Chronic renal failure
  E. Liver diseases
    1. Acute hepatitis
    2. Chronic hepatitis and cirrhosis
  F. Inflammatory diseases
    1. Connective tissue disease
    2. Inflammatory bowel disease
    3. Sarcoidosis
  G. Chronic pulmonary disease
  H. Chronic cardiovascular disease
  I. Neoplastic diseases
  J. Chronic fatigue syndrome
  K. Neuromuscular diseases (see Chapter 10, Weakness of Neuromuscular Origin)
  L. Miscellaneous causes
    1. Medications
    2. Alcoholism
    3. Drug abuse

Diagnostic Approach

History

I. Much can be learned from the history of a patient with fatigue. Because fatigue is most commonly psychic in origin and the result of anxiety, anger, or chronic conflict, a careful inquiry into the emotional state of the patient and his or her life situation is warranted. Depressive reactions, also a common cause of fatigue, are often associated with weakness, anorexia, weight loss, apathy, insomnia, withdrawal, lack of a desire to go on, and self-deprecation. The presence of such symptoms should alert the physician to the possibility of serious depression, with its attendant risk of suicide. Therapy should be instituted promptly, even before diagnostic studies are completed.

II. Clues to the etiology of fatigue may be found in the analysis of the symptoms itself.
  A. Patients with fatigue caused by anxiety are typically tired when they go to bed and just as tired when they wake up in the morning. As a general rule, the fatigue appears to lessen during the day. Many patients complain that they are "always tired" and that no amount of rest or sleep seems to improve their weariness or give them strength. Inquiry often discloses that there is considerable variation in the fatigue: At one time the patient feels exhausted, and at another time—sometimes only a few minutes later—full of energy and capable of any task confronting him or her. Motivation appears to be a large factor in the patient's ability to cope with the situations of everyday life. Headaches and other pains, as well as subjective weakness, commonly accompany the fatigue. The problem of anxiety is considered in detail later in this chapter.
  B. Fatigue caused by depression follows no set pattern but is almost invariably accompanied by other stigmata of the depressed state (namely, a persistent mood of sadness coupled with pessimism, cognitive changes, and physiologic disturbances). The problem of depression is discussed in detail later in this chapter.
  C. Fatigue caused by physical illness, on the other hand, is relieved by decreased activity and rest and sleep. The patient probably awakens refreshed in the morning, but less than ordinary activity causes fatigue.
  D. Denial or minimization of fatigue in a patient who looks tired or is described as being weak or tired by his or her family usually implies organic disease rather than a psychological disturbance.

Physical Examination

I. Fatigue per se is not associated with any specific physical findings.
II. The patient who is pale, wan, and sickly in appearance, who looks tired and worn, and whose face sags and body slumps should be suspected of having organic illness.
III. The facial expression of the depressed patient, once seen, is rarely forgotten.
IV. Most physical ailments that cause fatigue can be diagnosed by clinical observation alone.
V. A careful neurologic examination is indicated in all cases.

Diagnostic Workup

I. The major purpose of the diagnostic workup is to exclude organic disease. To this end, the following procedures are recommended.
  A. CBC
  B. Sedimentation rate
  C. Urinalysis
  D. Biochemical screening
  E. Thyroid function tests (e.g., TSH; T_4; T_3 resin uptake or T_3 RIA, or both)
  F. Two-hour postprandial glucose or glucose tolerance test
  G. Chest films
  H. Electrocardiogram
  I. HIV serology, if indicated
  J. ANA
II. If the initial workup is negative in a patient who is apparently well except for fatigue, organic disease usually can be excluded, and no further workup is necessary. The patient should be kept under observation until systemic illness can reasonably be excluded. Patients with fatigue of physical origin sooner or later develop other symptoms or signs. Should these occur, further investigation is warranted.

Chronic Fatigue Syndrome

H. Harold Friedman

The chronic fatigue syndrome is a symptom complex of unknown etiology that has received considerable attention recently. It is characterized by persistent or recurrent debilitating fatigue in association with other symptoms listed in the following under Diagnosis. It is found primarily in healthy, heterosexual teenagers and young adults, about three-quarters of whom are women. It has been attributed by some to a persistent mononucleosis infection owing to the Epstein–Barr virus, but this relationship has not been established. The diagnostic value of Epstein–Barr virus serologic tests

in patients with the syndrome is doubtful. Treatment is unsatisfactory. Some have suggested that a novel human retrovirus may be the cause of the syndrome.

Certain abnormalities found in patients with chronic fatigue syndrome suggest central nervous system (CNS) dysfunction. These include immunologic abnormalities, evidence of pituitary and hypothalamic involvement, abnormal levels of certain neurotransmitter metabolites, and cerebral perfusion abnormalities.

Diagnosis

According to Holmes and coworkers (*Ann Int Med* 1988;108:387), to establish the diagnosis, a case of chronic fatigue syndrome must fulfill major criteria 1 and 2 and the following minor criteria: six or more of the 11-symptom criteria and two or more of the three physical criteria, or eight or more of the 11-symptom criteria.

Major Criteria

I. A new onset of persistent or relapsing fatigue not previously present, sufficient to reduce daily activity by 50% or more, lasting at least 6 weeks
II. Exclusion, by appropriate means, of other conditions that could produce similar symptoms, including malignancy, autoimmune disease, infection, chronic psychiatric illness, chronic inflammatory disease, neuromuscular disease, endocrine disease, drug dependency or abuse, side effects of a medication or toxic substance, and chronic disease

Minor Criteria

I. Mild fever (37.5°C to 38.6°C) or chills
II. Sore throat
III. Painful cervical or axillary lymph nodes
IV. Unexplained generalized muscle weakness
V. Muscle discomfort or myalgia
VI. Prolonged (24-hour or more) generalized fatigue after previously tolerated exercise
VII. Generalized headaches unlike previous cephalalgia
VIII. Migratory arthralgia without joint swelling or redness
IX. Neuropsychiatric complaints, such as photophobia, scotomata, forgetfulness, irritability, confusion, inability to concentrate, difficulty in thinking, or depression
X. Sleep disturbance (hypersomnia or insomnia)
XI. Onset of the main symptom complex in hours or a few days

Physical Criteria

These must be documented by a physician on at least two occasions, at least 1 month apart.

I. Low-grade fever (see Minor Criteria)
II. Nonexudative pharyngitis.
III. Palpable or tender anterior or posterior cervical or axillary nodes (<2 cm in diameter).

The differential diagnosis includes the conditions in Table 1-1. Conventional laboratory tests listed in the Diagnostic Workup usually are normal.

Fever of Unknown Origin

H. Harold Friedman

Definition

Fever of unknown origin (FUO) is defined as continuous fever of at least 3 weeks' duration with daily temperature elevation above 101°F (38°C) and remaining undiagnosed after 1 week of intensive study in the hospital, or as temperature greater than 100.5°F persisting for at least 3 weeks in patients in whom the history, physical examination, blood count, urinalysis, and chest films fail to indicate the diagnosis (Sheon and Van Ommen). Regardless of which of these criteria is employed, the diagnostic approach to FUO must be individualized for each patient. No hard-and-fast rules can be set, because each patient with cryptic fever presents a unique problem in diagnosis. The

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requirement of fever of 3 weeks' duration for the diagnosis of FUO is most important because it eliminates from consideration most viral and bacterial infections as well as other self-limited diseases associated with fever.

Etiology

Most patients with FUO do not have rare diseases but usually suffer from common disorders that are difficult to diagnose because they present atypically. Most patients with FUO reveal that infections and neoplasm are the predominant causes. Connective tissue and autoimmune disorders, granulomatous disorders, and miscellaneous conditions are somewhat less frequent. In approximately 5% to 10% of cases, the cause is unknown. Table 1-2 lists most of the disease entities reported in the literature.

Table 1-2. Causes of fever of unknown origin

Disease category	Petersdorf and Beeson (100 patients, 1952–1957)	Howard et al. (100 patients, 1969–1976)	Larson et al. (105 patients, 1970–1980)
Infections	36	37	32
Tuberculosis	11	3	5
Abdominal abscess	4	9	8
Hepatobiliary	7	7	4
Endocarditis	5	9	0
Urinary tract	3	4	3
Cytomegalovirus	0	0	4
Osteomyelitis	0	0	2
Brucellosis	1	1	0
Others	5	4	6
Malignancies	19	31	33
Lymphoma	6	20	11
Leukemia	2	3	5
Solid tumors	9	8	6
Others	2	0	11
Collagen vascular and autoimmune disorders	13	13	8
Still's disease	2	1	4
Systemic vasculitis	0	5	1
Lupus erythematosus	5	3	0
Rheumatic fever	6	0	1
Others	0	4	2
Granulomatous disorders	6	7	9
Crohn's disease	0	4	2
Sarcoidosis	2	0	2
Giant cell arteritis	2	3	1
Miscellaneous	19	7	10
Factitious fever	3	0	3
Periodic fever	5	0	0
Pulmonary emboli	3	0	1
Hematoma	0	0	3
Drug fever	0	2	0
Others	8	5	3
Undiagnosed	7	5	13

From Petersdorf RG, Beeson PB. Fever of unexplained origin: report of 100 cases. Medicine (Balt) 1961;40:1; Howard P, et al. Fever of unknown origin: a prospective study of 100 patients. Tex Med 1977;73:56; Larson EB, Featherstone HJ, Petersdorf RB. Fever of undetermined origin: diagnosis and follow-up of 105 cases, 1970–1980. Medicine (Balt) 1982;61:269, with permission.

Diagnostic Clues

The type of fever curve (e.g., intermittent, remittent, or continuous), is of little or no help in the diagnosis of FUO.

Infections

I. *Tuberculosis* is the most common infectious disease responsible for FUO. It may be disseminated without radiologic evidence of pulmonary involvement, and the tuberculin test may be negative. Funduscopic examination may provide the first suggestion of this disease if choroid tubercles are demonstrable. However, the diagnosis is usually made by smear and culture of gastric aspirates or by demonstrating tubercles in biopsies of the liver, lymph nodes, bone marrow, or pericardium. Sometimes only a therapeutic trial with antituberculotic drugs can establish the correct diagnosis.

II. *Infective endocarditis* may manifest itself initially as FUO, particularly if the patient has received antibiotics in the early stages of the disease. *Atrial myxoma* may mimic endocarditis because it can occur with fever, a heart murmur, and embolic phenomena. Angiocardiography and echocardiography help distinguish between the two.

III. *Urinary tract infections* rarely cause FUO unless associated with intrarenal or perinephric abscess or obstructive uropathy. Rare organisms causing FUO are diagnosed primarily by blood cultures.

IV. *Liver abscess and subphrenic abscess* initially may appear as FUO without localized findings. Radioisotope scanning of the liver, CT scans, and ultrasonography are useful, safe procedures in diagnosing these entities. Arteriography also may be helpful in some situations.

V. *Miscellaneous causes* of FUO, in addition to bacterial infections, include some fungal pathogens, parasitic diseases, and such viral infections as infectious mononucleosis, anicteric hepatitis, and acquired immunodeficiency syndrome (AIDS).

Neoplasms

Most patients with cancer have fever at some time during the course of their illness. The fever may be related to concomitant infection, localized obstruction by the tumor, surgery and postoperative complications, or the neoplasm itself. The diagnosis is most often established by biopsy of the bone marrow, liver, lymph nodes, or tumor masses. Neoplasms that are most frequently associated with fever are Hodgkin's disease, non-Hodgkin's lymphomas, leukemia and preleukemia, hepatoma, and hypernephroma. Carcinoma of the stomach, colon, pancreas, breast, and hepatic metastases are examples of other malignancies that may cause fever.

Connective Tissue Diseases

It is not unusual for rheumatic fever, SLE, rheumatoid arthritis (particularly the juvenile variety), and polymyalgia rheumatica (temporal arteritis, giant cell arteritis) to present as FUO. On the other hand, scleroderma, dermatomyositis, and polyarteritis nodosa rarely appear in this manner. The clinical history, physical findings, and laboratory tests are more important than biopsy in establishing the diagnosis of connective tissue disease. One exception is temporal artery biopsy, which may establish the diagnosis of polymyalgia rheumatica.

Miscellaneous Causes

I. Drugs are an important cause of FUO. A careful inquiry must be made in every case of FUO to determine whether the patient is taking any medications, because elimination of the offending agent may solve the problem and eliminate the need for extensive workup.

II. Multiple pulmonary emboli may cause FUO. Lung scans and pulmonary angiography usually can establish the diagnosis.

III. Regional enteritis, granulomatous disease of the colon, and ulcerative colitis may occur as FUO in the absence of abdominal complaints.

IV. Patients who have altered immune responses because of disease (e.g., Hodgkin's disease, multiple myeloma) or chemotherapy frequently have fever owing to infection with organisms unlikely to be found in immunologically competent individuals.

Diagnostic Approach

I. Check the *history*.
   A. If other members of the family have been or are affected by a similar illness, exposure to a common etiologic agent may be involved or the disease may have a hereditary basis (e.g., familial Mediterranean fever).
   B. A past history of episodic illnesses over a period of years involving multiple organ systems suggests the possibility of connective tissue disease.
   C. The occupation of the patient may provide a clue to the cause of FUO. For example, a veterinarian, butcher, or one engaged in animal husbandry may suffer from a disease of animal origin.
   D. Inquiry about travel abroad is important because knowledge of the geographic locale where the patient has been may lead to a search for illnesses endemic to that area rather than those commonly found in the United States. For example, among U.S. military personnel in Vietnam, the causes of FUO included dengue, malaria, chikungunya, scrub typhus, and enteric diseases.
   E. A history of rodent bite during the 10 weeks before the onset of fever should suggest the possibility of rat bite fever.

II. Rule out *habitual hyperthermia*. This usually occurs in young, psychoneurotic women, and is characterized by afternoon temperatures between 100°F (37.7°C) and 100.5°F (38°C), vague complaints, vasomotor instability, and a normal sedimentation rate. Removal of the patient from her stressful life situation or the administration of tranquilizers, or both, will result in the disappearance of the fever.

III. Rule out *factitious fever* (malingering). Clues to the diagnosis are a history of medical or paramedical training, complicated and inconsistent histories, absence of weight loss, the failure of the temperature curve to follow the normal diurnal cycle, excessively high temperatures (106°F/31.4°C or 107°F/41.6°C, which is rare in adults), normal pulse and respiratory rates at the time of fever, and rapid defervescence unaccompanied by diaphoresis. If malingering is suspected, all temperatures should be taken by a nurse with a carefully checked thermometer, and the patient should be carefully observed throughout the procedure.

IV. Perform careful and repeated complete *physical examinations*.
   A. Pay particular attention to the eyes, because ocular manifestations of systemic disease may provide the first clue to the diagnosis of obscure fever. An ophthalmologist may be of great help in interpreting ocular findings.
   B. Examine carefully for lymphadenopathy, particularly in the area about the clavicles.
   C. Hepatosplenomegaly occurs more frequently in neoplastic than in infectious diseases, and especially in the lymphomas.
   D. Listen for bruits, which may provide evidence for malignant vascular tumors.
   E. Check for sternal and bony tenderness, which may suggest myeloproliferative disease or metastatic tumor.
   F. Check the navel, because intraabdominal neoplasms may metastasize early to the navel, where the presence is readily detected by palpation. Moreover, such metastases are easily biopsied under local anesthesia.
   G. Examine the skin for nodules that also may represent the earliest manifestation of metastatic malignancy.
   H. Rectal examination and proctosigmoidoscopy are indicated in all patients with FUO.

V. When there are symptoms or signs other than chills, fever, malaise, or weight loss (e.g., lethargy, disorientation, meningismus, rash, dyspnea, cough, cardiac murmurs, jaundice, visceromegaly, lymphadenopathy, dysuria or hematuria, arthritis or other joint manifestations, abdominal pain, nausea, vomiting, diarrhea), the initial investigation should be directed at those organ systems most likely to be the source of the FUO.

   Depending on circumstances, perform most or all of the following laboratory tests. It may be necessary to carry out these tests serially. Surgical procedures,

with the exception of easily performed biopsies, should be considered only after routine studies have failed to reveal the sources of FUO.

A. Routine laboratory tests
   1. CBC
   2. Sedimentation rate
   3. Urinalysis, and urine culture and sensitivity studies
   4. Stools for ova, parasites, occult blood, culture, and sensitivity studies
   5. Blood cultures: Take at least three sets of paired cultures from different sites. All specimens should be cultured aerobically and anaerobically and retained for several weeks.
   6. Blood smears for malaria parasites, if exposure to this disease within the previous year is possible
B. Serologic tests
   1. Febrile agglutinins (rarely of help)
   2. ASO and antistreptozyme titers to help in the diagnosis of rheumatic fever
   3. Rheumatoid factor
   4. ANA titer
   5. Mono test, heterophil agglutination, and Epstein–Barr antibody titer
   6. CEA
   7. Cytomegalovirus titer
   8. HIV antibody test
C. Blood chemistries
   1. Biochemical screening and thyroid function tests
   2. Serum protein electrophoresis and immunoglobulins
D. Miscellaneous tests
   1. Bone marrow core biopsy (not aspiration alone) and culture
   2. Gastric aspirate for acid-fast smear and culture
E. Skin tests: tuberculin, histoplasmin, coccidioidin, and possibly others, depending on circumstances
F. Radiographic procedures
   1. Chest films
   2. IVP
   3. Barium enema and upper GI series, including small bowel study
   4. Bone films to detect infection or neoplastic disease
   5. Computerized tomography (CT) for suspected intraabdominal or retroperitoneal disease
G. Ultrasonography, also for suspected intraabdominal and retroperitoneal lesions
H. Radioisotope scanning procedures
   1. Lung scan to detect pulmonary embolism
   2. Liver scan to detect hepatic lesions
   3. Bone scan to detect neoplastic disease
   4. Gallium scan to detect occult infection
I. Tissue examination
   1. Biopsy of lymph nodes or readily accessible tumor masses
   2. Needle biopsy of the liver, which often reveals the diagnosis if there is hepatic involvement
   3. Biopsy of the skin and skeletal muscle in suspected connective tissue disease. (Usually this procedure is not very helpful.)
   4. Biopsy of the temporal artery in suspected polymyalgia rheumatica, which may establish the diagnosis
J. Angiographic studies
   1. Lymphangiography to detect lymphomas
   2. Celiac aortography to detect hepatic, renal, and pancreatic tumors
   3. Angiocardiography to detect atrial myxoma
   4. Pulmonary angiography to detect pulmonary embolism
K. Surgical procedures
   1. Peritoneoscopy may be useful in detecting tuberculous peritonitis, peritoneal carcinomatosis, cholecystitis, and pelvic inflammatory disease
   2. Exploratory laparotomy should not be performed in FUO unless all noninvasive techniques have been exhausted and only if the clinical picture, roentgenographic studies, or laboratory findings point to the abdomen as the source of the fever.
   3. Bronchoscopy, bronchial brushing, culture, cytologic studies, and transbronchial biopsy should be carried out, and rarely, exploratory thoracotomy in the presence of unidentified pulmonary disease.
L. Therapeutic trials should be employed only as a last resort and only if they are reasonably specific. Shotgun mixtures of antibiotics, steroids, and other drugs are to be condemned because they usually solve nothing, confuse the clinical picture, and may be hazardous. Examples of more or less specific therapeutic trials include antituberculotic drugs for suspected tuberculosis; aspirin for rheumatic fever; heparin and anticoagulant therapy for pulmonary emboli; steroids for polymyalgia rheumatica, rheumatoid arthritis, or SLE; and penicillin and streptomycin for suspected bacterial endocarditis.

Unexplained Weight Loss

Harvey B. Karsh

Weight loss is often an early manifestation of many acute or chronic illnesses. It may occur in a broad spectrum of conditions, including endocrine or metabolic diseases, drug intoxication, neoplastic processes, and psychiatric disorders.

History

Special attention should be focused on the following:

I. Documentation that weight loss has actually occurred
II. An increased or decreased appetite
III. The composition of the diet and eating habits of the patient
IV. The presence of any gastrointestinal symptoms, regardless of how vague they might be
VI. A complete social and psychiatric history, in order to elicit sources of anxiety, fear, depression, or special situational problems

Weight Loss with Increased Appetite

Weight loss in spite of an increased appetite suggests the possibility of diabetes or hyperthyroidism.

Conditions Associated with Accelerated Metabolism and Weight Loss

I. Neoplasms. Unexplained weight loss in middle-aged or elderly persons should suggest the possibility of occult malignancy. Neoplasms produce weight loss by increasing the metabolic processes of the host even in the absence of complicating anatomic, endocrine, or metabolic abnormalities.
II. Fever. Infections, neoplasms, cerebrovascular accidents, and metabolic disorders may be accompanied by fever. Because the basal metabolic rate increases by 7% with each degree of temperature rise, fever by itself can cause weight loss. Moreover, the anorexia, dehydration, and increased protein catabolism that commonly accompany any febrile illness may also contribute to the weight loss. Fever of unknown origin is discussed in the preceding section.
III. Congestive heart failure
IV. Chronic infections
V. Excessive physical activity
VI. Periods of rapid growth

Conditions Primarily Associated with Anorexia or Decreased Food Intake

Psychogenic Disorders

I. Anxiety and depression are among the most common causes of weight loss. The importance of psychological and emotional problems as causes of weight loss should

not be underestimated. Depression, anxiety, hysteria, or serious psychosis may cause an unnoticed but nevertheless significant decrease in food intake. Correct diagnosis requires a thorough psychiatric and social history.

II. Anorexia nervosa
   A. *Definition.* Anorexia nervosa is a psychogenic disorder characterized by loss of appetite and refusal to eat. It occurs predominantly in young women between 11 and 35 years of age.
   B. Signs and symptoms
      1. Weight loss occurs, varying from 10% to 50% of the premorbid weight.
      2. Spontaneous or deliberate vomiting is a common occurrence.
      3. Overactivity is usual and is out of proportion to the degree of cachexia.
      4. Diarrhea may result from laxative abuse.
      5. The patient may sleep poorly but awaken refreshed (unlike the depressed individual, who is always tired).
      6. Acrocyanosis is often observed.
      7. Pubic and axillary hair growth is normal.
      8. Bradycardia and hypotension occur commonly.
      9. Because of malnutrition, gonadal function is diminished. Decreased urinary estrogens, absence of cornified cells on vaginal smears, and low urinary gonadotropins are common findings. Urinary 17-ketosteroids also may be decreased. The plasma cortisol levels are normal, however, a finding that helps to differentiate anorexia nervosa from panhypopituitarism. Thyroid function is normal.

Dietary Causes

With few exceptions, malnutrition is rare in the United States, but the possibility of nutritional deficiencies should be considered in drug addicts, alcoholics, poor people, elderly people (particularly those living alone), and food faddists. Physicians, in the treatment of certain diseases by special diets, may sometimes inadvertently prescribe nutritionally deficient diets and thereby initiate or perpetuate weight loss.

Affections of the Mouth and Pharynx

I. Mechanical. Ill-fitting dentures or a lack of dentures may so interfere with mastication that the quantity and quality of the food eaten is substandard.
II. Neurologic lesions. Neurologic disorders that affect the ability to taste, chew, or swallow food can result in an insufficient caloric intake and weight loss. Included in this group of diseases are such conditions as muscular dystrophy, strokes, amyotrophic lateral sclerosis, brainstem lesions, and syringomyelia.
III. Painful oral lesions
   A. Nutritional diseases, including vitamin deficiencies
   B. Painful lesions of the oropharynx owing to connective tissue disease or other diseases
   C. Candidiasis, which is often associated with the use of antibiotics
   D. Gingivitis owing to diphenylhydantoin or other drugs
   E. Heavy metal intoxication

Drug Effects

Drugs may cause weight loss as a byproduct of their actions. Drug dependence (e.g., narcotic or alcohol addiction) is a common cause of weight loss. Drugs may induce anorexia (e.g., digitalis), nausea, and vomiting by a direct effect on the gastrointestinal mucosa. Laxative abuse may result in malassimilation of necessary nutrients. Finally, some drugs may produce nutritional deficiencies, which in turn can cause anorexia, decreased food intake, and weight loss.

Anorexia and Weight Loss as Symptoms

Anorexia and weight loss may be early or prominent symptoms in the following disorders:

I. Infectious diseases (e.g., tuberculosis, endocarditis)
II. Metabolic disorders
   A. Hypopituitarism
   B. Hyperthyroidism
   C. Addison's disease
   D. Hyperparathyroidism
III. Blood dyscrasias
   A. Pernicious and other anemias
IV. Renal disease
V. Liver disease
   A. Acute hepatitis
   B. Chronic hepatitis and cirrhosis
VI. Malabsorptive states (Chapter 5, Diarrhea)
VII. Malignancy
   A. Carcinoma of the esophagus
   B. Carcinoma of the pancreas
   C. Carcinoma of the colon
   D. Lymphoma and leukemia
VIII. AIDS
IX. Chronic pain syndromes

Diagnostic Approach

I. It is manifestly impossible to investigate every possible cause of unexplained weight loss. Clues to the diagnostic approach should be sought in the history and physical examination.
II. When no obvious cause for weight loss can be discovered and when psychogenic disorders can be excluded, the initial workup should include, as a minimum, the following tests:
   A. CBC
   B. Sedimentation rate
   C. Urinalysis
   D. Biochemical screening, serum electrolytes, TSH, and HIV
   E. Fasting blood glucose
   F. Stools for occult blood, ova, and parasites
   G. Chest films
III. If the initial studies are unrevealing, further investigation is warranted in any patient who continues to lose weight without an adequate explanation. Consideration should be given to at least some of the following tests or procedures:
   A. Skin tests (tuberculin, histoplasmin)
   B. Serologic tests (syphilis, RA, LE, and ANA)
   C. Serum protein electrophoresis and immunoglobulins
   D. X-ray studies (appropriate CT, MRI, and ultrasonography studies)
   E. Tests to rule out endocrinopathies (e.g., Addison's disease, hypopituitarism)
   F. Tissue biopsy (bone marrow, liver, skin, and muscle)
   G. Radioisotope scanning procedures
   H. Angiographic studies
   I. Computerized tomography and ultrasonography when considered appropriate
   J. HIV serology, if indicated
IV. Unexplained weight loss is often multifactorial in elderly persons. Socioeconomic factors (e.g., loneliness and isolation), may lead to poor eating habits and malnutrition. Dementia, delirium, depression, drug reactions, and the presence of chronic diseases may be important etiologic factors. The normal aging process is manifested by periodic weight loss of 5 to 10 pounds. Often this causes great apprehension but may be part of the normal aging process.
V. Patients with unexplained weight loss should be kept under observation until systemic illness can be excluded. If the weight loss is owing to physical causes, other symptoms and signs almost invariably develop over a period of time. As these occur, additional diagnostic studies should be undertaken.

Anxiety States

David H. Rubinstein

Definition

Anxiety is a subjective feeling of apprehension, uneasiness, tension, or terror in response to danger. Anxiety should be distinguished from *fear,* which is an emotional reaction to a bona fide threatening situation. *Nervousness* and *worry* are terms commonly used by patients to describe anxiety.

Phobic disorders are characterized by the avoidance of certain situations that precipitate the symptoms of anxiety. There is a secondary constriction of normal life's activities that limit the individual's ability to function.

Anxiety neurosis is a chronic illness characterized by recurrent episodes of acute anxiety, often described as panic attacks.

Generalized anxiety disorder refers to persistent anxiety, worry, fears, ruminations, and anticipation of misfortune that has been continuous rather than intermittent.

Etiology

Anxiety is probably the most common complaint encountered in practice. Similarly, anxiety neurosis is the most common neurotic syndrome seen clinically. Both anxiety and anxiety neurosis may accompany or be associated with almost any illness.

An anxiety state may be a component of other, sometimes more serious disorders, such as those listed in the following:

I. Psychiatric disorders (e.g., schizophrenia, depressive illness)
II. Disease of the CNS (e.g., postconcussion syndrome, vascular disease, degenerative disorders, seizures)
III. Endocrine and metabolic disorders (e.g., hyperthyroidism and hypothyroidism, hyperparathyroidism and hypoparathyroidism, hyperadrenocorticism, hypoglycemia, pheochromocytoma)
IV. Drug effects (e.g., sympathomimetic agents, corticosteroids, alcohol)
V. Drug withdrawal syndromes (e.g., alcohol, barbiturates)
VI. Miscellaneous conditions
   A. Menopause
   B. Mitral valve prolapse (click-murmur syndrome)
   C. Porphyria

Clinical Features

Anxiety

I. Subjective symptoms of apprehension, worry, difficulty in concentration, insomnia, irritability, "nervousness," and panicky feelings
II. Somatic complaints such as giddiness, shakiness, restlessness, trembling, fatigability, cold clammy hands, dry mouth, dizziness, lightheadedness, tingling in hands or feet, frequent urination, nausea, stomach upset, diarrhea, symptoms of the hyperventilation syndrome, palpitations, tightness in the chest, chest pain, and muscle aches

Phobic Disorders

I. Agoraphobia is the most common phobic disorder found in women. Agoraphobic individuals avoid being alone in public places, particularly supermarkets, public highways, tunnels, and bridges, or other situations where they must be confined or have to wait. They often fear that they will lose control or will die. As a result, they may become housebound.
II. Episodes of panic may accompany phobic disorders.

Characteristics of Anxiety Disorders

I. Studies indicate that 10% to 20% of patients treated by general practitioners suffer primarily from symptoms related to functional anxiety. Anxiety disorders affect women twice as frequently as men. The onset is usually during adolescence or early adult life. It seldom begins after the age of 35. Chronically anxious individuals in older age groups frequently experience an exacerbation of symptoms as they become physically incapacitated and helpless.
II. Anxiety has a persistent and fluctuating course. Ten percent to 12% of patients recover spontaneously. Fifteen percent deteriorate and experience substantial disability as a result of their symptoms, and the remainder are evenly divided between those who are symptomatic with mild disability, and those who are symptomatic without disability. Individuals who medicate themselves with alcohol or other substances clearly fare more poorly.
III. Unhappiness, depression, and demoralization are common in patients who experience anxiety. Anxiety is a debilitating symptom that causes one to feel that one is not in control of one's life and severely limits life's forward progression.
IV. Episodes of acute anxiety typically have an abrupt onset. There is a sense of foreboding, fear, and apprehension; a sensation of panic; and often a feeling of being seriously ill or that one's life is threatened. Some patients experience feelings of depersonalization. Symptoms such as labored breathing, smothering, palpitation, blurred vision, tremulousness, and weakness frequently accompany the apprehension and foreboding. The hyperventilation syndrome with tachypnea, breathlessness, circumoral paresthesias, numbness and tingling of the fingers and toes, and even carpopedal spasm is a common feature. Objective signs of distress such as tachycardia, sweating, tachypnea, tremor, hyperactive deep tendon reflexes, and dilated pupils may be seen. The frequency of attacks and their severity vary considerably from one patient to another. Episodes of anxiety usually terminate spontaneously.
V. Although most patients commonly have cardiorespiratory complaints, others suffer from the manifestations of a functional bowel syndrome. In fact, anxiety neurosis is the psychiatric disorder most commonly associated with this syndrome. However, functional enterocolonopathies may occur during the course of other psychiatric illnesses, such as hysteria or depression.
VI. Complications are seen far less frequently than in other psychiatric disorders. Judgment is not impaired. Suicide is a rare occurrence.

Diagnostic Approach

I. The diagnosis of anxiety or anxiety neurosis can usually be established from the patient's history. The symptomatology is usually characteristic. Drug use and abuse should be excluded as possible causes of anxiety states. It is also important to be certain that anxiety is not a component of a more serious medical or psychiatric disorder and to be aware that it may coexist with such conditions.
II. A complete physical and neurologic examination is warranted to provide clues to the possible presence of CNS disease, endocrine disorders, cardiovascular disease, or other ailments.
III. The mental status should be evaluated in all patients with anxiety, to confirm the presence or absence of an underlying psychiatric disorder.
IV. In addition to the physical, neurologic, and mental examinations, some diagnostic workup is probably indicated, if only to reassure patients that their symptomatology is not organic in origin. The procedures chosen depend on circumstances and, to some extent, on the symptomatology. Some or all of the following tests may be justified:
   A. CBC
   B. Urinalysis
   C. Biochemical screening
   D. Thyroid function tests when thyroid dysfunction merits consideration
   E. A 5-hour glucose tolerance test, if the symptoms suggest hypoglycemia
   F. Urinary vanillylmandelic acid (VMA) determination to screen for pheochromocytoma in hypertensive patients with paroxysms of headaches, blurred vision, sweating, trembling, and pallor
   G. Chest films, an electrocardiogram, and possibly a treadmill study in suspected cardiac disease, especially when chest pain is a predominant symptom. Holter monitoring may be useful in determining whether or not palpitation is owing to cardiac arrhythmia.
   H. GI workup in patients with gastrointestinal somatization

Depression and Mania

David H. Rubinstein

Definition

Depression is "exaggerated sadness coupled with pessimism." Pessimism is the essential feature that distinguishes depression from the ordinary "blues" or feelings of dejection that everyone experiences from time to time. Depression varies greatly in intensity, from mild dejection to profound despair, but characteristically involves a degree of sadness or pessimism, or both, that is out of keeping with life circumstances. Not all depression involves sadness or a "blue feeling." The hallmark of depression ranges from lack of enthusiasm to hatred of one's life and existence.

Grief, unlike depression, is a reaction to a real loss. The most significant loss that humans can sustain is the death of a spouse, close relative, or friend. Normal acute grief lasts 4 to 6 weeks and involves marked sadness, crying spells, preoccupation with the deceased (including feelings of anger and guilt), and a reduced interest in external affairs. The entire process usually occurs over a period of months. Delayed grief may occur months or years after the loss, sometimes on the anniversary of the death or loss.

Mania is characterized by an elevated, expansive, or irritable mood associated with hyperactivity, over involvement in activities, diminished need for sleep, pressured speech, and a flight of ideas. An exaggerated sense of well being is usually present.

Classification

There is still no agreed-on method of classifying affective (mood) disorders. In the past, depressions were classified as endogenous or exogenous (reactive) depending on whether a precipitant could be identified. Another classification system distinguished neurotic depression, which was mild with no evidence of loss of reality testing, from psychotic depression, which was severe and included a depressed mood and signs and symptoms of depression, as well as loss of reality testing (e.g., hallucinations or delusions). Distinguishing between neurotic and psychotic depressive reactions, however, was often difficult. In yet another dichotomy, agitated depression referred to disorders characterized by a great increase in movement, restlessness, and anxiety, whereas retarded depressions were characterized by a decrease in psychomotor activity, as well as a great deal of lethargy and hypersomnia. The following classification system has been found to be clinically useful:

I. A *major affective disorder* is a disorder of mood, found in individuals who have not had other psychiatric disorders, in which depression or mania is the predominant problem.
   A. *Bipolar disorder—mixed type* has a tendency to recur, and there may be alterations in mood from depressive to manic or repeated episodes of mania. This is also referred to as the circular cyclothymic type of manic-depressive illness. The first manic episode of bipolar illness is likely to start before the age of 30. The first depressive episode may start at any age. Bipolar illness is more likely to occur in females and is likely to be familial. There is also a high incidence of alcoholism associated with bipolar illness. Those patients who are manic or have mania are classified as bipolar.
   B. *Bipolar disorder—manic* type and *bipolar disorder—depressed type* are disorders limited to a single or repeated episodes of mania or depression. Unipolar depressive illness may occur for the first time in the postpartum period. Depression that occurs for the first time in middle age or later is often referred to as involutional depression. Involutional melancholia refers to a specific entity that occurs in the elderly and is characterized by agitation, anxiety, delusional thinking of a dramatic nature (e.g., "I'm rotting"), obsessional concern with past misdeeds, and occasional delusions of a paranoid nature.
II. A *secondary affective disorder* is a disorder of mood that occurs in patients with a preexisting psychiatric illness other than depression or mania (e.g., the depression encountered in schizophrenia).

Clinical Features of Depression

Depression is a clinical syndrome. The diagnosis should be suspected when patients exhibit the following:

I. A persistent mood of sadness, apathy, irritability, or general loss of interest, enthusiasm, and pleasure in usual activities
II. Feelings of unworthiness, hopelessness, guilt, suicidal thoughts, and problems with memory and concentration
III. Physiologic or vegetative disturbances (e.g., anorexia, weight loss, sleep disturbances, fatigue, psychomotor retardation, emotional withdrawal and blunting)
   Depression may simulate, precede, accompany, or follow physical illness. Most depressed medical and surgical patients suffer from neurotic or reactive depressions. The incidence of depression is high in gastrointestinal disorders, such as functional bowel syndrome, colitis, regional enteritis, hepatitis, cirrhosis, pancreatitis, and carcinoma of the pancreas. Depression is common in obesity, especially following weight-reduction programs. Depression is particularly common in myocardial infarction and following cardiac surgery. Clinical depression may occur in any CNS disease but most commonly in subdural hematoma, frontal lobe tumor, and chronic neuralgic illness, such as multiple sclerosis or Parkinsonism. It frequently accompanies Alzheimer's and Pick's disease. Depressive symptoms may simulate or coexist with metabolic or endocrine disorders. Diseases in this group include hypothyroidism, adrenal insufficiency, Cushing's syndrome, acromegaly, hyperparathyroidism, hyponatremia, hypocalcemia, and hypomagnesemia. Chronic drug abuse (e.g., barbiturates, opiates, bromides, tranquilizers) may produce depression. Prescribed drugs, such as reserpine, methyldopa, propranolol, L-dopa, steroids, and digitalis, also can cause depression. Systemic diseases associated with depression include connective tissue disease, lymphomas, rheumatoid arthritis, carcinoma of the lung, and disseminated carcinomatosis. Depression occurs with alcoholism and withdrawal or cessation of cocaine usage. Use or misuse of opiates or cessation result in a depressive state.
IV. Cognitive changes, problems with memory and concentration, cognitive slowing

Subjective Symptoms

I. Apathy, lack of energy, tiredness
II. Feeling sad or blue occurs only in 50% of depressions
III. Loss of interest in work and family
IV. Crying spells
V. Sleep disturbances, such as difficulty in falling asleep, early morning waking, and sometimes hypersomnia or spending many hours in bed with difficulty facing the day's activities
VI. Appetite disturbances (anorexia, hyperphagia)
VII. Weight loss, weight gain
VIII. Constipation
IX. Diurnal variations in mood, typically worse in the morning with improvements as the day goes on
X. Decreased sexual interest
XI. Loss of ability to enjoy things, loss of sense of humor

Objective Findings

I. Sadness, tearfulness, irritability, flattening or constriction of emotional range
II. Expressions of hopelessness, helplessness, guilt, self-reproach, and shame
III. Psychomotor retardation
IV. Inattention to personal hygiene, emotional withdrawal or blunting
V. Difficulty in thinking and concentration; problems with memory, including decreased retention or recall of past events; decreased attention span, ability to concentrate
VI. Auditory hallucinations sometimes present
VII. Delusions sometimes present, such as somatic or nihilistic delusions or delusions of sin and punishment, worthlessness, and poverty or persecution.

VIII. Suicidal intent or ideation; expressed wish to be dead or fear of dying, wish for things to be over and to escape from life
IX. Preoccupation with or exaggerating physical problems and illnesses

Clinical Features of Mania

Subjective Symptoms

I. Marked optimism; inappropriate enthusiasm or altruism, or both
II. Feelings of unmitigated power, energy, hypersexuality
III. Feeling "entitled," or angry, and resentful toward those who try to set limits or oppose them
IV. Reduced need for sleep

Objective Findings

I. Euphoria or expansive mood
II. Irritability, rage, sudden severe marital problems
III. Pressured speech with rapid shifting of ideas
IV. Markedly social behavior often accompanied by inappropriate interactions with others, particularly in a person for whom this represents a significant change
V. Poor judgment and impulsive behavior in business matters. Engaging in spending sprees, impulsive financial decisions.
VI. Sexual promiscuity
VII. Delusions of grandeur or special powers; religious preoccupations
VIII. Reduced need for sleep. Reporting having been up several nights.
IX. Marked irritability, anger, and refusal to acknowledge that the behavior has changed or is abnormal
X. Impulsive traveling long distances

Mania may be associated with organic disease or drug-induced problems. Neurologic disease (e.g., multiple sclerosis) or endocrine disorders may mimic a manic episode. Amphetamines, methylphenidate, and scopolamine may also cause reactions that mimic mania.

Diagnostic Approach

I. The history taking and physical examination are directed at establishing the criteria for the diagnosis of depression and mania (e.g., disordered mood, cognitive changes, and physiologic disturbances, as outlined earlier in this section).
II. History. Inquiry should be made concerning the following:
   A. Past or present medical and psychiatric illness
   B. Current medications, including over-the-counter and illicit drugs that may be responsible for a depressed or euphoric state
   C. Alcoholism and drug abuse. Many patients resort to alcohol or drugs for relief from depression or mania. The risk of suicide is high among alcohol users.
   D. A family history of depression, nervous breakdown, highs, euphoria, and hyperactivity. The last three are associated with bipolar affective illness, which has been shown to have a genetic basis.
   E. A history of losses—death, divorce, separations from parents, children, siblings, lovers
III. Physical examination is directed at a search for the stigmata of depression and mania and at detecting the presence or absence of organic disease. A careful neurologic examination and an evaluation of the mental status should be performed.
IV. Workup. The major purposes of the diagnostic workup are to exclude organic illness as a cause of depression or mania and to determine the existence of organic disease that depression or mania may simulate, precede, accompany, or follow. The following guideline is suggested:
   A. CBC
   B. Urinalysis
   C. Biochemical screening
   D. Serum electrolytes when indicated
   E. Thyroid function tests should always be performed.
   F. Chest films
   G. Electrocardiogram
   H. GI workup when gastrointestinal symptoms need evaluation
V. Depression should also be considered a diagnostic possibility under the following circumstances:
   A. Symptoms and signs that remain unexplained in spite of a complete workup
   B. Symptoms and signs that do not respond to conventional treatment
   C. Multitudinous complaints involving many organ systems for which no obvious cause is demonstrable
   D. Unexplained chronic fatigue and lack of energy
   E. Excessive weight loss or gain
   F. Chronic alcoholism and drug abuse
   G. Decline in sexual interest and performance
VI. In the evaluation of any depressed patient, it is important to determine to what extent the depression has impaired the patient's ability to cope with his or her environment. The degree to which interpersonal relationships are altered should also be assessed. The physician should inquire directly of any depressed patient about suicide and assess the risk. Many factors are associated with an increased risk of suicide: lethal plan, old age, male sex, isolation, and lack of personal resources. Psychiatric consultation and usually hospitalization are warranted in potentially suicidal individuals.
VII. Once depression is diagnosed and classified, appropriate treatment should be initiated.

Acquired Immunodeficiency Syndrome

Steven R. Mostow and Wheaton J. Williams

Definition

The Centers for Disease Control (CDC) formerly defined acquired immunodeficiency syndrome (AIDS) as an illness characterized by one or more opportunistic diseases, diagnosed by reliable methods that are at least moderately indicative of underlying cellular immunodeficiency and absence of all known underlying causes of cellular immunodeficiency (other than infection with the virus[es] presumed to cause AIDS) as well as the absence of all other causes of reduced resistance reported to be associated with at least one of those opportunistic diseases.

AIDS is a condition of severe impairment in cell-mediated immunity owing to human immunodeficiency virus (HIV) infection, which predisposes patients to opportunistic infections and malignancies. In 1993, the CDC revised the case definition for AIDS to include any HIV-infected person with a CD4 cell count less than 200 mm^3 regardless of symptoms (Table 1.3).

The modes of transmission of HIV infection include sexual transmission, maternal–fetal transmission, injection drug use, and transfusion of HIV-contaminated blood or blood products. Globally, sexual transmission of HIV predominates. In developing countries, most cases of HIV infection are owing to heterosexual transmission. In western Europe and North America, homosexual transmission of HIV has been most common, but increasing numbers of cases of HIV infection are owing to heterosexual transmission and injection drug use. Rarely, health care workers acquire HIV infection through occupational exposure to blood or other bodily fluids.

HIV infection is a chronic viral infection, which causes progressive impairment of cell-mediated immunity. Without effective antiretroviral therapy, the majority of HIV-infected persons will develop AIDS several years after the initial infection. The rate of progression of HIV infection is related to the level of HIV RNA in plasma (the viral load). Combination antiretroviral therapy can suppress HIV replication to undetectable levels in plasma, and maintain or improve immune function in HIV-infected patients.

Clinical Features of AIDS

The number of asymptomatic HIV-infected individuals far exceeds the number of persons with AIDS. The clinical course of HIV infection and AIDS has changed dramatically

Table 1-3. Conditions included in the 1993 AIDS surveillance case definition

Candidiasis of bronchi, trachea, or lungs
Candidiasis, esophageal
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV-related
Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (greater than 1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
Pneumocystis carinii pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome due to HIV

since the availability of potent antiretroviral therapy, with striking reductions in the rates of hospitalizations, opportunistic infections, and death. Despite the availability of effective antiretroviral therapy, AIDS-defining illnesses continue to occur in HIV-infected persons who are not receiving or are not responding to antiretroviral therapy. Some of the more common clinical syndromes are outlined in the following:

I. *Constitutional symptoms.* Fatigue, night sweats, weight loss, intermittent diarrhea, and fever are relatively common complaints in patients with advanced HIV infection. It is important to exclude a specific cause for these symptoms before attributing them to HIV infection.

II. *Oral disease.* Oral abnormalities are extremely common in patients with AIDS, including oral candidiasis, oral hairy leukoplakia, oral ulcers, severe gingivitis and periodontitis, and Kaposi's sarcoma. Careful inspection of the oropharynx and routine dental care are important components of routine medical care for patients with AIDS.

III. *Cutaneous manifestations.* Skin disorders are also extremely common and include viral infections (herpes simplex, varicella zoster, molluscum contagiosum), bacterial infections (folliculitis, impetigo, bacillary angiomatosis), fungal infections (dermatophytosis, disseminated fungal infections), Kaposi's sarcoma, seborrheic dermatitis, eosinophilic folliculitis, and xerosis.

IV. *Hematologic disorders.* Leukopenia and lymphopenia occur commonly. Anemia also occurs frequently, and is usually owing to chronic HIV infection or the myelosuppressive effects of drug therapy. Less often, anemia is owing to opportunistic infection, blood loss, or decreased production of erythropoietin. HIV-related thrombocytopenia appears to be owing to both decreased platelet production by megakaryocytes, and increased platelet clearance. Treatment options for the thrombocytopenia include steroids, intravenous immunoglobulins, anti-rhesus antibodies, and splenectomy.

V. *Gastrointestinal disorders. Esophageal diseases* include *Candida* esophagitis, and esophageal ulcers owing to cytomegalovirus (CMV) or herpes simplex virus (HSV). Idiopathic esophageal ulcers can also occur. Evaluation of esophageal symptoms with esophagogastroduodenoscopy (EGD) is most useful, because the procedure allows for direct visualization of the esophagus with biopsy of any abnormalities. *Gastritis* owing to CMV or HSV can occur. Enterocolitis is a common problem, and is often owing to common pathogens such as *Salmonella, Campylobacter, Clostridium difficile,* or *Giardia lamblia,* but may be the result of opportunistic infection with organisms such as *Mycobacterium avium* complex (MAC), CMV, or *Cryptosporidium.* The evaluation of diarrhea in patients with AIDS includes collection of stool for ova and parasite examination, bacterial culture, and *C. difficile* toxin assay. Endoscopic evaluation with biopsy should be performed if patients have persistent symptoms and negative evaluation of stool samples. Proctitis owing to gonorrhea, chlamydia, HSV, or syphilis can occur in sexually active patients. Kaposi's sarcoma (KS) and lymphoma are *HIV-related tumors* that can occur within the gastrointestinal tract. *Bowel perforation* in AIDS patients is most often owing to CMV infection involving the distal small bowel or colon, but has also been associated with *Histoplasma capsulatum, C. difficile,* lymphoma, and KS.

VI. *Hepatobiliary and pancreatic disorders. Liver disease* is common in AIDS patients, usually due to drug toxicity or coinfection with hepatitis B or hepatitis C virus. Infection of the biliary tract with CMV, cryptosporidia, or microsporidia has been associated with the development of papillary stenosis or sclerosing cholangitis, bile duct disorders referred to as *HIV-associated cholangiopathy.* Patients with HIV-associated cholangiopathy may complain of fever and 1 RUQ abdominal pain. Acute *acalculous cholecystitis* is another cause of biliary tract disease in AIDS patients, and has been attributed to infection with CMV, cryptosporidia or Isospora belli. Pancreatitis in AIDS patients is generally caused by toxicity from alcohol or medications such as didanosine (ddI), zalcitabine (ddC), or pentamidine.

VII. *Pulmonary disorders.* Pulmonary infections occur frequently in patients with AIDS. *Pneumocystis carinii* pneumonia (PCP) and bacterial pneumonia are the most common etiologies of pneumonia, but infection with a variety of other organisms can occur, including *Mycobacterium* tuberculosis, atypical mycobacteria, *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis,* and CMV. Noninfectious causes of pulmonary disease include KS, lymphoma, and pulmonary embolism. The clinical presentation and radiographic appearance of pulmonary infiltrates cannot reliably determine the etiology of the pulmonary disease, so diagnostic tests need to be performed. Examination of induced sputum is often helpful for confirming the diagnosis of PCP, bacterial pneumonia, or mycobacterial infection. Occasionally, more invasive tests are necessary, such as bronchoscopy with bronchoalveolar lavage and/or transbronchial biopsy, or open lung biopsy.

VIII. *Renal disorders.* HIV-associated nephropathy is a condition characterized by massive proteinuria and rapidly progressive renal failure. Hypertension is uncommon. The typical histopathology is focal and segmental glomerulosclerosis. Acute renal failure in AIDS is usually owing to acute tubular necrosis (ATN) as a result of hypovolemia, drug toxicity, or radiocontrast agents.

IX. *Neurologic disorders. Focal intracranial lesions* are usually owing to *Toxoplasma gondii,* progressive multifocal leukoencephalopathy (JC virus), or primary CNS lymphoma. Uncommon causes of CNS mass lesions include *M. tuberculosis, C. neoformans, Nocardia asteroides,* and HSV. *Other CNS infections* include cryptococcal meningitis, syphilis, CMV, herpes zoster, coccidioidomycosis, and histoplasmosis. *HIV dementia* can result in cognitive dysfunction, behavioral changes such as social withdrawal, and organic psychosis. *Peripheral neuropathy* occurs frequently in AIDS, usually in the form of distal symmetric polyneuropathy (DSP). DSP has been associated with advanced immunosuppression as well as the toxic effects of medications such as didanosine, stavudine, and zalcitabine.

X. *Musculoskeletal disorders.* Rheumatologic manifestations of HIV infection include Reiter's syndrome, reactive arthritis, septic arthritis, polymyositis, zidovudine-related myositis, pyomyositis, and, rarely, vasculitis.

Laboratory Diagnosis

The laboratory diagnosis of HIV infection depends on the ability to detect HIV in blood or tissue by culture, polymerase chain reaction (PCR), or antigen detection. Alternatively, the diagnosis can be confirmed by detecting the presence of HIV-specific antibodies in serum.

I. *Enzyme-linked immunosorbent assay (ELISA).* The ELISA screening test detects antibody to HIV I and HIV 2. It is very sensitive (97%) and specific (99%). A positive test requires confirmation with Western blot assay.
II. *Western blot.* The Western blot is a very reliable confirmatory test that detects antibody to specific viral proteins. The test is reported as positive, negative, or indeterminate. Patients with indeterminate results are rarely infected with HIV I or HIV 2.
III. *PCR.* The PCR test detects specific DNA of HIV I and HIV 2 in both blood and tissue. Highly sensitive and specific, PCR detects virus in patients who have not made antibody.
IV. *Plasma HIV RNA* levels (viral load). Quantitative reverse transcriptase PCR (RT-PCR) accurately measures the number of copies of HIV RNA/mL plasma. Viral load assays are able to detect between 20 and 1,000,000 copies of HIV RNA/mL. Higher viral loads correlate with more rapid loss of CD4 cells and more rapid progression to AIDS. Viral load measurements are useful for making decisions regarding initiation of antiretroviral therapy, and following the response to antiretroviral therapy. Currently, the goal of antiretroviral therapy is to suppress HIV viral replication below the limit of detection.

Antiretroviral Therapy

Highly active antiretroviral therapy has proven clinical benefit in patients with advanced HIV infection including significant reductions in the rates of hospitalization, opportunistic infection, and mortality. Unfortunately, currently available antiretroviral therapy regimens are complex, are associated with numerous potential side effects and drug interactions, and may be difficult for patient adherence. Also, the field of antiretroviral therapy is rapidly evolving. For these reasons, patients with HIV infection or AIDS should receive treatment from health care providers experienced in the management of HIV infection.

The "Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents" are frequently updated by an expert panel convened by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation, and reflect the current state of knowledge of antiretroviral therapy. Table 1-4 summarizes the current indications for initiating antiretroviral therapy, and Table 1-5 summarizes the current recommendations for antiretroviral therapy of established HIV infection.

Table 1-4. Indications for the initiation of antiretroviral therapy in the chronically HIV-infected patient

Clinical category	CD4+ T-cell count and HIV RNA	Recommendation
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	CD4' T cells = 500/mm" OR HIV RNA = 20,000 (RT-PCR)	Treatment should be offered
Asymptomatic	CD4+ cells = 500/mm OR HIV RNA = 20,000	Many experts would delay therapy and observe; however, some experts would treat

Table 1-5. Recommended antiretroviral agents for treatment of established HIV infection

Preferred	Strong evidence of clinical benefit and/or sustained suppression of plasma viral load. One choice from column A and column B. Drugs are listed in random, not priority, order:	
	Column A	*Column B*
	Indinavir	ZDV + ddl
	Nelfinavir	d4T + ddl
	Ritonavir	ZDV + ddC
	Saquinavir-SGC	ZDV + 3TC
	Ritonavir + Saquinavir SGC or HGC	d4T + 3TC
	Efavirenz	ddl + 3TC
Alternative	Less likely to provide sustained virus suppression or data inadequate	
	Nevirapine or delavirdine + 2 NRTIs (column B, above), Abacavir + ZDV + 3TC	
Not generally recommended	Strong evidence of clinical benefit but initial virus suppression is not sustained in most patients	
	2 NRTIs (column B, above)	
	Saquinavir-HGC + 2 NRTIs (column B, above)	
Not recommended	Evidence against use, virologically undesirable, or overlapping toxicities	
	All monotherapies	
	d4T + ZDV	
	ddC + ddl	
	ddC + d4T	
	ddC + 3TC	

Sleep Disorders

Paul M. Cox, Jr. and George E. Bokinsky

Definition

Disorders of sleep can be grouped into four broad categories: (a) dyssomnias, a group of disorders that interfere with either the initiation or maintenance of sleep or produce excessive sleepiness; (b) circadian rhythm disorders, which reflect alterations in the daily sleep-wake cycle (e.g., secondary to jet lag or shift work); (c) parasomnias, which are disorders of arousal, partial arousal, and transition of sleep stages that intrude into otherwise normal sleep; and (d) sleep disorders associated with either medical or psychiatric illness.

Sleep-related disorders are common in Western society. A thorough review of questions concerning sleep should include the amount of quality of nocturnal sleep, whether nocturnal sleep is fragmented, and whether the patient experiences excessive daytime sleepiness. A history of snoring should be sought in patients complaining of poor sleep quality and excessive daytime sleepiness, because obstructive sleep apnea syndrome is likely to be present. Parasomnias usually do not present as the major complaint of sleep disorders; they are often diagnosed by the chief complaint and are not further considered here. Similarly, abnormal sleep–wake cycles usually are recognized by the individual and rarely are an etiologic problem presenting to the doctor. Occasionally, they present as either insomnia or excessive sleepiness. This section, then, considers excessive sleepiness and inadequate sleep, but other forms of disordered sleep must occasionally be considered.

Excessive Sleepiness

Etiology

Excessive daytime sleepiness may be caused by the sleep apnea syndromes, narcolepsy, and frequently by insufficient nocturnal sleep.

History

I. Patients with *sleep apnea syndrome* frequently complain of excessive daytime sleepiness and nonrestorative nocturnal sleep. As with normal sleepiness, excessive daytime sleepiness may be apparent in sedentary situations, such as reading or watching television, but may also occur during important tasks, such as operating a motor vehicle. Patients may not recognize their disordered breathing at night, but the spouses may complain of excessively loud snoring, often sufficient to cause them to sleep in a separate room. Excessive daytime sleepiness is the result of sleep deprivation and fragmentation at night. Disturbances of memory and vision and personality changes are frequent complaints. Falling asleep during important activities, such as driving or working, is also common in this condition. Nocturia and pharyngeal discomfort in the morning are frequent complaints expressed by sleep apnea patients, who are often middle-aged men with obesity and systemic hypertension. Alcohol intake frequently worsens symptoms. Lengthening night sleep seldom improves the symptoms of sleep apnea and, in fact, frequently makes matters worse.

II. Similarly, *narcolepsy* presents as excessive sleepiness. Periods of daytime sleep are usually brief. These patients characteristically have cataplexy, which is a sudden onset of muscle weakness brought on by excitement or emotion, most commonly laughter. Some patients may undergo complete paralysis of the upper extremity muscles, but momentary attacks lasting less than a minute and causing the patient to drop something are more common. Most patients develop sleepiness several months before their first episode of cataplexy. The third classic symptom is sleep paralysis (the inability to move during the onset of sleep) lasting up to 10 minutes. Hypnagogic hallucinations (hallucinatory experiences at the time of onset of sleep or awakening) occur in 60% of patients and are considered the fourth element in the classic tetrad.

III. *Insufficient sleep.* The amount of sleep needed to restore one's health is variable, and many people chronically live with what would be an inadequate amount of sleep in other people. Students, medical officers, individuals holding two jobs, and parents of infants are frequently and chronically sleep deprived and may complain of excessive daytime sleepiness. A careful sleep history should make this diagnosis obvious.

Physical Examination

I. *Obstructive sleep apnea.* Patients are often obese, and hypertension is present in over half of the patients. Twenty percent to 30% of patients with essential hypertension may have sleep apnea. The relationship of hypertension to sleep apnea is a current subject of investigation. Structural abnormalities of the upper airway are usually present to the careful examiner. Nasal pharyngeal obstruction, a relatively reduced caliber of the oropharyngeal airway, and structural abnormalities, such as micrognathia or tonsillar hypertrophy, may be seen. The uvula and soft palate may be unusually prominent and show evidence of chronic irritation. In patients with severe obstructive sleep apnea, signs of cor pulmonale may occasionally be seen, including distended neck veins, right ventricular lift and gallop, hepatomegaly, and peripheral edema.

II. Patients with narcolepsy and those suffering from insufficient sleep have a normal examination.

Roentgenographic Findings

Patients with obstructive sleep apnea may demonstrate narrowing of the upper airway on examination of soft tissue of the head and neck. Cephalometric studies may help to quantify the degree of obstruction.

Laboratory Data

I. CBC. The minority of patients with sleep apnea may have erythrocytosis.

II. Arterial blood gases. The usual arterial blood gas in obstructive sleep apnea syndrome is normal. Chronic hypoventilation (i.e., increased partial pressure of P_{CO_2} with low normal pH) may be seen in severe obstructive sleep apnea syndrome. The combination of hypoxemia with chronic hypoventilation in these patients generally indicates the presence of pulmonary hypertension.

III. Electrocardiogram. Patients with cor pulmonale may show the characteristic findings of right ventricular hypertrophy and right-axis deviation.

IV. Urinalysis is usually normal, but some patients with obstructive sleep apnea of severe degree, particularly with cor pulmonale, may have pathological degrees of proteinuria.

V. Other procedures. Patients with suspected sleep apnea syndrome should undergo formal overnight testing in an accredited laboratory. EEG, ECG, oxygen saturation, respiratory effort, and air flow should be continuously monitored. The prevalence and length of apneas should be recorded as well as degree of hypoxemia and cardiac dysrhythmias. It is important to look for evidence of transient arousals associated with changes in breathing patterns; even those not associated with desaturation. Duration and frequency of time in various stages of sleep should be recorded. Patients with suspected cataplexy should undergo the multiple sleep latency test. This test is performed during the day, and the patient is asked to try to sleep at 2-hour intervals, while onset of sleep latency and types of sleep are measured.

The HLA types HLA-DR2 and HLA-DQwl are present in an overwhelming majority of patients with narcolepsy

2. DERMATOLOGIC PROBLEMS

Pruritus

Kenneth H. Neldner

Itching is the most common uncomfortable sensation we experience in our skin—far more common than pain and frequently more distressing and more difficult to control.

Itch and pain sensations are believed to be transmitted by the same C fibers originating as free nerve nets at the dermal–epidermal junction and surrounding hair follicles. Through basically unknown physicochemical mechanisms, minimal stimulation of these fibers is thought to cause pruritus, whereas more intense stimulation of the same fibers causes pain. This long-held belief lacks full credibility because experimental electrical stimulation of the skin sufficient to induce pain does not gradually turn to itch as the stimulus is slowly reduced, suggesting that the skin may hold distinctive subsets of itch and pain receptors and transmitters.

The sensation of itch may be elicited by a wide variety of dermatologic disorders and infections or by external stimuli, such as changes in temperature, stroking, or exposure to noxious agents. Itching may also be one manifestation of a systemic disease. Most systemic and cutaneous (delayed-type hypersensitivity) allergic reactions cause pruritus and often present a challenging diagnostic problem.

At a molecular level, histamine is the best known chemical mediator of pruritus, although other chemical substances, such as papain, trypsin, serotonin, bradykinin, kallidin, and substance P are known chemical mediators of itch—but by unknown mechanisms. In its broadest sense, pruritus may be viewed as a uniform response to a wide variety of physical or chemical stimuli.

Etiology

The patient presenting with a significant complaint of itching should be viewed initially as falling into one of four broad categories: (a) itching associated with a visible skin rash; (b) itching secondary to an internal disorder and without a visible rash; (c) psychosomatic pruritus; and (d) neurologic and circulatory disturbances.

Itching Associated with a Visible Cutaneous Eruption

A complete discussion of itching skin rashes encompasses essentially the entire field of dermatology, because virtually any skin lesion may itch. This is beyond the purpose and scope of this text. Therefore, only the major categories and types of dermatoses that most commonly produce itching are summarized in Table 2-1.

The rapidly increasing incidence of AIDS has introduced a new spectrum of pruritic dermatologic disorders in which many of the common skin diseases present as an exaggerated and often grotesque replica of the more easily recognized disorder in non-AIDS patients. This occurs particularly when the CD4 lymphocyte count falls below 200 cells/mm^3. Two conditions that have received particular attention are seborrheic dermatitis with severe pruritus, covering large areas of the face, scalp, and chest, and eosinophilic folliculitis, which produces extremely pruritic, erythematous follicular papules on the chest. These two conditions are highly suggestive of AIDS until proved otherwise.

One of the most common and vexing causes for itching in infants and children is atopic eczema, which is most commonly seen in families in which asthma and hay fever are also present. The pruritus may be generalized and severe with secondary bacterial infection from scratching.

Itching Secondary to an Internal Disorder and without a Visible Skin Rash

Itching without an associated skin rash is more difficult to evaluate. First, it must be determined whether the patient has genuine pruritus or symptoms that are neurologic

Table 2-1. The most common itching dermatologic disorders

I. Papulosquamous skin diseases
  A. Eczema (atopic, nummular, dyshidrotic)
  B. Lichen planus
  C. Seborrheic dermatitis
  D. Psoriasis
  E. Pityriasis rosea
II. Vesicobullous diseases
  A. Dermatitis herpetiformis
  B. Erythema multiforme
III. Allergic reactions
  A. Contact dermatitis
  B. Systemic drug eruptions
  C. Urticaria
  D. Photoallergy
IV. Infestations
  A. Bites (lice, fleas, scabies, bedbugs, mosquitoes, chiggers)
  B. Nematodes (creeping eruption, onchocerciasis)
V. Infection
  A. Bacterial (impetigo, folliculitis)
  B. Viral (exanthem, herpes simplex, varicella, AIDS)
  C. Fungal (tinea capitis, tinea corporis, tinea pedis, *Candida*)
VI. Environmental causes
  A. Wool, fiberglass, pollen, dust
  B. Miliaria (prickly heat)
  C. Sunburn
VII. Miscellaneous conditions
  A. Purpura simplex
  B. Phototoxic reactions
  C. Urticaria pigmentosa
  D. Ichthyosis
  E. Juvenile rheumatoid arthritis
  F. Primary cutaneous amyloidosis
  G. Pruritus ani
  H. Pruritus vulvae

or psychosomatic in nature. A careful history and physical examination usually establish the presence of any existing neurologic defect. Psychosomatic problems are more difficult to assess. The major categories of internal disorders associated with itching are summarized in Table 2-2.

One of the most common causes of itching in the patient without a rash is simple dryness of the skin, followed in order of frequency by obstructive biliary disease and lymphoma, particularly Hodgkin's disease. Diagnostic workup, therefore, should concentrate initially on these areas and then proceed to less common possibilities, as the situation dictates.

I. Increasing *dryness* of the skin with age is common and may be considered a normal physiologic consequence of aging. It varies in severity from person to person and is generally aggravated in the winter, especially in geographic areas where prolonged heating decreases the humidity in the living and sleeping quarters. Dry skin pruritus is also called *senile pruritus, pruritus hiemalis, asteatosis,* or *xerosis.*
II. Pruritus associated with *liver disease* nearly always implies the presence of an obstructive condition, because pruritus seldom occurs in jaundice secondary to hemolytic anemia and only rarely in infectious hepatitis. The constituent of bile responsible for itching has not been identified with certainty, but it generally has been accepted that elevated serum, skin, and skin surface bile acids are responsible for the pruritus of cholestasis (intrahepatic obstruction). However, recent studies have shown equally elevated serum and skin bile acid levels in patients with cholestasis who do not have pruritus. Liver function tests also correlate poorly with the presence of pruritus. The cause of pruritus in cholestasis, therefore, remains unknown. The clinical effectiveness of methyltestosterone, which relieves pruritus while often causing a rise in serum bile acids and worsening of cholestasis, tends to confirm the negative role of bile acids as causative agents for pruritus. Similarly, the effectiveness of cholestyramine or external biliary drainage in controlling pruritus indicates that some pruritogenic substance other than bile acids is being removed. Intrahepatic obstruction may be induced by medications such as chlorpromazine, testosterone, and erythromycin estolate.
III. *Uremia* is a more common cause for itching in chronic renal diseases than in renal disorders producing acute nephropathy. The slow development of uremia generally correlates better with pruritus than do absolute levels of azotemia, although at least 75% of patients have pruritus when blood urea nitrogen (BUN) levels reach 100 mg/dL. The unrelenting itch of hemodialysis at times may become so severe as to be disabling. Topical capsaicin, a substance known to deplete substance P in peripheral sensory neurons, has been helpful in controlling the pruritus. This observation has raised the question about a role for substance P in other types of pruritus. Some hemodialysis patients develop prurigo nodularis papules, which they constantly excoriate to the point of bleeding. Treatment with the synthetic vitamin A derivative, etretinate, has helped these individuals, suggesting a currently unknown but possible role for vitamin A in

Table 2-2. The most common internal conditions associated with pruritus

I. Dry skin
II. Metabolic and endocrine causes
  A. Obstructive biliary disease
    1. Extrahepatic
      a. Common duct stones
      b. Common duct stricture
      c. Carcinoma of bile duct or pancreas
    2. Intrahepatic
      a. Biliary cirrhosis
      b. Carcinoma of liver
      c. Drug-induced cholestasis
      d. Viral hepatitis
  B. Uremia (especially dialysis uremic pruritus)
  C. Thyroid disease
  D. Hyperparathyroidism
  E. Diabetes mellitus
  F. Gout
III. Malignancy
  A. Lymphoma (Hodgkin's disease, mycosis fungoides, leukemia)
  B. Carcinoma
  C. Carcinoid
IV. Parasitosis
  A. Hookworm
  B. Pinworm
V. Drug reactions
  A. Opium derivatives
  B. Histamine liberators
  C. Any drug
VI. Miscellaneous causes
  A. Polycythemia vera
  B. Pregnancy

the mediation of pruritic symptoms. Xerosis also is common among patients having hemodialysis, as is secondary hyperparathyroidism, adding to the list of problems that may induce pruritus in the uremic patient.

IV. *Hypothyroidism* is commonly associated with generalized pruritus and is most likely related to the dry skin that characterizes this disease. *Hyperthyroidism* is seldom a cause for itching. When it does occur, it is believed to be related to the temperature changes of increased cutaneous circulation.

V. *Hyperparathyroidism* secondary to renal disease is the most common parathyroid disorder producing pruritus. Relief of itching with return of the elevated serum calcium and phosphorus levels to normal following parathyroidectomy suggests that increased blood and tissue levels of calcium may be the pruritogenic stimuli, but the etiologic factors are not completely clear because not all hypercalcemic disorders are accompanied by pruritus.

VI. *Diabetes mellitus* is a rare cause of itching, despite "common knowledge" to the contrary. The increased susceptibility of diabetics to cutaneous bacterial and yeast infections with secondary pruritus is a more common cause for itching than is the diabetes per se.

VII. *Gout* rarely causes itching. When it does, the itching is presumed to be owing to elevated blood and tissue levels of uric acid.

VIII. Of all the *malignancies* known to induce pruritus, Hodgkin's disease is the most common, and itching may be the first symptom in as many as 25% to 30% of cases. Mycosis fungoides may also be preceded by itching in areas where characteristic skin lesions subsequently develop. Chronic leukemia is less commonly pruritic; itching is somewhat more common in lymphatic leukemia than in the granulocytic types. Carcinoma of any organ may produce itching, but this is most frequently associated with involvement of the stomach, pancreas, bowel, bronchi, esophagus, ovaries, and prostate gland. The carcinoid syndrome is characterized by flushing of the skin, but pruritus is rare.

IX. Intestinal *parasitosis* with hookworm *(Ancylostoma duodenale* or *Necator americanus)* may produce generalized pruritus. The constitutional phase of the disease is preceded by evanescent skin lesions ("ground itch"), usually on the feet, at the sites where the *Ancylostoma* larvae penetrate the skin. Pinworm *(Enterobius vermicularis)* infestation is a common cause of pruritus ani, especially in children.

X. Virtually any ingested drug or chemical may cause an allergic pruritus, with or without a visible skin rash. The etiology of a low-grade chronic pruritus secondary to a subclinical drug eruption may be difficult to diagnose, particularly in elderly patients who commonly take 10 or more medications each day. The drug addict is another difficult category in that the history of using such pruritogenic drugs as opium, heroin, or cocaine may be difficult to elicit.

XI. Mild, generalized pruritus is a frequent complaint during *pregnancy* and, in some patients, is very severe and distressing. Approximately 65% of pregnant women have mild to moderate elevations in serum bilirubin level (0.75 to 3.0 mg/100 mL) during the last trimester, with a rapid return to normal after parturition. The degree of itching generally parallels the serum bilirubin level. If the pruritus does not disappear in the immediate postpartum period, underlying liver disease should be suspected.

XII. *Polycythemia vera* frequently is associated with itching. Here, the itching is unique in that it is markedly aggravated after a hot bath. Polycythemia vera is often accompanied by iron deficiency anemia. Correction of the iron deficiency relieves pruritus; however, iron deficiency by itself is seldom a cause for pruritus. The combination of generalized pruritus and low serum ferritin (with normal hemoglobin values) should raise suspicions of occult carcinoma, particularly in men.

XIII. Prodromal itching of the anterior neck and upper trunk may precede an attack of childhood asthma at times (in about 40% of cases). Recognition of this symptom allows institution of therapy that is able to abort the attack in some cases.

XIV. Aquagenic pruritus is an unusual but definite condition in which wetting the skin with water at any temperature causes itching. It normally occurs after a shower or tub bath and lasts about 1 hour. Sudden changes in air temperature may also trigger an attack. The disorder responds poorly to antihistamines. About one-third of the affected individuals have a family history for the condition.

Psychosomatic Pruritus

I. Patients suffering with neurotic excoriations (factitial dermatitis) have multiple, dug-out, superficial or deep ulcerations of the skin and complain of severe, intractable pruritus. Most individuals freely admit to deep scratching and relate the intensity of the itching to nervous tension. Some are more evasive and deny that they had anything to do with the obviously self-induced lesions; situations of this type generally indicate a more severe underlying neurosis.

II. Psychotic states. The usual complaint is that "bugs" or parasites are crawling in the skin, producing intense pruritus. *Delusions of parasitosis* and *acarophobia* are the terms applied to this condition. Deep, self-inflicted excoriations and ulcerations are the rule. This is one of the most intractable and incurable forms of pruritus. The patient readily reports that "bugs" are in his skin and adamantly refuses to accept any evidence or explanation to the contrary. Psychiatric treatment has been disappointing.

Neurologic and Circulatory Disturbances

I. Any neurologic disease with manifestations of cutaneous paresthesias, hypoesthesia, or hyperesthesia may produce sensations in these areas that the patient interprets as pruritus. Neurologic examination quickly establishes the presence or absence of such a neurologic defect in most instances. Neurologic disease of this type is actually a rare cause of itching. Circulatory disturbances secondary to cardiovascular disease are also uncommon causes for itching. When itching is present, the lower extremities are most frequently involved, with the pruritus secondary to ischemic changes.

Diagnostic Approach

I. Patients with obvious skin lesions should be clinically and, if necessary, histologically evaluated in order to establish a diagnosis. A trained observer should be able to diagnose most dermatologic disorders with a high degree of accuracy. Patients with urticaria present special problems because of the diverse nature of the possible etiologic factors. Urticaria therefore is considered separately (see the next section).

II. Pruritus without an associated cutaneous reaction presents the most challenging diagnostic problem. The initial history and physical examination should include a specific evaluation for possible low-grade jaundice and generalized dryness of the skin.

III. The diagnostic workup then proceeds according to the results of the history and physical examination. In some instances, the clinical findings alone establish a diagnosis with certainty and no laboratory studies are necessary. At other times, extensive laboratory evaluation is required. The procedures that may be indicated are listed in Table 2-3. This list is neither complete enough to cover all possible exigencies nor is it to be considered a routine workup for each and every case of pruritus of undetermined etiology. Each significant symptom or sign should be evaluated with an appropriate laboratory test, based on the clinical judgment of the examining physician.

IV. Simple therapeutic measures may at times not only aid in diagnosis but also provide immediate relief for the patient. Hydration and lubrication of the skin by daily bathing for 15 to 20 minutes in a tub of tepid water, followed by the immediate application of any moisturizing lotion to the wet skin, will afford marked and lasting relief if the pruritus is related to simple xerosis. The addition of table salt to the water (1 cup in tub of warm water) is often beneficial. Relief obtained by such measures, in conjunction with a normal brief history and physical examination, often precludes further diagnostic workup.

Role of Antihistamines

Even though histamine is the best known mediator of pruritus, therapy with conventional H_1-blocking antihistamines is generally disappointing. Combinations of H_1 and

Table 2-3. Procedures for evaluating pruritus of undetermined etiology

I. Hematologic studies
   A. Complete blood count
   B. Sedimentation rate
   C. Eosinophil count
   D. HIV and CD4 count
II. Gastrointestinal workup
   A. Liver profile
   B. Cholecystography
   C. Serum amylase
   D. Stool for ova and parasites
   E. Liver biopsy
III. Endocrine evaluation
   A. Blood sugar and glucose tolerance tests
   B. Thyroid function studies
   C. Serum calcium and phosphorus
IV. Genitourinary studies
   A. Urinalysis
   B. Blood urea nitrogen
   C. Serum creatinine
   D. Creatinine clearance
   E. Intravenous pyelogram
V. Evaluation for malignancy
   A. Lymph node biopsy
   B. Chest radiograph
   C. Bone marrow biopsy
   D. Upper gastrointestinal examination
   E. Barium enema
   F. Proctosigmoidoscopy
   G. Mammograms
   H. Papanicolaou test
   I. Skull radiograph
   J. Pelvic radiograph
   K. Serum acid phosphatase
VI. Miscellaneous studies
   A. Psychiatric evaluation
   B. Pregnancy test
   C. Blood and urine toxicology

H_2 blockers have been recommended but in general offer little or no enhanced antipruritic effect. In general, the relief of pruritus achieved by any conventional H_1 blocker is in direct proportion to its degree of sedation, which in itself soon becomes an intolerable side effect of therapy. Newer, so-called nonsedating H_1-blocking antihistamines (terfenadine, astemizole, cetirizine) may offer some advantage by permitting much higher doses without the undesirable side effect of sedation.

Urticaria and Angioedema

Alan A. Wanderer

Definition and General Information

Urticaria is characterized by transient erythematous pruritic wheals or papules, which affect the superficial layers of skin. Angioedema is a condition with well-demarcated, nonpitting edema that involves deeper dermal tissues and mucosal membranes. The pruritus that accompanies urticaria is conspicuously absent in angioedema because of the paucity of sensory fibers in the deeper dermal tissues. Vasodilation, vasopermeability, and edema in urticaria and angioedema can develop from similar pathophysiologic mechanisms (e.g., IgE-mediated immune complexes, direct nonimmune mast cell degranulation, complement activation) that cause release or generation of biologic active mediators such as histamine, leukotrienes, kallikrein, and platelet activating factor.

Urticaria and angioedema are arbitrarily defined as acute if the symptoms last less than 6 weeks and chronic if they persist longer than 6 weeks. Both conditions may occur independently or in association with each other. Approximately 20% of the general population experience at least one episode of urticaria or angioedema or both during their lifetime.

Most acute and chronic urticaria with and without angioedema are uncomplicated; however, there are exceptions to this generalization. For example, urticaria or angioedema reactions secondary to hymenoptera stings, cold urticaria, and hereditary angioedema may be complicated by shock symptomatology. In addition, urticaria and angioedema are occasionally associated with serious underlying diseases such as infectious diseases, serum sickness, malignancies, connective tissue disorders, and metabolic disorders.

Etiology

A wide variety of causative factors have been implicated in the induction of urticaria and angioedema. The following briefly characterize important diagnostic considerations.

I. *Drugs.* It is essential that a careful drug history include prescription, nonprescription, and illicit drugs administered around the onset of the symptoms because most medications have been associated with induction of urticaria or angioedema. In addition, drugs taken as long as 1 month prior to the onset of symptoms may induce urticaria with serum sickness disorders. Drugs most commonly associated with urticaria or angioedema include aspirin, antibiotics (e.g., penicillin and its congeners), and opiates. Angioedema can be associated with angiotensin-converting enzyme inhibitors (e.g., ACE-inhibitors).

II. *Foods.* Foods are frequently implicated as causes of acute and chronic urticaria or angioedema. Common offenders of acute urticaria or angioedema are fish, shellfish, nuts, and eggs. The causal relationship between foods and chronic urticaria and angioedema is more difficult to establish because of the vague temporal relationships between food ingestion and chronic symptomatology. Food additives such as metabisulfites, salicylates, and coloring dyes have also been implicated as causes of acute or chronic symptomatology; however, these are rare associations and most reports are anecdotal.

III. *Infection.* There is ample evidence to suggest that viral infections can cause urticaria or angioedema. Urticaria can develop in the prodromal phase of hepatitis B virus infections as a result of immune complex deposition. Epstein–Barr viral infections can induce primary acquired cold urticaria and systemic urticaria. Urticaria has been described with parasitic infestations such as giardiasis, amebiasis, and ascariasis. The association of chronic urticaria with *Candida albicans* or focal bacterial infections (e.g., sinusitis) remains poorly documented.

IV. *Inhalants.* Inhalation of animal danders, pollens, foods, and chemicals can induce urticaria or angioedema. Occasionally seasonal occurrences are observed in pollen-sensitive individuals who may also experience rhinitis, bronchospasm, or both.

V. *Insect stings.* The most common manifestation of hymenoptera stings is urticaria or angioedema, which may be localized or systemic. In general these reactions are mediated through IgE mechanisms. Urticaria or angioedema may also develop following stings or bites of spiders, fire ants, flies, and mosquitoes. Papular urticaria is frequently a manifestation of insect bites.

VI. *Contact urticaria.* Substances that directly contact the skin can occasionally induce urtication. Typical urticaria-inducing contactants include animal dander or saliva, foods, drugs, and direct mediator-releasing substances from insects (e.g., moths, caterpillars) and sea nettles.

VII. *Systemic disease.* Urticaria and angioedema may be manifestations of systemic disorders, such as those that follow:
- A. Connective tissue diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis)
- B. Neoplasms (e.g., lymphoma, leukemias, carcinomas). A rare association of acquired C1-esterase deficiency with lymphoma or carcinoma has been reported.
- C. Endocrine abnormalities (e.g., hyperthyroidism or hypothyroidism, hyperparathyroidism, diabetes mellitus, menopause, premenstrual, pregnancy-related).
- D. Systemic mastocytosis or urticaria pigmentosa
- E. Miscellaneous disorders
  1. Serum sickness (induced by heterologous serum, drugs, infectious illnesses)
  2. Urticarial vasculitis (with and without hypocomplementemia)
- F. Autoimmune etiology. Autoimmune disorders are occasionally associated with chronic urticaria and/or angioedema. Examples include: autoimmune-induced thyroiditis associated with antithyroid microsomal antibodies; systemic lupus erythematosus; and mixed connective tissue disorders. Autoimmunity may underlie chronic idiopathic urticaria. There is evidence of IgG anti-IgE autoantibodies and also IgG autoantibodies to the IgE receptor on the mast cell (i.e., IgG anti-FCεRIα). This mechanism may explain the persistence of chronic urticaria/angioedema despite the absence of IgE sensitizing antigen.

VIII. *Psychogenic.* The role of psychogenic factors as the sole cause of urticaria remains controversial. However, it is generally accepted that psychologic problems can exacerbate chronic urticaria. There is currently no accepted personality profile that is characteristic of patients with urticaria.

IX. *Genetic types.* There are several rare types of urticaria or angioedema that are inherited by autosomal dominant patterns such as hereditary angioedema, vibratory angioedema, and delayed cold urticaria. Other inherited forms of urticaria include Muckle–Wells syndrome (urticaria, deafness, amyloidosis), familial localized delayed heat urticaria, erythropoietic protoporphyria with solar urticaria, and C3b-inactivator deficiency with urticaria.

X. *Physical agents.* This category includes urticaria or angioedema that is induced by physical agents (e.g., thermal stimuli, pressure, vibration, light energy). Physical agents induce approximately 15% of all urticaria and angioedema. The following is an outline of the various entities:
- A. Mechanical
  1. Dermographism (immediate wheal and flare following pressure to skin)
     - a. Primary
     - b. Secondary (secondary to drug reactions, insect stings, chronic mastocytosis)
  2. Delayed dermographism (superficial wheal and flare evolves 4 to 6 hours after stroking skin.)
  3. Delayed pressure urticaria (deep painful swelling occurring 4 to 6 hours after pressure has been applied to a specific location; sometimes associated with constitutional symptoms such as fever, chills, arthralgias)
  4. Hereditary vibratory angioedema (autosomal dominant inherited disorder associated with development of angioedema following vibratory stimuli)
  5. Hereditary angioedema (autosomal dominant inherited swelling that is often triggered by trauma, such as dental manipulation, which can cause swelling of the oropharynx)
- B. Thermal stimuli
  1. Cold temperature
     - a. Acquired cold urticaria (urticaria, angioedema, and occasionally shock immediately after exposure to cold temperature). This can be documented by a positive immediate cold stimulation test (wheal develops immediately after application of 0°C stimulus). Some patients with a positive history of cold urticaria exhibit atypical responses to cold stimulation tests such as negative or delayed reactions. On occasion there are underlying diseases associated with acquired cold urticaria (e.g., cryoglobulinemia, infectious mononucleosis, syphilis, leukocytoclastic vasculitis, cold agglutinins, leukemia, and lymphomas).
     - b. Familial types of cold urticaria (autosomal dominant inheritance)
       - (1) Delayed cold urticaria
       - (2) Familial cold urticaria (actually a misnomer because the rash is maculopapular. Fever, arthralgia, and leukocytosis also develop after cold exposure)
  2. Heat
     - a. Cholinergic urticaria (pruritic papular urticaria with heat, exercise, emotional stress)
     - b. Localized heat urticaria (immediate wheal develops after contact with warm temperature)
     - c. Solar urticaria. Urticaria develops immediately after exposure to sunlight. There are six types, each dependent on the wavelength of light that induces the urticaria. Erythropoietic protoporphyria (type VI) is a genetic abnormality of porphyrin metabolism. Differential diagnosis should exclude lupus erythematosus, photosensitizing agents, and polymorphic light eruptions.

XI. *Miscellaneous factors*
- A. Aquagenic urticaria (urticaria develops after contact with water at body temperature)
- B. Episodic angioedema with eosinophilia and without cardiopulmonary involvement, differentiating it from hypereosinophilic syndrome
- C. Exercise-induced anaphylaxis (pruritus, urticaria, angioedema, and collapse can develop during or immediately following exercise)

XII. *Idiopathic.* Despite the best medical efforts, only 15% to 20% of all chronic urticaria or angioedema can be classified in one of the aforementioned categories.

Diagnostic Approach

History

I. A thorough history is essential and should include pertinent information relevant to diet, drugs taken presently and during the recent past (up to 1 month), environmental exposures, contactants, insect stings, activities such as exercise, relationship to physical agents, infectious illnesses, emotional stress, genetic patterns, and concomitant systemic illnesses. A complete review of systems should be included.

II. The patient should maintain a daily diary of skin lesions with particular emphasis on times of occurrence, food and drugs ingested, and activities.

Physical Examination

I. A complete physical examination should be performed to include evaluation for systemic illnesses such as infectious illnesses (hepatitis, infectious mononucleosis), endocrinopathies (hyperthyroidism, hyperparathyroidism), vasculitis, serum sickness, neoplasms, and connective tissue diseases.

II. A careful examination of skin lesions should be performed to definitively establish a diagnosis of urticaria (wheals of typical urticaria persist less than 24 hours, as compared to urticarial vasculitis in which the wheals persist longer than 24 hours).

Laboratory

I. A routine laboratory profile should include a complete blood count, erythrocyte sedimentation rate, liver function profile, and urinalysis.

II. Specific laboratory tests
- A. Cold urticaria. A cold stimulation test (e.g., ice cube in plastic bag applied to forearm for 5 minutes) typically induces wheal formulation. It is important

to note that some patients may still have cold urticaria, established by history, despite negative cold stimulation tests. Evaluation should include the following tests: cryoglobulins, syphilis serology, infectious mononucleosis panel, and ANA.

B. Other physical agents: dermographism (stroke the skin with a blunt object); solar urticaria (light testing at different wave lengths); cholinergic urticaria (methacholine skin test); heat urticaria (warm water stimulation of forearm); delayed pressure urticaria (this can be detected by placing a weight of approximately 15 pounds on the shoulder for a period of 15 minutes. Swelling that develops 2 to 6 hours after removal of the weight would implicate this diagnostic entity).

C. Infectious illness evaluation. When pertinent, the following tests should be ordered: infectious mononucleosis panel, hepatitis B panel, stool for ova and parasites, miscellaneous (viral cultures, bacterial cultures of throat, blood, urine).

D. Allergy evaluation. When appropriate, skin tests, or radioallergosorbent (RAST) test, or both, might be ordered for foods, inhalants, or insect venoms. In general, drug sensitivities cannot be accurately detected by these techniques except for penicillin skin testing for major and minor antigenic determinants. There are no accurate RAST tests for drug sensitivities, including penicillin.

E. Hereditary angioedema. Autosomal dominant pattern of angioedema (without urticaria), often triggered by trauma such as dental manipulation and occasionally associated with abdominal pain. Laboratory tests include complement levels (second and fourth component, which are low), and C1-esterase inhibitor (quantitative and functional assays).

F. Immunologic evaluation for connective tissue diseases, serum sickness, and urticarial vasculitis. When appropriate the following tests might be ordered: ANA, native DNA binding, rheumatoid factor, immune complex assays (C1q binding, Raji cell), total complement levels, complement components for classic and alternative pathways, and skin biopsy with immunofluorescent staining.

G. Neoplasm evaluation is occasionally indicated. Specific examples include evaluation for leukemia and lymphoma in cold urticaria with cryoglobulinemia, and lymphosarcoma with angioedema may exhibit decreased C1 and C1-esterase inhibitor levels.

H. Autoimmune-induction of chronic urticaria/angioedema requires laboratory confirmation. The copresence of antithyroid microsomal antibodies in euthyroid or hypothyroid states may implicate an autoimmune etiology. An evaluation for an underlying autoimmune mechanism may require panels for antinuclear antibodies and detection of IgG autoantibodies to IgE/IgE receptors. The latter tests are currently not commercially available.

I. A body of scientific evidence is emerging that recommends a punch skin biopsy be performed on patients with difficult to treat chronic idiopathic urticaria. Two groups of chronic urticaria have been defined by skin biopsy results, perivascular lymphocyte predominant urticaria and perivascular polymorphonuclear (i.e., neutrophils, eosinophils) predominant urticaria. Several interesting clinical observations have been associated with each group. Patients with lymphocyte-predominant infiltrates are more responsive to antihistamine therapy. Patients with polymorphonuclear cell-predominant infiltrates are relatively resistant to antihistamines and more likely require oral corticosteroid treatment. In addition, chronic urticaria patients, who have evidence of circulating IgG anti-IgE or IgE receptor autoantibodies, more usually exhibit evidence of perivascular polymorphonuclear cell-predominant infiltrates in skin biopsy results. Hence, the latter histopathology may suggest existence of an unrecognized autoimmune mechanism. The skin biopsy may also detect unsuspected urticarial vasculitis or mastocytosis (e.g., requires metachromatic stains such as Giemsa).

Empiric Procedures

I. Elimination diet as diagnostic tool

II. Challenge procedures. The preferred technique is double-blinded challenges using desiccated foods in capsules. This procedure is not suggested for patients with IgE-mediated food sensitivities who might develop anaphylaxis.

III. Referral to an allergist or dermatologist may be appropriate if patient exhibits chronic symptoms that are refractory to common therapeutic approaches.

3. CARDIOVASCULAR PROBLEMS

Chest Pain

Phillip S. Wolf

Chest pain may have its origin in the heart; the lungs or other organs of the chest; the musculoskeletal structures of the thorax, neck, or shoulders; or the upper abdominal viscera. The history, with particular attention to a detailed description of the pain and any associated symptoms, often provides most if not all of the essential information needed for a correct diagnosis. It is convenient for clinical purposes to classify chest pain into two categories: recurrent, often paroxysmal, pain, which is mild or moderate in intensity, and severe, prolonged pain, which is commonly associated with clinical evidence of acute, serious illness.

Recurrent Chest Pain

Angina pectoris is the most important but not the most frequent cause of recurrent chest pain. Musculoskeletal disorders, as a group, are responsible for more cases of chest pain than any other disease entity. They account for most errors in the diagnosis of angina pectoris, although they may coexist with this condition. By meticulous attention to the history and examination of the chest wall, especially by palpation, it is often possible to resolve the diagnostic difficulties.

Angina Pectoris

Atherosclerotic narrowing of one or more coronary arteries is the most common cause of angina pectoris. Other causes of angina include severe aortic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension, and cardiomyopathy. However, on rare occasions typical angina may occur in the absence of apparent heart disease or demonstrable abnormality of the coronary arteries. Spasm of the coronary arteries currently is considered an established cause of angina both in patients with anatomically normal arteries and underlying atherosclerosis. It is worth stressing that angina is uncommon in men younger than 35 years of age and in premenopausal women unless they have diabetes, hypertension, or hyperlipidemia.

Characteristics of Anginal Pain

I. Anginal pain is "visceral" (poorly localized) and squeezing, oppressive, burning, or heavy in quality.
II. It is of brief duration, usually lasting from 2 to 10 min, only rarely longer or shorter.
III. It is usually moderate in intensity.
IV. The pain is typically retrosternal, but it may occur in other locations. Even then, at least a portion of the pain is commonly beneath the sternum. The pain may be referred to the precordium, neck, lower jaws, shoulders, arms, back, and epigastrium. Radiation to the left shoulder and arm is especially common.
V. The pain is precipitated by effort or emotional stress, or both. It is most likely to occur after meals, on exposure to cold air or wind, and while walking uphill or climbing stairs. The pain often increases with recumbency. A key question to ask is, "Do you get discomfort behind your breastbone if you walk rapidly in cold air?"
VI. Anginal pain usually can be excluded under the following circumstances:
   A. If it can be localized with one finger
   B. If it consistently lasts less than 30 sec or longer than 30 min
   C. If the pain is sticking, jabbing, or throbbing
   D. If it occurs exclusively at rest, with two exceptions: (a) angina preceding myocardial infarction and (b) a variant form of angina, described by Prinzmetal,

that is characterized by pain at rest but not with exertion. Vasospasm of the coronary arteries is now considered to be the leading cause of this syndrome.

E. If the intensity of the pain is consistently severe

Coexistence of Angina with Pain of Different Origin

I. Anginal pain may coexist with chest pain owing to musculoskeletal disease. When this occurs, a history of a second type of chest discomfort, different in character from anginal pain, may be elicited. The finding of tenderness on palpation of the chest wall confirms the musculoskeletal origin of this additional pain.

II. Preexisting disease of the neck, arms, shoulders, thorax, or upper abdomen may so condition the nervous system that if angina pectoris develops subsequently, ischemic pain may erroneously be perceived as arising from these structures. This explanation probably accounts for at least some cases of atypical angina.

III. Some patients with longstanding chronic coronary artery disease, especially after open-heart surgery, may develop chronic burning precordial pain that is associated with tenderness of the anterior thoracic wall. This condition, which has been termed *cardiac causalgia,* is of unknown etiology.

IV. The diagnosis of angina can be established from the history alone in a majority of patients. When doubt exists or diagnosis is difficult, the procedures listed in the following may be helpful.

Diagnostic Approach

I. Physical examination. Examination of the heart seldom provides the information needed for an unequivocal diagnosis of angina pectoris. However, the physical findings listed in the following provide supportive evidence for the diagnosis of angina, especially if they occur during an episode of pain.

A. An audible or palpable fourth heart sound

B. A rise in blood pressure or pulse rate, or both

C. The appearance of the murmur of mitral regurgitation owing to papillary muscle dysfunction

D. A palpable dyskinetic area or bulge at or around the cardiac apex

E. Paradoxical splitting of the second heart sound

F. Relief of pain by carotid sinus massage (the Levine test). The relief of pain appears to be related to slowing of the heart rate produced by carotid sinus pressure. In performing the test, to avoid influencing the patient's interpretation of the result, the physician should ask whether the maneuver has made the pain worse. A reply that the pain was not made worse but was relieved constitutes evidence in favor of the diagnosis of angina.

II. Use of nitroglycerin. Sublingual nitroglycerin relieves anginal pain in 3 minutes or less in a large majority of cases, provided the tablets are potent (capable of inducing headache and flushing or producing a burning sensation under the tongue). Failure of nitroglycerin tablets (especially if taken at 3- to 5-min intervals) to relieve chest pain indicates either that the pain is not anginal or, if it is anginal, that it may represent unstable angina or myocardial infarction. On the other hand, a patient's more after taking nitroglycerin is evidence against, rather than for, the diagnosis of angina.

III. Electrocardiographic changes

A. No electrocardiographic changes are pathognomonic of angina pectoris. In fact, the resting ECG is frequently normal in patients with angina.

B. During anginal attacks, S-T segment depression is the most commonly noted abnormality and is caused by subendocardial injury and ischemia. However, this finding is nonspecific. If coronary artery spasm is present, S-T segment elevation (and, on occasion, increase in the R-wave amplitude) may be noted. S-T depression and T-wave changes have also been observed.

C. Exercise testing increases the accuracy of the electrocardiographic diagnosis if the ECG is recorded both during and after exercise. The presence of at least 1 mm of flat or downsloping S-T segment depression that is 0.08 to 0.12 sec in duration is the major criterion for a positive result. Exercise testing may be performed by climbing stairs, walking a treadmill, or pumping a stationary bicycle.

D. Exercise testing may be misleading in women under the age of 40 years. In this group, the incidence of coronary artery disease is remarkably low, but false-positive S-T segment depression is not uncommon.

E. ECG changes of ischemia are probably much more common without anginal symptoms. "Silent ischemia" can be demonstrated by exercise or ambulatory ECG monitoring.

F. The addition of radionuclide scanning with Thallium-201 or Technetium-99m has enhanced the accuracy of the exercise.

G. Scanning is especially useful when the exercise ECG is difficult to interpret (e.g., left bundle branch block, severe left ventricular hypertrophy, the Wolff–Parkinson–White syndrome), or when symptoms or ECG findings are not diagnostic with routine exercise testing.

IV. Selective coronary angiography. Coronary angiography is currently the most accurate method for diagnosing coronary artery disease during life and for determining its severity. The procedure carries a very low risk. As a general rule, the symptomatology of ischemic heart disease correlates exceedingly well with angiographic evidence of occlusive disease. Three exceptions are worthy of mention.

A. In some individuals, angiography may disclose severe arterial obstruction in the absence of symptoms; thus, the presence of an obstructive lesion does not necessarily mean that it is causally related to chest pain.

B. Spasm of proximal coronary arteries undoubtedly causes angina in some patients, but spasm is not always evident on angiography. Provocative maneuvers to induce spasm, including the intracoronary injection of ergonovine, have proven useful in some cases. In most cases, the absence of arterial narrowing on angiography helps to exclude angina as a cause of chest pain.

C. In some patients, typical anginal symptoms occur with ECG and radionuclide evidence of ischemia but without atherosclerotic narrowing or demonstrable vasospasm. Termed "syndrome X," the entity may represent inability of the coronary microcirculation to dilate with stress.

Musculoskeletal Pain

I. The musculoskeletal structures of the neck, shoulder, and thorax are the most common sources of chest pain.

II. Anterior or posterior chest pain, or both, may result from involvement of the nerve roots of the cervical and upper thoracic spine by osteoarthritis, disc disease, or deformities. The radicular nature of and posterior component to the pain help to differentiate it from angina. The pain tends to occur at night. It may be precipitated by fatigue, incorrect posture, and movement of the involved segments but not movement of the body as a whole. It may also intensify with coughing or sneezing. The discomfort is usually dull and aching in character but is often punctuated by brief sharp twinges of pain. The pain may last for hours at a time. Relief is often obtained through rest, analgesics, postural exercises, and local heat.

III. Costochondral and chondrosternal pain or swelling, or both (Tietze's syndrome), may stimulate angina. The pain is usually well localized, but it may radiate across the chest and over to the arms. Tenderness to palpation over the involved articulations, especially with reproduction of the pain, is the clue to the diagnosis.

IV. Rib pain in young people is usually the result of trauma. Fractures from trauma or hard coughing are easily recognized on examination, but other mechanical causes of rib pain may be subtle. For example, trauma may increase the mobility of the anterior ends of the lower ribs. The pain, which is described as sharp or burning, can be reproduced by local pressure. Rib tumors, when painful, are usually metastatic in origin.

V. Fleeting, jabbing, lancinating, or sticking pains are common in many normal individuals. They are easily differentiated from angina by their brevity and character and by the lack of any relationship to effort or emotional excitement. The cause of these pains is unknown.

VI. The thoracic outlet syndromes (e.g., the scalenus anterior, costoclavicular, hyperabduction, cervical rib syndromes) may cause chest pain. Symptoms depend on whether neural or vascular structures are compressed at the thoracic outlet. Nerve compression is more frequent; pain and paresthesias are the leading symptoms. Demonstrable weakness is infrequent. Vascular compression is quite rare. Signs of venous obstruction with thrombosis may be present. Arm and head movements may reproduce the discomfort and pain. It is often difficult to evaluate the effects of various maneuvers because they may produce signs of neurovascular compression in some normal persons. Decreased ulnar nerve conduction is currently considered the most reliable objective method for demonstrating thoracic outlet compression. Angiography may be indicated in patients with symptoms of vascular obstruction.

VII. Disorders of the shoulder may produce pain that is referred to the chest. Although the pain may increase with effort, careful analysis usually reveals that aggravation of the discomfort is related specifically to shoulder movement and not to body motion. Local tenderness, pain on passive movements, and limitation of motion are commonly present.

VIII. Less common and usually obvious causes of pain in the chest are herpes zoster and superficial phlebitis of the thoracic wall or breast.

Other Causes of Recurrent Chest Pain

I. The chest discomfort of angina may be mimicked by anxiety states. The discomfort may take various forms: (a) intermittent sharp, knifelike pains, (b) persistent precordial aching unrelated to effort, and (c) tight sensations in the chest. Typically, there is no constant relationship between the pain and exertion. The pain tends to appear some time after exertion or is associated with fatigue. The duration of the pain is variable. It may last for seconds, hours, or even days. Sighing respirations and symptoms owing to hyperventilation are commonly associated. A statement that "the pain is coming from my heart" is almost a giveaway for the diagnosis of psychogenic pain.

II. Pain owing to reflux esophagitis, with or without hiatal hernia, may closely simulate anginal pain. The discomfort is substernal and may radiate to the left arm or lower jaw. It may be precipitated by overeating, excessive alcohol intake, or consumption of highly seasoned foods. The pain is often nocturnal and most often triggered by recumbency. The patient may note a sour taste in his or her mouth. In severe cases, bending forward may cause the regurgitation of a mouthful of gastric contents. The pain may be relieved by assuming an upright position and the ingestion of antacids. Reproduction of the pain with an acid infusion, demonstration of reflux by barium swallow, esophageal motility studies, and esophagoscopy with biopsy provide substantiating evidence for this diagnosis.

Diffuse esophageal spasm may occur in the absence of reflux. The pain, often described as a pressure or squeezing sensation, may be quite variable. It may be mild or severe, very brief or quite prolonged. Location is usually retrosternal, and radiation may occur into the jaws, neck, through to the back, or down the arms. Often the pain occurs with meals and may be associated with dysphagia for both liquid and solid foods. Relief in many cases is obtained with nitroglycerin. In several respects, then, the pain of diffuse esophageal spasm may mimic that of angina pectoris. Appropriate esophageal manometric and barium studies may be required for the diagnosis.

III. Pulmonary hypertensive pain may resemble angina in that it is precipitated by effort. The association of moderate or severe dyspnea and evidence of pulmonary hypertension are clues to the diagnosis. The response to nitroglycerin is not as clear-cut as it is in angina pectoris.

IV. An association between chest pain and mitral valve prolapse has been cited, but recent reviews cast doubt on any such link. Chest pain in these patients is thought to be coincidental and not pathologically related.

Prolonged Chest Pain

Patients with severe, protracted chest pain may have serious underlying disease, such as myocardial infarction, dissecting hematoma (aneurysm) of the aorta, pulmonary embolism, and pericarditis; therefore, immediate hospitalization of such patients for diagnosis and therapy is almost always indicated.

Acute Myocardial Infarction

Characteristics of Pain in Myocardial Infarction

I. The pain in acute myocardial infarction is typically crushing, pressing, burning, aching, or viselike in quality. Although it may be mild or moderate in severity, it is more commonly quite severe.

II. If the patient has had angina previously, inquiry often discloses that the frequency and severity of the anginal pain were greater during the period preceding the acute attack.

III. The duration of the pain is variable. It may last from half an hour to several hours or longer.

IV. The pain is typically retrosternal but may be in the precordium or other locations. Radiation of the pain to the anterior thorax, lower jaws, neck, shoulders, and arms is common. There is a tendency for it to be transmitted to the left shoulder and arm.

V. Symptoms of dyspnea, a cold sweat, and "indigestion" commonly accompany the pain.

VI. In some instances, myocardial infarction is painless, but more often there are symptoms that the patient has overlooked or has attributed to "gas" or other nonspecific gastrointestinal complaints.

Physical Findings

I. The patient may appear cold, diaphoretic, pale, cyanotic, and in obvious distress from the pain. Cardiogenic shock may be present in severe cases.

II. Physical signs of myocardial ischemia may be noted (see Angina Pectoris).

III. Signs of congestive heart failure without peripheral edema may be noted on physical examination or in the chest roentgenogram.

IV. An evanescent pericardial friction rub is not an uncommon finding.

V. Disorders of the heartbeat occur in almost all cases. Ventricular premature contractions are the most common type of rhythm disturbance, but all types of arrhythmias, including conduction defects, may be seen.

Diagnostic Approach

I. The diagnosis of acute myocardial infarction is based primarily on objective evidence. Characteristic changes in the ECG and in serum enzyme activity, together with the clinical picture, establish the diagnosis.

II. The electrocardiographic diagnosis of myocardial infarction can be established with certainty in an appropriate clinical setting when abnormality of the initial 0.04 sec of the QRS complex (abnormal Q, QS, or R waves) is combined with characteristic S-T segment changes or typical T-wave abnormalities, or both. Unfortunately, ECG abnormalities that are usually considered diagnostic of myocardial infarction may sometimes occur in conditions such as left or right ventricular hypertrophy, cardiomyopathy, myocarditis, tumor of the heart, obstructive pulmonary emphysema, acute cor pulmonale, ventricular preexcitation, and left anterior fascicular block, and thus may lead to an erroneous diagnosis. It is also important to realize that the ECG may be normal or show only nonspecific abnormalities in myocardial infarction. Serial changes in the ECG may be significant, especially if the initial ECG is normal. It cannot be emphasized too strongly that a normal initial tracing does not necessarily rule out infarction.

III. Sometimes the diagnosis of infarction is obscured altogether, as in left bundle branch block. Echocardiography is useful when the ECG is nondiagnostic. The finding on echocardiogram of a localized contraction defect of the left ventricle is diagnostic of infarction or prolonged ischemia.

IV. Elevated serum levels of enzymes released from necrotic cardiac muscle support the diagnosis of myocardial infarction. The serum creatine phosphokinase (CPK) test is useful in this regard and has rendered other enzyme tests largely obsolete. The CPK level rises during the first 4 to 6 hours after myocardial infarction,

reaches a peak in about 12 hours, and generally returns to normal levels in 36 to 48 hours. The degree of enzyme elevation roughly corresponds to the size of the infarct. Other conditions may elevate the level. These include muscle trauma, intramuscular injections, recent surgery, muscle disease, cerebral infarction, hypothyroidism, and cardioversion. Isoenzymes of CPK are useful in distinguishing between CPK of cardiac and noncardiac origin. The MB fraction is virtually specific for cardiac necrosis and may be detected in the serum within the first 6 hours after the onset of infarction. Recently the serum troponin level has proven to be a valuable marker of acute myocardial infarction. A normal serum level obtained within 4 to 6 hours after pain onset is highly reliable in excluding necrosis. Falsely positive results, however, are not uncommon.

V. Fever, leukocytosis, and an elevated sedimentation rate are nonspecific abnormalities commonly associated with myocardial infarction. However, a persistently normal sedimentation rate suggests that infarction has not occurred.

VI. Acute pericarditis may occur as the presenting feature of acute myocardial infarction. There is a possibility of "silent" infarction causing pericarditis in middle-aged or elderly patients.

VII. Patients with prolonged bouts of anginalike pain unaccompanied by signs of myocardial necrosis are considered to have unstable angina, which may herald the occurrence of myocardial infarction.

VIII. Patients with a myocardial infarction or angina pectoris frequently have a second, coexisting, cause of chest pain arising from the chest wall. Demonstration of marked chest wall tenderness usually suffices for the diagnosis.

Dissecting Hematoma (Aneurysm) of the Aorta

Dissecting hematomas occur most frequently in hypertensive men between 40 and 70 years of age.

Characteristics of Pain in Dissecting Hematoma

I. The pain, which is inordinately severe and often unbearable, is usually described by the patient as having a sharp, tearing, or ripping quality. Large, repeated doses of narcotics are often needed to relieve the pain.

II. The location of the pain correlates with the site of intimal rupture. When the tear is above the aortic valve, the pain is located in the anterior chest; when the rupture is distal to the left subclavian artery, the pain is referred to the back. The pain may radiate along the pathway of aortic dissection.

Physical Findings

Usually the patient appears to be very sick but does not show signs of shock unless rupture through the aortic wall takes place. Dissection of the aorta may spread and occlude major arteries, resulting in characteristic findings.

I. Vertebral occlusion may lead to syncope, coma, hemiplegia, or blindness.

II. Interference with circulation to the arms or legs may cause vascular insufficiency of the involved limb, with loss of arterial pulsations.

III. Renal artery occlusion may cause acute hypertension and oliguria.

IV. Mesenteric artery occlusion may produce infarction of the bowel, with abdominal pain and ileus.

V. Dissection at the base of the aortic root may extend into the aortic ring and cause acute aortic regurgitation.

VI. Coronary artery occlusion, which occurs occasionally, may lead to myocardial infarction.

VII. External rupture of the aorta into the pericardial sac usually results in cardiac tamponade and death. External rupture into other sites, such as mediastinum, peritoneum, or retroperitoneum, may occur, and also may terminate life.

Diagnostic Approach

I. The diagnosis of dissecting hematoma is often suggested by the clinical picture, provided it is considered in the differential diagnosis of severe chest pain.

II. The chest roentgenogram usually reveals widening of the aortic shadow in the mediastinum. Progressive widening of this structure in serial films is strongly suggestive of the diagnosis.

III. Aortography is the most precise method for diagnosing aortic dissection. Under ideal circumstances, the points of entry and exit of the dissection can be seen in the films. The location and extent of the dissection may help in deciding between surgical and pharmacologic management. The initial decision to perform aortography should be postponed until the diagnosis of myocardial infarction has been excluded. As a general rule, no harm is done to the patient with aortic dissection who is treated palliatively, but serious harm can come to the patient with myocardial infarction who undergoes aortography. It is inappropriate, however, to subject the patient to a variety of other diagnostic procedures such as cervical spine films, upper gastrointestinal or gallbladder roentgen studies because undue delay in making the diagnosis of dissection may result in fatality.

IV. Transesophageal echocardiography offers a swift and reliable method for the diagnosis of proximal aortic tears.

V. CT or magnetic resonance (MRI) scanning have also proven of value in detecting dissection.

Pulmonary Embolism

Chest Pain in Pulmonary Embolism

Chest pain is present in the majority of patients with pulmonary embolism. Most often, the pain is pleuritic in nature. Occasionally, severe retrosternal discomfort may occur, simulating the pain of acute myocardial infarction. Dyspnea accompanies the chest pain in most patients with pulmonary embolism. Less frequently associated symptoms are apprehension, cough, and hemoptysis. On examination, the respiratory rate exceeds 16 per minute in nearly all cases of embolism. Audible rales and an accentuated pulmonary closure sound are common. Sinus tachycardia is the usual rhythm.

Diagnostic Approach

I. The diagnosis of pulmonary embolism is usually suggested by the clinical setting in which it occurs. Embolism should be suspected whenever dyspnea and chest pain develop suddenly in patients who have been immobilized or bedridden for long periods of time because of surgery, trauma, hip fracture, congestive heart failure, or malignancy. The susceptibility to thromboembolic phenomena apparently also is increased in women taking oral contraceptives.

II. Chest roentgenograms are usually not helpful in the diagnosis. In a minority of cases, signs of pulmonary infarction (consolidation, pleural effusion, atelectasis) may occur. With extensive embolization, distention of the proximal pulmonary arteries or localized areas of decreased vascularity may be observed.

III. The electrocardiogram is of relatively little diagnostic value in most cases of pulmonary embolism. The most common findings are nonspecific T-wave changes (chiefly inversion) and nonspecific S-T segment abnormalities. Disturbances in rhythm are uncommon. The following patterns, if present, are strongly suggestive of acute or pulmonale: an S1Q3T3 pattern with T-wave inversion in the right precordial leads; an S1T3 pattern or T-wave inversion in lead III and the right precordial leads; or an S1Q3T3 pattern with right bundle branch block. Unfortunately, signs of acute cor pulmonale are found in only about 25% of cases.

IV. Arterial blood gases often reveal some degree of hypoxemia and are of supportive value in the diagnosis of embolism.

V. Lung scanning is the diagnostic method of choice and should be performed in any patient with suspected embolism. (Further details may be found in Chapter 4, Acute Pulmonary Radiographic Abnormalities.)

VI. Pulmonary angiography is an accurate method for disclosing the presence of embolism, but because special techniques are required, angiography is less readily available than scanning. The procedure should be reserved for instances in which the information to be obtained is vital to proper diagnosis and treatment. Angiography may be indicated under the following circumstances: (a) when

massive embolism is believed to be present and pulmonary embolectomy is contemplated. It is then essential to verify the diagnosis by angiography lest a seriously ill patient be subjected to unnecessary thoracotomy; (b) when a high suspicion of embolism exists and conventional studies fail to provide a diagnosis; (c) when the use of anticoagulant or thrombolytic therapy carries a greater-than-usual risk, and an accurate diagnosis becomes essential.

VII. Digital subtraction angiography (DSA) offers a safer alternative to selective pulmonary angiography when the diagnosis is in doubt.

Acute Pericarditis

Nearly all patients with acute pericarditis have chest pain. Because only the lower portion of the external surface of the pericardium is pain sensitive, much of the pain is presumably owing to inflammation of the adjoining diaphragmatic pleura.

Pain in Acute Pericarditis

I. Three types of pain may occur in acute pericarditis.
   A. Pleuritic pain is the most common type.
   B. Steady, severe retrosternal pain of sudden onset, simulating that of myocardial infarction, may occur.
   C. The rarest type is pain at the cardiac apex felt synchronously with each heartbeat.

II. Characteristics of pericardial pain
   A. The pain is commonly sharp. It is normally increased by breathing deeply, rotating the trunk, swallowing, or yawning—maneuvers that have no effect on the pain of myocardial infarction. It is often worse in recumbency and is sometimes relieved by sitting up and leaning forward.
   B. The pain is most commonly located in the precordial region and may radiate to the neck or to the left shoulder and arm.

Diagnosis of Acute Pericarditis

I. The pericardial friction rub. On examination, the most important finding is the presence of a pericardial friction rub over the precordium. The rub is often very transient, but it may persist and may even last for weeks. Classically, it has a superficial quality and is grating or scratchy in character. It may have systolic, diastolic, and presystolic components. It is accentuated by deep breathing and may be heard only in certain body positions (e.g., with the patient sitting and leaning forward). Pericardial rubs are often quite changeable in character from minute to minute or hour to hour. When confined to either systole or diastole, a rub may be confused with a cardiac murmur. Repeated observation usually makes the distinction clear, because the friction rub either assumes a to-and-fro character or disappears.

II. Pericardial effusion. Acute pericarditis is often accompanied by pericardial effusion. The physical signs depend on the amount of fluid and, in the case of tamponade, on the rapidity of its accumulation. Signs of pericardial effusion include an increased area of cardiac dullness and muffling of the heart sounds. Signs of tamponade include decreased systolic pressure with a narrow pulse pressure, tachycardia, pulsus paradoxus, and inspiratory elevation of the jugular venous pressure. Echocardiography has emerged as the simplest, safest, and most accurate method for the diagnosis of pericardial effusion.

III. Electrocardiographic changes. The electrocardiographic diagnosis of acute pericarditis is based primarily on the presence of sequential changes in the S-T segments and T waves in multiple leads. The QRS abnormalities of myocardial infarction are absent. Low-voltage and electrical alternans may occur when effusions are large. The cardiac rhythm is usually a sinus tachycardia, but atrial arrhythmias may occur. P-R segment deviations are seen occasionally.

IV. Differential diagnosis of acute pericarditis and myocardial infarction. Because of the similarity in pain and, occasionally, in the ECG findings, it may be difficult to differentiate between acute pericarditis and myocardial infarction. The following points may be helpful:

   A. The presence of a pleuritic component to the pain favors pericarditis.
   B. The development of pathologic Q waves in the ECG occurs only with myocardial infarction.
   C. S-T segment abnormalities are more widespread in pericarditis than in infarction. When elevated, the S-T segment may be concave upward in pericarditis, whereas convex changes are more consistent with infarction. Reciprocal S-T changes are usually absent in the limb leads in pericarditis but are commonly present in infarction. In pericarditis, the T waves are usually not inverted until the S-T segment is isoelectric; in infarction, they begin to invert while the S-T segment is still elevated.
   D. Serum enzyme elevations are absent or minimal in acute pericarditis.
   E. A pericardial friction rub may occur in either condition but is far less likely in infarction. The rub is more persistent in pericarditis.
   F. Large pericardial effusions occur only in pericarditis.

Other Causes of Prolonged Chest Pain

Pneumothorax, mediastinal emphysema, acute pancreatitis, acute cholecystitis, peptic disease, and perforated ulcer sometimes may cause severe chest pain. Usually, local symptoms, signs, radiographic studies, and laboratory findings provide the information needed for correct diagnosis.

Venous Pressure

H. Harold Friedman

Measurement

I. The peripheral venous pressure is measured most accurately by manometry. For clinical purposes, however, an adequate approximation of the venous pressure can be obtained by inspection of the jugular pulsations.

II. Although internal or external jugular pulsations may be used to estimate venous pressure, the former are preferred for this purpose.

III. Right-sided pulsations are preferred for measurement because left-sided ones may be falsely elevated by kinking of the left innominate vein.

IV. The reference level for bedside evaluation of venous pressure is the sternal angle.

V. The height of the jugular pulsations varies with the position of the chest. For this reason, the patient should be examined in a position that is optimal for revealing the venous pulsations.

VI. The vertical distance between the top of the venous column and the sternal angle represents the venous pressure.

VII. The upper limits for normal venous pressure at various degrees of body elevation are:
   A. Recumbent, 2 cm
   B. 30 degrees, 3 cm
   C. 45 degrees, 4.5 cm
   D. Upright, at the level of the suprasternal notch
      These values are less than those obtained by manometry because the true zero value is at the level of the right atrium.

VIII. When the findings on inspection are equivocal, the 1-minute abdominal compression test (hepatojugular reflux) may unmask latent elevation of the venous pressure.
   A. The abdominal compression test is considered to give a positive result if abdominal pressure for 1 minute causes a rise of at least 1 cm in the level of venous pulsations.
   B. A positive response is usually indicative of right-sided heart failure.
   C. Pure left-sided heart failure usually elicits a normal or, at most, an equivocal response.
   D. False-positive results may occur in severe emphysema, superior vena cava obstruction below the azygos vein, hypervolemia, restrictive cardiomyopathy, pulmonary embolism, and increased sympathetic stimulation.

IX. The maximum normal antecubital venous pressure, as determined by manometry, is 12 cm when the zero level is located 5 cm below the sternal angle, and 15 cm when the zero level is 10 cm from the back.

X. The central venous pressure (CVP) can be determined by transvenous placement of a plastic catheter into the superior vena cava or right atrium. The CVP is primarily an indicator of right ventricular function. It reflects the approximate level of the pulmonary capillary or wedge pressure when right and left ventricular function are comparable, but not when the function of these chambers is different (e.g., left ventricular failure). The CVP may be elevated in congestive heart failure, circulatory overload, and when intrathoracic or intrapericardial pressure is increased. The CVP is low in hypovolemic states (e.g., shock). Serial determinations are useful in treating patients with hypovolemia and shock and in monitoring fluid replacement therapy. The normal range for CVP is between 5 and 15 cm of water.

Hemodynamic monitoring using the Swan–Ganz catheter permits measurement of the pulmonary capillary pressure (normal range, 5 to 12 mm Hg) and cardiac output (normal cardiac index, 2.7 to 4.3 L/min/m^2). This procedure has largely replaced measurements of the CVP. This type of monitoring has found its greatest usefulness in the management of seriously ill patients with acute myocardial infarction, cardiogenic shock, and severe left ventricular failure, in whom CVP measurements may be misleading.

Abnormalities of Venous Pressure

I. Unilateral nonpulsatile distention of the neck veins usually indicates venous obstruction. Unilateral distention of the left jugular veins, however, may be caused by compression of the left innominate vein, a condition that is clinically unimportant.

II. Bilateral nonpulsatile neck vein distention associated with venous collaterals in the upper thorax is strongly suggestive of superior vena caval obstruction in the absence of heart disease, hepatic congestion, or venous engorgement in the lower half of the body.

III. Bilateral pulsatile neck vein distention associated with generalized elevation of venous pressure is commonly found in the following conditions:
   A. Right-added congestive heart failure from any cause
   B. Pericardial effusion with tamponade
   C. Chronic obstructive pulmonary disease
   D. Bronchial asthma
   E. Pleural effusion
   F. Hyperkinetic circulatory states
   G. Tricuspid stenosis
   H. Tricuspid regurgitation
   I. Central circulatory congestion owing to noncardiac causes

IV. Inspiratory distention of the neck veins (Kussmaul's sign), formerly considered to be pathognomonic of chronic constrictive pericarditis or cardiac tamponade, may also occur in severe right ventricular failure and the restrictive cardiomyopathies.

V. Expiratory increase in venous pressure may occur in some cases of bronchial asthma and chronic obstructive pulmonary disease.

Jugular Venous Pulse

H. Harold Friedman

The Normal Jugular Venous Pulse

The normal visible jugular venous pulse (Fig. 3-1) consists of three positive waves (A, C, and V) and two negative waves (X and Y). The A wave is normally the tallest wave, exceeding both C and V waves in amplitude. The X wave is usually deeper than the Y wave. The heart sounds are preferable to the carotid pulse for timing the venous pulsations at the bedside.

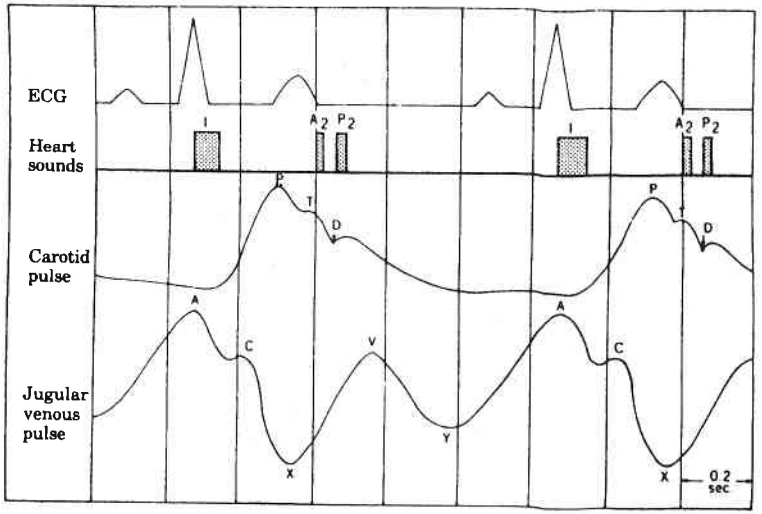

FIG. 3-1. Relationships between the electrocardiogram, heart sounds, arterial pulse, and jugular venous pulse. 1 = first heart sound; A_2 = aortic component of the second heart sound; P_2 = pulmonary component of the second heart sound; P = percussion wave; T = tidal wave; D = discrotic notch; A, C, X, V, and Y = waves and troughs of the jugular venous pulse.

The A Wave

The A wave is produced by right atrial contraction. It begins before S_1 and peaks just before or during this sound. If an S_4 is present, it coincides with the summit of the wave. It precedes the carotid pulse.

The C Wave

The C wave is probably produced by right ventricular systole and the bulging of the tricuspid value into the right atrium. Impact of the carotid pulse against the jugular vein may contribute to its genesis. It begins at the end of S_1 and peaks shortly thereafter. It coincides with the upstroke of the carotid pulse.

The X Descent ("Systolic Collapse" of the Venous Pulse)

The X descent is produced by right atrial relaxation and downward displacement of the base of the heart. It begins with the downslope of the A wave and terminates in the X trough. Some authorities divide it into the X and X′ descents, the C wave separating the two. The X trough occurs about 0.10 sec before S_2. The X descent occurs during the peak of the carotid pulse.

The V Wave

The V wave is produced by right atrial filling during right ventricular systole while the tricuspid valve is closed. It begins shortly before P_2 and peaks 0.06 to 0.08 sec after this sound. The peak of the V wave occurs after the dicrotic notch of the carotid pulse.

The Y Descent ("Diastolic Collapse" of the Venous Pulse)

The Y descent is produced by the rapid flow of blood into the right ventricle after the opening of the tricuspid valve. It begins with the end of the V wave and ends with the

Y trough. The Y trough occurs about 0.20 sec after P_2. The Y descent comes long after the carotid pulse is felt.

Abnormalities of the Jugular Venous Pulse

The types of abnormalities of the jugular venous pulsations and their causes are listed in the following:

The A Wave

I. Large or giant A waves are caused by increased resistance at the tricuspid valve or increased resistance to right ventricular filling in the following conditions:
   A. Tricuspid stenosis or atresia
   B. Ebstein's anomaly
   C. Pulmonary stenosis
   D. Pulmonary hypertension
      1. Primary
      2. Eisenmenger's syndrome (uncommon)
      3. Mitral stenosis
      4. Acute and chronic cor pulmonale
      5. Tricuspid regurgitation (nonrheumatic cases secondary to pulmonary hypertension)
   E. Cardiomyopathy
   F. Idiopathic hypertrophic subaortic stenosis
   G. Aortic stenosis (some cases)

II. Decreased A waves are seen in the presence of a markedly dilated right atrium.

III. Absent A waves are seen in atrial fibrillation and atrial flutter (A waves replaced by flutter waves).

IV. Cannon A waves are produced by fusion of giant A waves with C or V waves.
   A. Regular cannon waves
      1. Atrioventricular (AV) junctional rhythm
      2. First-degree AV block (some cases)
      3. 2:1 AV block
      4. Atrial tachycardia (some cases)
   B. Irregular cannon waves
      1. Premature systoles
         a. Ventricular (frequently)
         b. AV junctional (sometimes)
         c. Atrial (rarely)
      2. Complete AV dissociation
         a. Complete AV block
         b. AV junctional tachycardia (some cases)
         c. Ventricular tachycardia (some cases)
      3. Atrial flutter (difficult to detect)

The X Descent

The X descent is decreased in atrial fibrillation. It is partially or completely obliterated by a regurgitant wave (called the CV, S, or V wave) in tricuspid regurgitation. It may be deeper than the Y descent in some cases of chronic constrictive pericarditis.

The V Wave (Large V Wave)

I. Tricuspid regurgitation
II. Right-sided heart failure
III. Atrial septal defect (about 50% of cases)
IV. Anomalous pulmonary venous drainage

The Y Descent

I. A slow, shallow Y descent is seen in tricuspid stenosis.
II. A rapid, steep Y descent is seen in constrictive pericarditis and in severe right-sided heart failure.

Arterial Pulse

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The Normal Arterial Pulse

Routine examination of the arteries should include palpation of the carotid, arm, and leg pulses. The normal carotid pulse (Fig. 3-1) consists of a brief upstroke, a smooth dome-shaped summit, and a downstroke that is more gradual than the upstroke. The systolic percussion and tidal waves, as well as the dicrotic notch, are not normally palpable, but they can be recorded. Most pulse wave abnormalities are detected best in the carotid arteries.

Abnormalities of the Arterial Pulse

Hypokinetic Pulse (Weak Pulse, Pulsus Parvus)

A small pulse signifies a narrowed pulse pressure. It is usually produced by low cardiac output in association with increased peripheral resistance. The causes are listed in Table 3-1.

Hyperkinetic Pulse (Bounding Pulse)

A bounding pulse usually implies a widened pulse pressure. It is produced by varying combinations of increased stroke volume, increased cardiac output, and lowered peripheral resistance. The causes are listed in Table 3-2. A water-hammer pulse is an exaggerated type of bounding pulse. Corrigan's sign, as originally described, consists of visible abrupt distention and rapid collapse of the carotid pulse. It is therefore a sign detected by inspection, not by palpation. The sign is quite characteristic of aortic regurgitation.

Pulsus Parvus et Tardus

This is a pulse of low amplitude that rises slowly to a late summit. It is usually found in valvular aortic stenosis. Although it may occur with less frequency in subvalvular aortic stenosis because of a fibrous ring or diaphragm, it is not found in idiopathic hypertrophic subaortic stenosis. The anacrotic pulse, a variant of pulsus parvus et tardus, in which a notch is palpable on the upstroke of the pulse wave, is indicative of severe aortic stenosis.

Table 3-1. Causes of decreased pulse pressure[a]

Decreased cardiac output
Congestive heart failure
Shock
Hypovolemia
Acute myocardial infarction
Cardiac tamponade
Chronic constrictive pericarditis
Cardiomyopathy and myocarditis
Peripheral vasoconstriction
Shock
Hypovolemia
Mechanical
Valvular disease
Aortic outflow obstruction
Mitral stenosis or regurgitation, or both
Aortic disease
Coarctation of the aorta
Aortic arch syndrome

[a] More than one mechanism may be operative.

Table 3-2. Causes of increased pulse pressure[a]

Decreased distensibility of the arterial system
Atherosclerosis (most common)
Hypertension
Coarctation of the aorta
Increased stroke volume
Normal
Anxiety, exercise
Complete heart block
Aortic regurgitation
Increased cardiac output or decreased peripheral resistance, or both
Fever
Anemia
Thyrotoxicosis
Hyperkinetic heart syndrome
Arteriovenous fistula
Paget's disease
Beriberi
Cirrhosis of the liver

[a] More than one mechanism may be operative.

Pulsus Bisferiens
Pulsus bisferiens is a twice-beating pulse in which both peaks occur during systole. The initial, or percussion, wave is brisk and forceful. The second, or tidal, wave rises slower and is less prominent than the percussion wave. Pulsus bisferiens occurs most commonly in combined aortic stenosis and regurgitation, but it may occur in pure aortic regurgitation. Pulsus bisferiens is also characteristic of idiopathic hypertrophic subaortic stenosis.

Dicrotic Pulse
A dicrotic pulse is a double-peaked pulse in which the initial wave occurs during systole and the final (dicrotic) wave occurs during diastole. It occurs in some fevers, notably typhoid fever, and occasionally in mild or moderate aortic regurgitation.

Pulsus Alternans
Pulsus alternans is a condition in which the pulse waves during regular rhythm are alternately strong and weak. It may be detected by palpation but it is more accurately assessed by sphygmomanometry. To detect pulsus alternans, inflate the blood pressure cuff rapidly above the systolic pressure and then deflate it slowly until sounds are first audible. At this point, the beats are heard at one-half of the heart rate. When the cuff is deflated further, the rate doubles. There may be some variation in the intensity of the strong and weak beats. Pulsus alternans can be diagnosed only if the heart rate is regular. It is often accentuated when the patient is sitting or standing. Severe degrees may be palpable over the radial and other peripheral arteries.

Pulsus alternans is virtually diagnostic of left ventricular failure and is commonly associated with a ventricular (S_3) gallop rhythm. However, it may occasionally occur during or after paroxysmal tachycardia in an otherwise normal heart. Pulsus alternans must be differentiated from bigeminy produced by premature systoles. In pulsus alternans, the intervals between the strong and weak beats are equal. In extrasystolic bigeminy, weak ectopic beats occur prematurely and are followed by strong normal beats after pauses, resulting in ventricular cycles that are alternately short and long.

Pulsus Paradoxus
Pulsus paradoxus is a condition in which the inspiratory decline in systolic pressure exceeds 10 mm Hg (maximum normal value during quiet respiration). To detect pulsus paradoxus, inflate the cuff rapidly above the systolic pressure and then slowly deflate it. The difference between the systolic pressures at which sounds are first heard only

C. Oral contraceptive agents
D. Miscellaneous causes: polycythemia, burns, lead poisoning, CNS lesions (increased intracranial pressure, brain tumors, bulbar poliomyelitis)

Symptoms
I. The age and type of onset may provide clues to the etiology of hypertension.
   A. A gradual onset between the ages of 35 and 55 years is typical of essential hypertension.
   B. An acute onset in children or young adults suggests acute renal disease (e.g., acute glomerulonephritis).
   C. Moderate to severe hypertension in the young is usually indicative of chronic renal disease (e.g., chronic glomerulonephritis).
   D. A sudden onset in middle-aged or older persons suggests a renovascular cause.
   E. A rapid onset of severe, progressive hypertension, or sudden acceleration of preexisting hypertension may herald the onset of a malignant phase in either primary or secondary hypertension.
II. Elevated diastolic blood pressure per se is asymptomatic except possibly for morning occipital headache.
III. Symptoms in patients with essential hypertension are nonspecific or are related to the cardiovascular, cerebral, or renal complications of the disease.
IV. Some types of secondary hypertension, such as primary aldosteronism, Cushing's syndrome, or pheochromocytoma, may be associated with symptoms or signs that are strongly suggestive of its cause.
V. Muscular weakness in association with hypertension suggests coexistent hypokalemia.
VI. Symptoms of muscle weakness (sometimes with paralysis) in association with polyuria, nocturia, polydipsia, tetany, and hypertension are strongly suggestive of primary aldosteronism.
VII. Attacks of headache, blurring of vision, sweating, palpitation, nausea, trembling, and pallor with either paroxysmal or persistent hypertension are suggestive of pheochromocytoma.

Signs
I. Delayed femoral pulses and blood pressures in the legs that are lower than those in the arms suggest coarctation of the aorta.
II. Decreased or absent femoral pulses may be indicative of occlusive disease in the abdominal aorta or iliac arteries or of coarctation of the aorta.
III. An abdominal bruit, audible anteriorly in the epigastrium or over the flank, is strongly suggestive of renal artery stenosis.
IV. Bilaterally enlarged kidneys in patients with hypertension suggests polycystic disease.
V. An orthostatic drop in blood pressure suggests secondary rather than primary hypertension and is especially characteristic of pheochromocytoma.
VI. The physical findings in some types of secondary hypertension (e.g., Cushing's syndrome) may be sufficiently characteristic to permit or at least suggest the correct diagnosis.
VII. An assessment of the severity of hypertension can be made from the degree of cardiac, cerebral, retinal, and renal involvement, and from the blood pressure readings.

Category	Systolic	Diastolic
Normal	130 mm Hg	85 mm Hg
High normal	130–139 mm Hg	80–89 mm Hg
Hypertension		
Stage 1 (mild)	140–159 mm Hg	90–99 mm Hg
Stage 2 (moderate)	160–179 mm Hg	100–109 mm Hg
Stage 3 (severe)	180–209 mm Hg	110–119 mm Hg
Stage 4 (very severe)	210 mm Hg	120 mm Hg

The diagnosis should be based on an average of at least two readings separated by at least 2 min. It should be confirmed on at least two subsequent visits. With very severe hypertension, immediate treatment may be required.

VIII. The chronicity and severity of the hypertension may also be estimated by funduscopy. The normal arteriolar-venous (AV) diameter ratio is 3:4.

Grade I (mild): AV ratio 1:2, no hemorrhages, exudates, or papilledema.
Grade II (moderately severe): AV ratio 1:3, AV nicking, no hemorrhages, exudates, or papilledema.
Grade III (severe): AV ratio 1:4, hemorrhages or exudates, or both, but no papilledema.
Grade IV (malignant): AV ratio as in the preceding, marked arteriolar narrowing, hemorrhages, exudates, and papilledema.

Initial Evaluation
The initial workup in patients with hypertension has a threefold purpose: (a) to identify systemic complications of hypertension, (b) to establish an etiologic diagnosis, if possible, and (c) to screen for the fewer than 10% of hypertensive patients with potentially curable forms of the disease. Some workup is indicated in every patient with hypertension. Under *ideal* conditions, every hypertensive patient should have the comprehensive rather than the limited basic workup outlined in succeeding paragraphs. However, some selectivity is required because neither funds, personnel, nor facilities are available for a complete evaluation of every patient with hypertension. Furthermore, screening for the common causes of curable hypertension usually can be performed on clinical grounds with simple procedures.

Limited Basic Workup
In patients with stable, mild, or moderate hypertension beginning after the age of 35 years, many authorities believe that a satisfactory initial workup can be limited to the following:

I. Hematocrit
II. Urinalysis
III. Serum creatinine or BUN
IV. Serum potassium
V. Electrocardiogram

Other tests that may be helpful include chest films, CBC, and a biochemical profile.

Comprehensive Basic Workup
I. Urinalysis to screen for intrinsic renal disease. The urine usually shows no abnormalities in essential or renovascular hypertension and in primary aldosteronism unless the hypertension is severe, in which case there may be mild proteinuria or microscopic hematuria. On the other hand, it is rare to have primary renal disease without proteinuria and some abnormality of the urine sediment.
II. Urine culture and sensitivity studies to detect bacteriuria associated with pyelonephritis.
III. Biochemical screening, including the following:
   A. Serum electrolytes (Na, K, Cl, and CO_2) to detect hypokalemia and alkalosis caused by primary aldosteronism, Cushing's syndrome, or other diseases
   B. BUN and creatinine to screen for gross impairment of renal function
   C. Serum uric acid to detect hyperuricemia, gout, or related gouty nephropathy
   D. A 2-hour postprandial blood glucose or standard glucose tolerance test to detect diabetes mellitus or carbohydrate intolerance owing to such other causes as pheochromocytoma, primary aldosteronism, or Cushing's syndrome
IV. Urinary vanillylmandelic acid (VMA) determination to screen for pheochromocytoma
V. Urinary 17-hydroxycorticosteroid determination to screen for Cushing's syndrome

during expiration and later during both expiration and inspiration is a measure of the magnitude (in mm Hg) of the paradoxical pulse. Deep inspiration may cause a 10- to 15-mm fluctuation in the systolic pressure of a normal person but does not cause the radial pulse to disappear. Hence, disappearance of the radial pulse on deep inspiration suggests significant pulsus paradoxus.

Classic pulsus paradoxus occurs in cardiac tamponade and constrictive pericarditis, but it may also be found in chronic obstructive airway disease and occasionally in cardiomyopathy or shock. Pulsus paradoxus caused by constrictive pericarditis or cardiac tamponade is sometimes associated with an inspiratory increase in venous pressure (Kussmaul's sign), whereas pulsus paradoxus caused by pulmonary disease usually shows an expiratory increase in venous pressure.

Pulse and Pressure Differences Between the Arms and Legs
Normally, with a standard cuff, the systolic blood pressure in the legs is about 20 to 40 mm Hg higher than that in the arms. With a large cuff (18 cm), the systolic blood pressure in the lower extremities is about the same as that in the upper extremities (±10 mm Hg). A large cuff is more accurate than a standard cuff for measuring the blood pressure in the legs. The femoral pulse should occur slightly earlier than the radial pulse and should be of equal or greater intensity. A diminished and delayed femoral pulse is a classic finding in coarctation of the aorta. Decreased femoral pulses may also occur because of occlusive disease in the terminal aorta or iliac arteries, aortic dissection, or aneurysm of the abdominal aorta. Decreased or absent popliteal and pedal pulsations with good preservation of the femoral pulses are indicative of occlusive peripheral arterial disease.

Pulse and Pressure Differences Between the Arms
Normally there is a difference of less than 15 mm Hg of systolic blood pressure between the two arms. An aberrant radial artery is the most common cause of unequal radial pulses. Pulse and pressure differences between the arms may also be owing to other causes.

I. Acquired disease
   A. Subclavian steal syndrome
   B. Aortic arch syndrome (pulseless disease, Takayasu's syndrome)
   C. Thoracic outlet syndrome
   D. Arterial thrombosis and embolism
   E. Aneurysm of the thoracic aorta
   F. Dissection aneurysm
   G. Incompressible brachial artery
II. Congenital disease
   A. Coarctation of the aorta
   B. Supravalvular aortic stenosis. (In more than 50% of cases, the pressure difference between the arms exceeds 20 mm Hg, with the right arm pressure greater, except in dextrocardia.)
   C. Patent ductus arteriosus
   D. Anomalous subclavian artery

Arterial Hypertension

H. Harold Friedman

Normal Blood Pressure
The maximum normal blood pressure is 140/90 mm Hg. In normal persons in the recumbent position, the popliteal blood pressure exceeds the brachial pressure by 20 to 40 mm Hg when determined by sphygmomanometry.

Systolic Hypertension
Definition
Elevation of the systolic pressure without concomitant elevation of the diastolic pressure constitutes systolic hypertension.

Etiology

I. Decreased elasticity of the aorta owing to aortic atherosclerosis (most common)
II. Increased cardiac output owing to fever, anemia, thyrotoxicosis, hyperkinetic heart syndrome, arteriovenous fistula, Paget's disease, beriberi, or anxiety
III. Increased stroke volume owing to aortic insufficiency or complete heart block
IV. Coarctation of the aorta

Symptoms

Symptoms, if any, are produced by the underlying disease and are not attributable to the hypertension per se.

Signs

Systolic hypertension is signified by a persistently elevated systolic pressure.

Diagnostic Approach

I. Rule out coarctation of the aorta by checking the blood pressure and pulses in both the upper and lower extremities. If the blood pressure in the legs is 20 to 30 mm Hg less than that in the arms, or if the femoral pulse peak is delayed, or both, check further for evidence of aortic coarctation.
II. Rule out high-output states and conditions causing increased stroke volume.
III. If the foregoing conditions are excluded and the patient is middle-aged or elderly, aortic atherosclerosis is the most probable cause.

Diastolic Hypertension

Definition

Diastolic hypertension is defined as elevation of the diastolic pressure above normal values. It is almost always associated with concomitant elevation of the systolic pressure. The diagnosis of hypertension is not warranted unless blood pressure readings exceed normal values on at least three separate occasions after a 15- to 20-min period of rest.

Etiology

I. Primary, or essential, hypertension (90% of cases)
II. Secondary hypertension
   A. Endocrine disorders
      1. Adrenal
         a. Aldosteronism (1% to 2% of cases)
         b. Pheochromocytoma (0.1% of cases)
         c. Cushing's syndrome
      2. Thyroid: hypothyroidism
      3. Pituitary
         a. Cushing's disease
      4. Parathyroid: hyperparathyroidism
   B. Renal disease
      1. Renal artery lesions (7% of cases)
         a. *Intrinsic:* atherosclerotic plaque (most common); fibromuscular hyperplasia; aneurysm, thrombosis, or embolism; arteriovenous fistula; arteritis
         b. *Extrinsic compression:* tumor involving renal pedicle, congenital fibrous band, retroperitoneal fibrosis
      2. Parenchymal (0.5% of cases)
         a. *Unilateral:* congenital hypoplastic kidney; pyelonephritis (pyogenic, tuberculous); irradiation, trauma, renal neoplasm, unilateral renal vein thrombosis; obstructive nephropathy
         b. *Bilateral:* glomerulonephritis; pyelonephritis, polycystic disease, connective tissue disease, amyloidosis, gouty nephropathy, nephrocalcinosis, obstructive nephropathy
         c. Coarctation of the aorta
         d. Toxemia of pregnancy

VI. An ECG for evidence of left ventricular and left atrial enlargement. Other abnormalities owing to myocardial damage from associated coronary artery disease may also be discovered
VII. Chest films to estimate heart size, detect pulmonary complications, or diagnose aortic coarctation
VIII. A rapid-sequence IVP to help identify unilateral disease of the renal parenchyma, renovascular lesions, polycystic disease, or pyelonephritis. A normal result lends support to a diagnosis of essential hypertension.
IX. Renal arteriography may be useful in evaluating renovascular hypertension and determining appropriate treatment.
X. In patients not receiving antihypertensive drugs, renin profiling and the oral Captopril test have been suggested as office screening procedures for renovascular hypertension. Ultrasonic scanning and magnetic resonance angiography are too unreliable as screening tests for renovascular hypertension.

Subsequent Evaluation

Negative Initial Workup

Patients with mild to moderate hypertension that is familial and begins after the age of 35 years, with no abnormalities revealed by clinical history, examination, or initial limited or comprehensive workup, are assumed to have *essential hypertension* and should be treated accordingly. No further workup is necessary. When the initial workup suggests a potentially curable form of hypertension, additional studies are justified only if the results to be obtained will materially alter the treatment program. The evaluation must be tailored to each patient. Thus, a complete workup for pheochromocytoma is indicated if the clinical history and urinary VMA excretion suggest this diagnosis, because surgical removal of the tumor is necessary to effect a cure. On the other hand, a 65-year-old woman with a blood pressure of 160/100 mm Hg and no evidence of systemic complications does not need renal arteriography; even if renovascular disease were detected, surgical therapy probably would not be warranted.

Abnormal Laboratory Findings

I. If the urinalysis suggests *primary renal parenchymal disease* or if the BUN or serum creatinine is elevated, a creatinine clearance test should be performed to estimate the degree of renal function impairment and to provide a baseline for future studies. More comprehensive studies for the diagnosis of primary renal parenchymal disease are discussed elsewhere in this volume.
II. The presence of abnormal urinary findings such as proteinuria, white cells, and white cell clumps or casts, together with bacteriuria, suggests the diagnosis of *chronic pyelonephritis*, although urinalysis may yield negative findings in this disease. Bacteriuria with over 100,000 colonies/mL of urine (from a clean-voided specimen) is considered significant. In chronic pyelonephritis, the IVP usually shows bilaterally shrunken kidneys with scarred and clubbed calyces.

Hypokalemia and Hypertension

If the serum potassium level is low (≤33 mEq/L) or borderline, further investigation for possible causes of hypokalemia and hypertension (listed in the following) is warranted. For practical purposes, if cases of essential hypertension treated with diuretics or other potassium-depleting drugs are excluded, the most common cause of hypokalemia in hypertensive patients is primary aldosteronism. Adrenocortical hyperplasia and other rare syndromes of adrenocortical dysfunction are uncommon causes of hypokalemia in patients with hypertension.

Etiology

I. Essential hypertension with the following:
   A. Vomiting and diarrhea
   B. Diuretic therapy
   C. Oral contraceptive or estrogen therapy
   D. Steroid therapy

II. Renal disease
   A. Accelerated or malignant hypertension
   B. Renovascular hypertension
   C. Potassium-losing nephropathies (e.g., chronic pyelonephritis)
   D. Renin-secreting renal tumor
   E. Liddle's syndrome
III. Adrenocortical dysfunction
   A. Primary aldosteronism
      1. Aldosterone-producing adenoma
      2. Cortical hyperplasia
   B. Cushing's syndrome and the ectopic ACTH syndrome
   C. Endogenous mineralocorticoid excess (some adrenocortical tumors)
   D. Exogenous administration of mineralocorticoids
IV. Pseudoaldosteronism (excessive licorice ingestion syndrome)

Diagnostic Approach

The *first* step is to determine whether the potassium loss is the result of renal or extrarenal mechanisms. Extrarenal potassium depletion is easily recognized by the clinical picture and is correctable by replacement therapy with potassium salts. On the other hand, if there is renal potassium wasting, then diuretics, kidney disease (parenchymal or vascular), primary aldosteronism, or other rare forms of adrenocortical dysfunction may be responsible. Before proceeding with additional laboratory studies, it is well to recheck the history and physical examination for diagnostic clues.

History

I. Inquire specifically for possible causes of potassium depletion: Has the patient been taking diuretics, laxatives, steroids, estrogens, or oral contraceptive agents? Is there a history of vomiting or diarrhea? Has potassium intake been reduced?
II. Be sure that the patient is not a licorice ingestor, because the glycyrrhizic acid in licorice may mimic the action of aldosterone by producing hypertension, alkalosis, and suppressed renin activity (but with low aldosterone secretion). Measurement of urinary aldosterone excretion differentiates between primary aldosteronism and the syndrome of chronic licorice ingestion.
III. Ask whether the patient has been on a low-sodium diet, because salt restriction may mask the hypokalemia of primary aldosteronism.

Physical Examination

I. In primary aldosteronism, retinopathy is usually mild (grade I or II) and edema is absent.
II. A positive Trousseau's or Chvostek's sign in an untreated hypertensive patient is presumptive evidence of hyperaldosteronism.
III. Lack of an abdominal bruit is an important sign favoring aldosteronism over renovascular hypertension.
IV. The Valsalva maneuver in primary aldosteronism does not elicit the characteristic hypertensive overshoot and bradycardia found in other types of hypertension.

Determining the Mechanism of Potassium Loss

I. If the patient has been taking diuretics or other drugs that induce hypokalemia, these should be discontinued. Give 50 mEq of potassium (as the chloride) daily for 1 week. Stop the potassium chloride and recheck the serum potassium and sodium in 1 to 2 weeks. If the serum potassium is then normal, for practical purposes renal potassium wasting and the diagnosis of primary aldosteronism can be ruled out. On the other hand, if the serum potassium is borderline or low, proceed as in the paragraph that follows.
II. If the serum potassium is borderline or low and there is no obvious cause for the hypokalemia, check for potassium wasting. Measure the 24-hour urinary excretion of potassium while the patient is on a regular salt intake (as reflected in a urinary sodium level of approximately 100 mEq/24 hours). Urinary potassium excretion of less than 20 mEq/24 hours is strong evidence against renal potassium wasting and the diagnosis of primary aldosteronism, whereas a level of 60 mEq/24 hours or greater is strongly suggestive of renal potassium wasting.
III. If the serum potassium is initially low and the studies outlined in the preceding paragraphs show negative findings, it can be assumed that the patient does not have renal potassium wasting or primary aldosteronism, and further investigation for this diagnosis is not warranted.
IV. If the preliminary results, as outlined in the preceding paragraphs, are suggestive of nondiuretic renal potassium wasting, the two most likely possibilities are primary aldosteronism and renovascular hypertension. At this point the determination of plasma renin activity and aldosterone excretion are the next steps indicated.
   A. Plasma renin activity (PRA). The PRA test is carried out by comparing the plasma renin level under basal conditions with the level obtained after 4 hours of ambulation. The patient should be on a 20-mEq per day sodium diet for at least 4 days prior to the test. The normal response is a twofold or threefold rise in PRA after 4 hours of ambulation. Patients with primary aldosteronism show decreased plasma renin values, which typically fail to rise after activity. It must be remembered that about 25% of patients with essential hypertension have suppressed PRA, but aldosterone excretion is usually low or normal in these patients. PRA is decreased in patients with excessive production of deoxycorticosterone or corticosterone, and is normal or elevated in patients with secondary aldosteronism. The measurement of peripheral PRA 5 hours after the oral administration of 60 mg of furosemide is a somewhat simpler and more convenient screening procedure. However, the stimulation of renin activity is not as marked as that produced by a low-sodium diet.
   B. Aldosterone excretion. Measure the quantity of aldosterone in a 24-hour urine sample after the patient has been on a sodium intake of at least 200 mEq per day. Increased aldosterone secretion after salt loading is found in primary and secondary aldosteronism (it may also occur, rarely, in essential hypertension). When aldosterone excretion is increased, elevated PRA suggests renovascular hypertension, and low PRA suggests primary aldosteronism. Aldosterone secretion is reduced in the 17-alpha-hydroxylase and 11-beta-hydroxylase deficiency syndromes and in Liddle's syndrome.
   C. Adrenal arteriography and venography. If the diagnosis of primary aldosteronism is established, adrenal arteriography or venography may be advisable in the preoperative evaluation of the patient for tumor localization. In some medical centers, tumor localization is attempted by catheterization of the adrenal veins bilaterally. Usually, there is at least a twofold increase in the adrenal venous aldosterone levels on the side with the tumor.

Summary of the Results of Various Tests for Hypertension with Hypokalemia

I. If aldosterone excretion is increased and PRA is suppressed, the diagnosis is primary aldosteronism owing to an aldosterone-producing adenoma, nodular hyperplasia, or adrenocortical hyperplasia (glucocorticoid-remediable hypertension).
II. If aldosterone excretion is increased and PRA is normal or elevated, the diagnosis is secondary aldosteronism owing to accelerated or malignant hypertension, renovascular hypertension, essential hypertension with diuretic therapy, or essential hypertension with oral contraceptive medications.
III. If aldosterone excretion is reduced and PRA is suppressed, mineralocorticoids other than aldosterone, such as deoxycorticosterone and corticosterone, may be responsible for the hypertension.
   A. The 17-alpha-hydroxylase deficiency syndrome is characterized by hypertension, hypokalemic alkalosis, hypogonadism, primary amenorrhea, little if any 17-hydroxycorticosteroids or aldosterone in the urine, and responsiveness to glucocorticosteroids.
   B. The 11-beta-hydroxylase deficiency syndrome is characterized by hypertension, hypokalemic alkalosis, sodium retention and edema, virilization in

women, precocious puberty in men, reduced excretion of 17-hydroxycorticosteroids and aldosterone, and responsiveness to glucocorticosteroids.

Abnormal Intravenous Pyelogram
The rapid-sequence IVP is a screening procedure for determining the role played by the kidney in hypertension.

I. If the kidneys are reduced in size and scarred and the calyces are clubbed, *chronic pyelonephritis* is probable.
II. If the kidneys are shrunken with normal calyces and pelves, *chronic glomerulonephritis* or *nephrosclerosis* is likely.
III. Grossly enlarged kidneys with spidery calyces are virtually pathognomonic of *polycystic disease.*
IV. *Unilateral primary parenchymal disease*, not owing to vascular impairment, is characterized by clubbed calyces and a thinned cortex on the affected side. In addition to the urographic findings, the evidence for unilateral parenchymal disease, rather than renovascular disease, as the cause of hypertension includes a history of urinary tract infections, decreased urine osmolality, and increased sodium concentration by split-function studies, normal renal vasculature by arteriography (except that the vasculature size reflects the diminished function), and normal peripheral and renal plasma renin activity.
V. *Renovascular hypertension* is suggested by one or more of the following findings: (a) unilateral reduction in kidney size, exceeding 1.5 cm on the left or 1.0 cm on the right, (b) delayed appearance of the contrast medium on the affected side, (c) greater concentration of the radiopaque medium on the affected side when the contrast material finally does appear, and (d) notching of the pelvis or upper ureter on the affected side by collateral vessels. Even if renovascular hypertension is suggested by the urographic findings, it is unnecessary to do additional studies unless surgery is contemplated. Ancillary studies available for the diagnosis of renovascular hypertension in addition to the IVP are the radioactive renogram, determination of PRA, aortography, catheterization of the renal veins for PRA, and differential renal function tests.
   A. The radioactive renogram is a safe, easy test to perform. It is not a specific diagnostic study but provides a comparison of the blood flow to each kidney. Although positive renogram and IVP findings do not always coincide in the same patient, a combination of the two may identify renovascular disease in a larger number of cases than will either test alone.
   B. Digital subtraction angiography or aortography by the femoral route can be performed to visualize the renal arteries. The mere presence of anatomic renal arterial lesions does not establish their functional significance. Proof of their functional significance in the form of increased PRA should be obtained.
   C. PRA is usually increased in patients with renovascular hypertension both in the basal state and after 4 hours of ambulation.
   D. Some authorities believe that the best technique for confirming the diagnosis of curable renovascular hypertension is the determination of PRA in blood samples from the renal veins of both kidneys. A level of PRA on the involved side that is at least one and a half times greater than that on the uninvolved side is considered significant.
   E. Split kidney function tests, employing bilateral ureteral catheterization, are usually performed prior to surgery, primarily to be certain that if nephrectomy is required, the remaining kidney will function adequately. The diagnosis of renal ischemia may also receive additional support. Split kidney function tests generally show impairment of renal function on the affected side unless there are segmented lesions that are too small to produce measurable renal function impairment. In the interpretation of the tests, a 50% or greater decrease in urine volume, a 15% or greater decrease in sodium concentration, a lowered glomerular filtration rate, and an increased creatinine concentration on the affected side are considered diagnostic of renal ischemia. Bilateral lesions may not be detected with this technique, and both false-positive and false-negative responses may occur.

Increased Excretion of VMA
I. Urinary excretion of VMA that is twice the normal rate is virtually pathognomonic of *pheochromocytoma.* False-positive and false-negative results may be produced by interfering drugs.
II. Clinically, pheochromocytoma is characterized by one or more of the following features: paroxysmal or persistent hypertension; attacks of headache, blurred vision, sweating, palpitation, trembling, and pallor; hyperglycemia and glycosuria; orthostatic hypertension; a tendency to cholelithiasis; a familial incidence in some cases; and an association with such diseases as carcinoma of the thyroid gland, parathyroid adenoma, neurofibromatosis, and neuroectodermal diseases (e.g., Lindau–von Hippel disease and tuberous sclerosis). Ninety percent of pheochromocytomas occur in the adrenal gland, and of these about 10% are bilateral. Two percent of extramedullary tumors are multiple. Malignancy is present in fewer than 10% of cases.
III. If VMA excretion is increased, the diagnosis should be confirmed by assay of catecholamines or metanephrines, or both, in a 24-hour urine specimen.
IV. If excretion of VMA, catecholamines, or metanephrines is normal in a case with a high index of clinical suspicion, urine should be collected for a short, carefully timed period during and immediately after an attack and examined for catecholamines.
V. Pharmacologic tests such as the phentolamine, histamine, tyramine, and glucagon tests are unnecessary and inadvisable because they are hazardous and less accurate than urine assays.
VI. Extraabdominal location of the tumor can often be ruled out by physical examination of the neck and chest films. Computerized tomography of the abdomen is an excellent method for the localization of adrenal pheochromocytoma and may replace invasive procedures. However, invasive studies (arteriography and venography) together with the determination of catecholamine levels are indicated for the accurate localization of extraabdominal tumors.
VII. All patients with suspected pheochromocytoma should be evaluated preoperatively by an expert.

Precordial Pulsations and Movements

H. Harold Friedman

A great deal of useful clinical information is obtained by inspection and palpation of the precordium and chest wall. The apical impulse can be located and its characteristics defined. In addition, palpable sounds, murmurs, thrills, and abnormal pulsations as well as ventricular enlargement can be detected. For a complete examination, the patient should be examined while sitting, lying supine, and lying in the left lateral recumbent position. The heart sounds are the most useful reference points for timing cardiac pulsations.

Apical Impulse

Normal
I. The location of the apex beat is determined most accurately in the sitting position. The normal apical impulse lies in or about the fifth intercostal space inside the midclavicular line at a distance no greater than 10 cm from the left sternal border. The impulse is confined to a single area no greater than 2 or 3 cm in diameter.
II. The normal apex beat is a systolic outward movement of brief duration (from S_1 to before S_2) that has a light, tapping quality. A somewhat more forceful beat is not abnormal in tense or thin-chested individuals.
III. The outward thrust of the apex beat is accompanied by slight inward movement of the chest wall overlying the right ventricle.
IV. The apical impulse may not be palpable in many normal individuals.

Abnormal

I. Aside from its absence as a normal variant, the apical impulse may be impalpable because of disease (e.g., mitral stenosis, constrictive pericarditis). Thus, absence of the apex beat by itself has little diagnostic significance.

II. An apex beat that is not substantially displaced from its normal location but that is heaving, sustained (lasting from S_1 to S_2), forceful, and strong enough to lift the fingers against firm pressure, is indicative of left ventricular hypertrophy due to pressure loading (e.g., systemic hypertension, aortic stenosis). It is associated with increased systolic precordial retraction, producing the so-called *left ventricular rock.*

III. A sustained and abnormally bulging apical impulse, indistinguishable from the heave of left ventricular hypertrophy, may be encountered in myocardial infarction in the absence of hypertrophy.

IV. An apex beat that is displaced laterally and downward is indicative of left ventricular dilatation, with or without hypertrophy.

A. A sustained but weak apical impulse is indicative of dilatation.

B. A hyperdynamic impulse, meaning one that is forceful, exaggerated, and abrupt (although prolonged beyond normal), is indicative of combined dilatation and hypertrophy due to volume overloading (e.g., aortic or mitral regurgitation, left-to-right shunt). A hyperdynamic impulse is also associated with a left ventricular rock.

V. Double apical impulses may be associated with an S_3 or S_4 gallop. In such cases, the ventricular impulse is systolic, and the additional impulse is diastolic.

VI. Double apical thrusts, with both impulses occurring in systole, are strongly suggestive of idiopathic hypertrophic subaortic stenosis, but they may also occur in some cases of myocardial infarction, angina pectoris, left ventricular aneurysm, or the systolic click syndrome associated with prolapse of the mitral valve into the left atrium.

VII. The presence of asynchronous cardiac impulses palpable at both the xiphoid and apex suggests combined ventricular hypertrophy.

Left Parasternal Pulsations

I. A slight precordial lift may occur normally in children and young adults.

II. Bulging of the precordium in a child generally denotes longstanding right ventricular enlargement.

III. A localized, sustained, heaving lift in the lower left parasternal region is indicative of right ventricular hypertrophy owing to pressure loading (e.g., pulmonary hypertension from any cause, pulmonary stenosis). The lift is associated with conspicuous systolic retraction of the chest further to the left, producing the so-called *right ventricular rock.*

IV. A hyperdynamic impulse over a relatively large area parasternally is indicative of right ventricular enlargement owing to volume loading (e.g., atrial septal defect). This impulse is also associated with a right ventricular rock.

V. A left parasternal lift may be palpable in the absence of right ventricular hypertrophy or pulmonary hypertension when the right ventricle is pushed anteriorly by a giant left atrium.

VI. Marked right ventricular dilatation may displace the right ventricular beat leftward to the site of the normal cardiac impulse. In such cases, identification of the impulse as right rather than left ventricular in origin is supported by the presence of a right ventricular lift, an accentuated P_2, and the demonstration of a left ventricular impulse, or the thrill and murmur of mitral valvular disease, in the left axilla.

Other Systolic Precordial Pulsations and Movements

I. A diffuse systolic depression of the precordium followed by a brisk diastolic rebound and a palpable or audible "knock" is characteristic of chronic constrictive pericarditis.

II. A diffuse systolic depression at the left side of the chest accompanied by an opposite pulsation at the right side is characteristic of tricuspid regurgitation.

III. Systolic depression of the midportion and right side of the chest may be found in marked aortic regurgitation.

IV. Paradoxical sustained outward systolic movements, or bulges, are commonly palpable in patients with myocardial infarction or angina pectoris at some point medial to the apex beat. When present at the apex, however, they are indistinguishable from the apical thrust of a hypertrophied left ventricle. A bulge signifies the presence of ventricular asynergy or aneurysm.

Pulsations in the Left Second and Third Intercostal Spaces

I. A faint, nonlifting, systolic pulsation may be normal in young people and patients with pectum excavatum, and during tachycardia.

II. A systolic lifting pulsation in this area is indicative of pulmonary artery dilatation or increased pulmonary blood flow.

Pulsations in the Second Right Intercostal Space

Pulsation in the second right intercostal space suggests dilatation of the aorta.

Pulsations of the Sternoclavicular Joints and Sternum

I. Pulsation of the right sternoclavicular joint may indicate a right-sided aortic arch.

II. Pulsation of either sternoclavicular joint occurs in aortic dissection or aneurysm.

III. Systolic outward pulsation of the upper half of the sternum is generally due to aneurysm of the ascending aorta. Aneurysm of the transverse aorta is usually not associated with visible pulsations but may cause displacement of the trachea or a tracheal tug.

Epigastric Pulsations

I. Epigastric pulsations may be helpful in the diagnosis of ventricular hypertrophy in patients with emphysema.

II. Pulsations in the epigastric region may originate in the aorta or result from an overactive or hypertrophied heart.

III. The pulsations of a hypertrophied right ventricle are palpable high in the epigastric area beneath the rib cage; those of a hypertrophied left ventricle are palpable under the left costal margin. To be indicative of hypertrophy rather than simple overactivity or displacement, such pulsations should have a significant downward thrust.

Thoracic Arterial Pulsations

I. Visible arterial pulsations over the back of the chest occur frequently in coarctation of the aorta from an increased collateral circulation. They are seen best with the patient leaning forward and the back illuminated by a light from above shining obliquely downward.

II. Pulsations in the right lower neck beneath the sternomastoid muscle are usually owing to kinking of the common carotid artery rather than to aneurysm.

III. Other abnormalities of the arterial pulse are described in the section Arterial Pulse, earlier in this chapter.

Heart Sounds

The first sound and both components of the second sound, ejection sounds, the opening snap of mitral stenosis, pericardial friction rubs, and gallop sounds may all be palpable when present. They are identified by their characteristics and timing. Gallop sounds on occasion may be felt even when they are not heard. Left-sided gallops and the mitral opening snap may sometimes be felt more easily with the patient in the left lateral recumbent position.

Thrills

Thrills are palpable vibrations associated with murmurs. The presence of a thrill indicates only that the accompanying murmur is loud. It has no other significance.

Heart Sounds

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Normal Heart Sounds

Usually only two heart sounds, called the first sound and the second sound, are audible in normal persons (Fig. 3-1). The first sound (S_1) is ordinarily louder at the apex than at the base. The converse is true of the second sound (S_2). At the apex, S_1 is usually louder than S_2 but may be of the same or even lesser intensity than S_2. At the base, S_2 is louder than S_1. Decreased intensity of the heart sounds may be caused by poor conduction of the sounds because of such conditions as a thick chest wall, emphysema, or pericardial effusion. Increased intensity of the heart sounds may occur normally in children or thin-chested individuals. In the discussion that follows, only cardiac factors influencing the intensity of the heart sounds are considered.

The First Heart Sound (S_1)

I. The normal first heart sound is composed of audible mitral (M_1) and tricuspid (T_1) components.
II. *Increased intensity* of S_1 may be found in the following conditions:
   A. Sinus rhythm with a short P-R interval (0.08 to 0.12 sec)
   B. Hyperkinetic circulatory states
   C. Mitral stenosis
III. *Decreased intensity* of S_1 may occur when myocardial contractility is impaired or when hemodynamics are altered, as in shock, myocardial infarction, congestive failure, or terminal states. S_1 may be decreased in intensity in mitral or aortic regurgitation.
IV. *Variation in the intensity* of S_1 is a common occurrence in arrhythmias such as atrial fibrillation, AV dissociation, ventricular tachycardia with AV dissociation, and complete AV block. The term *cannon sounds* refers to the very loud first sounds that occur intermittently in the last three conditions.
V. *Normal splitting* of S_1 is audible in 85% of normal subjects. M_1 and T_1 have about the same pitch and intensity and are heard with about equal loudness at both the apex and left sternal border.
VI. *Wide splitting* of S_1 may result from mechanical delays in mitral or tricuspid valve closure (e.g., mitral stenosis, Ebstein's anomaly, atrial septal defect).
VII. S_1 may be *masked* by a loud systolic murmur (e.g., mitral regurgitation).

The Second Heart Sound (S_2)

The second heart sound (S_2) consists of aortic (A_2) and pulmonary (P_2) components. A_2 normally precedes P_2 and is the louder sound in adults. P_2 is usually audible in the pulmonary area; less commonly, it can be heard in the aortic area or left sternal border. It cannot normally be heard at the apex.

Intensity

I. P_2 is usually louder than A_2 up to the age of about 20 or 30 years; in persons above this age, A_2 is louder than P_2.
II. *Increased intensity of A_2* occurs when the systemic arterial pressure is elevated, as in essential hypertension. It may also be accentuated in aortic dilatation or aneurysm and in some cases of aortic regurgitation. A tambourlike A_2 is characteristic of syphilitic aortitis.
III. *Decreased intensity of A_2* is commonly observed in hypotension, shock, and congestive failure. In valvular aortic stenosis, A_2 is usually diminished or absent.
IV. *Increased intensity of P_2*, with P_2 louder than A_2, is found in pulmonary hypertension caused by such conditions as mitral stenosis, left-sided heart failure, primary pulmonary hypertension, pulmonary emboli, and left-to-right shunts. In these conditions, P_2 is sometimes audible at the apex.
V. *Decreased intensity of P_2* or absence of P_2 is noted in pulmonary stenosis.
VI. A_2 or P_2 may be masked by loud systolic murmurs (e.g., pulmonary stenosis and aortic stenosis, respectively).

Splitting

Normal Splitting

I. Normal or physiologic splitting of S_2 into earlier A_2 and later P_2 components is heard best in the pulmonary area or along the left sternal border.
II. The maximum normal split between A_2 and P_2 is about 0.03 sec in expiration and 0.06 sec in inspiration.
III. In normal young adults, in the recumbent position, S_2 is either single or narrowly split during expiration, and is audibly and more widely split during inspiration. However, in the upright position, expiratory splitting of S_2 should not be audible.
IV. Audible expiratory splitting of S_2 in the upright position, with rare exceptions, is suggestive of organic heart disease in adults.
V. S_2 is often single in both expiration and inspiration. This pattern is observed more frequently with advancing age and is quite common in normal adults above the age of 50 years.

Narrow Physiologic Splitting

Narrow physiologic splitting of S_2 owing to early P_2, relative to A_2, is common in patients with severe pulmonary hypertension when right ventricular systole is not prolonged with respect to left ventricular systole.

Wide Splitting

Splitting of S_2 that exceeds normal values may be caused by a delayed P_2, an early A_2, or a combination of the two.

I. The most common causes of wide splitting of S_2 with a *delayed* P_2 are as follows:
   A. Delayed activation of the right ventricle (e.g., complete right bundle branch block, left ventricular paced or ectopic beats)
   B. Prolonged right ventricular mechanical systole (e.g., valvular pulmonary stenosis with an intact interventricular septum, pulmonary hypertension, pulmonary embolism)
   C. Increased right ventricular stroke volume, as in left-to-right shunts (e.g., atrial septal defect, ventricular septal defect) and pulmonary insufficiency
   D. Decreased impedance of the pulmonary vascular bed (increased hangout) as, for example, in normotensive atrial septal defect, idiopathic dilatation of the pulmonary artery, and mild pulmonary stenosis
   E. Structural abnormalities such as pectus excavatum and the straight back syndrome
II. An *early A_2* may result from decreased resistance to left ventricular ejection or decreased left ventricular stroke volume, as in ventricular septal defect or mitral regurgitation.

Wide and Fixed Splitting

I. The term *fixed splitting* (of S_2) refers to an already widely split S_2 that splits no further or splits by not more than 0.02 sec during inspiration in either the recumbent or sitting position.
II. Wide and fixed splitting of S_2 may be observed in atrial septal defects and some other left-to-right shunts, severe right-sided heart failure, acute massive pulmonary embolism, and cardiomyopathy.
III. The widely split S_2 of right bundle branch block is not fixed.

Reversed or Paradoxical Splitting

I. Reversed splitting of S_2 is rarely a normal finding. It results from delayed aortic closure so that A_2 follows rather than precedes P_2 during the entire respiratory cycle.
II. Usually the splitting narrows during inspiration and widens during expiration.
III. The most common causes of paradoxical splitting of S_2 are as follows:
   A. Delayed closure of the aortic valve
      1. Delayed electric activation of the left ventricle (e.g., complete left bundle branch block, right ventricular paced or ectopic beats)
      2. Prolonged left ventricular mechanical systole (e.g., left ventricular outflow tract obstruction)

3. Decreased impedance of the systemic vascular bed (increased hangout) as in poststenotic dilatation of the aorta or patent ductus arteriosus
B. Early closure of the pulmonary valve. Early electric activation of the right ventricle as in the Wolff–Parkinson–White (WPW) syndrome, type B

Single Second Heart Sound

I. A single S_2 is a common normal variant in persons above the age of 50 years
II. S_2 may be single because of changes in P_2.
  A. P_2 is faint or not detected (e.g., tetralogy of Fallot, tricuspid atresia, pulmonary atresia, pulmonary stenosis).
  B. P_2 is synchronous with A_2 (e.g., ventricular septal defect with Eisenmenger's syndrome, some cases of aortic stenosis, occasional instances of left bundle branch block, pulmonary hypertension).
  C. P_2 is masked by a systolic murmur (e.g., aortic stenosis).
III. S_2 may be single because of changes in A_2.
  A. A_2 is faint or not detected (e.g., aortic stenosis).
  B. A_2 is synchronous with P_2 (see preceding paragraph).
  C. A_2 is masked by a systolic murmur (e.g., pulmonary stenosis).
IV. S_2 is single when there is only one semilunar valve (e.g., truncus arteriosus).

Abnormal and Extra Sounds

The various abnormal and extra sounds that may be encountered are discussed in the following; their differential diagnoses are summarized in Tables 3-3 and 3-4.

The Third Heart Sound (Ventricular Gallop, S_3)

Normal

I. The third sound (S_3) is commonly audible in normal children and young adults below the age of 30 years.
II. The normal S_3 is a soft, low-pitched sound that is usually localized to the apex. It is heard best with the bell of the stethoscope with the subject in the left lateral recumbent position. The sound is louder in expiration than inspiration.

Abnormal

I. S_3 is abnormal above the age of 30 years and probably at any age in the presence of heart disease.
II. S_3 occurs 0.12 to 0.18 sec after A_2 and coincides with the descending limb of the V wave of the jugular venous pulse.
III. S_3 may be accompanied by a palpable or visible apical shock or bulge.
IV. A left-sided S_3 (LS_3) is caused by left ventricular disease or failure; a right-sided S_3 (RS_3), by right ventricular disease or failure. LS_3 is heard best at the apex; RS_3, along the left sternal border, the tricuspid area, and occasionally in the right supraclavicular fossa. LS_3 is louder in expiration; RS_3, in inspiration.
V. An S_3 sound may be the earliest sign of myocardial failure.
VI. The intensity of S_3 is decreased by sitting or standing and increased by brief exercise.
VII. An LS_3 is absent in pure or predominant mitral stenosis, but RS_3 may occur when there is pulmonary hypertension. If an LS_3 is heard in a patient with both mitral stenosis and regurgitation, it can be assumed that regurgitation is the predominant lesion.
VIII. S_3 must be differentiated from the second component of a split S_2, an opening snap, and an S_4 (Table 3-4).
IX. The pericardial knock, a diastolic filling sound occurring somewhat earlier than the usual S_3 (0.06 to 0.12 sec after A_2), is found in most cases of chronic constrictive pericarditis; it coincides with the end of the Y descent in the jugular venous pulse.
X. S_3 may coexist with S_4, producing a quadruple rhythm, whereas either sound alone, when combined with S_1 and S_2, produces a triple rhythm. When S_3 and S_4 coincide, the condition is called a summation sound, or gallop. Transient slowing of the heart rate by carotid massage may separate a suspected summation sound into its S_3 and S_4 components.

Table 3-3. Differential diagnosis: S_4 preceding M_1 versus split S_1 (M_1 preceding T_1)

Parameter	LS_4 preceding M_1	RS_4 preceding M_1	Split S_1 (M_1 and T_1)
Characteristics of sound	Faint, low-pitched sound (S_4) followed by higher-pitched sound (M_1)	Faint, low-pitched sound (S_4) followed by higher-pitched sound (M_1)	M_1 and T_1 about same intensity and pitch
Effect of pressure with stethoscope diaphragm	LS_4 more faint or inaudible	RS_4 fainter or inaudible	M_1 and T_1 may be more faint but sharper and clicky
Area of maximum audibility	Apex, especially in left lateral recumbent position, with bell chest piece; faint or absent away from apex	Lower left sternal border, with bell chest piece	Lower left sternal border and medial to apex but not lateral to it, with bell or diaphragm; equal intensity at apex and LSB
Interval between sounds	Usually 0.05–0.10 sec	Usually 0.05–0.10 sec	Usually about 0.03 sec
Precordial pulsations	Presystolic and systolic apical impulses	Right ventricular lift or heave	Single systolic apical impulse
Effect of respiration	LS_4 louder in expiration	RS_4 louder in inspiration	Splitting somewhat more evident in expiration
Effect of change in venous return			
Increase (e.g., leg raising)	LS_4 louder	RS_4 louder	Little or no effect
Decrease (e.g., sitting)	LS_4 more faint or inaudible	RS_4 more faint or inaudible	Little or no effect

LS_4 = left-sided S_4, LSB = left sternal border, M_1 = first audible component of S_1, RS_4 = right-sided S_4, S_1 = first sound, T_1 = second audible component of S_1

The Opening Snap

I. The opening of the mitral or tricuspid valves is normally inaudible. Audible opening of an AV valve occurs when it is stenosed. The sound produced is called an opening snap (OS).
II. The OS of the mitral valve (OSMV) is virtually pathognomonic of mitral stenosis and indicates that the valve is pliable. The OS disappears when the valve becomes rigid, fixed, or calcified. It may also disappear in the presence of aortic insufficiency or when mitral regurgitation is the predominant lesion. Surprisingly, the OS persists after commissurotomy. It is audible both in sinus rhythms and atrial fibrillation.
III. The OSMV is a high-pitched, snapping sound that occurs between 0.04 and 0.12 sec after A_2. The severity of mitral stenosis may be roughly estimated from the A_2-OS interval. As a rule of thumb, the stenosis is severe when the interval is short, and mild when it is long.
IV. The OSMV is heard best at the lower left sternal border and at the apex, but it is also frequently audible at the base. The sound may be palpable as well as audible. Its timing coincides with the V wave of the jugular venous pulse. The intensity of the sound is not affected by respiration.

Table 3-4. Differential diagnosis of various heart sounds

Parameter	Split S_2, A_2 preceding P_2	Opening snap	S_3	S_4	Ejection sound
Characteristics of sound	P_2 soft unless accentuated	Relatively loud, high-pitched	Faint, low-pitched	Faint, low-pitched	Sharp, clicking
Interval between sounds	A_2-P_2, 0.03–0.05 sec during inspiration	A_2-OS, 0.04–0.12 sec	A_2-S_3, 0.12–0.18 sec; S_2-S_3, 0.18 sec	S_1-M_1, 0.05–0.10 sec; S_2-S_4, 0.20 sec	M_1-ES, 0.04–0.09 sec; M_1-T_1, 0.03 sec
Area of maximum audibility	Localized to pulmonary area and LSB	Widespread; OSMV: 4LICS, apex, and LSB; OSTV: lower LSB; OSMV: loud, snapping S_1 at apex and A_2, P_2, and OS audible in pulmonary area	Localized: LS_3: apex in LLRP; RS_3; LSB, tricuspid area, and supraclavicular fossa	Localized: LS_4: apex in LLRP, not transmitted; RS_4: lower LSB, sometimes lower RSB	Usually localized; PES: 2- and 3LICS; AES: apex, LSB, aortic area
Precordial pulsations	P_2 sometimes palpable if accentuated; other pulsations depend on underlying conditions	OS may be palpable; apical impulse often impalpable in pure mitral stenosis	LS_3 palpable or visible, or both; RS_3 may have right ventricular heave or lift	LS_4 presystolic and systolic apical impulses; RS_4: right ventricular heave or lift	ES not palpable; other pulsations depend on underlying conditions
Effect of respiration	Splitting increased unless fixed; P_2 louder on inspiration	OSMV louder on expiration; OSTV louder on inspiration	LS_3 decreased with inspiration; RS_3 increase with inspiration	LS_4 louder in expiration; RS_4 louder in inspiration	PES decreased and moves closer to S_2 with inspiration AES not affected by respiration
Effect of change in venous return					
Increase (e.g., leg raising)	P_2 louder, split increased	Little or no effect	Louder	Louder	Little or no effect
Decrease (e.g., sitting)	A_2 louder, split decreased	Little or no effect	Fainter	Fainter	Little or no effect

A_2 = aortic component of S_2, AES = aortic ES, ES = ejection sound, LICS = left intercostal space, LLRP = left lateral recumbent position, LS_3 = left-sided S_3, LS_4 = left-sided S_4, LSB = left sternal border, M_1 = mitral component of S_1, OS = opening snap, OSMV = OS mitral valve, OSTV = OS tricuspid valve, P_2 = pulmonary component of S_2, PES = pulmonary ES, RS_3 = right-sided S_3, RS_4 = right-sided S_4, RSB = right sternal border, S_2, = second heart sound, S_3 = third heart sound, S_4 = fourth heart sound, T_1 = tricuspid component of S_1

V. The mitral OS is associated almost always with a loud S_1 and frequently with a split S_2 and accentuated P_2.
VI. An OS of the tricuspid valve (OSTV) may be heard in some patients with tricuspid stenosis. The auscultatory characteristics of this sound are similar to those of the mitral OS, but there are some differences. The OSTV is heard best over the lower end of the sternum or at the right lower sternal edge. The tricuspid A_2-OS interval is shorter than the mitral A_2-OS interval. The tricuspid OS is not appreciably affected by respiration. An OSTV is occasionally heard in atrial septal defects in the absence of tricuspid stenosis.
VII. In severe MS, the A_2-OS interval may be so short that the OS cannot be clearly differentiated from the components of S_2. Under such circumstances, administration of phenylephrine may, by increasing the A_2-OS interval, separate the OS from S_2 enough to make it identifiable as a separate sound.

The Fourth Sound (Atrial Sound or Gallop, S_4)

I. The fourth sound (S_4) occurs about 0.12 sec after the P wave, preceding S_1 by about 0.05 to 0.10 sec when the P-R interval is normal. S_4 sounds, also called atrial or presystolic gallops, are usually indicative of myocardial abnormality. Atrial sounds are not audible in atrial fibrillation.
II. S_4 is usually a soft, low-pitched sound; hence, it is heard best with the stethoscope bell applied lightly to the chest wall. It may be audible with the diaphragm.
III. S_4 may be left-sided or right-sided in origin.

Left-Sided S_4

I. Left-sided S_4 (LS_4) is usually heard best at the cardiac apex with the patient in the left lateral recumbent position.
II. It is usually associated with a presystolic apical impulse.
III. LS_4 may wax and wane with respiration, becoming louder during expiration or becoming audible only during this phase of respiration.
IV. Maneuvers that increase venous return (e.g., leg raising, exercise) tend to increase the intensity of the sound; those that decrease venous return (e.g., sitting) have the opposite effect.
V. LS_4 has been reported to occur in some normal individuals over 50 years of age, but it is more commonly associated with one of the following conditions:
   A. Disorders characterized by decreased compliance of the left ventricle (e.g., systemic hypertension, aortic stenosis or insufficiency, cardiomyopathy)
   B. Acute myocardial infarction (LS_4 is heard in an overwhelming majority of cases)
   C. Attacks of angina pectoris
   D. AV block, of varying degrees
   E. Hyperkinetic circulatory states (e.g., hyperthyroidism, anemia)
VI. LS_4 is ordinarily not audible in mitral valve disease, but it may occur in acute mitral regurgitation owing to ruptured chordae tendineae.

Right-Sided S_4

I. Right-sided S_4 (RS_4) is usually heard along the lower left sternal border and sometimes over the right internal jugular vein.
II. RS_4 is usually associated with a sustained left parasternal heave and a giant jugular A wave.
III. RS_4 may wax and wane during respiration, becoming loudest during inspiration.
IV. Maneuvers that increase the venous return to the heart increase the intensity of S_4; those that decrease the venous return have the opposite effect.
V. RS_4 is heard in conditions in which there is either decreased compliance of the right ventricle or increased resistance to right ventricular filling:
   A. Pulmonary hypertension (e.g., atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary embolism, primary pulmonary hypertension)
   B. Pulmonary stenosis
   C. Cardiomyopathy

Systolic Sounds

Pulmonary Ejection Sounds

I. Pulmonary ejection sounds (PES) occur at the time blood is ejected from the right ventricle into the pulmonary artery. They follow M_1 by 0.04 to 0.09 sec (range 0.02–0.14 sec).
II. PES are heard best over the second or third left intercostal spaces. They are poorly heard or inaudible at the apex. They tend to decrease in intensity and move closer to S_1 during inspiration.
III. PES have a sharp clicking quality.
IV. PES occur in most cases of pulmonary stenosis and in many cases of primary and secondary pulmonary hypertension.

Aortic Ejection Sounds

I. Aortic ejection sounds (AES) occur at the time of ejection of blood from the left ventricle into the aorta. Their timing is similar to that of PES.
II. AES, in contrast to PES, are usually heard best at the apex and have no respiratory variation. They may also be heard along the left sternal border and in the aortic area.
III. AES are present in almost all cases of congenital valvular aortic stenosis, but not in infundibular, supravalvular, or idiopathic hypertrophic subaortic stenosis. AES may be heard in some cases of rheumatic aortic stenosis and in occasional instances of aortic insufficiency, coarctation of the aorta, aneurysm of the ascending aorta, and the tetralogy of Fallot.

Systolic Clicks

I. Clicks are systolic sounds. Although systolic clicks (SC) occur at any time during systole, they are more common in mid- or late systole. They are usually single, but sometimes two or more sounds may be heard.
II. Systolic clicks are heard best in the midprecordium or at the apex, and may show respiratory or positional variation in intensity or even in timing from beat to beat.
III. Systolic clicks associated with mid- or late apical systolic murmurs are indicative of mitral valve prolapse.

Pericardial Friction Rub

I. The pericardial friction rub is a rough, scratchy sound, often quite changeable in character from day to day or even minute to minute, audible over the precordium in most cases of acute pericarditis but rarely in chronic constrictive pericarditis. The rub is usually louder on inspiration. The sound may have systolic, diastolic, and presystolic components. When two or three components are present, the diagnosis is made easily. When the rub is heard only during systole, it may be mistaken for a murmur or an extracardiac sound. With continued observation, the friction rub either assumes a to-and-fro character or disappears.
II. A pericardial friction rub should be differentiated from: (a) a *pleuropericardial friction rub,* which is usually louder at the apex, often associated with a left pleural friction rub, and markedly affected by respiration; and (b) the to-and-fro *crunching sound of mediastinal emphysema,* which is coarser in quality and often associated with crepitus of the soft tissues of the neck.

Heart Murmurs

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Murmurs are related to several factors: (a) increased flow through normal or abnormal valves, (b) forward flow through narrowed or deformed valves, (c) backward or regurgitant flow through incompetent valves or septal defects, (d) more or less continuous flow through extracardiac and intracardiac shunts and narrowed or collateral vessels, and in vascular structures, and, less often, (e) vibration of loose structures within the heart. The following abbreviations are used in this section:

A_2 = aortic component of second heart sound
AES = aortic ejection sound(s) or click(s)
AR = aortic regurgitation
AS = aortic stenosis
ASD = atrial septal defect
CM = continuous murmur(s)
DM = diastolic murmur(s)
EM = ejection murmur(s)
ES = ejection sound(s) or click(s)
ICS = intercostal space
IE = infective endocarditis
IHSS = idiopathic hypertrophic subaortic stenosis
IPS = infundibular pulmonary stenosis
JVP = jugular venous pulse
LA = left atrium
LAE = left atrial enlargement
LICS = left intercostal space
LLRP = left lateral recumbent position
LLSB = lower left sternal border
LRSB = lower right sternal border
LSB = left sternal border
LV = left ventricle (ventricular)
LVE = left ventricular enlargement
MR = mitral regurgitation
MS = mitral stenosis
OS = opening snap
OSMV = OS mitral valve
OSTV = OS tricuspid valve
P_2 = pulmonary component of second heart sound
PA = pulmonary artery
PDA = patent ductus arteriosus
PES = pulmonary ejection sound(s) or click(s)
PH = pulmonary hypertension
PPH = primary pulmonary hypertension
PR = pulmonary regurgitation
PS = pulmonary stenosis
RA = right atrium
RAE = right atrial enlargement
RICS = right intercostal space
RM = regurgitant murmur(s)
RSB = right sternal border
RV = right ventricle (ventricular)
RVE = right ventricular enlargement
S_1 = first heart sound
S_2 = second heart sound
S_3 = third heart sound
S_4 = fourth heart sound
SC = systolic click(s)
SEM = systolic ejection murmur(s)
SM = systolic murmur(s)
SPH = secondary pulmonary hypertension
SRM = systolic regurgitant murmur(s)
T/F = tetralogy of Fallot
TR = tricuspid regurgitation
TS = tricuspid stenosis
ULSB = upper left sternal border
URSB = upper right sternal border
VAS = valvular aortic stenosis
VPS = valvular pulmonary stenosis
VSD = ventricular septal defect(s)

Types of Murmurs

There are three basic types of murmurs: systolic, diastolic, and continuous. An SM begins with or after S_1 and ends before, at, or slightly beyond S_2. A DM begins with or after S_2 and ends before S_1. A CM begins in systole, continues through S2 without interruption, and ends at some time in diastole.

Systolic Murmurs

Systolic Ejection Murmurs

I. *Midsystolic EM* are caused by normal or increased forward flow through either normal or abnormal right or left ventricular outflow tracts. They may be found in AS or PS, increased flow through a normal valve, ejection across a nonstenosed but deformed valve, dilatation of the aorta or PA, or combinations of these. The murmur of AS is the prototype of left-sided midsystolic EM, and the murmur of PS, of right-sided EM. Such murmurs begin after S_1 and end before A_2 if left-sided, and before P_2 if right-sided. The murmurs are of variable intensity, high- to medium-pitched, noisy, rough, or harsh in quality, and generally crescendo-decrescendo (diamond-shaped) in character.

II. *Early systolic EM* are primarily flow murmurs, beginning after S_1 and ending midway through systole. They tend to be decrescendo (kite-shaped) in character.

Systolic Regurgitant Murmurs

SRM are caused by flow from high- to low-pressure chambers or vessels. Thus, they occur in MR, TR, VSD, and some aortopulmonary communications. RM may be classified according to their timing as pansystolic (holosystolic), early systolic, midsystolic, or late systolic. *Pansystolic RM* start with S_1 and end with or beyond A_2. They are typical of the aforementioned conditions. *Early systolic RM* start with S_1 but end in midsystole. They occur in some VSD, in tight MS with slight MR, and in TR from IE. *Midsystolic RM* begin after S_1 and end before or at A_2. They are usually found in MR because of papillary muscle dysfunction, although any type of SRM may occur in this condition. *Late systolic RM* start about midsystole, often with an SC, and end at or beyond A_2. They occur most often in nonrheumatic MR associated with prolapse of one or both mitral leaflets into the LA, but they may be found in rheumatic MR and in calcification of the mitral annulus.

Diastolic Murmurs

DM may be classified as early diastolic, middiastolic, or late diastolic (presystolic). *Early DM* are caused by semilunar valve incompetence. *Mid- and late DM* are owing either to stenosis of the atrioventricular valves or to increased flow across these valves.

Continuous Murmurs

CM begin after S_1, continue through S_2 without interruption, enveloping it, and end at some time in diastole before S_1. The murmur need not persist through all of diastole to be considered continuous. CM occur in extracardiac and intracardiac shunts but may be caused by flow through narrowed or collateral vessels or by increased flow in vascular structures.

Description of Murmurs

Descriptions of murmurs should include their timing, intensity, pitch, quality, duration, location, and radiation. The most widely used system (Levine and Harvey) for grading the intensity of heart murmurs uses a six-point scale.

Grade 1: Very faint
Grade 2: Faint
Grade 3: Moderately loud
Grade 4: Loud
Grade 5: Very loud
Grade 6: Loudest possible

Physiologic and Pharmacologic Maneuvers

Physiologic and pharmacologic maneuvers may have effects on the intensity of murmurs that may have some diagnostic significance. The maneuvers and their effects on various murmurs are summarized in Table 3-5. Use of these maneuvers is often helpful in the differential diagnosis of specific auscultatory problems (Table 3-6).

Vasopressors increase peripheral resistance; vasodilators reduce it. Standing upright causes a decrease in venous return and a slight increase in heart rate and systemic arterial resistance. Squatting causes a transient increase in venous return and increased peripheral arterial resistance. Both of these effects increase the size of the left ventricle. The Valsalva maneuver obstructs venous return during the straining phase and diminishes the size of both the right and left ventricles.

Diagnostic Approach to Murmurs

The diagnostic evaluation of any heart murmur involves, first, a decision as to whether the murmur is innocent or organic, and second, if organic, a determination of the anatomic lesion and its cause. The workup of a patient with an organic murmur should include examination of the arterial and jugular venous pulses, inspection and palpation of the precordium and chest wall, and systematic auscultation of the heart, thorax, and related vascular structures. Also indicated in all cases are an ECG and chest films (preferably PA, lateral, and oblique views taken with a barium-filled esophagus). Cardiac fluoroscopy with image amplification is invaluable in studying motion and dynamic changes as well as in the detection of valvular or other calcifications.

Based on the aforementioned procedures, it is possible to make the correct cardiac diagnosis in the vast majority of cases. When this is not possible or for other legitimate reasons (e.g., confirmation of a diagnosis, preoperative evaluation), apexcardiography, external recordings of the jugular and carotid pulses, phonocardiography, echocardiography, cardiac catheterization, and angiocardiography may be indispensable tools for diagnosis, differential diagnosis, or the study of cardiovascular hemodynamics. As a general rule, preference should be given to noninvasive techniques when the information yielded is comparable to that obtainable by catheter intervention. Because all these supplementary techniques are highly technical and require special equipment, they usually are not performed by the nonspecialist in cardiology, and hence are not discussed here.

In the presentation that follows, primary consideration is given to the more frequent, uncomplicated murmurs encountered in adults, omitting discussion of many complex congenital or acquired lesions. The murmurs are described according to their timing and site of maximum intensity.

Innocent Murmurs

Innocent murmurs are those not caused by recognizable lesions of the heart. Although they may occur at any age, they are most common in children and adolescents. The characteristics of innocent murmurs in young people and their differential diagnosis are summarized in Tables 3-7 and 3-8. The aortic ejection murmur of middle and old age, although not innocent, is nevertheless benign. It is, so to speak, the innocent murmur of the elderly. It is discussed in the following.

Systolic Murmurs According to Site of Maximum Intensity

Second Right Intercostal Space (Aortic Area): Midsystolic Ejection Murmurs

Etiology

I. Left ventricular outflow obstruction
   A. Congenital aortic stenosis
      1. Valvular
      2. Subvalvular (discrete)
      3. Supravalvular
   B. Acquired aortic stenosis
      1. Rheumatic
      2. Nonrheumatic
   C. Idiopathic hypertrophic subaortic stenosis
      1. Aortic ejection murmur of middle and old age (probably owing to aortic valve sclerosis)
      2. Transmitted murmur of mitral regurgitation
      3. Aortic flow murmur in free aortic regurgitation

(*text continued on page 76*)

Table 3-5. The effects of physiologic and pharmacologic maneuvers on murmurs

Murmur	Inspiration	Sudden standing	Sudden squatting	Vasodilators (amyl nitrite)	Vasopressors (phenylephrine or methoxamine)	Valsalva and post-Valsalva effect	Effect of miscellaneous maneuvers on murmur
Aortic stenosis	NSC	D	I	I	D or NSC	D, with delayed return of intensity of murmur	I after extrasystole or pause, and leg raising
Idiopathic hypertrophic subaortic stenosis	NSC	I	D	I	D	I	I after extrasystole or pause, sitting, standing; D after leg raising
Pulmonary stenosis	I	NSC	I	PS: I (most cases) Tetralogy of Fallot: D	PS: NSC Tetralogy of Fallot: I	D, with immediate return of intensity of murmur	
Aortic regurgitation	D	NSC compared with sitting	I	D Austin Flint murmur: D	I Austin Flint murmur: I		I when sitting, when leaning forward, and in expiration
Mitral regurgitation Pansystolic	NSC or D	D or NSC	I	D	I	D, with later I	Beat after extrasystole or pause: NSC
Mid- to late systolic (click syndrome)	Murmur starts earlier; is longer	Murmur starts earlier; is longer	Murmur starts later; is shorter	Murmur starts earlier; is longer	I	I, with later D	Murmur starts later; is shorter
Papillary muscle dysfunction	NSC	NSC	Variable	Variable	Variable		D or NSC
Tricuspid regurgitation	I	D or NSC	I	I or NSC	NSC	D, with later I	
Ventricular septal defect without pulmonary hypertension	NSC	NSC	I	D	I	NSC	I after exercise and in left lateral recumbent position
Mitral stenosis	NSC or slight D; may reveal A_2-P_2-OS sequence	D	I	I	D; A_2-OS interval is widened	NSC	
Tricuspid stenosis	I	D	I	I	NSC	NSC	
Pulmonary regurgitation	I or NSC			NSC	NSC		

D = decreased intensity, I = increased intensity, NSC = no significant change in intensity
Source: Adapted from M. C. Dohan and M. G. Drisitiello, Physiologic and pharmacologic manipulations of heart sounds and murmurs. *Mod. Concepts Cardiovasc. Dis.* 39:121, 1970.

TABLE 3-6. Maneuvers helpful in the differential diagnosis of similar murmurs

Diagnostic problem	Useful maneuvers[a]
Mitral regurgitation versus tricuspid regurgitation	Respiration, amyl nitrite, vasopressors
Aortic stenosis versus idiopathic hypertrophic subaortic stenosis	Squatting, standing, Valsalva, amyl nitrite
Mitral regurgitation versus idiopathic hypertrophic subaortic stenosis	Squatting, standing, amyl nitrite, vasopressors
Aortic stenosis versus mitral regurgitation	Amyl nitrite, vasopressors, post-extrasystolic beat
Aortic stenosis versus mid- to late systolic murmur of mitral regurgitation	Standing, amyl nitrite
Mitral stenosis versus Austin Flint murmur	Amyl nitrite, vasopressors
Mitral stenosis versus tricuspid stenosis	Respiration, amyl nitrite, vasopressors
Pulmonary stenosis versus tetralogy of Fallot	Amyl nitrite
Pulmonary stenosis versus small ventricular septal defect	Amyl nitrite, vasopressors

[a] The responses to these maneuvers are shown in Table 3-5.
From Dohan MC, Drisitiello MG. Physiologic and pharmacologic manipulations of heart sounds and murmurs. *Mod Concepts Cardiovasc Dis* 1970;39:121, with permission.

4. Supraclavicular arterial bruit
5. Coarctation of the aorta (some cases)

Diagnostic Features

I. The murmur of AS is the prototype of left-sided SEM. When a crescendo–decrescendo, loud, noisy, harsh aortic EM, which is transmitted upward to the right and into the carotids, occurs in association with a thrill, a faint or absent A_2, and an anacrotic or small pulse with a delayed systolic peak, the diagnosis of AS is established. The presence of valvular calcification on fluoroscopy or radiograph is confirmatory.

II. Isolated AS in persons under the age of 30 years is usually congenital, particularly if the valve is calcified. The valve is usually unicuspid. Above this age to about the age of 60 years, congenitally bicuspid valves predominate. Rheumatic aortic stenosis is almost always associated with mitral valvular disease and often with severe AR. Isolated rheumatic AS is rare. Calcific AS in the elderly is believed to be degenerative in origin. The murmur of AS must be differentiated from the benign nonobstructive aortic EM of middle and old age.

III. The differential diagnosis of the various causes of AS is summarized in Table 3-8. It is especially important to differentiate between valvular AS and IHSS. Some important differences are as follows: The murmur of IHSS is medium-pitched and less rough than that of valvular obstruction. It is usually maximum at the LLSB or at the apex rather than in the 2RICS. The murmur, like that of AS, is ejection in type except at the apex, where it is likely to be holosystolic because of associated MR. Sudden squatting, the Valsalva maneuver, changes in position, amyl nitrite, and vasopressors may help differentiate between AS and IHSS when the auscultatory findings are similar. In IHSS, the thrill when present is maximum at the LLSB or at the apex, the ventricular impulse is sustained or double-peaked, the carotid pulse is brisk or bisferiens, S_3 and S_4 sounds are frequently audible, S_2 is single or paradoxically split, the murmur of AR is absent, and diagnostic abnormalities may be found in the ECG or echocardiogram, or on cardiac catheterization. IHSS must also be distinguished from MR owing to other causes; for this purpose, compare the features of each in Tables 3-9 and 3-10.

IV. The murmur of AS must also be differentiated from the benign nonobstructive aortic EM of middle and old age. The latter tends to be both less harsh and less intense than the murmur of AS. It shows little upward radiation but is commonly transmitted to the apex, where it may be louder than at the base. It retains the configuration of a midsystolic EM at all locations. The arterial pulse is normal unless the pulse pressure is increased by concomitant hypertension. The JVP, the apical impulse, and the heart sounds are normal. No extra sounds are audible. A thrill is rarely present. The diagnosis of this benign murmur is supported by the age of the patient, the presence of aortic dilatation or systemic hypertension, and the absence of murmurs of other valvular lesions. When the murmur is loudest at the apex, it may be mistaken for the murmur of MR, which differs in being higher-pitched, blowing, and pansystolic rather than midsystolic.

V. The differential diagnosis of the murmurs of AS and MR is discussed in Table 3-11.

VI. In free AR, it may be difficult to determine whether a midsystolic aortic EM is owing to flow or coexisting AS. Favoring stenosis over flow are the absence of peripheral signs of AR, a normal diastolic blood pressure, and the harshness and late peaking of the murmur. Either murmur may be loud and associated with a thrill.

VII. The differential diagnosis between aortic EM and innocent supraclavicular arterial bruits is given in Table 3-7.

VIII. The differential diagnosis of the murmurs of PS and AS is summarized in Table 3-12.

IX. Coarctation of the aorta usually produces a basal SEM that may be heard in the 2RICS but that is more commonly heard better in the 2LICS or, rarely, at the apex. The murmur is heard as well or even better posteriorly in an area medial to the left scapula.

Left Sternal Border: Midsystolic Ejection Murmurs

Etiology

I. Right ventricular outflow obstruction
   A. Congenital pulmonary stenosis
   B. Tetralogy of Fallot
   C. Acquired pulmonary stenosis
      1. Rheumatic fever
      2. Carcinoid syndrome
II. Idiopathic dilatation of the pulmonary artery
III. Atrial septal defect
IV. Ventricular septal defect (some cases with small left-to-right shunts)
V. Pulmonary hypertension
   A. Primary
   B. Secondary
      1. Left-to-right shunts
      2. Mitral stenosis
VI. Coarctation of the aorta
VII. Idiopathic hypertrophic subaortic stenosis
VIII. Pulmonary flow murmurs in hyperkinetic circulatory states (e.g., fever, anemia, thyrotoxicosis)
IX. Innocent murmurs
   A. Pulmonary ejection murmur
   B. Vibratory or Still's murmur
   C. Cardiorespiratory murmur

Diagnostic Features

I. As may be seen from the preceding, a large number of murmurs may have their sites of maximum intensity along the LSB. The murmur of VPS with an intact

(text continues on page 87)

Table 3-7. Innocent murmurs in young people and their differential diagnosis

Innocent murmur	Maximum site and transmission	Features of innocent murmur	Organic murmur to be differentiated	Features of organic lesion
Pulmonary ejection murmur	2LICS with radiation to LLSB and apex	Early to midsystolic, rough or blowing, low- to medium-pitched; increased in recumbency, held expiration, and after exercise; common in the straight back syndrome or pectum excavatum; S2 normally split; precordium quiet	Atrial septal defect Mild valvular pulmonary stenosis	Murmur louder, longer, with wide fixed splitting of S_2; right ventricular impulse hyperdynamic Murmur louder, longer, harsher with thrill; S_2 widely split; sustained right ventricular lift
Vibratory murmur	Apicosternal region; may be widely transmitted	Early to midsystolic, medium-pitched, crescendo–decrescendo, vibratory, twangy, or groaning; louder with amyl nitrite; no significant change with vasopressors	Small ventricular septal defect	Murmur high-pitched, blowing, holosystolic, with thrill in 3LICS or 4LICS; when early systolic, often no thrill, but murmur is high-pitched, blowing; softer with amyl nitrite; louder with vasopressors
			Mitral regurgitation	Murmur holosystolic apical, transmitted to left axilla and scapula; softer with amyl nitrite; louder with vasopressors
Supraclavicular arterial bruit	Maximum on the right side of neck, and louder above the clavicle than below it	Short, low-pitched early systolic; louder with slight compression of the subclavian artery; decreased or obliterated by marked compression of the subclavian artery or hyperextension of shoulders; sounds and precordium normal	Aortic stenosis	Murmur maximum in 2RICS or apex, often with thrill; A_2 decreased or absent; sustained left ventricular lift
Venous hum	Neck, especially on the right side with head turned away from side being examined	Continuous low- to medium-pitched, peaking after S_2; decreases or disappears with recumbency; obliterated by compression of jugular veins; louder with amyl nitrite; softer or no change with vasopressors	Patent ductus arteriosus	Maximum over pulmonary area; not affected by position change or compression of jugular veins; peaks at S_2; softer with amyl nitrite; louder with vasopressors
Mammary souffle	RSB or LSB from 2ICS to 4ICS	Medium- to high-pitched continuous, with systolic accentuation; occurs in late pregnancy and lactation, then disappears; obliterated by firm stethoscope pressure	Patent ductus arteriosus Arteriovenous fistula of chest wall	See venous hum Murmur louder, with thrill; usually not obliterated with stethoscope pressure; persists after pregnancy or lactation

From Castle RF. The innocent heart murmurs. *Rocky M Med J* 1972;69:45, with permission.

Table 3-8. Differential diagnosis of systolic ejection murmurs at left sternal border

Part I

Parameter	Congenital pulmonary stenosis (uncomplicated)	Tetralogy of Fallot (uncomplicated)	Idiopathic dilatation of pulmonary artery	Atrial septal defect	Innocent murmurs
Clinical features	Murmur present from birth; growth and development normal; chubby, round facies typical	Cyanosis present at rest or after exercise; most common type of cyanotic congenital heart disease above the age of 4 years; dyspnea and squatting common	Asymptomatic in healthy young people	Asymptomatic; F > M; mostly young people	Normal in young people; also in straight back syndrome (SBS) and pectum excavatum (PE)
Arterial pulse	Normal, or decreased if severe	Normal	Normal	Normal or small	Normal
Jugular venous pulse	Mild: normal A waves Moderate to severe: large A waves	Normal; large A waves occur if PS is severe and the VSD is small; large A and V waves in CHF	Normal	Usually normal; large A waves in PH or LV failure	Normal
Precordial pulsations	Valvular: sustained RV lift reaching to 3LICS; no impulse over 2LICS Infundibular: sustained RV lift, not reaching 3LICS	Slight RV lift below 3LICS	PA impulse palpable 2LICS; RV impulse not palpable	Hyperdynamic RV impulse: systolic pulsation of enlarged pulmonary trunk	Normal
Maximum thrill	Valvular: 2LICS or occasionally 3LICS Infundibular: 3LICS or more commonly 4LICS	Usually 3LICS	None	Usually absent, but may be felt over PA	None
Ejection sounds	Valvular: Mild: PES present or absent Moderate to severe: PES 2 LICS, which decreases and moves toward S_1 with inspiration Severe: may be absent Infundibular: absent	PES rare because PS is usually infundibular; AES present in 2RICS only in severe PS or atresia	PES 2LICS	Absent unless PH is present	None PES in SBS
Heart sounds	S_1: normal S_2: narrowly split in mild PS; widely split in more severe PS; widely split in infundibular PS P_2: valvular Mild: normal or increased Moderate to severe: decreased or absent Infundibular: usually absent RS_4: in moderate to severe PS	S_1: normal Mild: widely split S_2; P_2 decreased or absent Moderate: P_2 absent, A_2 loud Severe: P_2 absent, A_2 loud RS_4: absent	S_1: normal S_2: narrowly or widely split	S_1: normal, or loud and split with $T_1 > M_1$ S_2: wide, fixed splitting P_2: normal or increased and audible at apex RS_4: sometimes present RS_3: sometimes present	S_1: normal; may be loud in SBS or PE S_2: normally split; may be widely split with increased P_2 in SBS or PE RS_4: may be present in SBS or PE

continued

Table 3-8. *Continued.*

Part I

Parameter	Congenital pulmonary stenosis (uncomplicated)	Tetralogy of Fallot (uncomplicated)	Idiopathic dilatation of pulmonary artery	Atrial septal defect	Innocent murmurs
Systolic murmur	Harsh, long crescendo-decrescendo; Valvular Mild: ends before A_2 Moderate: ends with A_2 Severe: ends after A_2 Maximum: 2LICS or 3LICS, radiating upward and to the left Infundibular: maximum 3LICS or 4LICS Intensity increases with amyl nitrite; unchanged with vasopressors	Harsh, shorter than in VPS Mild: loud, late peak, ends at A_2 Moderate: loud, midsystolic peak, ends before A_2 Severe: short, early, faint If IPS, maximum in 3LICS or 4LICS If VPS (uncommon), PES with long systolic murmur Intensity decreases with amyl nitrite and increases with vasopressor	Shorter, maximum in 2LICS	Medium-pitched; short, or extends to S_2; usually maximum in 2LICS	EM: rough blowing; early to midsystolic, short, 2LICS Vibratory (Still's murmur): medium-pitched, groaning; in apicosternal region Cardiorespiratory: LSB or apex louder in inspiration; disappears with breath holding Murmurs widely transmitted
Other murmurs	Presystolic or PR murmurs occur, but are rare	Continuous murmur in pulmonary atresia	PR in some cases	Tricuspid diastolic flow murmur common in large shunts; murmur of PR in pulmonary hypertension	None
Electrocardiogram	RAD; RAE; RVE	RAD; RVE with dominant R wave in V_1	Normal	P waves: normal or peaked; P_3 may be inverted in sinus venosus defect QRS: rSr′ in V_1 Secundum: RAD, CW loop in FP; Primum: LAD, CCW loop in FP	Normal
X-ray findings	Valvular: normal or decreased pulmonary blood flow; poststenotic dilatation of main PA and LPA Infundibular: PA not dilated	Pulmonary vascularity normal or increased; coeur en sabot	Dilated pulmonary trunk	Pulmonary plethora, small aorta; marked dilatation of main PA and RPA; dilatation of RA and RV	Normal

Part II

Parameter	Flow murmurs (high output states)	Primary pulmonary hypertension	Secondary pulmonary hypertension	Small ventricular septal defect (uncomplicated)	Coarctation of the aorta in adults (uncomplicated)	Idiopathic hypertrophic subaortic stenosis
Clinical features	Hyperkinetic state; occurs at any age	Healthy, acyanotic young women; effort syncope, angina-like pain, dyspnea, fatigue common	Associated with left-to-right shunts (ASD, VSD, PDA) or mitral stenosis; cyanosis and clubbing common in congenital cases	Normal; usually recognized in childhood	Generally normal; M > F; arterial hypertension common	Mostly young adults, but occurs at any age

continued

Table 3-8. *Continued.*

Part II

Parameter	Flow murmurs (high output states)	Primary pulmonary hypertension	Secondary pulmonary hypertension	Small ventricular septal defect (uncomplicated)	Coarctation of the aorta in adults (uncomplicated)	Idiopathic hypertrophic subaortic stenosis
Arterial pulse	Bounding	Small; pulse pressure narrow	Normal	Normal	Small and delayed femoral pulse; blood pressure in arms greater than in legs; carotid pulses often prominent	Brisk and unsustained or bisferiens
Jugular venous pulse	Normal	Large A waves	Large A waves	Normal	Normal	Normal or increased A waves
Precordial pulsations	Brisk LV impulse	Presystolic distention of RV RV lift 2 LICS: systolic impulse of dilated main PA, palpable P_2 and sometimes palpable PES	Depends on underlying tension	Normal except for systolic thrill	Collaterals common around scapula LV impulse normal or sustained heave Pulsations of dilated ascending aorta often palpable in 2RICS or 3RICS	Sustained LV heave or double systolic apical impulse
Maximum thrill	None	None	Whether thrill is present depends on nature of primary lesion	Usually present at 3LICS or 4LICS near sternum; may be absent	Suprasternal common	LLSB or apex
Ejection sounds	None	PES in 2LICS and 3LICS, decreasing with inspiration	PES sometimes audible	Absent	AES commonly present and may be palpable; suggests bicuspid aortic valve	AES rare
Heart sounds	S_1: normal S_2: normally split as a rule	S_1: normal S_2: normally split, may be widely split in RV failure P_2: markedly accentuated RS_4: may be present RS_3: present in RV failure	S_1: normal S_2: narrow, or widely split P_2: markedly accentuated OS and increased S_1 when MS is present RS_4: common	S_1: normal S_2: normally split as a rule	S_1: normal S_2: single or normally split A_2: accentuated LS_3: common LS_4: occasionally present	S_1: normal S_2: usually single, but paradoxical splitting common A_2: normal or decreased LS_4: common
Systolic murmur	Short, early, maximum in 2LICS	Midsystolic EM in 2 LICS	Midsystolic EM in 2LICS	Soft, early, SEM; high-frequency; decrescendo or crescendo-decrescendo; ends in mid-systole, maximum at 3LICS or 4LICS Decreased by amyl nitrite and increased with vasopressors	Murmur most prominent at LSB and often transmitted to apex and along subclavian arteries; may be audible below clavicles on both sides Murmur often louder posteriorly than anteriorly Presence of AES and SEM in 2RICS and murmur of AR-bicuspid aortic valve	SEM maximum lower LSB or apex; may be pansystolic at apex Murmur decreased or disappears with squatting or vasopressors; increased with Valsalva or amyl nitrite

continued

Table 3-8. *Continued.*

Part II

Parameter	Flow murmurs (high output states)	Primary pulmonary hypertension	Secondary pulmonary hypertension	Small ventricular septal defect (uncomplicated)	Coarctation of the aorta in adults (uncomplicated)	Idiopathic hypertrophic subaortic stenosis
Other murmurs	None	May have PR and TR	Diastolic flow murmurs (mitral or tricuspid) common PR and TR may occur In MS: mild diastolic, with presystolic crescendo accentuation	None	AR (see above)	None
Electrocardiogram	Normal	Normal axis or *RAD; RAE; RVE*	Biatrial and *biventricular enlargement* common in shunts	Normal	Normal or LVE	LVE; S-T-T changes; left or *biatrial enlargement*; abnormal Q waves
X-ray findings	Normal	Dilatation of main PA and its branches; RVE, RAE clear peripheral lung fields	Depends on primary disease, but pulmonary plethora, biatrial and biventricular enlargement common in shunts	Normal or slight LVE: little or no increase in pulmonary vasculature	Notching of ribs, especially in 3rd to 8th posterior ribs; retrosternal notching due to dilated internal mammaries	LVE; no post-stenotic dilatation of aorta

CCW = counterclockwise, CW = clockwise, FP = frontal plane, LAD = left axis deviation, RAD = right axis deviation

ventricular septum is the prototype of the SEM of pulmonary outflow obstruction, but similar murmurs may occur in other conditions. By attention to the various parameters listed in Table 3-5, including physiologic and pharmacologic maneuvers, it is often possible to distinguish between them. There will remain nevertheless a fair number of cases in which the diagnosis can be established only by cardiac catheterization.

II. The differential diagnosis of innocent murmurs is considered in Tables 3-7 and 3-9.

III. At times it may be difficult to distinguish between the murmurs of PS and AS. The differentiating features are listed in Table 3-12.

Apex and Lower Left Sternal Border: Pansystolic Regurgitant Murmurs and Their Variants

Etiology

1. Mitral regurgitation
   A. Congenital: as an isolated lesion, part of an endocardial cushion defect, Marfan's syndrome, Ehlers–Danlos syndrome, IHSS, or anomalous left coronary artery arising from the pulmonary artery
   B. Acquired
      1. Rheumatic
      2. Nonrheumatic
         a. Papillary muscle dysfunction or rupture
         b. Infective endocarditis
         c. Ruptured chordae (rheumatic, infective endocarditis, trauma, unknown etiology)
         d. "Click" syndrome with prolapse of mitral leaflets into left atrium
         e. Calcification of the mitral annulus
         f. Left ventricular dilatation (e.g., cardiomyopathy, aortic valve disease)
         g. Tricuspid regurgitation
   A. Rheumatic (organic or relative, or both)
   B. Nonrheumatic
      1. Right ventricular dilatation (e.g., cardiomyopathy, severe left-sided heart failure)
      2. Pulmonary hypertension
      3. Trauma
      4. Carcinoid syndrome
   II. Ventricular septal defect
      A. Congenital
      B. Acquired (e.g., septal rupture in acute myocardial infarction)

Diagnostic Features

I. The murmur of rheumatic MR is the prototype of the pansystolic RM. The murmur starts with S_1, which is typically decreased or masked by the murmur, and ends with or beyond A_2. It is high- to medium-pitched, blowing, and usually plateau-shaped, although it may be crescendo, decrescendo, or crescendo–decrescendo. S_2 is split narrowly when MR is mild, and widely when it is moderate or severe. An accentuated P_2 is common and a loud S_3 is often present. For practical purposes, a holosystolic murmur that is maximal at the apex, regardless of its characteristics, is virtually diagnostic of MR.

II. The murmur of MR must be differentiated from the murmurs of TR and VSD (Table 3-10). MR owing to IHSS should be distinguished from MR owing to other causes (compare Tables 3-8 and 3-10).

III. The murmur of rheumatic TR should be distinguished from the usually coexisting murmur of MR. This may be difficult, but attention to the intensity of the murmur during inspiration and expiration usually provides the answer. The murmur of TR is louder in inspiration, whereas that of MR is unchanged or slightly diminished. Also, the former is louder at the LLSB, and the latter, at the apex.

(*text continues on page 95*)

Table 3-9. The differential diagnosis of systolic ejection murmurs in the second right intercostal space

Parameter	Congenital aortic stenosis: Valvular (75% of cases)	Congenital aortic stenosis: Subvalvular (discrete)	Congenital aortic stenosis: Supravalvular	Acquired aortic stenosis	Idiopathic hypertrophic subaortic stenosis	Aortic valve sclerosis (*non*-obstructive)	Supra-clavicular arterial bruit
Age	Youth	Youth	Youth	Adolescence to old age; rare below age 10	Mostly young adults, but occurs at any age	Middle and old age	10–20 years
Sex		M:F = 4 or 5:1		M:F = 2:1	Familial: M = F; Non-familial: M:F = 4:1	M = F	M = F
Physical appearance	Normal	Normal	Typical facies	Normal	Normal	Normal	Normal
Arterial pulse	Small; slow rise to late systolic peak	Small; slow rise to late systolic peak	Right brachial and carotid greater than left; blood pressure in right arm greater than in left arm	Small; slow rise to late systolic peak	Brisk and unsustained, or bisferiens	Normal	Normal
Jugular venous A wave	Normal or increased	Normal or increased	Normal or increased	Normal or increased	Normal or increased	Normal	Normal
Apical impulse	Sustained heave	Sustained heave	Sustained heave	Sustained heave	Sustained heave or bifid impulse	Normal	Normal
Maximum thrill	1st or 2nd RICS	1st or 2nd RICS	Just beneath right clavicle and right neck	1st or 2nd RICS	Lower left sternal border of apex	Uncommon; 1st or 2nd RICS	Supra-clavicular
Aortic ejection sound	Common	Rare	Rare	Rare	Rare	Absent	Absent
Splitting of S_2	Single of narrowly split; sometimes paradoxical	Single of narrowly split; sometimes paradoxical	Single of narrowly split; sometimes paradoxical	Single of narrowly split; sometimes paradoxical	Usually single, but paradoxical splitting common	Single or narrowly split	Normal
Intensity of A_2	Normal or increased	Normal or increased	Normal or increased	Usually decreased or absent, sometimes normal	Normal or decreased	Normal	Normal
Audible or palpable S_4	Uncommon in mild to moderate stenosis; common in severe	Uncommon in mild to moderate stenosis; common in severe	Uncommon in mild to moderate stenosis; common in severe	Uncommon in mild to moderate stenosis; common in severe and over age 40	Common	Absent	Absent
Systolic murmur	Maximum 1st or 2nd RICS; harsh; ejection	Maximum 1st or 2nd RICS; harsh; ejection	Often maximum 1st RICS; harsh; ejection	Maximum 1st or 2nd RICS; harsh; ejection	Maximum lower left sternal border or apex; less harsh, medium-pitched; ejection, but may be pansystolic at apex	Maximum 1st and 2nd RICS, but sometimes at apex; rough ejection; early peak, short duration	Maximum above rather than below clavicle; usually right-sided; rough ejection; early peak, short duration

continued

Table 3-9. *Continued.*

Parameter	Congenital aortic stenosis			Acquired aortic stenosis	Idiopathic hypertrophic subaortic stenosis	Aortic valve sclerosis (*non-*obstructive)	Supra-clavicular arterial bruit
	Valvular (75% of cases)	Subvalvular (discrete)	Supravalvular				
Murmur of aortic regurgitation	10–20% of cases	55–100% of cases	25% of cases	Common	Absent	Absent	Absent
Effect of maneuvers on systolic murmur						Maneuvers usually not performed	Maneuvers usually not performed
Sudden squatting	Increased	Increased	Increased	Increased	Decreased		
Valsalva	Decreased	Decreased	Decreased	Decreased	Decreased		
Amyl nitrate	Increased	Increased	Increased	Increased	Increased		
Vasopressors (phenylephrine or methoxamine)	Increased	Increased	Increased	Increased	Decreased or absent		
Electrocardiogram	Left ventricular enlargement (LVE) with S-T–T changes			LVE, later with S-T–T changes; left atrial abnormality; may mimic anteroseptal myocardial infarction (MI)	LVE, S-T–T changes; left or biatrial abnormality; abnormal Q waves simulating MI common	Normal	Normal
X-ray	Concentric left ventricular hypertrophy (LVH); post-stenotic dilatation of the aorta; valvular calcification common	Concentric LVH; post-stenotic dilatation usually absent	Concentric LVH; post-stenotic dilatation absent	Concentric LVH; post-stenotic dilatation of aorta may be present; valvular calcification common, increasing with advancing age	LVH; post-stenotic dilatation of aorta absent	Normal	Normal

Table 3-10. Differential diagnosis of pansystolic regurgitant murmurs

Parameter	Mitral regurgitation	Tricuspid regurgitation	Ventricular septal defect
Arterial pulse	Abrupt and collapsing	Reflects associated left-sided lesions	Brisk, bounding, or bisferiens
Jugular venous pulse	Normal	Large V waves with a rapid Y descent, often with systolic expansion of liver	Normal; large A waves in PH
Precordial pulsations	Hyperdynamic LV impulse; apical systolic thrill	Hyperdynamic RV impulse; diffuse systolic depression on left side of chest with opposite pulsation on right; systolic thrill LLSB	Hyperdynamic LV impulse; systolic thrill at 3LICS or 4LICS
Heart sounds	S_1: normal or decreased S_2: wide expiratory splitting that is not fixed P_2: often accentuated LS_3: common LS_4: rare OS: rare	S_1: normal, increased, or decreased in tricuspid area S_2: normal or wide splitting; paradoxical in early pulmonary closure OS: rare RS_3: common RS_4: rare	S_1: normal S_2: normal, or widely split with large shunts; with PH, P_2 increased and splitting normal or narrow LS_3: often present LS_4: absent
Systolic murmurs	Typical pansystolic, maximum at apex; high- to medium-pitched, blowing, and usually plateau-shaped. May be crescendo, decrescendo, or crescendo-decrescendo, radiation to left axilla and scapula Mid- or late nonpansystolic	Murmur is similar to that of MR but maximum at 4LICS or 5LICS; radiation to xiphoid, LRSB, and pulmonary area, but when RVE is marked, may be heard at apex	Harsh, plateau-shaped, maximum at 3LICS or 4LICS; with high VSD, may be maximum at 2LICS; the murmur may be early systolic rather than holosystolic when the VSD is small
Diastolic murmurs	Rumbling middiastolic flow murmur may be heard at apex in pure, severe MR	Rumbling middiastolic flow murmur may be heard at LLSB in pure, severe TR	A rumbling middiastolic flow murmur may be heard at apex in large shunts. Murmur of AR indicates incompetence of medial aortic cusp
Effect of maneuvers on systolic murmur:			
Inspiration	Unchanged or decreases slightly	Increased	Unchanged
Amyl nitrite	Rheumatic: softer Mid to late (click syndrome): softer, starts earlier, lasts longer Papillary muscle dysfunction: variable effect	Increased	Small with PH: decreases Large with hyperkinetic PH: louder Large with pulmonary vascular disease: little change
Vasopressor (phenylephrine or methoxamine	Rheumatic: louder Mid to late (click syndrome): increased Papillary muscle dysfunction: variable effect	NSC	Small: louder Large: unchanged or paradoxical increase
Electrocardiogram	Atrial fibrillation common; LVE and LAE, and sometimes RVE	Atrial fibrillation usual; RVE and sometimes LVE	Small: normal Large: LVE, RVE, LAE, RAE
X-ray findings	LVE and LAE	RVE, RAE, often with prominent great veins	Small: normal Large: pulmonary plethora, large PA, LVE, RVE, LAE, RAE

Table 3-11. Differential diagnosis of aortic stenosis and mitral regurgitation, masquerading one for the other

Parameter	Aortic stenosis	Mitral regurgitation
Arterial pulse	Small, delayed upstroke and peak	Brisk, collapsing
Precordial pulsations	Sustained LV heave; thrill over carotid arteries or 2RICS	Hyperdynamic LV impulse; apical thrill
Heart sounds	S_1: normal S_2: usually decreased or absent; may be single, narrowly split, or paradoxically split AES: may be present LS_3: may be present in LV failure LS_4: may be present	S_1: decreased or masked by murmur S_2: normal or widely split AES: absent LS_3: commonly present without LV failure LS_4: absent; present only in MR owing to ruptured chordae
Systolic murmur	Ejection type regardless of location; transmitted to carotid arteries even with apical radiation Murmur usually louder after long pauses (as in ventricular premature contractions or atrial fibrillation)	Holosystolic in pure rheumatic mitral regurgitation; usually transmitted to left axilla; radiates to base when posterior mitral leaflet is incompetent Mid- to late systolic murmur almost always maximal at apex Murmur unchanged after long pauses
Phonocardiogram	Murmur ends before A_2	Murmur ends at or after A_2
Amyl nitrite	Murmur louder	Murmur softer
Phenylephrine	Murmur softer	Murmur louder

Table 3-12. Differential diagnosis of murmurs of pulmonary and aortic stenosis

Parameter	Pulmonary stenosis	Aortic stenosis
Effect of inspiration on murmur with patient standing	Louder	Fainter
Maximum site	Left sternal border	2RICS or apex
Post-Valsalva effect	Immediate return of intensity of murmur	Delayed return of intensity of murmur
Effect of inspiration on ejection sound	Pulmonary ejection sound may decrease and move toward S_1 or disappear	Aortic ejection sound unchanged
S_2	Usually widely split except in very mild stenosis, when splitting is narrow	Usually single or narrowly split; reversed splitting may be present in severe stenosis
S_4	Right-sided S_4 often present	Left-sided S_4 often present

IV. Sometimes the murmurs of AS and MR masquerade for one another, as occurs when the former is louder at the apex or the latter is louder at the base. Table 3-11 should help in differential diagnosis of the two.

V. Once the diagnosis of MR is established, its cause should be determined.

A. The congenital varieties, with the exception of IHSS, are usually found at an early age and are rarely problems in adult medicine.

B. Rheumatic valvulitis is by far the most common cause of MR, and a history of rheumatic fever or chorea can almost always be obtained.

C. MR owing to IE is characterized by symptoms of systemic infection, embolic phenomena, and valvular vegetations.

D. MR caused by ruptured chordae tendineae is usually acute if the etiology is nonrheumatic, as in IE, trauma, or idiopathic cases. Rheumatic fever and IE account for about half the cases, but in about one-third the cause is unknown. In addition to the loud holosystolic murmur, distinctive features of ruptured chordae (in contrast to conventional rheumatic MR), include the sudden onset of dyspnea and pulmonary edema, sinus rhythm, minimal left atrial enlargement, mild cardiomegaly, and a fourth heart sound. Radiation of the murmur to the base and carotid arteries is produced by rupture of the posterior leaflet. When the anterior leaflet ruptures, the murmur radiates to the axilla, posterior thorax, and vertebral column.

E. MR caused by rupture of a papillary muscle is most commonly caused by myocardial infarction. If the patient survives, congestive heart failure dominates the clinical picture. Survival depends not only on the severity of the MR but also on the state of the myocardium. Coronary and left ventricular angiography are indicated whenever MR is acute to assess the severity and possible causes of the lesion with a view to surgical intervention. The differential diagnosis between a ruptured papillary muscle and perforation of the interventricular septum in myocardial infarction is discussed in the following text.

F. MR caused by papillary muscle dysfunction is common in coronary artery disease—both in angina pectoris and myocardial infarction. The murmur is variable. It may be pansystolic or midsystolic (simulating an SEM), and it may change from time to time in the same patient. Atrial sounds are commonly audible. When the murmur is midsystolic, S_1 is often normal and SC may be heard.

G. The midsystolic click-late systolic murmur syndrome is characterized by nonejection SC, late SM, or both. The etiology is unknown in most cases, but the syndrome has been reported in patients with atrial septal defects, rheumatic heart disease, and papillary muscle dysfunction. Although the condition can occur at any age and in both sexes, the incidence is strikingly high (6% to 10% or more) in presumably healthy young women. The auscultatory findings are the result of prolapse of one or both mitral leaflets into the left atrium: the SC, to tensing of the redundant leaflets and elongated chordae tendineae; and the SM, to MR. The diagnosis can be confirmed by echocardiography, angiocardiography, or both. Complications are infrequent, but include ruptured chordae tendineae, infective endocarditis, ventricular arrhythmias, calcification of the valve, and sudden death (about 1.2% of cases). Overall, however, the syndrome should be considered benign and is associated with a good prognosis.

H. Nonrheumatic calcification of the mitral annulus is a not unusual cause of MR in elderly women. The hallmark of this condition is a J-, U-, or oval-shaped calcification at the site of the mitral annulus, demonstrated best by fluoroscopy under image amplification.

I. MR or TR, or both, may occur in cardiomyopathy. In this condition, there are usually "unexplained" cardiomegaly and S_3 and S_4 gallops, accompanied by congestive failure. The RM of cardiomyopathy, whether mitral or tricuspid, tends to become fainter or vanish when failure ceases, whereas the murmurs of MR and TR owing to other causes remain the same or become louder with restoration of compensation.

J. MR may result from LV dilatation. The mechanism is not clear, but it may involve such factors as dilatation of the mitral annulus and papillary muscle

dysfunction. The presence of a quiet precordium, marked lateral displacement of the cardiac apex, a nondynamic LV impulse, little left atrial enlargement, and a soft pansystolic murmur suggests LV dilatation rather than valvular disease as the cause of MR.

K. TR is most often rheumatic and is more a functional than an anatomic lesion. Rheumatic TR is always associated with mitral and often with aortic valvular disease. Thus, its cause is established by the company it keeps. In pulmonary hypertensive TR, there is usually good evidence of obliterative pulmonary vascular disease, persistent wide splitting of S_2 on expiration, and prominent A as well as V waves in the JVP (versus prominent V waves only in rheumatic TR). Traumatic TR is rare. TR is sometimes caused by the carcinoid syndrome.

L. VSD is congenital but may sometimes result from rupture of the interventricular septum in myocardial infarction. A postinfarctional VSD must be distinguished from a papillary muscle rupture with a similar cause. With septal rupture, the murmur and thrill are usually maximum at the LLSB, with the clinical picture dominated by right-sided heart failure. In papillary muscle rupture, the murmur is usually not as intense and is loudest at the apex. A thrill is uncommon, and left-sided heart failure is the dominant clinical manifestation. Often the correct diagnosis can be made only by cardiac catheterization.

M. Systolic whoops and honks are short, loud, somewhat inconstant, systolic murmurs, often preceded by systolic clicks, having auscultatory characteristics corresponding to the descriptive terms. Most whoops and honks are caused by MR.

Diastolic Murmurs

Early Diastolic Murmurs at the Base and Sternal Borders

Etiology

I. Aortic regurgitation
   A. Rheumatic fever
   B. Infective endocarditis
   C. Calcific aortic stenosis
   D. Senile aortic dilatation
   E. Disease of the aorta
      1. Dissecting aneurysm
      2. Arterial hypertension
      3. Marfan's syndrome
      4. Miscellaneous diseases
   F. Syphilis
   G. Congenital lesions
      1. Bicuspid aortic valve
      2. Coarctation of the aorta
      3. Ventricular septal defect
      4. Other congenital defects
   H. Postsurgical and posttraumatic
   I. Miscellaneous causes (e.g., ankylosing spondylitis, other rheumatoid variants)

II. Pulmonary regurgitation
   A. Congenital
      1. Congenital pulmonary valve incompetence
      2. Absence of the pulmonary valve
      3. Idiopathic dilatation of the pulmonary artery
   B. Acquired
      1. Disease of the pulmonary valve
         a. Rheumatic
         b. Postsurgical
         c. Infective endocarditis
      2. Pulmonary hypertension
         a. Primary
         b. Secondary: mitral stenosis (most common cause of PR), cor pulmonale, or Eisenmenger syndrome

Diagnostic Features

I. The murmur of AR is the prototype of the murmur of semilunar valve incompetence. The diagnosis is based on the presence of a high-pitched, blowing, but sometimes harsh or musical DM, beginning immediately after A_2 and lasting through most or all of diastole. The murmur is heard best at the 3LICS with the patient seated, leaning forward, and holding his breath in expiration. Transmission of the murmur is to the LSB, the apex, and sometimes to an area above the apex in the anterior axillary line. The murmur may also be audible in the 2RICS. Radiation of the murmur along the RSB rather than the LSB should suggest an uncommon cause of AR, such as disease of the proximal aorta or of the aortic valve, in association with dilatation and displacement of the aortic root. In the former category are such conditions as aneurysm, dissection, Marfan's syndrome, cystic medial necrosis of the aorta, and aneurysm of the sinus of Valsalva. The latter group comprises cases of aortic valve disease owing to IE, trauma, VSD with AR, and syphilis. A musical murmur of AR is usually caused by eversion of an aortic cusp, most commonly of syphilitic or rheumatic origin. AR causes widening of the pulse pressure, except in mild cases, giving rise to peripheral signs such as a bounding or collapsing arterial pulse, pistol-shot sounds or double sounds (Traube's sign) over large superficial arteries, Duroziez's to-and-fro murmur, and capillary pulsation; none of these findings is specific for AR. Pulsation in the 2RICS is usually owing to dilatation of the aorta. Pulsation of the sternoclavicular joints suggests aortic aneurysm or dissection. The apical impulse is hyperdynamic, and in some severe cases may show a double outward movement in diastole. In marked AR, systolic depression of the midportion and right side of the chest may be seen. S_1 may be diminished or absent. A_2 is commonly accentuated but may be decreased when AS is present. An AES may be audible. Other murmurs that may occur in AR include an aortic SEM owing to flow or concomitant AS, an apical holosystolic murmur owing to anatomic or relative MR, and the rumbling Austin Flint middiastolic murmur, probably owing to relative MS.

II. The murmur of PR, originally described by Graham Steell, must be distinguished from the murmur of AR, which has similar characteristics. Acquired PR is almost always caused by dilatation of the pulmonary valve ring secondary to PH. In the presence of MS, the differentiation of AR from PR may be difficult or impossible. Aortic valvulography may be useful in establishing the diagnosis of AR but not in ruling PR in or out. Amyl nitrite may be of some help because it decreases the intensity of the murmur of AR but has no effect on the murmur of PR. In general, a basal DM should be attributed to AR if there are peripheral signs of AR, AS is present, the murmur is decreased with amyl nitrite, LVE is noted, or the aorta is large and pulsatile; and to PR if there is an accentuated P_2, RVE but not LVE is present, the murmur is unaffected by amyl nitrite, or the lesion is secondary to PPH. PR may occur in the absence of PH following surgical treatment of VPS or IE, or from congenital incompetence of the pulmonary valve.

III. The Austin Flint murmur of AR must be distinguished from the murmur of MS, which is often associated with rheumatic AR. The patient with both AR and MS is more likely to be female, fibrillating, and having marked exertional dyspnea, hemoptysis, or both. Usually S_1 is accentuated, P_2 is loud, an OS is present unless the valve is calcified or inflexible, S_3 is absent, and the murmur is longer. An apical DM associated with calcification of the mitral valve should be attributed to MS whether an OS is present or not. In the absence of mitral valvular calcification or an OS, an apical DM should also be considered of stenotic origin if the SM of MR is audible. In contrast to the foregoing, the patient with the Austin Flint murmur is typically male, usually in sinus rhythm, with only moderate exertional dyspnea, and no history of hemoptysis. The murmur is early to middiastolic and relatively short, S_1 is decreased, P_2 is commonly normal or only slightly accentuated, and S_3 is often present. No OS is audible. If a rheumatic origin can be excluded, an apical DM in AR should be considered an Austin Flint murmur. The Austin Flint murmur is decreased, and the murmur of MS

increased, with amyl nitrite. In MS, the ECG is more likely to show RAD and RVE; in AR, LVE.

IV. For practical purposes, AR is most commonly caused by rheumatic fever, IE, calcific AS, or senile ectasia of the aorta, with rheumatic cases constituting about 75% of the total. Clues to the cause of AR may be found in the history, especially with respect to the time of discovery of the murmur. Murmurs beginning in childhood suggest a congenital origin; those discovered in the second or third decade are most often rheumatic; those found in the fourth or fifth decade or somewhat later are usually owing to calcific disease of the aortic valve; and those discovered late in life are usually caused by aortic dilatation. A history of rheumatic fever is helpful when positive, but it is often absent in rheumatic cases. When mitral valvular disease coexists with AR, the cause is almost certainly rheumatic. A history of syphilis or of its treatment, a positive serology, calcification of the ascending aorta, and a tambourlike A_2 suggest a syphilitic origin. IE is diagnosed by the usual criteria for the disease. In the presence of familial disease, particularly if supported by appropriate clinical data, Marfan's syndrome, the mucopolysaccharidoses, and the Ehlers–Danlos syndrome should be considered as causes of AR. Ankylosing spondylitis and other rheumatoid variants sometimes cause AR. AR owing to aortic dilatation is not associated with other valvular lesions, but systemic hypertension is a common accompaniment. It is probably the most common cause of AR in elderly patients.

Mid- and Late Diastolic Murmurs at the Apex and Lower Left Sternal Border

Etiology

I. AV valve obstruction
   A. Mitral stenosis
   B. Tricuspid stenosis
   C. Atrial myxomas
   D. Left atrial ball-valve thrombus
II. Increased flow across the AV valves without obstruction (relative stenosis)
   A. Mitral valve
      1. Active rheumatic valvulitis (Carey Coombs murmur)
      2. Mitral regurgitation (some cases)
      3. AR with the Austin Flint murmur
      4. Patent ductus arteriosus
      5. Ventricular septal defect
   B. Tricuspid valve
      1. Tricuspid regurgitation
      2. Atrial septal defect
III. Miscellaneous causes
   A. Hyperthyroidism
   B. Anemia
   C. Complete heart block
   D. Left ventricular dilatation secondary to hypertensive or arteriosclerotic heart disease, or both
   E. Atypical verrucous endocarditis
   F. Chronic or adhesive pericarditis
   G. Eisenmenger syndrome
   H. Primary pulmonary hypertension
   I. Coarctation of the aorta with aortic stenosis

Diagnostic Features

I. The murmur of MS is typically a low-pitched, rumbling, middiastolic murmur with presystolic crescendo accentuation. The earliest murmur is usually a middiastolic murmur, although sometimes it is only presystolic. In atrial fibrillation, the presystolic component disappears. S_1 is loud and sharp. P_2 is normal or accentuated, and an OS is present unless the valve is rigid, fibrosed, or calcified. S_3 and S_4 sounds are not present. The murmur is maximum at the apex and often confined to its vicinity. It is heard best with the bell chest piece at the site of the apical impulse with the patient lying in the left lateral recumbent position. When not clearly audible, it may become more discernible after exercise. The murmur is generally unaffected by respiration but may decrease slightly with inspiration. In pure MS, the apical impulse is often normal. An RV lift means PH or TR.

II. When MS and MR are combined, SM and DM are usually audible, but S_3 and S_4 sounds and an OS are not heard. S_1 is usually decreased. If an S_3 sound is present, it can be assumed that MR is the predominant lesion.

III. The differential diagnosis between the Austin Flint murmur and that of MS is discussed elsewhere in this text.

IV. The murmur of MS must be distinguished from that of left atrial myxoma, a condition in which, contrary to the situation in MS, the DM tends to vary with body position, and an OS is not present. There is often a variable and at times musical SM. Irregular clicks may be heard throughout systole and diastole. Fever and embolic phenomena are common. Left atrial myxoma can be diagnosed by echocardiography or angiocardiography.

V. An atrial ball-valve thrombus may simulate MS but should be suspected if severe pulmonary congestion and embolic phenomena are associated with syncope, relief of symptoms in the upright position, murmurs changing with body position, tachycardia, and at times, episodes of coldness, cyanosis, and numbness of the hands and feet.

VI. The differential diagnosis of true MS and relative MS is summarized in Table 3-13. Also helpful in the diagnosis of relative rather than true MS is evidence of a primary condition capable of causing the relative stenosis.

VII. The presence of a DM in patients with MR may raise the question of whether the DM is owing to the MR itself or is the result of associated MS. Favoring pure MR as the cause of the DM is clinical evidence of severe regurgitation manifested by a large LV, a hyperdynamic apical impulse, wide splitting of S_2 on expiration, a soft S_1, and a DM that is loud and blowing and that starts with the S_3 sound. Favoring coexisting MS as the cause of the DM are the following: an earlier, longer, rumbling DM that begins after the OS, absence of S_3, normal splitting of S_2, a normal or increased P_2, calcification of the valve, and a normal-size or minimally enlarged heart.

VIII. The murmur of TS is similar in its characteristics to that of MS. It differs in that it is maximal at the LLSB rather than at the apex and is louder on inspiration. The murmur of MS is unaffected or decreases slightly with inspiration.

IX. The carcinoid syndrome is commonly associated with stenotic or regurgitant lesions of the tricuspid and pulmonary valves. Systemic manifestations, such as cutaneous flushing and telangiectasia, intestinal hypermotility, bronchoconstriction, and hypotensive crises, in association with RV failure, are clues to the diagnosis. Confirmation may be obtained by finding increased urinary excretion of 5-hydroxyindoleacetic acid.

Table 3-13. Differential diagnosis of true and relative mitral stenosis

Parameter	Mitral stenosis	Relative mitral stenosis
Right ventricular lift	Often present	Absent
Left ventricular lift	Absent	Present
Apical thrill	Sometimes present	Absent
Loud, sharp S_1	Present	Absent
P_2	Usually increased	Variable
OS	Present	Absent
S_3	Absent	Present
Diastolic murmur	Rumbling; starts after opening snap; longer	Blowing; starts with S_3; shorter

Continuous Murmurs Over the Thorax

Etiology and Site of Maximum Intensity

I. Extracardiac shunts
   A. Patent ductus arteriosus (2LICS or immediately below left clavicle)
   B. Pulmonary AV fistula: congenital or acquired (lower lobes or right middle lobe)
   C. Systemic AV fistula (directly over the fistula)
   D. Some cases of aortopulmonary septal defect (2LICS or 3LICS)
   E. Postsurgical shunts in the tetralogy of Fallot (to the right or left of the upper sternum)

II. Intracardiac shunts
   A. Sinus of Valsalva aneurysm with rupture into right atrium or ventricle (4LICS)
   B. Coronary arteriovenous fistula with connection to the right atrium or ventricle (apicosternal region)
   C. Small atrial septal defect with tight mitral stenosis: Lutembacher's syndrome (LLSB)
   D. Total anomalous pulmonary venous drainage (ULSB)

III. Arterial stenosis
   A. Coarctation of the aorta (posterior chest)
   B. Pulmonary artery branch stenosis (SM or CM over site of stenosis)
   C. Aortic arch syndrome (over affected vessel)

IV. Increased flow through normal or dilated vessels
   A. Jugular venous hum (neck, above the clavicle)
   B. Mammary souffle (2LICS to 4LICS, or 2RICS to 4RICS)
   C. Increased bronchial collateral circulation (posterior chest)
      1. Truncus arteriosus
      2. Severe tetralogy of Fallot
      3. Other congenital malformations

Diagnostic Features

I. The murmur of PDA is the prototype of CM associated with extracardiac shunts. It starts with S_1, continues through S_2 without interruption, and fades steadily during diastole. Systolic accentuation of the murmur is quite characteristic. The murmur usually has a machinerylike quality. It is loudest in the 2LICS or immediately below the left clavicle. A thrill may be present. When PDA is associated with moderate to large left-to-right shunts, a DM owing to flow may be heard at the apex. S_1 is usually normal. An S_3 sound is common. If PH develops, the diastolic component of the CM decreases or disappears, so that only an SM remains. P_2 becomes accentuated, a PES may be heard, and the murmurs of PR and TR may appear.

II. When a patient has the clinical picture of a left-to-right shunt with PH and only an SM at the 2LICS or 3LICS, the diagnostic possibilities include PDA, VSD, ASD, and an aortopulmonary window.

III. With CM, the location of the maximum site of the murmur may be of some diagnostic significance.

IV. Rupture of an aortic sinus with a right-sided communication is suggested by the sudden appearance of a CM in a young adult following trauma or exertion. The murmur is maximal at the LLSB.

V. Coronary arteriovenous fistula with connection to the RA or RV is manifested by a superficial CM with diastolic accentuation, loudest in the apicosternal region, and is commonly associated with a thrill. The murmur is decreased by the Valsalva maneuver. In contrast, the CM of extracardiac shunts (e.g., PDA) shows systolic accentuation and is unaffected by the Valsalva maneuver.

VI. The to-and-fro murmurs of AS and AR, or of PS and PR, may be mistaken for CM. The chief differentiating point is that CM envelop S_2, but to-and-fro murmurs do not. By careful auscultation in to-and-fro murmurs, it will be found that the SEM ends before S_2 and the DM begins after S_2. There is thus a hiatus between the two murmurs, a condition that does not exist in CM.

VII. The characteristics and differential diagnosis of the jugular venous hum and the mammary souffle, both of which are innocent CM, may be found in Table 3-7.

Cardiac Enlargement and the Cardiomyopathies

Lane D. Craddock

Cardiac Enlargement

Cardiac enlargement, with few exceptions, is a sign of organic heart disease. Its cause can usually be ascertained from the history, physical examination, and laboratory data (including the ECG, chest films, echocardiogram, radioisotope scanning, and angiocardiography). Assuming that artifactitious enlargement is excluded (e.g., cardiac displacement, transverse position of the heart, thoracic deformity, pericardial fat pads, cysts, faulty roentgenographic techniques) cardiomegaly, in actual clinical practice, is most often due to the conventional causes of heart disease—congenital malformations, coronary artery disease, hypertension, rheumatic fever, and pericardial disease. However, there remain a significant number of cases of cardiomegaly that are not owing to the usual causes. Many of these appear to be the result of some type of cardiomyopathy. This section briefly considers the more common causes of cardiac enlargement that are well known to the reader, but considers in some detail the etiology, classification, clinical features, and differential diagnosis of the less well-known cardiomyopathies.

In actual clinical practice, enlargement of the heart is usually detected by physical examination, electrocardiography (including vectorcardiography), radiographic techniques, or combinations of these methods, rather than by esoteric techniques. It is to be stressed that enlargement should rarely be missed by physical examination alone. Cardiac enlargement may be owing to hypertrophy, dilatation, or a combination of the two. It may be generalized, or it may affect individual chambers in various combinations.

Etiology

Generalized cardiac enlargement is most often caused by congestive heart failure. Although initially, enlargement may take place in one or more of the heart chambers, eventual progression to involvement of all chambers is common. Thus, a patient with arterial hypertension may develop, successively, left ventricular enlargement and failure, enlargement of the left atrium, pulmonary vascular congestion, and finally, enlargement of the right ventricle and atrium. In other circumstances, a disease process may affect all chambers more or less simultaneously and thereby produce diffuse cardiomegaly (e.g., anemia, myocarditis, cardiomyopathy). Individual chamber enlargement is usually a consequence of a single congenital or acquired lesion.

The major causes of cardiomegaly in the adult are listed in the following. It should be borne in mind that in some patients more than one etiologic factor may play a role.

I. Generalized cardiac enlargement
   A. Congenital diseases
   B. Acquired diseases
      1. Alcoholism
      2. Anemia
      3. Cardiomyopathy (Table 3-14)
      4. Coronary artery disease (late stage)
      5. Hypertension (late stage)
      6. Rheumatic fever (late stage or with multivalvular involvement)
      7. Syphilis
      8. Pericardial disease (Table 3-15)
      9. Neoplasm
      10. Endocrinopathies
      11. Incessant automatic supraventricular tachycardia in the young (rare)
   C. Inherited abnormalities—incompletely understood, but they include defects in myocardial energetics that result in CMP

Table 3-14. Etiologic and clinical classification of the cardiomyopathies

Primary cardiomyopathy
Dilated (formerly referred to as congestive)
Idiopathic
Familial
Peripartal
Hypertrophic (familial and nonfamilial)
Obstructive
Nonobstructive
Restrictive
Endomyocardial fibrosis
Endocardial fibroelastosis
Secondary cardiomyopathy[a]
Connective tissue disease (e.g., systemic lupus erythematosus, scleroderma, dermatomyositis, rheumatoid arthritis)
Neuromuscular disease (e.g., Friedrich's ataxia, myotonia atrophica, progressive muscular dystrophy, Duchenne's and Becker's muscular dystrophy)
Vascular disease (e.g., ischemic cardiomyopathy)
Metabolic disease (e.g., hyperthyroidism, hypothyroidism, hemochromatosis, glycogen storage disease, mucopolysaccharidoses, amyloidosis)
Neoplastic disease (e.g., lymphomas, eukemia, metastatic carcinoma)
Nutritional disease (e.g., beriberi, kwashiorkor)
Myocarditis
  Viral
  Parasitic
  Protozoal
  Other
Sarcoidosis
Inherited mechanisms due to genetic defects (e.g., abnormalities in activity of myocyte mitochondria)
Drugs, chemicals, and toxins (e.g., emetine, arsenic, carbon monoxide poisoning)
Posttraumatic disorders

[a] Secondary cardiomyopathies usually give a clinical picture of congestive failure; less often, with symptoms resembling those of constrictive pericarditis. Ischemic heart disease may be seen clinically as a congestive or dilated cardiomyopathy, hence its inclusion in the classification.

II. Left ventricular enlargement
  A. Congenital or familial diseases
    1. Aortic stenosis
    2. Idiopathic hypertrophic subaortic stenosis
    3. Coarctation of the aorta
    4. Patent ductus arteriosus
    5. Tricuspid atresia
  B. Acquired diseases
    1. Arterial hypertension
    2. Coronary artery disease
    3. Aortic stenosis, regurgitation, or both
    4. Mitral regurgitation
III. Left atrial enlargement
  A. Congenital diseases
    1. Ventricular septal defect
    2. Patent ductus arteriosus
    3. Coarctation of the aorta
    4. Congenital mitral stenosis
  B. Acquired diseases
    1. Left ventricular hypertrophy or dilatation

Table 3-15. Hemodynamics of myocardial and pericardial disease

Parameter	Constrictive pericarditis	Cardiomyopathy
Left atrial pressure	Tends to equal RAP	10–20 mm Hg = RAP
Right atrial pressure	Usually = 15 mm Hg with prominent Y trough	Usually = 15 mm Hg: normal if wedge pressure normal
Cardiac output	Tends to normal with normal AV difference	Usually low with increased AV difference
Right ventricular pressure	Consistent early diastolic dip	Early diastolic dip may disappear with therapy
Diastolic right ventricular pressure	Tends to equal or exceed ⅓ of systolic pressure	Usually does not equal ⅓ of systolic pressure
Pulmonary artery pressure	Systolic pressure usually = 40 mm Hg	Systolic pressure often 45–65 mm Hg
Respiratory variation in pressures	Tends to be absent	Usually present
Diastolic pressure plateau	RAP = RVDP = PADP = PWP	PWP = RAP

AV, arteriovenous; *PADP*, pulmonary arterial diastolic pressure; *PWP*, pulmonary wedge pressure; *RAP*, right atrial pressure; *RVDP*, right ventricular diastolic pressure.
From: Fowler NO. Pericardial disease. In: Hurst JW, Logue RB, eds. *The Heart*, 2nd ed. New York: McGraw-Hill, 1970:1267, with permission.

    2. Mitral stenosis, regurgitation, or both
    3. Infective endocarditis of mitral valve
    4. Left atrial myxoma
    5. Mitral valve prolapse (late stage or with rupture of the chordae tendineae)
IV. Right ventricular enlargement
  A. Congenital diseases
    1. Ventricular septal defects
    2. Atrial septal defects
    3. Transposition of the great vessels
    4. Tetralogy of Fallot
    5. Eisenmenger complex
    6. Anomalous pulmonary venous return
  B. Acquired diseases
    1. Left ventricular hypertrophy or dilatation
    2. Mitral valve disease (especially stenosis)
    3. Chronic obstructive pulmonary disease
    4. Primary pulmonary hypertension
    5. Tricuspid regurgitation
    6. Pulmonary vascular disease (especially pulmonary embolism)
    7. Chronic alveolar hypoventilation (Pickwickian syndrome)
V. Right atrial enlargement
  A. Congenital diseases.
    1. Ebstein's anomaly.
    2. Tricuspid regurgitation.
    3. Atrial septal defect with large left-to-right shunt.
    4. Valvular pulmonic stenosis.
    5. Multiple pulmonary coarctation.
  B. Acquired diseases.
    1. Right ventricular hypertrophy and dilatation (usually secondary to pulmonary hypertension).
    2. Tricuspid stenosis, regurgitation, or both.
    3. Right atrial tumors (most often myxoma).
    4. Tricuspid valve prolapse (rare).

Evaluation

1. It should be possible in the vast majority of cases, based on the history, physical examination, clinical picture, ECG, chest films, and appropriate ancillary techniques, such as echocardiography (including transesophageal), exercise stress when appropriate, cardiac catheterization, angiography, and radioisotope scanning, to determine both the mechanism (e.g., valvular stenosis, regurgitation) and the cause (e.g., rheumatic fever, arterial hypertension) of cardiac enlargement. A discussion of these procedures, their interpretation, and the criteria for the diagnosis of the various etiologic types of heart disease is beyond the scope of this text.
2. Should the cause of cardiac enlargement in any patient remain undetermined in spite of meticulous clinical and laboratory evaluation, careful consideration should be given to the diagnosis of a cardiomyopathy.
3. Primary consideration should also be given to the diagnosis of cardiomyopathy as the explanation of heart disease in patients with the diseases listed in Table 3-14.

The next section deals with various features and differential diagnosis of the cardiomyopathies.

Cardiomyopathy

Definition

The terms *cardiomyopathy, myocardosis,* and myocardiopathy refer to disease of the heart muscle. It is characterized anatomically by cardiomegaly due to hypertrophy or dilatation, or both, and functionally by a clinical picture consistent with congestive failure (congestive cardiomyopathy), cardiac hypertrophy with or without ventricular outflow obstruction (hypertrophic cardiomyopathy), or simulating constrictive pericarditis (restrictive or obliterative cardiomyopathy). All forms may involve systolic or diastolic dysfunction, or both.

Etiology

Cardiomyopathy may be primary (idiopathic) or secondary. The primary cardiomyopathies are myocardial diseases of unknown cause, probably due to multiple causes and not related to any known systemic disorder. Immune mechanisms in dilated cardiomyopathy have received much attention recently, and studies strongly suggest a relationship, at least in some patients. Although a causative role has not been established, further work should clarify the issue. Inherited mechanisms have been clarified and include genetic defects in energy metabolism in myocardial cells; their importance and incidence remain to be determined. Secondary cardiomyopathies are those in which the myocardial involvement is secondary to a systemic illness even when the cause of this disease is not understood (e.g., amyloidosis). It should be noted that some authorities use the term *primary myocardial disease* to indicate any myocardial disorder, idiopathic or secondary, in which cardiac involvement is the major clinical manifestation. A combined etiologic and clinical classification of the cardiomyopathies is shown in Table 3-14. The author prefers this classification to that published by the WHO/ISFC in the August 1981 issue of *Circulation*.

Clinical Features

Dilated Cardiomyopathy

The clinical presentation is most commonly that of biventricular failure, although sometimes the picture of left or right ventricular failure predominates. Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and dependent edema are thus common symptoms. Other presentations include syncope (due to arrhythmia or heart block), arrhythmia, embolic phenomena, and occasionally, angina. Sudden death is distressingly frequent. On physical examination, the usual signs of congestive failure may be noted. Cardiomegaly (predominantly left ventricular in most cases), reduced intensity of the heart sounds, regurgitant systolic murmurs, and galloprhythm (S_3, S_4, or summation gallop) are characteristic. A decreased arterial pulse with a narrow pulse pressure is common. Cyanosis is rare.

Hypertrophic Cardiomyopathy

I. Obstructive (idiopathic hypertrophic subaortic stenosis):
   A. Patients in this group have left ventricular hypertrophy in association with muscular ventricular outflow obstruction. The disease is often familial and is common in young and middle aged adults.
   B. Many cases are discovered before the onset of symptoms because of the detection, on routine examination, of left ventricular enlargement or a heart murmur, or both. Individuals with symptoms generally complain of exertional dyspnea, syncope, or angina.
   C. On physical examination it is observed that the apical impulse is typically forceful and often bifid, the arterial pulse is brisk and bisferiens, an S_4 is present, a systolic ejection murmur is audible at either the mid or lower left sternal border, and a mitral regurgitant murmur is often heard at the apex (see the preceding section, Heart Murmurs).

II. Nonobstructive.
   A. In addition to the aforementioned clinical patterns, there are patients with myocardial disease who present primarily with evidence of hypertrophy (usually concentric) of the left ventricle. A history of syncope, palpitation, angina, or dyspnea may be obtained. Most such cases are familial, although isolated nonfamilial cases do occur. There are no characteristic murmurs. An atrial gallop is commonly heard.
   B. Some of these patients eventually develop evidence of left ventricular outflow obstruction. It would thus appear that hypertrophic cardiomyopathy can exist with or without obstruction. Recent echocardiographic observations suggest that asymmetric septal hypertrophy is the pathognomonic anatomic abnormality and the common denominator of both the nonobstructive and obstructive forms.

Restrictive Cardiomyopathy

I. A very small number of patients with myocardiopathy, notably those with diseases such as amyloidosis, leukemia, and polyarteritis nodosa, may have symptoms resembling those of constrictive pericarditis.
II. The major features are an elevated venous pressure, deep X and Y descents in the jugular venous pulse, severe right-sided heart failure, clear lung fields, and only moderate cardiomegaly.
III. Endomyocardial fibrosis and endocardial fibroelastosis are also primary cardiomyopathies. The former condition is seen almost exclusively in Africans; the latter, in children.

Laboratory Studies

Electrocardiogram

I. The ECG is almost invariably abnormal in the cardiomyopathies.
II. Nonspecific S-T segment and T-wave abnormalities are common.
III. Almost any type of arrhythmia may occur, but ventricular premature systoles and atrial fibrillation are seen most frequently. Abnormalities of AV conduction are not uncommon.
IV. P-wave abnormalities, especially left atrial and biatrial enlargement, are often present.
V. Left ventricular hypertrophy is quite common, but right ventricular hypertrophy is infrequent. All types of ventricular conduction defects, especially left bundle branch block and left anterior fascicular block, are often present. Ventricular preexcitation is a common accompaniment of familial forms of cardiomegaly.
VI. Pseudoinfarction patterns occur frequently in idiopathic hypertrophic subaortic stenosis and amyloidosis.

Chest Films

I. The chest x-rays usually reveal only cardiomegaly.
II. When congestive heart failure supervenes, evidence of pulmonary vascular congestion and pleural effusion may appear.

Echocardiography

I. This has become virtually routine in most centers and is of great value for evaluation of cardiac structure and function.
II. It is without risk, therefore useful as a followup test.
III. It may yield information as to etiology (eg, valvular disease, pericardial disease, amyloidosis).
IV. It has reduced the need for cardiac catheterization overall.

Cardiac Catheterization

I. Cardiac catheterization is of greater value in ruling out valvular, congenital, and other types of heart disease than in establishing the diagnosis of a cardiomyopathy.
II. Hemodynamic studies may be helpful in differentiating between obstructive and nonobstructive forms of cardiomyopathy.
III. The finding of restricted filling (secondary to a noncompliant ventricle or a partially obliterated ventricular cavity, or both) supports the diagnosis of a restrictive cardiomyopathy but it is also seen in constrictive pericarditis.
IV. Coronary arteriography may be helpful in differentiating ischemic heart disease from other types of myocardial disease. A normal arteriogram excludes coronary artery disease as a cause of cardiomyopathy.

Endomyocardial Biopsy

I. By no means routine, may be helpful in selected patients.
II. Primarily of value in evaluation of myocarditis, cardiotoxicity from various agents (eg, doxorubicin); differentiation of restrictive vs. constrictive disease; evaluation of tumors.
III. Its main routine use is in post-cardiac transplantation

Criteria for the Diagnosis of Cardiomyopathy

I. Cardiomegaly due to left ventricular or biventricular enlargement without evidence of valvular calcification.
II. An abnormal ECG.
III. The presence of an S3 or S4 gallop rhythm, or both.
IV. Absence of sustained arterial hypertension and, almost always, absence of diastolic murmurs.
V. Exclusion of other causes of heart disease; rheumatic or other valvular disease, congenital heart disease, constrictive pericarditis, pericardial effusion, cor pulmonale, hypertensive heart disease, and coronary artery disease.
VI. Genetic studies: the ability to detect inherited defects of myocardial metabolism in a clinical setting is anticipated in the near future.

Differential Diagnosis of Cardiomyopathy

Coronary Heart Disease

Ischemia of the myocardium may produce a clinical picture indistinguishable from that found in other types of cardiomyopathy. An unequivocal, documented history of myocardial infarction or angina pectoris, or both, establishes the diagnosis of coronary artery disease. However, it should be recognized that typical or atypical angina may occur in cardiomyopathy. Ischemic cardiomyopathy is usually found in older patients. When it occurs in younger patients, the premature coronary heart disease is most often familial and is generally associated with abnormal, serum lipid concentrations and abnormal lipoprotein electrophoretic patterns. Many such patients are diabetic or at least show abnormal findings on glucose tolerance tests. Physical findings are rarely helpful, although the presence of systolic precordial bulges due to ventricular asynergy or aneurysm is indicative of ischemic heart disease. The ECG may be helpful if diagnostic infarction patterns are present; but pseudoinfarction patterns are occasionally seen in cardiomyopathy. When it is not possible to distinguish between coronary heart disease and cardiomyopathy on clinical grounds, selective coronary arteriography, ventriculography, and hemodynamic studies may be of assistance.

Congenital Heart Disease

Congenital heart disease is rarely a problem in differential diagnosis. Patients with hypertrophic cardiomyopathy and either left or right ventricular outflow obstruction may have murmurs mimicking aortic or pulmonary stenosis, respectively (see preceding section, Heart Murmurs, for further details).

Echocardiography may establish the diagnosis; bubble study or TEE may be necessary. These patients may require cardiac catheterization and angiography to confirm diagnosis. In rare instances, an Eisenmenger complex of long duration (e.g., with atrial septal defect) may show marked cardiomegaly without the identifying features of the congenital lesion and thus may be mistaken for a cardiomyopathy. However, cardiac catheterization will reveal the bidirectional shunting. Moreover, the associated arterial oxygen unsaturation will not be corrected by the administration of 100% oxygen. Sometimes the mitral regurgitant murmur of a cardiomyopathy may be mistaken for the murmur of a ventricular septal defect. Here again, cardiac catheterization and angiocardiography will establish the correct diagnosis.

Rheumatic Heart Disease

The diagnosis of rheumatic heart disease is based on a history of rheumatic fever accompanied by a characteristic structural lesion of the heart (e.g., mitral stenosis or on evidence of a characteristic structural lesion even in the absence of a history of rheumatic fever. Rheumatic heart disease is often suspected as the cause of murmurs of mitral or tricuspid regurgitation in patients with congestive heart failure. When compensation is restored in such patients, murmurs due to cardiomyopathy tend to diminish or disappear, whereas rheumatic murmurs tend to become louder. The murmur of mitral stenosis is virtually diagnostic of rheumatic heart disease, although diastolic rumbles have been reported in a few patients with cardiomyopathy. Other diastolic murmurs (e.g., due to aortic insufficiency) virtually exclude cardiomyopathy. The presence of valvular calcification also eliminates cardiomyopathy. In doubtful cases, cardiac catheterization may be indicated. Echocardiography is very helpful, often definitive, in distinguishing between primary and secondary valvular involvement, establishing presence or absence of CMP. In doubtful cases, cardiac catheterization may be indicated.

Hypertensive Heart Disease

Occasionally confusion occurs between cardiomyopathy and hypertensive heart disease when the blood pressure is elevated. However, the arterial hypertension is much milder (diastolic pressure 90–110 mm Hg) in cardiomyopathy and is not sustained. It tends to disappear when congestive heart failure improves. In patients with systemic hypertension, it is usually possible to document a long history of elevated blood pressure with corroborative changes in the ocular fundi. In hypertensive heart disease, there is a rough correlation between the heart size and the severity and duration of the hypertension, whereas in cardiomyopathy the cardiomegaly is out of proportion to the mildness of the hypertension.

Pericardial Disease

Patients with cardiomyopathy often have a clinical picture that may be confused with constrictive pericarditis or pericardial effusion. Some clinical features may be of assistance in the differential diagnosis. An apical impulse that is displaced downward and to the left favors myocardial rather than pericardial disease. The presence of the pansystolic murmurs of mitral or tricuspid regurgitation also supports the diagnosis of cardiomyopathy rather than pericarditis. Gallop rhythms are common in cardiomyopathy, although they must be differentiated from the early diastolic knock of pericarditis. In pericardial disease, there is a tendency to low voltage in the ECG; in cardiomyopathy, the findings are as described previously. Echocardiography is definitive with effusion; may be helpful in diagnosis of constrictive disease by showing limited diastolic filling, absence of valvular disease, and a thickened pericardium.

Radioisotope scanning, cardiac catheterization, and angiocardiography may be of assistance in making the diagnosis. Sometimes the problem can be resolved only by exploratory thoracotomy. The differences in hemodynamics between restrictive cardiomyopathy and constrictive pericarditis are listed in Table 3-15.

Primary Pulmonary Hypertension
Primary pulmonary hypertension may be seen with cardiac enlargement and right-sided heart failure, simulating a cardiomyopathy. Clues to the diagnosis are an accentuated P_2, dilated pulmonary arteries and clear lung fields in the chest films, and electrocardiographic evidence of right ventricular enlargement.

Care should be taken to detect a murmur of tricuspid regurgitation and this may, as with the pericardial knock, require squatting for its induction.

Echocardiogram may confirm elevated PA pressure and tricuspid regurgitation.

Hyperkinetic Heart Syndrome
This is an uncommon entity. It is uncertain at present whether it should be regarded as a cardiomyopathy. The distinguishing features are a high cardiac output, an increased rate of ventricular ejection slight cardiac enlargement, and a wide pulse pressure with brisk pulses.

Differential Diagnosis of Primary and Secondary Cardiomyopathy
Because the clinical features of primary and secondary cardiomyopathy are similar, the differentiation is made only by excluding those systemic ailments known to produce myocardial disease. Some of the more important secondary cardiomyopathies and their distinguishing features are discussed below.

Connective Tissue Diseases
The diagnostic features of these diseases are described in the sections Peripheral Joint Arthritis and Myalgia.

Neuromuscular Diseases

I. *Friedreich's ataxia* is characterized by ataxia, progressive skeletal deformities, and speech disturbances, beginning in adolescence and terminating in congestive failure or infection within 20 years of its onset. Heart disease occurs in 30 to 50 percent of cases and may be the initial manifestation of the disease.
II. *Myoteria atrophica* is characterized by atrophy involving primarily the muscles of the face, neck, forearms, and thighs, increased muscle tone cataracts, premature baldness, and gonadal atrophy. Although the neuromuscular defects are usually apparent before evidence of heart disease appears, the latter may be seen first.
III. *Progressive muscular dystrophy* is characterized by weakness of the proximal musculature of the extremities, a waddling gait, a "climbing up the legs" phenomenon when arising from a sitting position, muscles that are hypertrophied or atrophied, and skeletal deformities.
IV. Duchenne's and Becker's muscular dystrophy, though usually characterized by skeletal muscle abnormalities, may occasionally present with the clinical picture of CMP.

Hyperthyroidism
Thyrotoxic heart disease is characterized by goiter, tachycardia, exophthalmos, warm moist skin, tremor, and arrhythmia, notably atrial fibrillation. The diagnosis can be confirmed by thyroid function tests.

Myxedema
Myxedema commonly causes pericardial effusion and is often associated with coronary artery disease. Whether it can cause myocardial disease is disputed. Clinically, myxedema is suggested by cold intolerance; hoarseness; a low-pitched voice; sluggishness, weakness, and fatigue; a dry, yellow, puffy skin; hair loss; a thick tongue; slow pulse; and decreased tendon reflexes. It is easily confirmed by determination of the serum T_4 level, the radioactive iodine uptake, or other thyroid function tests.

Acromegaly
Acromegaly is associated with an increased incidence of clinical cardiovascular disease. Marked cardiac hypertrophy, particularly of the left ventricle, is a common finding. Hypertension and congestive heart failure are the major clinical manifestations. About one-third of patients have a diabetic glucose tolerance test. Typically, there is persistent elevation of plasma growth hormone levels that cannot be suppressed by an oral glucose load.

Hypoparathyroidism
Clinical heart disease is uncommon in hypoparathyroidism. The major cardiac manifestations are electrocardiographic and result from the hypocalcemia. The changes noted include prolongation of the Q-T interval (due to lengthening of the S-T segment); sometimes with a prolonged P-R interval, nonspecific T-wave abnormalities; and changes in the QRS duration. Congestive heart failure may occur but responds to restoration of normal serum calcium levels. Sensitization of the myocardium by hypocalcemia to the effects of catecholamines may precipitate arrhythmias, angina, and even sudden death.

Pheochromocytoma
Pheochromocytoma is quite rare. The usual clinical presentation consists of hypertension (sometimes paroxysmal), sweating, palpitation, headaches, pallor, and episodes of collapse. Cardiomyopathy with congestive failure may occur. The cardiomyopathy may be caused by focal cellular damage and fibrosis, possibly related to an imbalance between coronary blood flow and increased need. The diagnosis is based on finding excessive catecholamine production and demonstration of the tumor.

Hemochromatosis
This disease is characterized by a combination of liver disease, diabetes mellitus, hyperpigmentation of the skin, and heart disease. Plasma iron levels are increased; endomyocardial biopsy may be diagnostic.

Amyloidosis
Amyloidosis is one of the less common causes of cardiomyopathy. It should be considered in any elderly patient with unexplained cardiac enlargement and congestive failure. Purpura, waxy skin deposits, peripheral neuropathy, macroglossia, and nephrosis are other features of the disease. The presence of a disease known to cause secondary amyloidosis (e.g., rheumatoid arthritis, ulcerative colitis, chronic suppuration, tuberculosis) should alert the physician to this type of cardiomyopathy. The combination of low voltage in ECG and thickening of ventricular wall by echocardiogram suggest the diagnosis.

The diagnosis can often be established by gingival or rectal biopsy, or may require endomyocardial biopsy.

Neoplasms
The presence of lymphoma, leukemia, or neoplasm should raise the question of secondary cardiomyopathy if the heart is enlarged or if it shows pericarditis. Arrhythmias are common; pericardial effusion may occur with danger of tamponade.

Myocarditis and Pericarditis
Myocarditis may occur in association with many viral, bacterial, rickettsial, and parasitic diseases. The clinical evidence of myocarditis generally appears as the initial manifestations of the systemic infection begin to subside. Fever is characteristic. Fatigue, dyspnea, palpitation, and precordial discomfort may occur. Cardiac enlargement, murmurs, tachycardia, arrhythmias, and conduction defects are commonly observed. Embolic phenomena may be evident. Cardiomyopathy with congestive failure may occasionally occur in the wake of the benign idiopathic pericarditis syndrome. Echocardiogram may be helpful and endomyocardial biopsy may be diagnostic.

Sarcoidosis
Cardiomyopathy due to sarcoidosis should be considered in heart disease of obscure origin in young African Americans, Tachycardia, cardiac enlargement, pericarditis, heart block, arrhythmias, and congestive heart failure may be noted. Cutaneous lesions,

hilar and cervical adenopathy, and pulmonary infiltrates are common. Hyperglobulinemia and hypercalcemia may occur. Endomyocardial biopsy may be diagnostic.

Alcohol Cardiomyopathy
The consumption of large quantities of alcohol over a period of many years may cause myocardial disease in some individuals. The clinical spectrum is wide. Cardiac beriberi occasionally occurs in the alcoholic. It is manifested by moderate cardiomegaly, congestive failure, nutritional deficiencies, and responsiveness to thiamine. Beer-drinkers' cardiomyopathy, characterized by right-sided heart failure, massive cardiac dilatation, and other symptoms, is no longer seen since the addition of cobalt to beer was discontinued. The most common manifestations of alcoholic cardiomyopathy are cardiac dilatation and congestive failure, neither of which is responsive to thiamine. This type of cardiomyopathy may be observed in heavy drinkers who are malnourished or obese.

Diabetic Cardiomyopathy
Diabetes mellitus is associated with a specific cardiomyopathy in the absence of large-vessel coronary artery disease. Noninvasive studies have shown alterations in systolic and diastolic function that may ultimately lead to congestive heart failure. These findings have been most prominent in diabetics with evidence of microvascular disease and hypertension. Pathologic studies have revealed myocardial hypertrophy and fibrosis with arteriolar and capillary basement membrane thickening in some patients. Autonomic neuropathy may play a role in the genesis of the left ventricular dysfunction.

There is an important, large subset of diabetic patients with the combination of insulin resistance, dyslipidemia, hypertension, progressive vascular disease, left ventricular enlargement, and CMP with CHF (now called syndrome X).

Inherited Disorders
Inherited disorders, which heretofore may have been labeled idiopathic, are known to involve abnormal myocardial energy metabolism as a cause of CMP. Their incidence is uncertain, but their elucidation represents a significant advance, since it may lead to further understanding of genetically based myocardial disorders.

Diagnostic Approach to Cardiomyopathy

I. The diagnosis of cardiomyopathy should be considered in all cases of heart disease of obscure cause.
II. The diagnosis of cardiomyopathy is made by excluding other causes of heart disease and is based on the criteria listed earlier in this section.
III. Once the diagnosis of cardiomyopathy is established, one must make every effort to distinguish between primary and secondary forms. In the examination of the patient, search carefully for systemic illness that may produce myocardial involvement. Each of the causes of secondary cardiomyopathy should be excluded. This can usually be accomplished through the history and physical examination, supplemented by selected laboratory tests.
IV. The following workup is suggested for cardiomyopathy:
   A. CBC.
   B. ESR.
   C. Urinalysis.
   D. Chest films.
   E. Electrocardiogram.
   F. Biochemical screening.
   G. Protein electrophoresis.
   H. Immunoglobulins.
   I. Serologic test for syphilis.
   J. ANA.
   K. Rheumatoid factor.
   L. Muscle enzymes (CPK, aldolase).
   M. T4 or other thyroid function tests.
   N. Echocardiogram (including doppler, stress echocardiography, and transesophageal study).

V. Other procedures sometimes needed to establish an etiologic diagnosis follow:
   A. Tissue biopsy (lymph nodes, bone marrow, skin, muscle, rectal mucosa, gingiva).
   B. Cardiac catheterization.
   C. Angiocardiography.
   D. Radioisotope scans.
   E. Pulmonary function studies.
   F. Endomyocardial biopsy. Specimens of myocardium obtained by endomyocardial biopsy are utilized more commonly, both for establishing the diagnosis and determining the prognosis in cardiomyopathy. At present, the procedure is most useful in inflammatory disorders (e.g., myocarditis), infiltrative disease such as amyloidosis, and drug-induced toxicity. Studies in progress at present should, when completed, clarify its role.
   G. Magnetic resonance imaging. In the gated mode, it yields sharper delineation of the ventricular wall. Its use is increasing.
   H. Positron emission tomography (PET) scanning. PET scans are probably most useful in disorders of myocardial metabolism, such as genetic defects in myocardial energetics.

Palpitation and Disorders of the Heartbeat

David Shander

Definition
The term *palpitation* refers to any conscious sensation of cardiac activity. It is generally an unpleasant feeling. Palpitation is not necessarily an indication of the presence of heart disease or of any specific arrhythmia. It may occur even when the heartbeat is normal.

Etiology
Normal
Palpitation may occur normally as a result of increased heart rate and vigor of myocardial contraction associated with physical activity or emotional stress. The cardiac rhythm is sinus tachycardia and needs no further discussion. Awareness of cardiac activity is common at night in many individuals who sleep on their sides. The heartbeat frequently is audible in the dependent ear and is probably the result of direct sound transmission to the ear. The sounds made by implanted synthetic prosthetic valves may cause annoyance when heard by the patient.

Neurocirculatory Asthenia (Cardiac Neurosis)
An awareness of the heartbeat occurs in some individuals in the absence of physical exertion or consciousness of any emotional stress. Such symptoms and other psychosomatic complaints may be an indication of neurosis. The episodes of palpitation are commonly associated with shortness of breath, lightheadedness, and precordial pain. The respiratory difficulty is frequently described as an inability to "get enough air in" or a feeling of suffocation. There may be an overwhelming sense of terror, which tends to perpetuate the symptoms. In some instances, deliberate hyperventilation may reproduce all of the symptoms. It is well to remember that cardiac neurosis is often associated with real cardiovascular disease. Such patients are understandably anxious, and sometimes perceive minor symptoms out of proportion to their significance, precipitating an acute anxiety reaction associated with palpitation and breathlessness. Very loud murmurs of aortic stenosis, ventricular septal defect, and mitral regurgitation are sometimes heard by patients, especially when at rest.

Palpitation Not Associated with Cardiac Arrhythmia
The conditions that may cause palpitation in the absence of arrhythmia are listed in Table 3-16.

Table 3-16. Causes of palpitation without arrhythmia

Noncardiac disorders
Anxiety
Anemia
Fever
Thyrotoxicosis
Hypoglycemia
Pheochromocytoma
Aortic aneurysm
Migraine
Arteriovenous fistula
Drugs (e.g., beta agonists, vasopressors, theophylline, vasodilators)
Diaphragmatic flutter
Cardiac disorders
Aortic regurgitation
Aortic stenosis
Patent ductus arteriosus
Ventricular septal defect
Atrial septal defect
Marked cardiomegaly
Acute left ventricular failure
Hyperkinetic heart syndrome
Tricuspid insufficiency
Pericarditis
Prosthetic valves
Electronic pacemakers

Palpitation Associated with Cardiac Arrhythmia

Cardiac arrhythmias, including premature contractions, paroxysmal and nonparoxysmal tachycardias, and marked bradycardias are the most common causes of palpitation. Some patients with artificial pacemakers have diaphragmatic or intercostal twitching produced by the pacemaker stimulus. This may be interpreted as palpitation. Other patients are aware of a change in cardiac activity when spontaneous beats are replaced by a pacemaker-induced rhythm.

Premature Contractions

I. Many patients with premature contractions (Fig. 3-2) do not use the term *palpitation* to describe their complaint, but rather describe the premature systoles as flip-flop sensations in the chest, stoppage of the heart, or skipped beats. Brief chest pain may be associated.

II. Premature contractions may occur in the presence or absence of organic heart disease. They may be ventricular or supraventricular in origin. The clinical significance of such beats varies. Some are completely benign, whereas others may have serious or even grave prognostic importance. The presence of premature beats in an ECG may provide a clue to the identification of a paroxysmal tachycardia not otherwise recorded. It is usually presumed that they are of similar origin. Although physical examination and close scrutiny of the jugular venous pulse may assist in determining the origin of the beats, the final diagnosis of their etiology is based on the electrocardiographic findings. Criteria for the electrocardiographic identification of the various types of premature beats are summarized in Table 3-17 and Fig. 3-2.

III. Supraventricular premature contractions (atrial and AV junctional) may occur in normal individuals. Other important causes include infectious disease and other febrile states, organic heart disease, particularly with atrial involvement (e.g., mitral valvular disease, pericarditis), chronic obstructive airway disease, and digitalis administration. Atrial premature beats are frequent precursors of atrial fibrillation, tachycardia, or flutter.

IV. Ventricular premature beats are also frequently benign, but underlying myocardial disease or drug effects should be suspected if they occur frequently (>1 or 2/min), are paired or grouped, arise from more than one focus in the ventricles, are very closely coupled to the preceding beat, or are very wide (≥0.16 sec). Ventricular premature beats in myocardial infarction may be harbingers of ventricular fibrillation, especially if they encroach upon the vulnerable period (the region at or about the peak of the T wave). In general, ventricular premature beats in nonischemic conditions are less ominous, and the risk of sudden death

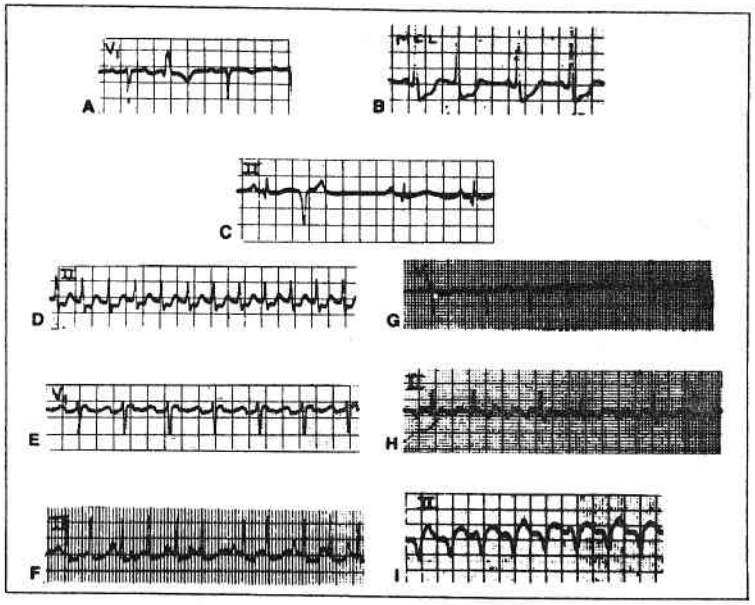

FIG. 3-2. Arrhythmias associated with palpitation. **A.** Atrial premature contraction (second beat) with berrant ventricular conduction exhibiting the pattern of right bundle branch block. **B.** AV junctional premature contraction (second ventricular complex). The ectopic beat is similar in configuration to that of the conducted beats but is not preceded by a P wave. **C.** Ventricular premature contraction (second QRS complex). A sinus P wave deforms the T wave of the ectopic beat. **D.** Paroxysmal supraventricular tachycardia. Atrial activity cannot be identified. The QRS complexes are of normal duration. **E.** Paroxysmal atrial tachycardia with 2:1 AV block. **F.** Multifocal atrial tachycardia. Note the multiform P waves, the irregular P-P intervals, and the variable P-R durations. **G.** Atrial fibrillation with a moderate ventricular response. The P waves are replaced by small irregular oscillations, called f waves. The ventricular rhythm is irregular. **H.** Atrial flutter with alternating 2:1 and 4:1 AV conduction. The P waves are replaced by regular oscillations exhibiting a sawtooth pattern (F waves). **I.** Probable ventricular tachycardia. The QRS complexes are wide and bizarre. The T waves of the first, fourth, and seventh ventricular complexes are peaked due to superimposed independent atrial activity indicative of AV dissociation. An AV junctional tachycardia with aberrant ventricular conduction can produce the same appearance. The absence of fusion or capture beats or both does not rule out ventricular tachycardia.

Table 3-17. Electrocardiographic differential diagnosis of premature contractions

Premature contractions	Initial deflection	P wave	P-R interval	QRS complex	Compensatory pause
Atrial (APC)	P wave	Premature; different from sinus P wave; usually upright but may be retrograde (inverted in leads II, III, and aVF, and upright in lead aVR)	Normal or prolonged	May be absent if APC is nonconducted; usually normal but may be aberrant ventricular conduction	Not fully compensatory unless sinoatrial (SA) node is suppressed by discharge of the APC
AV junctional (JPC)	P wave or QRS complex	Retrograde	0.10 sec to negative; R-P interval variable; diagnostic if R-P interval is > 0.10 sec	Usually normal but may demonstrate RBBB or less commonly LBBB ducts aberrant ventricular conduction or preexisting intraventricular block	Not fully compensatory unless SA node is suppressed by discharge of the JPC
Ventricular (VPC)	QRS complex	Sinus if dissociated from QRS; retrograde if ventricular impulse is conducted to atria	Absent if P and QRS are dissociated; if retrograde, R-P interval is = 0.10 sec	Wide (= 0.12 sec)	Fully compensatory unless retrograde conduction is present or beat is interpolated

Note: It is not always possible by surface leads to distinguish absolutely between VPCs and JPCs with aberrant ventricular conduction.

is considerably less. An exception to this statement is the presence of ventricular premature beats owing to digitalis intoxication.

Paroxysmal Tachycardias

Most patients who experience bouts of paroxysmal tachycardia complain of palpitation, yet some, surprisingly, are completely unaware of their existence. Paroxysmal tachyarrhythmias occur in normal individuals as well as in those with diseased hearts. Some are drug-induced; digitalis is the most notable offender in this group. Patients taking antiarrhythmic agents, especially of class I type, may be prone to arrhythmia exacerbation. These proarrhythmias may occur in as many as 30% of patients on such drugs.

Attacks of paroxysmal tachycardia may last from less than a minute to hours or days, and may be recurrent. As in the case of prematurities, paroxysmal tachycardias may be supraventricular or ventricular in origin. Prolonged episodes of paroxysmal tachycardia may give rise to faintness, lightheadedness, syncope, dyspnea, angina, or congestive heart failure. The clinical evaluation of paroxysmal tachycardia is summarized in Table 3-18. The electrocardiographic differential diagnosis is considered in the following.

Bradycardias

Bradycardias may produce consciousness of the heartbeat when cardiac contraction is forceful as a result of increased stroke volume. Should the cardiac output decline, as a result of either very slow rates or weakened myocardial contractility, faintness or syncope may occur. The major causes of a slow pulse rate are sinus bradycardia, sinoatrial block, AV junctional rhythms, extrasystolic bigeminy, and AV block. Beta blockers, calcium channel blockers, digitalis, and amiodarone are cardiac drugs known to be associated with various types of bradycardia.

Preexcitation Syndromes (Wolff–Parkinson–White, Lown–Ganong–Levine)

Paroxysmal supraventricular tachycardia occurs commonly with preexcitation. The ECG in the Wolff–Parkinson–White (WPW) syndrome demonstrates a short P-R interval caused by prolongation of the QRS duration, the early portion of which is most prolonged and referred to as a delta wave. Secondary repolarization changes are the rule. In the Lown–Ganong–Levine (LGL) syndrome a short P-R interval (≤0.10 sec) is associated with a normal QRS duration and absence of delta waves. The recognition of preexcitation as a cause of supraventricular tachycardia is important because conventional forms of therapy may be ineffective.

Sick Sinus Syndrome

A common cause of palpitation, dizziness, and syncope, at all ages (but most commonly in patients over 60) and in numerous clinical states, is the tachycardia–bradycardia syndrome commonly called the sick sinus syndrome (SSS). The term is somewhat of a misnomer because most of these patients also have disease of other portions of the conduction system. A spectrum of arrhythmias is seen, including SA block, sinus arrest, sinus pauses, sinus bradycardia, supraventricular tachycardias, and AV conduction disturbances. Failure to elicit a tachycardia with 1 mg of atropine intravenously in a patient with sinus bradycardia suggests the possibility of the sick sinus syndrome.

Diagnostic Approach

History and Physical Examination

I. As a first step, disorders not associated with arrhythmia and neurocirculatory asthenia should be ruled out as causes of palpitation (Table 3-16). This can usually be accomplished through the history, physical examination, and selected laboratory tests.
II. All patients in whom arrhythmia is suspected as the cause of palpitation should be evaluated for the presence or absence of heart disease. Chest films and an ECG should be included in such an evaluation.
III. In any patient complaining of palpitation, specific inquiry should be made as to whether the symptom is continuous when present or is related to isolated beats.
IV. When rapid heart action is suggested by the history, additional features may help to distinguish between sinus and ectopic rhythms. A tachycardia with a rate

(text continues on page 119)

TABLE 3-18. Clinical differential diagnosis of the tachycardias

Tachycardias	Rate: Atrial	Rate: Ventricular	Regularity	Onset and Termination
Sinus tachycardia	100–150 but may be faster	100–150 but may be faster	Regular	Gradual
Paroxysmal reentrant supraventricular tachycardia	140–200	140–200	Usually regular	Abrupt
Paroxysmal automatic atrial tachycardia	100–180	100–180	Usually regular	Usually abrupt
Paroxysmal atrial tachycardia with block	120–250; usually 120–180 with 2:1 block	Variable	Regular or irregular	Gradual
Multifocal atrial tachycardia (chaotic atrial rhythm)	100–180	100–180	Irregular	Gradual
Atrial flutter	220–350	Variable; 2:1 block usually present if untreated	Regular or irregular	Abrupt
Atrial fibrillation	350	Variable	Irregular; if regular, indicative of advanced or complete AV block	Abrupt
Paroxysmal automatic AV-junctional tachycardia	100–180; with AV dissociation, usually NSR	100–180	Regular	Usually abrupt
Nonparoxysmal AV-junctional tachycardia	Depends on atrial mechanism; AV dissociation often present	65–130	Regular	Gradual
Paroxysmal ventricular tachycardia	With AV dissociation, usually NSR; may have retrograde atrial activation	140–200; may be slower with idioventricular or parasystolic ventricular tachycardia	Regular or slightly irregular	Abrupt
Accelerated idioventricular rhythm	Indeterminate	80–110	Regular	Abrupt

Arrhythmia	Etiology	Physical signs: Jugular venous pulsations	Physical signs: Heart sounds	Response to carotid sinus massage
Sinus tachycardia	Physical or emotional stress; increased sympathetic tone; decreased vagal tone; drugs; hypoxemia; shock; hyperkinetic circulatory states; congestive heart failure; myocardial disease	Normal	Normal	Gradual slowing with return to previous rate
Paroxysmal reentrant supraventricular tachycardia	Organic heart disease or normal subjects	Normal or cannon A waves	S_1 usually constant in intensity	No effect, or abrupt termination
Automatic atrial tachycardia	Most commonly associated with organic heart disease	Normal	S_1 constant in intensity	No effect, or AV block may appear, P waves unaffected
Paroxysmal atrial tachycardia with block	Most often caused by combination of digitalis excess and potassium depletion; may also occur in coronary heart disease, rheumatic heart disease, and pulmonary disease	A waves at rapid, slightly irregular rate, exceed ventricular rate	S_1 may vary in intensity	May increase degree of AV block and slow ventricular rate; contraindicated in most situations
Accelerated idioventricular rhythm	Coronary heart disease, acute ischemic syndromes, digitalis toxicity	Regular cannon A waves	S_1 constant, S_2 widely split	No effect
Multifocal atrial tachycardia	Acute and chronic pulmonary disease, especially with respiratory failure and hypoxia; organic heart disease may be associated.	May not be visible	S_1 may vary in intensity	No effect, or gradual slowing

continued

TABLE 3-18. *Continued.*

Arrhythmia	Etiology	Physical signs: Jugular venous pulsations	Physical signs: Heart sounds	Response to carotid sinus massage
Atrial flutter	Almost always associated with organic heart disease; hypoxemia; shock; acute or chronic pulmonary disease	Flutter waves may be visible at multiples of ventricular rate	S_1 may vary in intensity if rhythm is irregular	May increase degree of AV block, slow ventricular rate, and reveal flutter waves
Atrial fibrillation	Almost always associated with organic heart disease (especially rheumatic or coronary heart disease); hyperthyroidism	Irregular pulsations	S_1 varies in intensity	Gradual slowing, with return to previous rate
Paroxysmal AV junctional tachycardia	Same as for paroxysmal atrial tachycardia	Regular or irregular canon A waves may occur	S_1 constant; varies in intensity if AV dissociation is present	No effect, or abrupt termination
Nonparoxysmal AV junctional tachycardia	Digitalis toxicity; coronary heart disease, especially inferior infarction; rheumatic carditis; post-cardial surgery	Regular or irregular canon A waves commonly present	S_1 constant; varies in intensity if AV dissociation is present	No effect, or gradual slowing, with return to previous rate; contraindicated in most situations
Ventricular tachycardia	Coronary heart disease, especially myocardial infarction; congestive heart failure; drug toxicity (digitalis, quinidine, epinephrine)	Irregular cannon A waves when AV dissociation is present	S_1 varies in intensity; S_2 widely split	No effect

AV = atrioventricular, NSR = normal sinus rhythm, S_1 = first heart sound, S_2 = second heart sound.

above 140/min that starts and ends abruptly, and that can be terminated by vagal maneuvers performed by the patient (e.g., swallowing, coughing, breath-holding), suggests the diagnosis of paroxysmal rather than sinus tachycardia.

V. Cardiac arrhythmia is a not uncommon cause of syncope.

VI. The use of coffee, tobacco, alcohol, and drugs should be quantified. It should be remembered that arrhythmias may be exacerbated in some instances by antiarrhythmic drugs.

VII. Supraventricular arrhythmias, such as paroxysmal atrial tachycardia (PAT), are quite common in young women during pregnancy.

VIII. Associated symptoms or signs may provide clues to the presence of coexisting disease (e.g., hyperthyroidism, pheochromocytoma) that may be responsible for palpitation and dysrhythmia. Viral illnesses, especially influenza, may give rise to ventricular premature beats that may last for weeks or months after recovery.

IX. During auscultation of premature beats, splitting of the heart sounds is wider with ventricular or aberrantly conducted beats than with premature beats in which the QRS complexes are of normal duration.

X. The jugular venous pulse may be of considerable help diagnostically (Table 3-18).

XI. The click-murmur syndrome of mitral valve prolapse is commonly associated with frequent premature contractions, both ventricular and supraventricular, and bouts of paroxysmal tachycardia. Palpitation is a common complaint. A careful physical examination and an echocardiogram may be helpful in diagnosis.

XII. The hyperkinetic heart syndrome is an ill-defined condition consisting of a resting tachycardia associated with palpitation. It occurs in otherwise normal healthy individuals and appears to be different from simple neurocirculatory asthenia.

Electrocardiographic Findings

When a patient is seen during an arrhythmic episode, an ECG should be recorded at once. The diagnosis may then be obvious from the ECG. Not infrequently, however, particularly in paroxysmal tachycardias, the ECG may present diagnostic problems. Under such circumstances, attention to the points listed in the following may be helpful in unraveling the correct diagnosis. It is useful to divide paroxysmal tachycardias into those characterized by normal QRS duration and those in which the QRS duration is prolonged (≥0.12 sec).

I. Tachycardia with normal QRS duration

A. The supraventricular origin of a tachycardia is virtually established if the QRS complexes are of essentially normal configuration and duration. However, supraventricular tachycardia may be associated with abnormal QRS complexes. This variety is considered separately in the following.

B. The identification of P waves or other atrial activity is crucial in diagnosing arrhythmias by ECG. Lead V_1 is often the most useful in this regard, but leads II, III, aVF, or V_6 may also be helpful. For this reason, a 12-lead ECG should be obtained whenever possible. Esophageal or intracardiac leads may be necessary in complex cases.

C. A tachycardia is atrial in origin if it is initiated by a premature, ectopic P wave and followed by a QRS complex at a normal or slightly prolonged P-R interval.

D. A tachycardia is AV junctional in origin if the P waves are inverted (retrograde) in leads II, III, and aVF, and upright in lead aVR; if the P-R interval is 0.10 seconds or less; if retrograde P waves follow the QRS complexes; or if P waves are not detectable in the ECG.

E. During a continuous tachycardia with unidentified or retrograde P waves, it is not possible to determine whether the tachycardia is atrial or AV junctional in origin. *Supraventricular* is then the appropriate term for this arrhythmia.

F. Atrial flutter is recognized by the sawtooth appearance of the baseline (F waves) with an atrial rate usually greater than 250/min. Flutter waves may sometimes be separated by a flat baseline. F waves are usually best seen in leads II, III, and aVF, where they are usually inverted.

G. Atrial fibrillation is characterized by absence of P waves, rapid irregular oscillations of the baseline (f waves), and an irregularity of the ventricular

response (unless advanced or complete AV block or a nonparoxysmal AV junctional tachycardia is present). Fibrillatory waves may be fine or coarse in appearance, and when coarse may appear regular for brief periods, when they may be confused with flutter waves.

H. Carotid sinus massage, vagal maneuvers, and cholinergic drugs are often helpful in the diagnosis. Vagal maneuvers other than carotid sinus massage (e.g., eyeball pressure, induction of vomiting, etc.) are not recommended. Carotid sinus massage should always be performed with caution, particularly in the elderly, and with ECG monitoring. The procedure is contraindicated in patients with carotid artery disease, heart block, and in suspected digitalis intoxication.

Adenosine (6 or 12 mg intravenously) is the pharmacologic agent most commonly used currently for the termination of supraventricular tachycardias. It should be given with caution to patients with reactive airway disease or asthma. Verapamil 5 mg IV may be used as an alternative. The use of a pressor agent (e.g., phenylephrine) to abruptly raise the systolic blood pressure is still a useful alternative, especially in patients who present with hypotension. All of these agents have a diagnostic as well as a therapeutic potential, for if the arrhythmia does not convert to sinus there may be sufficient slowing for the underlying atrial rhythm to be detected. Atrial flutter is often easily recognized under these circumstances.

II. In patients with suspected sick sinus syndrome, the measurement of corrected sinus node recovery time (CSNRT) has been suggested. Atrial pacing is performed at 130 to 140 beats/min for 1 to 2 min. On cessation, the ensuing pause (before the first sinus beat) minus the prepacing P-P interval is suggestive of the sick sinus syndrome if it exceeds 525 msec. Unfortunately, false-negative results are common.

III. Tachycardia with abnormal QRS duration (≥0.12 sec) (Figs. 3-2 through 3-4)

A. Tachycardia with abnormally wide QRS complexes may be supraventricular or ventricular in origin. All the electrocardiographic manifestations of ventricular arrhythmia may be mimicked by supraventricular arrhythmia associated with QRS complexes that are abnormally wide as a result of aberrant ventricular conduction, bundle branch block, ventricular preexcitation, or hyperkalemia.

B. Tachycardias with abnormal QRS complexes are supraventricular in origin if they are initiated by premature, ectopic P waves, regardless of the configuration of the QRS complexes.

C. Tachycardias initiated by abnormal QRS complexes may be ventricular or AV junctional in origin. In the latter case, the QRS complexes may be bizarre because of the presence of the conditions listed in the preceding.

D. A tachycardia that occurs after a premature QRS complex and interrupts the T wave of the preceding beat (R on T phenomenon) is regarded as ventricular in origin.

E. The regularity of the tachycardia and its rate are of limited help in differential diagnosis.

F. The configuration of the QRS complexes may provide a clue, but it rarely permits absolute differentiation between aberrant ventricular conduction and ventricular ectopy. Favoring aberrant conduction are a triphasic RBBB pattern with an rsR′ pattern in V_1 and a qRS pattern in V_6. Favoring ectopy are the following: (a) a duration greater than 0.14 seconds; (b) concordance of the QRS complexes in the precordial leads, either all positive or all negative (preexcitation excluded); (c) AV dissociation; (d) early nonaberrant capture or fusion beats; (e) VA association (retrograde conduction of P waves); (f) electrical axis markedly superior and rightward; (g) morphology unlike either RBBB or LBBB; (h) absence of RS complexes in the V leads or the presence of any RS with a duration greater than 0.10 seconds (measured from the beginning of the complex to the nadir of the S wave); (i) the presence in V_1 of a qR, RsR′ with a taller left peak, a single-peak R, QR, or RS complexes; (j) with an LBBB pattern, a broad R wave (0.03 sec) or slurred downstroke to a late nadir (≥0.06 sec); (k) the presence in V_6 of rS, QS or QR complexes, and S or QS more than 15 mm deep, or a peak or nadir greater than 0.07 seconds. If the configuration of the QRS complexes during the tachycardia is the same as that during a known supraventricular rhythm, the tachycardia is considered supraventricular in origin.

G. In the presence of AV dissociation, an atrial arrhythmia can be excluded, and a ventricular rhythm is the most likely diagnosis, although a junctional mechanism with aberration or preexisting block is possible.

H. Retrograde conduction to the atrium may occur in AV junctional or ventricular tachycardias.

I. The most useful criterion for the diagnosis of ventricular tachycardia in the conventional ECG is the presence of early ventricular capture or fusion beats, or both. Absence of fusion or capture beats does not rule out ventricular tachycardia.

J. Because ventricular tachycardia is unaffected by carotid sinus massage, a response to this maneuver (such as termination of the tachycardia or slowing of the ventricular rate) is virtually diagnostic of supraventricular arrhythmia.

K. The most precise method available for differentiating between supraventricular and ventricular arrhythmias is the His bundle electrogram. With this recording, in supraventricular rhythms, an H deflection is seen to precede each QRS complex at a normal or prolonged H-V interval; and in ventricular rhythms, the QRS complexes are not preceded by H deflections. Esophageal or intracardiac leads may establish the diagnosis of supraventricular arrhythmia if a definite relationship between atrial and ventricular activity can be demonstrated.

L. Reversion of a tachycardia with wide QRS complexes to normal sinus rhythm with low voltage, direct current, cardioversion (10 W/sec or less), or by a mechanical blow to the chest is suggestive of ventricular tachycardia. Similarly, reversion with lidocaine suggests a ventricular origin. Hence, these procedures may aid in diagnosis as well as therapy.

M. Wide QRS tachycardias may be monomorphic (all complexes of the same configuration) or polymorphic (changing complex configuration). Such tachycardias may be nonsustained or sustained (lasting 30 sec). It is now recognized that sustained and polymorphic ventricular tachycardias are potentially more life-threatening than nonsustained and monomorphic forms. A unique polymorphic form exists, known as torsades de pointes, in which a rapidly occurring complex appears to rotate its vector about a point. Such rhythms are very malignant and are sometimes the result of the proarrhythmic effects of antiarrhythmic drugs or severe metabolic disturbances.

Recent studies have suggested that suppression of ventricular ectopy and asymptomatic nonsustained ventricular tachycardia, using antiarrhythmic agents, may not consistently reduce the risk of sudden death.

N. The diagnosis of arrhythmia may pose a real problem if the arrhythmia is not present at the time of examination. One solution, if the condition is not serious, is to ask the patient to return when the rhythm disturbance returns. However, if the episodes occur infrequently or are of brief duration even when frequent, it may not be possible to catch the patient during an arrhythmic episode. Under such circumstances, either the diagnosis must await a more propitious opportunity for examination, or the patient may be monitored.

Electrocardiographic Monitoring

Patients with serious arrhythmia problems, particularly when associated with other cardiovascular symptoms and organic heart disease, should be monitored if the rhythm disturbance cannot be diagnosed in any other way. Monitoring can be performed either on an inpatient or an outpatient basis. In the hospital, radiotelemetry (if available) is the most suitable method for monitoring patients, because it permits them to be ambulatory. Direct connection to a nonportable unit is less desirable because the patient must be confined to bed. For outpatients, a portable apparatus is available that can tape record continuously for 24 hours the patient's ECG while he or she goes about

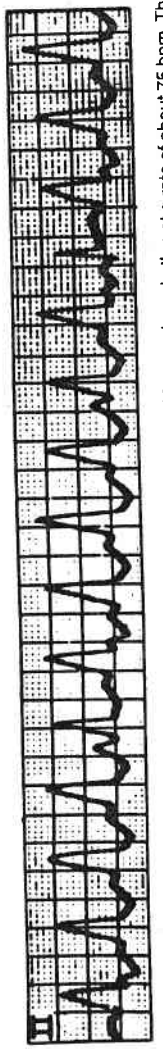

FIG. 3-3. Relatively slow paroxysmal ventricular tachycardia, at a rate of 128 bpm, dissociated from a sinus rhythm at a rate of about 75 bpm. The twelfth ventricular complex is a ventricular capture, and its pattern is that of inferior myocardial infarction. The fifth and tenth QRS complexes are ventricular fusion beats (Dressler beats).

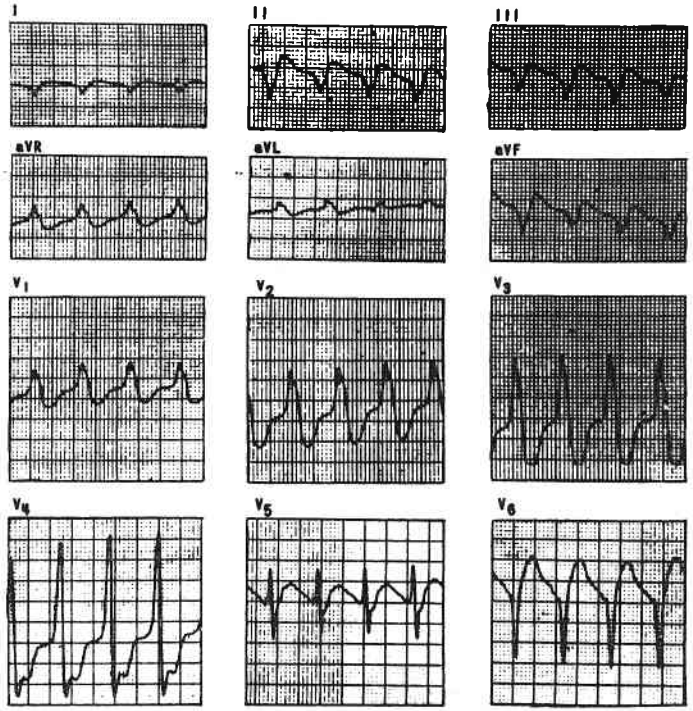

FIG. 3-4. Left ventricular paroxysmal tachycardia. The broad slurred R waves in lead V_1 and QS complexes in lead V_6 strongly suggest left ventricular ectopy. The marked superior axis in the limb leads also suggest ventricular arrhythmia, because this is an uncommon axis for conducted beats. The atrial mechanism cannot be identified.

normal activities. When the tape is played back later, the arrhythmias that occurred can be identified and reproduced on electrocardiographic paper to obtain permanent records. Exercise testing may elicit arrhythmias not present at rest or during normal activity and thereby provide a clue to the presence of symptomatic cardiovascular disease or indicate an increased risk of sudden death.

Small, portable, and even surgically implantable (for longer periods of monitoring) battery-operated devices are now available that allow the patient to record the heartbeat by placing the device on the chest. The electrocardiogram can then be transmitted by telephone to the patient's physician or to a central recording station. Many of the units have a memory capacity and can store fleeting arrhythmias for later transmission.

Electrophysiologic Testing

In patients who have experienced life-threatening arrhythmias and episodes of sudden death with successful resuscitation, programmed electrical stimulation of the ventricles has been shown to be of value in subsequent management of the patient. The ability to induce sustained ventricular tachycardia, which is no longer inducible after administration of an antiarrhythmic agent, may be the best predictive test of anti-

arrhythmic effectiveness. Failing this, implantation of an automatic implantable cardioverter defibrillator (AICD) is the only other fail-safe approach to the prevention of sudden death from ventricular tachycardia or ventricular fibrillation. The new devices are capable of recording the arrhythmic event that triggered the device and to pace the heart when needed. In fact, recent studies have demonstrated that the AICD may be preferable to antiarrhythmic drugs in these situations. (See Syncope in Chapter 10 for use of upright tilt testing in evaluating palpitations.) Signal-averaged electrocardiography that detects low-amplitude late potentials may be a useful method for predicting the future development of life-threatening arrhythmias in patients after acute myocardial infarction.

Peripheral Vascular Disorders

Michael A. Cooper and Richard J. Sanders

Introduction

The peripheral vascular system constitutes a delivery system for blood and blood products to various tissues and organs. It is divided into three major areas: arterial, venous, and lymphatic. Disorders of the arterial system constitute an inability to supply tissues with oxygen and other nutrients required for their functions. Venous disorders typically result in congestion of fluid and waste products as blood flow exiting tissues is impeded. Lymphatic disorders are also congestive in nature.

Arterial Disease

Acute Arterial Occlusion

Etiology

I. Embolism: Any material traveling in a blood vessel of sufficient size to occlude blood flow is defined as an embolus. Although organized thrombus originating in the heart represents the most common source, arterioarterial embolization of atherosclerotic debris or even foreign bodies from trauma may occlude vessels. Although the femoral artery constitutes the level of embolic occlusion in greater than one-third of the cases, any vessel may be affected.

II. Thrombosis: Obliteration of the lumen of any artery by atherosclerosis represents the most common underlying etiology for acute arterial thrombosis. This clinical scenario may present with less occlusive disease in patients with hypercoagulability. Often a history of chronic arterial insufficiency precedes the thrombotic event.

III. Trauma: Complete transection of an artery is typically followed with retraction and spasm to minimize blood loss. The resultant effect is thrombosis. Blunt trauma, however, may produce intimal separation or dissection progressing to thrombosis.

Symptoms and Signs

I. Pain: Pain occurs immediately and is often debilitating if there is insufficient collateral flow.

II. Pulselessness: Loss of pulse in the involved limb, especially if the contralateral limb has palpable pulses, is a key finding.

III. Paresthesia: Sensory nerves are more sensitive to ischemia than motor nerves. Initially pain is marked but paresthesia develops as ischemia advances.

IV. Paralysis: Motor nerve dysfunction is typically a late finding and represents a more guarded prognosis.

V. Pallor: Loss of flowing blood in the capillary bed is responsible for this white color.

VI. Poikilothermia: Coldness develops with abrupt arterial occlusion.

Diagnostic Tests

I. Doppler: A 5-MHz hand-held bedside model is useful for identifying and characterizing flow within vessels.

II. Duplex ultrasonography: This technology combines an ultrasound image and Doppler.

III. Segmental pressures and pulse volume recording: This physiologic examination determines the blood pressure at various levels in an extremity and then provides a wave form at each level.

IV. Arteriography: Although this radiographic examination provides minimal physiologic information, it represents the gold standard for defining anatomy.

V. Magnetic resonance imaging: Both physiologic and anatomic information of large, medium, and small vessels may be defined by newer generation MRIs.

VI. Laboratory: Tests that define muscle damage based on acute extremity ischemia include CPK, WBC, pH, and electrolytes. Ischemia of other end organs may be represented by their specific function tests (i.e., renal ischemia by BUN and creatinine).

Treatment

Rapid restoration of arterial blood supply to the end organ or tissue is mandatory. It is helpful, but not always achievable, to identify the etiology of acute ischemia to assist in planning the method for reestablishing blood flow.

I. Operation: Removal of thrombus or embolic material by directly opening the artery constitutes the most rapid method. This is the method of choice for embolic occlusions. A balloon catheter is typically employed but can be damaging or impossible to pass in vessels with significant occlusive disease.

II. Endovascular: Advancements in guidewire and catheter techniques in combination with fibrinolytic medications has enhanced the ability to infuse medication directly into the thrombus or embolus. Although this method typically takes longer to reconstitute blood flow, it is preferred over operative methods in patients with thrombosis of chronic occlusive disease.

Chronic Arterial Occlusive Disease

Etiology

I. Atherosclerosis: Lipid deposition in the intimal and medial layer of elastic arteries resulting in plaque formation represents the most common etiology of chronic occlusive disease. Hypertension, hyperlipidemia, tobacco abuse, and diabetes mellitus augment this process.

II. Vasculitis: Autoimmune disorders may target the vascular endothelium as an antigenic source. Deposition of these complexes may lead to an obliterative process of the lumen of the vessel. This inflammatory process may characteristically be confined to large, medium, or small arteries. A unique form affects young smokers targeting small and medium sized arteries of the upper and lower extremities and is called thromboangiitis obliterans or Buerger's disease.

III. Vasospasm: Vasoconstriction and/or vasospasm may completely impede arterial flow. Raynaud's phenomenon is frequently used to describe this entity and is augmented by cold or emotional stimuli. Tissue necrosis may occur in vasospasm that is associated with collagen vascular disease but is atypical of vasospasm alone.

Symptoms

I. Pain

A. Intermittent claudication: Claudication is derived from the Greek language and means "to limp." Thus it is technically confined to the lower extremity but other muscle groups demonstrate similar findings. The demand for increased blood flow as a muscle group works is met by vasodilatation but a proximal flow limiting occlusive process may inhibit flow. The muscle mass thus tires and cramping, weakness, or pain is demonstrated. The complaint is generally alleviated within a few minutes after resting.

B. Ischemic rest pain: A dull aching or intense pain demonstrated in the digits of the leg, the dorsum of the foot, the arch of the foot or occasionally the pretibial region while the patient is supine may represent end-stage ischemia. The pain is typically alleviated with dependency and indicates a threat of tissue loss.

II. Ischemic ulceration: Ulcers that develop traumatically or de novo on a dysvascular foot require significant blood flow for healing. If there is not evidence of granulation following proper debridement and wound care, the limb is in jeopardy of amputation.
III. Gangrene: This represents tissue death due to lack of sufficient arterial blood flow.

Signs
I. Pulses: Although pulses are occasionally palpable owing to collateralization, they are typically absent below the level of occlusion.
II. Capillary refill: End-stage occlusive disease typically is manifest by rubor or redness in the dependent position and loss of color or pallor with elevation.
III. Temperature: Ischemic limbs are characteristically cooler; however, temperature is controlled by a number of factors. All cool limbs are not ischemic.
IV. Trophic changes: Loss of hair growth, thinning of the skin, and nail hypertrophy are all characteristics of chronic ischemia.
V. Bruits: Turbulence produced as blood flows over a flow constrictive lesion can frequently be heard by auscultation. Not all bruits indicate hemodynamically significant occlusive disease. For example, only 30% of cervical bruits indicate carotid stenosis in excess of 50% diameter reduction.

Diagnostic Procedures
I. Doppler: A 5-MHz, hand-held, bedside Doppler should be considered part of the physical examination of the vascular system. Single sound or monophasic signals are typically indicative of proximal occlusive disease while multiphasic (biphasic or triphasic) signals are considered normal.
II. Segmental pressures and pulse volume recordings: This objective, noninvasive examination measures blood pressure at three or four levels in the extremity and then gives a confirmatory waveform (pulse volume recording) at each level. An ankle index or ankle brachial index represents the ratio of the ankle blood pressure and the brachial blood pressure. Medial calcinosis, which is frequent in the diabetic population, may require increased pressure in the occluding cuff at the ankle level and therefore may artificially elevate the ankle index.
III. Duplex ultrasonography
IV. Arteriography
V. Magnetic resonance imaging

Treatment
I. Medical management: Non–limb-threatening occlusive disease is best managed with risk factor treatment and ambulation. If claudication is debilitating (usually one block before the symptom onset) and threatens the patient's job, then invasive intervention may be considered.
II. Endovascular intervention: Balloon angioplasty, with or without stent placement, is indicated for short segment, flow-limiting lesions with sufficient symptoms to warrant intervention. The common iliac works well but long-term patency without restenosis in the infrainguinal location has been disappointing.
III. Operation: Limb-threatening ischemia (ischemic rest pain, ischemic ulcer, or gangrene) constitutes the main indication for operative intervention. Endarterectomy or removal of the diseased intima and media with the associated plaque may be utilized for localized disease but the mainstay of reconstruction is arterial bypass. Although prosthetic material such as PTFE or Dacron may be used for larger vessel bypass, the conduit affording the best patency rate in the infrainguinal location is vein.

Carotid Occlusive Disease
Pathology
The majority of neurologic events that occur secondary to carotid pathology are related to an embolic focus but carotid occlusion may also be etiologic.

I. Atherosclerosis: The bifurcation of the cervical carotid artery provides a luminal flow pattern characterized by turbulence, reversal of flow, and shear forces on the posterior–lateral wall of the carotid bulb. This becomes the most common location for atherosclerotic plaque formation.
   A. Thromboemboli: Irregularity in the plaque leads to platelet deposition and poorly adherent clot that may embolize.
   B. Plaque hemorrhage: Erosion of the plaque into vas vasorum may lead to bleeding into the wall of the plaque with eruption and emboli from the debris.
II. Fibromuscular dysphagia: Multiple frail webs form in the intimal surface of the internal carotid artery followed by small dilatations giving rise to the "chain of beads" appearance. These serve as the source for thrombus formation and emboli.
III. Carotid arterial dissection: Pulsatile blood flow that violates the intimal barrier may lift the intima and part of the media. Although trauma, hypertension, and fibromuscular dysphagia are risks, spontaneous idiopathic dissections are not rare.

Clinical Presentation
I. Transient ischemic attack: This is a unilateral neurologic deficit that must totally clear to normal within 24 hours.
   A. Unilateral sensory motor defect: This may involve the feet but the upper extremities are more common.
   B. Amaurosis fugax: Emboli in the ophthalmic artery as it arises from the internal carotid will produce retinal ischemia and transient blindness in the ipsilateral eye.
   C. Expressive aphasia: Emboli that lodge in the speech area of the dominant hemisphere produces an inability to articulate the thought that is appropriately produced.
II. Stroke: A neurologic deficit that persists longer than 24 hours is often referred to as a reversible ischemic neurologic deficit (RIND). Longer persistence of the deficit is a stroke.

Treatment
I. Medical management: Antiplatelet agents such as aspirin are the mainstays of conservative therapy.
II. Operation: Carotid endarterectomy has shown clinical efficacy for both symptomatic and asymptomatic disease.
   A. Transient ischemic attack (TIA): For lesions 70% diameter stenosis, operation is preferable.
   B. Stroke with good recovery: (same as TIAs)
   C. Asymptomatic stenosis: Although there is support in the literature for operation in patients with 60% stenosis, most vascular surgeons have continued to reserve operation for "high-grade" stenosis (usually 80%).

Aneurysms
Etiology
I. Medial degeneration: Atherosclerosis is by far the most common cause; however, certain abnormalities of elastin tissue may be included.
II. Trauma: Penetrating and blunt trauma may lead to aneurysm formation. This is most commonly a false or pseudoaneurysm. Pseudoaneurysms do not contain all layers of the vessel wall like a true aneurysm.

Symptoms
I. Asymptomatic: The majority of true aneurysms are asymptomatic. Pseudoaneurysms may either be symptomless or present with subtle pressure symptoms.
II. Pain: This generally indicates rupture or rapid expansion with impending rupture. In the infrarenal abdominal aortic position, abdominal and back pain are characteristic.
III. Hypotension: Shock indicates rupture until proven otherwise.
IV. Distal arterial ischemic symptoms: Thrombosis or distal embolization may produce symptoms in the peripheral extremity.

Signs
I. Pulsatile mass: Although this is the hallmark of aneurysms, they may be difficult to palpate and ultrasound may be required.
II. Hematoma: This may be identified with rupture. Aortic or iliac aneurysms may produce flank, groin, or even scrotal hematomas.

Diagnostic Tests
I. Abdominal plain films: Although generally performed for other diagnostic purposes, the medial calcification frequently is visualized as a thin, white ring adjacent to the spine.
II. Ultrasonography: This noninvasive test is useful for diagnosis in both peripheral and abdominal aneurysms or may be used to serially follow small aneurysms.
III. Computed tomography: This radiographic examination provides superior detail concerning size, perianeurysmal bleeding, mural thrombus, and surrounding anatomy.
IV. Arteriography: This invasive radiographic examination provides anatomic detail regarding branch or outflow vessels. Because only the lumen of the vessel is imaged, mural thrombus may make the aneurysm look smaller than it actually is.

Operative Treatment Options
I. Abdominal aortic aneurysms: Although the general medical status and anticipated longevity of the patient must be taken into consideration, aneurysms of 5 cm or larger are repaired. Straight or bifurcated Dacron or PTFE grafts are utilized.
II. Peripheral aneurysms: Because peripheral aneurysms are more likely to thrombose or embolize, they are typically repaired at the time of diagnosis, especially if mural thrombus is identified.

Endovascular Options
Certain aortoiliac aneurysms may be treated with a new device that combines a graft material with stents in a low-profile carrier device introduced via femoral artery cutdown. Long-term outcome data are not yet available regarding this procedure.

Venous Disease

Deep Venous Thrombosis

Etiology
I. Stasis
II. Trauma
III. Hypercoagulability

Symptoms
I. Pain: This is related to the inflammatory response that occurs around the thrombosed vessel.
II. Swelling: The loss of fluid into the subcutaneous tissue related to the venous hypertension produces swelling.

Signs
I. Homan's sign: Pain with active dorsiflexion of the foot owing to muscle stretching around the inflamed veins is referred to as Homan's sign.
II. Color changes: A bluish discoloration of the leg related to iliofemoral venous thrombosis might indicate a limb-threatening condition called phlegmasia cerulea dolens. Worsening of this condition to complete venous outflow obstruction and capillary to arterial thrombosis may lead to limb loss.

Diagnostic Tests
I. Duplex ultrasonography: This noninvasive examination is highly accurate and has replaced venography in most circumstances.

II. Venography: Although still considered the gold standard, this invasive examination is reserved for nondiagnostic ultrasonography, visualization of iliac venous or vena caval abnormalities, or in conjunction with endovascular treatment.

Treatment
I. Anticoagulation: Intravenous heparin sulfate with conversion to oral warfarin represents the standard treatment. Fractionated heparin may be given by a twice-daily subcutaneous administration without serial partial thromboplastin time monitoring. Approximately 80% of uncomplicated deep venous thrombotic segments will recanalize with anticoagulant treatment alone. Valvular function may not be salvaged and may lead to chronic venous insufficiency.
II. Fibrinolytic therapy: Administration of fibrinolytic drugs via a catheter directed route might improve valvular salvage and thus diminish the risk of chronic venous insufficiency. This form of therapy has nearly completely replaced surgical thrombectomy. Although treatment of lower extremity DVT remains controversial, iliofemoral and subclavian venous thrombosis frequently employ this form of therapy.
III. Operation: Surgery is indicated for subclavian venous thrombosis caused by venous narrowing from the repetitive trauma of the first rib, clavicle, subclavius muscle, and costoclavicular ligament. This condition, called Paget-Schroeder syndrome or effort thrombosis, is initially treated with fibrinolytic therapy followed by first rib resection with venolysis with or without direct repair of the vein.

Chronic Venous Insufficiency

Etiology
I. Primary valvular insufficiency: Dysfunction of the veins of the lower extremity may result secondary to genetic factors and prolonged standing.
II. Secondary valvular insufficiency: Deep venous thrombosis may occlude the involved vein permanently or more commonly leads to valvular dysfunction.

Symptoms
I. Swelling
II. Pain

Signs
I. Varicose veins: Insufficiency of the superficial system or in combination with deep and communicating vein insufficiency may lead to varicose veins in the branches of the greater or lessor saphenous system.
II. Stasis dermatitis: Chronic swelling may lead to deposition of hemoglobin breakdown products and protein rich fluid in the subcutaneous tissues.
III. Ulceration: Chronic swelling leads to an unhealthy microenvironment at the skin and subcutaneous level, which may lead to an ulcer.

Diagnostic Tests
I. Duplex ultrasonography: This examination accurately defines deep, superficial, and perforator incompetence while investigating for venous occlusion.
II. Photoplethysmography

Treatment
I. External support: Compression stockings are indicated for treatment of varicose veins, swelling, and symptoms associated with deep and superficial venous insufficiency.
II. Operation: Stripping of the offending venous system and its branch varicosities is often curative.

Lymphatic Disease

Etiology
I. Congenital: Underdevelopment or obstruction of lymphatics (lymphedema praecox) is usually seen in young women age 12 to 30 years of age.

II. Cancer: Tumor growth may obstruct lymphatic flow either directly or by deposition of tumor cells in lymph nodes.
III. Trauma: Surgical dissection of the popliteal or femoral arteries disrupts the associated lymphatics and thus leads to transient lymphedema.

Signs and Symptoms
I. Edema: The swelling is classically spongy in nature and may extend into the toes.
II. Pain: Although swelling may be uncomfortable, pain may indicate infection (lymphangitis).

Treatment
External compression in the form of weighted stockings or pneumatic compression boots are the mainstay of therapy.

4. RESPIRATORY PROBLEMS

Dyspnea

Paul M. Cox, Jr. and Marvin I. Schwarz

Definition

Dyspnea is the subjective complaint of shortness of breath. Other forms of breathlessness, such as sighing respirations and the subjective sensation of inability to take deep breaths, are thus not included in this discussion.

Other terms frequently confused with dyspnea but having distinctly different meanings include hyperventilation, which is excessive breathing with or without the sensation of dyspnea; tachypnea, which is rapid breathing; and hyperpnea, which is rapid and abnormally deep respirations.

Orthopnea refers to dyspnea in recumbency that is at least partially relieved by assuming an upright position. Paroxysmal nocturnal dyspnea (PND) is the term applied to attacks of severe breathlessness that generally occur at night and usually awaken the patient from sleep. Relief from or termination of the attack is frequently obtained when the patient sits up.

Acute Dyspnea

Etiology (9)

I. The more common pulmonary diseases that are accompanied by acute dyspnea include pneumonia, pulmonary embolus, spontaneous pneumothorax, asthma, foreign body aspiration, noncardiac pulmonary edema (including noxious gas inhalation, high-altitude pulmonary edema, and neurogenic pulmonary edema), and the acute respiratory distress syndrome.
II. The major nonpulmonary cause of acute dyspnea is cardiogenic pulmonary edema. Orthopnea and PND are commonly associated with cardiogenic pulmonary edema.
III. Acute hyperventilation syndrome is a relatively frequent neuropsychiatric cause of dyspnea.

History

I. Pneumonia. Patients with pneumonia from any cause (viral, bacterial, or mycoplasmal) may have cough, sputum, pleuritic chest pain, fever, and chills after a prodrome of upper respiratory tract symptoms.
II. Acute pulmonary embolism. Patients with pulmonary embolism may have a characteristic clinical setting, such as prolonged immobilization, recent surgery, congestive heart failure, or recent trauma (particularly to the lower extremities). A predisposition to thromboembolism occurs in patients with a previous history of thrombophlebitis, women taking oral contraceptives, individuals with sickle cell anemia or polycythemic states, and individuals with congenital reduction in normally present anticoagulant proteins (antithrombin III, protein C, protein S, or Leiden Factor V).
III. Acute bronchial asthma. Acute asthma may begin at any age but is more frequent in patients with a past or family history of atopic disease. The asthma may be seasonal and may be associated with specific events or inciting agents.
IV. Cardiogenic pulmonary edema. The patient usually has the characteristic symptoms of congestive heart failure—dyspnea, orthopnea, PND, nocturia, ankle edema—which may precede the acute dyspnea by days or weeks. Acute dyspnea may accompany the characteristic chest pain of acute myocardial infarction or be its sole manifestation. A previous history of heart disease should be sought. Occasionally, previously undetected mitral stenosis may be discovered after an initial episode of pulmonary edema.

V. Spontaneous pneumothorax. Spontaneous pneumothorax is more likely to occur in young, tall, thin individuals. The patient usually gives a history of sudden onset of chest pain and dyspnea brought on by strenuous exertion, coughing, or air travel. Predisposing factors include emphysema, recent chest trauma, and interstitial lung disease.

VI. Foreign body aspiration. In the patient who has aspirated a foreign body, the history is usually obvious. The patient may not recall the event, however, especially if under the influence of alcohol or unconscious at the time or, as is frequently the case, the patient is a child and unable to relate any history.

VII. Noncardiogenic pulmonary edema
- A. Acute respiratory distress syndrome. Patients with this condition have insidious onset of dyspnea 24 to 72 hours after a severe, usually nonpulmonary, illness (e.g., hemorrhagic or septic shock, acute pancreatitis, multiple trauma, near drowning, overwhelming pneumonia).
- B. Noxious gas inhalation. There is usually a history of accidental exposure to a poisonous gas (e.g., chlorine, phosgene, smoke).
- C. High-altitude pulmonary edema. This condition usually occurs in young adults engaging in vigorous activity at a high altitude prior to acclimatization.
- D. Neurogenic pulmonary edema. This type of edema may be seen in epileptic patients during the postictal period and in patients with increased intracranial pressure.

VIII. Hyperventilation. This usually occurs in young people without other symptoms of cardiopulmonary disease, often in the presence of a recent emotional upset. Circumoral and carpopedal dysesthesias (tingling sensations) and carpopedal spasm may occur. Acute metabolic acidosis (diabetic ketoacidosis, ASA toxicity) should be considered in the differential.

Physical Findings

Tachycardia, tachypnea, cyanosis, and fever may be noted in patients with acute dyspnea.

I. Pneumonia. In the bacterial pneumonias, there are signs of consolidation, including bronchial breath sounds, increased tactile and vocal fremitus, and egophony. There may be an associated decrease in breath sounds and fine rales heard over the involved area. If a pleural effusion accompanies the pneumonia, the physical findings may include a pleural friction rub, decreased to absent breath sounds, decreased fremitus, and flatness to percussion. In contrast, the viral and mycoplasmal pneumonias characteristically show a paucity of physical findings. Sometimes only rales are heard.

II. Acute pulmonary embolism. Pulmonary emboli show a variety of physical findings. The examination may reveal such signs as rales heard over the involved area, a pleural friction rub, and evidence of pleural effusion. Splinting of the involved side may be present and manifested in elevation of the diaphragm and a generalized decrease in breath sounds. Cardiac examination may reveal signs of right ventricular failure, including a right-sided third heart sound, the murmur of pulmonary regurgitation, or increased intensity of the pulmonary component of the second heart sound. Evidence of deep venous thrombosis may be present. Frequently, however, there are only the nonspecific findings of tachypnea and tachycardia.

III. Pneumothorax. The physical findings of pneumothorax are decreased breath sounds, increased resonance, and increased fremitus on the involved side. There may be a shift of the trachea and heart to the opposite side. Distention of the neck veins may be visible if the pneumothorax is under tension, and hypotension may occur. Hamman's sign (mediastinal crunch) may be heard in the presence of a left-sided pneumothorax.

IV. Bronchial asthma. Patients with asthma have hyperresonance to percussion and wheezing during their attacks. A prolonged expiratory phase is common. If bronchospasm is severe, the chest may be silent to auscultation.

V. Foreign body aspiration. A patient who aspirates a foreign body may have localized wheezing and decreased breath sounds on the involved side. There may be air trapping during expiration (hyperresonance to percussion on the affected side following forced expiration).

VI. Noncardiogenic pulmonary edema
- A. Acute respiratory distress syndrome. Clinical evidence of shock may be present. Conjunctival and axillary petechiae are commonly seen in fat embolism, and central nervous system (CNS) changes are also common. Rales may be heard but are less prominent than in other forms of pulmonary edema.
- B. Noxious gas inhalation. Such patients usually have conjunctivitis, pharyngitis, acute bronchitis, and wheezing. Later on, diffuse, bilateral moist rales appear as the clinical picture of pulmonary edema evolves.
- C. High-altitude pulmonary edema. Fine, moist bibasilar rales are commonly audible, although there is no evidence of heart failure.
- D. Neurogenic pulmonary edema. The findings are as in the preceding entry in association with evidence of neurologic injury. Acute systemic hypertension may be present.

VII. Cardiogenic pulmonary edema. There may be evidence of previous hypertension or heart disease. Cardiomegaly is suggested by lateral and downward displacement of the apical impulse. A third heart sound or summation gallop and murmurs may be heard. Examination of the lungs may reveal fine moist rales, particularly at the bases. Wheezes also may be heard. Peripheral edema, hepatomegaly, and distended neck veins suggest coexisting right-sided failure.

VIII. Hyperventilation. Fever and cyanosis are never present, and evidence of anxiety frequently exceeds the objective evidence for cardiopulmonary disease. Physical findings are normal except for tachypnea and occasionally tachycardia.

Roentgenographic Findings

I. Pneumonia
- A. Lobar consolidation with air bronchograms is usually present in bacterial pneumonia. Pleural effusion, which may be infrapulmonary or interlobal, is sometimes seen.
- B. Viral and mycoplasmal pneumonias may be lobar in distribution but are more likely to be diffuse and nonlobar in character. Pleural effusions occur less frequently than in bacterial pneumonias. Uncommonly, hilar adenopathy may occur.

II. Acute pulmonary embolism. The chest roentgenogram may be normal or may show evidence of splinting (a raised diaphragm and basilar atelectasis). Pleural effusion or pulmonary infiltrates may be seen after infarction of the lung. A lobar consolidation similar to bacterial pneumonia may be present. Vascular changes occur frequently in acute pulmonary embolism but are difficult to interpret. Vascular cutoffs and decreased blood flow may be demonstrated, particularly if previous x-ray films are available for comparison. With large central pulmonary emboli, a sausage-shaped dilation of the involved pulmonary artery may be seen. Most patients with pulmonary embolism have normal chest radiographs or nonspecific findings.

III. Spontaneous pneumothorax. Findings on the chest roentgenograms are virtually diagnostic of pneumothorax if the films are examined carefully. Occasionally, a small pneumothorax is not seen unless inspiratory and expiratory films are evaluated. It is necessary to determine whether or not the pneumothorax is under tension. The classic findings of a tension pneumothorax are depression of the diaphragm on the affected side and shift of the mediastinum to the opposite side.

IV. Bronchial asthma. In asthma, there may be radiologic signs of hyperinflation, such as flat diaphragm and increase in the retrosternal and retrocardiac air spaces. When an infectious process precipitates an asthmatic attack, evidence of pneumonia may be seen on the chest roentgenogram.

V. Foreign body aspiration. Rarely, the foreign body is radiopaque and can be visualized. The chest roentgenogram usually shows nothing abnormal. There may be evidence of unilateral air trapping, which is demonstrated best by fluoroscopy and expiratory films. Consolidation collapse of the lung distal to the foreign body may occur after a period of time.

VI. Noncardiogenic pulmonary edema. Early in the course of noxious gas inhalation, neurogenic and high-altitude pulmonary edema, and the adult respiratory distress syndrome, the chest radiograph may be normal. Within hours to a few days, the films show evidence of pulmonary edema without cardiomegaly.
VII. Cardiogenic pulmonary edema. The chest roentgenogram shows cardiomegaly except in mitral stenosis and some cases of acute myocardial infarction. Specific chamber enlargement is seen in valvular and congenital heart disease. An alveolar infiltrate showing a butterfly pattern is typical of this form of pulmonary edema. Distended veins to the upper lobes, Kerley's lines, and a peripheral or hilar haze, or both, may also be seen.
VIII. Hyperventilation. The chest film is normal.

Laboratory Data

I. CBC. The hematocrit and hemoglobin values are normal in all of these conditions unless altered by coexisting disease. The white blood cell (WBC) count is usually elevated, with a shift to the left, but it is rarely above 16,000/mm^3, except in bacterial pneumonias. Asthma may be associated with a significant eosinophilia. Marked derangements in all formed blood elements may be seen in severely ill patients with acute adult respiratory distress syndrome (ARDS). Moderated thrombocytopenia is often seen in embolism, and severe thrombocytopenia is seen in the disseminated intravascular coagulation (DIC) that may accompany ARDS.
II. Urinalysis. Hematuria, proteinuria, formed elements, and casts may be seen in the pneumonias, congestive heart failure, and conditions associated with ARDS. All these findings are nonspecific.
III. Serum electrolytes. A low serum sodium level may be seen in any infectious pneumonia. This may be associated with increased excretion of sodium in the urine.
IV. Electrocardiogram. The classic pattern of acute myocardial infarction on the electrocardiogram may be diagnostic. Findings of right-axis deviation, an $S_1Q_3T_3$ pattern, or right ventricular strain provide supportive evidence for the diagnosis of pulmonary embolism but do not distinguish this condition from other acute causes of dyspnea associated with increased pulmonary vascular resistance, such as severe airway resistance or hypoxemia. Atrial arrhythmias may be seen with any cause of respiratory failure.
V. Examination of the sputum.
   A. Gross examination. Pink frothy sputum is often seen in the cardiogenic or noncardiogenic pulmonary edema. Blood streaking is usually not helpful. The presence of mucous plugs may suggest asthma. Grossly purulent sputum suggests a bacterial pneumonic process, whereas a mucoid sputum is seen more frequently in viral and mycoplasmal pneumonias.
   B. Gram stain. An adequate, freshly obtained sputum sample should be examined in patients with pneumonia. The gram stain should demonstrate large numbers of polymorphonuclear leukocytes. Only if a predominant or intracellular organism can be identified should it be tentatively considered the etiologic agent.
   C. Acid-fast stain. Acid-fast organisms should be sought carefully under oil immersion.
   D. Wright's stain. Eosinophilia may predominate in the sputum samples of asthmatic patients.
   E. Sputum cultures. Routine cultures for bacteria should be obtained. Facilities for culture of viruses, Legionella, and mycoplasmas are not usually available except in specialized laboratories.
VI. Blood cultures. Blood cultures should be drawn from the febrile patient with acute dyspnea.
VII. Arterial blood gases. Arterial blood gas results are no value in differentiating among the various entities under consideration, but they are helpful in patient management because all of these conditions may include varying degrees of hypoxemia, hypercarbia, or both.

VIII. Serologic studies. Cold agglutinins may be elevated in mycoplasmal pneumonia. Rises in specific titers may be seen in viral pneumonias and pneumonia owing to *Legionella pneumophila*.

Further Studies

When the aforementioned studies are completed, the most likely diagnosis should be apparent and treatment instituted. If pulmonary embolism is a prime consideration, perfusion and inhalation lung scans should be performed. A pulmonary angiogram is usually indicated if the lung scan is abnormal. Impedance plethysmography, Doppler examination, and venography of the lower extremities may be helpful in selected cases. If foreign body aspiration is suspected, early bronchoscopy is indicated. If asthma is the apparent diagnosis, treatment should be instituted and the workup completed when the patient's condition has stabilized. Severe hypoxemia or acute hypercarbia may require intubation and mechanical ventilation.

Chronic Dyspnea

Etiology

I. Pulmonary causes of chronic dyspnea
   A. Chronic obstructive airway disease
      1. Emphysema
      2. Chronic bronchitis
      3. Chronic bronchial asthma
         Note: Although there is usually considerable overlap among these three entities, the classic forms are described in the discussion that follows.
   B. Restrictive lung disease
      1. Interstitial lung diseases (the most common of which are sarcoidosis, rheumatoid lung, scleroderma lung, the pneumoconioses, histocytosis X, lymphangitic carcinomatosis, and idiopathic pulmonary fibrosis)
      2. Chest wall deformities (e.g., kyphoscoliosis and thoracoplasty)
      3. Pleural fibrosis
      4. Alveolar-filling disease (alveolar proteinosis, alveolar cell carcinoma, desquamative interstitial pneumonia, and alveolar microlithiasis)
      5. Neuromuscular disease (e.g., myasthenia gravis, amyotrophic lateral sclerosis)
II. Nonpulmonary causes of chronic dyspnea
   A. Congestive heart failure and other low-output states
   B. Anemia
   C. Hyperthyroidism
   D. Upper airway disease
   E. Obesity
   F. Neurosis

History

I. Pulmonary causes
   A. Chronic obstructive airway disease
      1. Patients with emphysema usually give a long history of steadily worsening dyspnea. There may be a family history of emphysema or other obstructive lung disease.
      2. In chronic bronchitis, a productive cough is present for at least 3 months of every year for a consecutive 2-year period. Chronic bronchitis is usually associated with a long history of cigarette smoking, "smoker's cough," wheezing, and repeated pulmonary infections.
      3. The history of patients with chronic asthma is similar to that of patients with acute asthma.
   B. Restrictive lung disease
      1. A complete discussion of all the causes of interstitial lung disease is beyond the scope of this text. In some conditions, diagnostic clues may be found in the history. In the connective tissue diseases, such as scleroderma, rheumatoid arthritis, and polymyositis, there may be a history or

symptoms suggestive of the diagnosis. Sometimes, however, these diseases are first manifested by interstitial fibrosis, and the systemic manifestations develop later. Patients with eosinophilic granuloma may have a history of recurrent pneumothorax or diabetes insipidus, or both. Patients with sarcoidosis may have arthralgias and painful erythematous nodules on the shins. In the pneumoconioses, the occupational history is of prime importance. In lymphangitic carcinomatosis, symptoms caused by a primary carcinoma of the stomach, breast, prostate, lung, or other organ may be the presenting complaint.

2. The history is clear in patients with thoracic deformities.
3. Patients with pleural fibrosis may give a history of previous tuberculosis, severe bacterial pneumonia, chest trauma, surgery for tuberculosis, or asbestos exposure.
4. Among the alveolar-filling diseases, alveolar proteinosis and alveolar cell carcinoma may have significant sputum production. In lipoid pneumonia, there may be a history of use of oily nose drops.
5. Neuromuscular diseases rarely present as dyspnea. Diaphragmatic involvement may cause dyspnea that worsens lying down.

C. Pulmonary vascular disease. Pulmonary hypertension, either primary or secondary to recurrent pulmonary emboli, usually presents as slowly progressive dyspnea.

II. Nonpulmonary causes

A. Congestive heart failure. See Cardiogenic Pulmonary Edema under Acute Dyspnea.
B. Anemia. Progressive dyspnea is a common symptom of anemia; it should be considered, particularly, if the patient complains of blood loss, pallor, and/or weakness.
C. Hyperthyroidism. In thyrotoxic patients, dyspnea may be the predominant presenting symptom. Usually these patients have classic symptoms of thyrotoxicosis.
D. Upper airway disease. Patients with upper airway disease may have a history of endotracheal tube intubation or tracheostomy. Occasionally, bronchogenic carcinoma presents with tracheal obstruction. Such patients may complain of audible wheezing or upper airway rattling.
E. Obesity. Corpulence is seldom the sole reason for a patient's complaint of dyspnea unless the obesity is severe or the weight gain rapid.
F. Neurosis. See Hyperventilation under Acute Dyspnea. This is clearly a diagnosis of exclusion.

Physical Examination

I. Pulmonary causes

A. Chronic obstructive airway disease
1. Emphysema. Usually the emphysematous patient is thin and asthenic, the AP diameter of the chest is increased, and hypertrophy of the accessory muscles of respiration is visible. There is hyperresonance to percussion with depressed immobile diaphragm. Auscultation reveals decreased breath sounds and a prolongation of the expiratory phase of respiration. Faint expiratory wheezes may be heard.
2. Chronic bronchitis. Chronic bronchitis is diagnosed by the history. The patient may have findings of airway obstruction. Patients with severe disease may be cyanotic or plethoric or have signs of cor pulmonale.
3. Chronic bronchial asthma. Wheezing is one characteristic physical finding, and it may be associated with signs of hyperinflation of the lungs.

B. Restrictive lung disease
1. Interstitial lung disease. In interstitial fibrosis, clubbing is frequent. The chest examination may be normal except for dry inspiratory bibasilar rales. Signs of associated systemic diseases may be seen (e.g., arthritis, skin rash, lymphadenopathy, splenomegaly). Evidence of a primary carcinoma may be found in lymphangitic carcinomatosis.

2. Thoracic deformities. Kyphoscoliosis or a previous thoracoplasty is evident on inspection.
3. Pleural fibrosis. There may be diminished expansion of the chest wall. Dullness to percussion, decreased fremitus, and decreased breath sounds may be noted on the involved side.
4. Alveolar-filling diseases. There are no specific physical findings. Rales may be heard in occasional cases.

C. Pulmonary hypertension. Normal lung examination with right ventricular lift and accentuated pulmonary valve closure are usually seen. Peripheral edema may be seen late in the course.

II. Nonpulmonary causes

A. Congestive heart failure. Elevated venous pressure, gallop rhythm, bibasilar rales, and dependent edema are the cardinal signs.
B. Anemia. Aside from pallor, there are no specific signs of anemia, although specific signs are associated with different causes of anemia.
C. Hyperthyroidism. A goiter in association with tremor, moist skin, exophthalmos, hyperreflexia, and tachycardia is a classic sign of Graves' disease.
D. Upper airway disease. Wheezing or stridor may be audible, and a tracheostomy scar may be present.
E. Obesity. Excess adiposity is usually obvious on inspection.

Roentgenographic Findings

I. Pulmonary causes

A. Chronic obstructive airway disease. Severe obstructive disease of any etiology is frequently accompanied by a normal chest radiograph.
1. The patient with emphysema may show bullous changes, evidence of hyperinflation of the lungs, and attenuation of the pulmonary vasculature on the chest roentgenogram.
2. Chronic bronchitis may be associated with roentgenographic evidence of cor pulmonale (right ventricular hypertrophy associated with pulmonary hypertension).
3. In chronic bronchial asthma, the chest roentgenogram may show signs of hyperinflation and sometimes diffuse fibrosis or chronic segmental fibrosis secondary to old infectious processes. Occasionally, evidence of mucoid impaction of the bronchi may be seen.

B. Restrictive lung disease
1. In the interstitial lung diseases, the chest roentgenogram demonstrates a linear, fibronodular, or fibroreticularis infiltrate. Lytic lesions of the ribs or pneumothorax may be seen in histiocytosis X. Kerley's lines, pleural effusion, and mediastinal lymph node enlargement may be seen in lymphangitic carcinomatosis. A lung mass may also be demonstrable. In the interstitial lung disease owing to connective tissue disease, pleural effusion or scarring may be seen. Hypomotility and dilation of the esophagus owing to scleroderma may be manifested by a mediastinal air–fluid level. In sarcoidosis, hilar lymphadenopathy may be present. Silicosis is usually a predominantly upper lobe disease, with multiple interstitial nodules that often coalesce. Cavitary disease owing to superimposed mycobacterial infection may be present. Asbestosis is a predominantly lower lobe disease—a linear interstitial pattern that may be associated with calcified plaques in the diaphragmatic pleura or lateral wall pleural thickening, or both.
2. Obvious skeletal deformity may be seen on the chest films in kyphoscoliosis or after thoracoplasty.
3. In pleural fibrosis, the pleural line is thickened and may be calcified.
4. Alveolar-filling diseases demonstrate a characteristic acinar-filling pattern with air bronchograms, rosettes, and obliteration of the vascular markings. Early lipoid pneumonia and desquamative interstitial pneumonitis involve primarily the lower lobes.

C. Pulmonary hypertension usually shows enlarged central pulmonary arteries with or without cardiomegaly.

II. Nonpulmonary causes
A. Congestive heart failure. The radiographic picture of congestive heart failure is described in the section on Acute Pulmonary Radiographic Abnormalities.
B. Anemia. The chest roentgenogram is usually normal, although cardiomegaly may be present.
C. Hyperthyroidism. The chest film is usually normal, although the heart may be enlarged.
D. Upper airway disease. The chest roentgenogram may be normal, or there may be evidence of air trapping. The tracheal air shadow may be narrowed.
E. Obesity causes no significant pulmonary parenchymal infiltration, although cardiomegaly may be present. Because of the adiposity, the lung parenchyma may appear diffusely infiltrated if the chest film is underpenetrated. Increased soft tissue is obvious.

Laboratory Data

I. CBC. Erythrocytosis may be seen with any pulmonary cause of chronic dyspnea if hypoxemia is present. (Erythrocytosis may be seen in patients with sleep apnea or chronically high carboxyhemoglobulin, which may or may not be related to chronic dyspnea.) Low hemoglobin and hematocrit values are the diagnostic features of anemia. Leukocytosis may be seen in patients with chronic airway disease who have superimposed infection; it may also be seen in chronic congestive heart failure. Lymphocytosis is common in thyrotoxicosis, anemia, and connective tissue diseases. Abnormalities of the WBCs may be seen in certain types of anemia. Eosinophilia may occur in chronic asthma.
II. Urinalysis. Changes in urine sediment may be seen in the various connective tissue diseases, but these are nonspecific.
III. Blood chemistries. The serum bicarbonate level may be increased in severe chronic lung disease with alveolar hypoventilation. Dilutional hyponatremia may be seen in congestive heart failure. The serum calcium value may be elevated in sarcoidosis. Serum creatinine and BUN may be elevated in renal failure because of connective tissue diseases.
IV. Sputum examination. In chronic asthma, eosinophils are usually seen with Wright's stain. The periodic acid-Schiff stain is frequently positive in alveolar proteinosis. Sputum cytologic findings may be abnormal in alveolar cell carcinoma. In lipoid pneumonia, the Sudan III stain may be positive for fat-laden macrophages.
V. Electrocardiogram. In all forms of chronic pulmonary disease there may be evidence on electrocardiogram of right-axis deviation, right ventricular enlargement and strain, atrial dysrhythmias, and right atrial enlargement. Evidence of left ventricular disease may be seen in chronic left-sided heart failure, and atrial and ventricular ectopy are common. Sinus tachycardia is frequently present in thyroid toxicosis and anemia.
VI. Blood gases. In all pulmonary causes of chronic dyspnea, hypoxemia may be present. Hypoventilation (PCO_2 45 mm Hg) is seen more commonly in chronic bronchitis, thoracic cage deformities, and neuromuscular disease. Hyperventilation (low PCO_2) may be seen in interstitial lung disease and pulmonary hypertension. Hypoxemia, with or without CO_2 retention, may be seen in congestive heart failure. Arterial blood gases are normal in anemia, thyrotoxicosis, or upper airway disease, although O_2 content is low in anemia. There may be mild hypoxemia in obesity.
VII. Serum protein electrophoresis. Electrophoresis occasionally shows a decrease or absence of alpha-1-globulin, particularly in younger patients with emphysema. If the alpha-1-globulin level is low, specific assays for alpha-1 antitrypsin deficiency are indicated.

Further Studies

From the foregoing data it should be possible to determine whether dyspnea is of pulmonary or nonpulmonary origin. Patients with pulmonary dyspnea should have pulmonary function studies performed. In chronic obstructive airway disease, the ventilator functions show evidence of airway obstruction (e.g., diminished FEV_1 and MMEF), vital capacity may be normal or decreased, and there is usually an increase in the residual volume. In patients with a predominantly restrictive component (e.g., interstitial fibrosis, chest wall deformities, and pleural diseases), ventilatory function usually shows a reduction in vital capacity, total lung capacity, and diffusing capacity, but good flow rates are maintained. CT scanning of the lung may differentiate among various interstitial lung diseases and provide better "targets" for open lung biopsy. Lung biopsy may be indicated when the diagnosis of interstitial lung disease is not apparent from the clinical findings.

Wheezing

Paul M. Cox, Jr. and Marvin I. Schwarz

Wheezing is a common complaint in patients with pulmonary disease. It may be caused by any of the following:

I. Large airway obstruction
A. Laryngeal obstruction—tumor, vocal cord paralysis, inflammation, laryngospasm
B. Tracheal obstruction—stenosis, tumor
C. Foreign body aspiration
II. Endobronchial tumors and granulomas
III. Bronchial asthma
IV. Acute bronchitis
V. Chronic airway obstruction
VI. Acute left ventricular failure (cardiac asthma)
VII. Pulmonary embolism

Table 4-1 presents the differential diagnosis of wheezing.

Cough

Paul M. Cox, Jr. and Marvin I. Schwarz

All the causes of acute dyspnea, with the possible exception of pneumothorax, may also present with cough of acute onset or even with acute cough without dyspnea. The most frequent cause of acute cough without dyspnea in a previously healthy patient is acute bronchitis. The diagnosis of acute bronchitis is based on evidence of a preceding upper respiratory infection, followed by cough productive of mucoid or purulent sputum. Myalgias, headaches, malaise, fever, and an influenza syndrome may be associated. The physical examination usually reveals nothing abnormal except evidence of respiratory tract inflammation, including the presence of rhonchi on auscultation. The chest roentgenogram is normal. Laboratory abnormalities, if any, are nonspecific.

Chronic Cough

Etiology

Chronic cough is frequently found in the pulmonary conditions causing chronic dyspnea. However, patients with pure emphysema, thoracic wall deformities, and pleural fibrosis, as well as those with nonpulmonary causes of dyspnea, may not have associated cough. Additional causes of chronic cough are bronchogenic carcinoma, benign endobronchial tumors, and chronic granulomatous diseases, including tuberculosis, sarcoidosis, fungal diseases, and lung abscess. For discussion of bronchiectasis, an important cause of chronic cough, see the section on hemoptysis.

History

I. Bronchogenic carcinoma. Patients with bronchogenic carcinoma usually have a history of cigarette smoking of greater than 10 pack-years. In addition to cough,

Table 4-1. Differential diagnosis of wheezing

Disease	Clinical presentation	Laboratory findings	Chest roentgenogram	Associated clinical findings
Large airway obstruction: laryngeal stridor; tracheal stenosis; foreign body aspiration	Acute onset of dyspnea except in tracheal stenosis; previous history of intubation; atopic history in laryngeal stridor		A narrowed air tracheogram and the demonstration of air trapping on expiration films	Other allergic phenomena (e.g., urticaria). In laryngeal stridor, wheezing heard over the major airways, obstruction to air flow greater on inspiration
Endobronchial tumors or granulomas	Gradual onset of dyspnea	Positive sputum cytologic findings or acid-fast smears; hypergammaglobulinemia and hypercalcemia with sarcoidosis	A hilar mass with or without lobar collapse; typical tuberculous infiltrates in the upper zone; bilateral hilar adenopathy with or without pulmonary infiltrates	History of tobacco consumption; weight loss, fever, cough; wheezing is localized
Asthma	Subacute or acute onset of dyspnea	Sputum and systemic eosinophilia; arterial blood gases demonstrate hypoxia and hyperventilation; FEV1 reduced and responds to bronchodilators	May show hyperinflation or mucoid impaction	History of similar episodes and an atopic state
Acute bronchitis	Cough and purulent sputum, other symptoms of URI	Purulent sputum; elevated WBC with shift to the left	Usually normal unless pneumonia develops	
Chronic obstructive pulmonary disease	Chronic cough, dyspnea, and sputum production	Purulent sputum with elevated WBC and shift to the left. Arterial blood gases may demonstrate hypoxemia and hypoventilation, or both; elevated hematocrit; FEV1 diminished	May show evidence of emphysema and pulmonary hypertension	History of tobacco use; signs of cor pulmonale
Cardiac asthma	Acute onset of dyspnea, associated with paroxysmal nocturnal dyspnea and orthopnea	ECG may show evidence of acute myocardial infarction, ischemic changes, changes consistent with LVH, or P mitrale	Cardiac enlargement, diffuse alveolar filling; venous hypertension; Kerley's B lines; or left atrial enlargement	History of coronary, hypertensive, or rheumatic heart disease; physical exam may demonstrate a third heart sound gallop and systolic or diastolic murmurs
Pulmonary embolus	Acute onset of dyspnea, pleuritic chest pain, and cough	ECG may show evidence for acute right heart strain; arterial blood gases may demonstrate hypoxemia and hyperventilation; abnormal lung scan; positive angiogram	May be normal, or may demonstrate a pleural effusion, atelectatic lines, or an ill-defined pulmonary infiltrate	Evidence of lower extremity venous thrombosis

URI, upper respiratory infection; LVH, left ventricular hypertrophy

they may have hemoptysis and weight loss. Exposure to asbestos or radioactive materials, such as in uranium mining, increases the risk of developing bronchogenic carcinoma, particularly in smokers.

II. Bronchial adenoma. Systemic symptoms are usually absent. Patients may complain of wheezing or give a history of recurrent pneumonia. Hemoptysis may be present.

III. Chronic granulomatous disease. Persistent cough may be the only symptom, but increased sputum production, hemoptysis, weight loss, fever, and night sweats are commonly associated. Patients with endobronchial sarcoidosis may have the same symptoms as those with fungal or tuberculous granulomatous disease. They may also have systemic symptoms, such as arthralgias, arthritis, erythema nodosum, or skin rash. Erythema nodosum may also occur in histoplasmosis.

IV. Lung abscess. Recent dental procedures, episodes of unconsciousness, and history of recent pneumonia owing to staphylococci or Gram-negative bacilli, in particular, are common antecedents. Halitosis, foul-smelling sputum, and fever are frequent complaints. There is often a history of excessive alcohol intake.

Physical Examination

I. Bronchogenic carcinoma. There may be evidence of recent weight loss in bronchogenic carcinoma. Lymphadenopathy may be present in the supraclavicular and infraclavicular areas. Bony metastases may be noted in the chest wall. Auscultation of the chest may reveal evidence of endobronchial obstruction manifested by localized wheezing, atelectasis, or pneumonia. Clubbing may be present. Evidence of metastatic disease may be noted in other organs, including the skin, liver, and brain.

II. Bronchial adenoma. In bronchial adenoma, abnormal physical findings are unusual. Occasionally, there is evidence of unilateral or localized wheezing. Evidence of atelectasis is sometimes found on physical examination.

III. Granulomatous diseases. These diseases may be present without abnormal physical findings. Because the distribution of such disease is usually apical and posterior, rales may be heard in these areas. When large cavities are present, characteristic cavernous breath sounds may be present. Sarcoidosis patients may show evidence of uveitis, arthritis, skin rash, erythema nodosum, or hepatosplenomegaly.

IV. Lung abscess. Clubbing, halitosis, rales, and cavernous breath sounds may be present.

Roentgenographic Findings

1. Bronchogenic carcinoma. The chest roentgenograms of patients with bronchogenic carcinoma usually demonstrate a hilar mass or a single coin lesion. Mediastinal lymphadenopathy may be present. If the tumor partially or totally occludes a bronchus, evidence of volume loss in the form of elevation of the diaphragm or a shift of the lung fissures and hilar structures may appear. Another radiographic sign is pneumonia distal to the obstruction. Pleural effusion is often present, and lytic lesions in the ribs occasionally may be seen. If there is lymphangitic spread of the tumor, evidence of diffuse interstitial disease and Kerley's lines may be seen.

II. Bronchial adenoma. The most characteristic appearance of bronchial adenoma is that of a centrally placed, circumscribed mass with atelectasis distal to the lesion. A small number of cases may present as peripheral coin lesions.

III. Granulomatous diseases. Evidence of a primary complex (i.e., a calcified mediastinal or hilar node on the same side as the calcified parenchymal lesion) may be noted in tuberculosis. Posterior and apical infiltrative disease or cavity disease, or both, may be present. An apical pleural reaction and pleural effusion are commonly seen. In the more chronic cases, there may be evidence of upper lobe volume loss, such as fibrotic streaking and retracted hilar structures. The roentgenographic findings are variable in sarcoidosis. Bilateral and symmetric mediastinal and hilar lymphadenopathy is the most common radiographic presentation. This may be associated with alveolar or interstitial infiltrates, or both, early in the course of the disease. Pleural disease or cavities are rarely seen. In the more chronic states of the disease, there is usually a diffuse interstitial infiltrate that may be linear or nodular, or a combination of the two. With further progression of the disease, bilateral upper lobe retraction with fibrotic streaking and cystic transformation may be seen.

IV. Lung abscesses. These are seen radiographically as cavitary lesions, usually with air-fluid levels. An infiltrate may surround the cavity.

Laboratory Data

I. CBC. Anemia may be seen in bronchogenic carcinoma, tuberculosis, fungus diseases, sarcoidosis, or lung abscess. The anemia may be hemolytic or, more frequently, have the characteristics of anemia of chronic disease. The WBC count may be elevated in all of these disorders, particularly if there is an associated infectious process. Leukemoid reactions have been reported in tuberculosis.

II. Urinalysis. WBCs with blood cell casts, proteinuria, and hematuria may be seen singly or in any combination in patients with renal tuberculosis. In the rare patients who have bronchogenic carcinoma associated with inappropriate antidiuretic hormone (ADH) secretion, concentrated urine with high specific gravity and increased osmolality may be found.

III. Electrolyte and serum enzyme abnormalities

A. Hyponatremia may occur in bronchogenic carcinoma with inappropriate ADH secretion or, rarely, when adrenal insufficiency occurs as a result of adrenal metastasis. Hyponatremia is frequent in tuberculosis. Although it may be secondary to inappropriate ADH secretion or adrenal insufficiency owing to tuberculous involvement of the adrenal cortex, frequently no specific cause can be found. It usually disappears when treatment of the tuberculosis is instituted.

B. Hypercalcemia may be seen in bronchogenic carcinoma, sarcoidosis, and certain bronchial carcinoid tumors.

C. In bronchogenic carcinoma, sarcoidosis, and tuberculosis, abnormalities of liver function may occur as a result of liver involvement.

IV. Sputum examination. Sputum cytologic study may lead to diagnosis in carcinoma of the lung, but should rarely be performed if bronchoscopy is readily available. Acid-fast stains are frequently positive in active tuberculosis, but they may be negative even when the culture is positive. Fungal organisms may be seen with special staining techniques. The sputum should be cultured for *Mycobacterium tuberculosis* and fungi. Gram stains may reveal the likely etiologic organism in lung abscess, but aerobic bacterial cultures should be obtained. Anaerobic cultures may be misleading because of contamination by anaerobes normally in oral secretions.

V. Electrocardiogram. Electrocardiographic evidence of pericarditis may be seen in tuberculosis, sarcoidosis, and bronchogenic carcinoma with pericardial involvement. In sarcoidosis, the electrocardiogram may rarely resemble that of myocardial infarction. Arrhythmias and atrioventricular conduction disturbances are seen occasionally.

VI. Skin testing and serologic study. PPD-S (Tween stabilized, TU, or intermediate strength): Greater than 10-mm induration at 48 to 72 hours is strong evidence of infection with tuberculosis. However, a positive result does not necessarily indicate active tuberculosis or prove that tuberculosis is the cause of the patient's symptoms. False-negative findings may be caused by anergy, improper technique, and other factors that are poorly understood. A negative skin test finding does not rule out tuberculosis. First- and second-strength PPD are not useful in the diagnosis of tuberculosis and should not be employed. In high-risk patients with negative initial tests, a second PPD should be placed 7 to 14 days after the initial test to evaluate the booster effect.

VII. Other diagnostic procedures

A. Fiberoptic bronchoscopy is a safe and relatively comfortable procedure. It should be performed whenever the aforementioned tests do not lead to diagnosis and to determine the extent and resectability of tumors. A biopsy should be performed at the time. Bronchial brushings also may be obtained.

Transtracheal and transcarinal needle aspiration may also be helpful to stage or diagnose tumors. Postbronchoscopy sputa for cytologic study, acid-fast and fungus stains, and cultures are probably not indicated routinely, although occasionally they may be positive even when bronchoscopy is negative. Bronchoscopy and "protected brush" sampling may be necessary in lung abscess to restore drainage and obtain cultures.

B. Computerized tomography of the thorax is useful to detect or rule out mediastinal disease or to localize enlarged nodes to direct transtracheal needle aspiration or mediastinoscopy.

C. Mediastinoscopy is useful for determining the resectability of bronchogenic carcinoma and for the diagnosis of sarcoidosis.

D. In rare instances, the procedures listed above may not lead to a diagnosis. Diagnostic video-assisted or open thoracotomy may then be necessary.

E. Bronchography is no longer indicated in routine evaluation of the airways.

Hemoptysis

Paul M. Cox, Jr. and Marvin I. Schwarz

Definition

Hemoptysis is the expectoration of blood or bloody sputum.

Etiology

Some of the important causes of hemoptysis have been described in earlier sections. These include infectious pneumonias, pulmonary embolism, bronchogenic carcinoma, mitral stenosis, chronic obstructive pulmonary disease, and tuberculosis and other granulomatous diseases. Other causes of hemoptysis include bronchiectasis, pulmonary arteriovenous malformations, pulmonary sequestration, idiopathic hemosiderosis, Goodpasture's syndrome, coagulation disorders, and intracavitary fungus balls (aspergillosis). Bronchitis is the most common cause.

History

I. Bronchiectasis. Characteristically, there is a history of repeated episodes of pneumonia or bronchitis. Long-term production of foul-smelling sputum is a classic finding, but it is not always present. Sinusitis is common. There may be a history of pertussis, measles, or other causes of severe childhood pneumonia. Patients with cystic fibrosis may have a personal or family history of failure to thrive or meconium ileus. Patients with immune disorders may have had recurrent nonpulmonary infections.

II. Pulmonary sequestration. The history may be similar to that of bronchiectasis. In other instances, the patient may have been asymptomatic previously.

III. Idiopathic pulmonary hemosiderosis. This condition usually occurs in children and young adults. Cough and hemoptysis are the usual symptoms. Anemia is a common accompaniment and may cause the presenting symptoms.

IV. Goodpasture's syndrome. The symptoms are similar to those in idiopathic pulmonary hemosiderosis, although symptoms and signs of uremia also may be present. The symptoms of renal disease may antedate those of pulmonary disease, or vice versa.

V. Coagulation disorder. Patients with known coagulopathies or those undergoing anticoagulant therapy may have respiratory tract bleeding. Usually there is a history of bleeding from other sites (e.g., the skin, gastrointestinal tract, the nares).

VI. Intracavitary fungus balls. Aspergillomas are found only in patients with preexisting cavitary disease owing to tuberculosis or other causes. They are more likely to be seen in older, debilitated patients.

VII. Pulmonary arteriovenous malformations. A family history of pulmonary arteriovenous malformations can be elicited in 60% of cases. Dyspnea is a common complaint. In addition to hemoptysis, the patient may have experienced epistaxis, hematemesis, cerebral hemorrhage, melena, or unexplained anemia.

Physical Examination

I. Halitosis and clubbing are frequent in bronchiectasis. Examination of the chest may reveal signs of chronic airway obstruction, but the most consistent findings are coarse, "sticky" bibasilar rales. In localized bronchiectasis, the findings are confined to the area of involvement. Patients with Kartagener's syndrome have a triad of bronchiectasis, sinusitis, and situs inversus. Patients with cystic fibrosis may have evidence of malnutrition.

II. In pulmonary sequestration, there may be localized rales over the site of sequestration.

III. In idiopathic pulmonary hemosiderosis, diffuse or localized rales may be heard. Pallor secondary to anemia is common.

IV. Patients with Goodpasture's syndrome demonstrate physical findings similar to those of idiopathic pulmonary hemosiderosis; signs of uremia may be present.

V. Coagulation disorders frequently show evidence of bleeding from multiple sites. Ecchymoses or petechiae may be present. Examination of the chest may reveal diffuse or localized rales.

VI. Aspergilloma produces no characteristic physical findings, although findings of the preexisting condition (e.g., tuberculosis, lung abscess) may be present.

VII. The physical findings associated with pulmonary arteriovenous malformations include clubbing, cyanosis, and telangiectasis in the skin and mucous membranes. On examination of the chest, continuous murmurs may be heard over the malformations.

Roentgenographic Findings

I. In bronchiectasis, the chest roentgenogram may be normal, or evidence of basilar fibrosis, with or without cystic changes, may be noted. Localized changes are found in some cases. In more severe cases, the fibrotic and cystic changes may be diffuse. Cavity formation with air–fluid levels may be present. Situs inversus is evident in Kartagener's syndrome.

II. Pulmonary sequestration is shown radiographically as a circumscribed shadow, usually in the left lower lobe and continuous with the diaphragm. Air–fluid levels may be present if cavitation has occurred.

III. During the acute phase of idiopathic pulmonary hemosiderosis, evidence of diffuse or localized acinar-filling process may be seen. There may be resolution of these abnormalities or progression to an interstitial fibrotic pattern.

IV. The roentgenographic findings in Goodpasture's syndrome are similar to those of idiopathic pulmonary hemosiderosis. The "butterfly" pattern of uremic pulmonary edema may be seen if the renal disease is severe.

V. The roentgenogram in hemoptysis owing to coagulation disorders is similar to that of idiopathic pulmonary hemosiderosis and Goodpasture's syndrome.

VI. Aspergilloma typically presents a round mass within a cavity. When the patient is placed in the lateral decubitus position, movement of the mass may be noted.

VII. A pulmonary arteriovenous malformation appears radiographically as a sharply defined, round or oval, homogeneous mass 1 to 5 cm in diameter. It is usually in the lower lobes, and vascular structures may be continuous with the mass.

Laboratory Data

I. CBC. This is usually normal in hemoptysis. Iron deficiency anemia may be seen in idiopathic pulmonary hemosiderosis and Goodpasture's syndrome. Pulmonary arteriovenous malformations may have iron deficiency anemia secondary to recurrent bleeding, but more commonly, erythrocytosis secondary to chronic hypoxemia is seen. Massive hemoptysis rarely produces anemia, and other etiologies for the anemia should be considered.

II. Urinalysis. Urinalysis is helpful in the diagnosis of Goodpasture's syndrome and may demonstrate evidence of nephritis.

III. Blood chemistries. Laboratory findings of uremia may be present in Goodpasture's syndrome.

IV. Examination of the sputum. Patients with Goodpasture's syndrome or idiopathic pulmonary hemosiderosis show hemosiderin-laden macrophages in their sputa.

V. Electrocardiogram. If pulmonary hypertension is present, there may be evidence of right axis deviation, right ventricular hypertrophy, and right atrial enlargement.
VI. Other diagnostic procedures.
   A. Pulmonary function tests are of little value in differentiating between the various disorders. However, in bronchiectasis there may be evidence of obstruction to air flow. A patient with idiopathic pulmonary hemosiderosis or Goodpasture's syndrome may have a restrictive defect and reduction of the diffusing capacity.
   B. Computerized tomography has replaced bronchography to diagnose bronchiectasis.
   C. Arteriography. In a patient with suspected pulmonary sequestration, aortography should be done.
   D. Biopsy. In patients with suspected Goodpasture's syndrome, a lung or renal biopsy should be performed, with immunofluorescent staining of the tissue. Patients with suspected idiopathic pulmonary hemosiderosis should have a lung biopsy.
   E. Serologic tests. Precipitating antibodies may be present in aspergillosis.
   F. Coagulation screening should be performed when coagulopathies are suspected.
   G. Miscellaneous studies. Sweat chlorides are elevated in cystic fibrosis, iontophoresis is more specific. Increased fecal excretion of fat may be noted in cases of untreated cystic fibrosis and in some immune disorders. Serum globulin values are usually abnormal in immunologic diseases. Isolated deficiency of IgA may be associated with bronchiectasis or recurrent bronchitis.
   H. Bronchoscopy should be performed when it is necessary to rule out intraluminal disease.

Cyanosis

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Definition

Cyanosis is a bluish color of the skin and mucous membranes, usually owing to the presence of at least 5 g of reduced hemoglobin in the arterial blood. Although cyanosis frequently indicates arterial oxygen unsaturation, it reflects the degree of hypoxemia imperfectly. Not all cyanosis is related to the presence of increased amounts of reduced hemoglobin in the blood. Severe cyanosis, for example, may be owing to the presence of abnormal pigments (methemoglobin or sulfhemoglobin) within the red blood cells.

Etiology

Cyanosis may be classified as central or peripheral. Central cyanosis usually results from arterial hypoxemia caused by right-to-left cardiac shunt, pulmonary arteriovenous fistula, or acute or chronic pulmonary disease. It may occur in polycythemia vera in the absence of arterial oxygen unsaturation, because of the presence of an increased amount of reduced hemoglobin in the blood. In central cyanosis, both the skin and mucous membranes are blue. Polycythemia and digital clubbing are commonly present when cyanosis is severe and chronic. Peripheral cyanosis is caused by stagnant circulation and vasoconstriction through the peripheral vascular bed. Arterial oxygen saturation is normal unless cardiopulmonary disease is also present. The cyanosis primarily affects the exposed portions of the body, such as the hands, ears, nose, cheeks, and feet. Peripheral cyanosis may be caused by exposure to cold, nervous tension, reduced cardiac output, or vascular obstruction. The most common cause of central cyanosis in the adult is pulmonary disease, especially chronic obstructive airway disease. Intracardiac right-to-left shunts are less common causes. Peripheral cyanosis is most commonly owing to exposure to cold or emotional tension.

Central Cyanosis
I. Cyanotic congenital heart disease (e.g., tetralogy of Fallot, Eisenmenger's syndrome, trilogy of Fallot, tricuspid atresia, Ebstein's anomaly, transposition of the great vessels, pulmonary arteriovenous fistula)
II. Pulmonary disease
   A. Acute (e.g., pneumonia, pulmonary embolism, atelectasis)
   B. Chronic
      1. Obstructive airway disease
      2. Restrictive lung diseases
      3. Hemoglobin abnormalities
         a. Congenital
         b. Acquired

Peripheral Cyanosis
I. Reduced cardiac output (e.g., congestive heart failure, cardiogenic shock, mitral stenosis)
II. Exposure to cold, including Raynaud's phenomenon
III. Arterial obstruction
IV. Venous obstruction

History

Central Cyanosis
I. Cyanotic congenital heart disease. There may be a history of cyanosis, dyspnea, heart murmur, syncope, squatting, congestive heart failure, or other cardiac symptoms dating from birth or childhood.
II. Pulmonary disease. The most common symptoms are dyspnea, cough, sputum production, wheezing, hemoptysis, and recurrent pulmonary infections.
III. Hemoglobin abnormalities
   A. Congenital (deficiency of NADH diaphorase, hemoglobin M disease): A history of cyanosis from birth may be elicited in these types of methemoglobinemia.
   B. Acquired (methemoglobinemia, sulfhemoglobinemia): A history of exposure to chemicals or drugs may be obtained. The chief offenders are nitrates, nitrites, chlorates, quinones, certain aniline dyes, acetanilid, sulfonamides, and phenacetin.

Peripheral Cyanosis
I. Decreased cardiac output. A history of pulmonary embolus, mitral stenosis, myocardial infarction, or other heart disease usually can be elicited. In cases owing to shock, evidence of hemorrhage, sepsis, or other underlying disease may be obtained.
II. Exposure to cold (including Raynaud's phenomenon). A history of exposure to cold is usually obvious. In Raynaud's phenomenon, paroxysmal pain, pallor, and cyanosis, followed by redness, usually involving the fingers, occur on exposure to cold or emotional stress.
III. Arterial obstruction. A history of antecedent intermittent claudication is often obtainable from patients with arterial occlusion. Diabetes predisposes individuals to arterial insufficiency. When arterial obstruction is embolic, the source is often a mural thrombus from mitral stenosis or myocardial infarction, or, in infective endocarditis, a bacterial vegetation.
IV. Venous obstruction. There may be a long history of varicose veins, thrombophlebitis, edema, leg trauma, or immobilization.

Physical Examination

Central Cyanosis
There is bluish discoloration of the skin and mucous membranes.

I. Right-to-left shunt. Cardiac murmur(s) and evidence of right-sided cardiac enlargement are present.
II. Pulmonary disease. See Dyspnea, earlier in this chapter.

III. Clubbing is common in severe central cyanosis but is absent in cyanosis owing to hemoglobin abnormalities.

Peripheral Cyanosis
There is discoloration of only the distal extremities or nail beds.

I. Decreased cardiac output. Hypotension, tachycardia, cold moist extremities, decreased urinary output, and mental confusion are common. Signs of shock may be noted. Evidence of underlying heart disease may be present.
II. Raynaud's phenomenon. Evidence of underlying disease, such as scleroderma, systemic lupus erythematosus, and the cryoglobulinemias, may be noted unless the condition is idiopathic (Raynaud's disease).
III. Arterial obstruction. Signs of arterial occlusion are present (absent pulses, cool skin, skin mottling, and ulcers).
IV. Venous obstruction. Signs of venous disease, such as varicose veins, edema, ulceration, and increased pigmentation of the skin, may be noted.

Chest Roentgenographic Findings
Characteristic roentgenographic findings may be noted in certain types of heart disease and in pulmonary disease. Otherwise, chest films are of little or no diagnostic help in the evaluation of cyanosis.

Laboratory Data
I. CBC. Erythrocytosis may be seen in right-to-left shunts and in the chronic pulmonary disease and in any patient with chronic hypoxemia.
II. Urinalysis. This may be abnormal in Raynaud's phenomenon, which is associated with connective tissue disease and renal involvement. The abnormal findings include proteinuria, hematuria, and cylindruria.
III. Serum electrolytes and biochemical screening. The serum bicarbonate level may be elevated in a patient with chronic alveolar hypoventilation. The BUN may be elevated in circulatory collapse and decreased cardiac output and in patients with renal hypoperfusion. Acute hepatic injury may be reflected in abnormal liver function tests in patients with circulatory collapse. Liver function tests may also be abnormal in patients with cor pulmonale and chronic passive congestion of the liver. Serum levels of LDH, SGOT, and CPK may be elevated in patients with arterial and venous obstruction, because of skeletal muscle damage. In these patients, the serum bilirubin, serum proteins, and prothrombin time usually are normal.
IV. Electrocardiogram. In patients with right-to-left shunt, the electrocardiogram may show findings related to the underlying disease. In patients with pulmonary disease, there may be evidence suggestive of chronic obstructive pulmonary disease with or without cor pulmonale. The electrocardiogram is usually normal in patients with Raynaud's phenomenon, but in those with connective tissue disease, evidence of pericardial or myocardial involvement may be noted. In patients with circulatory collapse, a pattern simulating myocardial infarction is sometimes seen.
V. Arterial blood gases. Hypoxemia is seen in all conditions causing central cyanosis except those with abnormal hemoglobins. Usually the arterial oxygen tension is normal in patients with peripheral cyanosis. Determination of PO_2 is thus useful in differentiating between central and peripheral causes of cyanosis. The arterial PCO_2 level is elevated in patients who are cyanotic from chronic or acute alveolar hypoventilation. Arterial saturation is low in patients with hypoxemia. Abnormal hemoglobins variably affect the apparent arterial saturation, depending on the method used. Pulse oximetry is not helpful in patients with cyanosis of any etiology.
VI. Ventilatory function tests. Ventilatory function tests demonstrate a characteristic obstructive pattern in patients with chronic obstructive pulmonary disease. A restricted pattern is observed in patients with interstitial fibrosing diseases of the lung. A restrictive or obstructive pattern, or both, may be seen in patients with left ventricular failure. D_LCO is low in interstitial disease and emphysema and high in left ventricular failure.
VII. Other procedures
A. Arterial blood gases drawn while the patient is breathing 100% oxygen often show large alveolar–arterial gradients (100 mm Hg) in patients with right-to-left shunts and pulmonary arteriovenous fistulas. Smaller alveolar–arterial gradients are seen in advanced obstructive or restrictive pulmonary disease. These are easily differentiated from shunts by the association of markedly abnormal ventilatory-function test results.
B. Cardiac catheterization and pulmonary angiography may be indicated for the diagnosis of congenital cyanotic heart disease and pulmonary arteriovenous fistulas.
C. Mass spectroscopy of a hemoglobin sample is employed to confirm the diagnosis of methemoglobinemia or sulfhemoglobinemia. Determination of the P_{50} by simultaneous measurements of PO_2 and SO_2 confirms the presence of abnormal hemoglobins.

Consolidation Collapse of the Lung

Stanley B. Reich

Definition
Occasionally, routine chest roentgenograms show consolidation collapse, or atelectasis, of the lung. This loss of volume of a segment, a lobe, or the whole lung is shown primarily by increased density of the area because of replacement of the air by fluid and displacement of the fissures because of the volume loss. Secondary changes include displacement of the hilum, elevation of the diaphragm, shift of the mediastinum, approximation of the ribs, and overinflation of the remainder of the lung, shown by alteration of vascular shadows. This condition is also called atelectasis, but consolidation collapse is a more precise and descriptive term.

Etiology
I. The most serious cause is an endobronchial lesion, such as bronchogenic carcinoma, which causes absorption of air and collection of secretions. The symptoms and signs of infection or irritation may or may not be present.
II. Another cause is passive collapse secondary to adjacent disease, such as pleural effusion, pneumothorax, or thoracoplasty. These conditions usually can be identified easily on the roentgenogram.
III. Adhesive collapse occurs in conditions in which surfactant is diminished, as in the acute respiratory distress syndrome of infants or adults, or following cardiac bypass surgery. These entities usually can be recognized clinically, but radiographic studies are useful in following the progress of the disease.
IV. Cicatrization as a result of prior infection and fibrosis may also cause this radiographic appearance. Patients may be asymptomatic at the time of examination but may recall the previous infection responsible for the condition.
V. Occasionally, an acute or subacute inflammatory lesion or a pulmonary embolus may cause consolidation and loss of volume of a lung. Improvement and ultimate clearing of the involved lung may take from days to months.
VI. Other causes include aspirated foreign bodies, intubation of the right mainstem bronchus, and atelectasis complicating surgery.

Diagnostic Approach
I. As a first step, all prior films should be obtained if they are available. They may help in determining the time of onset of the disease process.
II. If the changes were present previously and are slowly progressive, a neoplasm must be excluded by bronchoscopy, bronchial brushing, cytologic study, and transbronchial biopsy.
III. If the lesion was present previously but has remained unchanged for a period of 6 months to 1 year, bronchoscopy, transbronchial biopsy with brushing for

cytologic and bacteriologic study, and possible CT scans are indicated to exclude an indolent neoplasm or a chronic inflammatory lesion with fibrotic changes.

IV. If the lesion was present previously but had remained unchanged for a year or two, further observation with film taken at 2- to 3-month intervals is probably warranted. During this time, noninterventional investigation can be carried out (e.g., sputum cytologic and bacteriologic studies).

V. If the lesion was not present previously, it may be observed for a 2- to 3-week period while the usual clinical noninterventional investigation is pursued. If the lesion clears completely in that period, no further studies may be necessary except for follow-up films in approximately 3 months. If a residual infiltrate remains or if symptoms persist, it becomes necessary to perform bronchoscopy, bronchial brushing, cytologic study, and clearing of an associated inflammatory reaction.

VI. If pulmonary embolism is suspected, compression ultrasound of the legs should be carried out to look for venous thrombosis. If positive, anticoagulation can be performed; if negative or inconclusive, a CT angiogram should be completed to look for clots in the pulmonary arteries.

Acute Pulmonary Radiographic Abnormalities

Stanley B. Reich

Acute pulmonary lesions often pose problems in differential diagnosis. Pneumonia, pulmonary edema, pulmonary infarction, pulmonary hemorrhage, atelectasis, and pulmonary embolism are the entities usually involved.

Acute Parenchymal Infiltrates

Excluding neoplasm, parenchymal infiltrates are of three basic types: alveolar, interstitial, and mixed. This differentiation is frequently of considerable help in determining the cause of an infiltrate. On chest films, interstitial infiltrates are linear-nodular, or nodular, with the nodules generally less than 5 mm in diameter. Alveolar infiltrates tend to be fluffy in appearance, with poorly defined borders; they commonly involve segments of lobes or entire lobes, and they frequently demonstrate air bronchograms and loss of blood vessel margins.

Simply because infiltrates are seen on chest roentgenograms does not necessarily mean they are acute. For example, alveolar infiltrates, usually seen in acute processes, also can be seen in chronic processes, such as alveolar cell neoplasm, sarcoidosis, and desquamative interstitial pneumonia. Similarly, interstitial infiltrates are often chronic and may be caused by disparate entities, such as usual interstitial pneumonia, connective tissue disease, granulomatous disease, eosinophilic granuloma, and fibrosis from chronic bronchitis and previous pneumonia. In all the preceding instances, previous chest films for comparison and serial films for follow-up are of enormous help in arriving at an accurate diagnosis.

Pneumonia

Although the radiographic patterns are quite variable and nonspecific, the following points may prove helpful in the diagnosis of pneumonia. Pneumonia owing to aspiration may involve any or all segments of both lungs but is more generally seen in the most dependent portions of the lung. Thus, with the patient lying supine, the most dependent parts of the lung are the posterior segments of the upper and lower lobes. Bacterial pneumonia is likely to present an alveolar pattern and involve segments of the lungs asymmetrically. Viral pneumonia tends to be interstitial in pattern and more symmetric and diffuse in distribution. It should be emphasized that these are generalities and that overlapping of patterns and exception may occur.

Pulmonary Edema

Pulmonary edema is most commonly caused by left-sided heart failure, but it may also be the result of other conditions, such as iatrogenic fluid overloading, allergic reaction to medications (particularly blood transfusions), or the acute adult respiratory distress syndrome (ARDS).

The lung changes in left-sided heart failure usually include the following: (a) pulmonary congestion, manifested by distended upper lobe veins; (b) interstitial edema, demonstrated primarily as narrow, linear strands perpendicular to the nearest pleural surface in the lower lobes; lamellar markings in the upper lobes; a hilar or peripheral haze or both; and at times, thickened interlobar fissures; and (c) alveolar edema, appearing typically as a fluffy infiltrate that tends to involve both lungs symmetrically but is nonetheless quite variable in appearance. Pleural effusions are usually present.

Atelectasis

Atelectasis, or consolidation collapse of the lung, is discussed separately in the next section. It is important to realize, however, that atelectasis is the most common postoperative respiratory complication. Plate, disc, or focal atelectasis is that of a rather thin, streaky density, usually located toward the lung bases. These densities are approximately perpendicular to the long axis of the body, but considerable variation is seen. Parenchymal scars from previous inflammatory disease or infarcts are the major differential possibilities. Large areas of atelectasis involving segments, lobes, or entire lungs are seen less frequently, but it is important to recognize them because they may represent serious disease. The major condition to be differentiated from lobar collapse, particularly in the lower lobes, is an encapsulated pleural effusion. The differentiation may be difficult or impossible, but two points may be helpful: (a) Signs of lobar collapse are usually not associated with encapsulated effusions; and (b) decubitus films may occasionally demonstrate fluid shifts with a change in body position. CT differentiates combinations of collapse and fluids, whether free flowing or loculated. Ultrasound helps to localize loculated pleural effusions for diagnostic taps.

Pulmonary Embolism with Infarction

Pulmonary embolism that goes on to infarction may show an area of alveolar infiltrate near a pleural surface. Sometimes an infarct may be seen as a homogeneous density with its base adjacent to a pleural surface and its convexity directed toward the hilum. A resolving infarct may appear as a rather broad, streaky density, much like an area of plate atelectasis. The roentgenographic findings in infarction and infection may be identical, and the differentiation between the two entitles cannot be made on the basis of chest films alone.

Pulmonary Embolism without Infarction

Pulmonary embolism without infarction frequently shows little or no abnormality in chest roentgenograms. Plain films may show pleural effusion, decreased vascularity of a lobe or a segment of a lobe, serial changes in the main pulmonary arteries owing to alterations of blood flow, or a parenchymal infiltrate. None of these findings is specific for embolism.

Pulmonary angiography, although an accurate method for the diagnosis of pulmonary embolism, is not completely free of hazard and is difficult to perform in an emergency. Its major drawback diagnostically is its frequent failure to demonstrate small peripheral emboli satisfactorily. Nevertheless, it remains the most sensitive test.

Ultrasound and Doppler examination of the legs may be used as a screening test for thrombosis. Noncompressibility of the veins and abnormal flow are signs of thrombus. If found, they indicate anticoagulation, and further workup for pulmonary embolus is not necessary.

Lung scans are often of value in the diagnosis of pulmonary embolism. The commonly performed perfusion scan consists of the intravenous injection of a myriad of tiny particles labeled with a radioisotope to permit detection of their distribution. The particles act like microemboli that ultimately lodge in the capillaries and precapillary arterioles. Although the procedure is safe and there are no contraindications to its use, abnormal perfusion scans are not specific for embolism. Such conditions as pneumonia, chronic bronchitis, emphysematous bullae, asthma, neoplasm, pleural effusion, and congestive heart failure may also produce abnormal scans. When interpreting lung scans, it is imperative to have a current chest film available for comparison. The perfusion scan is most useful when the chest film is normal or, if abnormal, when no lesion is demonstrable at the site of the abnormal scan.

Table 4-2. Perfusion and ventilation scans in the differential diagnosis of pulmonary lesions

Disease	Perfusion area	Ventilation scan
Embolism without infarction	No perfusion	Normal ventilation
Pneumonia	No perfusion	No ventilation
Embolism with infarction (infiltrate in lungs)	No perfusion	Decreased to no ventilation
Emphysematous bullae	No perfusion	Delayed ventilation; delayed washout
Chronic bronchitis	Decreased perfusion	Normal to delayed ventilation; delayed washout

Ventilation lung scans are performed simultaneously. In this procedure, the patient inhales a radioactively labeled gas, usually xenon, and its distribution in the lungs (ventilation pattern) is recorded. Rapid sequence images are then made serially during quiet respiration to reveal the pattern and rapidity of washout of the gas. Normally, most of the xenon is gone from the lungs in about 1 minute. Chronic obstructive pulmonary disease characteristically shows a slight delay in ventilation but a marked delay in the washout from involved areas. As with perfusion scans, ventilation scans may be abnormal in the presence of a parenchymal infiltrate.

An abnormal perfusion scan with a normal ventilation scan indicates pulmonary embolism. The number and size of defects can be quantified into low, intermediate, or high probability of embolus. In pulmonary embolus with infarction, both perfusion and ventilation scans are abnormal. Table 4-2 lists the results of perfusion and ventilation scans in pulmonary lesions.

If the ultrasound of the legs and the lung scan are indeterminate, a CT angiogram performed with intravenous injection of contrast medium usually shows significant emboli. Delayed CT examination of the legs and abdomen with the same contrast shows thrombi in veins that are not apparent on ultrasound. This should also be done in a patient whose chest radiograph shows widespread or multiple abnormalities, and some institutions are doing the CT angiogram without a nuclear lung scan.

Recently, a nuclear scanning agent has become available for testing that adheres to activated platelets. This would identify new clots and differentiate new from old clots. This may change the sequence of workups in the future.

The Solitary Pulmonary Nodule

James H. Ellis, Jr.

Definition

The solitary pulmonary nodule is usually defined in radiographic terms as a lesion that is single, round, or ovoid, and less than 6 cm in diameter. It has distinct margins (i.e., it is surrounded by aerated lung parenchyma) and does not abut the chest wall, diaphragm, or mediastinum. It may or may not contain calcium. Although it is most often asymptomatic, cough, hemoptysis, or both may occur. Painful clubbing and endocrinopathy are extremely rare manifestations of solitary pulmonary nodules that subsequently prove to be bronchial carcinomas.

Etiology

The most common causes of solitary pulmonary nodules are healed granulomas, primary pulmonary malignancies, pulmonary metastases, arteriovenous malformations, and pulmonary hamartomas.

The true incidence of such nodules is difficult to establish and varies greatly with such factors as the availability of routine or screening chest radiographs, the age of the population examined, and the incidence of endemic fungal infections (especially histoplasmosis and coccidioidomycosis). The same factors also influence the percentage of bronchial carcinomas in most reported series. For example, one mass x-ray screening program in 1949, involving 673,218 individuals in an area in which histoplasmosis was endemic, revealed only a 3% incidence of cancer in patients with solitary pulmonary nodules. (This was a period when the true frequency of bronchial carcinomas was lower than it is today.) On the other hand, the incidence of bronchial carcinoma was 63% in a series of highly selected "older" patients who had undergone thoracotomy for solitary nodules. In most series of patients with solitary nodules who have undergone thoracotomy, the reported incidence of bronchial carcinoma is about 36%.

Most lung cancers are initially detected on chest radiographs, but many benign lesions have radiologic characteristics similar to malignant lesions. Thus, additional studies are required for further evaluation. CT is most frequently used to provide additional anatomic and morphologic information about lesions, but it is limited in distinguishing between benign and malignant abnormalities. Because of the indeterminate results obtained from anatomic images, biopsy procedures, including thoracoscopy and thoracotomy, may be used even though one-half of the lesions removed are benign and do not need to be removed. High-resolution CT can help differentiate benign solitary pulmonary lesions from malignant solitary pulmonary lesions. Circumscribed pleural thickening, the density of the lesion, and the length of spicules can help differentiate benign from malignant lesions. CT scanning confirms that the lesion is spherical and intrapulmonary and helps assess the diameter, calcification pattern, presence of otherwise undetectable intranodular calcium, and the type of nodule margin. In some cases of solitary nodular hamartoma, the CT pattern is diagnostic, and CT with contrast may demonstrate that the lesion is an arteriovenous fistula. CT can visualize additional nodules in some instances, suggesting that the underlying problem is a metastatic tumor. It also detects the presence, severity, and distribution of mediastinal and hilar adenopathy, which is helpful in staging the tumor. However, metastases strongly resemble benign lesions in terms of size and edge type. MRI currently offers no advantages over CT in staging of the mediastinum.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) measures focal metabolic activity and can make a qualitative statement (benign or malignant) about a tumor. FDG pet imaging may provide physiologic and metabolic information that characterizes lesions that are indeterminate by CT, may accurately stage the distribution of lung cancer, and provide prognostic information. FDG pet imaging takes advantage of the increased accumulation of FDG in transformed cells and is sensitive (approximately 95%) to the detection of cancer in patients who have indeterminate lesions on CT. The specificity (approximately 85%) of PET imaging is slightly less than its sensitivity because some inflammatory processes, such as active granulomatous infections, avidly accumulate FDG. FDG PET cannot generally be considered as a replacement for diagnostic thoracoscopy of thoracotomy at the present time. However, by combining FDG PET with radiological follow-up, clinical applications may evolve in patients at low risk for a malignant tumor or at a high risk for surgical complications. It is noteworthy that bronchioloalveolar carcinoma may show false-negative results for malignancy on FDG pet scanning.

Diagnostic Approach

I. The primary problem confronting the physician when a solitary nodule is discovered is to determine whether nonsurgical measures or thoracotomy should be employed to establish the diagnosis. The decision, of course, depends on whether the lesion is benign or malignant. Benign nodules rarely require surgical removal. On the other hand, if the nodule is a bronchial carcinoma or adenoma it is potentially "curable" surgically, provided no metastases have occurred. Solitary pulmonary metastases from a primary extrapulmonary malignancy should seldom be removed and then only when the original tumor and other metastases have been controlled.

Four factors generally determine the diagnostic approach: the age of the patient, the age and rate of growth of the lesion, the presence or absence of calcification within the nodule, and the patient's smoking history.

A. Statistical studies indicate that below the age of 30, solitary nodules are infrequently malignant. Thereafter, the incidence of malignancy increases with advancing age.

II. A second important consideration is the age and rapidity of growth of the lesion. If previous chest films can be obtained, the growth rate or stability of the patient's nodule often can be determined. An exhaustive search should be made for previous chest radiographs. Comparison of current and previous films may even obviate the need for invasive procedures and hospitalization. Earlier films are helpful because of the well-known and highly predictable growth rate of primary bronchial carcinomas. The "doubling time" of the nodule refers to the doubling in volume of the nodule. From the volume of a sphere ($V = 4\pi r^3$), it can be seen that a tumor doubles in volume when its diameter or radius increases by a factor of 1.26 (the cube root of 2). Thus, when a 10-mm nodule has increased in size to 12.6 cm (10 mm 1.26), its volume has doubled. The mean doubling time of untreated primary bronchial carcinoma in a series of 41 patients was about 41.1 months for undifferentiated neoplasms, 4.2 months for squamous cell carcinomas, and 7.3 months for adenocarcinomas. The range of doubling times for primary bronchial carcinomas was 1 to 15 months. Single pulmonary nodules that double in size in less than 1 month are almost always either benign inflammatory lesions or, less often, solitary metastases of rapidly growing tumors such as chorionic carcinomas, testicular tumors, and osteogenic sarcomas.

A. The presence of calcification within the lesion makes it extremely unlikely that the lesion is a primary bronchial cancer. A ring-shaped or target pattern of calcification is usually indicative of a histoplasmoma. A "popcorn" pattern is highly characteristic of a hamartoma. Both patterns are reliable signs of a benign lesion. Nodules with small "flecks" of calcium are most likely to be benign, but if the patient has other high risk factors, such as age over 35 years and a heavy smoking history, such nodules should be observed by repeated chest films at 1- to 3-month intervals.

B. Cigarette smoking is also an important consideration. The overwhelming majority of bronchial carcinomas occur in cigarette smokers. However, bronchial adenocarcinomas occasionally occur in nonsmokers, particularly in women. Alveolar cell carcinoma also does not bear a particularly specific relationship to smoking.

III. The workup of the patient can be performed on either an outpatient or inpatient basis. A complete history and physical examination plus routine laboratory tests, such as CBC, urinalysis, and biochemical screening, may suggest additional studies. A tuberculin stain test probably should be performed. Although a positive skin test confirms previous infection with the organism, it does not necessarily establish the cause of the nodule. Sputum specimens should be obtained for cytologic smears and cultures, for conventional pathogens as well as for acid-fast bacilli and fungi.

IV. Bronchial carcinomas unfortunately metastasize early and extensively by hematogenous, lymphangitic, and direct extension. The latter mechanism is essentially ruled out by the definition of solitary nodule (i.e., surrounded by aerated lung parenchyma). Lymphatic extension outside of the thorax most frequently goes to supraclavicular and cervical lymph nodes. Occasionally, infraclavicular and axillary nodes are involved. Careful palpation of these areas is essential. Biopsy of any hard or enlarged nodes usually is indicated and, if positive, will abort the need for more invasive and risky tests. Hematogenous spread of bronchial carcinoma has a high incidence and a preference for organs with a rich blood supply, such as the brain, other areas of the lung, the liver, adrenals, bone, and even the skin (e.g., subcutaneous nodules). Except for pain from far advanced metastasis, bony involvement is often silent. Serum calcium, phosphorus, and alkaline phosphatase levels are not very sensitive screening procedures for bony involvement. Bone scans are much more sensitive indicators of bony metastasis and should be obtained before thoracotomy. Since bone scans sometimes give false-positive results, an otherwise indicated thoracotomy should not be ruled out without careful consideration.

Between 80% and 88% of patients with a solitary metastasis from an extrathoracic primary carcinoma give a history of previous diagnosis of the neoplasm. Most of the remainder have symptoms and signs or abnormal screening test results that suggest an extrapulmonary primary malignancy.

If there is no evidence of extrathoracic cancer, then preoperative evaluation to determine if the patient can reasonably tolerate thoracotomy and lobectomy is indicated. This simply means careful attention to the cardiopulmonary history, particularly the patient's exercise tolerance. Current spirometry, arterial blood gas analysis, and an electrocardiogram are indicated. Ventilation-perfusion scanning, formal treadmill exercise, and cardiac catheterization are usually reserved for patients with unusual situations or borderline cardiopulmonary reserve.

V. Patients with a nodule of less than 1.5 cm in diameter seldom have mediastinal node involvement. Unless the hila are obviously enlarged on chest x-ray, mediastinoscopy does not seem necessary or indicated. On the other hand, the larger the nodule, the more likely it is that mediastinal node involvement will occur. Mediastinoscopy should be performed routinely, if possible, to avoid thoracotomy in patients who are beyond the stage of surgical care. Most experts agree that contralateral, "high" ipsilateral, or subcarinal nodal involvement is a contraindication to thoracotomy. Positive nodes limited to "low" ipsilateral or intralobar positions, although certainly a poor prognostic sign, may not be an absolute contraindication to surgery, especially if combined with irradiation.

VI. The most valuable diagnostic procedure is fiberoptic bronchoscopy performed under fluoroscopic control, provided the lesion is accessible to the bronchoscope. Bronchial brushing should be done, specimens collected for cytologic study and cultures, and a transbronchial biopsy obtained.

Fiberoptic bronchoscopy with brush and transbronchial biopsy has a diagnostic accuracy of approximately 80%, with very acceptable morbidity and probably less than 0.1% mortality. Fluoroscopic-guided, percutaneous needle-aspiration biopsy approaches 80% accuracy for diagnosing malignant nodules, with a risk that is only slightly increased over that of bronchoscopic biopsy. The "borderline" patient and the conservative surgeon may be willing to accept the high risks of lobectomy even when cancer is present. Also, even when thoracotomy is not a consideration, a positive diagnosis helps in choosing therapy and increasing accuracy of prognosis.

VII. Transthoracic needle aspiration techniques can improve diagnostic accuracy. The technique can be fluoroscopically or CT guided, and using coaxial needles safely allows multiple passes with the inner biopsy needle.

VIII. If all studies including cultures are negative, radiologic studies should be performed 1 month later to determine the progress of the lesion. If after 1 month of study the cause of the nodule is undetermined, and the lesion has either remained unchanged in size or grown larger, surgical resection is indicated. If the lesion becomes smaller during the 1-month observation period, it is likely that the nodule represents an atypical inflammatory or embolic lesion rather than a neoplasm. Under these circumstances, a more conservative approach is probably warranted. It is then appropriate to continue chest films once a month for an additional 3-month period, and, when the lesion stabilizes, at intervals of 6 months or longer.

If investigation, including biopsy, proves the lesion to be benign, surgical removal is rarely necessary. However, if the etiology cannot be determined or malignancy is established, the lesion should be resected unless there are contraindications to its removal.

IX. Major errors in the management of a solitary pulmonary nodule are failure to (a) follow a logical workup owing to predetermined bias, (b) obtain old films, (c) provide a basic workup for metastatic disease, (d) observe the patient and nodule for 30 days when the lesion is new, (e) make any decision, and (f) recommend thoracotomy with conviction when indicated.

Mediastinal Masses

Matthew J. Fleishman

The mediastinum is the extrapleural space of the thorax. It is bounded by the lungs laterally, the chest wall anteriorly, the paraspinous gutters posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly. Division of the mediastinum into discrete compartments is arbitrary, but aids in the development of differential diagnoses for lesions that occur within this space. A useful scheme divides the mediastinum into three compartments, based on anatomic landmarks found on the standard lateral chest radiograph.

The anterior mediastinum is bounded anteriorly by the sternum and defined posteriorly by a line drawn vertically from the thoracic inlet to the diaphragm along the anterior margins of the brachiocephalic veins and superior vena cava, ascending thoracic aorta and pericardium. The thymus, internal mammary vessels, and fat are contained within the anterior mediastinum.

The middle mediastinum contains the heart and pericardium, ascending aorta, central pulmonary arteries and veins, tracheobronchial tree and lymph nodes.

The posterior mediastinum is bounded anteriorly by the posterior margin of the pericardium and extends posteriorly to the paraspinous gutters. The posterior mediastinum contains the descending thoracic aorta, esophagus, azygos and hemiazygos veins, fat, and autonomic and intercostal nerves.

Mediastinal Pathology

The compartmental boundaries of the mediastinum do not prevent contiguous spread of disease, however, specific masses do have a predilection for one or more of the three mediastinal compartments. Table 4-3 lists the most common mass lesions for each region of the mediastinum. Approximately 55% of mediastinal masses arise from the anterior mediastinum, 30% from the middle mediastinum, and 15% from the posterior mediastinum. Half of all mediastinal tumors are malignant.

The most common masses of the anterior mediastinum are benign thyroid goiters, followed by lymphomas, thymomas, and teratomas. The most common middle mediastinal mass is adenopathy, which may be malignant or reactive to inflammatory or granulomatous disease. Bronchopulmonary foregut malformations, specifically bronchogenic cysts, are also common middle mediastinal masses, but these lesions may occur in any compartment of the thorax, including intrapulmonary locations. The most common posterior mediastinal masses are of neurogenic origin.

Table 4-3. Mediastinal masses by compartment

Anterior mediastinum	Middle mediastinum	Posterior mediastinum
Thyroid goiter	Adenopathy	Neurogenic tumor
Lymphoma	Bronchogenic cyst	Hiatal hernia
Thymoma, other thymic tumors, and cysts	Pericardial cyst and fat	Esophageal masses
Teratoma and other germ cell tumors	Pericardial effusion	Descending aortic aneurysm
Ascending aortic aneurysm	Aortic aneurysm	Anterior meningocele
Parathyroid tumors	Bronchogenic carcinoma	Extramedullary hematopoesis
Morgagni hernia	Coronary and pulmonary aneurysm	Bochdalek hernia
	Vascular rings and slings	Neurenteric cyst
		Azygos continuation of IVC

Diagnostic Approach

Pulmonary symptoms of dyspnea, chest pain, cough, and hemoptysis are nonspecific. History and physical examination may occasionally direct a search for a specific lesion, such as myasthenic symptoms secondary to thymoma or fever and night sweat secondary to lymphoma. Mediastinal masses are often discovered incidentally on routine chest radiographs.

The standard PA and lateral chest radiograph is adequate for the initial detection and localization of mediastinal mass lesions. After their initial identification, CT is the preferred method for further evaluation of mediastinal masses. CT readily discriminates between densities of fat, water, soft tissue and calcium, often providing for a specific radiologic diagnosis. Intravenous contrast is useful to characterize primary vascular lesions and to assess the relationship of other masses to the adjacent vascular structures of the mediastinum. CT angiography, which uses new techniques of helical or spiral scanning, can replace conventional angiography in assessing many lesions of the thoracic aorta and central pulmonary vessels. In cases where bronchogenic cyst is a differential diagnostic consideration, CT scanning should be performed with pre- and postcontrast enhanced imaging. Whereas usually near-water in attenuation on CT, bronchogenic cysts may contain proteinaceous fluid or even milk of calcium. A lack of contrast enhancement in a rounded or ovoid lesion with contents that are greater than water in attenuation can be helpful in establishing the diagnosis of bronchogenic cyst. CT may also provide a means for image-guided percutaneous biopsy of some mediastinal masses.

Magnetic resonance imaging (MRI) is the primary imaging method for posterior mediastinal masses, almost always being of neurogenic origin. The relationship of a posterior mediastinal mass to the spinal canal and neural foramina is essential, both for diagnosis and surgical treatment planning. MRI is often used as a problem-solving tool for lesions that remain difficult to characterize on CT. MRI is particularly helpful in identifying cystic and fatty components of lesions and for characterizing congenital and acquired vascular abnormalities, especially those involving the aorta. Calcification, exquisitely demonstrated on CT, is not well shown by MRI.

Barium swallow will demonstrate primary esophageal pathology to advantage, such as mass lesions and hiatal hernia. The esophagram is occasionally helpful in the assessment of congenital vascular lesions, such as aberrant vessels, vascular rings, and slings, which form characteristic impressions upon the contrast-filled esophagus. Catheter-directed angiography is rarely necessary to characterize vascular lesions of the mediastinum owing to the current abilities of CT and MRI. Ultrasound, primarily in the form of echocardiography, is useful in assessing pericardial effusions and paracardiac masses.

Common Lesions

Intrathoracic thyroid goiters are commonly identified on chest radiographs. These may significantly displace or even compress the trachea. CT generally demonstrates a heterogeneous mass with regions of calcification and low attenuation necrosis. A thin communication of the mass with the cervical thyroid can nearly always be identified on CT.

The *thymus*, quite large in infants, is gradually replaced with fat, usually undetectable after young adulthood. The normal thymus has a bilobed, triangular configuration with concave borders.

Thymomas are rounded masses in the anterior mediastinum, usually solid soft tissue, but occasionally with areas of calcification and necrosis. If encapsulated, without spread to other regions of the chest, they are regarded as noninvasive. If the lesion spreads into the mediastinum or to the pleural space, the lesion is regarded as invasive, with a poorer prognosis. Only 15% of patients with symptoms of myasthenia gravis have a detectable thymoma, but of those patients with a thymoma, 40% have myasthenic symptoms.

Germ cell tumors arise in the anterior mediastinum and are more often benign than malignant. Many lesions contain fat. Malignant tumors grow rapidly, with local invasion of the mediastinum and distant metastases.

Lymphoma often arises in the anterior mediastinum and extends to contiguous nodal groups in the neck and chest. Usually of soft tissue attenuation, lymphomatous masses, and nodes may calcify after treatment.

Bronchopulmonary foregut cysts arise from abnormal budding of the tracheobronchial tree and primitive foregut. *Bronchogenic cysts* are the most common manifestation, usually appearing as a middle mediastinal cyst, close to the carina and in the right paratracheal region, although they may appear in any compartment of the thorax, including intrapulmonary locations. *Esophageal duplication cyst* is a related but distinct entity, usually adjacent to the esophagus in the posterior mediastinum. *Neurenteric cysts* are another group of related cystic lesions located in the posterior mediastinum and associated with vertebral body anomalies.

Anterior meningocele is a posterior mediastinal mass that communicates with the cerebrospinal fluid space of the spinal canal, demonstrable by MRI or myelography.

Pericardial cysts usually occur in the right cardiophrenic angle and are of no clinical significance.

Neurogenic tumors arise from the nerves of the autonomic nervous system, intercostal regions or roots emanating from the neural foramina and are the most common posterior mediastinal mass. Neurofibromas, schwannomas, and ganglioneuromas are most common. Paragangliomas arise from the sympathetic ganglia and may be regarded as "extraadrenal pheochromocytomas."

Thoracic aortic aneurysms are acquired, secondary to atherosclerosis, longstanding hypertension, connective tissue disorders such as Marfan and Ehlers–Danlos syndromes, trauma, and syphilis.

Thoracic aortic pseudoaneurysm is the result of deceleration trauma, typically at the region of the ligamentum arteriosum, where the aorta focally ruptures, but is fortuitously contained by some compartment of the mediastinum, forming a mass.

Thoracic aortic dissection is an entity distinct from aneurysm, in which the intrinsic walls of the aorta are separated by blood and hematoma. The aorta may or may not increase in overall caliber.

Management

A specific diagnosis is required to undertake proper management for mediastinal mass lesions. Many mediastinal masses can be confidently classified as benign based on their imaging features. Thyroid goiters, uncomplicated bronchogenic cysts, pericardial cysts, and prominent fat pads require no therapy. Many congenital vascular lesions are of no clinical significance. Benign patterns of calcification in lymph nodes may obviate the need for invasive biopsy.

Mediastinal adenopathy generally requires histologic identification to discriminate malignant from non-neoplastic reactive processes and to select specific treatment regimens. Percutaneous CT guided biopsy or mediastinoscopy may accomplish sampling of suspicious lymph nodes. Occasionally, mediastinotomy or thoracotomy is required.

Surgical management may follow for specifically identified lesions without the need for biopsy, such as thymoma and other thymic tumors, germ cell tumors, and neurogenic tumors. Surgical management is indicated, often emergently, for many acquired diseases of the thoracic aorta, such as large aneurysms, all pseudoaneurysms, and dissections that involve any portion of the ascending aorta.

Differential Diagnosis of Pleural Effusion

Paul M. Cox, Jr. and Marvin I. Schwarz

The diagnostic features of pleural effusions are shown in Table 4-4. In the evaluation of pleural effusion, it is important first to determine whether it is an exudate or transudate. If it is believed to be an exudate, additional diagnostic studies (e.g., cytologic study, culture, biopsy) must be undertaken. If the fluid is a transudate, attention should be directed to the underlying cause of the effusion (e.g., congestive heart failure, cirrhosis of the liver, nephrotic syndrome, hypoproteinemia). Exudates are characterized by one or more of the following features: a pleural fluid:serum protein ratio greater than 0.5, a pleural fluid lactic dehydrogenase (LDH) greater than 200 IU, and a pleural fluid:serum LDH ratio greater than 0.6. Transudates exhibit none of these abnormalities.

Table 4-4. Differential diagnosis of pleural effusion

Etiology	Characteristics of effusion	Clinical findings	Laboratory findings and diagnostic procedures
Transudates: Protein less than 3 g/100 mL with normal serum protein concentration, LDH <200 IU, LDH ratio <0.6			
Congestive heart failure	Usually right-sided but may be bilateral; may be localized to an interlobar fissure	Orthopnea, paroxysmal nocturnal dyspnea, tachycardia, cardiomegaly, gallop rhythm, murmurs, rales, peripheral edema	Chest films; electrocardiogram
Cirrhosis	Right-sided, occasionally left-sided or bilateral	Ascites, peripheral edema, physical signs of cirrhosis	Liver function tests; liver biopsy
Nephrotic syndrome	Bilateral or unilateral	Generalized edema; periorbital edema is characteristic; pallor	Cylindruria and proteinuria, hypoalbuminemia, hyperlipidemia
Meigs' syndrome	Usually right-sided, occasionally left-sided or bilateral; rarely, effusion is bloody; no malignant cells present	Benign or malignant ovarian tumor, rarely uterine fibroma; ascites always present	Removal of the tumor resolves the effusion and ascites
Exudates: Protein greater than 3 g/100 mL with normal serum protein concentration, LDH >200 IU, LDH ratio ≧0.6			
Bacterial or viral pneumonia (parapneumonic effusion)	Same side as infiltrate; polymorphonuclear leukocytes; no organisms seen; may be loculated	Pleuritic pain; friction rub may be present; may see recurrence of fever	Precedes clinical picture of pneumonia; usually resorbed within 2 weeks
Pulmonary infarction	May be serosanguinous; polymorphonuclear leukocytes	Pleuritic pain; friction rub, fever (<101°F); right ventricular heave; murmur of pulmonary insufficiency; increased P_2, right-sided S_4 or S_3	Positive radioisotope scans; pulmonary angiography may also provide diagnosis
Tuberculosis	Lymphocytic pleural effusion; may be serosanguinous; acid-fast organisms rarely seen; increased cholesterol content if chronic	Usually pleuritic pain and fever in young adults; frequently asymptomatic	Positive skin test; pleural biopsy with histopathologic and bacteriologic studies

continued

Table 4-4. *Continued.*

Etiology	Characteristics of effusion	Clinical findings	Laboratory findings and diagnostic procedures
Rheumatoid arthritis	Polymorphonuclear leukocytes; glucose low; cholesterol may be elevated; LDH markedly elevated; complement low; low pH	More common in males; other systemic rheumatoid involvement (e.g., arthritis, subcutaneous nodules)	Positive serum rheumatoid factor; biopsy of subcutaneous nodule or synovium rarely indicated
Lupus erythematosus	Polymorphonuclear leukocytes; fluid glucose equals blood glucose; may be transudate if associated with heart failure or the nephrotic syndrome	Arthritis, skin rash, renal disease; superficial thrombophlebitis	Positive serologic results; urinary sediment abnormalities; renal or skin biopsy
Lymphoproliferative disorders	Polymorphonuclear leukocytes, lymphocytes, rarely eosinophils; occasionally transudate; rarely chylothorax	Night sweats, fever, pruritus; adenopathy; hepatosplenomegaly; chest roentgenogram may reveal hilar and mediastinal lymphadenopathy or parenchymal nodules or infiltrates	Lymph node, skin, pleural, liver, or bone marrow biopsy leads to diagnosis
Primary lymphedema		Yellow fingernails, peripheral lymphedema; may follow upper respiratory illness	Normal cardiac, renal, and liver function
Myxedema	Frequently bilateral; may be transudate if associated with myocardial or pericardial disease	Clinical findings of myxedema; large heart on radiograph	Abnormal thyroid function test results
Subphrenic abscess	Polymorphonuclear leukocytes, occasionally a transudate ("sympathetic" effusion)	May follow ruptured viscus; amebic abscess; complication of abdominal surgery	Liver–lung radioisotope scan; CT scan or ultrasound
Peritoneal dialysis	No specific characteristics	Clinical picture is evident	Disappears following drainage of peritoneal cavity
Hydronephrosis	No specific characteristics	Picture of urinary obstruction	Disappears with relief of obstruction
Leakage through a subclavian vein catheter	Reflects characteristics of the intravenous fluid; may be transudate		
Malignancy	Malignant cells; lymphocytes or polymorphonuclear leukocytes; major cause of hemorrhagic pleural effusions	History and physical findings of a primary or metastatic cancer; history of asbestos exposure in suspected mesothelioma	Pleural biopsy frequently positive
Pancreatitis	Polymorphonuclear leukocytes; high amylase; usually on left, but may be bilateral; occasionally it is transudate	Severe abdominal pain with radiation to back	Elevated serum and urine amylase
Pneumothorax	May contain inflammatory cells	Sudden onset of pain, dyspnea, cough; chest radiogram demonstrates an air-fluid level	
Chest trauma	May contain inflammatory cells; frequently hemorrhagic	May be closed or open; chest radiograph may demonstrate fractured ribs or a pulmonary contusion	
Chylothorax			
Chest trauma; lymphoma; postsurgical complication	Milky fluid; normal cholesterol; increased lipid content; positive Sudan III stain	Recent trauma or chest surgery; findings of lymphomatous disease	Lymph node biopsy indicated for palpable nodes
Empyema			
Bacterial, fungal, or tuberculous pneumonia; chest trauma; thoracic surgery; mediastinitis; lung abscess; ruptured subdiaphragmatic abscess	Polymorphonuclear leukocytes; may be lymphocytic in tuberculosis; organisms may be seen by Gram stain; may be loculated; low pH; grossly purulent	Fever, pleuritic chest pain, and findings associated with underlying etiology	Fluid culture positive (fungus, tuberculous, aerobic or anaerobic cultures); blood cultures occasionally positive

LVH, left ventricular hypertrophy.

5. GASTROINTESTINAL PROBLEMS

Abdominal Pain

Sunder J. Mehta

Pain is the most common complaint of patients with gastrointestinal (GI) disorders. There is enormous individual variation in reaction to pain, and this important challenge to the physician can be met only by a thorough history and careful objective analysis.

Types

Classically, abdominal pain is separated into three categories: visceral, parietal, and referred. Visceral pain is felt at the site of primary stimulation. It is usually dull, aching, and poorly localized, and frequently difficult to describe. It may or may not be associated with referred pain. Parietal pain is a deep somatic pain that arises from irritation or inflammation of the parietal peritoneum or the root of the mesentery. It is more definite and easier to describe than visceral pain. Referred pain is pain felt at a site other than that stimulated, but in an area supplied by the same or adjacent neural segments. The location of pain arising from specific organs is outlined in Table 5-1.

Clinical Syndromes

The acuteness of abdominal pain determines the clinical approach to this important symptom and is therefore discussed under the separate headings of Acute Abdominal Pain and Chronic and Recurrent Abdominal Pain.

Acute Abdominal Pain

Many diseases, some of which are nonsurgical, may cause acute abdominal pain (Table 5-2). The most common causes of acute abdominal pain are acute gastroenteritis, inflammatory disease (appendicitis, cholecystitis, diverticulitis, pancreatitis, salpingitis), renal and biliary colic, intestinal obstruction, and perforation of a viscus.

Clinical Features

The salient findings of the more common conditions are outlined in the following. However, it must be borne in mind that many of these entities exhibit variant or atypical patterns.

I. Acute gastroenteritis (viêm DD - một cấp)
   A. Anorexia, nausea, vomiting (common)
   B. Crampy, rather poorly localized abdominal pain and tenderness
   C. Diarrhea (common)
   D. Fever and leukocytosis (common)

II. Acute appendicitis (VRT)
   A. Perforation is uncommon before 24 to 36 hours from the onset of symptoms. Initially, pain is diffuse epigastric or periumbilical, eventually shifting to the right lower quadrant (RLQ) of the abdomen.
   B. Nausea and acute loss of appetite are common; vomiting less so.
   C. Constipation or diarrhea is an inconsistent symptom.
   D. Tenderness, muscle spasm, and rebound tenderness in RLQ are frequently absent at the outset but become more evident after 24 hours.
   E. Fever is usually slight to moderate, especially during the first 12 hours.
   F. Moderate leukocytosis with neutrophilia is a late finding.
   G. With a retrocecal appendix, pain, vomiting, and RLQ muscular rigidity are less common.

Table 5-1. Location of pain from specific organs

Organ	Location
Esophagus	Substernal; occasionally neck, jaw, arm, or back
Stomach	Epigastrium; occasionally left upper quadrant and back
Duodenal bulb	Epigastrium; occasionally right upper quadrant and back
Small intestine	Periumbilical; occasionally above the lesion
Colon	Below umbilicus, on the side of the lesion
Splenic flexure	Left upper quadrant
Rectosigmoid	Suprapubic region
Rectum	Posteriorly, over the sacrum
Pancreas	Epigastrium or back
Liver and gallbladder	Right upper quadrant, right shoulder, and posterior chest

Table 5-2. Some important causes of acute abdominal pain

I. Pain originating in the abdomen
- A. Parietal peritoneal inflammation
  - 1. Bacterial contamination (e.g., perforated appendix, pelvic inflammatory disease) (NK)
  - 2. Chemical irritation (e.g., perforated ulcer, pancreatitis, mittelschmerz)
- B. Mechanical obstruction of hollow viscera
  - 1. Obstruction of the small or large intestine
  - 2. Obstruction of the biliary tree
  - 3. Obstruction of the ureter
- C. Vascular disturbances
  - 1. Embolism or thrombosis causing intestinal ischemia
  - 2. Nonocclusive intestinal ischemia
  - 3. Rupture of an abdominal aortic aneurysm
  - 4. Sickle cell anemia
- D. Abdominal wall disorders
  - 1. Distortion or traction of mesentery (co cơ mạc treo)
  - 2. Trauma or infection of muscles
  - 3. Distention of visceral surfaces (e.g., hepatic or renal capsules) (chấn)

II. Pain referred from extraabdominal sources
- A. Thorax (e.g., pneumonia, referred pain from coronary occlusion)
- B. Spine (e.g., radiculitis from arthritis) (viêm Rễ dây TK, tk viêm khớp)
- C. Genitalia (e.g., torsion of the testicle)

III. Metabolic causes
- A. Exogenous
  - 1. Black widow spider bite
  - 2. Lead and other poisoning
  - | độc chất x nọc côn trùng.
- B. Endogenous
  - 1. Uremia
  - 2. Diabetic ketoacidosis
  - 3. Porphyria
  - 4. Allergic factors (C'1-esterase deficiency)

IV. Neurogenic causes
- A. Organic
  - 1. Tabes dorsalis
  - 2. Herpes zoster
  - 3. Causalgia
- B. Functional

From: Silen W. Abdominal pain. In: Thorn GW, et al., eds. *Harrison's principles of internal medicine*, 8th ed. New York: McGraw-Hill, 1976:34, with permission.

- H. Plain radiograph of the abdomen may occasionally show a calcified appendolith. Ultrasound may be useful if perforation has occurred. Barium enema radiographs are not needed.

III. Acute cholecystitis (Viêm TM cấp) (đau hữu)
- A. Previous history of fatty food intolerance, flatulence, postprandial fullness, and RUQ discomfort (common, but nonspecific)
- B. Steady, severe pain in RUQ or epigastrium
- C. Tenderness, muscle guarding, and rebound tenderness (common). The gallbladder may be palpable.
- D. Anorexia, nausea, and vomiting (common)
- E. Fever and leukocytosis (common)
- F. Radiopaque gallstones occasionally revealed by plain abdominal radiographs. Imaging of the gallbladder and biliary tree with either ultrasonography or isotope scanning with HIDA or PIPIDA is very helpful for a quick and accurate diagnosis. Oral cholecystography, although useful for the diagnosis of gallstones, requires 12 to 36 hours to be completed. Endoscopic retrograde cholangiopancreatography (ERCP) may be needed if acute cholangitis is suspected. Intravenous cholangiography is obsolete.
- G. Mild hyperbilirubinemia and bilirubinuria (common)

IV. Acute diverticulitis (viêm túi thừa cấp)
- A. Lower abdominal pain, especially in the LLQ (common)
- B. Tenderness, muscle guarding, and rebound tenderness (common)
- C. Fever and leukocytosis (common)
- D. Constipation (common)
- E. Nausea, sometimes vomiting (common)
- F. Findings like those of acute appendicitis, but left-sided

V. Acute pancreatitis (viêm tụy cấp)
- A. Common in alcoholic patients
- B. Common in patients with cholelithiasis
- C. May occur in patients with hyperlipidemia
- D. Abdominal pain variable, ranging from ~~mild to severe~~, typically epigastric with radiation to the back. May be accompanied by prostration, sweating, and shock
  - hiệt sử
- E. Nausea and vomiting (common)
- F. Abdominal tenderness in epigastrium (common)
- G. Elevated serum or urinary amylase levels, or both (not pathognomonic). Elevated serum lipase (common)
- H. Hyperbilirubinemia and hypocalcemia may occur.
- I. Fever, leukocytosis (common)

(Tắc ruột) VI. Acute intestinal obstruction. The symptomatology depends on the site and completeness of the obstruction.
- A. Crampy abdominal pain (common)
- B. Vomiting (more common with obstruction of the proximal gut)
- C. Constipation; eventually complete inability to pass feces or flatus (common)
- D. Abdominal distention and tenderness (common)
- E. Hyperperistalsis and borborygmi are inconsistent symptoms.
- F. Radiographic evidence of bowel distended with gas proximal to the site of obstruction. Air–fluid levels common

VII. Perforated viscus (thủng tạng rỗng)
- A. Most commonly produced by perforation of a peptic ulcer
- B. Sudden onset of severe abdominal pain, aggravated by movement
- C. Tenderness, abdominal rigidity, and rebound tenderness (common)
- D. Abdominal distention (uncommon initially)
- E. Obliteration of hepatic dullness (uncommon)
- F. Air demonstrable below the diaphragm in the roentgenogram (common)
- G. Hypotension and shock are common later on.

VIII. Mesenteric vascular infarction (NM mạc treo)
- A. Clinical setting often that of congestive heart failure, atrial fibrillation, or visceral hypoperfusion

B. Moderate to severe abdominal pain (common)
C. Vomiting (inconstant)
D. Bloody diarrhea (inconstant)
E. Abdominal distention, tenderness, and rigidity in severe cases
F. Hypotension and shock in severe cases

IX. Acute salpingitis
A. Lower abdominal pain
B. Chills and fever
C. History of sexual exposure
D. Vaginal discharge
E. Adnexal mass(es)
F. Demonstration of gonococcal infection or chlamydial infection

X. Abdominal pain in patients with AIDS
A. Abdominal symptoms are common, but surgical illness is not the cause in most.
B. Etiology of abdominal pain is often an infectious gastroenteritis.
C. Other common clinical syndromes include peritonitis, secondary to cytomegalovirus enterocolitis, perforation, non-Hodgkin's lymphoma or Kaposi's sarcoma of the GI tract, and *Mycobacterium avium* infection of the retroperitoneum and spleen.
D. Abnormal serum liver function tests, right upper quadrant abdominal pain, and fever may be owing to acalculous cholecystitis, sclerosing cholangitis, or papillary stenosis, often caused by cytomegalovirus or cryptosporidiosis.

Diagnostic Approach

It is of the utmost importance to diagnose early. The most important question facing the clinician caring for a patient with severe acute abdominal pain is "Is prompt surgery needed?" Thorough history and physical examination are far more valuable than laboratory or radiologic tests. Surgical consultation should be promptly sought and analgesics withheld until the surgeon completes evaluation of the patient.

All acute abdominal crises give rise to one or more of the following main symptoms and signs: pain, collapse, vomiting, or abdominal wall rigidity. Some main clinical presentations are as follows:

I. Abdominal pain by itself. Often this is the only symptom in the earliest stages of a number of serious conditions of simple intestinal colic, acute appendicitis, small-bowel obstruction, and acute pancreatitis.
II. Severe central abdominal pain with muscular rigidity (e.g., acute pancreatitis, ruptured aortic aneurysm, and mesenteric thrombosis)
III. Pain with vomiting and increased distention but no rigidity usually indicates intestinal obstruction.
IV. Pain with constipation, increased distention, and perhaps vomiting may indicate large-bowel obstruction.
V. The presence of fever, tachycardia, perspiration, and hypotension suggests a serious disorder, such as sepsis or a perforated viscus.
VI. Severe abdominal pain with collapse and generalized rigidity of the abdominal wall usually signifies perforation of a viscus. Stomach and duodenum are more likely sites than colon.
VII. Right hypochondrial pain and rigidity indicate acute cholecystitis or a perforated duodenal ulcer. Left hypochondrial pain and rigidity indicate acute pancreatitis, perforated gastric ulcer, or splenic rupture. Right lower quadrant pain, tenderness, and rigidity indicate acute appendicitis or tuboovarian disease or ileitis. Left iliac fossa pain, tenderness, and rigidity indicate diverticulitis. Hypogastric pain and rigidity indicate perforated appendicitis, diverticulitis, or tuboovarian disease.
VIII. Pelvic, genital, and rectal examinations are mandatory. Pelvic inflammatory disease, a twisted ovarian cyst, or an ectopic pregnancy may be found. Torsion of the testicle may be uncovered in men. Rectal examination may reveal an abscess or neoplasm.

History

I. In eliciting the history of pain, it is important to know its character, severity, localization, radiation, duration, frequency, times of occurrence, and the factors that alleviate or aggravate it.
II. Information about associated symptoms, both GI and systemic, may be helpful in elucidating the cause of pain.
III. Careful inquiry should be made concerning the presence or absence of disorders that may cause referred abdominal pain (e.g., pneumonia, pericarditis, myocardial infarction, spinal-arthritis).
IV. Ask about symptoms that are associated with endogenous or exogenous metabolic causes of pain, as well as those of neurogenic origin (Table 5-2).
V. Check the menstrual history. Midcycle follicular rupture is a frequent, harmless cause of abdominal pain. A history of a missed period followed by abdominal pain should suggest possible rupture of an ectopic pregnancy.
VI. The family history may provide a clue to the cause of abdominal pain. Such familial disorders as hyperlipidemia, familial Mediterranean fever, thalassemia, sickle cell anemia, and acute intermittent porphyria are commonly associated with abdominal pain.
VII. Anticoagulants may be responsible for intraabdominal or retroperitoneal hemorrhage and thereby produce abdominal pain.
VIII. A history of syphilis or gonorrhea may be helpful in elucidating the cause of abdominal pain. Ask about risk factors for AIDS, such as homosexuality and intravenous drug abuse.

Abdominal Examination

I. Abdominal examination is of paramount importance.
A. Inspect the abdomen for distention and visible peristalsis.
B. Check for hernia at all potential sites.
C. Abdominal auscultation, although valuable, is probably one of the least rewarding aspects of the physical examination, because perforation and strangulation of the gut can occur in the presence of normal peristalsis.
D. Palpation of the abdomen must be thorough but gentle.
1. Check for masses, ascites, and splanchnomegaly.
2. Tenderness, rebound tenderness, and involuntary guarding are important signs of peritonitis.

Physical Examination

I. A complete physical examination is indicated.
II. The status of the cardiovascular and respiratory systems and the state of hydration of the patient should be evaluated.

Laboratory Studies

Overreliance on lab tests often misleads the clinician. Useful tests include:

I. CBC
II. Urinalysis
III. Stool for occult blood
IV. SMA 12- or 22-type screens
V. Serum and urinary amylase and lipase
VI. Chest upright and decubitus radiographs of the abdomen. Rarely, contrast studies of the GI tract may be indicated. Occasionally, abdominal ultrasound, abdominal CT scan, or HIDA scans are very useful in older patients.
VII. Electrocardiogram
VIII. Upper or lower endoscopy is rarely indicated.
IX. Abdominal paracentesis may be useful.

Comments: As a general rule, the majority of severe abdominal pains that occur in previously healthy patients and last more than 6 hours are caused by diseases of surgical importance.

Laboratory examination, although important, rarely establishes the diagnosis. Leukocytosis should never be the sole deciding factor as to whether or not surgery is indicated.

A peripheral white blood cell count greater than 20,000/mm² may be seen with perforation, but also with pancreatitis. Conversely, the count may be normal with a perforated viscus. Routine urinalysis, serum electrolytes, and biochemical screening are of value in assessing the state of hydration and in ruling out renal disease, diabetes, or other complications. Serum amylase testing is overrated because disorders other than pancreatitis (e.g., perforated peptic ulcer, strangulated gut) may be associated with marked elevations.

Sometimes, a definite diagnosis cannot be made at the time of the initial examination. The possibility that a patient has an "acute abdomen" requires immediate consultation with a surgeon. If doubt exists, watchful waiting with repeated questioning and examination often indicates the proper course of action.

X. HIV test in patients with risk factors of homosexuality and intravenous drug abuse.

Chronic and Recurrent Abdominal Pain

When pain has been present for weeks or months, the workup can be more deliberate and planned. The patient must be questioned carefully about the location, intensity, character, chronology, and setting of the pain; aggravating or alleviating factors; and associated signs and symptoms. Generally, it is the relationship in which pain occurs that is important. Each organ has its "usual" pain pattern—the location of pain being less useful information than its association with activity or the involved organ. Common pain patterns are described in the following.

I. Peptic ulcer disease. Epigastric pain, described as burning, gnawing, hunger, or aching, occurs 1 to 3 hours after a meal; about one-third of patients are awakened at night with pain. Most often it is quickly relieved with food or antacid, resulting in a pain-food-relief pattern. Some patients with gastric ulcer have increased pain after food, thus presenting a pain-food-pain-relief pattern. Pain is almost always episodic, lasting several days to weeks and is followed by a remission of months.
II. Biliary tract disease. Major symptoms include nausea, vomiting, and epigastric or RUQ abdominal pain that is steady (not colicky). Postprandial fullness, eructations, flatulence, and fatty food intolerance are nonspecific symptoms that are commonly associated with many other abdominal disorders.
III. Pancreatic disease. A history of chronic, heavy alcohol ingestion or evidence of stones in the biliary tree are highly suggestive of pain of pancreatic origin.
IV. Small intestinal disease. Characteristically located in the periumbilical region, the pain is crampy and may be associated with vomiting and changes in bowel habits. With proximal mechanical intestinal obstruction, vomiting occurs early in the clinical course; constipation and inability to pass flatus are more likely to occur with distal intestinal obstruction.
V. Irritable bowel syndrome (IBS). Abdominal pain is present at some time in most patients. It is generally located in the hypogastrium or LLQ. It rarely awakens the patient from sleep, unlike the pains previously discussed. The pain may be aggravated by food and is usually relieved by passage of flatus or a bowel movement. It may be associated with constipation or alternating diarrhea and constipation.
VI. Colonic cancer. Abdominal pain is a common complaint with tumors proximal to the sigmoid. It occurs less frequently with rectal neoplasms and lesions of the distal portion of the sigmoid colon. It may be associated with a recent change in bowel habits. Bleeding per rectum is common. Mild anemia is common.
VII. Miscellaneous causes
   A. Chronic diverticulitis
   B. Intermittent or chronic intestinal obstruction
   C. Tuberculous peritonitis
   D. Systemic diseases and intoxication (e.g., connective tissue diseases, lead poisoning, diabetes, porphyria, tabes dorsalis)
   E. Carcinoma of the pancreas
   F. AIDS

Diagnostic Approach
I. History
II. Physical examination
III. Characteristics of the pain
IV. Associated symptoms, especially weight loss and change in bowel habits
V. Laboratory studies
   A. CBC
   B. Urinalysis
   C. Stool examination for occult blood, ova, and parasites
   D. Biochemical screening
VI. GI endoscopy (proctosigmoidoscopy, colonoscopy, upper GI endoscopy)
VII. Roentgenographic studies
   A. Plain films of the abdomen and chest films
   B. Contrast studies of the GI tract
   C. Cholecystography
   D. CT scan
VIII. Abdominal ultrasonography
IX. Special studies for obscure pain
   A. Urinary porphyrins
   B. Hemoglobin electrophoresis
   C. Abdominal angiography
   D. HIV test

Comments: Few disorders produce pain with distinctive pathognomic features. Clinical history usually only provides enough clues to supply some possibilities. Occasionally physical examination may provide the answer. Laboratory and radiologic studies are generally needed to confirm a tentative diagnosis.

Nausea and Vomiting

H. Harold Friedman

Definition

Even though nausea and vomiting may occur independently, they are so closely related that they are considered together. *Nausea* may be defined as the urge to vomit. *Vomiting* or *emesis* is the forceful expulsion of gastric contents. With few exceptions, nausea is a premonitory symptom of vomiting. *Retching* refers to the spasmodic respiratory activity that precedes emesis. Retching not followed by the expulsion of significant amounts of vomitus is often referred to as the "dry heaves." Vomiting should be distinguished from *regurgitation*, the term applied to the ejection of small quantities of gastroduodenal or esophageal contents not preceded by nausea and not accompanied by the abdominal muscular activity that characterizes the act of vomiting.

Etiology

Nausea and vomiting are common manifestations of organic and functional disorders. The more common causes are listed in Table 5-3.

Nausea without vomiting may occur in uremia, x-ray therapy, alcoholism, liver disease, hypercalcemia, and pregnancy, and as a side effect of drug therapy (e.g., digitalis, opiates, antibiotics, oral contraceptives). Persistent nausea in otherwise healthy persons is frequently psychogenic in origin.

Vomiting may be owing to any acute or chronic illness, or to a functional or nervous disorder. Vomiting may be the first sign of an acute abdominal emergency or of a serious systemic disease.

In everyday clinical practice, the most common causes of nausea and vomiting are acute gastroenteritis, febrile systemic illnesses, drug effects, and GI disease.

Clinical Features

I. Nausea and vomiting are rarely isolated phenomena. They are usually accompanied by other symptoms and signs.

Table 5-3. Causes of nausea and vomiting

I. Neurologic
   A. Migraine
   B. Labyrinthine disorders (Ménière's disease, motion sickness)
   C. Cerebral lesions (especially if associated with increased intracranial pressure)
II. Psychogenic
   A. Emotional and environmental stress
   B. Surreptitious vomiting
   C. Cyclic vomiting (infants and children)
II. Metabolic and endocrine
   A. Renal failure
   B. Metabolic acidosis
   C. Drugs and chemicals
   D. Electrolyte abnormalities (hyponatremia, hypercalcemia, hyperkalemia)
   E. Hepatic failure
   F. Hypothyroidism
   G. Adrenal insufficiency
   H. Pregnancy
   I. Food allergy
   J. Diabetes mellitus
III. Alimentary
   A. Gastroduodenal
      1. Peptic ulcer
      2. Gastric outlet obstruction
      3. Gastric atony
      4. Postgastric surgery
   B. Gastrointestinal
      1. Gastroenteritis, including food poisoning
      2. Appendicitis
      3. Intestinal obstruction
      4. Paralytic ileus
   C. Hepatobiliary
      1. Cholecystitis and cholelithiasis
      2. Acute hepatitis
      3. Cirrhosis of the liver
   D. Pancreatic
      1. Acute pancreatitis
      2. Carcinoma of the pancreas
   E. Peritoneal
      1. Peritonitis
      2. Carcinomatosis
IV. Miscellaneous
   A. Acute febrile illness
   B. Myocardial infarction
   C. Congestive heart failure
   D. Chronic obstructive pulmonary disease
   E. Reflex (e.g., renal, colic, salpingitis)

II. Migraine headaches are commonly preceded or accompanied by nausea and vomiting.
III. The headache of intracerebral disease, notably that of increased intracranial pressure, is sometimes accompanied by vomiting that may be projectile in character.
IV. Labyrinthine disease is typically manifested by vertigo, nausea, and vomiting.
V. Early morning vomiting before eating is seen in pregnancy, alcoholism, uremia, obstructive airway disease of heavy smokers, and sometimes, psychoneurosis.

VI. Psychogenic vomiting is characterized by one or more of the following features:
   A. A lengthy history of vomiting
   B. Maintenance of adequate nutrition despite the vomiting (except in anorexia nervosa)
   C. Vomiting during or shortly after meals
   D. Surreptitious vomiting, often self-induced
   E. Evidence of psychologic disturbances (e.g., anxiety, depression)
VII. Delayed and recurrent vomiting 1 hour or more after meals, with large residues of gastric contents containing food particles, is usually indicative of gastric retention.
VIII. Esophageal obstruction is associated with regurgitation rather than vomiting.
IX. The character of the vomitus may provide clues to an etiologic diagnosis.
   A. Odor. Vomitus with an acrid odor suggests the secretion of hydrochloric acid, easily confirmed by the laboratory. A fecal odor is characteristic of intestinal obstruction or gastrocolic fistula, but it is sometimes noted in paralytic ileus. A putrid odor is a sign of bacterial overgrowth of retained gastric contents or necrosis of a fungating gastric carcinoma.
   B. Contents. "Coffee ground" or bloody emesis is of upper GI origin. Bile usually appears in the vomitus when emesis is repeated. Its presence implies patency of the gastric outlet. Vomiting of bile is not uncommon following gastric surgery. The presence of food particles in vomited material is discussed in the preceding.
X. Persistent vomiting may have serious consequences (e.g., aspiration pneumonia, dehydration, electrolyte and acid-base disturbances, and hemorrhaging owing to tears at the esophagogastric junction).

Diagnostic Approach

I. The multiplicity of causes of nausea and vomiting makes it virtually impossible to follow a specific diagnostic approach.
II. Foremost in the evaluation of nausea and vomiting is the history. Special attention should be paid to the following:
   A. The temporal relationship between emesis and food intake; the character of the vomitus; and the onset, duration, and persistence of the nausea and vomiting
   B. A past or present history of GI disease or surgery
   C. The presence or absence of specific GI symptoms such as abdominal pain, hematemesis, melena, indigestion, heartburn, dysphagia, abdominal swelling, jaundice, diarrhea, and constipation
   D. Inquiry concerning symptoms that would suggest a systemic illness or metabolic disorder capable of producing nausea and vomiting
   E. Careful questioning about the use of medications that can cause nausea and vomiting
   F. A history of weight loss
   G. Background information about the patient's psychological and social history and of symptoms that may indicate a psychological disorder
III. The physical examination may provide evidence of the organ system primarily involved.
   A. Fever may suggest infection but is nonspecific.
   B. Neurologic abnormalities, papilledema, and altered consciousness point to disease of the central nervous system (CNS).
   C. An alimentary origin is suggested by a history of abdominal pain and findings of tenderness, distention, splanchnomegaly, altered peristalsis, and abdominal masses on abdominal examination.
   D. Metabolic disorders may be suggested by the physical findings (e.g., in Addison's disease, thyrotoxicosis) usually required for the diagnosis of these conditions.
IV. An isolated episode of emesis, or at most a few bouts of nausea and vomiting, associated with anorexia, malaise, aching, little or no fever, abdominal cramping, diarrhea, and negative physical findings, is virtually diagnostic of acute gastroenteritis. Little or no workup is necessary because the disease is usually

self-limited. However, persistent of symptoms may mandate diagnostic studies. (See Acute Diarrhea.)

V. The initial workup for all patients with *persistent or recurrent nausea and vomiting, or both,* should include:
   A. CBC
   B. Urinalysis
   C. Serum electrolytes
   D. Biochemical screening
   E. Serum and urinary amylase
   F. Arterial blood gases (when an acid-base disturbance is suspected)
   G. Survey films of the abdomen
   H. Chest films
   I. Electrocardiogram

VI. If the GI tract is believed to be at the root of the problem, as is most often the case with persistent and repetitive nausea and vomiting, additional tests are warranted. The procedures chosen should be based on the best clinical judgment of the physician. Such studies might include gastric aspirations, esophagogastroduodenoscopy, barium studies, cholecystography, and proctosigmoidoscopy. Stool examination for occult blood, ova, and parasites and stool cultures may be advisable. The presence of jaundice suggests a special approach. (See Jaundice.)

VII. The choice of other investigative procedures depends primarily on the clinical findings, but tests are sometimes performed for purposes of exclusion. Included in this group are pregnancy tests in amenorrheic women, special studies to elucidate the cause of unexplained anemia, thyroid function tests in suspected thyrotoxicosis, skull films, and other localizing procedures to rule out cerebral disease.

Heartburn (Pyrosis)

Barry W. Frank

Definition

Heartburn, or pyrosis, is a painful or burning sensation located retrosternally or in the subxiphoid region. The discomfort may radiate to the lateral anterior chest, jaws, and arms. Heartburn is frequently worse after meals and aggravated by recumbency or bending forward. It is almost always relieved within 15 minutes by the ingestion of an antacid.

Mechanism

Heartburn arises from alterations in the esophageal epithelium induced by the reflux of acid and pepsin, or bile and pancreatic juice, or both. Motor abnormalities of the esophagus may contribute to its production. However, because pyrosis may be experienced when esophageal motility is normal, it seems likely that chemical stimulation from esophageal reflux is the most important factor in its pathogenesis.

Gastroesophageal Reflux

The primary determinant of gastroesophageal reflux is the tone of the lower esophageal sphincter (LES). Other factors of importance are diet, medications, and smoking. Although the LES cannot be identified anatomically, its presence can be verified by physiologic means. Modern manometric methods have established that the LES possesses a resting tone that causes the intraluminal esophageal pressure to exceed that of the stomach. Thus, in the normal individual, an intact LES prevents the reflux of gastric contents into the esophagus, even when stomach pressures are high. The role of hiatal hernia remains controversial but may, in some cases, be associated with decrease in LES pressure. The following are some of the complications of gastroesophageal reflux:

I. Esophagitis (histologic alteration of the esophageal mucosa)
   A. With bleeding
   B. With ulceration
   C. With stricture

II. Tracheal aspiration with chemical laryngitis, chronic cough, pneumonitis, and fibrosis

Etiology

I. Gastroesophageal reflux owing to an incompetent sphincter, with or without hiatal hernia
II. Medications
III. Scleroderma, with involvement of the lower esophageal sphincter
IV. Barrett's syndrome (lower esophagus lined by columnar epithelium with ulceration at the transitional zone)
V. Tumor, by affecting sphincter function or altering motility
VI. Diet
VII. Tobacco
VIII. Excess alcohol

Diagnostic Approach

Initial Evaluation

I. In many patients, treatment can be initiated on the basis of symptoms without resorting to diagnostic testing. If symptoms subside, the diagnosis is secure.
II. Endoscopy with biopsy has replaced barium radiographs as the initial diagnostic test in patients with severe symptoms not responding to reasonable therapy. A significant number of heartburn patients (30% to 50%) have negative endoscopy findings. In addition to esophagitis, endoscopy can detect stricture formation, Barrett's esophagus, tumor, and other causes of inflammation.
III. Further investigation is warranted in the presence of negative endoscopy and persistent heartburn unresponsive to therapy.

Subsequent Evaluation

I. Continuous 24-hour intraesophageal monitoring is the most sensitive and specific test for diagnosing gastroesophageal reflux. Reflux patients can be categorized as upright, recumbent, or bipositional refluxes. It is most useful when endoscopy is negative and in patients with atypical symptoms.
II. Esophageal acid perfusion test (Bernstein test). The acid perfusion test determines whether the esophagus is sensitive to acid but does not necessarily prove that reflux is present. It is designed to reproduce the symptoms created by acid reflux. A nasogastric tube is passed into the midesophagus and positioned by fluoroscopy. With the patient seated upright, normal saline is administered via the nasogastric tube at a rate of 6 to 7.5 mL/min. Then, without the patient's knowledge, 0.1 N HCl is substituted for the saline. This is perfused at the same rate until pain is produced or until 15 minutes have elapsed. The solutions are again interchanged without notifying the patient. The test is considered to give a positive result if heartburn is elicited by acid perfusion but not by saline. A high incidence of false-positive and false-negative results, ranging between 5% and 15%, makes it necessary to interpret the results with caution.
III. Esophageal motility studies and measurement of the intraesophageal pH. Gastroesophageal reflux is demonstrated best by measurement of the intraluminal pH combined with simultaneous measurement of the intraesophageal pressure. To perform the test the patient swallows an assembly consisting of a pH electrode and three manometric catheters whose tips are placed 5 cm apart. The LES is located and its pressure characteristics noted. The motility of the esophagus is then recorded, and the reflux is measured by the pH electrode.

Dysphagia

Barry W. Frank

Definition

Dysphagia is nonpainful difficulty in swallowing. It is a subjective sensation experienced during the act of deglutition. There is usually a sticking sensation retrosternally

as the bolus descends. In most instances, dysphagia is experienced at the same level as the lesion or above it, but not below it. *Odynophagia* is the term applied to painful swallowing. Dysphagia is a highly specific and significant symptom of organic disease. It should never be considered functional without an exhaustive evaluation. Dysphagia can be differentiated by a careful history from globus hystericus, which is a functional complaint. Globus hystericus is a sensation of a "lump in the throat." It is not necessarily associated with deglutition. The symptom is intermittent and is not associated with regurgitation. Foods and liquids can be swallowed without difficulty.

Oropharyngeal dysphagia is difficulty in emptying material from the oral pharynx into the esophagus. It occurs in disorders proximal to the esophagus, most often of neurologic or muscular origin. Esophageal dysphagia is usually the result of obstructive or motor abnormalities.

Etiology

Oropharyngeal Dysphagia

I. Loss of tongue function (myasthenia gravis, myotonia dystrophica)
II. Pharyngeal dysfunction (myasthenia gravis, vascular brainstem disease, dermatomyositis, hyperthyroidism)
III. Mechanical obstruction
  A. Zenker's diverticulum
  B. Tumor
  C. Inflammatory stricture

Esophageal Dysphagia

I. Intraluminal obstruction
  A. Esophageal webs
  B. Lower esophageal ring (Schatzki's ring)
  C. Tumor
  D. Lower esophageal sphincter spasm (hypertensive sphincter)
  E. Inflammatory stricture
  F. Caustic stricture
  G. Foreign body
II. Extraluminal obstruction
  A. Compression by tumors, enlarged lymph nodes, or substernal thyroid gland
  B. Vascular abnormalities (aortic aneurysm, aberrant right subclavian artery, right-sided aortic arch)
III. Motility disorders
  A. Achalasia
  B. Scleroderma
  C. Diabetic neuropathy
  D. Diffuse esophageal spasm
  E. Amyloidosis
  F. Parasitic infection (Chagas's disease)
IV. Miscellaneous causes
  A. Infections (candidiasis)
  B. Crohn's disease

Symptoms

I. A detailed history may provide a significant clue to the etiology of dysphagia and hence aid in its evaluation.
II. Dysphagia of oropharyngeal disease is characterized by difficulty in moving a bolus of food from the mouth to the pharynx. There may be instant regurgitation of food through the nares, choking, and repetitive swallowing, particularly in neuromuscular disorders.
III. Esophageal dysphagia usually presents as a sticking sensation. It may be intermittent, as in the case of a lower esophageal ring, or progressive, as in the presence of a tumor. Regurgitation of undigested food may occur minutes to hours after a meal. Patients find that they must chew their foods thoroughly and that fluids may be required to "wash the food down." The time taken to eat frequently is prolonged.

IV. The presence of weight loss suggests marked obstruction owing to benign disease or a malignancy.
V. Respiratory symptoms, most often nocturnal, may occur from tracheal aspiration of esophageal contents. Esophageal disease should always be considered as a possible cause of recurrent unexplained pneumonia.
VI. Heartburn suggests an inflammatory stricture or disease that involves the lower esophageal sphincter.
VII. Raynaud's phenomenon suggests a connective tissue disease as the cause of dysphagia, which in turn is owing to a motility disorder.
VIII. Halitosis and postprandial neck fullness should suggest the presence of a Zenker's diverticulum.

Physical Examination

The physical examination is of little value in the diagnosis of dysphagia except in the presence of neuromuscular disorders, scleroderma, diabetes mellitus, cervical lymphadenopathy, or malnutrition.

Diagnostic Approach

I. X-ray examination
  A. Barium swallow is the most valuable procedure. It often reveals the cause and site of an obstruction, but a normal result should not deter further investigation, particularly by endoscopy.
  B. The addition of a marshmallow or barium-coated tablet is useful in an attempt to reproduce the dysphagia or define more precisely the location, type, and degree of obstruction.
II. Esophagoscopy and biopsy are essential in the diagnosis of esophagitis, strictures, rings, webs, and tumors. Therapeutic dilation, when indicated, can be performed under the same sedation.
III. When properly performed, exfoliative *cytologic studies* and biopsies may be expected to yield the correct diagnosis in 95% of patients with esophageal carcinoma.
IV. Esophageal motility study, as described in the preceding section, is essential to the diagnosis of motility disorders. It is the only technique that elucidates the status of the lower esophageal sphincter as well as the overall motility of the esophagus.
V. The esophageal acid perfusion test (Bernstein test) is of little value in the evaluation of dysphagia except when esophageal reflux is suspected.

Irritable Bowel Syndrome

Sunder J. Mehta

Irritable bowel syndrome (IBS) is a common disorder producing abdominal pain and disordered defecation. There are no biologic markers or diagnostic tests to define this disorder. Therefore, a set of criteria arrived at by consensus among investigators worldwide, known as the Rome criteria, are used to define it.

IBS is a combination of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities that is attributed to the intestine and associated with symptoms of pain and disturbed defecation and/or symptoms of bloating and distention.

Etiology

IBS affects 14% to 24% of women and 5% to 19% of men, with a decrease in reporting frequency among older persons. The prevalence appears similar in Whites and African Americans but may be lower in Hispanics. It accounts for 12% of primary care and 28% of GI specialty practices.

No physiologic mechanism unique to IBS has been identified. The types of motility patterns seen in the colon and small intestine are qualitatively similar to the contractions seen in healthy controls. There is no consensus on the dysmotility responsible for

diarrhea or constipation. Some patients with diarrhea-predominant IBS have accelerated transit in the small bowel and/or colon; others with constipation-predominant IBS have delayed transit. Most have increased contractions in response to environmental or enteric stimuli, such as psychological stress or meals.

Clinical Features

Rome Diagnostic Criteria for IBS

At least 3 months of continuous or recurrent symptoms of the following:

Abdominal pain or discomfort
Relieved with defecation, or
Associated with a change in frequency of stool, or
Associated with a change in consistency of stool

Two or more of the following, at least on one-fourth of occasions or days:

Altered stool frequency (for research purposes altered may be defined as more than three bowel movements each day or fewer than three bowel movements each week), or
Altered stool form (lumpy/hard or loose/watery stool), or
Altered stool passage (straining, urgency, or feeling of incomplete evacuation), or
Passage of mucus, or
Bloating or feeling of abdominal distention

Diagnosis

The key to diagnosis is a good history. The diagnosis is generally one of exclusion because there are no confirmatory tests.

I. Features that support the diagnosis of the IBS include the following:
   A. Onset below the age of 40 years, often in early adult life
   B. Symptoms present for at least 3 months, most prominent during periods of emotional stress and often associated with multiple complaints
   C. Consistent pattern of symptoms, although they may vary in severity
   D. Abdominal pain, typically increased after meals, and at least partially relieved by defecation
   E. Discomfort typically felt during the day
   F. Excessive mucus in the stools
   G. Negative physical findings except for tenderness usually noted in the lower quadrants
II. Features that militate against the diagnosis of IBS include the following:
   A. Onset above the age of 50 years
   B. Relatively short duration of symptoms
   C. A steadily progressive downhill course, especially if associated with constitutional manifestations
   D. Voluminous diarrhea (500 mL/day), weight loss, nocturnal symptomatology, rectal bleeding, and the presence of pus or fat in the stools
III. As a group, patients have an increased prevalence of personality disorders, anxiety, depression, or somatization.

Diagnostic Approach

I. A careful history and physical examination, including pelvic and rectal examinations, should be performed to rule out organic disease. Careful inquiry should be made into the use of dairy- and sorbitol-containing products (sugar-free gum, pears, prunes, and apple juice).
II. Initial workup
   A. CBC
   B. Urinalysis
   C. Stools for ova and parasites, occult blood, and fecal leukocytes if diarrhea is the predominant symptom
   D. Thyroid function tests if diarrhea is the predominant symptom

   E. Proctosigmoidoscopy in all patients over 40 years old and in younger patients with diarrhea or tenesmus
   F. Trial of milk-free diet or crude screening procedure for lactose intolerance
III. Subsequent workup. If symptoms persist and the initial workup is negative, additional studies are advisable to exclude malabsorptive states, inflammatory bowel disease, infections (e.g., amebiasis, giardiasis), and carcinoma of the colon.
   A. Barium enema, upper GI series, and small bowel study
   B. Screening for malabsorption
   C. Colonoscopy—frequently needed in older patients
   D. Lactose tolerance test or hydrogen breath test (rarely needed)
IV. Other procedures. When the symptomatology is persistent or intractable and the workup is negative, additional investigation, such as abdominal CT scan, may be warranted. Having patients keep a 1-week diary of food intake, chronological occurrence, and symptoms can be useful.

Gastrointestinal Bleeding

Andrew Mallory

Definitions

Hematemesis is the vomiting of red blood or "coffee ground" material. *Melena* is the passage of black, sticky stools. *Hematochezia* is the passage of fresh red blood per rectum. Upper GI bleeding is defined as bleeding from a source proximal to the ligament of Treitz; lower GI bleeding is from a source distal to this point.

Etiology

Some causes of GI bleeding are listed in Table 5-4.

Clinical Features

Acute massive GI hemorrhage results in the following hemodynamic changes: decreased cardiac output, rise in pulse rate, and drop in blood pressure. The latter is first detectable as an orthostatic change. A drop in systolic blood pressure of more than 10 mm Hg or an increase in heart rate of more than 20 beats/min when sitting (with the legs "dangling") or standing usually indicates a loss of at least 1,000 mL of blood. It should be remembered that the hematocrit may be normal and may grossly underestimate the amount of blood lost if volume readjustment to blood loss has not yet taken place. It may take as long as 24 hours for this phenomenon to occur.

Recovery of bright red blood from the stomach usually indicates a brisk rate of bleeding; recovery of dark blood indicates a slower rate of bleeding. However, fresh blood can be converted to dark-colored hematin in a highly acidic environment in a matter of seconds.

Diagnostic Approach

History

A carefully taken history usually helps to define both the site and cause of GI bleeding.

I. Vomiting of blood or coffee ground material localizes the source to the upper GI tract.
II. A history of epistaxis or hemoptysis raises the possibility of sources other than the GI tract causing bleeding in a patient with hematemesis.
III. Vomitus containing no gross blood or coffee ground material in a patient with melena or rectal bleeding does not rule out an upper GI source, because bleeding may have stopped before vomiting occurred or because bleeding into the duodenum may not have refluxed into the stomach. However, the presence of bile in the gastric aspirate indicates that reflux has occurred.
IV. Melena usually means that the site of bleeding is proximal to the midtransverse colon.
V. Gross blood from the rectum usually means that the source of bleeding is located more distally in the large bowel. However, upper GI sources may cause gross

Table 5-4. Causes of massive gastrointestinal bleeding in adults

Area	Disease or disorder
Upper gastrointestinal tract	
Common	Ulcer (duodenal, gastric)
	Gastritis (stress, alcohol, drugs)
	Mallory-Weiss tear
Uncommon	Esophagitis
	Angiodysplastic or other vascular malformations (e.g., hereditary hemorrhagic telangiectasia)
	Gastric or esophageal carcinoma
	Duodenitis
	Hemobilia
	Aortoduodenal fistula
	Bleeding diathesis (including iatrogenic)
Lower gastrointestinal tract	
Common	Diverticular disease of the colon
	Angiodysplasia
	Inflammatory bowel disease
	Colorectal carcinoma and polyps
Uncommon	Ischemic bowel disease
	Meckel's diverticulum
	Postirradiation enteritis
	Hemorrhoids (common cause of minor bleeding; massive bleeding rare except in presence of portal hypertension)

From: Reller LB, et al., eds. *Clinical internal medicine.* Boston: Little, Brown, 1979:197, with permission.

rectal bleeding if the hemorrhage is massive and bowel transit is rapid. Under these circumstances, the vital signs deteriorate rapidly.

VI. Although there is a past history of ulcer disease in most patients with bleeding ulcers, bleeding may be the initial manifestation in up to 10% of cases of ulcer disease. Disappearance of ulcer pain often heralds the onset of bleeding.

VII. A history of ingestion of particular drugs increases the likelihood of gastritis or ulcer disease. The evidence implicating salicylates is convincing. Other drugs, such as phenylbutazone, nonsteroidal antiinflammatory drugs (NSAIDs), and steroids also may cause bleeding.

VIII. A history of cirrhosis of the liver increases the likelihood that esophageal varices are the source of the bleeding. However, in several studies approximately 50% of hemorrhages in cirrhotic patients were owing to other lesions.

IX. Stools may appear red in some persons after the ingestion of beets. Black stools may result from the ingestion of iron, bismuth-containing compounds (e.g., Pepto-Bismol), or charcoal.

X. A source of blood loss is often not found in the bleeding patient who is receiving anticoagulant therapy. A diagnostic workup is nevertheless indicated, especially in the patient who bleeds while his anticoagulation is in the "therapeutic range."

Physical Examination

I. The initial examination may have to be limited in a patient with massive hemorrhage and deteriorating vital signs.

II. Particular attention should be directed to the following:
   A. Vital signs: for evidence of orthostatic pulse and blood pressure changes
   B. Skin: for vascular spiders, palmar erythema, and jaundice in chronic liver disease; pigmented macules on the lips in the Peutz–Jeghers syndrome; telangiectasia on the face, palms, soles, or on the buccal or nasal mucosa in hereditary hemorrhagic telangiectasia; purpura or ecchymoses in bleeding diathesis; erythema nodosum in inflammatory bowel disease
   C. ENT: for possible epistaxis
   D. Abdomen: for hepatosplenomegaly, ascites, and caput medusae in cirrhosis epigastric tenderness in ulcer disease or gastritis; the presence of a mass in Crohn's disease or malignancy
   E. Rectal examination: to detect masses, hemorrhoids, or fissures; to confirm the presence of rectal bleeding or melena. It should be remembered that stools may remain tarry and tests for occult blood may remain positive for several days after bleeding has stopped.

Diagnostic Studies

I. Initial laboratory studies should include:
   A. CBC
   B. Coagulation studies (prothrombin time, partial thromboplastin time, platelet count)
   C. Liver function tests
   D. Electrolytes in selected cases, especially if vomiting or diarrhea has been present or if liver disease is likely
   E. Serum creatinine, blood urea nitrogen (BUN), and blood glucose
   F. Blood for typing and cross matching. At least three units of blood should be available at all times.

II. A large-bore (e.g., 24F) nasogastric tube should be inserted into the stomach even if only bright red rectal bleeding is present. The presence or absence of bile in the gastric aspirate should be noted. If no blood or coffee-ground material is recovered in 30 minutes, the tube can be removed. If blood is present, the tube should remain for purposes of lavage. Although lavage has not proved effective in lessening bleeding, it helps cleanse the upper GI tract of blood and thus facilitates further diagnostic studies.

III. Additional procedures depend on the diagnostic facilities available to the physician.
   A. Panendoscopy is employed early in many patients with upper GI tract bleeding. Its high accuracy, ease (at patient's bedside), safety, and therapeutic potential (injection, cautery, variceal bleeding) probably make it the procedure of choice. It is generally preferable to delay endoscopy until resuscitative measures restore vital signs and the stomach can be cleared of blood clots with a nasogastric tube. In many instances, the rate of bleeding slows during this period of time. Endoscopy can then be undertaken. However, if bleeding continues and especially if immediate surgery is contemplated, endoscopy may be performed.

      Panendoscopy is very safe in experienced hands. Relative or absolute contraindications are coma, an uncooperative patient, or the presence of severe cervical arthritis.
   B. Upper GI series is less sensitive than panendoscopy in diagnosing the source of upper GI tract bleeding but may be better tolerated. It should not be performed until the vital signs are stable. It is the procedure of choice when panendoscopy is unavailable or contraindicated.
   C. Arteriography is seldom necessary in the diagnostic evaluation of upper GI bleeding. It is usually reserved for the patient with continuous brisk bleeding (at least 0.5 to 1.0 mL min) after other diagnostic measures have failed. More commonly, however, patients with continued bleeding from the upper GI tract and negative diagnostic studies are explored surgically after five to six units of blood have been transfused.
   D. Gastric or esophageal tamponade with a tube such as the Sengstaken-Blakemore may occasionally prove useful diagnostically as well as therapeutically in a patient with suspected varices.
   E. If bleeding appears to originate in the lower GI tract (e.g., hematochezia with a negative nasogastric aspirate), proctosigmoidoscopy should be carried out

promptly. If this procedure is unrevealing, a period of observation is usually recommended during which blood transfusions may be administered if indicated. If bleeding continues and the patient is hemodynamically stable, technetium 99m-labeled RBC scanning may prove useful in localizing the bleeding source. If positive, further identification and perhaps treatment can be offered by arteriography, or colonoscopy, or both. If negative, colonoscopy is usually indicated after adequate preparation.

F. If bleeding is especially massive, prompt arteriography for localization and treatment (e.g., embolization, vasopressin infusion) should be performed. Even if successful therapy cannot be carried out, localization of the bleeding source may greatly aid the surgeon should surgery become necessary. Colonoscopy carried out during massive lower GI bleeding on occasion may prove useful, especially if the colon can be rapidly prepared by administration of an oral electrolyte solution beforehand.

Diarrhea

Barry W. Frank

Definition

Diarrhea may be defined as an increase in the fluidity, or frequency, or both, of the stool. The 24-hour stool weighs less than 250 g and contains about 150 mL of water. When daily stool weight exceeds 200 g (approximately 250 mL water) diarrhea is usually present. Whether acute or chronic, diarrhea results from or is associated with water and electrolyte malabsorption. There are four basic pathophysiologic mechanisms involved in the production of diarrhea. One or more of these factors may play a significant role in any given diarrheal state. They include the following: (a) abnormal intestinal motility, (b) increased vascular or mucosal permeability, resulting in fluid and electrolyte exsorption, (c) impaired intestinal absorption, and (d) intraluminal nonabsorbable osmotically active solutes. It is important to bear in mind that patients with inflammatory disease of the rectum may refer to the frequent passage of small quantities of blood and mucus as diarrhea.

Acute Diarrhea

Acute diarrhea is usually of abrupt onset and short duration.

Etiology

I. Infectious diarrhea
   A. Bacterial: *Salmonella, Shigella, Campylobacter fetus, Vibrio cholerae;* enteropathogenic: *Escherichia coli, Clostridium difficile, Yersinia enterocolitica, Vibrio parahaemolyticus*
   B. Viral: enterovirus, hepatitis-associated virus, parvoviruslike agents, orbivirus, Norwalk virus
   C. Fungal: *Candida, Actinomyces, Histoplasma*
   D. Protozoal: *Giardia lamblia, Entamoeba histolytica, Cryptosporidium, Isospora belli, Blastocystis hominis*
   E. Helminthic: *Ascaris lumbricoides, Ancylostoma duodenale, Necator americanus, Trichuris trichiura, Strongyloides stercoralis*
II. Toxic diarrhea
   A. Bacterial toxins (food poisoning): *Staphylococcus, Clostridium perfringens, E. coli, Clostridium botulinum, Bacillus cereus, Pseudomonas*
   B. Chemical poisons: arsenic, lead, mercury, mushrooms
III. Dietary causes: Irritating foods, alcohol, drugs, food allergies, nonspecific food intolerance, nonabsorbable sugar substitutes (sorbitol, mannitol)
IV. Miscellaneous causes: Appendicitis, diverticulitis, GI hemorrhage, Schönlein–Henoch purpura, Stevens–Johnson syndrome, pseudomembranous enterocolitis, fecal impaction, ischemic colitis

Symptoms

The symptoms are usually abdominal cramps, urgency, tenesmus, nausea and vomiting, and watery stools with or without blood and mucus. Systemic symptoms, particularly fever and myalgias, may be present.

Signs

The signs vary with the cause and severity of the disease, but diffuse abdominal tenderness and active bowel sounds are usually present. The temperature may be elevated. Involuntary guarding, localized tenderness, and rebound tenderness of the abdomen are rare. Dehydration may be evident.

Diagnostic Approach

Acute diarrhea frequently is self-limiting. The etiology is generally established by the history and physical examination. However, immediate evaluation is necessary in the presence of severe abdominal pain, systemic symptoms, dehydration, bloody stools, or when symptoms persist beyond 24 hours. Under these circumstances, the following studies should be performed:

I. CBC
II. Rectal swab for bacterial culture and sensitivity studies
III. Immediate examination of a freshly passed stool for ova and parasites
IV. Serum electrolytes to aid in the diagnosis and management of dehydration
V. Stool smears stained with Löffler's alkaline methylene blue for the presence of leukocytes. Fecal leukocytes are commonly present in bacterial infections and chronic inflammatory disease of the colon but are usually not seen in the stools of patients with diarrhea secondary to viruses, toxicogenic bacteria, and parasites.
VI. Stool for *Clostridium difficile* titer when antibiotic-induced pseudomembranous colitis is suspected.
VII. Sigmoidoscopic examination, which is helpful in the diagnosis of shigellosis, amebic colitis, and acute ulcerative colitis. It should be considered as a part of the immediate evaluation in any patient with bloody diarrhea.
VIII. A three-way abdominal x-ray examination should be obtained if there is bloating, severe abdominal pain, or obstructive-type bowel sounds on auscultation, or if obstruction or perforation is suspected.

Chronic Diarrhea

Patients who report having diarrhea for more than 4 weeks should be evaluated for chronic diarrheal disease.

Etiology

Table 5-5 lists the many causes of chronic diarrhea. Cases of diarrhea seen in office practice are caused most often by the following conditions: (a) functional disorders (IBS, emotional diarrhea), (b) disease of the colon (diverticulitis, ulcerative colitis, Crohn's colitis, carcinoma), (c) disease of the small intestine (malabsorption syndromes, Crohn's disease), (d) diarrhea secondary to laxative abuse, and (e) gastrogenic diarrhea, including the postgastrectomy and postvagotomy syndromes. Other diseases are encountered less frequently. It is beyond the scope of this text to consider more than a few of these conditions.

Functional Bowel Disorders

Patients with functional motility disorders ordinarily have a long history of intermittent or chronic diarrhea. Exacerbations may be precipitated by emotional stress and anxiety. Diarrhea is most likely to occur in the morning or after meals. The stools may be large or small, semiformed or liquid, and mucus- or non–mucus-containing. Blood is not found in the stool unless produced by a complicating anorectal lesion. Systemic symptoms are absent, and nutrition is usually good. The diagnosis is made on the basis of history and by exclusion. The findings on physical examination, study of the feces, proctosigmoidoscopy, and barium enema are negative.

Table 5-5. Causes of chronic diarrhea

I. Disease of the stomach
   A. Postgastrectomy (dumping syndromes)
   B. Postvagotomy
   C. Hypertrophic atrophic gastritis (Ménétrier's disease with hypoalbuminemia)
   D. Pernicious anemia with associated megalocytosis of the intestinal mucosal cells
   E. Zollinger—Ellison syndrome
II. Disease of the small intestine
   A. Inflammatory disease
      1. Crohn's disease
      2. Radiation enteritis
      3. Whipple's disease
      4. Collagen disease (polyarteritis, systemic lupus erythematosus, scleroderma)
      5. Amyloidosis
   B. Malabsorption diarrhea
      1. Gluten-sensitive enteropathy (nontropical sprue)
      2. Tropical sprue
      3. Disaccharidase deficiency
      4. Intestinal lymphoma
      5. Intestinal amyloidosis
      6. Intestinal scleroderma
      7. Hypogammaglobulinemia
      8. Intestinal lymphangiectasia
      9. Pancreatic insufficiency
      10. Diarrhea of intestinal stasis (blind-loop syndrome, small bowel diverticula, postgastrectomy steatorrhea, intestinal pseudoobstruction)
      11. Small bowel resection with loss of absorptive surface
      12. Malabsorption associated with chronic skin disease (dermatitis herpetiformis, atopic dermatitis)
      13. Chronic giardiasis
III. Disease of the colon
   A. Ulcerative colitis
   B. Crohn's disease
   C. Ulcerative proctitis
   D. Diverticulitis
   E. Colonic carcinoma
   F. Villous adenoma
IV. Diarrhea in AIDS
   A. Cryptosporidium infections
   B. Amebiasis
   C. Giardiasis
   D. Isospora belli infections
   E. Herpes simplex infections
   F. Cytomegalovirus infections
   G. Mycobacterium avium-intracellulare infections
   H. Salmonella typhimurium
   I. Cryptococcus infections
   J. Candidiasis
   K. AIDS enteropathy
V. Miscellaneous causes
   A. Superior mesenteric artery insufficiency
   B. Addison's disease
   C. Diabetes mellitus associated with visceral neuropathy

continued

Table 5-5. *Continued.*

   D. Endocrine tumors (carcinoid tumor, Zollinger–Ellison syndrome, non-beta islet cell tumor of the pancreas with watery diarrhea, hypokalemia and hypochlorhydria, medullary thyroid carcinoma)
   E. Hyperthyroidism
   F. Drugs
      1. Antacids
      2. Antibiotics
      3. Hypotensive agents
      4. Cholinergic agents
      5. Cathartics
      6. Alcohol
      7. Quinidine
      8. Antidepressants
   G. Functional bowel syndromes
   H. Small bowel tumors
   I. Eosinophilic gastroenteritis
   J. Parathyroid disease
   K. Biliary, gastric, or duodenal colic fistula
   L. Infections
      1. Giardiasis
      2. Amebiasis
      3. Tuberculosis
      4. Clostridium difficile
      5. Helminthic Infections
   M. Laxative abuse

Diseases of the Colon and Small Intestine

I. Diverticulitis. Diverticula of the colon occur more frequently with advancing age; they are usually asymptomatic unless complicated by inflammation. The resulting diverticulitis may be manifested by acute attacks of left lower quadrant pain, tenderness, and fever. A palpable tender mass may be present. Constipation is usual, but diarrhea may occur with bloody stools. Symptoms may disappear after the acute episode subsides. In patients with low-grade inflammation, diarrhea is likely to occur intermittently, although it may be chronic. Crampy lower-abdomen pain is often a feature. The diagnosis is usually established by barium enema.

II. Ulcerative colitis. This is primarily a disease of youth, although it may occur at any age. Its course is characterized by remissions and exacerbations. During the acute phase, the diarrhea may be quite severe, with daily passage of as many as 30 or more bloody, mucus- and pus-containing stools. Fever, weight loss, abdominal griping, and tenesmus are common accompaniments. Complications include pericolitis, perforation of the bowel, malignant transformation, perianal disorders, arthritis, spondylitis, iritis, pericholangitis, and pyoderma gangrenosum. The diagnosis in over 90% of cases can be established by sigmoidoscopy and confirmed by rectal biopsy and barium studies. The sigmoidoscopic findings may be positive even when the contrast examination is negative.

III. Crohn's disease. This disorder occurs most frequently in adolescence and early adult life. Like ulcerative colitis, its course is marked by remissions and exacerbations. During acute attacks, there may be right lower quadrant pain, diarrhea, low-grade fever, and weight loss. The clinical picture of acute appendicitis is simulated in some patients. During periods of remission, constipation may be present but with otherwise normal function. Fistula formation and intestinal obstruction are common sequelae. Nutritional deficiency and malabsorption are less frequent complications. The diagnosis is usually established by radiography. Abnormality of the terminal ileum and skipped areas of involvement are typical. At times the clinical picture is indistinguishable from that of ulcerative

colitis. Differentiating features that are helpful when present include sharp demarcation between diseased and healthy areas of bowel, absence of rectal and sigmoidal lesions in early cases, and evidence of involvement of all layers of the bowel wall.

IV. Malabsorption. Diarrhea manifested by the passage of pale, bulky, greasy, frothy, foul-smelling stools, in association with evidence of nutritional deficiency and weight loss, suggests malabsorption. Fever, hypermetabolism, and significant loss of appetite do not occur. The diarrhea can usually be made to disappear in a 1- to 2-day period if oral feedings are withheld. The laboratory studies most useful in the diagnosis of malabsorption are listed in the following. Evidence of increased fecal excretion of fat is the most important factor in establishing the presence of steatorrhea. The differential diagnosis of various causes of malabsorption is beyond the scope of this discussion.

Diagnostic Approach

History

The history may provide clues to the etiology of the diarrhea and the localization of the disease process.

I. Age. Diarrhea beginning in adolescence or early adult life suggests diseases such as ulcerative colitis, Crohn's disease, and functional disorders. In middle-aged and elderly persons, carcinoma of the colon, diverticulitis, and pancreatic disease are among the more common causes.

II. Diarrhea patterns. Diarrhea alternating with constipation suggests functional enterocolonopathies and excessive use of laxatives. Continuous diarrhea may be seen in intestinal fistulas, laxative abuse, and gastric disease. Intermittent diarrhea is a common feature of functional disorders, diverticulitis, allergies, and malabsorption.

Relief of abdominal cramping by defecation suggests colonic disease; persistence after bowel movements suggests disease of the small intestine. Large-stool diarrhea suggests disease of the small bowel or proximal colon; small-stool diarrhea, involvement of the distal colon. Diarrhea with rectal tenesmus suggests inflammatory disease of the bowel combined with anorectal lesions. Diarrhea associated with abdominal distention should raise the possibility of partial obstruction.

III. Diurnal variations and relationship to meals. Diarrhea occurring primarily in the morning and after meals is found in emotional disorders, Crohn's disease, and ulcerative colitis. Diarrhea that is not related to normal diurnal variations in colonic activity is often found in infectious disease. Nocturnal diarrhea is characteristic of diabetic neuropathy but is not specific for this diagnosis. When inflammatory disease of the bowel is severe, diarrhea may occur at night as well as during the day. Nocturnal diarrhea should always suggest an organic cause.

IV. Weight loss. In the presence of undiminished appetite, weight loss suggests hyperthyroidism or malabsorption. Weight loss in association with fever and other systemic symptoms implies inflammatory disease of the bowel. Weight loss preceding the onset of diarrhea suggests carcinoma of the pancreas or other malignancy, tuberculosis, diabetes, hyperthyroidism, or malabsorption. Weight loss is uncommon in carcinoma of the colon until late in the course of the disease. Diarrhea without weight loss or other systemic manifestations is often functional in origin.

V. Characteristics of the stools. Watery stools with little fecal material occur commonly in psychophysiologic disturbances, severe inflammatory disease of the bowel, and shortened intestines (after surgery). Semiformed, bulky, pale, foul-smelling, frothy, greasy stools indicate malabsorption. Chronic bloody diarrhea with gripping abdominal pain and rectal tenesmus may result from amebic or bacillary dysentery, ulcerative colitis, Crohn's disease, and less often, other conditions. It should be remembered that in any diarrhea, bloody rectal discharge may occur from an associated proctitis or anusitis. Frequent, soft, nonfatty stools should suggest gastrogenic diarrhea. Stools that contain large amounts of mucus without pus or blood are a feature of functional bowel disorders. Semiformed or liquid stools with a greenish color because of excessive amounts of bile may result from excessive use of cathartics or from an infection. Voluminous, watery stools associated with hypokalemia suggest diarrhea produced by the abnormal production of GI hormones (e.g., vasoactive intestinal polypeptide).

Physical Examination

There are few signs that have specific diagnostic value in chronic diarrhea. Evidence of weight loss, malnutrition, dehydration, and anemia point to disease of a serious nature. The physical examination may provide clues to specific disease: reddish-purple flushing of the skin suggests metastatic carcinoid tumor; mucocutaneous pigmentation—Addison's disease or the Peutz–Jeghers syndrome; ecchymosis—malabsorption or Schönlein–Henoch's purpura; erythema nodosum or pyoderma gangrenosum—ulcerative colitis; Argyll Robertson pupils in the absence of syphilis—diabetic neuropathy; exophthalmos—Graves' disease; macroglossia—amyloidosis; lymphadenopathy—lymphoma; tuberculosis, metastatic carcinoma, or Whipple's disease; lymphedema—lymphangiectasia; peripheral arthritis or spondylitis—ulcerative colitis, regional enteritis, or Whipple's disease; uremic breath—renal failure; and clubbing—sprue or ulcerative colitis. In the abdominal and rectal examination, special attention should be paid to tenderness, masses, gaseous distention, bowel sounds, organomegaly, anal fistulae, and the presence of a rectal shelf or frozen pelvis. A palpable mass in the left lower quadrant should arouse suspicion of carcinoma or diverticulitis; on the right side of the abdomen, carcinoma and Crohn's disease. A palpable, stiff descending colon is common in ulcerative colitis and diverticulitis, but this may result from spasm.

Proctosigmoidoscopy

This procedure is indicated in all patients to detect rectal and colonic inflammatory disease, neoplasm, and parasitic disease.

Colonoscopy

Colonoscopy is indicated when hemoccult tests are positive, when right colon lesions are suspected, and to diagnose collagenous colitis.

Radiologic Studies

Roentgenographic examination is warranted in all patients. It should include plain abdominal films as well as a barium enema, upper GI series, and small bowel study. The routine abdominal films may reveal visceromegaly, partial obstruction, pancreatic calcification, and postoperative foreign bodies.

Laboratory Procedures

I. CBC to screen for anemia that may suggest blood loss, malabsorption, infection, or neoplasia. Eosinophilia suggests parasitic disease, allergic reaction, eosinophilic gastroenteritis, or neoplasia. Megaloblastic anemia suggests malabsorption of folic acid or vitamin B_{12}.

II. Stool, examined immediately for culture, ova and parasites, occult blood, and fecal leukocytes. An enzyme-linked immunosorbent assay for *Giardia* antigen in stool has largely supplanted intestinal biopsies and duodenal fluid studies.

III. Serum electrolytes and BUN for electrolyte disturbances or uremia

IV. Serum protein electrophoresis to detect GI protein loss, evidence of chronic inflammation, or hypogammaglobulinemia

V. Serum carotene to screen for fat malabsorption. The results may be invalid if the patient has had either a limited or an excessive intake of vegetables.

VI. Serum calcium, phosphorus, and alkaline phosphatase to detect parathyroid disease

VII. Thyroid function tests (T_4, T_3 resin uptake) to detect hyperthyroidism

VIII. Fasting or 2-hour postprandial blood sugar tests to detect diabetes

IX. Serum folate and vitamin B_{12} levels to detect deficiency that may be owing to malabsorption

Specialized Tests in the Evaluation of Chronic Diarrhea

The initial evaluation may well provide the proper diagnosis so that treatment can be instituted. Often, however, the initial evaluation only suggests the cause or the anatomic site of the lesion. More specialized procedures, such as those that follow, are then required.

I. Serum level of vitamin B_{12} and a Schilling test. These may identify pernicious anemia associated with chronic diarrhea.
II. Seventy-two-hour fecal fat test. This test, although time consuming, is invaluable in documenting a malabsorption problem as a cause of diarrhea. The patient must be on a diet containing a minimum of 80 g of fat/day. All feces excreted during a 72-hour period are collected and analyzed for lipid content. A normal individual should excrete no more than 5 to 7 g of fat every 24 hours. Increased fecal excretion of fat only indicates a significant abnormality in fat absorption; additional studies are necessary to establish its cause.
III. D-Xylose absorption. D-xylose (25 g dissolved in 250 mL of water) is administered orally. The ability of the small intestine to absorb this carbohydrate is measured by determining the amount of xylose excreted in a 5-hour period. An abnormally low excretion of xylose (less than 5 g in 5 hours) suggests jejunal mucosal disease. The accuracy of the test is increased by measuring serum D-xylose levels 2 hours after the oral dose is administered. The normal levels are less than 20 mg/dL.
IV. Lactose tolerance test. This test is indicated when the history suggests that the diarrhea is related to milk intolerance. Following oral administration of lactose (100 g, or 1.75 g/kg of body weight for patients weighing less than 100 lb), patients with lactase deficiency show a rise in blood glucose to a peak of less than 30 mg/100 mL (expressed as glucose) associated with bloating, flatulence, cramps, and diarrhea. The most discriminatory finding using a noninvasive procedure is increased hydrogen excretion in the breath after a test dose of lactose.
V. Bentiromide test. This test is of value when pancreatic exocrine insufficiency is suspected. The principle underlying this noninvasive test is an adequate duodenal concentration of chymotrypsin to cleave para-aminobenzoic acid (PABA) from the synthetic peptide bentiromide. After a 500-mg oral dose of the peptide, PABA is released in the duodenum, absorbed, conjugated in the liver, and excreted in the urine. Normally there is less than 57% arylamine excretion in a 6-hour urine sample. Modifications of the test involving PABA levels have increased its accuracy.
VI. Small bowel culture. A number of derangements of the GI tract, such as multiple strictures, surgical blind loops, afferent loop partial obstruction, multiple jejunal diverticula, diabetic neuropathy, and scleroderma, may give rise to the intestinal stasis syndrome. The common feature is massive bacterial proliferation in the proximal small bowel. Aspirates of small bowel contents are cultured on appropriate aerobic and anaerobic media. Cultures showing greater than 1 million colonies/mL of intestinal fluid should be regarded as abnormal.
VII. Bile acid breath test. This procedure has been recommended for the detection of intestinal malabsorption in the blind-loop syndrome with bacterial overgrowth and in ileal disease or resection. A test is considered positive if there is increased pulmonary excretion of $^{14}CO_2$ following the oral administration of glycine-1-^{14}C glycocholate.
VIII. Peroral small bowel biopsy. Many types of suction and hydraulic biopsy instruments are now available for procuring mucosal specimens to demonstrate histologic abnormalities peculiar to certain diseases. Extreme care must be taken to ensure proper orientation and processing of the biopsy material.
IX. Dye-marker transit time. The time required for ingested food to be eliminated in the stool may at times be useful in correlating the symptoms with the laboratory evaluation. Ingestion of an intense dye (50 mg brilliant blue mixed with 350 mg methylcellulose) along with a regular meal provides a means of measuring the mouth-to-anus transit time.

X. Arteriography. Judicious use of celiac arteriography may be helpful in the diagnosis of arterial insufficiency, suspected tumors, or obscure submucosal abnormalities on routine barium studies.
XI. Colonoscopy. See previous section on colonoscopy.
XII. To test for factitious laxative abuse, a stool specimen should be brought to a pH of 8.0. A maroon color indicates the presence of phenolphthalein, a common ingredient in laxative preparations. Urine tests are available to demonstrate the presence of aloes, senna alkaloids, and bisacodyl.
XIII. Elevated serum gastrin levels suggest the Zollinger–Ellison syndrome. They may also be elevated in chronic atrophic gastritis.

Constipation

H. Harold Friedman

Definition

Constipation may be defined as the passage of excessively dry, small (less than 50 g/day), or infrequent stools (less often than every other day). When a patient complains of constipation, it is well to ask what he means by the term, because the symptom may be imagined. For example, patients who equate good health with regularity of bowel movements often believe they are constipated even when stools are normal. Most patients, however, consider themselves constipated if they have hard stools, small stools, infrequent bowel movements, or stools that are difficult to expel.

Etiology

The more common causes of constipation are listed in Table 5-6. Constipation results when filling or emptying of the rectum is impaired. Inadequate rectal filling may be a consequence of such diverse conditions as intestinal disease, systemic illness, functional bowel disorders, drug effects, and neurologic abnormalities. Emptying of the rectum depends on the integrity of the defecation reflex, which may be disturbed by anorectal disease, poor bowel habits, laxative abuse, neurologic illness, physical inactivity, old age, and other conditions.

Clinical Features

Chronic Constipation

I. Chronic habitual constipation with the passage of hard or infrequent stools is usually caused by improper eating habits, poor bowel habits, inadequate fluid intake, lack of exercise, medications, laxatives, or a combination of these factors. It may also occur in patients with IBS, who often complain of alternating constipation and diarrhea, abdominal distress, and the passage of scybalous stools that may or may not contain mucus. Constipation is sometimes the manifestation of an anxiety neurosis or depression. In all of the foregoing conditions, the GI findings are negative. The diagnosis is made by exclusion.
II. Chronic constipation may be owing to rectal insensitivity, which in many cases appears to be the result of persistent suppression of the urge to defecate or laxative abuse. In such individuals, the desire for bowel movement often is lacking even when the rectum is filled with feces.
III. Chronic constipation may be associated with anorectal disease, such as fissures, ulcers, or hemorrhoids. The diagnosis is usually evident from the history, examination, and proctosigmoidoscopy.
IV. Lifelong obstipation (severe refractory constipation) is sometimes owing to megacolon.
V. Chronic constipation may also result from a variety of GI or systemic disorders, as outlined in Table 5-6.

Acute Constipation

I. Constipation of fairly recent onset in a previously healthy individual, particularly if progressive, may be indicative of a serious disorder.

Table 5-6. Causes of constipation

I. Impaired rectal filling
  A. Dysfunction owing to intrinsic gastrointestinal disease
    1. Narrowing of the lumen
      a. Tumors (benign or malignant)
      b. Inflammatory bowel disease
        (1) Crohn's disease
        (2) Ulcerative colitis
        (3) Chronic amebiasis
        (4) Diverticulitis
      c. Irritable bowel syndrome
      d. Congenital aganglionic megacolon (Hirschsprung's disease)
  B. Dysfunction secondary to systemic disorders
    1. Pregnancy
    2. Hypothyroidism
    3. Hyperparathyroidism and other hypercalcemic states
    4. Hypokalemia
    5. Diabetes mellitus
    6. Porphyria
    7. Lead poisoning
  C. Dysfunction secondary to drug effects
    1. Opiates
    2. Ganglionic blocking agents
    3. Anticholinergic drugs
    4. Nonabsorbable antacids
    5. Antidepressants
    6. Hematinics
    7. Diuretics
II. Impaired rectal emptying
  A. Segmental disturbances in the defecation reflex
    1. Anorectal disorders
      a. Anal ulcer
      b. Fissure-in-ano
      c. Fistula-in-ano
      d. Proctitis
      e. Hemorrhoids
      f. Increased anal sphincteric tone
    2. Neurologic disease
    3. Physical inactivity
    4. Weak abdominal musculature
    5. Old age
  B. Suprasegmental disturbances in the defecation reflex
    1. Poor toilet training
    2. Poor bowel and eating habits
    3. Laxative abuse
    4. Psychiatric disorders

II. The most common cause of acute constipation, particularly in elderly persons, is fecal impaction. The clinical setting is usually that of a feeble, weak, or debilitated individual, lying in bed and receiving frequent doses of sedatives or narcotics. It may also follow barium studies of the GI tract. Soiling and involuntary passage of stools around the impaction may be interpreted erroneously as diarrhea. Rectal discomfort may be severe. The diagnosis is made by rectal examination.

III. Other causes of constipation of recent or acute onset are neoplasm of the rectum and large bowel, mesenteric vascular occlusion, painful anorectal lesions, drugs, intestinal obstruction, urinary tract disease, neurologic disorders, and systemic illness.

Diagnostic Approach

I. Digital rectal examination is of major importance in the diagnosis of fecal impaction, anal and perianal disease, and lesions of the rectum. In a patient who is constipated at the time of examination, absence of stool in the rectum suggests a disorder of rectal filling rather than one of rectal emptying.

II. Habitual constipation of long duration does not require extensive workup if the patient is otherwise in good health. The diagnosis of its cause may be apparent from the history. The physical findings are negative, as are those of rectal and stool examinations. Proctosigmoidoscopy and barium enema should probably be performed once to exclude organic disease.

III. When constipation is of recent origin, once fecal impaction has been excluded, a thorough investigation is warranted to rule out carcinoma of the rectum and colon. The digital rectal examination is an important procedure because about one-fourth of cancers are within reach of the examining finger. If rectal findings fail to explain the constipation, then stool examination for occult blood, proctosigmoidoscopy or colonoscopy, and plain abdominal films followed by barium enema, upper GI series, and small bowel study are indicated. If the GI workup is unrevealing, the systemic causes of constipation listed in Table 5-5 should be excluded by appropriate means.

Functional Bowel Disease

Sunder J. Mehta

Syndromes of functional bowel disease include nonulcer dyspepsia (NUD) and the IBS. They are the most common GI disorders seen by primary care doctors and gastroenterologists. NUD is characterized by chronic or recurrent upper abdominal symptoms in the absence of peptic ulcer. IBS comprises chronic abdominal pain or an abnormal bowel habit in the absence of structural or biochemical abnormality. About 20% of individuals have symptoms consistent with functional bowel disease, and about one-fourth of them seek medical care, generally before the age of 35 years.

Etiology

The cause of IBS is unknown. The disorder is attributed to an abnormality of intestinal motility combined with a heightened pain response to bowel distention rather than to an increased volume of intraluminal gas. Paradoxically, decreased colonic motility is associated with diarrhea, and increased motility with constipation. The bowel musculature exhibits increased reactivity to parasympathomimetic drugs and cholecystokinin. Anxiety or depression is frequently associated with this disorder.

Clinical Features

A multinational committee recently developed consensus criteria for epidemiologic and clinical use. The criteria are based on the following symptoms, continuous or recurrent, for at least 3 months.

I. Abdominal pain or discomfort, relieved with defecation or associated with a change in frequency or consistency of stool

II. An irregular pattern of defecation at least 25% of the time that is associated with at least three of the following: altered frequency or form or passage of stool, mucus per rectum, abdominal distention

III. The likelihood of the syndrome increases as the number of these symptoms increases. The predictive value of these symptoms diminishes with increasing age.

IV. Additional features include symptoms not referable to the lower GI tract: heartburn, dysphagia, globus sensation, noncardiac chest pain, urologic dysfunction, fatigue, and gynecologic problems.

Diagnosis

The key to diagnosis is a good history. The diagnosis is generally one of exclusion, because there are no confirmatory tests.

I. Features that support the diagnosis of the IBS include the following:
   A. Onset below the age of 40 years, often in early adult life
   B. Symptoms present for at least 3 months, most prominent during periods of emotional stress, and often associated with multiple complaints
   C. Consistent pattern of symptoms, although they may vary in severity
   D. Abdominal pain, typically increased after meals, and at least partially relieved by defecation

Gastrointestinal Gas Syndromes

Sunder J. Mehta

I. Complaints of too much "gas" are a common clinical problem. The more common causes of indigestion, gaseousness, and flatulence are listed in Table 5-7. Surprisingly, patients with this complaint have normal volumes of bowel gas whose composition is no different from that of normal subjects.

Clinically, three syndromes are seen: (a) excessive belching, (b) abdominal pain and bloating, and (c) excessive flatulence.

Table 5-7. Causes of indigestion, gaseousness, and flatulence

I. Functional or psychosomatic
II. Organic
   A. Disease of the esophagus
      1. Gastroesophageal reflux with or without hiatal hernia
      2. Achalasia
      3. Esophageal obstruction
   B. Disease of the stomach and duodenum
      1. Gastritis
      2. Gastric ulcer
      3. Duodenal ulcer
      4. Carcinoma of the stomach
   C. Disease of the biliary tract
      1. Cholecystitis
      2. Cholelithiasis
      3. Choledocholithiasis
   D. Disease of the pancreas
      1. Pancreatitis
      2. Carcinoma of the pancreas
   E. Disease of the intestines
      1. Malabsorptive states
      2. Intermittent intestinal obstruction
      3. Irritable bowel syndrome
      4. Abdominal angina
   F. Systemic illness
      1. Tuberculosis
      2. Heart disease
      3. Renal failure
      4. Chronic liver disease (e.g., cirrhosis)
      5. Diabetes mellitus

Source: L. B. Reller, et al. (eds.), *Clinical Internal Medicine*. Boston: Little, Brown, 1979:211.

A. Aerophagia, which is the excessive swallowing of air, is usually associated with abdominal fullness, gaseous eructations, and the presence of a large air bubble in the fundus of the stomach. Belching ordinarily relieves the discomfort. Pain is uncommon but when present may mimic coronary artery disease. Aerophagia is usually a habit, although it may be associated with organic disease. Many aerophagics are not aware that they are air-swallowers. Swallowed air that is not eructed passes down to the small bowel and colon. Should the air become trapped in the splenic flexure, left upper quadrant (LUQ) discomfort, which radiates to the left side of the chest, left shoulder, and sometimes the left arm, may occur. This is the splenic flexure syndrome. Relief of the pain is characteristically obtained by defecation. The diagnosis is suggested by showing large amounts of air in the LUQ on plain abdominal radiographs.

B. Abdominal pain and bloating. The primary problem is not too much gas but rather an irritable gut caused by some sort of motility disorder that causes these patients to perceive pain when the gut is distended by gas.

C. Flatulence is probably the result of a disturbance in bowel motility sometimes associated with an abnormal pain response to gaseous distention of the bowel. The possible routes by which gas may enter the GI tract are air-swallowing, bacterial fermentation in the bowel, and diffusion from the blood. Food intolerance appears to play a role in the genesis of flatulence. Milk products may cause bloating, flatulence, and diarrhea in patients with lactase deficiency. Gluten-containing foods exacerbate the symptoms of nontropical sprue. Intolerance to fatty foods is a common occurrence in patients with biliary tract or pancreatic disease. Some food intolerances are undoubtedly allergic in origin, but in the majority of cases the mechanism is not understood. Flatulence is often a noteworthy, but never the sole, symptom of malabsorptive states or intestinal disease.

Diagnostic Approach

The diagnostic approach here is similar to that discussed in the Functional Bowel Syndrome section. Identify the specific gas problem to see whether the patient is a belcher, a bloater, or a gas passer. Workup should be sufficient to convince the patient and physician that no organic gut lesion is overlooked.

Generalized

I. Ascites (discussed later in this section)
II. Intestinal obstruction
   A. Adynamic ileus
   B. Mechanical obstruction
   C. Idiopathic intestinal pseudoobstruction
III. Large intraabdominal cyst
IV. Diffuse peritonitis from any cause
V. Extreme constipation with fecal impaction
VI. Neurogenic obstruction (Hirschsprung's disease)
VII. Large retroperitoneal mass

Diagnostic Approach

I. *Initial procedures.* In addition to the history and physical examination, a hemogram, urinalysis, liver function tests, and serum and urinary amylase determinations should be performed on every patient.
II. X-ray studies
   A. Four-way abdominal films. Such films are indicated in virtually all cases, especially if intestinal obstruction is suspected. With this procedure, evaluation of the size of the liver is inaccurate, but splenomegaly can be recognized. The kidneys are usually seen as well-defined shadows on each side of the spine at approximately the level of the third lumbar vertebra. The psoas shadows extend obliquely and laterally toward the pelvis. Distortion of these shadows suggests retroperitoneal disease. A clearly defined line in the flank represents the translucent area occupied by the properitoneal fat; this line

is obliterated in the presence of abscess or infection. It is important to note the character of the gas patterns in the intestinal tract. Fluid levels, abnormal calcium deposition, intraperitoneal air, and organ displacement are also important. The nature and diagnostic implications of the many abnormalities that can occur are beyond the scope of this text, but proper interpretation is essential to accurate diagnosis.

B. Barium studies of the GI tract. When intestinal obstruction is suspected, regardless of its cause, barium x-ray studies should not be performed without consultation with the radiologist and not without detailed consideration of the clinical problem. Barium should not be used orally when perforation is suspected, when intestinal obstruction is complete, or when vomiting is persistent. Water-soluble contrast material, such as Gastrografin, should be used cautiously in patients susceptible to aspiration, to avoid pulmonary edema. With a skilled radiologist, barium enemas can be of great value in the diagnosis of colonic obstruction. If obstruction is not present, barium radiographs are indicated to look for intrinsic lesions or for displacement or alterations produced by extrinsic lesions. Unless the clinical history and physical examination strongly suggest the upper or lower GI tract, a barium enema should be obtained first because it makes subsequent preparation for upper GI and small bowel series easier for the patient.

C. Intravenous pyelogram. Retroperitoneal abnormalities often do not produce alterations of the barium radiographs. An intravenous pyelogram may be of value in defining renal pathology as well as disease in the retroperitoneum.

D. Ultrasonic scanning. This may be helpful in the diagnosis of ascites of intra-abdominal and retroperitoneal cysts, pancreatic pseudocysts, pancreatic carcinoma, aortic aneurysms or other fluid-filled lesions, and solid tumors. The procedure is most effective for upper abdominal and pelvic pathology because intestinal gas significantly interferes with sound waves.

IV. Computerized tomography (CT). CT scans, if available, may be valuable in the detection and evaluation of intraabdominal and retroperitoneal masses and liver disease, and in the diagnosis of pancreatic disease, including carcinoma.

V. Laparoscopy. This relatively safe, simple procedure is being used more frequently as a method for internal inspection of the upper and lower abdomen. The technique involves three basic steps: induction of a pneumoperitoneum, insertion of the instrument, and inspection of the superficial structures of the abdominal cavity. Best seen are significant portions of the liver, the peritoneum, the anterior wall of the stomach, the uterus, and the ovaries. The ability to obtain biopsies is an added diagnostic dimension that may save the patient from the need for surgical laparotomy.

VI. Abdominal angiography. This diagnostic procedure, although rarely needed, may be of assistance in the diagnosis of suspected masses. Vascular abnormalities of significance include vascular occlusion, vessel displacement or straightening, and the presence of a vascular blush.

VII. Paracentesis

VIII. Upper, lower GI endoscopy panendoscopy and colonoscopy can be helpful in clarifying tumors and panendoscopy can usually identify the cause of gastric outlet obstruction.

Ascites

Barry W. Frank

Definition

Ascites may be defined as an accumulation of fluid in the peritoneal cavity. The fluid is most often serous in nature.

Symptoms and Physical Examination

See Abdominal Distention.

Etiology

The most common causes of ascites are cirrhosis of the liver and congestive heart failure. Ascitic fluid may be a transudate or an exudate, or it may be chylous. The causes are listed in the following.

Transudative Ascites

I. Prehepatic causes
   - A. Right-sided heart failure
   - B. Constrictive pericarditis
   - C. Venous occlusion
     1. Supradiaphragmatic occlusion of the inferior vena cava
     2. Budd–Chiari syndrome (hepatic vein occlusion owing to thrombosis, tumor, or venous web)
     3. Venoocclusive disease secondary to hepatotoxins (e.g., seneciosis)

II. Hepatic causes
   - A. Cirrhosis of the liver
     1. Micronodular
     2. Macronodular
     3. Cardiac
   - B. Tumors of the liver (rarely)

Exudative Ascites

I. Peritonitis
   - A. Ruptured viscus
   - B. Tuberculosis
   - C. Pancreatitis
   - D. Bile peritonitis
   - E. Pelvic inflammatory disease (rarely)
   - F. Spontaneous bacteria peritonitis (SBP)

II. Tumors. Metastatic to the liver or peritoneum, or both

Chylous Ascites

I. Trauma to the cisterna chyli in the abdomen
II. Tuberculosis (occasionally)
III. Cirrhosis of the liver (occasionally)
IV. Chronic inflammation, fibrosis, or hyperplasia of the major intestinal lymphatics
V. Tumor involving the major intestinal lymphatics

Miscellaneous Causes

I. Meigs' syndrome (ovarian fibroma)
II. Myxedema
III. Endometriosis
IV. *Pseudomyxoma peritonei*
V. Anasarca with hypoalbuminemia
VI. Connective tissue diseases (rarely)

Diagnostic Approach

I. Liver function tests. Because the most common cause of ascites is liver disease, the initial laboratory tests should include a serum bilirubin, alkaline phosphatase, AST, ALT, gamma glutamyl transpeptidase, prothrombin time, and protein electrophoresis. If acute or chronic hepatitis is suspected, the serum should be examined for the presence of antigens and antibodies as outlined in the section on jaundice.

II. Diagnostic paracentesis. Diagnostic paracentesis is a valuable procedure with ascites because the character of the fluid is often helpful diagnostically. The procedure should be performed under sterile conditions. Ordinarily, 100 to 200 mL of fluid is adequate for the studies outlined in the following. It should always be performed if there is fever or abdominal pain.
   - A. Appearance of the fluid. Clear, straw-colored fluid is usually seen in liver disease or prehepatic obstruction. Bloody fluid suggests malignancy but may

occur in nonmalignant liver disease. Turbid fluid implies infection or inflammation. Milky fluid is virtually pathognomonic of chylous ascites.

B. Specific gravity. Ascitic fluid with a specific gravity greater than 1.017 is indicative of an exudative process.

C. Protein content. Ascites has been classified by measuring the ascites/serum albumin gradient that involves concomitant determinations of the albumin concentration in the two fluids. If the gradient is high (over 1.1 G/dL), it almost always indicates liver disease or cardiac failure. If the gradient is less than 1.1 G/dL, the cause is the peritoneum. This simple test has over 90% sensitivity and specificity.

D. WBC count. White counts are often variable. However, when the count is greater than 900/mm^3, peritonitis is probable. A predominance of lymphocytes suggests tuberculosis.

E. Amylase. Amylase levels above 500 U suggest pancreatitis or pancreatic ascites.

F. Serum electrolytes. Electrolyte determinations are of little diagnostic value.

G. Stains and cultures for bacteria. A Gram stain should be performed routinely to detect suspected or unsuspected infection of the peritoneum. Routine cultures for aerobic and anaerobic organisms, acid-fast bacilli, and fungi are advisable.

H. Triglycerides. Although frank chylous ascites is detectable by the naked eye, a slightly turbid fluid may pose a diagnostic problem. The presence of chylous ascites is confirmed by finding elevated triglyceride levels in the fluid.

I. Cytologic study. When intraabdominal malignancy is seen with "studding" of the peritoneum by tumor nodules and ascites, confirmation of the diagnosis can be obtained by histologic study of smears prepared from a centrifuged specimen of ascitic fluid.

III. Barium studies of the GI tract. Contrast examinations are often necessary in the patient with ascites of unknown cause. In addition to disclosing intrinsic disease of the GI tract and varices, displacement of the gut by extrinsic lesions may be revealed.

IV. Abdominal CT scan or ultrasound studies. These may be helpful in the diagnosis of intraperitoneal masses, organ enlargement or displacement, and enlarged lymph nodes. When the physical examination is equivocal, ultrasound is the best test to confirm the presence of ascites.

V. Needle biopsy of the liver. Percutaneous liver biopsy should be considered in most cases when liver abnormality is suspected as the cause of ascites. It is useful in establishing the histologic diagnosis in primary disease of the liver, detecting malignancy, and revealing hepatic manifestations of systemic disease (e.g., tuberculosis). Significant ascites is a contraindication to percutaneous liver biopsy.

VI. Selective angiography and retrograde venous catheterization. Selective arteriography of the hepatic and splenic arteries with delayed films to visualize the portal vein may be helpful in ascites of obscure cause. Retrograde venous catheterization may be useful in the diagnosis of cardiac and pericardial disease.

VII. Laparoscopy. The introduction of pneumoperitoneum, insertion of a laparoscope, and inspection of the abdominal contents are useful for the direct visualization of the liver, gallbladder, pelvic organs, omentum, and peritoneal surfaces. Biopsies can be taken for histologic examination and culture. This procedure should be strongly considered when ascites is associated with a pelvic tumor, positive cytologic examination result, or suspected tuberculous peritonitis.

VIII. Exploratory laparotomy. In the vast majority of cases, it is possible to discover the cause of ascites by means of the foregoing procedures. However, should the cause remain undetermined after adequate study, exploratory laparotomy may be necessary to establish a correct diagnosis.

Physical Examination

I. Inspection may reveal localized enlargement (e.g., abscess, tumor).

II. Auscultation may reveal a bruit (tumor), venous hum (portal hypertension with collateral flow), or friction rub (tumor).

III. Percussion (punch) may detect tenderness (hepatitis, biliary tract disease, congestion).

IV. Palpation may reveal the firm liver edge of cirrhosis or the "rock hard" edge of malignancy. Nodularity suggests cirrhosis or tumor. Pulsations suggest tricuspid regurgitation. A palpable gallbladder suggests pancreatic carcinoma with bile duct obstruction.

Laboratory Data

See Jaundice.

Hepatomegaly

Andrew Mallory

Definition

Hepatomegaly is defined as an enlarged liver. Defining only the location of the inferior edge of the liver on physical examination is inadequate in assessing liver size. Liver size can be best estimated on physical examination by gentle percussion in the midclavicular line during quiet breathing. The inferior margin may also be located by palpation. The normal range of size varies with height and sex. Hard percussion results in smaller estimations. In one study, normal liver size was defined as 8 ± 2 cm for females and 10 ± 2 cm for males.

Liver scans and abdominal CT scans can also give useful indications of liver size. Plain films and barium studies are often misleading.

Etiology

Common causes of hepatomegaly are listed in Table 5-8.

Table 5-8. Causes of hepatomegaly

Venous congestion of the liver
Congestive heart failure*
Obstruction of vena cava or hepatic veins (e.g., tumor, thrombosis)
Constrictive pericarditis
Obstruction of the common bile duct*
Gallstones
Tumors
Pancreatitis
Infectious diseases
Localized infections (e.g., amebic or pyogenic abscess)
Diffuse infections (e.g., viral hepatitis,* tuberculosis, schistosomiasis)
Hepatitis associated with systemic infections
Infiltrative diseases
Fatty liver (e.g., alcohol,* diabetes)
Amyloidosis
Sarcoidosis
Glycogen storage diseases
Neoplasms (e.g., primary, metastatic*)
Other
Toxin- and drug-induced hepatitis (including alcohol*)
Autoimmune hepatitis
Cirrhosis (e.g., alcoholic,* postnecrotic, biliary)
Wilson's disease
Hemochromatosis

* Most common causes.

Source: L. B. Reller, et al. (eds.), *Clinical Internal Medicine.* Boston: Little, Brown, 1979. P. 211.

Diagnostic Approach

History
A history of heart failure, alcoholism, febrile illness, gallstones, foreign travel, diabetes, drug-taking, or symptoms suggesting malignancy is helpful. A family history of liver disease suggests Wilson's disease, hemochromatosis, or alpha-1-antitrypsin deficiency.

Physical Examination
1. Inspection may reveal localized enlargement (e.g., abscess, tumor).
2. Auscultation may reveal a bruit (tumor), venous hum (portal hypertension with collateral flow), or friction rub (tumor).
3. Percussion (punch) may detect tenderness (hepatitis, biliary tract disease, congestion).
4. Palpation may reveal the firm liver edge of cirrhosis or the "rock hard" edge of malignancy. Nodularity suggests cirrhosis or tumor. Pulsations suggest tricuspid regurgitation. A palpable gallbladder suggests pancreatic carcinoma with bile duct obstruction.

Laboratory Data
See Jaundice, next section.

Jaundice

Andrew Mallory

Definition
Jaundice is the yellow discoloration of the tissues caused by retention of bilirubin. When serum bilirubin exceeds 3 mg/100 mL, jaundice is usually present.

Etiology
I. Increased quantity of bilirubin presented to the liver (e.g., hemolysis, transfusion of stored blood, hematoma with resorption)
II. Decreased hepatobiliary excretion of bilirubin
   A. Defective uptake and transport of bilirubin by the liver cell (e.g., drug effects).
   B. Defective conjugation of bilirubin by the liver cell (e.g., Gilbert's syndrome, drug effects, breast feeding jaundice)
   C. Defective excretion of bilirubin by the liver cell (e.g., drug effects, Dubin–Johnson syndrome, idiopathic cholestasis of pregnancy)
   D. Defective transport of bilirubin by the biliary system (e.g., common bile duct stone, pancreatic carcinoma, bile duct tumors)

   The examples given are conditions thought to arise exclusively from the mechanism stated. Many common causes of jaundice are owing to combinations of these mechanisms. In clinical practice, the most common causes of jaundice are hemolysis, viral hepatitis, alcoholic liver disease, drugs, bile duct calculi, pancreatic carcinoma, and carcinoma metastatic to the liver.

Clinical Features
History
I. The insidious onset of anorexia, nausea, malaise, and fever in a young patient prior to the onset of jaundice suggests viral hepatitis
II. Recurrent episodes of epigastric or right upper quadrant pain prior to the onset of jaundice in a middle-aged or elderly patient suggest biliary tract disease. These symptoms together with high fever and appropriate physical signs suggest cholangitis.
III. A long history of alcohol abuse is consistent with alcoholic liver disease.
IV. Chronic weight loss and weakness preceding jaundice suggest malignancy. These symptoms, when accompanied by depression, phlebitis, or epigastric pain, point to pancreatic carcinoma.

V. The onset of jaundice in relation to the administration of certain drugs or anesthetic agents suggests drug-induced liver disease. The occupational history may suggest a toxin-induced liver disease.
VI. A family history of jaundice raises the possibility of hemolytic disorders, Wilson's disease, Gilbert's syndrome, and alpha-1-antitrypsin deficiency.

Physical Examination
Physical findings helpful in evaluating jaundice and the diseases suggested by these findings are listed in the following.

I. Spider nevi, gynecomastia, white nails, palmar erythema, and Dupuytren's contractures suggest cirrhosis.
II. Ascites, splenomegaly, dilated abdominal wall veins, and periumbilical venous hum suggest portal hypertension.
III. Kayser–Fleischer rings and neuropsychiatric changes suggest Wilson's disease.
IV. Gray pigmentation suggests hemochromatosis.
V. Excoriations and xanthomas suggest primary biliary cirrhosis.
VI. Severe left- or right-sided heart failure suggests passive congestion or hepatocellular ischemia.
VII. Palpable nontender gallbladder suggests pancreatic carcinoma.

Diagnostic Approach
I. Biochemical assessment
   A. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) (formerly serum glutamic-oxaloacetic transaminase [SGOT] and serum glutamic-pyruvic transaminase [SGPT], respectively). AST is found in the following organs in order of decreasing concentration: heart, liver, skeletal muscle, kidney, and pancreas. ALT, although widely distributed in the body, is predominantly confined to the liver and is, therefore, more specific for liver disease. These two tests are sensitive indicators of hepatocellular necrosis. In general, levels greater than 10 times the upper limit of normal indicate acute hepatocellular injury as seen, for example, in viral hepatitis, drug- or toxin-induced hepatitis (other than alcohol), ischemic liver disease, or, transiently, cholangitis. Lesser elevations are nonspecific and may be seen with virtually any other form of liver injury, including cholestasis or infiltrative liver disease. Alcoholic liver disease is only rarely associated with AST elevations in excess of 10 times normal. AST:ALT ratio greater than two suggests alcoholic liver disease. In general, the degree of elevation of AST or ALT has little prognostic value.
   B. Serum alkaline phosphatase (SAP). This normally derives from liver, bone, placenta, and intestine. The main clinical value of SAP is its sensitivity in detecting early intrahepatic or extrahepatic bile duct obstruction (often before jaundice develops) and in pointing to the presence of infiltrative diseases (tuberculosis, sarcoidosis) or space-occupying lesions (abscess, neoplasm). In addition, SAP helps differentiate hepatocellular from obstructive jaundice: high values (five times normal) favor obstruction, and a normal SAP virtually excludes this diagnosis.

      SAP also rises in diseases of bone and in pregnancy. Greater specificity for liver disease can be provided by the serum gamma glutamyl transpeptidase, which is not elevated by bone disease or pregnancy. The serum 5-nucleotidase is also elevated in liver disease but not in bone disease, although it may increase in pregnancy. The heat-inactivation test is less helpful in assessing the source of SAP.
   C. Serum gamma glutamyl transpeptidase (SGGT). This enzyme is found in kidney, liver, and pancreas. Elevated values are most closely associated with SAP elevations. The main clinical value of this enzyme determination is its specificity for liver disease. In patients with elevated SAP owing to bone disease or pregnancy, SGGT levels are usually normal.

D. Serum bilirubin. An elevated serum bilirubin connotes either the presence of hepatobiliary disease, overproduction of bilirubin, or both. The direct-reacting (conjugated) bilirubin is specific for the presence of hepatobiliary disease and is a sensitive index of mild hepatic disease; elevations are found in more than 30% of patients with liver disease whose total serum bilirubin is normal. A mild increase in serum direct bilirubin results in urinary excretion of bilirubin: hence, a urine bilirubin determination may prove sensitive in detecting mild hepatic disease.

The height of the serum bilirubin is of only limited diagnostic value in the individual patient. Elevations over 35 mg/100 mL generally indicate the presence of renal insufficiency in addition to hepatobiliary disease. Uncomplicated hemolysis seldom causes a total serum bilirubin of more than 5 mg/100 mL unless hepatobiliary disease is also present.

E. Prothrombin time (PT). The PT reflects the activities of fibrinogen, prothrombin, and factors V, VII, and X. It is dependent on hepatic synthesis of these factors and intestinal absorption of vitamin K. Malabsorption of vitamin K occurs with impaired lipid absorption, as is commonly seen with bile salt deficiency secondary to prolonged cholestasis.

The PT is helpful in assessing the extent of liver damage and in the prognosis. Little diagnostic significance should be given to a prolonged PT (3 sec above control) unless it is measured at least 24 hours after parenteral injection of vitamin K. Hypoprothrombinemia related to bile salt deficiency will be corrected, whereas that secondary to hepatocellular disease will not.

F. Serum proteins. The serum albumin concentration, like the PT, is a good indicator of hepatic functional reserve, but because of its half-life (20 to 26 days), changes are slow in reflecting liver damage. The alpha-1-globulins tend to be low in hepatocellular disease. An absent alpha-1-globulin suggests a homozygous alpha-1-antitrypsin deficiency. The gamma globulin concentration tends to increase with most forms of chronic liver disease. Marked increases (e.g., serum levels 3 g/100 mL) are suggestive of autoimmune chronic active hepatitis.

II. Serologic tests

A. Antimitochondrial antibody. Significant titers of antimitochondrial antibody are seen in over 85% of patients with primary biliary cirrhosis. Although not specific for this disease (e.g., elevated titers are occasionally seen with chronic active hepatitis), absence of the antibody is strong evidence against the diagnosis of primary biliary cirrhosis.

B. Hepatitis antigens and antibodies

1. Hepatitis A
   a. IgM hepatitis A antibody (IgM Haab). This antibody is present in the serum at the onset of symptoms and usually disappears within 3 to 6 months.
   b. IgG hepatitis A antibody (IgG Haab). This antibody appears during convalescence and persists indefinitely.
2. Hepatitis B
   a. Hepatitis B surface antigen (HBsAg). This antigen is the first serologic marker to appear and usually disappears within 3 months.
   b. Hepatitis B surface antibody (HBsAb). This antibody becomes detectable in the serum at a variable time after disappearance of the antigen and usually persists for life.
   c. Hepatitis B core antibody (HBcAb). This antibody usually appears shortly after HBsAg and usually persists for life. It is present during the "window" between disappearance of HBsAg and appearance of HBsAb. IgM hepatitis B core antibody titers can also be determined. High serum titers usually are present early in the course of hepatitis B and disappear within 3 to 4 months.
   d. Hepatitis Be antigen (HBeAg). This antigen appears within a few days of the appearance of HBsAg in most primary infections. It usually disappears just before the disappearance of the HBsAg in self-limited infections. Persistence of this antigen suggests chronic infection and is associated with a high degree of contagiousness. If this antigen does disappear from the serum, it is replaced by the hepatitis Be antibody.
3. Hepatitis C. Hepatitis C virus commonly causes both posttransfusion and community-acquired non-A, non-B hepatitis. The recombinant immunoblot assay (RIBA) is more specific than the original ELISA antibody test, but may take several months to become detectable and does not identify all cases. The most specific indication of infection is the presence of HCV RNA, detected by polymerase chain reaction, but this test is expensive.
4. Delta hepatitis. The delta agent is a defective virus that requires the presence of hepatitis B virus. Infection with this virus may occur simultaneously with hepatitis B or can present as a superinfection in an individual who is a chronic carrier of hepatitis B virus. Sensitive serologic assays for delta antibody are available.

III. Other tests

A. Upper GI series may reveal enlargement of the head of the pancreas.

B. Ultrasound has become the procedure of choice for detecting gallstones within the gallbladder. Ultrasound and CT scanning are useful in detecting bile duct enlargement, pancreatic tumors, and space-occupying lesions in the liver. Magnetic resonance imaging (MRI) is comparable to CT scanning for assessing the liver, but is usually more expensive. Spiral CT and MRI cholangiography are becoming more widely available and hold promise for increased sensitivity in detection of bile duct stones.

C. A radionuclide biliary scan (e.g., HIDA scan) is especially useful in evaluating the patient with suspected acute cholecystitis. Visualization of the bile ducts but not the gallbladder on acute and delayed films suggests cystic duct obstruction.

D. Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiopancreatography provide more detailed information regarding the cause of extrahepatic obstruction. With the latter technique, the pancreatic duct usually can be examined also. Choosing between these two procedures depends on such variables as blood coagulation studies, the general condition of the patient, the need to visualize the pancreatic duct, and local expertise.

E. Percutaneous liver biopsy is useful in diagnosing the cause of jaundice when the preceding tests have failed and in assessing the activity of disease (e.g., in chronic active hepatitis).

General Comments

In most cases of jaundice, a detailed history and careful physical examination will establish the diagnosis. Biochemical tests usually serve to confirm the diagnosis. More sophisticated (and expensive) tests should be required only in the minority of cases, when the diagnosis remains in doubt.

6. HEMATOLOGIC PROBLEMS

Anemia

Robert G. Chapman

Definition

I. Anemia is a subnormal total red cell volume. The normal volume in men is 32 ± 6.5 mL/kg; in women it is 25 ± 6.5 mL/kg. Persons living at elevations higher than 8,000 to 9,000 feet above sea level have an increased total red cell volume. Below this altitude, normal increases are of smaller magnitude and difficult to detect.

II. The total red cell volume can be measured with ^{51}Cr- or ^{32}P-labeled red cells or it can be calculated from the measured plasma volume and hematocrit reading. Simple tests measuring red cell concentration (hemoglobin and hematocrit values, red cell count) are usually used in place of the expensive and time-consuming total volume determinations. A normal plasma volume is assumed in evaluating the results.

Normal Values

I. The normal hemoglobin concentration in men is not less than 13.8 g/100 mL; in women it is not less than 12 g/100 mL. The normal hematocrit value in men is not less than 41%; in women, not less than 36%. The normal red cell count in men is not less than 6.9 million/mm^3; in women, not less than 6.3 million/mm^6. Of these, the red cell count is the least reliable. Automated determinations calculate the hematocrit value from the red cell count and the average individual red cell volume. Hematocrit readings obtained by this method are not as reliable as those measured directly by centrifugation. The ratio of hematocrit value to hemoglobin value is close to 3:1. Significant deviations from this ratio on automated counts should be questioned.

II. Dehydration, such as occurs in vomiting and diarrhea, may deplete the plasma volume and produce a rise in hemoglobin or hematocrit value without changing the total red cell volume. Pregnancy and congestive heart failure, on the other hand, have the opposite effect. When there is a rapid loss of blood, the hemoglobin and hematocrit values do not reflect the degree of blood loss until readjustment of the plasma volume has taken place. Therefore, under all of the foregoing circumstances, caution must be employed in using the hemoglobin and hematocrit values as indicators of the red cell volume.

Causes of Anemia

Inadequate Erythropoiesis

I. Lack of essential nutrient (e.g., vitamin B_{12}, folic acid, iron)
II. Injury to the marrow (e.g., ionizing radiation)
III. Marrow inhibition (e.g., drug, immunologic agent)
IV. Marrow replacement (e.g., neoplasm, fibrosis)
V. Hereditary defect
VI. Endocrine deficiency (e.g., hypothyroidism, hypopituitarism, renal failure)
VII. Idiopathic ("refractory")

Bleeding

I. Acute
II. Chronic, with secondary iron deficiency

Hemolytic

I. Intracorpuscular defect
   A. Abnormal hemoglobin (S, C, D, E, unstable)
   B. Defective globin synthesis (thalassemia)
   C. Defective heme synthesis (porphyria)
   D. Defective carbohydrate enzyme (G-6-PD, pyruvate kinase)
   E. Membrane defect (hereditary spherocytosis, elliptocytosis)
   F. Paroxysmal nocturnal hemoglobinuria
II. Extracorpuscular defect
   A. Secondary to:
      1. Physical agent (e.g., water, thermal injury, microangiopathy)
      1. Chemical agent (e.g., venom, drug)
      2. Infection (e.g., malaria, septicemia)
      6. Neoplasm (especially lymphoma)
      4. Connective tissue disease (e.g., lupus)
      5. Splenomegaly
      6. Isoimmunization (newborn, transfusion)
      7. Paroxysmal cold hemoglobinuria
   B. Primary, idiopathic (no underlying disease), usually autoimmune

Diagnostic Approach

I. In order to arrive quickly and efficiently at a correct diagnosis of the kind of anemia, a logical, stepwise procedure should be followed.
   A. Study the history and physical findings.
   B. Attempt to classify the anemia into hemolytic, blood loss, or bone marrow failure types, based on the pathophysiologic mechanism responsible for the red cell deficit.
   C. Perform more detailed tests and, at times, institute a therapeutic trial to determine the specific cause.
II. The initial laboratory evaluation reports hemoglobin, hematocrit, and red cell count and calculates the mean red cell volume (MCV), mean hemoglobin per red cell (MCH), and the mean concentration of hemoglobin in red cells (MCHC). These red cell indices have the following values normally: MCV 90 ± 12 fL, MCH 30 ± 3 pg/cell, and MCHC 34 ± 2 g/dL mL of red cells. Values are the same for men and women. Red size variability is 11.5% to 14.5%. Listed in the following is a classification of anemias based on these indices.

MCV	Etiology of Anemia
Increased	Vitamin B_{12} or folic acid deficiency owing to pernicious anemia (lack of intrinsic factor), malabsorption, tapeworm, or drug (phenytoin [Dilantin], antifolate)
	Alcoholism and liver disease
	Refractory anemia
	Increased reticulocytes
Normal	Acute blood loss
	Uremia
	Chronic disease
	Hemolysis, including hereditary spherocytosis
	Marrow failure (aplasia, x-ray or drug, invasion)
Decreased	Chronic disease
	Toxin (e.g., lead)
	Low MCHC (iron deficiency, thalassemia, sideroblastic, refractory)

Electronic sizing of red cells (MCV) is more sensitive than microscopic evaluation in detecting macrocytosis. When MCV is increased without obvious cause, it is worth evaluating the patient for vitamin B_{12} or folic acid deficiency.

III. Microscopic examination of the peripheral blood smear is an important supplement to the indices in evaluating red cell abnormalities. The smear should be examined in a systematic way for red cell size, shape, and color. The thin feathered edge is a good place to see polychromatophilic cells (reticulocytes) as well as platelet clumps and the larger white cells. Other features of red cell morphology are better evaluated in the body of the smear, just proximal to the feathered part, where cells are more evenly distributed but not overlapping. Red cell size varies mildly. Greater than normal variation (anisocytosis) is seen in some hemolytic anemias owing to the contrast between spherocytes and large reticulocytes. Size also varies because of fragmentation (schistocytes) seen in disseminated coagulation or abnormally functioning prosthetic heart valves.

Red cell shape is normally round to slightly oblong. Abnormal variation in shape (poikilocytosis) is a prominent feature of thalassemia and, to a lesser degree, of severe iron deficiency. It is seen also in patients with extramedullary blood formation (myelogenous leukemia, myeloid metaplasia) or those without spleens. Red cells may lose their smooth surface to become burr- or spur-shaped echinocytes because of liver disease or, rarely, secondary to hereditary plasma lipid abnormalities (acanthocytes). They can be elliptical (hereditary elliptocytosis).

Red cell color reflects the amount and distribution of hemoglobin within cells. Normally the central third of red cells is quite pale compared to the periphery, reflecting the cell's biconcave shape. The size of the pale center increases in both iron deficiency and thalassemia. This is also seen in a portion of the red cells in refractory anemias. An unusual hemoglobin distribution in liver disease (and hemoglobin C disease) gives the cells a targetlike appearance. This is because of the extra cell membrane surface area from uptake of extra unesterified cholesterol in liver disease. Other cell color abnormalities include distorted central pallor (stomatocytes), seen for both hereditary and alcoholic reasons, and basophilic cell inclusions. Fine blue stippling is seen in thalassemia (excess alpha chains), coarser stippling in toxic conditions (lead poisoning). Larger, round multiple Heinz bodies suggest drug damage in enzyme deficient cells, whereas single inclusions (Howell–Jolly bodies) are seen in the absence of a spleen. The presence of nucleated red cells suggests marrow stress or invasion by abnormal tissue and warrants bone marrow biopsy.

IV. Anemia results from the inadequate formation of red cells, excessive blood loss, increased destruction of red cells, or a combination of these factors. Determination of the reticulocyte count and the serum bilirubin level, together with an assessment of the rate of development of the anemia, suggests the mechanism in most cases.

V. The reticulocyte count, carried out better by flow cytometry than manually on smear, and better expressed as the number per cubic millimeter than as a percentage (normal, 25,000 to 75,000/mm^3), indicates the rate of red cell formation. As red cell formation increases, reticulocytes are released earlier from the marrow. Division of the reticulocyte number by a factor increasing from 1.0 to 2.5 as the severity of anemia increases has been suggested as a method to derive a red cell production index corrected for the distortion caused by this increasingly premature release. A high count, especially if there is no improvement in the anemia over a week or more, is good evidence for excessive red cell loss. A low count, especially in the face of anemia to which a normal marrow should respond, is very good evidence for bone marrow failure. It should be noted, however, that it takes 5 to 7 days after sudden hemorrhage or hemolysis before reticulocytosis occurs. The marrow response to a hemolytic anemia may be blocked temporarily by an inflammatory process, resulting in a temporary depression of the reticulocyte count and a rapid worsening of the anemia.

VI. The serum bilirubin (unconjugated) level, which normally does not exceed 0.8 mg/100 mL, is an indicator of red cell destruction. It is also affected by liver function. Increased red cell destruction (hemolysis) may raise the bilirubin level to 2 or perhaps 3 mg/100 mL but not higher unless liver function is also impaired. Mild hemolysis may not elevate the serum bilirubin at all. Hemoglobin loss from the body by hemorrhage or hemoglobinuria, of course, does not result in increased production of bile pigments. It should be remembered that anemia without

increased hemolysis produces less than normal quantities of bilirubin. Hence, serum bilirubin levels in nonhemolytic anemias should be below 0.8 mg/100 mL.

VII. Mild hemolytic disease with a normally functioning bone marrow may not cause anemia. This so-called compensated hemolysis may produce a reticulocytosis and possibly an elevated serum bilirubin level.

VIII. In the acutely ill patient who must be treated before a cause for anemia can be established, it is important to draw blood samples before therapy is begun. In all cases, the reticulocyte count and the serum bilirubin should be determined at the time of the initial hemogram. Blood samples should also be retained for the following tests: (a) serum iron and iron-binding capacity and serum ferritin, (b) serum haptoglobin, (c) serum B_{12} and folate levels (red cell folate even better than serum level), (d) serum protein electrophoresis, and (e) hemoglobin electrophoresis. Because other red cell studies (e.g., fragility, autohemolysis, enzyme activity) require relatively fresh samples of blood, it is impractical to save blood for them. The first three tests listed are markedly affected by transfusion and treatment with vitamin B_{12} or folic acid. It is therefore essential to hold the pretreatment blood samples until it is decided whether these tests should be performed.

Initial Evaluation

History

Many facets of the history and physical examination are potentially helpful in the evaluation of anemia. Only the most important and useful ones are given here.

I. Any past anemia, the therapy employed, and the response to treatment should be reviewed in order to ascertain whether the present and previous anemia are related. Chronic anemia or recurrent episodes of anemia over a period of years suggests a hereditary disease, whereas anemia of recent onset suggests an acquired disorder. Acceptance of any explanation for prior anemia must be predicated on objective evidence of an adequate response to specific measures. Anemia that is insidious in onset and gradual in development suggests bone marrow failure. Because of the relatively long lifespan of the red cell (4 months), failure of effective erythropoiesis takes some time to become apparent. Anemia that is rapid in its onset suggests either bleeding or hemolysis as a probable cause.

II. Inquiries should be made concerning diet, alcohol intake, medications used by the patient, and possible blood loss. An inadequate diet and excessive use of alcohol suggest possible folic acid deficiency. A review of the patient's medications is important because drugs, including recreational nitrites, may cause hemolysis, megaloblastic anemia, or bone marrow depression. Questions related to bleeding are especially important. Black stools, especially if they are foul-smelling and sticky, may indicate intestinal bleeding, unless the patient is taking iron. Previous subtotal gastrectomy, often for bleeding ulcer, is frequently associated with continued iron deficiency anemia owing to either iron malabsorption or persistent bleeding. In women, menorrhagia may be responsible for excessive iron loss. This symptom is difficult to evaluate because many women do not know what "normal" bleeding is. Large menstrual blood losses may result in iron deficiency anemia. Measurements have shown that women who bleed heavily may lose about 1 pint of blood per period, representing a loss of about 200 mg of iron. Pregnancy requires additional iron intake and nursing thereafter will remove additional iron stores. Intensive exercise, especially distance running, is associated with mild anemia, possibly owing to trauma or minor blood loss associated with an iron deficiency that is still poorly understood.

III. The family history is important in the hereditary anemias, especially in those with an autosomal dominant or sex-linked pattern. Inquiry should be made about anemia, jaundice, gallbladder disease, and splenectomy in blood relatives.

Symptoms

I. Dyspnea, palpitation, and fatigue are common, although nonspecific, complaints.

II. Pallor may be noted by the patient or family, but frequently is missed by both.

III. Jaundice, similarly, may be present but overlooked.

IV. Symptoms of postural hypotension are likely to occur when whole blood is lost rapidly.

V. Lifelong hemolysis may be asymptomatic except for the development of cholelithiasis at an early age and the occurrence of crises of abdominal pain or jaundice and weakness, or both.

Physical Examination

The physical examination may be helpful in detecting anemia, bleeding, jaundice, or hemolysis, and perhaps its cause. Most often, however, the cause of the anemia is left unresolved by examination. Marked postural changes in pulse and blood pressure usually indicate rapid loss of whole blood. These signs may occur before changes in hemoglobin or hematocrit values become apparent. Estimation of the patient's state of hydration is necessary for the proper evaluation of these parameters. Pallor, of course, suggests anemia; when associated with jaundice, it may be indicative of hemolysis. Petechiae or purpura suggests the presence of a disorder that is also thrombocytopenic. Hemorrhages in the eyegrounds may occur in severe anemia from any cause. Glossitis is often seen in pernicious anemia or severe iron deficiency. Hemic murmurs are commonly heard in many severe anemias. Careful palpation for splenomegaly is important in all patients with anemia. Splenomegaly may be owing to congestion (e.g., cirrhosis of the liver), hemolytic disorders, infections, connective tissue disease, or infiltrate or neoplastic disorders. The presence of lymphadenopathy suggests the possibility of infectious disease, connective tissue disorders, or infiltrative lesions. Poorly healing shin ulcers suggest chronic hemolytic disease. Assessment of proprioception, best determined by position sense in the toes, may provide a clue to spinal cord involvement in vitamin B_{12} deficiency. Examination of the stool for occult blood is mandatory. A negative result, however, does not exclude the possibility of slight or intermittent bleeding. Iron therapy makes the stools black but does not invalidate the test for blood (Fig. 6-1).

Anemia Caused by Bone Marrow Failure

Diagnostic Approach

Peripheral Blood Count and Smear

I. Abnormality of peripheral blood cells other than red cells indicates a widespread marrow disorder. Vitamin B_{12} deficiency and folic acid deficiency both produce thrombocytopenia and neutropenia. Hypersegmented neutrophils with more than five nuclear lobes occur commonly in both conditions. Pancytopenia may also occur in bone marrow injury or marrow replacement. The peripheral blood smear may also be helpful in differentiating between leukemia and neoplasm metastatic to the marrow. Although there are exceptions, the presence of immature white cells in the smear suggests leukemia, whereas a mature white cell population indicates metastatic malignancy.

II. The red cell structure is not always abnormal in marrow failure anemia. Thus, in the anemia of renal disease, usually responsive to treatment with erythropoietin, the red cells look normal, but there is a lack of polychromatophilic cells (reticulocytes on Wright's stain). Hypochromia (MCHC 31 g/100 mL RBC) indicates hemoglobin deficiency, not iron deficiency. Its most common causes are iron deficiency and thalassemia. The presence of basophilic stippling in the large polychromatophilic red cells strongly favors the diagnosis of thalassemia over that of iron deficiency. The finding of similar blood smears in the patient's blood relatives, together with the demonstration of increased hemoglobin A_2 or F on hemoglobin electrophoresis, helps to establish the diagnosis of -thalassemia. A mixed population of normal and hypochromic red cells is sometimes seen in untreated patients with poorly defined refractory anemias, some of which may terminate in acute granulocytic leukemia. Anisocytosis (abnormal variation in red cell size) is not a common feature of marrow failure anemia unless there is considerable poikilocytosis (abnormal variation in red cell shape). Marked poikilocytosis is a feature of thalassemia and, to a lesser degree, of iron deficiency. It may also be seen in severe vitamin B_{12} or folic acid deficiency and in the hemoglobinuric hemolytic diseases (artificial heart valve-induced, paroxysmal nocturnal

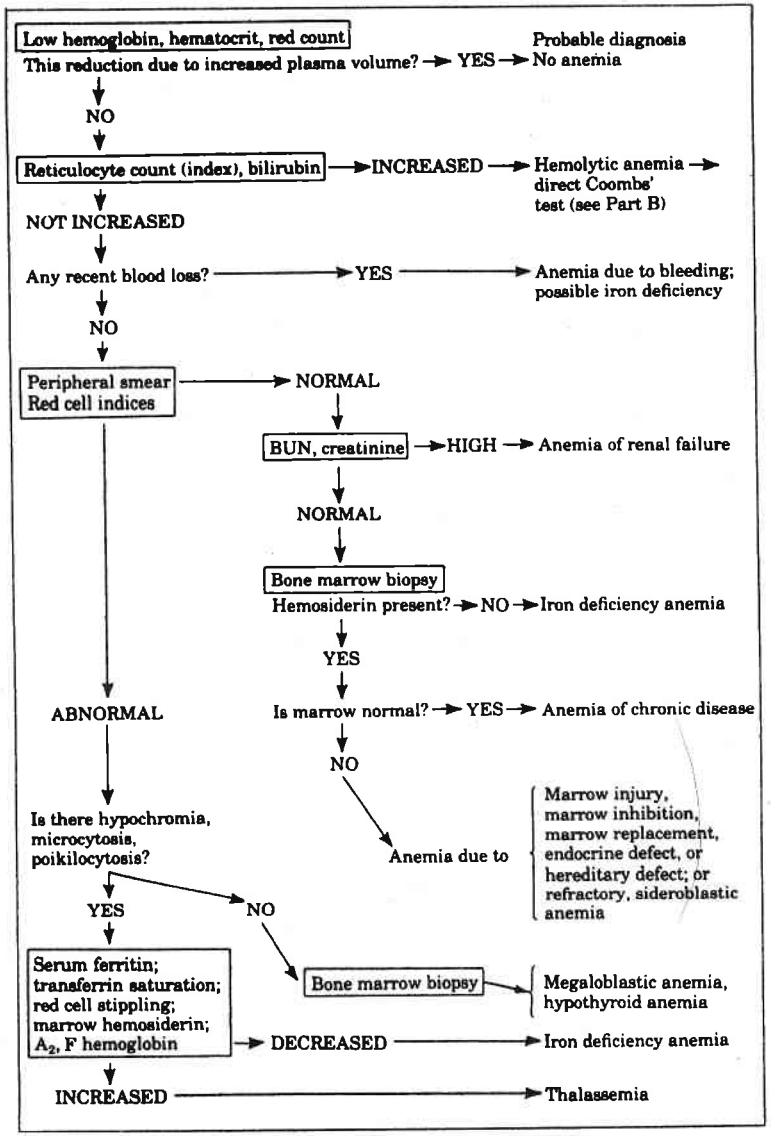

Fig. 6-1. A, B: Laboratory approach to the diagnosis of anemia.

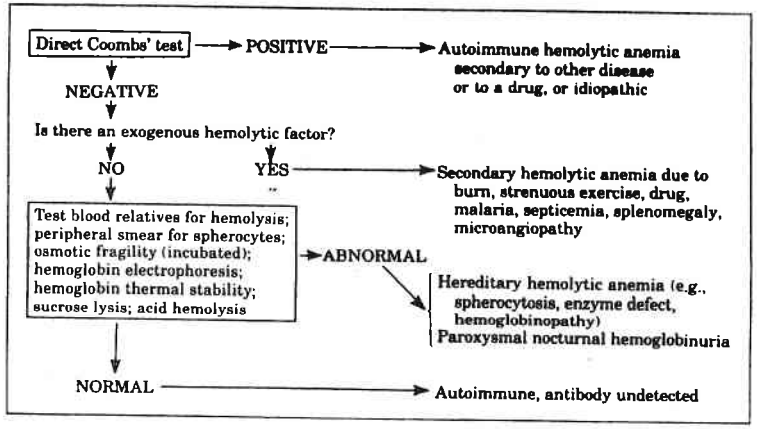

Fig. 6-1. *Continued.*

hemoglobinuria, hemolytic uremic syndrome), especially if iron deficiency becomes a secondary effect. Macrocytosis is good evidence for vitamin B_{12} or folic acid deficiency, but concomitant iron deficiency will diminish the distinctive red cell changes in these conditions.

Bone Marrow Biopsy

Bone marrow biopsy is a most important procedure in the diagnosis of marrow failure anemia. Although marrow smears are useful in detecting the abnormal megaloblastic maturation of vitamin B_{12} or folic acid deficiency, histologic sections of the marrow, obtained preferably by core biopsy rather than by aspiration, are of much greater value. Sectioned material is the only reliable method for evaluating general marrow cellularity and the distribution of cell types. Fibrosis and the serous fat atrophy of malnutrition or hypothyroidism can be detected only in sections. Packed tumor cells, which may not aspirate for smearing, are readily identified. Moreover, the reticulum cells, in which hemosiderin is stored, do not appear readily in aspirates. Thus, it is essential to have sectioned material, stained with Prussian blue, for the evaluation of iron stores. The bone marrow findings in various types of marrow failure anemia are as follows:

I. Generalized hypocellularity suggests a toxic injury to the marrow by drugs, chemicals, ionizing radiation, or possibly autoimmune mechanisms. It may also be seen in hypothyroidism or malnutrition.
II. Normal cellularity, except for a lack of erythroid tissue, suggests an immunologic cause, as may occur occasionally in thymoma; it may also be drug related.
III. Any cellularity with a lack of hemosiderin establishes the diagnosis of iron deficiency.
IV. General hypercellularity of all marrow elements is seen in vitamin B_{12} and folic acid deficiency, which would also display abnormal megaloblastic cell maturation. Patchy hypercellularity is also a finding in marrow fibrosis.
V. Hypercellularity with large numbers of abnormal cells is found in acute leukemia, lymphoma, multiple myeloma, and metastatic malignancy.
VI. Hypercellularity owing to increased erythroid tissue is observed in thalassemia and is often striking in the idiopathic refractory marrow failure anemias.

Routine Laboratory Tests

I. Most important are renal function tests (blood urea nitrogen [BUN] or serum creatinine). Marrow suppression, with its concomitant anemia, is a common

occurrence in renal failure. Sometimes the anemia is severe before other symptoms and renal insufficiency are evident.

II. Mild anemia resulting from marrow suppression is also a frequent finding in chronic illness, such as rheumatoid arthritis or infectious disease. An increased sedimentation rate and varying degrees of diffuse hpergammaglobulinemia frequently are associated findings.

Special Laboratory Tests

I. Decreased blood levels of vitamin B_{12} and folic acid may indicate which substance is lacking in a megaloblastic anemia. The normal values for serum vitamin B_{12} and folate exceed 180 pg/mL and 6.1 ng/mL, respectively, and red cell folate over 125 ng/mL.

II. The serum iron and iron-binding capacity, from which the saturation of the iron-binding globulin is calculated, may help demonstrate inadequate iron stores. Saturation less than 16% is seen in iron deficiency anemia, especially when the hemoglobin is under 8 g/100 mL. Similar desaturation may also occur in a wide variety of inflammatory conditions (e.g., rheumatoid arthritis, infections). Serum ferritin determination (normal, 12 to 300 ng/mL) can be a more reliable indicator of iron stores in the presence of inflammation, but low normal levels (13 to 20 ng/mL) can be seen with iron deficiency, and the levels rise in liver and other diseases. Bone marrow sections stained for hemosiderin are the most reliable indicators of iron stores. Lack of marrow iron in anemia is diagnostic of iron deficiency anemia.

X-Ray Examination

The demonstration of metastases suggests neoplastic marrow replacement as the cause of anemia. The finding of increased density of all bones is indicative of myelosclerosis, a condition in which fibrous tissue replaces the marrow. Chest films may show evidence of a thymoma, a tumor often associated with a lack of erythroid tissue in the marrow, resulting presumably from the effects of thymic humoral factors on red cell formation. The anemia is cured or relieved by removal of the tumor.

Therapeutic Trials

Diagnosis by a well-designed therapeutic trial is appropriate in selected instances. In all trials, one agent at a time should be used. A rise in the hemoglobin and hematocrit values or an increase in the reticulocyte count is indicative of a positive response. When reticulocytosis is too slight to be detected, as may occur when the anemia is mild, one must rely on a rise in the hemoglobin and hematocrit values. Such changes are usually evident by the end of 2 weeks of treatment. A negative response does not necessarily preclude the possibility that the patient is deficient in the substance tested. For example, a patient with iron deficiency anemia may not respond to orally administered iron because of intestinal malabsorption or because a concomitant inflammatory process interferes with the marrow response to iron. Only iron that is not enteric coated should be used in these trials to ensure absorption.

I. Therapeutic trials with vitamin B_{12} or folic acid should employ very small doses (1 and 200 μg/day, respectively, administered parenterally) to avoid the cross-responsiveness of the marrow to these agents. However, when the patient is severely anemic, it is impractical to wait 1 or 2 weeks to observe the response to either folic acid or vitamin B_{12}. Therefore, large doses of both substances are often used simultaneously while waiting for the results of the serum folate and B_{12} levels to be reported.

II. Some cases of refractory marrow failure anemia, with increased iron stores and significant numbers of ring sideroblasts in the marrow, may respond slowly to large doses of pyridoxine. Because no laboratory test is currently available to predict pyridoxine responsiveness, an empiric trial of this vitamin (daily oral dosage of 200 mg) is worthwhile in this type of anemia.

III. There are also other refractory anemias (presumably based on an immune mechanism, with a predominant incidence in older women) that respond to treatment with corticosteroids. A trial with steroid therapy is probably warranted in otherwise unresponsive refractory anemias.

Specific Etiology

Once a diagnosis of a specific deficiency anemia is made, the cause of the deficiency must be sought.

I. Folic acid deficiency may be the result of decreased intake, increased requirements, or interference with the metabolic activity of folic acid. It is usually the result of an insufficient intake of dietary sources (fresh green vegetables) because of poor diet, alcoholism, or intestinal malabsorption. Increased requirements of folic acid occur during pregnancy, and if intake is inadequate, a megaloblastic anemia may occur. Chronic hemolysis may also exhaust folic acid stores. Folic acid metabolism may be impaired by drugs such as diphenylhydantoin, methotrexate, and AZT. In such cases, the megaloblastic anemia generally improves when the drug is stopped.

II. Dietary deficiency of vitamin B_{12} occurs rarely. Although decreased intake may occur from intestinal disease or from competition for vitamin B_{12} by intestinal organisms and parasites, it is usually caused by interference with B_{12} absorption from autoantibodies directed against intrinsic factor (IF), which binds B_{12}, or against the binding B_{12}–IF complex to the absorbing ileal receptors. This absorptive defect is demonstrable with the Schilling test. A small dose of cobalt 60-labeled vitamin B_{12} is given orally; this is followed by the parenteral administration of a large amount of nonradioactive vitamin B_{12}. The urine is collected for 24 hours. Kidney function must be normal. If excretion of the labeled substance is normal, there is no indication for vitamin B_{12} therapy. If excretion is low, the test may be repeated with the addition of intrinsic factor given orally. If the poor excretion in the first test is owing to intrinsic factor deficiency, the result of the second test should be normal; if it is abnormal, other causes account for the malabsorption of the vitamin.

III. Iron deficiency in adults is rarely owing to dietary deficiency alone. Intestinal malabsorption of iron is also an uncommon cause of iron deficiency, except in malabsorption syndromes or after gastrointestinal (GI) surgery. Bleeding is by far the most common cause of iron deficiency in adult men and postmenopausal women. In adult women, iron deficiency is most commonly owing to unreplaced iron losses from menstruation, repeated pregnancies, or prolonged nursing. When bleeding is occult, it is usually of GI origin. Every effort must be made to demonstrate the source of the bleeding. Stools should be examined repeatedly for occult blood. Proctosigmoidoscopy, colonoscopy, and radiologic examination of the GI tract are also indicated. Body iron stores can be estimated by assays for ferritin and serum iron. Prussian blue stains of bone marrow biopsies give the most reliable estimate of ferritin. If anemia is owing to causes other than iron deficiency, ferritin is easy to find in the marrow. In iron deficiency, on the other hand, ferritin is absent. Serum ferritin levels are less reliable measures of tissue iron stores but are still useful and much simpler to obtain. Levels at or below 12 ng/mL indicate iron deficiency, 13 to 20 ng/mL is borderline, and 20 to 300 ng/mL is normal. Serum iron itself can be measured, with normal levels being 50 to 150 g/dL. The serum iron level as an indicator of iron stores is better evaluated by also determining the total serum iron binding capacity (TIBC) and expressing the result as the percentage of the TIBC that is saturated with iron. Levels below 16% saturation suggest deficient iron stores, but similarly low levels can be seen in inflammatory states, probably reflecting a block in the release of tissue iron into the plasma in such conditions. Newer tests for elevated plasma transferrin receptor concentration may prove to be helpful in detecting iron deficiency in the presence of inflammatory conditions. Elevation of TIBC above its normal 250 to 400 g/dL supports a diagnosis of iron deficiency.

Anemia Caused by Bleeding

I. Bleeding may be rapid and massive or slow and hidden; it may be internal or external. Bleeding is most commonly external, arising from the GI or genito-

urinary tract, from sites of trauma, or in hospitalized patients, from whom multiple tests can withdraw 200 to 400 mL or more of blood in a week. When hemorrhage takes place internally into the body tissues, the red cell iron is usually recovered and used again in hemoglobin synthesis. The degradation of heme leads to increased bile pigment production and hyperbilirubinemia.

II. Routine blood counts may fail to indicate the degree of blood loss when hemorrhage occurs rapidly, because cells and plasma are lost together. Significant blood loss (500 mL) is suggested by symptoms and signs of postural hypotension or shock. Direct measurement of the total plasma or red cell volume provides the only accurate assessment of anemia in such cases.

III. Recovery from bleeding can occur when the bleeding is slow or controlled and tissue stores of iron are adequate. During recovery, a reticulocytosis is seen. The hemoglobin may rise as much as 1 g/100 mL per week.

IV. Protracted bleeding results in exhaustion of the iron stores. Reticulocytosis then stops, and iron deficiency anemia develops. Hemosiderin is absent from marrow sections and serum transferrin iron saturation falls. Typical peripheral blood cell and serum iron changes may not be evident unless the anemia is severe (hemoglobin 8 g/100 mL).

V. Frequent testing of stools for occult blood is an excellent way to detect mild bleeding, but negative results do not rule out intermittent or a very slow rate of bleeding (4 mL of blood loss per day).

VI. Aspirin and nonsteroidal antiinflammatory drug (NSAID) ingestion is a frequent cause of low-grade bleeding. If continued long enough, iron deficiency anemia may result.

VII. Menstrual blood loss is seldom rapid enough to cause either hypovolemia or acute anemia, but it may result in iron deficiency anemia, as mentioned previously.

Anemia Caused by Hemolysis

Definition and Etiology

Human red blood cells have a normal lifespan of 120 days. A decrease in this lifespan for reasons other than bleeding is termed *hemolysis*. If the bone marrow is normal, it can compensate for a fourfold to sixfold decrease in the red cell lifespan and prevent anemia, producing what is called *compensated* hemolytic disease.

There are many causes of hemolysis. It is convenient to consider them in two categories: (a) intracorpuscular defects, nearly always hereditary, in which the red cell is abnormal from the time it is formed in the marrow, and (b) extracorpuscular defects, nearly always acquired after birth, in which the red cell is formed normally in the marrow but is injured by something in the circulation in which it lives.

The presence of an *intracorpuscular hemolytic disorder* is suggested by the following:

I. Evidence of a similar hemolytic disorder in a blood relative

II. A history of lifelong anemia, recurring jaundice, poorly healing shin ulcers, or the development of gallstones before the age of 30 years

III. A negative Coombs' test result

IV. Ancestry that is Jewish, Black, Mediterranean, or Southeast Asian, because of the higher incidence of sickle hemoglobin, thalassemia, and glucose 6-phosphate dehydrogenase (G-6-PD) deficiency in specific populations.

Hereditary hemolytic disease may not be discovered until later in life, either because it is episodic (e.g., the drug-induced group with G-6-PD deficiency) or because it is well compensated until the vicissitudes of age compromise the marrow's ability to maintain compensation (e.g., hereditary spherocytosis).

Extracorpuscular hemolytic disease is frequently associated with an antierythrocytic antibody that is demonstrable by the direct Coombs' test. A positive Coombs' test result means only that the red cells are coated with gamma globulin; it does not necessarily imply that hemolysis is present.

A seldom used but very sensitive method for distinguishing intracorpuscular from extracorpuscular defects is the measurement of the survival of ^{51}Cr-labeled compatible normal red cells in the patient. The lifespan of the donor cells is normal in patients with intracorpuscular defects but is shortened in those with extracorpuscular disorders. Red cell donors for such a test must be screened like regular blood donors to minimize any risk of transmitting infections, such as hepatitis and HIV.

Hemolytic Anemia Caused by Intracorpuscular Defects

Laboratory Tests

I. Peripheral blood smear

II. Sickle cell preparation

III. Hemoglobin electrophoresis for abnormal hemoglobin and for measurement of A_2 and F hemoglobins

IV. Incubated sample for Heinz body formation or precipitation of unstable hemoglobin

V. Screening for heat-unstable hemoglobin

VI. Tests for osmotic fragility (including incubation) and autohemolysis

VII. Enzyme screening for G-6-PD and pyruvate kinase (PK) deficiencies

VIII. Urinary hemosiderin and sucrose lysis test; if positive, acid hemolysis test

All of these tests should not be performed at once, because some, such as the acid hemolysis and osmotic fragility tests, are time consuming and expensive. The peripheral smear should be examined carefully first, because it may provide excellent clues to the cause.

Interpretation of Findings

I. Increased numbers of spherocytes with only mild to moderate anisocytosis suggests hereditary spherocytosis. In most instances, blood smears of parents and siblings detect at least one other similar case.

II. Basophilic stippling, best detected at high magnification in the large polychromatophilic red cells, suggests abnormal RNA. This phenomenon is common in thalassemia and greatly helps to distinguish this disease from iron deficiency anemia, which produces an otherwise similar smear.

III. Sickling of the red cells may occasionally be seen in the smear, indicating the need for a sickle cell preparation and hemoglobin electrophoresis.

IV. The presence of many target cells with little or no anemia and in the absence of liver disease suggests hemoglobin C abnormality, a condition in which mild hemolysis may occur.

V. Neutropenia occurs in the later stages of paroxysmal nocturnal hemoglobinuria (PNH). In addition, the continued loss of iron because of the hemoglobinuria may lead to iron deficiency and to changes in the peripheral smear owing to this type of anemia.

VI. Howell–Jolly bodies in the red cells occur in the absence of splenic function, most often the result of previous splenectomy. However, they may also be seen late in the course of sickle cell disease when "autosplenectomy" has taken place because of repeated splenic infarctions.

VII. Other red cell inclusions, some evident only with vital staining (methylene blue), may be seen in patients with abnormal unstable hemoglobins (e.g., Zurich, Köln).

VIII. If the peripheral smear suggests a specific disease, additional tests to support that diagnosis should be made:

A. The autohemolysis test or incubated osmotic fragility test is indicated for the diagnosis of hereditary spherocytosis or enzyme deficiency. Increased hemolysis is almost always observed, but the addition of glucose before incubation does not always prevent it.

B. Hemoglobin electrophoresis is performed for the measurement of A_2 and F hemoglobins in suspected thalassemia. Elevations of one or both of these hemoglobins may be seen in this disease. However, failure to find them increased does not exclude the possibility of thalassemia. Hemoglobin A_2 should not exceed 8% in this test. If greater levels are reported, one must suspect that hemoglobin E is present. This by itself causes only mild disease, but if present in thalassemia, the combined disease can be severe, so-called thalassemia intermedia with severe anemia and splenomegaly.

C. Sickle cell preparation and hemoglobin electrophoresis are performed for the diagnosis of sickle cell disease.
D. Hemoglobin electrophoresis is required for the diagnosis of hemoglobin C disease.
E. If PNH is suspected, the first tests should be a sucrose lysis test and an examination of the urine for hemoglobin and of its sediment for hemosiderin. Hemoglobinuria in PNH is intermittent, but, as in any condition with recurring hemoglobinuria, hemosiderin is present at all times in the shed cells of the urinary sediment. If the hemosiderin and sucrose lysis test results are positive, the diagnosis of PNH should be confirmed by a carefully performed Ham acid hemolysis test. The Ham test is reliable but is being replaced by fluorescence-activated cell sorting using antibodies for DAF (decay accelerating factor, CD55) and MIRL (membrane inhibitor of reactive lysis, CD59). These membrane constituents are deficient in the PNH clone of red cells, contributing to the enhanced susceptibility of these cells to the actions of complement.
F. The suspicion of an unstable hemoglobin may be confirmed by the examination of a heated (50°C) hemolysate for a precipitate or by incubating a methylene blue-stained red cell suspension to search for Heinz bodies or precipitate hemoglobin.

IX. Red cell enzyme deficiencies produce what have been called hereditary nonspherocytic hemolytic anemias. They generally produce no characteristic morphologic change visible in the routine blood smear. Red cells deficient in G-6-PD undergoing oxidative damage have been shown to be rigid, with their hemoglobin confined to one part of the cell, leaving a bitelike clear area on the opposite side of the cell. Such cells can contain Heinz bodies visible in appropriately stained blood smears. An enzyme deficiency should be suspected if the problem appears to be intracorpuscular and no other causes of intracorpuscular hemolytic disorders are found. Although most frequently associated only with episodic hemolysis related to drug exposure or infection, some variants of red cell G-6-PD deficiency found in non-Mediterranean Caucasians may produce chronic hemolysis in the absence of exogenous factors. Because of its sex-linked inheritance, G-6-PD disease is expressed mainly in men. Screening tests for G-6-PD deficiency are available, but unfortunately they may be normal during the hemolytic episodes when many young red cells are present. Under such circumstances, the test should be repeated several months after recovery to confirm the diagnosis. Much rarer is the autosomally recessive red cell PK deficiency. Enzyme assays for red cell PK for the confirmation of this diagnosis should be performed with both high and low levels of substrate in order to detect the variants of the disorder.

X. The most common cause of intracorpuscular hemolytic anemia is hereditary spherocytosis (HS). Because of a membrane defect, the red cells in this disorder have a decreased surface area. The spherocytosis is the result of a decreased surface-to-volume ratio. The mean red cell diameter (not the volume) is decreased, and the mean corpuscular hemoglobin concentration is increased above 35 g/dL. Autohemolysis and osmotic fragility of the red cells, especially after incubation, are increased. No test is absolutely pathognomonic for the diagnosis of HS, but the demonstration of similar changes in a parent or sibling provides adequate proof in most cases. If splenectomy fails to eliminate evidence of hemolysis, the accuracy of a diagnosis of HS should be seriously questioned.

Hemolytic Anemia Caused by Extracorpuscular Defects

Laboratory Tests

I. Laboratory procedures that are useful in the evaluation of these disorders include the following:
A. Peripheral blood smear
B. Plasma haptoglobin and perhaps plasma hemoglobin
C. Urine hemosiderin
D. Fibrinogen and fibrin split products or, better, a measure of D-dimer
E. RA factor and antinuclear antibody (ANA) test
F. More specific immunohematology tests in addition to Coombs' test
G. Donath–Landsteiner test and serologic test for syphilis
H. Various additional studies needed to detect underlying infections, neoplasms, or other disorders

II. The choice of tests for the evaluation of extracorpuscular disease depends to some extent on the clinical features. The history and physical examination are likely to be more helpful in evaluating these disorders than the hereditary diseases. A disease associated with acquired hemolysis may be evident before anemia becomes a problem. On the other hand, hemolysis may present a problem well in advance of other manifestations of the disease (e.g., SLE).
A. The peripheral smear may be very helpful. Abnormalities of white cells and platelets may indicate the presence of another condition, such as leukemia or disseminated intravascular coagulation. The latter diagnosis is suggested by the occurrence of red cell fragmentation in the smear. Fragmentation is also seen in other conditions characterized by mechanical damage to the cell (e.g., abnormally functioning artificial aortic heart valves). Spherocytosis of the red cells suggests coating of the cells by antibody, but it may also result from thermal injury in burned patients. Spherocytosis, neutropenia, and varying degrees of thrombocytopenia may occur in systemic lupus erythematosus or in any condition in which the spleen is large enough to trap and destroy blood cells. In malaria, the parasites are seen within the affected red cells.
B. When intravascular hemolysis is suspected because of red cell fragmentation in the peripheral blood or because of the occurrence of hemoglobinuria without hematuria, absence of haptoglobin and elevation of free hemoglobin levels in the plasma confirm the diagnosis. Plasma haptoglobin tends to be diminished in other hemolytic processes, but its complete absence in these conditions is rare. Significant intravascular hemolysis can often be detected by simple visual inspection of the patient's plasma for red hemoglobin or brown methemoglobin. As mentioned previously, the urine sediment contains hemosiderin in cases of recurrent hemoglobinuria. The loss of iron in the urine may be sufficient to cause the superimposition of iron deficiency on the original anemia. Intravascular hemolysis is accompanied by an elevation of the serum bilirubin, LDH, and SGOT levels. These findings may lead to confusion with liver disease. Mechanical injury to red cells in the feet of distance runners (march hemoglobinuria) can produce similar changes.
C. When intravascular coagulation is suspected, fibrinogen levels and fibrin degradation products (D-dimer) should be assayed. The finding of decreased fibrinogen levels and thrombocytopenia in association with red cell fragmentation is most suggestive of this disorder. An increase in fibrin split products helps to confirm the diagnosis, as does D-dimer levels over 0.5 μg. Other clotting factors also tend to be at low levels; these may be measured for confirmation, if available. This illness, formerly associated with syphilis, but more now with recent viral infection or the presence of non-Hodgkin's lymphoma, is diagnosed by the Donath–Landsteiner.

White Blood Cell Abnormalities

John H. Saiki

Neutropenia

Definition

Neutropenia (granulocytopenia) is defined as an absolute neutrophil count of 1,500/mm³) (Fig. 6-2).

Clinical Significance

I. Host resistance is related to the degree of neutropenia.
A. More than 1,500 neutrophils/mm³ is associated with normal host resistance.
B. One thousand to 1,500 neutrophils/mm³ is associated with mildly impaired host resistance.
C. Five hundred to 1,000 neutrophils/mm³ is associated with moderately impaired host resistance.

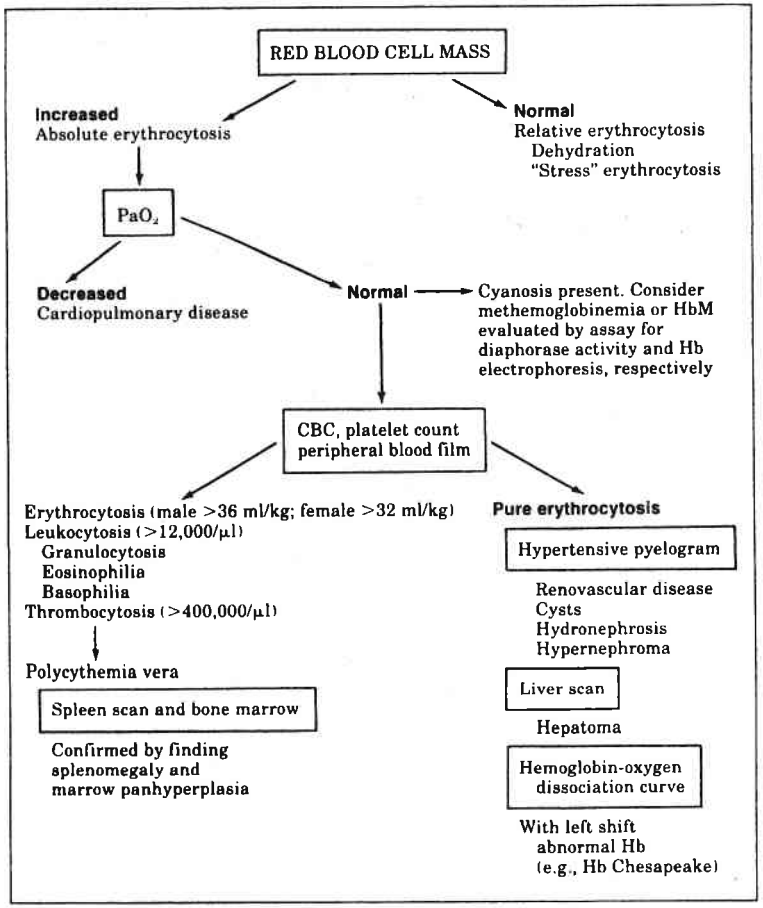

Fig. 6-2. Laboratory approach for evaluation of erythrocytosis.

II. Neutropenia results in increased susceptibility to infection. The usual clinical manifestations of infection in the setting of severe neutropenia are often absent because of the lack of granulocytes. Thus, pneumonia may be present without a significant infiltrate, meningitis may occur without pleocytosis, and pyelonephritis occurs without pyuria.

III. The three *most important* clinical disorders associated with neutropenia are: (a) aplastic anemia, (b) acute leukemia, and (c) drug-induced agranulocytosis. Each of these requires immediate therapeutic measures.

IV. Chronic neutropenias (e.g., Felty's syndrome) and chronic idiopathic neutropenia are uncommonly associated with severe infections, because the bone marrow is associated with increased proliferation and delivery of granulocytes.

V. When neutropenia is associated with anemia and thrombocytopenia, the term pancytopenia is used. This is associated with aplastic anemia, bone marrow infiltration (e.g., acute leukemia, and marrow injury such as aggressive chemotherapy).

Normal Granulocyte Kinetics

Granulocytes are produced within the bone marrow and maintained in a reserve or storage compartment from which they are released into the circulation on demand. Intravascular cells are equally divided between circulating and marginated pools. Granulocytes then make their way into body tissues, perform their function, and die (Fig. 6-3).

Mechanisms of Neutropenia

Neutropenia can result either from decreased production, ineffective production, accelerated destruction or consumption, and a distribution change from the circulating to the marginated pool (increased margination).

Etiology

I. Proliferation defects (hypoproliferation)

II. Marrow injury (e.g., radiation, drugs, PNH, hepatitis, HIV, idiopathic), or marrow infiltration (e.g., acute leukemia, and myelofibrosis). Severe hypoproliferation of erythrocytes, granulocytes, and megakaryocytes is called aplastic anemia.

II. Maturation defects (ineffective proliferation)
   A. The production of defective cells, which are purged from the marrow by macrophages, as in the megaloblastic anemias (vitamin B_{12} and folate deficiency), myelodysplastic syndromes

III. Distribution abnormality (increased margination):
   A. Endotoxin. This mechanism is of little clinical significance.

IV. Survival defects
   A. Accelerated consumption (e.g., severe sepsis)
   B. Accelerated destruction (e.g., immune mechanisms) as seen with the drug clozapine; and with autoimmune disease (e.g., Felty's syndrome), and hypersplenism. This mechanism can sometimes result in severe agranulocytosis (Fig. 6-4).

V. Evaluation of the CBC, platelet count, and peripheral blood smear are essential. A bone marrow aspiration is necessary in patients with unexplained neutropenia. The peripheral blood film and bone marrow findings are illustrated in Table 6-1.

VI. When aplastic anemia is identified, a history of exposure to drugs (e.g., chloramphenicol, phenylbutazone, hydantoin analogs, sulfonamides, sulfonylureas,

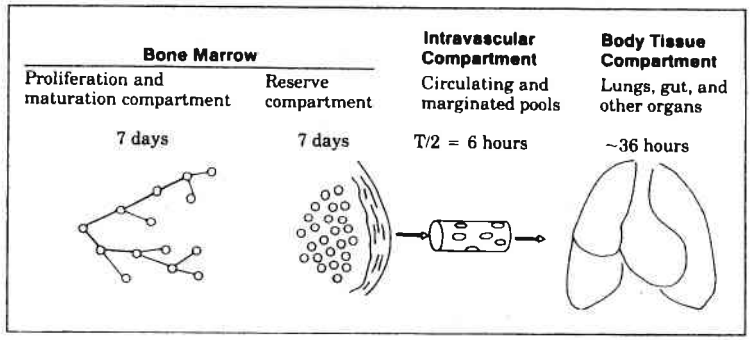

Fig. 6-3. Normal granulocytic kinetics.

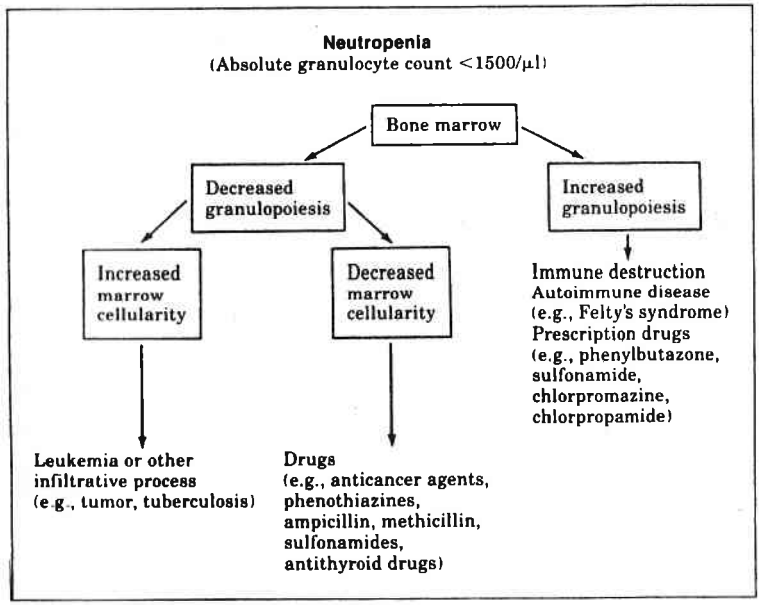

Fig. 6-4. Diagnostic approach to neutropenia.

gold compounds, and quinacrine); insecticides (e.g., DDT, lindane, chlordane); and solvents (e.g., benzene) must be determined. A hepatitis profile screen and a sugar water test for PNH should be performed.

Leukocytosis

Definition

Leukocytosis is defined as a white blood cell (WBC) count in excess of 10,000/mm^6.

Clinical Significance

Most frequently leukocytosis is reactive to an inflammatory process. The differentiation between a reactive leukocytosis and leukemia is most important.

Diagnostic Approach

History

Patients with a reactive leukocytosis are symptomatic with fever and other manifestations of infection. Typically, the patient with chronic granulocytic or lymphocytic leukemia is asymptomatic. Acute leukemia usually presents with weakness, fever with infection, and bleeding manifestations with epistaxis and bruising.

Physical Examination

A perfectly healthy-appearing patient strongly favors chronic granulocytic or lymphocytic leukemia. An ill-appearing patient with pallor, fever, and bleeding manifestations (petechia and bruises) is characteristic of acute leukemia. Hepatosplenomegaly is commonly seen in both acute and chronic leukemia. Generalized lymphadenopathy is most characteristic of acute and chronic lymphocytic leukemia.

Laboratory Studies

I. Evaluation of the peripheral blood film is the most important procedure:

Table 6-1. Diagnostic features of neutropenia of various origins

Disorder	Peripheral blood findings	Bone marrow findings
Proliferation defects		
Marrow injury	Pancytopenia; toxic changes in granulocytes; large reticulocytes	Hypocellularity; vacuolation of cytoplasm in precursor cells
Marrow infiltration	Pancytopenia; leukoerythroblastic reaction	Hypercellularity; reduced normal hematopoiesis; infiltration by fibrous tissue, tumor cells, or leukemia
Maturation defects	Macroovalocytes; Howell-Jolly bodies; hypersegmentation of granulocytes; pancytopenia	Hypercellularity; panhyperplasia; megaloblasts; giant metas and bands
Distribution abnormality	Pseudoneutropenia; normal smear	Normal
Survival defect		
Accelerated consumption (infection)	Left shift; toxic granulation; Dohle inclusion bodies; neutropenia	Increased granulocytic proliferation; depleted reserve compartment
Accelerated destruction (immune)	Left shift; neutropenia	Increased granulocytic proliferation; depleted reserve compartment

Leukocytosis

Predominantly mature cells (See sections on neutrophilia and lymphocytosis)	Predominantly blast forms
Reactive versus chronic leukemia	Acute leukemia

II. CBC and platelet count: The hemoglobin and hematocrit are more likely to be normal or near normal in reactive leukocytosis and in the chronic leukemias. The platelet count is normal or elevated in reactive leukocytosis and chronic leukemia, but invariably markedly reduced in the acute leukemias. Mature leukocytes favor a reactive process or chronic leukemia (See Neutrophilia). Predominantly blast forms are consistent with acute leukemia.

III. Bone marrow aspiration contributes little to the diagnosis of a reactive leukocytosis or chronic leukemia and is seldom necessary for diagnostic purposes. However, it is often essential for the diagnosis of acute leukemia. The marrow in acute leukemia is hypercellular with greater than 30% blasts. Not uncommonly leukemia is suspected, and the proportion of blast cells is only moderately increased. In this setting close observation of peripheral blood counts and the proportion of blasts in the bone marrow will allow the diagnosis to be established.

III. Specific etiology: The chronic leukemias are discussed more appropriately under the sections on neutrophils and lymphocytosis. Acute leukemia is classified according to cell type by morphology, special stains, and immunologic markers. The specific cell type is identified by individual morphologic features (e.g., Auer rods in myeloblastic and monocytic leukemias), and "the company they keep," which reflects maturation in any given cell line (e.g., the finding of promyelocytes in acute myeloblastic leukemia). Frequently, morphologic features are inconclusive and special stains are required (e.g., PAS positivity in lymphoblastic leukemia), or flow cytometry for specific surface antigen markers (e.g., CD-33 in acute

myeloblastic leukemia), cytogenetics, and molecular markers. From a therapeutic standpoint it is important to differentiate lymphoblastic leukemia from the nonlymphoblastic forms, and to identify acute promyelocytic leukemia. Hyperuricemia is common in all acute leukemias. Disseminated intravascular coagulation may occur in any of the acute leukemias, but is of particular significance in acute promyelocytic leukemia. A PT, PTT, fibrinogen level, and D-dimer should always be determined.

Neutrophilia

Definition

Neutrophilia is defined as an absolute granulocyte count in excess of 7,500/mm^6.

Clinical Significance

A neutrophilic leukocytosis most frequently is a nonspecific manifestation of inflammation. An absolute granulocytosis must be differentiated from chronic granulocytic leukemia and other myeloproliferative disorders.

Etiology

I. Increased production of granulocytes
   A. Reactive (e.g., infection, steroids, Hodgkin's disease, lung cancer)
   B. Myeloproliferative (e.g., chronic granulocytic leukemia)
II. Increased release of granulocytes from reserve compartment
   A. Etiocholanolone, corticosteroids
   B. Endotoxin
III. Decreased margination of granulocytes: epinephrine (endogenous or exogenous), physical activity, stress
IV. Decreased degrees of granulocytes from the blood
   A. Adrenal corticosteroids
   B. Prednisone

Diagnostic Approach

In the clinical setting the practical problem is the differential diagnosis of reactive and malignant granulocytosis (Table 6-2).

Basophilia

Definition

Basophilia is defined as an absolute basophil count of more than 100/mm^6.

Clinical Significance

Basophilia of itself seldom presents as a clinical problem, but may be a clue to diagnosis. Most important, basophilia is a significant marker of the myeloproliferative disorders.

Associated Conditions

I. Hypersensitivity states
II. Myxedema
III. Ulcerative colitis
IV. Myeloproliferative disorders
   A. Polycythemia vera
   B. Chronic granulocytic disorders
   C. Essential thrombocythemia
   D. Myelofibrosis with myeloid metaplasia

Eosinophilia

Definition

Eosinophilia is defined as an absolute eosinophil count of more than 500/mm^6

Clinical Significance

Counts between 500 and 1,000/mm^3 are nonspecific and should not be pursued as a clinical problem. Counts >4000/mm^3 have specificity.

Table 6-2. Differential diagnosis of chronic granulocytic leukemia and reactive granulocytosis

Parameter	Reactive granulocytosis	Chronic granulocytic leukemia
Clinical picture	Usually no symptoms, or symptoms related to splenomegaly	Often exhibited overt manifestations of underlying disease (e.g., carcinoma, infection)
Peripheral blood findings	Leukocytosis related to spleen size; few blasts common; giant platelets; basophils increased	Leukocytosis unrelated to spleen size; myeloblasts rarely present; platelets normal in appearance; basophils not increased
Bone marrow findings	Hypercellular; megakaryocytes increased (early); myeloid; erythroid = 10:1; myelocyte dominates granulocytic series; basophils increased	Cellularity variable; megakaryocytes usually normal; myeloid; erythroid usually greater than normal; granulocytic "pyramid" intact; basophils not increased
Leukocyte alkaline phosphatase activity	Decreased or absent	Increased
Serum B_{12}	Marked increase	Slight increase
Karyotype abnormality PH,[a] BCR-ABL gene rearrangement	Always present by definition[a]	Absent

[a] The new classification of leukemias requires the presence of the BCR-ABL gene rearrangement to be present for the diagnosis of chronic granulocytic leukemia.

Associated Conditions

I. Allergic disorders (e.g., hayfever, bronchial asthma)
II. Parasitic infestation with tissue invasion (e.g., trichinosis)
III. Skin diseases (e.g., dermatitis herpetiformis)
IV. Tumors (e.g., Hodgkin's disease)
V. Granulomatous disease (e.g., tuberculosis, coccidioidomycosis)
VI. The hypereosinophilic syndromes
   A. Eosinophilic leukemia
   B. Fibroplastic endocarditis
   C. Systemic vasculitis
   D. Loffler's syndrome
   E. Tropical eosinophilia

Lymphocytosis

Definition

Lymphocytosis is defined as an absolute lymphocyte count in excess of 4,500/mm^6.

Clinical Significance

Lymphocytosis is most common in childhood and is usually a nonspecific finding associated with viral infections. In the adult, lymphocytosis has greater specificity and therefore greater diagnostic value.

Etiology

I. The etiologic mechanisms of lymphocytosis are not well known. Significantly, not all cases are a result of increased proliferation. In pertussis, the mechanism is thought to be related to a blockade of lymphocyte entry into lymph nodes.

II. Causes of nonactivated lymphocytosis (normal inactive small lymphocytes)
  A. Infectious lymphocytosis
  B. Mumps
  C. Varicella
  D. Rubeola
  E. Herpes simplex
  F. Influenza
  G. Tuberculosis
  H. Pertussis
  I. Chronic lymphocytic leukemia
III. Causes of activated lymphocytosis (atypical lymphocytes)
  A. Infectious mononucleosis
  B. Infectious hepatitis
  C. Toxoplasmosis
  D. Cytomegalovirus
  E. Posttransfusion syndrome
  F. Drug-induced: para-aminosalicylic acid, diphenylhydantoin, Mesantoin (Fig. 6-5)
IV. Lymphocytosis uncommonly presents as a clinical problem and is usually a manifestation of an associated infection.
V. When it does present as an isolated problem, evaluation of the peripheral blood film and determination of the CBC and platelet count are important.
  A. If the cells identified are blasts, then the diagnosis of acute lymphoblastic leukemia is made and confirmed by bone marrow aspiration.
  B. If the lymphocytes are small or medium-sized with many "activated" (atypical) forms, then a monospot test, HAA, toxoplasma immunofluorescent titer, and CMV titer should be obtained in addition to inquiry into clinical history (e.g., use of analeptic drugs, transfusion history, hepatitis, or recent history of a URI).
  C. If the lymphocytes are small and "mature" and the patient is an older asymptomatic adult, the diagnosis of chronic lymphocytic leukemia is most likely. Evaluation for lymphadenopathy, splenomegaly, bone marrow aspiration for lymphocytic infiltration, and a serum protein electrophoresis for hypogammaglobulinemia will confirm the diagnosis.

Splenomegaly

Definition

Clinically, a palpable spleen represents an enlarged spleen. Enlargement must be confirmed by scan measurements. Remember that when you think you feel the spleen, you have not felt it, for when you feel it, you know.

Clinical Significance

I. Splenomegaly may represent a manifestation of associated disease or may represent primary disease (lymphoma).
II. Impaired gastric filling with early satiety may lead to weight loss. There may be increased susceptibility to rupture from trauma because of lack of protection by the rib cage.
III. Hypersplenism with cytopenia (single or multiple) occasionally is associated with increased susceptibility to infection and hemorrhage. Normally the spleen pools one-third of total body platelets and when enlarged, proportionately up to 90% of total body platelets.

Etiology

I. Congestion
  A. Congestive heart failure
  B. Portal hypertension

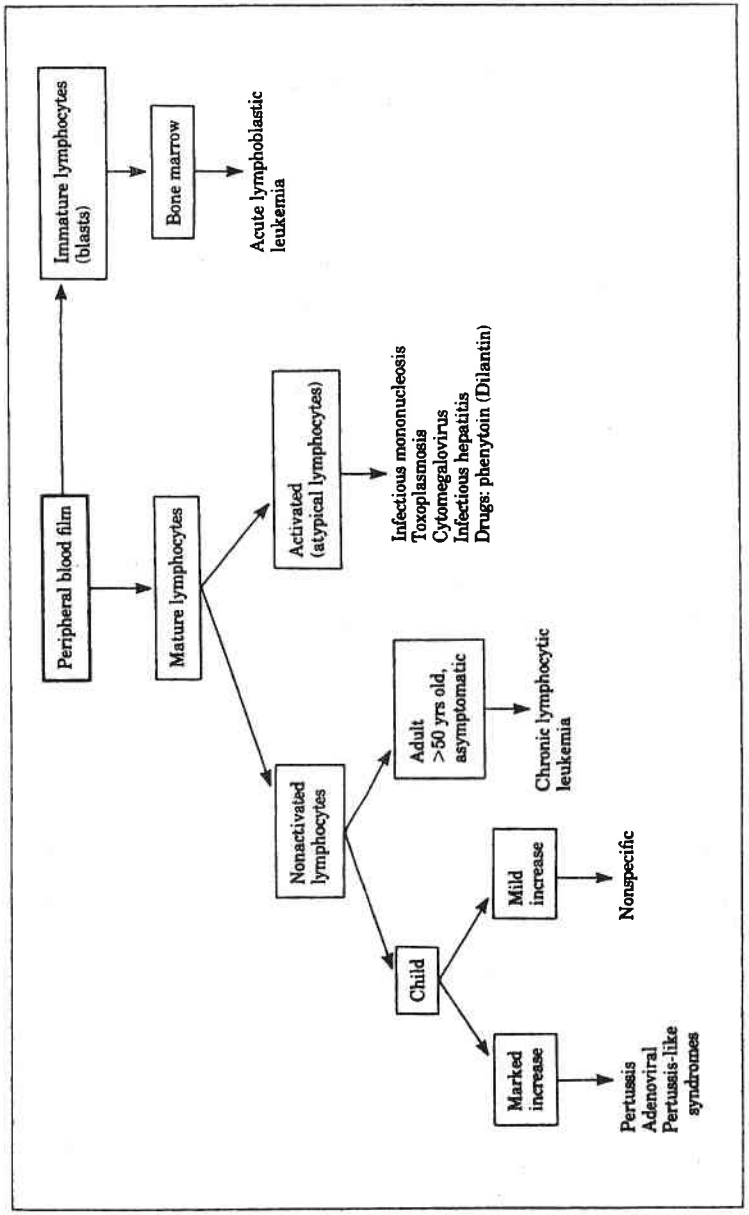

Fig. 6-5. Diagnostic approach to lymphocytosis.

II. Reactive hyperplasia
  A. "Work hypertrophy" (e.g., hemolytic anemia)
  B. Infections
    1. Bacterial (e.g., tuberculosis, infective endocarditis, brucellosis)
    2. Viral (e.g., cytomegalovirus, infectious mononucleosis)
    6. Fungal
    4. Parasitic (e.g., malaria, toxoplasmosis)
  C. Connective tissue diseases (e.g., SLE, RA)
  D. Serum sickness
III. Infiltrative diseases
  A. Nonneoplastic
    1. Lipidosis (Gaucher's disease)
    2. Sarcoidosis
    6. Amyloidosis
  B. Neoplastic diseases
    1. Lymphoproliferative disorders (acute and chronic lymphocytic luekemia and lymphoma)
    2. Myeloproliferative disorders (polycythemia vera, chronic granulocytic leukemia, and myelofibrosis with myeloid metaplasia)
    6. Metastatic tumor is extremely rare (Fig. 6-6).

History

Has the patient had a recent history of a febrile illness to suggest an infectious etiology? Does he or she have fever, sweating, itching, weight loss, and lymphadenopathy, which represent the clinically important symptoms of lymphoma? Is there a history of congestive heart failure or alcoholism to suggest passive congestion of the spleen? Is there pallor and weakness from a chronic hemolytic anemia (e.g., autoimmune hemolytic anemia, hereditary spherocytosis)?

Physical Examination

I. Very thorough examination for lymphadenopathy, hepatomegaly, or evidence of infection
II. Confirmation of splenomegaly by CT scan of the abdomen
III. Initial screening studies
  A. CBC, reticulocyte count, and platelet count
  B. Serum bilirubin (total and direct), alkaline phosphatase, GGT, ALT, SGOT, LDH, serum electrophoresis, acid phosphatase
  C. ANA and RF
  D. Serologic tests for fungi, complement fixation test for toxoplasmosis, Hepatitis screen (B and C), monospot test, and heterophile antibody titer
  E. Radiographs: PA and lateral films of chest, barium swallow for evaluation of varices, and CT scan of abdomen and pelvis
  F. Bone marrow aspiration and biopsy for culture, cytologic and histologic evaluation, staining for amyloid, fibrous tissue, bacteria (including acid fast bacilli), and fungi
IV. If the patient has asymptomatic splenomegaly and the spleen is mildly to moderately enlarged (estimated < 400 gm), continued observation at monthly intervals is a reasonable approach, particularly in the age group < 35 years without symptoms, close observation is imperative. If there is no significant change over a period of 2 years, no further evaluation is necessary.
V. If the patient is symptomatic with fever, profuse sweating, anorexia, and weight loss, or the patient remains asymptomatic, but documented continued enlargement of the spleen is noted, then further investigations are imperative. These include monitoring splenomegaly and potentially evidence of developing lymphadenopathy or hepatomegaly by periodic abdominal and pelvic CT scan. Even if these studies are negative, an exploratory laparotomy must be very seriously considered for diagnostic splenectomy, liver biopsy (core and wedge), and multiple lymph node biopsies.

Lymphadenopathy

Definition

Lymphadenopathy is an abnormal increase in size or altered consistency of lymph nodes. It can be a clinical manifestation of regional or systemic disease and serves as an excellent lead to the underlying etiology.

Etiology

I. Reactive
  A. Infectious
    1. Bacterial (e.g., pyogenic, tuberculosis)
    2. Viral (e.g., cytomegalovirus, infectious mononucleosis, HIV)
    6. Fungal (e.g., coccidioidomycosis)
    4. Parasitic (e.g., toxoplasmosis)
  B. Noninfectious
    1. Sarcoidosis
    2. Connective tissue disease
    6. Dermatopathic
    4. Drug-induced (e.g., diphenylhydantoin)
II. Infiltrative
  A. Benign (e.g., histiocytosis, lipidosis)
  B. Malignant (e.g., primary lymphoma, metastatic carcinoma) (Fig. 6-7)

History

Has the patient systemic manifestations of fever, sweating, weight loss, and itching, which represent the most important symptoms of malignant lymphoma? Has the patient had a recent febrile illness or contact with pets (e.g., transmission of toxoplasmosis from the excrement of cats)? Is the patient taking analeptic drugs (e.g., Dilantin)?

Physical Examination

I. Very thorough examination of all lymph node regions and evaluation for hepatosplenomegaly

Regional Lymphadenopathy

I. Cervical and supraclavicular lymphadenopathy: Careful examination of the head and neck region for a primary squamous cell carcinoma in the older adult by an ENT specialist prior to biopsy is important. Thirty-five percent of head and neck tumors initially manifest as a metastatic tumor to regional lymph nodes. Only after thorough ENT examination of these patients should the node be biopsied. In the young adult with URI symptoms and rapid onset of lymphadenopathy, infectious mononucleosis must be given first consideration. The presence of splenomegaly, the finding of activated "atypical" lymphocytes on the peripheral blood film, and a positive monospot test, confirm the diagnosis. The patient with unexplained significant lymphadenopathy must undergo lymph node biopsy, particularly if otherwise asymptomatic.
II. Mediastinal and hilar lymphadenopathy: Asymptomatic bilateral hilar adenopathy has been considered *a priori* evidence of sarcoidosis, but it is probably wisest to confirm this by transbronchial biopsy, or scalene fat pad biopsy. Mediastinal lymphadenopathy almost invariably represents tumor. In the young adult, Hodgkin's lymphoma is most likely, next would be a large cell lymphoma (with sclerosis) or a primary germ cell tumor (extragonadal). In the older adult, thymoma or metastatic carcinoma (usually a lung primary) are likely. In the absence of peripheral lymphadenopathy, a biopsy by mediastinoscopy or a parasternal mediastinotomy will establish the diagnosis.
III. Axillary lymphadenopathy: In a woman careful examination of the breast, including mammography, is imperative. Unexplained axillary adenopathy must be biopsied. Lymphomas are always a possibility, but if the biopsy reveals an adenocarcinoma, a primary breast cancer is almost certain.

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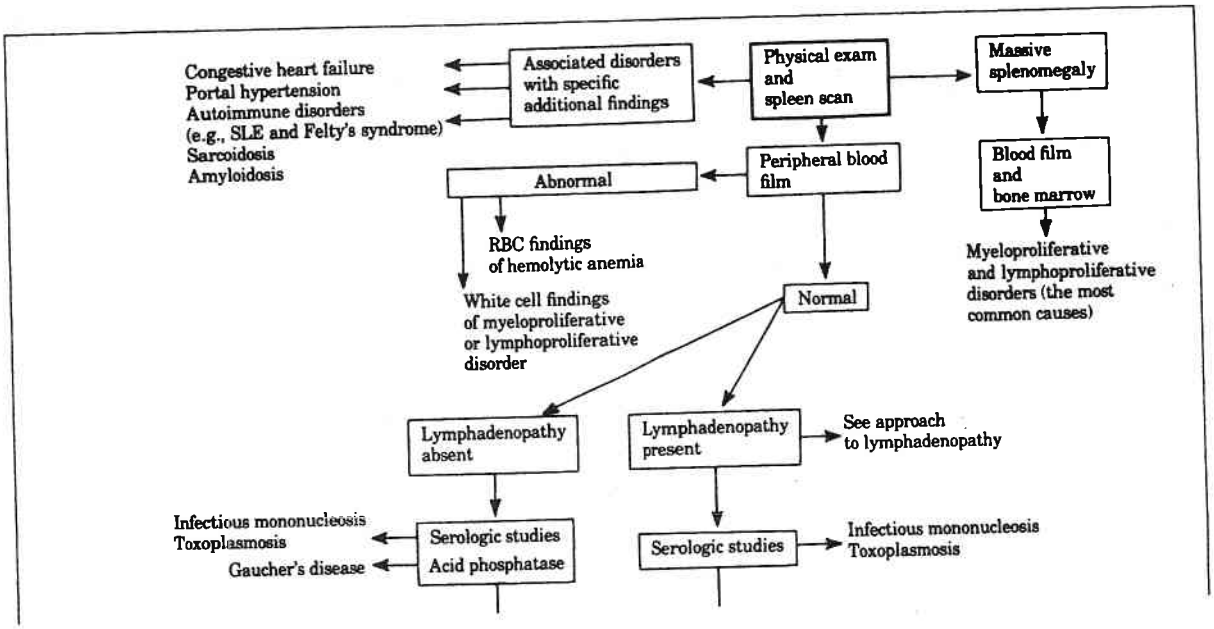

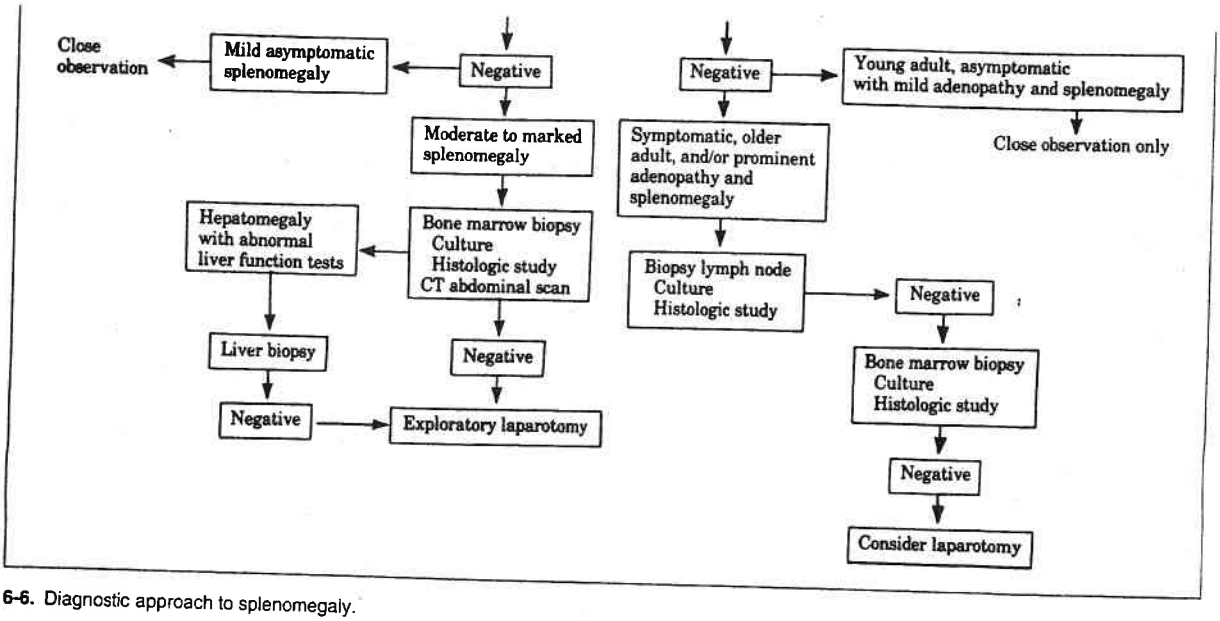

Fig. 6-6. Diagnostic approach to splenomegaly.

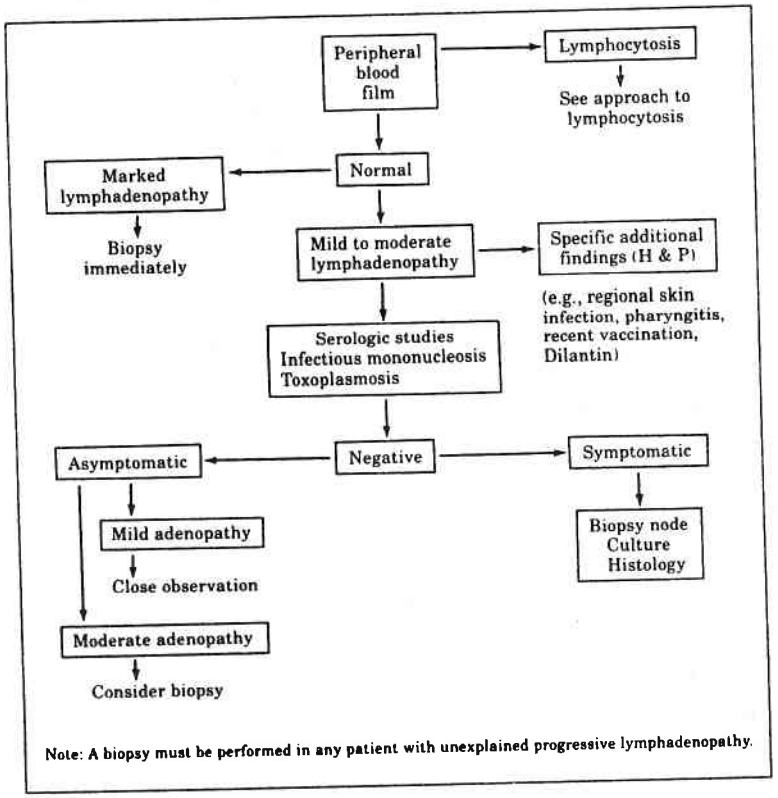

Fig. 6-7. Diagnostic approach to lymphadenopathy.

IV. Inguinal and femoral lymphadenopathy: These regions are characteristically more difficult to evaluate, as lymphadenopathy of a mild degree is common in the normal individual. Asymmetrical lymphadenopathy should arouse greater concern. If there is no evidence of regional cutaneous or subcutaneous inflammatory disease, a biopsy must be performed.

Generalized Lymphadenopathy
Generalized lymphadenopathy is a manifestation of a systemic illness (e.g., toxoplasmosis, serum sickness, rheumatoid arthritis, dilantin-induced hyperplasia), and the lymphoproliferative disorders (chronic lymphocytic leukemia and the low-grade lymphomas). If it has evolved over a few weeks, an infectious etiology is most likely. If it has evolved over several months or longer, a low-grade lymphoma is most likely, especially in the older adult (> 50 years of age). Diagnostic procedures, depending on the patient's history, might include the following: CBC, platelet count, liver function tests, toxoplasma immunofluorescent test, heterophile antibody titer, CMV titer, and chest radiograph. If these studies are not revealing, then a lymph node biopsy should be performed.

Table 6-3. Staging of the malignant lymphomas

Stage	Criteria
I	Single lymph node region (I) or a single parenchymal lesion (I-E)
II	Two or more lymph node regions (II) or localized parenchymal disease with one or more node regions on the same side of the diaphragm (II-E)
III	Lymph node involvement above and below diaphragm (III) Above criteria plus splenic involvement (III-S) Above criteria plus localized parenchymal involvement (III-E) plus splenic involvement (III-SE)
IV	Disseminated foci of one or more parenchymal organs with or without lymph node disease. A single lesion in liver or bone marrow is defined as IV.
Subclassification	*A*, asymptomatic; *B*, symptomatic
Symptoms	Fever and weight loss in excess of 10% of body weight within the previous 6 months. Pruritus and drenching sweats are not of prognostic significance.
	Karyotype abnormality PH,[a] Always present by definition[a]
	Absent BCR-ABL gene rearrangement

[a] The new classification of leukemias requires the presence of the BCR-ABL gene rearrangement to be present for the diagnosis of chronic granulocytic leukemia.

Specific Etiology
Malignant Lymphomas
The first step following a diagnosis of lymphoma is assessment of extent of disease for determination of the clinical stage (Table 6-3). Treatment is based on the clinical stage. The following studies should be performed:

I. History (especially symptoms of fever, sweating, and weight loss) and physical examination (especially lymph node areas, liver, and spleen)
II. Hematologic studies: CBC and platelet count, ESR, and bone marrow aspiration *and* biopsy (bilateral in the non-Hodgkin's lymphomas)
III. Liver: alkaline phosphatase, GGT, and CT scan
IV. Renal: urinalysis, creatinine, and BUN
V. Lymph node regions
   A. External: Physical examination
   B. Mediastinal: Chest radiograph and CT scan of chest
   C. Retroperitoneal and mesenteric: CT scan of abdomen and pelvis
VI. ^{67}Gallium scans of chest and abdomen are sometimes performed primarily for their potential benefit in assessing disease activity for residual masses noted on follow-up.
VII. Bone: ^{99}Technetium (polyphosphate) bone scan
VIII. Exploratory laparotomy is performed only if the diagnostic imaging studies reveal equivocal findings and significant therapeutic differences will be altered by the findings of an exploratory laparotomy.

Erythrocytosis (Polycythemia)

Definition
Erythrocytosis is defined as an elevation in hemoglobin and hematocrit above 18 gm% and 54%, respectively.

Etiology (Mechanisms)
I. Relative erythrocytosis: Red cell mass is normal and plasma volume is reduced (hemoconcentration) as occurs in dehydration and "stress" erythrocytosis (Gaisbock's syndrome).
II. Absolute erythrocytosis: Red cell mass is increased.
   A. Primary (autonomous proliferation; polycythemia rubra vera)
   B. Secondary (increased erythropoietin production)

1. Associated with systemic hypoxia
2. Reduced PaO_2: Chronic lung disease, chronic CHF, and congenital heart disease with right-to-left shunts
6. Normal PaO_2: impaired oxygen carrying capacity of methemoglobinemia and hemoglobin M, impaired hemoglobin-oxygen dissociation with increased oxygen affinity as in hemoglobin Chesapeake
4. Local renal hypoxia with renovascular disease
5. Autonomous erythropoietin production
   a. Benign lesions: renal cysts, hydronephrosis, uterine fibroids
   b. Malignant lesions: hypernephroma, hepatoma, cerebellar hemangiblastoma

C. Exogenous androgen administration

Diagnostic Approach

History

A careful inquiry must be made regarding manifestations of chronic heart or lung disease, family history of high hemoglobin levels, chronic ingestion of androgens, and general well-being, appetite, weight loss, bleeding, and thrombotic problems.

Physical Examination

A careful evaluation of cardiovascular and respiratory systems for hepatosplenomegaly and evidence of cyanosis must be carried out. In the absence of significant abnormalities identified by history or physical examination, the following schematic laboratory approach is pursued.

Specific Etiology

Polycythemia vera is a member of the myeloproliferative disorders, manifesting with erythrocytosis, leukocytosis, thrombocytosis, panhyperplasia of the bone marrow, and extramedullary hematopoiesis with hepatosplenomegaly. Symptoms of fatigue, headache, pruritus, and occasionally erythromelalgia are seen. Physical findings of plethora and hepatosplenomegaly are common. Complications of peptic ulcer disease, congestive heart failure from hyperviscosity, and thrombotic and bleeding problems are common and of major importance. The diagnostic criteria established by the National Polycythemia Vera Study Group are identified in the chart that follows.

Diagnostic criteria of polycythemia vera

Category A	Category B
1. Red cell mass Male >36 mL/kg Female >32 mL/kg	1. Thrombocytosis Platelet count >400,000/mL
2. Normal arterial O_2 saturation 92%	2. Leukocytosis >12,000/mL without fever or infection
6. Splenomegaly	6. LAP 8 (<100) without fever or infection
	4. ↑ serum B_{12} (<900 pg/mL or unsaturated B_{12} binding capacity (>2,200 pg/mL)

Diagnosis of P. Vera established with the following combinations:

$A_1 + A_2 + A_3$, or $A_1 + A_2$ + any two from Category B

Bleeding and Clotting Disorders

Jerome S. Nosanchuk

Definition and Characteristics

Bleeding is defined as a breakdown in hemostasis. Hemostasis depends on vascular integrity, the number and quality of platelets, plasma coagulation factors (procoagulants), and the counterbalancing activity of anticoagulants. Clotting requires the conversion of soluble plasma fibrinogen into an insoluble fibrin clot (Fig. 6-8). This conversion is mediated by a protease enzyme thrombin; the end product, fibrin, is rendered stable by factor XIII (fibrin stabilizing factor). Bleeding occurs when there is impairment of the hemostatic mechanism owing to either defective synthesis or excessive utilization of clotting factors. Coagulation may also be impaired by circulating inhibitors of clotting factors or the proteolytic action of plasmin. The degree of bleeding is related to both the nature and severity of the deficiency. A thorough history and physical examination are adequate to identify most bleeding disorders. The characteristics of bleeding in hemorrhagic disorders are given in Table 6-4.

Most operative and postoperative hemorrhage is caused by inadequate surgical hemostasis. Patients with delayed bleeding or those whose bleeding is controlled initially, but who subsequently bleed again, are more likely to have intrinsic defects in coagulation factors than platelet abnormalities. This type of bleeding, especially if acquired, is more frequently owing to multiple factors rather than a single cause.

The final diagnosis of a coagulation disorder rests heavily on laboratory support (Fig. 6-8; Table 6-5). Functional deficiency or inhibition of a factor in the intrinsic pathway is generally detected by the activated partial thromboplastin time (APTT). Factors involved in the extrinsic system are usually detected by measuring the one stage prothrombin time (PT). Both of these times are prolonged when fibrin formation is defective (e.g., low fibrinogen). Neither the PT nor the APTT detects abnormalities in factor XIII or platelets. It requires a significant reduction in any single factor to affect either the PT or the APTT. For example, pure factor VIII or IX deficiency must be reduced to a level that is 30% or less of normal before the APTT is prolonged. Paradoxically, severe deficiencies of factor II may not prolong the PT, because most reagent test systems are relatively insensitive to low factor II levels. However, a modest combination of multiple factor deficiencies usually prolongs the clotting times.

Because clotting studies are very method dependent, it is critical that samples be properly drawn using two-syringe or multiple Vacutainer techniques and that the specimens be brought promptly to the laboratory for analysis.

If the specimen needs to be shipped to a reference laboratory, the plasma should be promptly separated and frozen, preferably at –60°C. A sample of a normal patient's plasma should be obtained in the same fashion and shipped on dry ice with the patient's sample to serve as a control on the quality of the shipping because thawing of the normal sample will cause it to test abnormally also.

Consultation with the clinical hematology laboratory director or clinical pathologist is not only advisable but often mandatory for correct diagnosis and appropriate therapy.

I. The most important initial step is to obtain an adequate history and physical examination. It is also important to ascertain whether the patient has experienced abnormal bleeding or bruising in the past. The site, extent, and duration of previous hemorrhagic phenomena, and the response to treatment, may be helpful. Specific questions should be asked concerning bleeding with minor injuries, lacerations, circumcision, tooth extraction, appendectomy, tonsillectomy, pregnancy, menses, and umbilical cord, as well as delayed bleeding and keloid formation. The patient should also be questioned concerning the use of drugs that may interfere with hemostasis (e.g., oral contraceptives, aspirin-containing medicines, NSAIDs, antibiotics, sodium warfarin [Coumadin], or heparin). A positive family history of bleeding suggests the presence of sex-linked or autosomal dominant disorders.

II. Knowledge of the patient's underlying disease may provide a clue to potential bleeding problems. A patient with significant hepatic disease, neoplasia, or uremia is at greater risk than a patient who is otherwise well.

III. The incidence of coagulation hazard is increased in some surgical operations. Cardiopulmonary bypass procedures and hypothermia may cause inactivation or destruction of clotting factors and platelets. Prostate surgery is associated with an increased frequency of fibrinolysis. The use of water rather than saline irrigation in bladder surgery can provoke hemolysis. Cardiovascular surgery, trauma, and other situations in which massive bleeding and replacement transfusion

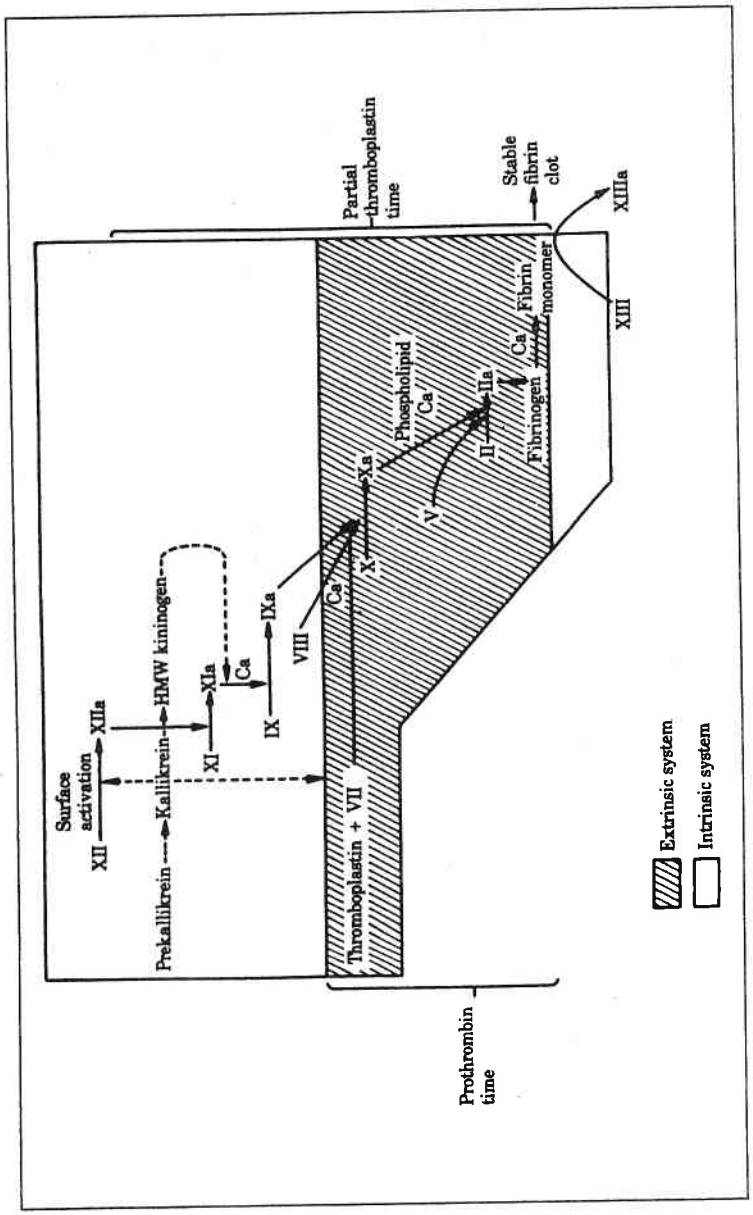

Fig. 6-8. Simplified clotting sequence.

Table 6-4. Characteristics of bleeding in hemorrhagic disorders

Type of bleed	Definition	Location	Cause
Petechia	Smallest; punctate; about 1 mm in diameter	On extremities, usually absent over pressure point	Vascular or platelet abnormality
Purpura	1 mm to 1 cm	Generally truncal, occasionally extremities	Vascular abnormality
Ecchymosis	Larger bleed with local extravasation	Soft tissues, joints	Factor deficiency or open blood vessel
Generalized	Diffuse or generalized ecchymosis	Large areas, mucous membranes, wounds	Disseminated intravascular clotting or primary fibrinolysis

occur also have an increased potential for hemorrhage because of deficiencies in various clotting factors.

IV. If, despite negative history and physical findings, a preoperative coagulation screen is still deemed necessary, the following studies are recommended. Negative findings with these tests virtually exclude, with the rarest of exceptions, the presence of a clinically significant preexisting coagulopathy.

Table 6-5. Diagnosis of clotting deficiencies

	Test			
Deficient factor	PT	APTT	Platelet count	Bleeding time
Fibrinogen (I)	A	A	N	N
Prothrombin (II)	A	A	N	N or A
Tissue thromboplastin (111)				
Calcium (IV)				
Labile factor (V)	A	A	N	N or A
(Not assigned) (VI)				
Stable factor (VII)	A	N	N	N
Antihemophilic globulin (VIII)	N	A	N	N
Christmas factor (IX)	N	A	N	N
Stuart-Prower factor (X)	A	A	N	N or A
Plasma thromboplastin antecedent (XI)	N	A	N	N
Hageman factor (XII)	N	A	N	N
Fibrin stabilizing factor (XIII)	N	N	N	N
Prekallikrein (Fletcher factor)	N	A	N	N
HMW kininogen (Fitzgerald factor)	N	A	N	N
von Willebrand's (VIIIag)	N	N or A	N	N or A
Thrombocytopenia	N	N	A	N or A
Functional platelet defect	N	N	N or A	A
Vascular defect	N	N	N	N or A
Antithrombin III	N	N	N	N
Protein C	N	N	N	N
Protein S	N	N	N	N

A, abnormal; *N*, normal.

A. APTT
B. PT
C. Fibrinogen
D. Platelet count
E. Bleeding time (preferably by a standardized template method). This test is seldom helpful and should only be ordered selectively.

V. Normal screening tests may occur in von Willebrand's disease, mild hereditary factor deficiencies, hereditary coagulation disorders (heterozygotic carriers), factor XIII deficiency, prekallikrein deficiency, some dysfibrinogenemias, some platelet function disorders, hemorrhagic telangiectasia, and vascular purpuras.

Evaluation of a Bleeding Patient

The approach to the problem of a bleeding patient should be logical. A history and physical examination are mandatory. The following laboratory studies should detect the cause(s) and permit guidance in therapy for all but extremely rare coagulation defects.

I. PT and APTT: If abnormal, correction studies with pooled normal plasma, absorbed plasma, and serum reagent may be helpful.
II. Platelet count
III. Fibrinogen level
IV. Fibrin split products or D-dimer, or both
V. Bleeding time (This is rarely useful.)
VI. Hemoglobin or hematocrit, or both
VII. Peripheral blood smear
VIII. Clot for blood typing and antibody screen
IX. If excess heparin is suspected, either a protamine sulfate correction or a heparin resin absorption assay can rapidly establish the correct diagnosis.
X. Special studies, usually available only in larger laboratories, include specific factor assays, assays for inhibitors and antibodies, and platelet aggregation and antibody studies.

Most operative and postoperative bleeding is caused by inadequate local control of a severed blood vessel. Once a patient begins to hemorrhage, it is mandatory to stop this bleeding because massive blood loss (usually greater than 15 to 20 units of blood in 24 hours) itself may deplete certain procoagulants. Only rarely are coagulation factor deficiencies responsible for this type of hemorrhage.

Identifying the Cause of the Bleeding

Specific factor assays will be suggested by the laboratory consultant based on the preceding screening studies. Isolated deficiencies are usually hereditary, whereas those that are acquired frequently involve multiple factors.

Hereditary Factor Deficiencies

I. Classic hemophilia (hemophilia A) or factor VIII deficiency, a sex-linked hereditary disorder, is the most common hereditary factor deficiency. It is detected by the presence of an abnormal APTT that is corrected by barium sulfate-adsorbed normal plasma and will not correct with known factor VIII-deficient plasma. It appears to be caused by the production of normal amounts of nonfunctional factor VIII molecules, because factor VIII antigen (VIIIag) levels are normal. It should be noted that up to 40% of classic hemophilia patients have a negative family history for the disease.
II. Hemophilia B (Christmas disease), or factor IX deficiency, is less common. It also is a sex-linked, autosomally recessive inherited condition. The APTT is prolonged, but in contrast to hemophilia A, the abnormality is not corrected by barium sulfate-adsorbed plasma, although normal stored plasma or serum can correct the APTT.
III. The remaining numbered factor deficiencies are extremely rare.
IV. Factor deficiencies must be confirmed by performing a specific factor assay using known factor-deficient control material.

V. Although infrequent, acquired factor deficiencies can occur in a variety of diseases, including lymphomas, plasma cell dyscrasias, amyloidosis, and nephrotic syndrome.
VI. Clotting factor inhibitors may be associated with some disease states, notably the connective tissue disorders. They also have occurred in ulcerative colitis, postpartum, and in association with some drug reactions. Occasionally, they occur in the absence of any identifiable disease. Special laboratory tests are necessary for their identification.

Vascular Defects and von Willebrand's Disease

I. Vascular disorders are poorly defined and not well understood. The etiology of vascular "fragility" is not always apparent. These patients have prolonged bleeding times. With the exception of vascular pseudohemophilia (von Willebrand's disease), the bleeding is rarely severe.
II. von Willebrand's disease (VWD) exhibits autosomal dominant inheritance. It is characterized by a decreased factor VIII antigen (in contrast to classic hemophilia A in which factor VIII antigen is normal), and failure of platelets to aggregate in the presence of ristocetin. Other common findings include a prolonged bleeding time, elevated APTT, and a low factor VIII level. Platelet adhesion may also be defective. Not all patients will manifest all of these laboratory abnormalities at any one time in their disease.
III. Testing for VWD
A. Ristocetin cofactor assay of VWF function (VWF:RCoF)
B. Useful additional test: VWF antigen (VWF:Ag)
C. VWF multimeric assay
IV. Defines VWD variants
V. Important to identify type I VWD because the drug desmopressin acetate (DDAVP: a vasopressin analog that causes transient release of VWF from body storage sites) can be used to prevent bleeding in type I VWD patients.
VI. DDAVP is contraindicated in type II and III VWD.
VII. Factor VIII deficiency in VWD differs from that found in hemophilia A. Infusion of plasma concentrates causes a prolonged elevation of factor VIII levels in VWD but not in classic hemophilia A, in which factor VIII activity disappears rapidly. Similarly, plasma from a classic hemophilia A patient corrects the VWD patient's ristocetin platelet aggregation defect.
VIII. Aspirin causes an exaggerated prolongation of the bleeding time in VWD. Many other drugs can also adversely affect platelet function.
IX. VWF can increase with physiologic stress (e.g., exercise, pregnancy, blood loss) and cause false normal results in mildly deficient VWD patients.

Platelet Defects

Bleeding can occur because of too few or too many platelets. Platelets that are qualitatively defective may be unable to react normally in the clotting process even when present in adequate numbers. The normal platelet count is about 150,000 to 400,000/mm^6. One-third of the platelet mass is sequestered in the spleen. It takes 5 to 7 days for platelets to mature from megakaryocytes. The platelet survival time in the circulation is about 10 days. Transfused platelets survive 4 to 5 days in the absence of antiplatelet antibodies.

Platelets adhere to injured vascular endothelium by contact with subendothelial collagen. The adenosine diphosphate (ADP) released from the cytoplasmic granules of the platelets participates in the induction of aggregation and cohesion. Meanwhile, the phospholipids (platelet factor 3), and other cellular constituents that are discharged, activate Hageman factor (XII), which in turn activates the intrinsic clotting pathway. Thrombin and perhaps ADP cause consolidation of the platelet plug.

Laboratory Tests

I. If bleeding is thought to be owing to a platelet abnormality, the following quantitative and qualitative platelet tests are indicated. The first three tests are available in most laboratories. The remainder may not be generally available.

A. Direct examination of the stained smear
B. Platelet count
C. Bleeding time (template method preferred)
D. Prothrombin consumption time with and without inositin
E. Adhesion
F. Aggregation
G. Assay for platelet factor 3
H. Platelet sizing (volume)
I. Clot retraction, although simple, is too nonspecific and takes too long. It is not recommended when a bleeding time can be obtained.

II. The probability of bleeding is related to the results of the quantitative and functional tests.
A. Functionally normal platelets in numbers greater than 50,000/mm³ ordinarily prevent hemorrhage during surgical procedures.
B. Major spontaneous hemorrhage is decidedly unusual with functionally normal platelet counts in excess of 20,000/mm⁶.
C. Spontaneous hemorrhage may occur with counts of 10,000/mm³ or less, but it is not unusual for patients with such levels and lower to go for long periods without serious complications, especially when the etiology of the thrombocytopenia is on an immune basis. The major threat at this low platelet level is intracranial hemorrhage, particularly in infants and young children. Patients with both anemia and thrombocytopenia are more likely to bleed than those with thrombocytopenia alone.
D. In patients with depressed platelet counts, it may be important to have some idea of the functional integrity of the platelets. The best, simplest, readily available test of platelet function is the standardized (template) bleeding time. Studies of platelet adhesiveness and aggregation sometimes may be pertinent but are not widely available. These patients should be guarded from taking drugs that affect platelet function, particularly aspirin.

Quantitative Platelet Abnormalities

Definition

Thrombocytopenia is said to exist when the platelet count is below 100,000/mm⁶. Thrombocytosis, usually a transient state, is present when the platelet count is greater than 400,000/mm⁶. Thrombocythemia is a condition in which the platelet count exceeds 900,000/mm⁶.

Etiology

The following is not an all-inclusive list.

I. Thrombocytopenia
A. Diminished or defective platelet production
1. Congenital
a. Wiskott–Aldrich syndrome
b. May–Hegglin syndrome
c. Chediak–Higashi anomaly
2. Acquired
a. Aplastic anemia
b. Marrow infiltration
c. Radiation toxicity
d. Chemotherapy
e. Direct toxicity to platelet production (e.g., thiazides, alcohol, estrogens)
f. Cyclic thrombocytopenia (premenstrual)
6. Nutritional
a. Vitamin B_{12} deficiency
b. Folic acid deficiency
c. Iron deficiency
4. Viral infections

5. Paroxysmal nocturnal hemoglobinuria
6. Splenic disorders
a. Congestive
b. Neoplasms
c. Infiltrations
d. Infections
7. Miscellaneous
a. Heat stroke
b. Burns
c. Endocrine
B. Increased platelet destruction
1. Giant cavernous hemangioma (Kasabach–Merritt syndrome)
2. Infection (viral, bacterial, rickettsial, fungal, mycobacterial)
6. Disseminated intravascular coagulation
4. Thrombotic thrombocytopenic purpura
5. Hemolytic-uremic syndrome
6. Drug-induced
a. Immunologic (e.g., quinine, quinidine, heparin)
b. Nonimmunologic
7. Posttransfusion
8. Idiopathic thrombocytopenic purpura
9. Connective tissue disorders
10. Extracorporeal circulation

II. Thrombocythemia
A. Myeloproliferative disorders
B. Chronic inflammatory states
C. Acute inflammation
D. Acute hemorrhage
E. Iron deficiency
F. Hemolytic anemias
G. Malignant diseases
H. Postoperative (especially splenectomy)
I. Drug-induced
J. Postexercise

III. Thrombocytopenic purpura
A. Acute idiopathic thrombocytopenic purpura (ITP) is usually a disease of childhood. Onset is usually preceded by infection (viral more frequently than bacterial). Spontaneous recovery within a 1- to 2-month period from onset is the general rule.
B. Chronic idiopathic thrombocytopenic purpura is more often a disease of women between the ages of 20 and 50 years. Onset is usually insidious. The disease is characterized by the presence of a purpuric or petechial eruption. Splenomegaly is minimal if present at all. The platelet counts may range from 10,000 to 75,000/mm⁶. Counts as low as 1,000/mm³ may be seen. Bleeding is rare unless the platelet count falls below 20,000/mm⁶. The number of megakaryocytes in the bone marrow is normal or increased, but the megakaryocytes are less granular and more basophilic than normal. These patients typically do not respond to platelet transfusions. Drug sensitivity, sepsis, TTP, disseminated intravascular coagulation, systemic lupus erythematosus, tuberculosis, sarcoidosis, and lymphoma must be excluded.
C. Platelet sequestration (hypersplenism). Many conditions may cause splenomegaly with hypersplenism and thrombocytopenia.
D. Other causes. Hemorrhage, multiple transfusions, and extracorporeal circulation may result in platelet losses and thrombocytopenia.

IV. Thrombocythemia. Platelet counts above 1,000,000/mm³ are likely to be dangerous. An exception to this is the thrombocythemia occurring after splenectomy for trauma or staging. Bleeding from the mucous membranes may occur, and thrombotic phenomena are common. The cause of the bleeding is presumed to be mechanical interference with the normal clotting mechanisms by the presence

of excessive numbers of platelets and by the excessive release of platelet procoagulant factors.

Qualitative Platelet Disorders

I. Drug-induced disorders: Drugs are the single most common cause of qualitative platelet defects, and aspirin is the single most common offender. Aspirin inhibits aggregation by irreversible acetylation of platelet cyclooxygenase (prostaglandins). One adult-dose aspirin may prolong the bleeding time for up to a week. Other drugs affecting platelet function include other antiinflammatory drugs (except acetaminophen [Tylenol]), antibiotics, antidepressants, and many other miscellaneous agents.
II. Thrombasthenia (Glanzmann's disease): This is a rare disorder with autosomal recessive transmission characterized by a prolonged bleeding time and failure of the platelets to aggregate in the presence of ADP and thrombin. Bleeding occurs because platelets are unable to bind fibrinogen and hence to aggregate.
III. Thrombocytopathic purpura (platelet factor 3 deficiency): In this condition, the platelets lack clot-promoting activity because of defective phospholipid release. The bleeding time is prolonged and aggregation of platelets by ADP and thrombin may be impaired.
IV. Thrombocytopathy (Bernard–Soulier syndrome): This is a rare disorder characterized by a prolonged bleeding time, impaired aggregation by thrombin but not ADP, and normal phospholipid release. There are characteristically giant platelets with large, prominent, dense granules giving a pseudonucleated appearance.
V. Paraproteinemia: Numerous manifestations of platelet dysfunction occur with myelomas and macroglobulinemias, which may be owing in part to the protein covering the surface of the platelets.
VI. Myeloproliferative disorders and leukemia: Multiple defects occur in these disorders.
VII. Anemia: Anemia, by itself, can cause a prolonged bleeding time in some patients. Correction of the anemia can correct the bleeding time.

Acquired Disorders

Vitamin K-Dependent Factors

I. Factors II, VII, IX, and X are synthesized by the liver. All are dependent on vitamin K for their synthesis. Deficiencies in these factors are detected by measuring the prothrombin time. It should be noted that different methods of PT determination exhibit different sensitivities to deficiencies in these factors.
II. Vitamin K is naturally synthesized by intestinal bacteria. It is absorbed only in the presence of bile salts because of its lipid solubility.
III. Depletion of vitamin K-dependent factors may occur in patients receiving antibiotics (especially for "bowel preps"), in obstructive jaundice, malabsorption states (e.g., sprue), and hepatic parenchymal disease.
IV. Parenteral vitamin K therapy can alleviate vitamin K deficiency unless hepatic cellular function is too severely compromised. In an emergency, rapid reversal can be achieved with infusion of fresh frozen plasma.
V. Protein C and protein S, important in hypercoagulability, are also vitamin K dependent.

Liver Disease

I. Deficiencies may be noted in factors VII, IX, X, V, II, and I, in the order given. The degree of deficiency is related to the severity and duration of the hepatocellular disease.
II. Factor VIII paradoxically rises to extremely high levels.
III. Plasminogen and antithrombin III deficiencies may occur.
IV. Fibrin split products are poorly cleared, thus predisposing to fibrinolysis.
V. Abnormal fibrinogens (dysfibrinogenemia) and antithrombin V may also be produced.
VI. Marrow platelet production may be depressed. Excessive sequestration of platelets may occur in the spleen, which may involve as much as 80% of the platelet mass in some hypersplenic states.

Renal Disease

I. Uremic thrombocytopathy may occur when the BUN exceeds 100 mg/100 dL.
II. The thrombocytopathy is manifested by an adhesive abnormality that is correctable by dialysis.
III. Urinary loss of procoagulants, especially factor IX, may occur.
IV. In connective tissue disease with renal involvement, pathologic inhibitors of procoagulants may appear in the circulation.

Massive Transfusions

I. Bank blood is deficient in platelets and factor V. Factor VIII is also variably depleted. Clinical problems related to deficiencies in bank blood virtually never occur unless at least 10 units of stored blood have been transfused.
II. Empiric replacement with fresh frozen plasma, or platelets, or both, should not be initiated without first measuring PT, APTT, and platelet count. Where readily available, fibrinogen, FSP (and/or D-dimer), plasminogen, and AT III can be useful.
III. It is not uncommon for a previously healthy patient to receive 20 or more units of blood in less than 24 hours without requiring any component (platelets, FFP) therapy.
IV. Hypocalcemia and/or hypomagnesemia are almost never a cause of bleeding because electroconductive defects (e.g., cardiac arrhythmias) will occur before bleeding develops.

Reaction to Heparin Therapy

I. Heparin is a naturally occurring substance; its greatest concentration is found in lung tissue. It interferes with clotting by a variety of actions: inhibition of factors V, IXa, and XIII; inhibition of the proteolytic activity of thrombin (antithrombin); increased inactivation of factor Xa; and, in large doses, inhibition of platelet aggregation.
II. Heparin prolongs the Lee–White whole blood clotting time (an obsolete test), plasma or whole blood recalcification time, APTT, thrombin time, and even (but unpredictably) PT. The correlation of the heparin dosage with the results of these tests is imperfect.
III. No single test of heparin activity now available is clearly superior to any other. The most commonly used tests are the APTT and recalcification time. The optimum level of anticoagulation for heparin therapy varies with the indication for use.
IV. Low molecular weight heparin therapy does not require monitoring by APTT or whole blood recalcification time.

Reaction to Coumarin Compounds

I. Coumarin derivatives are drugs with similar mechanisms of action but with variable rates of absorption and duration of activity. Their principal action is inhibition of the hepatic synthesis of vitamin K-dependent factors (II, VII, IX, and X) either by interference with vitamin K transport in the liver or by direct competition with vitamin K. It is also possible that these compounds cause the liver to produce abnormal forms of factors II, VII, IX, and X, perhaps by interference with a late step in peptide chain formation.
II. Factor VII is depressed first by the action of these drugs. The PT is affected most by deficiency of this factor. Subsequently, factor IX (not measured by the PT) falls, followed by decline in factors II and X. The last two factors reach their lowest levels in about 5 to 10 days. Reversal of drug effects by intravenous vitamin K usually occurs in 6 to 12 hours, provided liver function is normal. However, factor II may remain depressed for some time after the PT and APTT become normal.
III. Coumarin drugs may prolong the APTT as well as the PT.
IV. The PT is the test of choice for monitoring therapy with this group of drugs. The absolute PT compared to a control is more meaningful than "percent activity."
V. The International Normalized Ratio (INR) is a calculated value derived from the PT. It is intended to standardize PT results among laboratories regardless of differences in reagent systems and instruments. Because the INR is dependent

on the ISI (International Sensitivity Index) of the reagent system, the lower the ISI (closer to 1.0), the more sensitive the INR.

VI. The INR is intended for standardized monitoring of coumadin anticoagulation. INRs should not be used to diagnose coagulation deficiencies or the effectiveness of correcting congenital factor deficiencies.

Surreptitious Bleeding

Self-administered sodium warfarin (Coumadin), heparin, and aspirin have all been implicated in causing bleeding. Self-inflicted trauma has produced urinary tract, vaginal, rectal, upper GI, and cutaneous bleeding. Patients with these manifestations usually have significant psychiatric disorders.

Circulating Anticoagulants

Circulating anticoagulants are found most often in association with hemophilia A or systemic lupus erythematosus. In both instances the substances, which may be IgG autoantibodies, are active against factor VIII. Circulating anticoagulants that are active against other factors or that are found in other diseases have been described. Occasionally, circulating anticoagulants may occur in patients who are otherwise free of identifiable disease. Inhibitors can cause prolongation of either the PT or APTT. The lupus anticoagulant, which causes a prolonged PT or APTT, generally does not cause clinical bleeding, but is associated with hypercoagulable states (see the following).

Defibrination Syndromes

Classification

I. Defibrination syndromes may be divided into three major categories: disseminated intravascular coagulation, primary fibrinolysis and therapeutic fibrinolysis.
   A. Disseminated intravascular coagulation (DIC) occurs when thromboplastin-like material enters the circulation in sufficient quantities to cause excessive deposition of fibrin in the microcirculation. The physiologic response to the fibrin deposition is extensive fibrinolysis, with the formation of soluble fibrin degradation products (fibrin split products). Some of the fibrin split products, particularly fragments X and Y, are themselves potent anticoagulants.
   B. Primary fibrinolysis, in contrast, occurs in the presence of excessive plasmin, which is a potent digester of fibrinogen. This disorder may also result in the production of fibrin split products.
   C. Therapeutic thrombolysis or thrombolytic therapy is a medically induced clot lysis using pharmacologic agents. It is used for coronary artery and selected peripheral vascular thromboses.

II. DIC is a relatively common hemorrhagic disorder. It constitutes more than 90% of the defibrination syndromes. It is often associated with a treatable predisposing disease such as bacteremia, abruptio placentae, retained dead fetus, incomplete abortion, burns, and snakebite. Other less directly treatable causes include transfusion reactions, giant hemangiomas, surgical manipulations, acute promyelocytic leukemia, and carcinoma.

III. Primary fibrinolysis is rare. It is associated most frequently with prostatic adenocarcinoma and cirrhosis of the liver.

Diagnosis of Acute Disseminated Intravascular Coagulation and Primary Fibrinolysis

I. The clinical situation generally is urgent. Bleeding is extensive and characteristically occurs from multiple sites, such as the mucous membranes, incisions and wounds, needle puncture sites, the GI tract, and the genitourinary tract.

II. In both diseases the pathophysiologic process is essentially the conversion of plasma to serum *in vivo*. Thus, variable depressions of plasma fibrinogen level, platelet count, and procoagulants are seen. The PT and APTT are usually prolonged. The fibrin split products (FSP) that are produced can be measured directly or estimated from the thrombin time. Measurement of D-dimer can supplement or replace FSP measurements.

III. The tests listed in Table 6-6 (shown with "typical" results) are recommended for the diagnosis of diffuse intravascular clotting. All but the last three tests are widely available and generally can be completed within 1 hour. Other tests are useful but less available.

Table 6-6. Tests for the diagnosis of diffuse intravascular clotting

Test	DIC	Primary Fibrinogenolysis
Platelets	↓↓↓	Normal (↓)
Fibrinogen	↓↓	↓↓
PT	↑↑	Normal (↑ if cirrhosis)
APTT	↑↑	Normal (↑ if fibrinogen ↓)
FSP (FDP)	↑ (Normal)	↑↑
D-dimer	↑↑	Normal
AT III	↓↓	↓ (Normal)
Plasminogen	↓↓	↓ (Normal)

IV. Comments
   A. Fibrinogen is considerably elevated in women during the third trimester of pregnancy and in many men and women under stress. Thus, in such individuals a "normal" fibrinogen level may actually represent a depressed one when compared to fibrinogen concentrations in the prehemorrhagic state.
   B. Not all cases show all of the features of the respective disorders; for example, the PT or APTT may be relatively normal.
   C. The red blood cell morphology in advanced DIC is often abnormal, with the formation of schistocytes and helmet cells. However, DIC may occur in the absence of these changes, especially early in this process.
   D. FSP detects lysis of both fibrin clot and fibrinogen.
   E. D-dimer detect lysis of fibrin clot only.

V. Additional studies.
   A. In both DIC and primary fibrinolysis, factor V is depleted. Assay for this factor may not be readily available and is generally not helpful.
   B. Factor VIII is low in both of these entities. However, factor VIII, like fibrinogen, is a stress factor and may be elevated before or concomitant with the bleeding episode. Thus, a normal level may be misleading. Low levels may occur in liver disease.
   C. Cryofibrinogen may be detectable in DIC, but its determination is time consuming. It is useful only retrospectively.
   D. Antithrombin III is depleted in DIC according to some, but not all, methods.
   E. Plasmin and plasminogen assays are decreased.
   F. Plasma paracoagulation tests (ethanol gelatin and protamine sulfate precipitation) for fibrin monomers—increased in DIC but not fibrinolysis—have proved unreliable.

Thrombolytic Therapy

I. Although PT, APTT, and TT, are frequently ordered prior to administration of therapy, there are no guidelines to adjust therapy based on values obtained. Thus pretherapy testing is probably useless.

II. When postthrombolytic clotting parameters are measured, they are markedly prolonged. There are no established criteria, however, to adjust therapy based on the results.

III. There may be some value to obtaining coagulation studies if concurrent heparinization is anticipated.

Transfusion Therapy

Although there is insufficient space here to review this subject adequately, the primary purpose of blood transfusion is for oxygen-carrying capacity. Most patients do not need transfusion for an acute bleed without a hemoglobin of less than 8 gm/dL unless they are in shock or have angina or known cardiac disease. Component therapy—platelets,

fresh frozen plasma, factor concentrates, or albumin—should not be administered without documentation of indication and informed patient consent. Every hospital should have audit criteria for monitoring appropriate use of blood and component therapy.

Hypercoagulable State (Thrombophilia)

I. Patients with a hypercoagulable state (i.e., predisposition to thromboemboli), usually have a clinical history of one or more prior thrombotic episodes.
II. Hypercoagulability occurs in congenital (familial) and acquired forms.
III. The most common cause of inherited venous thrombosis is a deficiency owing to a point mutation in factor V, known as factor V Leiden, which results in increased resistance to activated protein C. Next in frequency is a prothrombin mutation (factor II G20210A).
IV. Causes of hypercoagulability
  A. Low factor V Leiden
  B. Prothrombin gene mutation
  C. Hyperhomocystinemia
  D. Low protein C
  E. Low protein S
  F. Low AT III
  G. Antiphospholipids
  H. Lupus anticoagulant
  I. Plasminogen deficiency
  J. Dysfibrinogenemia
  K. High platelet count
  L. Abnormally short APTT
  M. Spontaneous platelet aggregation
  N. Circulating platelet micro aggregates
  O. Abnormal thrombin generation time
V. Acquired hypercoagulability may be seen in postinflammatory states, malignancy, antiphospholipid syndrome, myeloproliferative disorders, and following L-asparaginase therapy heparin-induced thrombopathy.
VI. Laboratory studies to support the diagnosis of hypercoagulability or to identify patients at risk may be unrewarding, but one or more of the following tests may be abnormal in some of these patients:
  A. Factor V Leiden (Activated Protein C resistance) (FV R506Q)
    1. This appears to be the most common cause of hereditary hypercoagulability.
    2. Mutation in factor V causes activated protein C resistance which inactivates cofactors FVa and FVIIIa.
    6. Heterozygous fivefold to tenfold increased risk, homozygous 50- to 100-fold increased risk for venous thrombosis
    4. Uncertain if FV Leiden is arterial risk factor
    5. Other factor V mutations were recently discovered (e.g., FV Cambridge), which also produces APC resistance.
    6. Testing
      a. Screening patients may be on warfarin (Coumadin) for a screening test, but must be off of heparin for at least 72 hours.
      b. DNA probe for factor V mutation (FV Leiden) should only be ordered if:
        (1) The screening test is positive, or
        (2) You cannot wait 72 hours, or
        (3) You cannot take the patient off heparin.
  A. Prothrombin gene mutation
    1. Factor II is a critical precursor of thrombosis.
    2. G20210A point mutation increases venous thromboembolism threefold.
    6. Patients have increased plasma prothrombin concentrations.
    4. After factor V Leiden, prothrombin mutation is the second most frequent cause of inherited increased risk for thromboembolic disease.
    5. The patient should be off anticoagulants for testing.

  A. Hyperhomocystinemia
    1. May be hereditary or acquired (mostly nutritional disorders)
    2. Affected by creatinine and folic acid levels
    6. Increased incidence venous and arterial thrombosis
    4. Measure plasma homocysteine level
    5. Testing: assays *not* affected by anticoagulants

Protein C Deficiency

I. Heterozygous are at a sevenfold increased risk for thrombotic disease.
II. Heterozygous manifests venous thromboemboli or warfarin-induced skin necrosis, or both.
III. Homozygous produces purpura fulminans neonatalis.
IV. Acquired (liver disease, DIC, adult respiratory distress syndrome, postsurgical) causes venous thromboemboli.
V. Draw sample for protein C prior to heparinization of patient.

Protein S Deficiency

I. Heterozygous is associated with venous and possibly arterial thromboemboli.
II. Homozygous is associated with venous thromboemboli.
III. Acquired liver disease, pregnancy, DIC, nephrotic syndrome, or SLE causes venous thromboemboli.
IV. Warfarin-induced skin necrosis.
V. Draw sample for protein S before heparinizing patient.

Antithrombin III Deficiency

I. It has autosomal dominant inheritance with AT III levels of 25% to 50% of normal.
II. It frequently manifests thrombophlebitis and pulmonary emboli.
III. Pregnancy, oral contraceptives, surgery, trauma, and infection predispose to thrombosis.
IV. Because of low AT III level, patients appear to be heparin resistant and require large amounts of heparin to prolong APTT.

Pulmonary Emboli and D-Dimer Testing

I. Use of D-dimer in screening for pulmonary emboli is controversial and not uniformly accepted.
II. Normal D-dimer levels have been reported to correlate with a high negative predictive value for pulmonary emboli.
III. Elevated D-dimer levels do not have any positive predictive value for pulmonary emboli.

Indications for Testing for Thromboembolic Disease

I. Positive family history
II. Recurrent idiopathic thrombosis
III. Early age of onset
IV. Fetal loss
V. Warfarin (Coumadin) skin necrosis
VI. Purpura fulminans
VII. Unusual site

When to Test

I. It is best to test in the baseline state, not during or immediately after an acute event.
II. Patients who are nonanticoagulated, nonpregnant, and not taking oral contraceptives
III. Levels of AT III, PC and PS affected by anticoagulation, liver disease, pregnancy, inflammation, medicines
IV. If you must test while the patient is anticoagulated, take the patient off oral anticoagulation and place him or her on heparin for at least 10 days.

Antiphospholipid Syndrome

Jerome S. Nosanchuk

I. The syndrome is associated with circulating antibodies to phospholipid binding plasma proteins (cardiolipins).
II. Patients are frequently found because of false-positive test for syphilis.
III. It is associated with venous and arterial thrombosis, recurrent fetal loss, and thrombocytopenia; less often with pulmonary hypertension, valvular heart disease, retinal thrombosis, and central nervous system (CNS) disorders.
IV. It may be induced by some drugs, including phenytoin, quinidine, sulfadoxine with pyrimethamine, procainamide, phenothiazine, and cocaine.

Laboratory Tests

I. Anticardiolipin or antiphospholipid antibody
II. Circulating anticoagulant
III. False-positive test for syphilis

7. RENAL, ELECTROLYTE, BLOOD-GAS, AND ACID-BASE PROBLEMS

Renal and Urinary Tract Disorders

Michel B. Chonchol and Isaac Teitelbaum

In the diagnostic approach to diseases of the kidney and urinary tract, it is important to determine if the decline in glomerular filtration rate (GFR) is owing to prerenal, postrenal, or intrarenal disease. Intrinsic renal disease is best approached by categorizing the primary pathologic process into glomerular or nonglomerular disorders (e.g., tubules, interstitium, vascular system). It is also important to differentiate between primary renal disease and renal disease that is secondary to a systemic disorder. Special attention should be paid to those diseases that are either preventable or treatable.

Kidney and urinary tract disease may be discovered in a number of ways.

I. In many cases, a renal abnormality is suspected because the patient's complaints are directly related to the urinary tract or urine formation. Examples of such symptoms are frequency, dysuria, burning on urination, urgency, colic, polyuria, nocturia, hematuria, oliguria, and anuria.
II. Some patients are discovered to have renal disease because of the finding of laboratory abnormalities (e.g., proteinuria, microscopic hematuria, elevated plasma creatinine concentration, electrolyte and acid-base disturbances) during the course of a routine examination or an investigation for another purpose.
III. Occasionally patients present with symptoms and signs of renal failure (e.g., uremia, anuria, hypertension, edema) without any prior known kidney disease.
IV. Disease of the kidney and urinary tract may also become evident because of the manifestations of a systemic illness that involves the kidney secondarily. Examples of such conditions are as follows:
   A. Metabolic diseases (e.g., diabetes mellitus)
   B. Connective tissue diseases (e.g., systemic lupus erythematosus, polyarteritis nodosa, scleroderma)
   C. Infectious diseases (e.g., Gram-negative sepsis, infective endocarditis, tuberculosis, malaria)
   D. Cardiovascular diseases (e.g., hypertension, congestive heart failure)
   E. Infiltrative diseases (e.g., multiple myeloma, amyloidosis, lymphoma)

Frequency, Urgency, and Dysuria

General Considerations

I. This triad of symptoms is most often associated with infection of the urinary tract. However, care must be taken to evaluate each symptom, because any one may represent a diverse group of conditions other than urinary tract infection.
II. Frequency is defined as voiding at intervals of 2 hours or less, or more than seven times per day. A wide variety of nonpathologic factors may affect voiding intervals, including fluid intake, drugs, and consumption of bladder irritants (e.g., alcohol, caffeine). Patients with polyuria from any cause may complain of frequent voiding with an increased urine flow. In contrast, bladder inflammation may cause frequency without an increase in urine flow.
III. Urgency is typically described as a powerful sensation to void, regardless of bladder volume. Not uncommonly, the voided volumes of these patients are small—much less than the patient's normal maximum cystometric capacity. Urgency is most often caused by bladder inflammation, although prostatic enlargement may also cause this symptom. External compression of the bladder by masses, as in pregnancy, may also generate the feeling of urgency.

IV. Dysuria (painful urination) suggests irritation or inflammation in the bladder neck or urethra, usually because of bacterial infection.

History

I. A history of recurrent urinary tract infections suggests underlying anatomic or physiologic abnormality of the urinary tract.
II. Vaginal infections and sexually transmitted diseases may mimic urinary tract infections; therefore, they should be excluded.
III. Chills, fever, and back pain in addition to symptoms of bladder irritation almost always indicates upper urinary tract involvement.

Physical Examination

I. A complete physical examination is indicated.
II. The presence of costovertebral angle tenderness is compatible with inflammation of the kidney or distention of the renal pelvis or ureter.
III. The most common cause of bladder pain is bacterial cystitis; the discomfort is usually suprapubic and referred to the distal urethra during urination. Acute urinary retention causes agonizing pain in the suprapubic area.
IV. Abnormalities of the urethral meatus and along the course of the urethra may cause dysuria; specific attention should be given to these areas during examination.
V. Prostatic disease is usually painless, but an acutely inflamed prostate (prostatitis) may cause urethral symptoms. This gland should be examined carefully in all men with urinary symptoms.

Laboratory Findings

I. Pyuria and bacteriuria are consistent with the diagnosis of urinary tract infection. Leukocyte casts are pathognomonic of renal parenchymal infection.
II. Bacteriuria with over 100,000 colonies/mL of urine (from clean-voided specimens) is considered abnormal. Urine culture and sensitivity tests should be performed. Positive cultures recovered from catheterized or suprapubic puncture specimens are significant.
III. Further evaluation of these symptoms may require ultrasonography, excretory urography, voiding cystourethrography, retrograde urography, cystoscopy, and other, more specialized tests.
IV. If the patient has symptoms of cystitis, but the urine does not contain bacteria (sterile pyuria), consider the possibility of renal tuberculosis.

Renal and Ureteral Colic

Definition

Renal colic, which is most often unilateral, is characterized by excruciating intermittent pain, usually originating in the flank or kidney area, which radiates across the abdomen toward the hypochondrium. The pain of ureteral colic has similar characteristics but typically radiates along the course of the ureter, frequently into the region of the genitalia and inner thigh.

Etiology

Renal colic is usually produced by acute inflammation or bleeding within the kidney with stretching of the renal capsule; it results from conditions such as acute pyelonephritis or an expanding cyst. Ureteral colic is most often associated with the passage of a renal calculus.

Associated Symptoms

The pain is commonly associated with gastrointestinal (GI) symptoms (nausea, vomiting, abdominal distention). Chills, fever, hematuria, and frequency of urination are common, particularly as a calculus passes down the ureter.

Physical Examination

The physical examination is usually unremarkable except for the presence of flank tenderness.

Laboratory Findings

I. Urinalysis. The urine may be normal despite multiple calculi. Macroscopic or microscopic hematuria is common. Pyuria with or without bacteria may be seen.
II. Radiograph. Most urinary calculi contain calcium and are demonstrable on abdominal films. If no stone is seen, and further investigation is desired, excretory urography (XU) should be performed. This may reveal opaque or nonopaque calculi, as well as the extent and degree of the obstruction. An XU also shows masses and cysts. If the affected kidney is not visualized, delayed films should be taken. When XU is contraindicated (e.g., because of allergy to dye, renal insufficiency, or pregnancy), renal ultrasonography may help locate stones and rule out obstruction.

Nephrolithiasis

Etiology

I. Calcium oxalate and calcium phosphate stones. Hypercalciuric states and hyperoxaluria are the main remediable causes of calcium stones. Hypercalciuric (150 mg/24 hr) states that causes calcium stones include: primary hyperparathyroidism, sarcoidosis, renal tubular acidosis, vitamin D excess, idiopathic hypercalciuria, absorptive hypercalciuria, prolonged immobilization, Cushing's syndrome, and excessive milk intake. Hyperoxaluric states that cause calcium stones include: primary hyperoxaluria, ileal resection, jejunoileal bypass, and dietary oxalate excess.
II. Struvite stones (ammoniomagnesium phosphate). These stones are formed in the presence of infection by urea-splitting organisms.
III. Cysteine stones. These stones occur in patients with the inherited transport disorder cystinuria.
IV. Urate stones. These are usually associated with hyperuricemic states (primary gout, secondary gout, and idiopathic hyperuricemia). However, many patients with uric acid calculi do not have hyperuricemia or increased uric acid excretion.

Diagnostic Approach

History and Physical Examination

I. The history should include information concerning the following: the age at which symptoms of stones were first noted; family history of nephrolithiasis; history of fractures or prolonged immobilization; previous urinary tract infections or manipulations; and the intake of milk, alkali, salt, and vitamins A, D, and C.
II. The physical examination should include investigation for the band keratopathy associated with hypercalcemic states.

Laboratory Procedures

I. At least two determinations of serum calcium should be performed. In addition, serum levels of phosphorus, alkaline phosphatase, total protein and albumin, uric acid, creatinine, and electrolytes should be obtained.
II. A midstream urine specimen should be collected for culture and sensitivity studies because urinary tract infections are commonly associated with nephrolithiasis.
III. The urinary pH should be determined, ideally by metering the pH of urine collected under mineral oil. A persistently alkaline urine in the presence of hyperchloremic acidosis suggests renal tubular acidosis.
IV. Quantitative calcium and uric acid determinations should be performed on two separate 24-hour urine specimens while the patient is on a regular diet with a known calcium intake. This allows detection of hypercalciuria or increased uric acid excretion. Hyperuricemia and increased urinary uric acid excretion favor the formation of calcium oxalate and phosphate calculi as well as uric acid stones. Urinary oxalate and citrate excretion should also be measured, as hyperoxaluria or hypocitraturia may predispose to stone formation.
V. The urine should be examined for the presence of cysteine crystals. The diagnosis of cystinuria is based on the demonstration of such crystals in cold acidified urine, a positive nitroprusside test, increased urinary excretion of cysteine (300 mg/24 hr), or the demonstration of the specific aminoaciduria by urinary chromatography.

VI. Architectural and chemical analyses should be performed on all stones that are passed.
VII. Plains films of the abdomen should be obtained routinely. If further definition is desired, excretory urography or ultrasonography should be performed.

Polyuria

Polyuria is defined as an excessive output of urine (more than 3 L/day). It is an important symptom or sign because of its potential severity, diverse causes, and interesting pathophysiology. Polyuria may occur in association with many normal or pathologic states. Polyuria per se is not hazardous, provided the lost fluid and solutes are replaced. However, polyuria may become deleterious if such losses are excessive and replacement is inadequate. Hypotension and cardiovascular collapse may then ensue.

Etiology

I. Polyuria may represent an appropriate physiologic response to osmolar, sodium, or fluid loads, or it may be secondary to diuretic therapy.
   A. Osmolar loads may result in the excretion of isotonic urine. The following are examples of solute loads that may produce an osmotic diuresis and polyuria:
      1. Glycosuria, as in diabetes mellitus or hyperosmolar nonketotic coma
      2. Administration of mannitol or urea
      3. Hyperalimentation therapy with amino acids or glucose
      4. Administration of IV contrast
   B. Sodium loads that are accompanied by increased water intake may result in a sodium diuresis and the excretion of isotonic urine. This may occur under the following circumstances:
      1. High dietary intake of sodium (rare)
      2. Administration of excessive quantities of salt and water by intravenous or tube feedings
      3. Rapid resorption of edema fluid
   C. Polyuria may sometimes be the result of compulsive water drinking, so-called psychogenic polydipsia. Some patients with psychogenic polydipsia drink 7 to 43 L of water daily. The condition is usually associated with psychiatric disturbances. Typically, both the plasma and urine osmolalities are low, and the secretion of the human antidiuretic hormone arginine vasopressin (AVP) is completely suppressed. Occasionally, dilutional hyponatremia and water intoxication may occur. When plasma osmolality is normal, the diagnosis can be made by a normal response to water deprivation.
II. Polyuria may represent the response to a pathologic state.
   A. Central diabetes insipidus. This disorder represents a complete or partial defect in the pituitary secretion of AVP, which results in impaired renal concentrating ability and attendant polyuria. The characteristic features are mild serum hyperosmolality, a dilute urine, and responsiveness to vasopressin.
   B. Nephrogenic diabetes insipidus. In this condition, there is a urinary concentrating defect that is unresponsive to AVP.
      1. Renal disease. The inability to concentrate urine adequately may result in obligatory polyuria. The most common causes are listed in the following.
         a. Chronic renal failure, particularly if associated with interstitial disease
         b. Recovery from acute renal failure or urinary tract obstruction
         c. Acute pyelonephritis
      2. Hypercalcemia
      3. Hypokalemia
      4. Congenital nephrogenic diabetes insipidus
      5. Drug-induced disease (e.g., methoxyflurane anesthesia, lithium carbonate, demeclocycline, potent diuretics)

The diagnosis of nephrogenic diabetes insipidus is based on the following criteria: the occurrence of dilute urine in the presence of normal or increased serum osmolality; an inability to concentrate urine adequately with fluid restriction; and a lack of responsiveness to vasopressin.

Table 7-1. Water-deprivation test[a]

	Urinary osmolality with water deprivation (mOsm/Kg of H_2O)	Plasma AVP after dehydration	Increase in urinary osmolality with exogenous AVP
Normal	800	2 pg/mL	Little or no increase
Complete central diabetes insipidus	300	Undetectable	Substantial increase
Partial central diabetes insipidus	300–800	1.5 pg/mL	Increase of greater than 10% of urinary osmolality after water deprivation
Nephrogenic diabetes insipidus	300–500	5 pg/mL	Little or no increase
Primary polydipsia	500	5 pg/mL	Little or no increase

[a] Water intake is restricted until the patient loses 3% to 5% of his or her body weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. (Caution must be exercised to ensure that the patient does not become excessively dehydrated.) Aqueous AVP (5 units subcutaneously) is given, and urinary osmolality is measured after 60 minutes. The expected responses are given in the preceding.
From Jacobson HR, Striker GT, Klahr S, eds. *The principles and practice of nephrology*: 2nd ed. St. Louis: Mosby, 1995, with permission.

Diagnostic Approach

I. Rule out administered fluid or solute loads, or both, and psychogenic polydipsia as possible causes of polyuria by the history and a review of the fluid and electrolyte balance.
II. Determine the urine and serum osmolality.
   A. If the urine osmolality is elevated above that of the serum, rule out glycosuria.
   B. If the urine is isosmotic with respect to serum, check for evidence of renal disease, and exclude glycosuria, administered diuretics, and solute loads as possible causes.
III. If the urine is hypotonic compared to serum osmolality, test for renal concentrating ability by restricting the fluid intake.
   A. If the urine becomes concentrated with fluid restriction, it can be concluded that fluid intake was excessive and that it was either psychogenic or iatrogenic in origin.
   B. If the ability to concentrate urine is impaired, it can be assumed that the nephron is unable to conserve water adequately, indicating either nephrogenic or true diabetes insipidus. The diagnosis of central or nephrogenic diabetes insipidus may be made by the water deprivation test (Table 7-1).

Oliguria and Anuria

Definition

Oliguria is that amount of urine output below which the normal load of metabolic waste products (usually 400–500 mL/24 hours) cannot be excreted. Anuria is arbitrarily defined as a urinary output below 50 mL/24 hr. True anuria (i.e., no urine obtained with a bladder catheter in place) raises concerns of a bilateral renal vascular catastrophe (arterial or venous) or of bilateral ureteral obstruction.

Etiology

I. Prerenal or functional impairment of renal perfusion. The response of the kidneys to renal hypoperfusion is appropriate.

A. Absolute volume depletion (e.g., shock and dehydration)
B. Diminished "effective" circulating blood volume without total volume depletion
   1. Congestive heart failure
   2. Cirrhosis of the liver
   3. Nephrotic syndrome
   4. "Third space" losses (e.g., peritonitis, bowel obstruction)

II. Obstructive uropathy
   A. Bladder outlet obstruction (e.g., prostatic, urethral, or neuropathic)
   B. Bilateral ureteral obstruction

III. Vascular disease
   A. Acute arterial obstruction
   B. Renal vein obstruction

IV. Renal parenchymal disease
   A. Diffuse acute glomerular disease (e.g., acute glomerulonephritis, acute vasculitis, disseminated intravascular coagulation)
   B. Acute tubular necrosis (e.g., prolonged prerenal failure, abruptio placentae, nephrotoxins, sepsis, shock, myoglobinuria)
   C. Acute interstitial nephritis
      1. Hypersensitivity type (e.g., sensitivity to methicillin, ampicillin, nonsteroidal antiinflammatory drugs (NSAIDs), cephalosporins, or other agents)
      2. Acute urate nephropathy
      3. Hypercalcemic nephropathy
   D. Postcontrast media (e.g., multiple myeloma, diabetes mellitus)
   E. Any of the preceding superimposed on chronic renal failure
   F. NSAIDs or angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers

Diagnostic Approach

The history, physical examination, and course of the disease are as important as laboratory studies in establishing the diagnosis and differentiating between renal and extrarenal causes of oliguria and anuria.

History

I. A history of previous surgery, GI bleeding, dehydration, or other fluid losses may provide clues to the etiology of acute renal failure.
II. Inquiry should be made concerning the use of potentially nephrotoxic drugs or combinations of drugs that may act synergistically to cause acute renal failure.
III. The possible use of drugs capable of causing hypersensitivity interstitial nephritis (e.g., penicillins, NSAIDs, cephalosporins) should be reviewed.
IV. Because anuria occurs more frequently in obstructive uropathy and the nephritides than in acute tubular necrosis, evidence of these conditions should be sought.
V. It is necessary to establish evidence of previous renal insufficiency to confirm the diagnosis of acute renal failure superimposed on chronic renal disease.

Physical Examination

The most important aspect of the physical examination is the evaluation of the condition of the circulation and the state of hydration. Findings such as poor tissue turgor, postural hypotension, tachycardia, and weight loss support the diagnosis of hypovolemia and prerenal azotemia. On the other hand, edema, distended neck veins, and pulmonary congestion suggest an adequate or increased circulatory volume, as may occur in congestive heart failure or cirrhosis of the liver. Decreased "effective" renal blood flow nevertheless may occur in these conditions.

Laboratory Findings

I. Urinalysis
   A. Heavy proteinuria, hematuria, and red blood cell casts suggest primary glomerular disease.

   B. Mild proteinuria, the presence of eosinophils on a Hansel's stain, and epithelial cell casts support the diagnosis of hypersensitivity interstitial nephritis.
   C. Trace to mild proteinuria with renal tubular epithelial cells, broad deeply pigmented granular casts, and cellular debris support the diagnosis of acute tubular necrosis, but may occur in severe prerenal failure.
   D. Myoglobinuria, hemoglobinuria, or urate crystals may be seen in some specific types of acute renal failure.

II. Serum chemistries
   A. A rising serum creatinine above 2.5 mg/100 mL suggests established renal failure as opposed to prerenal disease.
   B. The BUN to creatinine ratio is usually less than 15:1 in renal parenchymal disease but is often greater than 20:1 in prerenal disease.

III. Determination of urinary sodium, chloride, osmolality, urea, and creatinine
   A. These procedures are most helpful in differentiating between prerenal (physiologic) oliguria and established acute renal failure. As a rule, with functional oliguria a normal kidney responds to hypoperfusion by retaining salt and water in an effort to maintain circulating blood volume.

      In prerenal failure, urinary sodium is usually less than 10 mEq/L, urine is concentrated (osmolality 500 mOsm/kg), and a urine/plasma urea to creatinine ratio greater than 14:1 is present. The fractional excretion of sodium is less than 1%. The urine sodium may be greater than 10 mEq/L in states of prerenal failure associated with metabolic alkalosis. The urine chloride remains low, however.
   B. In established acute renal failure, tubular destruction and dysfunction are present. Urinary sodium exceeds 20 mEq/L, the urine is isosmotic (approximately 300 mOsm/kg) and the U/P urea and creatinine ratios are less than 14:1. The fractional excretion of sodium is greater than 4%. A "prerenal" picture may occur with early acute glomerulonephritis.
   C. Because most diuretics impair tubular function, pretreatment with these drugs causes the appearance of a urine consistent with renal failure, although, in actuality, prerenal failure may be present. This may also occur in patients with chronic renal insufficiency.

IV. Administration of fluids and diuretics
   A. A fluid challenge with the administration of 500 to 1,000 mL of normal saline over a 30-minute period to a patient who does not have congestive heart failure or is not fluid overloaded may be helpful in differentiating between prerenal and established renal failure. The occurrence of diuresis favors the diagnosis of prerenal failure.
   B. Should volume expansion fail to induce diuresis, diuretic agents should be administered. Unresponsiveness to a large dose of furosemide (5 mg/kg, up to 500 mg) plus a thiazide diuretic supports the diagnosis of established renal failure. However, adequate diuresis may sometimes occur when established oliguric acute renal failure reverts to a nonoliguric phase.

V. Radiographic diagnosis. Technetium scanning is most helpful in distinguishing vascular occlusion from obstructive uropathy and renal parenchymal disease. Bladder catheterization with a large residual urine suggests bladder outlet obstruction. CT scan, radioisotope scan, or ultrasound can be used to demonstrate the presence of disease in both kidneys and to look for signs of obstruction. Retrograde pyelography should be performed if a question of obstruction still remains after these procedures.

VI. Serial observations: A definitive diagnosis cannot always be made at the time of the initial evaluation of the oliguric patient. Serial measurements of various parameters of renal function, particularly the serum creatinine levels, usually establish the diagnosis of acute renal failure.

Nonoliguric Renal Failure

Although oliguria is considered a cardinal feature of acute renal failure, nonoliguric acute renal failure has been recognized since 1943. Large series of patients with acute

renal failure have emphasized that the nonoliguric form is an unusual variety of acute renal failure, and may be caused by a variety of renal insults. The prognosis of nonoliguric acute renal failure is substantially better than that of oliguric acute renal failure; however, nonoliguric acute renal failure is still associated with significant morbidity and mortality.

The laboratory abnormalities are similar to those found in oliguric acute renal failure except for the maintenance of a "good urinary output," usually about 1,000 mL in 24 hours.

The diagnostic approach is the same for other types of acute renal failure.

Uremia

Definition

Uremia refers to the final stages of progressive renal insufficiency when the complex, multiorgan system derangements become clinically manifest. The GI, cardiovascular, and central nervous systems are particularly involved. A variety of metabolites of proteins and amino acids have been considered possible uremic toxins, but the clinical symptoms of uremia correlate to their blood levels rather poorly. Uremia generally results from the accumulation of such metabolites. A uremic individual may also have symptoms and signs related to altered fluid and electrolyte balance. Unfortunately, patients often seek medical attention only when their disease has progressed to the uremic stage.

Clinical Features

A patient with uremia may have some or all of the following manifestations:

I. GI symptoms include loss of appetite, nausea, vomiting, diarrhea, and hiccups. Nausea and vomiting are sometimes severe enough to cause volume depletion and negative caloric balance, which results in weight loss. The patient may awake feeling reasonably well but have nausea and vomiting at the very sight, smell, or taste of food.
II. The spectrum of nervous system manifestations is broad. Tiredness, insomnia, poor concentration, and psychological symptoms including agitation, irritability, and depression, are common. Peripheral neuropathy is also common. Clinical manifestations include painful paresthesias of extremities, twitching, restless leg syndrome, muscular weakness, and occasional sensory deficits.
III. Cardiovascular complications in patients with chronic renal failure include atherosclerosis, hypertension, and pericarditis. Pulmonary edema and circulatory volume overload may occur.
IV. Other uremic signs include the Kussmaul breathing of metabolic acidosis, increased cutaneous pigmentation, pruritus, anemia, and a uremic breath odor.
V. The insidious onset of weakness and anemia may be the only clue to severe renal insufficiency.
VI. Severe azotemia and elevated serum creatinine levels are a reflection of decreased renal function.

General Principles

I. A primary question in the evaluation of the patient with renal failure is whether the renal failure is chronic or acute. Chronicity implies stability and thus presents less of an immediate threat to the patient than does acute renal failure. Acute renal failure often implies reversibility, whereas chronic renal failure is often irreversible. The diagnostic approach to uremia is basically the same as that outlined in the section Oliguria and Anuria.
II. In patients with uremia, it is essential, as a first step, to attempt to correct the biochemical abnormalities either by medical means or dialysis. When uremia is severe, dialysis is the therapy of choice and should be instituted without delay. Diagnostic studies can then be initiated. Other indications for acute dialysis are the presence of hyperkalemia, metabolic acidosis, fluid overload, drug intoxication, hypercalcemia, or hyperuricemia.

Diagnostic Approach

History

I. A history of hypertension, proteinuria, anemia, hematuria, analgesic abuse, debilitation, and chronic weight loss supports the diagnosis of long-standing renal disease.
II. Recent exposure to nephrotoxins, a major bleeding episode, or hypotensive states are helpful in establishing the diagnosis of acute renal failure.
III. Symptoms of obstructive uropathy (e.g., urinary tract infections, symptoms of prostatism), particularly in the elderly, are helpful in the diagnosis of obstructive uropathy.

Physical Examination

I. The state of hydration and the condition of the circulation should be evaluated.
II. Hypertension may occur in either acute or chronic disease.
III. Hypotension commonly accompanies dehydration and volume depletion.
IV. A distended urinary bladder suggests bladder outlet obstruction.
V. The physical findings specifically related to uremia are described under Clinical Features.

Laboratory Studies

I. The diagnosis of renal failure is established by documenting an elevation in blood urea nitrogen (BUN) and serum creatinine concentrations. With stable chronic renal failure, the BUN and creatinine rise proportionately, and a ratio of BUN to creatinine of 10:1 typically is observed.
II. When the GFR falls below 25 to 30 mL/min, other laboratory abnormalities may be seen. These include anemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, and hyperuricemia. Hyperkalemia is a late manifestation.
III. Useful diagnostic modalities are ultrasound and CT scan. The presence of small kidneys implies chronic renal failure. Normal-sized or large kidneys suggest acute disease. However, some patients with chronic disease (e.g., diabetes mellitus or amyloidosis) may have normal or even large-sized kidneys. Bone films may reveal the punched out lesions of multiple myeloma or characteristic changes of renal osteodystrophy.
IV. Urinalysis and the other diagnostic test outlined in the section Oliguria and Anuria are helpful in determining whether the renal failure is owing to glomerular, vascular, obstructive, or interstitial disease.
V. A percutaneous renal biopsy is sometimes necessary to establish a definitive diagnosis.

Laboratory Abnormalities in Renal Disease: Urinalysis

It is not unusual for a patient with renal disease to have no history or physical findings suggestive of renal disease. Many patients are discovered to have kidney disease because of abnormal findings on routine urinalysis. The analysis of urine was actually the beginning of laboratory medicine. Urinalysis is an inexpensive, readily available, easily collected, and often informative laboratory procedure that should be a component of any initial evaluation. The urine should be a first morning, clean catch, and ideally midstream specimen. The two most common urinary abnormalities that suggest renal disease are hematuria and proteinuria. These conditions are discussed separately from other aspects of the urinalysis.

A number of important parameters should be measured. These will be described sequentially.

I. Appearance. Appearance is a general term that refers to the clarity of a urine specimen. Cloudiness or turbidity on standing is usually secondary to the precipitation of urates and phosphates. Besides amorphous crystals, the four most common substances that cause turbidity in urine are white blood cells, red blood cells, epithelial cells, and bacteria.
II. Color. The color of urine may vary from almost colorless to black. These variations may be owing to pathologic conditions. A noticeable change in color is often

the reason a patient seeks medical advice. Normal urine is yellow to amber in color. A deep yellow color usually signifies a normal concentrated urine but may be caused by the presence of the abnormal pigment bilirubin. The presence of bilirubin is suspected if a yellow foam appears when the specimen is shaken. Bile may also produce a cola-colored urine.

One of the most common causes of abnormal urine color is the presence of blood. Red blood cells, hemoglobin, and myoglobin impart a red or reddish brown color to the urine. Many abnormal urine colors are of a nonpathogenic nature and are caused by the ingestion of highly pigmented foods, medications, and vitamins. A white foam may occur when urine is shaken. Foaming is increased with proteinuria.

III. Specific gravity. Specific gravity is defined as the density of a substance compared with the density of a similar volume of distilled water at a similar temperature. It therefore is a measure of the weight of solutes in water. Thus, urine with a specific gravity of 1.010 is 1% heavier than water. Normal random specimens may range from 1.001 to 1.035, depending on the patient's degree of hydration. Therefore, a single determination of specific gravity is of limited usefulness unless the results are related to the clinical setting.

The specific gravity can be easily measured using either a urinometer, a refractometer, or a reagent strip. When an accurate measure of urine concentration is desired the urine osmolality should be determined.

IV. pH. The urinary pH does not measure net acid excretion but only the unbuffered ion concentration. This, in turn, is affected by many variables, including diet. Urine is almost always acid except during the alkaline tide following meals or when there is infection with a urea-splitting organism. The overall clinical situation must be known for such a measurement to be useful. For example, an alkaline urine in the presence of systemic acidosis suggests renal acidification defect, whereas an alkaline urine with systemic alkalosis is appropriate.

V. Glucose. Glucose oxidase reagent strips measure urinary glucose. Under normal circumstances, almost all of the glucose filtered by the glomerulus is reabsorbed in the proximal convoluted tubule. The blood level at which tubular reabsorption stops and glucose appears in the urine is termed the "renal threshold," which for glucose is 160 to 200 mg/dL. The glucose test is of great value in the detection and monitoring of diabetes mellitus except in rare cases of renal glycosuria.

VI. Other substances. Ketonemia results in a positive finding for acetone in the urine. This occurs most commonly in diabetic ketoacidosis. Ketonuria alone may be found in starvation or fasting, in methanol poisoning, and in alcoholic ketoacidosis.

VII. Microscopic examination. Examination of the urinary sediment is essential for the evaluation of renal disease.

A. Red blood cells. More than 5 to 10 RBCs/high-power field (HPF) are significant. Additional workup should proceed as indicated under Hematuria.

B. White blood cells (WBCs). Usually, fewer than 5 WBC/HPF are found in normal urine. An increase in urinary white blood cells is called pyuria and indicates the presence of an infection or inflammation in the genitourinary system. The presence of eosinophils on a Hansel's stain is helpful in diagnosing interstitial nephritis. When WBCs are found together with vaginal epithelial cells, it can be assumed that the collection technique was poor.

C. Epithelial cells. It is not unusual to find epithelial cells in the urine, as they are derived from the linings of the genitourinary system. Unless they are present in large numbers or in abnormal forms, they represent normal sloughing of old cells. Renal tubular cells are the most significant of the epithelial cells because the finding of increased numbers indicates tubular necrosis.

D. RBC casts. Red cell casts are primarily associated with glomerulonephritis; however, any condition that damages the glomerulus, tubules, or renal capillaries may cause the production of RBC casts.

E. WBC casts. These casts are indicative of renal infection (e.g., pyelonephritis) or inflammation (e.g., SLE).

F. Hyaline and granular casts. Such casts may be normal when only 1 to 2/HPF are seen in a concentrated urine. Showers of such casts (20–30/HPF) may be seen in acute renal failure.

G. Waxy casts. Waxy casts are nonspecific and may be found in both normal and pathologic urine.

H. Mixed cellular casts. Casts of this type generally occur in inflammatory renal disease.

I. Crystals. Crystalluria may occur in normal or pathologic urine. Most are not significant. Cysteine crystals are abnormal, as are massive precipitations of sulfonamide or uric acid crystals in oliguric patients.

J. Tissue fragments. Pieces of the renal papillae are diagnostic of papillary necrosis.

K. Bacteria. The presence of bacteria may indicate infection.

Proteinuria

General Principles

I. Proteinuria is often the first and occasionally the only abnormality in patients with renal disease. Proteinuria in excess of 3 g/day represents glomerular damage and is often associated with gross or microscopic hematuria.

II. Most individuals excrete between 30 and 150 mg/day of total protein (normal upper limit 200 mg/day). Sixty percent of this urinary protein is plasma protein (two-thirds of it is albumin). The remaining 40% is synthesized and secreted into the urine by the renal tubules as well as by the more distal portions of the urogenital tract.

III. The dipstick measurement detects mostly albumin; globulins or parts of globulins (heavy or light chains, Bence Jones protein) may be missed. Because of these last two limitations, alternative methods of screening for proteinuria should include the heat and acetic acid method or sulfosalicylic acid.

Currently dipsticks are available to measure microalbuminuria (30–200 mg/L), an early marker of glomerular disease.

IV. The measurement of the 24-hour protein excretion is of the utmost importance in the evaluation of any patient with proteinuria.

V. An excellent correlation exists between 24-hour urinary protein excretion and the protein: creatinine concentration ratio (mg/dL of protein ÷ mg/dL of creatinine), determined in a random sample of urine. A ratio of greater than 0.2 is considered abnormal.

Etiology and Classification

I. Heavy proteinuria (nephrotic proteinuria). Heavy proteinuria is defined as the excretion of more than 3.5 g of protein in 24 hours. It is most often associated with the nephrotic syndrome.

The cause of idiopathic nephrotic syndrome varies according to age; minimal change disease is the most common cause in children, whereas focal segmental glomerulosclerosis and membranous glomerulonephritis are more common in adults.

Other causes of nephrotic range proteinuria and the nephrotic syndrome include: systemic illnesses (e.g., connective tissue disease, diabetes mellitus, and multiple myeloma); amyloidosis; allergic disorders (e.g., bee sting and drug reactions); infections (e.g., malaria, cytomegalic inclusion disease, typhus, herpes zoster, hepatitis B, bacterial infections); solid tumors; and lymphomas.

II. Moderate proteinuria (nonnephrotic proteinuria). Moderate proteinuria is defined as a 24-hour excretion of 1.0 to 3.5 g of protein in 24 hours. The causes of moderate proteinuria may be the same as those causing heavy proteinuria. Moderate proteinuria may reflect an interstitial nephritis.

III. Minimal proteinuria (nonnephrotic proteinuria). Minimal proteinuria is defined as the excretion of less than 1.0 g of protein in 24 hours. The causes include:

A. Mild glomerular disease, pyelonephritis, nephrosclerosis, obstructive uropathy, nephrocalcinosis, acute tubular necrosis, and congestive heart failure

B. Isolated proteinuria. Isolated proteinuria is diagnosed when urine protein excretion is under 1 g/day in the absence of other abnormalities of renal function or evidence of systemic disease in apparently healthy asymptomatic people. Isolated proteinuria may be subdivided into benign varieties:
   1. Functional proteinuria. Functional proteinuria is transient proteinuria associated with conditions such as high fever, strenuous exercise, stress, congestive heart failure, or other acute medical illnesses.
   2. Orthostatic proteinuria. Orthostatic (postural) proteinuria refers to proteinuria that is present only when the patient is in the upright position and is absent when in the recumbent position.
   3. Asymptomatic persistent proteinuria. Persistent isolated proteinuria is almost always indicative of renal disease.

Diagnostic Approach

History

Because proteinuria may be the result of primary or secondary renal disease, evidence of systemic illness that may involve the kidney should be sought and excluded (e.g., connective tissue disease, diabetes mellitus). A careful drug history should be taken to exclude potentially nephrotoxic agents (e.g., gold salts, NSAIDs).

Physical Examination

Physical examination should be reviewed for the presence of signs that may be associated with the cause of renal disease (such as diabetic retinopathy; abdominal masses suggestive of polycystic kidneys; or rashes, murmurs, or arthropathy indicative of systemic illness) or that may result from renal disease (such as edema) or both (such as hypertension).

Laboratory Studies

I. Urinalysis. The presence of fatty casts, oval fat bodies, and doubly refractile fat globules suggests the lipiduria of the nephrotic syndrome. Red cell casts are virtually pathognomonic for glomerulonephritis but may be seen in diabetes. Glycosuria suggests diabetes mellitus.
II. The 24-hour urinary excretion. The 24-hour urine collection is the most accurate method of quantifying urinary protein excretion. Patients exhibiting minimal to moderate proteinuria should be checked routinely for postural or orthostatic proteinuria. The combined study can be performed as follows: The patient voids at 7 AM and discards the urine. All urine thereafter is collected in a single bottle. At 9 PM the patient assumes the recumbent position in bed. At 11 PM he or she voids into the same bottle without getting out of bed. At 7 AM the next morning, without rising, the patient voids into another bottle. The urine in the two bottles is the 24-hour urine collection, the second bottle representing the urine voided during recumbency. In patients with postural proteinuria, the total urinary protein excretion usually exceeds 150 mg (but is less than 2 g), but the protein excreted during recumbency should not be greater than 50 mg.
III. Serum and urinary electrophoresis should be performed in every patient suspected of having a plasma cell dyscrasia. Monoclonal light chains, either kappa or lambda, are commonly seen in the urine in multiple myeloma.
IV. Hypercholesterolemia and hypoproteinemia with a decreased albumin fraction are seen in most cases of the nephrotic syndrome.
V. An abnormal serum glucose test and glycosuria may be the only other manifestations of diabetes mellitus in a patient with diabetic nephropathy.
VI. Serologic tests for streptococcal antibodies, HBsAg, HepC Ab, connective tissue disease, syphilis, and serum complement (C3, C4) should be performed.
VII. Radiologic examination. Ultrasonography may be useful to evaluate renal size as an indicator of disease duration; it may occasionally reveal other abnormalities as well.
VIII. Renal biopsy is indicated when all other studies fail to reveal the etiology of renal disease, when the findings will influence the management of the disease (e.g., systemic lupus erythematosus), and as an aid in determining the prognosis. If performed, the biopsy should be examined by light and electron microscopy as well by immunofluorescent techniques.

Hematuria without Proteinuria

Hematuria may be macroscopic (red in color) or microscopic (more than three to five erythrocytes per HPF). It may occur with or without proteinuria or the presence of formed elements in the urine. It is important to differentiate between glomerular hematuria, renal nonglomerular hematuria, and extrarenal causes of hematuria (disorders of the clotting mechanism). Red cells in glomerular hematuria tend to be spiculated and have many sizes and shapes, whereas in nonglomerular hematuria the red blood cells are nonspiculated and uniform in size; a polarizing microscope is frequently needed to detect the dysmorphic red cells.

Gross hematuria can be confused with bile pigments, porphyrins, hemoglobin, or myoglobin. The finding of red cells in the urinary sediment establishes the diagnosis of hematuria. The other conditions are identified by specific laboratory tests. It should be recognized that either extremely concentrated or extremely dilute urine may cause lysis of red cells with resultant hemoglobinuria.

In a patient with gross hematuria, the rate and amount of blood loss can be estimated by performing serial urinary hematocrit readings. A hematocrit value of less than 1% indicates the blood loss is slight. Unless blood loss is massive, hematuria does not cause anemia. If anemia is present, other causes, such as chronic renal failure, tuberculosis, neoplasm, and blood dyscrasias, should be considered.

Etiology

I. Systemic. Fever, anticoagulant therapy, hemoglobin S-related diseases, strenuous exercise, and coagulopathies
II. Kidney. Glomerulopathies (particularly Ig A nephropathy), interstitial nephritis, infarct, tuberculosis, cystic disease, papillary necrosis, neoplasm, trauma, and vascular malformations
III. Urinary collecting system. Calculi, foreign bodies, neoplasm, endometriosis, trauma, and infections

History

I. A careful menstrual history should be obtained from any woman with a history of blood in the urine to be sure that bleeding is from the urinary tract and not vaginal in origin.
II. Frequency, urgency, dysuria, or urethral discharge suggests bladder or urethral involvement
III. Flank pain or colic may be seen with stones, obstruction, infarction, or polycystic kidney disease.
IV. Bleeding at the beginning of urination suggests an origin in the posterior urethra, whereas the source of terminal hematuria is usually the prostate gland or the trigonal area of the bladder.
V. Rectal or perineal pain or discomfort may occur with prostatitis.
VI. Weight loss may signal a malignancy.
VII. Inquiry concerning the presence of a blood dyscrasia or the use of anticoagulants is warranted in any patient with hematuria. Patients taking anticoagulants who develop hematuria should be investigated because they often turn out to have a significant lesions of the urinary tract.
VIII. A family history of polycystic kidney disease or sickle cell anemia suggests these conditions as possible causes of hematuria.
IX. Upper respiratory tract infections or gastroenteritis may trigger an exacerbation of IgA nephropathy.
X. Hemoptysis is important because of the link with antiglomerular basement membrane disease.
XI. Systemic symptoms such as fever, arthralgia, and easy bruising may suggest a particular entity such as systemic lupus erythematosus, Henoch–Schönlein purpura, or vasculitis.

Physical Examination

I. Elevated blood pressure and peripheral edema may indicate a renal lesion.
II. Bilaterally enlarged kidneys are often found in polycystic disease.
III. A unilateral renal mass suggests neoplasm or cyst.
IV. Costovertebral angle tenderness and fever suggest pyelonephritis.
V. A tender prostate gland suggests prostatitis.
VI. The presence of atrial fibrillation or valvular heart disease suggests renal embolism and infarction as possible causes of hematuria.
VII. The presence of petechiae, ecchymoses, lymphadenopathy, or splenomegaly may be indicative of a blood dyscrasia or clotting disorder.

Laboratory Studies

I. A complete urinalysis is often helpful in establishing a diagnosis. The presence of irregular erythrocytes is strongly associated with a glomerular lesion. Erythrocyte casts and heavy proteinuria are also typically seen with glomerular diseases. Dysuria and bacteriuria suggest infection of the urinary tract. Hematuria and pyuria without bacteriuria suggest the possibility of renal tuberculosis.
II. Blood count. The presence of anemia suggests renal failure or a systemic illness. Polycythemia is sometimes seen with renal cell carcinoma, polycystic disease, isolated renal cysts, uterine leiomyomata, and other conditions.
III. Excretory urogram. Patient with hematuria should undergo excretory urography before cystoscopy or other urinary tract manipulations are performed. The urogram is important in the diagnosis of nephrolithiasis and tumors. It is especially indicated in children in whom renal neoplasms are frequent causes of hematuria. Ultrasound is a good method for diagnosing renal cysts and differentiating between cystic and solid tumors. CT scan may be helpful to characterize any solid mass identified on ultrasound.
IV. Cystoscopy. Performed after urinalysis and intravenous pyelography, cystoscopy is the best procedure for evaluating the lower urinary tract.

Tests of Renal Function

The best clinical guide for evaluating renal function is the creatinine clearance. This test estimates the GFR. The urea clearance is less reliable. Clearance procedures are particularly useful in detecting early renal function impairment and in following the course of renal disease. However, clearance tests are of little help in determining the cause of kidney disease. The BUN and serum creatinine have limited usefulness as indicators of the GFR; the serum creatinine has some advantages over the BUN.

Endogenous Creatinine Clearance

I. Clearance is defined as the volume of blood from which a substance is eliminated per unit of time. It is reported in milliliters per minute.
II. Creatinine clearance is commonly employed to estimate renal function in patients with renal disease. Since creatinine is excreted primarily by glomerular filtration with only a small component of tubular secretion, as a rule, the creatinine clearance tends to overestimate the true GFR, especially when the GFR is low. However, serial determinations of creatinine clearance regularly parallel the rise and fall of the actual GFR.
III. A patient in a steady state excretes a constant amount of creatinine in 24 hours: 20 to 25 mg/kg per day for men and 15 to 20 mg/kg per day for women. Omissions in urine collection or sudden changes in renal function are possible causes of reduced excretion of creatinine. Sometimes, a patient with a small muscle mass has a lower than normal total urine creatinine excretion. Whenever the 24-hour urine creatinine excretion is below normal, the test should be repeated. It should also be rechecked if urine creatinine excretion is not comparable to that determined in previous studies.
IV. The creatinine clearance is measured by the formula C = U V/P, in which C is clearance in milliliters per minute, U is the urine creatinine concentration in milligrams per 100 milliliters, V is urine flow in milliliters per minute, and P is the serum creatinine concentration in milligrams per 100 milliliters.

V. Normal values of the creatinine clearance range from 100 to 150 mL/min in men and 85 to 125 mL/min in women. The GFR declines slowly above the age of 40. By the age of 70, the creatinine clearance may be 50% of normal even in the absence of renal disease.

Serum Creatinine

I. The normal serum creatinine level is approximately 0.6 to 1.3 mg/100 mL. The serum creatinine provides a reasonable estimate of the GFR; however, the serum creatinine is not always sensitive to changes in GFR. Patients with a small muscle mass may have a "normal" creatinine level in spite of significant impairment of renal function.
II. For patients in a steady state the creatinine clearance may be estimated from the serum creatinine by using the following formula:

$$C_{cr} = \left[\frac{(140 - \text{age})(\text{wt Kg})}{S_{cr} \times 72}\right] \times 0.85 \text{ for women}$$

Blood Urea Nitrogen

The normal range for BUN is 10 to 20 mg/100 mL. Because up to 50% of the filtered BUN is eventually reabsorbed, it does not provide a reliable estimate of the GFR. Many conditions may affect the BUN but not the GFR. Conditions that will increase the BUN include: high-protein diet (e.g., in patients on TPN), GI bleeding, corticosteroids, tissue trauma, or tetracycline compounds. Certain conditions will decrease the BUN: low-protein diet, liver disease, or sickle cell anemia. Therefore, BUN is not a satisfactory method for evaluating small changes in renal function early in the course of renal failure.

Concentration Tests

I. The normal kidney can produce urine with an osmolality that is three to four times that of plasma.
II. The most reliable test of the concentrating ability of the kidney is the determination of the osmolality of urine by freezing point depression.
III. To perform a concentration test, examine at hourly intervals freshly voided urine obtained after an overnight fast until the highest urine concentration is obtained. The fast is continued until the test is completed. A specific gravity greater than 1.020 or an osmolality greater than 800 mOsm/kg of water is considered normal. In patients with known or suspected azotemia, no attempt should be made to concentrate the urine by dehydrating the patient because it may be hazardous to do so.
IV. Factors that affect renal medullary hypertonicity (e.g., high fluid intake prior to the test, diuretics, low-protein diet, sodium restriction) may interfere with the concentration test.
V. Concentrating defects may be early findings in essential hypertension, diabetic nephropathy, hypokalemia, hypercalcemia, nephrogenic diabetes insipidus, sickle cell disease, interstitial nephritis, treatment with lithium, and polycystic kidney disease. Renal concentrating ability is also reduced with advancing age.

Urine Electrolytes

The clinical significance of urinary electrolyte determination has become more apparent. Measurement of urinary sodium or chloride is especially useful in attempting to differentiate between etiologies of hyponatremia (e.g., volume contraction versus conditions associated with increased salt loss), as seen with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), salt losing nephropathy, or adrenal insufficiency.

Urinary potassium determination is important in the evaluation of patients with either hypokalemia or hyperkalemia. The urinary concentration of these electrolytes varies depending on intake (dietary, parenteral, or both), the presence or absence of renal disease, and the responsiveness of the body to such conditions as hypovolemia, hyperosmolality, and hypoosmolality.

Hypernatremia

Definition

Hypernatremia is defined as an abnormally high serum sodium concentration (145 mEq/L). In hypernatremia, total body sodium content is high relative to total body water. Hypernatremia is usually caused by excessive water loss and rarely to increased total body sodium.

Etiology

I. Hypernatremia with increased total body sodium (usually iatrogenic). Physical examination reveals signs of increased total body sodium (e.g., increased jugular venous pressure, edema).
   A. Administration of hypertonic sodium bicarbonate
   B. Hyperalimentation by intravenous or nasogastric tube feeding
   C. Ingestion of large quantities of sodium chloride tablets
   D. Seawater drowning
   E. Mineralocorticoid excess

2. Hypernatremia with low total body sodium. Patients who sustain losses of both sodium and water but with a relatively greater loss of water are classified as having hypernatremia with low total body sodium. Hypernatremia ensues if the fluid losses are not adequately replaced. This condition is usually averted in the conscious patient because thirst causes the patient to drink until the water deficit is corrected. Physical examination reveals signs of decreased total body sodium (e.g., poor skin turgor, postural hypotension).

   In the evaluation of hypernatremia owing to excessive water loss, both the urine and serum osmolality should be determined.

   A. Urine maximally concentrated (hyperosmotic) in response to the hyperosmolar state
      1. GI losses
      2. Perspiration

Note: Elderly persons and patients with renal insufficiency may not be able to concentrate the urine maximally even though the hypernatremia is owing to one or more of the preceding causes.

   B. Urine not maximally concentrated (isoosmotic or hypoosmotic) in response to the hyperosmolar state
      1. Diuretic therapy
      2. Hypercalcemic nephropathy
      3. Hypokalemic nephropathy
      4. Osmotic diuresis
         a. Glycosuria owing to diabetes mellitus
         b. Other solutes (e.g., mannitol, radiocontrast)
      5. Polyuric phase of acute tubular necrosis
      6. Postobstructive uropathy

III. Hypernatremia with normal total body sodium. Physical examination is consistent with euvolemia. Diabetes insipidus (large urine volume, dilute urine). See Table 7-1 for diagnostic approach.
   A. Central diabetes insipidus (secondary to hypothalamic or pituitary disease), responsive to vasopressin
   B. Nephrogenic diabetes insipidus, not responsive to vasopressin

Diagnostic Approach

I. Rule out iatrogenic causes of hypernatremia. If iatrogenic causes are excluded, the hypernatremia is almost always owing to excessive extrarenal or renal fluid losses.

II. Measure the serum and urine osmolality.
   A. If the urine is hypertonic (osmolality increased), the fluid was lost by an extrarenal route (e.g., the GI route or perspiration).

   B. If the urine is isotonic (isoosmotic) or hypotonic (hypoosmotic), the fluid losses were probably sustained through the kidney. The renal disorders that may be responsible for this type of abnormality are listed in the preceding.

Hyponatremia

Definition

Hyponatremia is defined as an abnormally low serum sodium concentration (135 mEq/L). Because the ionic components of the serum are largely responsible for its osmolality, hyponatremia results in a lowered serum osmolality. The symptoms of hyponatremia are essentially those of reduced serum osmolality. Hyponatremia may occur in a variety of clinical disorders. Because treatment of these conditions may differ markedly, it is always important to determine the cause of hyponatremia. All hyponatremic states, with the exception of hyperlipidemia and hyperglycemia, are associated with low osmolality of the serum and extracellular fluids. In other words, total body sodium is inappropriately low with respect to total body water.

Etiology and Classification

I. Pseudohyponatremia
   A. Hyperlipidemia. Hyperlipemic states may be associated with spurious hyponatremia. The diagnosis is established by finding a high lipid content in the serum and normal serum osmolality. Also, the serum sodium will be normal if measured by direct potentiometry.
   B. Hyperglycemia. Every 100 mg/100 mL rise in the serum glucose concentration produces a decline of approximately 1.6 mEq/L in the serum sodium level. The diagnosis is based on finding hyponatremia and hyperglycemia together with a normal or elevated serum osmolality.

II. Hyponatremia with increased total body sodium. This is a state in which an excess of total body sodium and an even greater excess of total body water results in edema or ascites, or both. Serum osmolality is low. Hyponatremia with excess total body sodium occurs in congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. Increased water intake continued with marked sodium restriction or diuretic therapy, or both, may aggravate any of these conditions.

III. Hyponatremia with decreased total body sodium. Conditions associated with both sodium and water depletion are characterized by the absence of edema or ascites. Symptoms and signs of extracellular fluid volume depletion, tachycardia, decreased central venous pressure, a high hematocrit, and elevated serum total proteins may be noted. The history and urine sodium concentrations are important diagnostically.
   A. Decreased urine sodium concentration (10 mEq/L), usually associated with a decreased chloride concentration
      1. GI losses
         a. Vomiting or nasogastric suction, or both, commonly associated with hypokalemic alkalosis
         b. Diarrhea, commonly associated with hypokalemic acidosis
      2. Excessive perspiration with replacement of water but not of the sodium losses
      3. Volume depletion without replacement of lost fluids and electrolytes after diuretic therapy
   B. Increased urine sodium concentration (10 mEq/L). Causes include adrenocortical insufficiency and salt losing nephropathy. Occasionally, urinary sodium concentration may be increased after severe vomiting but the urinary chloride concentration will be low.

IV. Hyponatremia with normal total body sodium: The disorders included in this category are not associated with edema or volume depletion.
   A. Hypothyroidism or glucocorticoid deficiency may be associated with euvolemic hyponatremia.
   B. SIADH. This condition may be idiopathic or may be associated with one of the following disorders: diseases of the central nervous system (e.g., strokes, mass lesions, meningitis), pulmonary disease (e.g., tuberculosis, pneumonia,

bronchogenic carcinoma), and drugs (chlorpropamide, narcotics, barbiturates, vincristine, antidepressants, and clofibrate).

1. Criteria for the diagnosis
   a. Hypotonicity of the body fluids
   b. Urine osmolality greater than 100 mOsm/kg of water
   c. Normal renal, adrenal, and thyroid function
   d. Increased urinary excretion of sodium (30 mEq/L) during volume expansion
   e. Elevated serum concentration of ADH
   f. Reversal of the syndrome by adequate fluid restriction
2. Comment. When a steady state is reached, some of the abnormalities described may not be present.

Diagnostic Approach

Once the diagnosis of hyponatremia is made, the serum sodium level should be rechecked and the serum osmolality determined.

I. If the serum osmolality is normal or high in the presence of confirmed hyponatremia, the possibility of hyperlipidemia or hyperglycemia, or both, should be investigated.
II. If the serum osmolality is low, confirming the diagnosis of true hyponatremia, the status of the extracellular fluid volume should be assessed.
   A. The presence of edema, ascites, rales, and S3 gallop, or increased jugular venous pressure indicates an excess of total body sodium.
   B. Postural pulse and BP changes, decreased skin turgor, dry mucous membranes, or decreased jugular venous pressure indicate decreased total body sodium.
   C. In the absence of signs of either increased or decreased total body sodium, TSH and cortisol should be checked before entertaining the diagnosis of SIADH.

Hyperkalemia

Definition

Hyperkalemia is defined as an abnormally high serum potassium concentration (5.5 mEq/L).

Etiology

I. Pseudohyperkalemia (tourniquet on an exercising extremity), hemolysis, leukocytosis (70,000/mm^3), or thrombocytosis (10^6/mm^3)
II. Redistribution (e.g., acidosis, exercise, insulin deficiency, or hypertonicity). A number of drugs may cause hyperkalemia by this mechanism (e.g., succinylcholine, alpha-adrenergic agonists, beta-adrenergic antagonists, digitalis intoxication).
III. Decreased renal excretion of potassium (e.g., oliguric renal failure, potassium blocking diuretics, interstitial nephritis, Addison's disease, isolated hypoaldosteronism). Another important cause is volume contraction with avid proximal sodium retention. This results in decreased distal delivery of sodium that prevents Na-K exchange. Drugs that may cause hyperkalemia by preventing renal excretion include heparin, ACE inhibitors, NSAIDs, pentamidine, and cyclosporine.
IV. Increased potassium intake (e.g., salt substitute or potassium penicillin) or cellular destruction (hemolysis or rhabdomyolysis)

Symptoms and Signs

I. Neuromuscular symptoms and signs predominate; they include weakness, occasionally paralysis, loss of deep tendon reflexes, irritability, and confusion.
II. The following more or less sequential changes may be seen in the electrocardiogram: progressive increase in the amplitude of the T waves, decreased amplitude of the R wave with concomitant increased depth of the S wave, S-T segment depression, and prolongation of the QRS and P-R intervals; continued widening of the QRS and T waves, and their eventual replacement by a sine curve; and finally, ventricular tachyarrhythmia or asystole.

Diagnostic Approach

When hyperkalemia is severe (7.0 mEq/L), diagnostic investigations should be postponed until the life-threatening situation is controlled or corrected. A detailed approach to the diagnosis of hyperkalemia is beyond the scope of this text; however, the following is a brief outline.

I. Check simultaneous plasma and serum K^+ to eliminate factitious causes (plasma K^+ is normal)
II. Review medications.
III. Check blood pH and bicarbonate concentration.
IV. Assess renal function, volume status, urinary flow rate, urine sodium, and potassium excretion.
V. Other specialized tests that are occasionally necessary include measurements of renin or aldosterone, renal tubular K^+ secretion, and K^+ uptake by extrarenal tissues.

Hypokalemia

Definition

Hypokalemia is defined as an abnormally low serum potassium concentration (3.5 mEq/L).

Etiology

I. Nonrenal causes
   A. Decreased potassium intake
   B. GI losses of potassium
      1. Associated with alkalosis and volume depletion
         a. Gastric suctioning and vomiting
         b. Chronic laxative abuse (may be associated with acidosis or normal pH as well)
      2. Associated with acidosis
         a. Diarrheal states (including villous adenoma or Zollinger–Ellison syndrome)
         b. Ureterosigmoidostomy
II. Renal causes
   A. Potassium wasting associated with metabolic acidosis
      1. Renal tubular acidosis
      2. Postobstructive uropathy
      3. Diuretic phase of acute tubular necrosis
      4. Chronic pyelonephritis
   B. Potassium wasting associated with metabolic alkalosis
      1. Diuretic therapy (e.g., furosemide, ethacrynic acid, thiazides). Treatment with potent diuretics may cause hypochloremic alkalosis, which is usually associated with volume depletion.
      2. Disorders with increased aldosterone secretion and hypertension (e.g., primary aldosteronism, malignant hypertension, renovascular hypertension, and essential hypertension with vomiting and diarrhea, diuretic therapy, oral contraceptives, steroid therapy)
      3. Disorders with increased aldosterone secretion without hypertension (e.g., salt losing nephropathy, juxtaglomerular hyperplasia)
      4. Disorders with normal or decreased aldosterone and hypertension (e.g., licorice ingestion, Cushing's syndrome, certain congenital enzyme deficiency syndromes, Liddle's syndrome)

Symptoms and Signs

I. Most symptoms are nonspecific. They include anorexia, nausea, vomiting, abdominal distention, ileus, weakness, decreased deep reflexes, and a depressed sensorium.
II. The electrocardiographic finding include lowering, flattening, notching, or inversion of the T waves; prominent U waves; depression of the S-T segments; and arrhythmias.

III. Nephrogenic diabetes insipidus, rhabdomyolysis, and aggravation of hepatic coma may also occur.

Diagnostic Approach

I. Patients with hypokalemia require a thorough investigation to determine whether the potassium loss is the result of renal or extrarenal mechanisms. Extrarenal potassium depletion is easily recognized by the clinical picture and is correctable by appropriate treatment with potassium salts and fluids.
II. To determine whether potassium depletion is renal in origin, the 24-hour urinary excretion of potassium should be measured while the patient is on a regular salt intake. Urinary potassium excretion of less than 20 mEq/24 hours in a hypokalemic individual is excellent evidence against renal potassium wasting. On the other hand, urinary potassium excretion greater than 20 mEq/24 hours, especially if it is more than 60 mEq, is strongly suggestive of renal potassium wasting.
III. The problem of hypokalemia with hypertension is discussed in Chapter 3.
IV. In patients with both metabolic alkalosis and potassium wasting, volume depletion may cause the abnormal state to persist. Every effort should be made not only to ascertain the cause of the metabolic alkalosis but also to determine whether volume depletion is a contributing factor, and if it is, to correct it.

Hyperphosphatemia

Hyperphosphatemia in the adult is defined as an elevation of serum phosphate levels above normal (3.0–4.5 mg/100 mL). Elevation of serum phosphorus occurs predominantly in acute or chronic renal insufficiency and is aggravated by catabolic stress. Hyperphosphatemia has been reported to occur frequently in lactic acidosis. Large amounts of phosphate administered orally, parenterally, or rectally may cause transient hyperphosphatemia even in the presence of normal renal function.

The association of hyperphosphatemia and hypocalcemia has been reported to occur following the administration of large quantities of phosphate, in acute and chronic renal failure, from cytolysis during chemotherapy for neoplastic disease, and in hypoparathyroidism.

Hypophosphatemia

Hypophosphatemia is defined as a serum phosphate level below 3.0 mg/100 mL. Hypophosphatemia is considered severe when serum phosphorus levels are less than 1.5 mg/100 mL.

The clinical conditions most often associated with hypophosphatemia are alcoholism, diabetic ketoacidosis, the healing phase of severe burns, liver disease, and respiratory alkalosis.

Etiology

I. Intracellular shifts
   A. Respiratory alkalosis
   B. Carbohydrate loading
   C. Hyperalimentation
   D. Nutritional recovery syndrome
II. Decreased intake of phosphorus
III. Increased phosphorus excretion
   A. Hyperparathyroidism
   B. Renal tubular disorders
   C. Acidosis
IV. Impaired absorption of phosphate (e.g., aluminum hydroxide, carbonate antacids)

Clinical Features

I. Acute depletion
   A. Hemolytic anemia
   B. Rhabdomyolysis
   C. Increased susceptibility to infection (defective leukocyte function)
   D. Petechiae (defective platelet function)
   E. Metabolic encephalopathy

II. Chronic depletion
   A. Anorexia, weakness, bone pain, and pathologic fractures owing to osteomalacia
   B. Increased urinary concentration of calcium, magnesium, and bicarbonate
   C. Augmented intestinal calcium absorption
   D. Usually normal serum calcium levels
   E. Normal or low plasma parathyroid hormone levels

Hypermagnesemia

Hypermagnesemia is defined as an elevation of serum levels of magnesium above normal values (1.5–2.4 mEq/L). The only state in which there is chronic excess of total body magnesium is chronic renal failure. It is aggravated by increased intake of magnesium, especially magnesium-containing antacids and laxatives. Symptoms include paresthesias, vasodilatation, mild hypotension, and, at very high levels, decreased tendon reflexes, muscle weakness, and even flaccid paralysis.

Hypomagnesemia

Hypomagnesemia is defined as a decrease in serum levels of magnesium below normal values (1.5–2.4 mEq/L).

Etiology

I. Decreased intake of magnesium (e.g., parenteral alimentation, alcoholism)
II. Defective GI absorption of magnesium
   A. Malabsorption syndromes
   B. Short bowel syndromes
   C. Intestinal bypass surgery
   D. Laxative abuse
   E. Frequent enemas
   F. Malnutrition
   G. Isolated magnesium malabsorption
III. Excessive renal loss of magnesium
   A. Drugs (e.g., diuretics, aminoglycoside antibiotics, cyclosporine, *cis*-platinum)
   B. Ketoacidosis
   C. Hyperaldosteronism and Bartter's syndrome
   D. SIADH secretion
   E. Hypercalciuria
   F. Salt-wasting states
   G. Primary magnesium wasting
IV. Intracellular shift of magnesium (e.g., nutritional recovery)
V. Miscellaneous
   A. Alcoholism
   B. Primary hyperparathyroidism
   C. Postparathyroidectomy

Clinical Features

I. Malnutrition
II. Cardiac arrhythmias
III. Muscle weakness
IV. Neurologic dysfunction (e.g., myoclonus, hyperreflexia, positive Trousseau sign, tremor, spasticity)
V. Hypokalemia and hypocalcemia are commonly associated with hypomagnesemia.

Blood-Gas and pH Abnormalities

N. Balfour Slonim

Abnormalities of blood O_2, Co_2, and pH are diagnostically revealing as well as clinically significant. If values are extreme or changing rapidly, such abnormal laboratory findings

may be of critical importance. These three vital, interrelated blood parameters should not be ignored in any diagnostic situation.

For the purpose of blood-gas and pH determination there is no substitute for arterial blood. When reliable information is most needed—in the care of the critically ill patient—blood samples from nonarterial sources are least reliable. Discussion of the anaerobic technique of analysis of arterial blood samples for O_2, Co_2, and pH is outside the scope of this chapter, but it should be emphasized that all techniques in present use, whether they involve physical or chemical principles, are a challenge to the precision and skill of the analyst; respiratory gas exchange occurs in the pulmonary capillaries in a fraction of a second.

Pathophysiology

In the interpretation of blood-gas and pH abnormalities, physiologic principles provide the conceptual framework. Hypoxemia always precedes Co_2 retention in the course of diffuse bronchopulmonary disease for the following reasons: (a) Co_2 is about 20 times as diffusible across the pulmonary alveolocapillary membrane as O_2, and (b) the slopes of the O_2 and Co_2 dissociation curves differ so that regional hyperventilation in ventilation-perfusion mismatching can compensate for regional hypoventilation with respect to Co_2 but not with respect to O_2.

Hypoxemia

Definition

Hypoxemia is an arterial blood Po_2 that is less than the normal value of 100 ± 10 mm Hg for a healthy resting person at sea level. Arterial Po_2 decreases with age and is lower at higher altitudes.

Symptoms and Signs

Hypoxemia is a common clinical occurrence and should be suspected when a patient exhibits tachycardia, cyanosis, dyspnea, restlessness, impaired cerebral function, and polycythemia. Unfortunately, cyanosis does not appear until arterial oxyhemoglobin saturation falls to 83% and the arterial Po_2 to 48 mm Hg. At least 5 g of deoxygenated hemoglobin per 100 mL of blood must be present in the systemic capillary circulation to produce the color that characterizes cyanosis. Hence, cyanosis is seen at Po_2 levels higher than 48 mm Hg in polycythemia and at Po_2 levels lower than 48 mm Hg in anemia. Indeed, patients who have chronic severe anemia may die of hypoxemia without cyanosis. Good illumination is required to detect cyanosis, and it may be obscured by skin pigmentation. Acrocyanosis, as well as other regional cyanosis, may reflect only local conditions and not arterial hypoxemia.

Etiology

Clinical arterial hypoxemia results from any of four pathophysiologic mechanisms, which may occur singly or in combination (Table 7-2).

I. The most common mechanism is ventilation-perfusion (V_A/Q_c) abnormality, or mismatching of the distribution of inspired gas with the distribution of pulmonary capillary blood flow. This occurs in acute and chronic diffuse bronchopulmonary diseases:
   A. Chronic bronchitis
   B. Pulmonary emphysema
   C. Asthma
   D. Extensive acute and chronic pneumonias: infectious, chemical, allergic, aspiration
   E. Pulmonary embolism with or without infarction
   F. Adult respiratory distress syndrome
   G. Acute severe bronchitis or bronchiolitis
   H. Pulmonary atelectasis
   I. Extensive pulmonary tuberculosis
   J. Pneumoconiosis (e.g., silicosis, asbestosis, coal workers' pneumoconiosis)
   K. Pneumothorax
   L. Kyphoscoliosis

Table 7-2. The four pathophysiologic mechanisms of arterial hypoxemia and patterns of response to oxygen breathing and physical exercise

		PO_2		PCO_2
Mechanism	Condition[a]	Alveolar	Arterial	Alveolar
Ventilation-perfusion mismatching	Initial	Normal to high	Low	Normal to low
	Oxygen	Marked increase	Variable increase	Normal to low
	Exercise	Normal to high	Slight increase	Normal to low
Generalized alveolar hypoventilation	Initial	Low	Low	High
	Oxygen	Marked increase	Marked increase	Increase
	Exercise	Varies	Varies	Varies
Pulmonary diffusing capacity decrease	Initial	High	Low	Low
	Oxygen	Marked increase	Marked increase	Increase
	Exercise	Slight increase	Decrease	Decrease
Right-to-left shunt	Initial	Normal to high	Low	Normal to low
	Oxygen	Marked increase	Slight increase	Increase
	Exercise	Slight increase	Decrease	Slight decrease

[a] Initial: spontaneous initial condition, physiologic measurement; Oxygen: effect of breathing 100% O_2 for 15 minutes, oxygen breathing test; Exercise: effect of physical exercise, exercise test

   M. Mucoviscidosis or fibrocystic disease
   N. Fibrothorax
   O. Extensive pulmonary neoplasm
   P. Extensive pulmonary granulomata
   Q. Diffuse bronchiectasis
   R. Primary pulmonary hypertension
   S. Radiation fibrosis
   T. Acute anterior poliomyelitis with respiratory paralysis
   U. Unilateral bronchostenosis

II. The second most common mechanism is generalized alveolar hypoventilation (not to be confused with the regional hypoventilation that occurs in ventilation-perfusion mismatching) because of one of the following:
   A. Structural thoracic abnormalities (e.g., kyphoscoliosis, chest trauma)
   B. Neuromuscular diseases affecting breathing
   C. Obesity-hypoventilation (Pickwickian) syndrome
   D. Sleep-apnea syndrome
   E. Drugs or toxins decreasing respiratory drive

III. A less common mechanism of hypoxemia is decreased pulmonary diffusing capacity. There are two types:
   A. Decreased alveolocapillary membrane surface area
      1. Loss or destruction of lung tissue (e.g., lung resection)
      2. Compression of lung or restriction of lung expansion (e.g., pneumothorax, "vanishing lung" syndrome)
   B. Increased length of the gas diffusion pathway—alveolocapillary block syndrome. This occurs in diffuse parenchymatous bronchopulmonary diseases and certain cardiovascular conditions:

1. Acute or chronic diffuse interstitial pneumonitis (e.g., Hamman–Rich syndrome); interstitial pulmonary fibrosis
2. Pulmonary edema
3. Pulmonary sarcoidosis
4. Mitral stenosis with chronic pulmonary vascular congestion
5. Pulmonary berylliosis
6. Lymphangitic carcinomatosis
7. Pulmonary adenomatosis
8. Alveolar proteinosis

IV. The least common mechanism of hypoxemia is right-to-left cardiac or pulmonary circulatory shunt. Although there are innumerable small shunts that cause venous admixture in ventilation-perfusion mismatching, the term cardiac or pulmonary circulatory shunt refers to discrete gross anatomic shunts.
- A. Congenital right-to-left shunts
- B. Acquired right-to-left shunts
- C. Pulmonary hemangioma
- D. Hepato-pulmonary syndrome. This syndrome is defined as the triad of (a) chronic diffuse liver disease, (b) intrapulmonary vascular dilation, and (c) increased alveolar-arterial P_{O_2} difference while breathing room air. Clinical features of this syndrome include dyspnea, orthopnea, right-to-left intrapulmonary shunt, orthodeoxia, platypnea, alveolar hyperventilation, hypocapnia and, frequently, spider nevi. Essential to the diagnosis is the demonstration, by imaging modalities, of intrapulmonary vascular dilation. Such modalities include contrast-enhanced echocardiography, perfusion lung scanning, and pulmonary arteriography.

Diagnostic Approach

Unfortunately, a given bronchopulmonary disease may produce hypoxemia by more than one of these four mechanisms. Differential diagnosis of the diseases that produce hypoxemia proceeds as follows:

I. Ventilation-perfusion mismatching is established and quantified by the following tests and procedures:
- A. Single-breath nitrogen test
- B. Closed-circuit helium equilibration mixing index
- C. Distribution of inhaled radioactively labeled gas (e.g., xenon)
- D. Distribution of intravenously injected solution of radioactively labeled gas (e.g., xenon)
- E. Lung scan after intravenous injection of radioactively labeled particulates (e.g., radioiodinated macroaggregated serum albumin)

II. Generalized alveolar hypoventilation is established and quantified by the following tests:
- A. Spirometry. The minute volume of breathing is less than predicted.
- B. Analysis of an alveolar gas sample reveals low P_{O_2} and high P_{CO_2}.

III. Decreased pulmonary diffusing capacity is established and quantified by any of several carbon monoxide diffusing capacity tests. Tests of pulmonary diffusing capacity can measure a decrease but cannot distinguish between the conditions listed in the preceding. Unfortunately, the validity of these tests is decreased in patients who have ventilation-perfusion mismatching, generalized alveolar hypoventilation, or both.

IV. Right-to-left shunt is established by the following tests and procedures:
- A. Chest roentgenography with special views and techniques, as indicated (e.g., tomography)
- B. O_2 breathing test with analysis of arterial blood sample. A physiologic diagnosis of right-to-left shunt
- C. Angiocardiography. An anatomic diagnosis of the structure and location of a right-to-left shunt
- D. Cardiac catheterization, with calculation of right-to-left shunt flow

V. Identification of the mechanism of arterial hypoxemia may require the O_2 breathing test and an exercise test. Table 7-2 shows the characteristic responses of each of the four pathophysiologic mechanisms of clinical arterial hypoxemia to these two tests.

VI. The *alveolar-arterial* P_{O_2} difference [$P(A\text{-}a)_{O_2}$] is of diagnostic value in certain clinical situations.
- A. To obtain this difference, subtract the measured arterial blood P_{O_2} from the mean alveolar gas P_{O_2}, which is calculated using the *alveolar gas equation*. In health, $P(A\text{-}a)_{O_2}$ is a function of age. The diagnostic sensitivity of $P(A\text{-}a)_{O_2}$ depends on the selection of an appropriate normal range of values for the particular patient.
- B. $P(A\text{-}a)_{O_2}$ is used clinically in the following situations.
  1. The differential diagnosis of acute pulmonary embolism, considering also the arterial blood gases; increased $P(A\text{-}a)_{O_2}$, decreased arterial P_{CO_2}, and decreased arterial P_{O_2} all favor the diagnosis of acute pulmonary embolism.
  2. To determine the presence or absence of parenchymal lung disease
  3. To assess arterial hypoxemia in coma, for example, in drug overdose situations, where it is used to distinguish hypoventilation from parenchymal lung disease.

Positional Hypoxemia

In a healthy subject at rest, arterial blood P_{O_2} is slightly higher in the supine position than it is in the sitting position. This P_{O_2} difference results from the differential effect of gravity on lung gas and lung *blood*. Thus, alveolar ventilation and pulmonary perfusion (V/Q) are less well matched when a subject is sitting or standing quietly. Increased pulmonary arterial pressure (physical activity, pulmonary arterial hypertension, alveolar hypoxia) tends to abolish the supine recumbent/chest erect difference.

The body position of patients who have *unilateral* lung disease may greatly affect arterial blood P_{O_2}. In the *lateral* recumbent position with the diseased lung down, arterial blood P_{O_2} falls, whereas with the healthy lung down, it rises. When the diseased lung is down, blood gravitates preferentially to it and perfusion increases, but ventilation of this lung cannot increase appropriately (V/Q mismatching). If the unilateral disease process resolves, this type of positional hypoxemia no longer occurs.

If disease is evenly distributed throughout both lungs, then arterial blood P_{O_2} is slightly higher when the right side is down, because the right lung is larger than the left. In the supine position, the arterial blood P_{O_2} is usually closer to that in the less favorable lateral position than it is to that in the alternative lateral position. These facts are relevant for the interpretation of arterial blood-gas and pH data, optimal positioning of patients, and prescription of supplemental oxygen therapy.

Abnormalities of Blood P_{CO_2}

Definition

The arterial blood P_{CO_2} of a healthy resting man breathing air spontaneously at sea level is 40 ± 2 mm Hg. Arterial blood P_{CO_2} is promptly and strongly affected by changes in alveolar ventilation rate. Although arterial P_{CO_2} equals alveolar P_{CO_2} over a wide range of clinical conditions, in moderate to severe ventilation-perfusion mismatching, arterial P_{CO_2} is greater than alveolar P_{CO_2}, and hypoxemia is always already present. Although hypoxemia is the only clinically important blood P_{O_2} abnormality, hypocapnia and hypercapnia are both clinically important.

Hypocapnia

Pathophysiology

The clinical signs of hypocapnia are always the result of alveolar hyperventilation. Significant physiologic responses are:

I. Slightly decreased systemic arterial blood pressure
II. Systemic venoconstriction

III. Cerebral vasoconstriction and decreased cerebral blood flow
IV. Respiratory alkalosis with decreased concentration of ionized calcium in extracellular body fluids
V. The respiratory alkalosis of chronic hypocapnia induces the kidney to excrete HCO_3^-, producing a compensatory metabolic acidosis that corrects the pH abnormality

Symptoms and Signs
I. Dizziness
II. Numbness and tingling of hands and feet
III. Psychomotor impairment
IV. Signs of tetany
V. Carpopedal spasm

Etiology
I. Exposure to high altitudes (physiologic)
II. Normal pregnancy (physiologic)
III. Psychogenic hyperventilation
  A. Hysterical
  B. Voluntary
IV. Passive hyperventilation with mechanically controlled or assisted ventilation
V. Compensatory alveolar hyperventilation in response to primary metabolic acidosis
VI. Salicylates
VII. Progestogens
VIII. Primary central nervous system disease
IX. Severe anemia
X. Pneumonia, asthma, or pulmonary edema
XI. Gram-negative sepsis
XII. Restrictive lung diseases, such as pulmonary fibrosis
XIII. Hepatic failure

Diagnostic Approach
The cause of hyperventilation is usually readily apparent from the following:

I. History
II. Physical examination
III. Mental status and neurologic examination
IV. Routine laboratory workup
V. The presence of primary metabolic acidosis, shown by low arterial blood pH
VI. Consideration of altitude and ambient pressure
VII. Rarely, cerebrospinal fluid acidosis, stimulating the central chemoreceptors (resulting in hyperventilation and arterial hypocapnia)

Hypercapnia
Pathophysiology
I. Responses to *mild hypercapnia*:
  A. Breathing frequency increases
  B. Tidal volume increases
  C. Body heat loss increases
  D. Acute hypercapnia produces respiratory acidosis; chronic respiratory acidosis induces the kidney to retain HCO_3^-, producing compensatory metabolic alkalosis
II. Responses to *moderate hypercapnia*:
  A. Cerebral vasodilation and increased cerebral blood flow
  B. Intracranial and cerebrospinal fluid pressure increase
  C. The sympathoadrenomedullary system discharges, but catecholamines are inhibited by the concomitant respiratory acidosis.
  D. Hyperbaric oxygen convulsions are inhibited.

III. Responses to *severe hypercapnia*:
  A. Body core temperature decreases.
  B. Narcosis
  C. Unconsciousness
  D. Death

Symptoms and Signs
I. Transient, throbbing headache
II. Flushed face
III. Nausea
IV. Sweating
V. Tachycardia
VI. Palpitation
VII. Insomnia
VIII. Somnolence
IX. Tunnel vision

Etiology
I. Acute or chronic obstructive bronchopulmonary conditions
  A. Pulmonary emphysema
  B. Chronic bronchitis
  C. Status asthmaticus
  D. Bronchiolitis: infectious or chemical
  E. Mechanical obstruction of trachea or bronchi by water (drowning), blood (hemorrhage), bronchial secretions, or pus
II. Obstruction of the upper respiratory tract
III. Generalized alveolar hypoventilation
  A. Thoracic skeletal conditions, chest wall disease, or chest trauma affecting breathing (e.g., kyphoscoliosis, flail chest, ankylosing spondylitis)
  B. Neuromuscular conditions affecting breathing
    1. Muscular dystrophy
    2. Myasthenia gravis
    3. Intoxications (e.g., pesticides, curare, nerve gas)
    4. Acute or chronic infectious diseases (e.g., poliomyelitis, Guillain-Barré syndrome, diphtheria, tetanus)
  C. Obesity-hypoventilation (Pickwickian) syndrome
  D. Central nervous system conditions affecting breathing
    1. Cerebrovascular accident
    2. Increased intracranial pressure (e.g., intracranial tumor, head trauma)
    3. Meningitis or encephalitis
    4. Pharmacologic depression of respiratory centers (e.g., barbiturates, morphine, tranquilizers, alcohol)
  E. Hypoventilation with mechanical respirator
  F. Extreme abdominal distention or pain, traumatic or postsurgical, interfering with diaphragmatic breathing
  G. Other causes
    1. Severe hypothyroidism
    2. Starvation cachexia
    3. Severe electrolyte disturbance
    4. Acute intermittent porphyria
IV. Restrictive and other bronchopulmonary conditions
  A. Pneumothorax, hemothorax, hydrothorax
  B. Restrictive disease of the pleurae (e.g., fibrosis, calcification)
  C. Extensive infiltrative disease or fibrosis of lung parenchyma
  D. Severe pulmonary edema
V. Sleep apnea syndrome
VI. Oxygen therapy for chronic lung failure

Diagnostic Approach
The precise diagnosis of the disease or condition producing primary hypercapnia is established as follows:

I. Arterial hypoxemia is always also present, unless the patient is breathing oxygen.
II. If the simultaneously determined arterial blood pH is low, then respiratory acidosis is either uncompensated or partially compensated by metabolic alkalosis. If the pH is within normal limits, then either (a) respiratory acidosis is completely corrected by compensatory metabolic alkalosis, or, rarely, (b) a primary coexisting metabolic alkalosis may be just sufficient to correct fully the low pH of hypercapnia. The combination of high P_{CO_2} and normal pH indicates chronicity and stability of the inciting etiologic agent.
III. If respiratory acidosis is the only primary acid-base disturbance present, differential diagnosis is then made by the following procedures:
   A. History
   B. Physical examination
   C. Routine laboratory studies
   D. Chest roentgenography
   E. Electrolyte profile
   F. Pulmonary function tests
   G. Neurologic examination
   H. Special laboratory studies as indicated (e.g., porphyria, hypothyroidism)

Abnormalities of Blood pH

Definition
In clinical use, the term "blood pH" means plasma pH. The normal arterial blood pH of a healthy resting man at sea level is 7.40 ± 0.05. Deviations of arterial blood pH from this range of normal values result from one or more primary acid-base disturbances, which induce the pH homeostatic mechanisms to respond with secondary pH-compensating processes. Such responses always tend to restore pH toward normal. Acidemia means low blood plasma pH, and alkalemia means high blood plasma pH. Note that the terms acidemia and acidosis (similarly, alkalemia and alkalosis) are not synonymous.

Etiology
Metabolic (Nonrespiratory) Acidosis
Metabolic acidosis is the result of acid excess (metabolic overproduction or ingestion of acid), impaired renal excretion of the daily acid load, or loss of body base (HCO_3^-). Acid overproduction is often the result of diabetic ketoacidosis. Impaired renal excretion of acid results in retention of nonvolatile acids (acids other than H_2CO_3, which is excreted by the lungs as CO_2) and uremic acidosis. In ambulatory patients, diarrheal loss of body base stores (base deficit) is the most common cause of hyperchloremic (normal anion gap) metabolic acidosis. The second most common cause of hyperchloremic metabolic acidosis is renal tubular acidosis, which may be primary (hereditary) or secondary (the result of kidney injury from toxic chemical substances or drugs).

Regardless of cause, metabolic acidosis is characterized by decreased plasma pH (acidemia), decreased plasma HCO_3^- concentration, and decreased arterial blood P_{CO_2}. The hypocapnia moderates but does not fully correct the acidemia. Severe acidosis may impair myocardial contractility and dilate peripheral arterioles, causing circulatory shock. The symptoms of acidosis—fatigue, anorexia, nausea, vomiting, and dyspnea—may be difficult to distinguish from those of the underlying disorder that produced the acidosis.

I. Hyperchloremic (normal anion gap)
   A. Diarrhea
   B. Renal tubular acidosis
   C. Dehydration
   D. Interstitial renal disease
   E. Ureterosigmoidostomy
   F. Carbonic anhydrase inhibitor (e.g., acetazolamide)
   G. Arginine hydrochloride
   H. Ammonium chloride
II. Increased undetermined anion (high anion gap)
   A. Diabetic ketoacidosis
   B. Renal failure with uremic acidosis
   C. Alcoholic ketoacidosis
   D. Salicylate intoxication
   E. Methanol intoxication
   F. Ethylene glycol intoxication
   G. Paraldehyde intoxication
   H. Starvation ketoacidosis
   I. Heavy physical exercise, especially at altitude (physiologic)
   J. Lactic acidosis (may occur in the clinical setting of severe hypoxemia or impaired hepatic function)

Lactic acid is formed in an anaerobic glycolysis by the enzyme lactate dehydrogenase, which reduces pyruvate to lactate. In terms of metabolism, however, lactate is a blind alley. Once formed, it can only provide energy under aerobic conditions by reversal of the lactate dehydrogenase reaction. This reaction regenerates pyruvate, which is then available for oxidative metabolism in the tricarboxylic acid cycle. Unlike the phosphorylated intermediates of glycolysis, lactate diffuses out of the glycolyzing muscle cells within which it is formed. It is then transported by the circulation to the liver where it is metabolized through pyruvate to be stored as liver glycogen. Lactic acid accumulates when energy demand exceeds the rate of aerobic energy production, or when liver function is so impaired that circulating lactate is not removed and converted to liver glycogen.

Lactic acidosis is the acid-base disorder associated with elevated blood lactate levels and metabolic acidemia. Type A (hypoxic) lactic acidosis may occur in the clinical setting of asphyxia, sepsis, circulatory shock, cardiac arrest, and acute respiratory failure.

The causes of type B (nonhypoxic) lactic acidosis include hepatic disease, diabetes mellitus, thiamine deficiency, toxins, genetic metabolic disorders, and drugs (e.g., biguanidines). Acetaminophen overdose is a cause of fulminant hepatic failure. Lactic acidosis may occur in severely poisoned patients, even during the early phase of intoxication. Lactic acidosis associated with the oral antihyperglycemic drug metformin is rare, but mortality is high. The risk is increased in patients who are in renal failure.

Metabolic (Nonrespiratory) Alkalosis
Metabolic alkalosis is an acid-base disturbance characterized by increased plasma HCO_3^- concentration and alkalemia. This disturbance is often partially compensated for by respiratory acidosis. The pH increase results from decreased H^+ concentration, increased HCO_3^- concentration, or both.

Metabolic alkalosis may result from either base excess or acid deficit. The clinical causes of metabolic alkalosis include the following:

I. Chloruretic diuretics
II. Nasogastric suction
III. Vomiting
IV. Alkali therapy or excessive use of antacids
V. Mineralocorticosteroid excess
   A. Endogenous (e.g., aldosteronism)
   B. Exogenous (e.g., deoxycorticosterone acetate, licorice intoxication)
VI. Glucocorticosteroid excess
   A. Endogenous (e.g., hyperadrenocorticism, Cushing's syndrome)
   B. Exogenous (e.g., therapy with glucocorticosteroids, ACTH)
VII. Severe K^+ deficit (usually depletion)
VIII. Cl^- deficit (usually restriction of Cl^- intake)
IX. Intravenous phosphate or sulfate salts in a Na^+-depleted patient

Diagnostic Approach
Precise diagnosis, and thus proper therapy, of acid-base disorders requires identification of the primary inciting—as opposed to secondary compensatory—process. Usually one, but sometimes more than one, of the four possible primary acid-base disturbances is found; any primary disturbances and their etiologic agents must be identified and distinguished from any secondary compensatory responses. First, make a clinical assessment of the patient and try to predict what acid-base disorders will be found. The clinical setting is often useful in diagnosing acid-base disorders.

Graphic Approach

I. Review the history for potential causes of acid-base disturbance.
II. Review the physical examination for signs of acid-base disturbance.
   A. Nasogastric tube
   B. Cyanosis
   C. Evidence of bronchopulmonary disease
   D. Fever
   E. Hypotension
   F. Jaundice
   G. Signs of alkalemic tetany
III. Review the laboratory values for blood Co_2 content and K^+ concentration, and calculate the undetermined anion concentration (anion gap) as follows:

Undetermined anion concentration = $[Na^+] - [Co_2] - [Cl^-]$

The value is normally less than 12 to 14 mEq/L and consists of phosphates, anionic proteins, sulfates, and anions of various organic acids. Slight elevations to 15 or 16 mEq/L sometimes occur in respiratory alkalosis. Increased undetermined anion concentration indicates metabolic acidosis. However, the converse is not true; metabolic acidosis may be hyperchloremic as in normal anion gap acidosis: diarrhea, renal tubular acidosis (proximal and distal), hyperalimentation acidosis, acetazolamide effect, early renal failure acidosis, and possibly, hyperparathyroidism. Larger undetermined anion gaps are more likely owing to increased organic acids. Values greater than 25 mEq/L occur only in diabetic ketoacidosis; methanol, ethylene glycol, or salicylate intoxication; and lactic acidosis.

Acidosis is usually associated with hyperkalemia unless (a) the acidosis develops in a patient already K^+-depleted or (b) the acidosis is due to loss of $KHco_3$ from the body (e.g., in diarrhea, acetazolamide therapy, or renal tubular acidosis). Alkalosis is usually associated with hypokalemia, except when K^+ loading predominates due to increased K^+ intake or increased rate of tissue breakdown.

IV. Review other laboratory data for acid-base clues.
   A. Polycythemia
   B. Hyperglycemia
   C. Elevated BUN
   D. Elevated NH_3
   E. Decreased pulmonary function
   F. Positive blood culture
V. Analyze and interpret pH, Pco_2, and Hco_3^- as follows. Plot Pco_2 and pH on any of the three available two-dimensional graphs (Fig. 7-1) or on the three-dimensional acid-base surface model of the Henderson-Hasselbalch buffer equation. Visual inspection of the position of this plotted acid-base point relative to both the isobar $Pco_2 = 40$ (line of pure metabolic disturbance) and the patient's Co_2 titration, or blood buffer, curve (line of pure respiratory disturbance) indicates either an apparently (but not necessarily) pure primary respiratory or metabolic disturbance or an obviously mixed disturbance consisting of one or more primary components with or without secondary compensatory responses. Using the other clinical information from the preceding, deduce the nature, sequence, and cause of acid-base events.

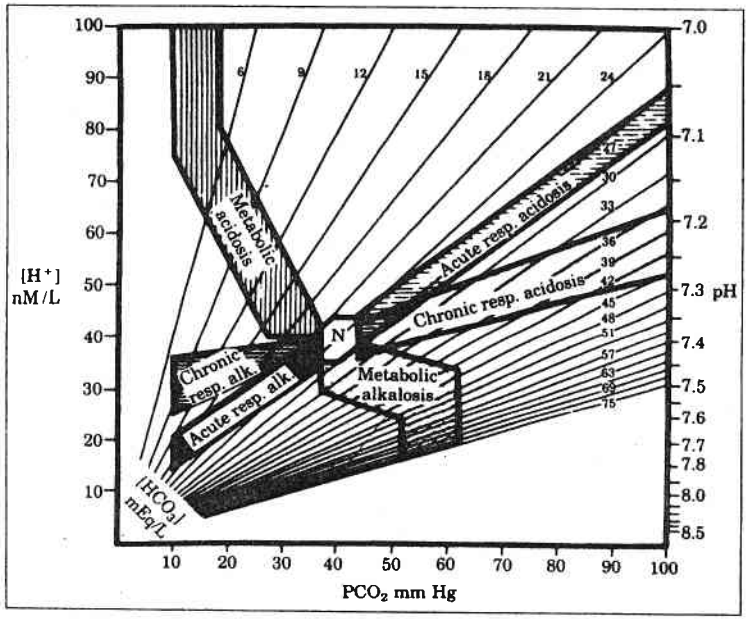

Fig. 7-1. Acid-base map showing the usual compensatory range of pH, Pco_2, and plasma Hco_3 concentration in simple acid-base disorders. Values on the vertical axis represent plasma H^+ concentration (*left*) in nanomoles/L, or pH (*right*). Values on the horizontal axis represent Pco_2 in mm Hg. Diagonal lines are isopleths for the plasma Hco_3 concentration in mEq/L. The clear area in the center of the graph is the range of normal. Note that the metabolic component (plasma Hco_3 concentration) and the respiratory component (arterial blood Pco_2) of the acid-base equation always change in the same direction. (Reprinted by permission from Goldberg M, et al. Computer-based instruction and diagnosis of acid-base disorders: a systemic approach. *JAMA* 1973:223–269.)

Tabular Approach
See Table 7-3.

Rules of Thumb for Interpretation of Acid-Base Disorders
Rules of thumb provide a useful alternative to the graphic method of interpretation. However, it must be remembered that such rules are linear approximations of nonlinear relationships and assume normal in vivo buffering, including normal hemoglobin concentration (Table 7-4).

Principles of Acid-Base Interpretation

I. We live on the brink of acidosis. Failure of either lungs or kidneys precipitates acidosis. Body buffer systems neutralize acid more effectively than they neutralize base. Thus, a base challenge is tolerated more poorly. In health, metabolism of dietary and endogenous protein produces about 1 mEq/kg per day of acid. However, critical illness may increase the rate of endogenous acid production by a factor of 2 to 3.

Table 7-3. Diagnosis of acid-base disorders

P_{CO_2}	Low pH	Normal pH	High pH
High	Respiratory acidosis with or without incompletely compensating metabolic alkalosis or coexisting metabolic acidosis	Respiratory acidosis and compensatory metabolic alkalosis	Metabolic alkalosis with coexisting respiratory acidosis or incompletely compensating respiratory acidosis
Normal	Metabolic acidosis	Normal	Metabolic alkalosis
Low	Metabolic acidosis with coexisting respiratory alkalosis or incompletely compensating respiratory alkalosis	Respiratory alkalosis and compensatory metabolic acidosis	Respiratory alkalosis with or without incompletely compensating metabolic acidosis or coexisting metabolic alkalosis

Table 7-4. Rules of thumb for interpretation of acid-base disorders

Metabolic acidosis	Arterial P_{CO_2} decreases by about 1 to 1½ times the decrease of plasma HCO_3^- concentration.
Metabolic alkalosis	Arterial P_{CO_2} increases by about ½ to 1 times the increase of plasma HCO_3^- concentration.
Respiratory acidosis	P_{CO_2} above 50 mm Hg suggests a *primary* respiratory disorder.
Acute	In acute uncompensated respiratory acidosis, plasma HCO_3^- concentration increases but does not exceed 30 mEq/L. For each mm Hg that P_{CO_2} increases above 40, pH decreases about ¾ of a point below 7.40 in the second decimal place.
Chronic	In fully compensated respiratory acidosis, for each mm Hg that P_{CO_2} increases above 40, plasma HCO_3^- concentration increases about ⅓ of a mEq/L and pH decreases about ¼ point below 7.40 in the second decimal place. For each 10 mm Hg increment of arterial P_{CO_2} above 40, plasma HCO_3^- concentration increases by about 4 mEq/L.
Respiratory alkalosis	
Acute	In primary acute respiratory alkalosis, for each mm Hg that P_{CO_2} decreases below 40, pH increases about 1 point above 7.40 in the second decimal place. For each 10 mm Hg decrement of arterial P_{CO_2}, plasma HCO_3^- concentration decreases by about 2.5 mEq/L, but is rarely less than 18 mEq/L.
Chronic	Plasma HCO_3^- concentration decreases by at least as much as it does in acute respiratory alkalosis but is rarely less than 15 mEq/L.

From Kaehny WD. Pathogenesis and management of respiratory and mixed acid base disorders. In: Schrier RW, ed. *Renal and electrolyte disorders*, 2nd ed. Boston: Little, Brown, 1980:170, with permission.

II. The *law of electroneutrality* states that in any solution the sum of the anionic (−) charges equals the sum of the cationic (+) charges. The concept of anion gap, the undetermined anion concentration, is based on the law of electroneutrality.
III. Acid-base disturbances are chemically additive, but their pathophysiologic effects may be multiplicative.
IV. H^+ concentration is a regulated variable. The pH-compensating response to a primary acid-base disturbance results from the operation of physiologic processes that regulate H^+ concentration in extracellular fluid.
V. Because anemia, hypoproteinemia, and decreased muscle mass reduce body buffering capacity, patients who have these conditions are vulnerable to wider pH swings for a given acid-base challenge.
VI. Respiratory acid-base changes occur in minutes, whereas metabolic acid-base changes require hours or days.
VII. Alveolar ventilation rate is the ultimate regulator of alveolar P_{CO_2}. One minute of apnea increases P_{CO_2} about 4 mm Hg.
VIII. Arterial hypoxemia always precedes CO_2 retention in the course of diffuse bronchopulmonary disease.
IX. CO_2 retention occurs only when the function of both lungs is impaired or when both lungs are diseased. Unilateral pneumonectomy does not result in CO_2 retention if the remaining lung is healthy. CO_2 retention results from hypoventilation, V/Q mismatching, or extensive loss of lung tissue.
X. Respiratory compensation for metabolic disturbances is incomplete. The respiratory compensation for metabolic alkalosis is unpredictable.
XI. Plasma Cl^- and HCO_3^- concentrations tend to change in opposite directions. In metabolic alkalosis Cl^- falls and HCO_3 rises, whereas in metabolic acidosis HCO_3 falls, but Cl^- seldom rises much above normal.
XII. A pH rise of 0.1 U is associated with a corresponding fall in plasma K^+ concentration of about 0.5 mEq/L and a pH fall of 0.1 U is associated with a plasma K^+ rise of the same extent.
XIII. Acid urine in a patient who is alkalemic is often evidence of hypokalemia or intracellular K^+ deficit, or both.

Comments

Rational therapy requires an understanding of the mechanism, nature, extent, and significance of the acid-base abnormality. It is important to identify mixed acid-base abnormalities when present and to distinguish a compensatory change from a coexisting primary disorder. Rational therapy also requires knowledge of the time-course of acid-base changes and often involves prediction of the reversibility of the underlying disorder producing a primary acid-base abnormality. It is also important to recognize certain patterns of arterial blood-gas derangement. For example, the pattern seen in venous thromboembolism, a common clinical dilemma, may facilitate an otherwise difficult diagnosis.

8. MUSCULOSKELETAL PROBLEMS

Clubbing

H. Harold Friedman

Definition

Clubbing is a condition characterized by bulbous enlargement of the distal phalanges of the fingers and toes. Hypertrophic osteoarthropathy is a more advanced stage of clubbing associated with periosteal proliferation of the long bones, often with arthralgia or joint swelling. Both conditions may occur at any age.

Clinical Features

I. Clubbing usually occurs first in the thumb and index finger, and later spreads to the other fingers. The earliest evidence of clubbing is thickening and sponginess of the nail bed, manifested by increased ballotability and curvature of the nail in its bed and an increase in the angle made by the nail and the dorsum of the distal phalanx. The normal base angle when viewed from the side (profile view) is 160 degrees.

   In early clubbing, the base angle is obliterated and becomes 180 degrees or greater. Later there may be warmth and redness and sometimes tenderness of the distal phalanges. Sometimes the patient has a burning sensation in the affected areas, but pain is uncommon. Hypertrophic osteoarthropathy should always be looked for in the presence of clubbing. It may precede the detection of pulmonary neoplastic disease by weeks or months. Clubbing and hypertrophic osteoarthropathy may disappear and reappear synchronously with remission and exacerbations of the underlying disease.

II. When the periosteum of the long bones is involved, there may be pain near the joints as well as redness, warmth, and tenderness.

III. The joints adjacent to long bone involvement may be swollen.

IV. Early on, the radiographs are normal. Later, there is flaring of the ungual process and demineralization. The long bones may reveal periosteal thickening, especially near the joints.

Differential Diagnosis

Clubbing should be differentiated from (a) exaggerated curving of the nail, a normal variant, particularly in African Americans, (b) Heberden's nodes, (c) cysts of the bony phalanges, and (d) infectious processes.

When joint symptoms predominate, confusion with arthritis may occur. If there is superficial warmth, redness, and tenderness in a lower extremity, thrombophlebitis or cellulitis may be considered.

Associated Conditions

Clubbing and hypertrophic osteoarthropathy are relatively innocuous, but they are important because of their frequent association with significant underlying disease. The hereditary forms are not related to any systemic disorder. The major conditions associated with clubbing and hypertrophic osteoarthropathy are listed in the following. Their incidence is as follows: pulmonary disease, 75% to 80%; cardiovascular abnormalities, 10% to 15%; diseases of the gastrointestinal tract, including the liver, 5% to 15%; and miscellaneous disorders, 5% to 15%.

I. Pulmonary disease
   A. Bronchogenic carcinoma (rare with metastatic lung tumor)
   B. Pleural neoplasms

C. Chronic infections other than tuberculosis (e.g., bronchiectasis, abscess, empyema)
D. Emphysema with cor pulmonale
E. Mediastinal lesions

II. Cardiac disorders
A. Cyanotic congenital heart disease
B. Infective endocarditis
C. Pulmonary arteriovenous fistula

III. Chronic liver disease (cirrhosis)

IV. Gastrointestinal disorders
A. Ulcerative colitis
B. Granulomatous colitis
C. Regional enteritis
D. Neoplasms
E. Steatorrhea of unknown cause

V. Hyperthyroidism

VI. Hemoglobinopathies

VII. Unilateral clubbing is usually caused by local vascular disease (e.g., anomalies of the aortic arch, aortic or subclavian aneurysm, pulmonary hypertension with persistent patency of the ductus arteriosus).

Diagnostic Approach to Bilateral Clubbing

History

A family history of clubbing and long duration of clubbing without evidence of associated illness suggest that it is of the hereditary type. Specific information related to associated illnesses should be sought in the history: cough, dyspnea, cigarette smoking, cyanosis, fever, jaundice, alcoholism, diarrhea, and tremulousness.

Physical Examination

Specific points related to associated illness should be sought: wheezes, rales, supraclavicular nodes, murmurs, jaundice, vascular spiders, palmar erythema, enlarged liver, abdominal mass (regional enteritis), thyromegaly, and thyroid eye signs.

Laboratory Studies

I. CBC
II. Urinalysis
III. Chest films
IV. Electrocardiogram
V. Liver function tests
VI. T_4; T_3 resin uptake or T_3 RIA, or both
VII. Arterial blood gases
VIII. Stools for occult blood
IX. Sigmoidoscopy, barium enema, and upper GI and small bowel study if the history suggests GI disease or if stools are positive for blood

Peripheral Joint Arthritis

Kenneth P. Glassman and Herbert Kaplan

The diagnostic challenge presented by the patient with pain or swelling in the elbows, knees, or the joints of the hands and feet is considered in this section. Although disorders that affect the peripheral articulations may also involve the shoulders, hips, and spine, these disorders are covered separately. The following abbreviations are used in this chapter.

ANA = Antinuclear antibody
ARF = Acute rheumatic fever
AS = Ankylosing spondylitis
CTD = Connective tissue disease(s)

DIP = Distal interphalangeal
DNA = Deoxyribonucleic acid
ECM = Erythema chronicum migrans
ESR = Erythrocyte sedimentation rate
HB_sAg = Hepatitis B surface antigen
IP = Interphalangeal
JRA = Juvenile rheumatoid arthritis
MCP = Metacarpophalangeal
MCTD = Mixed connective tissue disease
MTP = Metatarsophalangeal
NSAID(s) = Nonsteroidal antiinflammatory drug(s)
OA = Osteoarthritis
PAN = Polyarteritis nodosa
PIP = Proximal interphalangeal
PMR = Polymyalgia rheumatica
PSS = Primary Sjögren's syndrome
RA = Rheumatoid arthritis
RF = Rheumatoid factor
RNP = Ribonucleoprotein
SLE = Systemic lupus erythematosus

Etiology

The more common causes of peripheral joint disease diagnosed in office practice, listed in order of decreasing frequency, are as follows:

I. Osteoarthritis
II. Bursitis, tendinitis
III. Connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, polymyalgia rheumatica, scleroderma, dermatomyositis, polyarteritis nodosa, acute rheumatic fever)
IV. Crystalline arthropathies (gout, pseudogout)
V. Rheumatoid variants (ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, palindromic rheumatism, enteropathic arthropathy, juvenile rheumatoid arthritis)
VI. Infectious arthritis (bacterial and viral)
VII. Joint trauma
VIII. Lyme disease
IX. Miscellaneous disorders (sarcoidosis, hyperparathyroidism, myxedema, chronic active hepatitis, hemophilia, neuropathic arthropathy, pharmacologic arthritis, Behçet's syndrome, Whipple's disease, malignancy, pigmented villonodular synovitis, foreign body synovitis, amyloidosis, AIDS and other immunodepressant syndromes)

Diagnostic Approach

History

Mode of Onset

An acute, dramatic onset suggests crystalline arthropathy or infectious arthritis. However, acute rheumatic fever, rheumatoid arthritis, juvenile rheumatoid arthritis, Reiter's syndrome, and psoriatic arthritis may also begin suddenly. The chronic course of rheumatoid arthritis and osteoarthritis frequently is punctuated by acute exacerbations of painful, swollen, and occasionally warm joints. An acute onset of painful muscles in the proximal upper or lower extremities, or both, suggests PRM, which may be associated with mild synovitis of small joints.

Trauma

I. A history of trauma, recent or remote, may be significant in predisposing to osteoarthritis, tendinitis, or bursitis.
II. Acute gouty or pseudogout arthritis is often triggered by relatively mild trauma to the involved joint and is also a cause of acute arthritis in the first week after a major surgical procedure.

Antecedent Infection

I. A history of an infected skin laceration or any other bacterial focus may be the clue to infectious arthritis.
II. An antecedent streptococcal pharyngitis or scarlet fever should arouse suspicion of acute rheumatic fever.
III. Recent urethritis suggests gonococcal arthritis or Reiter's syndrome. The onset of gonococcal arthritis may also be associated with a menstrual period. Enteric infections causing diarrhea frequently precede the articular complaints by 1 to 3 weeks.
IV. Fever and skin rash followed by polyarthritis suggests rubella, infectious mononucleosis, arthritis associated with viral hepatitis, Lyme disease, or juvenile or adult-onset Still's disease.
V. An acute arthritis at the site of a total joint replacement in a patient with recent genitourinary instrumentation or dental cleaning should arouse suspicion of a septic joint.

Drugs

I. A history of intravenous drug abuse should suggest the possibility of infectious arthritis.
II. Penicillin, sulfonamides, and horse serum injections are common causes of foreign protein reactions (serum sickness) typified by urticaria and polyarthritis.
III. Antihypertensive drugs, diuretics, and L-dopa produce hyperuricemia and are common causes of secondary gout. Chemotherapy agents used in malignant disease may also cause secondary gout.
IV. Anticonvulsant drugs, hydralazine, procainamide, isoniazid, and some antibiotics may cause an SLE-like syndrome with polyarthritis.
V. Acute joint swelling in patients taking anticoagulants suggests hemarthrosis. However, hemarthrosis may also occur in patients with hereditary clotting disorders or trauma.

Previous Responses to Therapy

I. A therapeutic response or failure to respond to a specific drug may be of some diagnostic significance.
II. A good result from the administration of colchicine is almost pathognomonic of gout, although a beneficial response has also been reported in sarcoid arthritis, rheumatoid arthritis, and pseudogout.
III. A dramatic response to large doses of salicylates may be obtained in most acute joint inflammations. These drugs are less effective in Reiter's syndrome, crystalline arthropathy, and infectious arthritis.
IV. Systemic steroids may alleviate the arthritis of connective tissue disease and gout, but they are less effective in infections, osteoarthritis, Reiter's syndrome, and psoriatic arthritis. They are not indicated in infectious arthritis.
V. The response to drugs with a broad spectrum of antiinflammatory and analgesic activity is of little or no diagnostic value in either acute or chronic arthritis. A striking response to indomethacin or phenylbutazone in patients with severe lower back pain suggests the presence of ankylosing spondylitis or another seronegative spondyloarthropathy.

Family History

I. A family history of "arthritis" is generally of little diagnostic significance.
II. A well-documented family history of rheumatoid arthritis, connective tissue disease, gout, Heberden's nodes, psoriasis, ankylosing spondylitis, hemoglobinopathy, or abnormal bleeding may be of value.

Travel History

A travel history to regions where Lyme disease is endemic is pertinent. These areas are (primarily) the northeast seaboard, Wisconsin, Minnesota, northern California, and Oregon.

Physical Examination

In the physical examination, extraarticular manifestations of rheumatic disorders may provide important clues to specific diagnoses. Some of the more important of these findings are listed in the following.

I. Mucocutaneous lesions
   A. Patchy alopecia may be seen in SLE and RA. The hair of the forehead is characteristically short and brittle in SLE.
   B. A combination of painful oral and genital ulcers with iritis suggests Behçet's syndrome. Ulcerative lesions of the penis and scrotum, or of the vulva and vagina, are commonly observed. Pyoderma may be noted.
   C. Painful oral ulcers, balanitis circinata, and keratoderma blennorrhagica are features of Reiter's syndrome.
II. Cutaneous lesions
   A. Erythematous cutaneous lesions, a malar butterfly rash (especially one precipitated by sun exposure), and erythematous lesions of the fingertips should suggest SLE.
   B. Subcutaneous nodules in the olecranon bursa, along the extensor surface of the forearm or along bony protuberances, are almost pathognomonic of RA, but they also are seen, although rarely, in patients with acute rheumatic fever and SLE. Subcutaneous nodules may be indistinguishable from the tophi of gout. Tophi commonly occur in the cartilage of the helix of the ear, the olecranon and patellar bursae, and the tendons.
   C. Indolent ischemic ulcers on the distal portion of the leg occur in RA with Felty's syndrome or vasculitis, and in SLE.
   D. Pyoderma gangrenosum as well as erythema nodosum is often associated with the arthropathy of ulcerative colitis.
   E. The presence of cutaneous psoriasis suggests the possibility of psoriatic arthritis, as do multiple pitted lesions of the nails with or without subungual keratoses and onycholysis.
   F. Edematous, indurated, and atrophic changes in the skin, fingertip ulcerations, and hyperpigmentation are features of scleroderma.
   G. Erythema over the knuckles, a dusky erythematous eruption in a "shawl" distribution over the shoulders, a lilac or heliotrope discoloration of the upper eyelids, and diffuse or localized muscle induration should suggest dermatomyositis.
   H. A small red macule at the site of a tick bite that expands to form a large annular lesion with bright red outer border and partial central clearing may suggest ECM of Lyme disease.
   I. Sweaty palms with thenar and hypothenar erythema are common in RA.
   J. A salmon-colored macular, evanescent rash is characteristic of juvenile and adult-onset Still's disease.
   K. Raynaud's phenomenon on examination or a convincing history of finger blanching suggests scleroderma, RA, or SLE.
III. Ocular lesions
   A. Keratoconjunctivitis sicca, xerostomia, nasopharyngeal ulceration, and parotid enlargement are manifestations of Sjögren's syndrome, which may be primary or associated with RA in about half the cases and less commonly with other connective tissue disease.
   B. Conjunctivitis and iritis occur in Reiter's syndrome, sarcoidosis, AS, JRA, and Behçet's syndrome.
   C. Retinal cytoid bodies are a manifestation of SLE. Retinal granulomata may be observed in sarcoidosis and tuberculosis.
IV. Lymphadenopathy. A nonspecific abnormality, lymphadenopathy is not uncommon in SLE, RA, JRA, sarcoidosis, Lyme disease, and the arthritis seen in lymphomas.
V. Cardiopulmonary abnormalities
   A. Wheezing, cough, and shortness of breath may occur as a result of the pulmonary parenchymal disease sometimes found in RA, SLE, scleroderma, polymyositis, polyarteritis nodosa, and sarcoidosis.

B. Pleurisy with or without effusion may occur early in RA and SLE.
C. Cardiac involvement (pericarditis, heart block) may be a feature of any of the connective tissue diseases, Reiter's syndrome, or Lyme disease.
D. Aortic insufficiency may occur in acute rheumatic fever, RA, AS, Reiter's syndrome, and Behçet's syndrome.
E. Decreased chest expansion is a feature of ankylosing spondylitis.

VI. Hepatosplenomegaly may be found in CTD, sarcoidosis, infections, Lyme disease, and chronic active hepatitis. Splenomegaly is a feature of Felty's syndrome, systemic JRA, and SLE.

VII. Neurologic abnormalities
A. Polyneuritis or mononeuritis multiplex may occur in the connective tissue diseases and neuropathic arthropathies.
B. Long tract signs and motor weakness may result from cervical cord compression, most commonly owing to C1-C2 subluxation in RA, ankylosing spondylitis, and, less commonly, SLE.
C. Peripheral nerve entrapment syndromes may occur in RA, myxedema, and gout.
D. Neurologic manifestations of Lyme disease are protean and include cranial neuritis (Bell's palsy), meningitis, motor and sensory radiculoneuritis, chorea, and myelitis.

Etiology of Peripheral Joint Disease

The mode of onset, clinical course, and pattern of joint involvement provide a convenient basis for classifying the clinical patterns of peripheral joint disease. Four major categories can be identified: (a) acute polyarthritis, (b) chronic polyarthritis, (c) acute monarthritis, and (d) chronic monarthritis. It should be recognized that although this classification is useful in the diagnostic approach to joint disease, it is not all-encompassing. Moreover, it should not be implied that all cases can be grouped into these categories. The most common causes of these clinical patterns are listed in the following.

Acute Polyarthritis

I. Acute rheumatic fever (frequently migratory)
II. Rheumatoid arthritis
III. Other connective tissue diseases
IV. Seronegative spondyloarthropathies
V. Infectious arthritis (especially gonococcal)
VI. Gout
VII. Pseudogout
VIII. Foreign protein reaction (serum sickness)
IX. Palindromic rheumatism
X. Sarcoidosis

Chronic Polyarthritis

I. Rheumatoid arthritis
II. Other connective tissue diseases
III. Seronegative spondyloarthropathies
IV. Chronic gouty arthritis
V. Osteoarthritis
VI. Sarcoidosis
VII. Malignancy
VIII. HIV-associated arthritis

Acute Monarthritis

I. Gout
II. Pseudogout
III. Traumatic joint disease
IV. Infectious arthritis (bacterial, tubercular, fungal)
V. Rheumatoid arthritis

VI. Osteoarthritis
VII. Seronegative spondyloarthropathies
VIII. Lyme disease
IX. Intermittent hydrarthrosis

Chronic Monarthritis

I. Infectious arthritis (bacterial, tubercular, fungal)
II. Traumatic arthritis
III. Osteoarthritis
IV. Gout
V. Pseudogout
VI. Neuropathic arthropathy
VII. Neoplasms (pigmented villonodular synovitis, osteochondromatosis, synovioma, metastatic)
VIII. Lyme disease

Clinical Features of Peripheral Joint Disease

The clinical manifestations and the pattern of joint involvement may provide useful clues to the diagnosis of arthritis.

Acute Polyarthritis

I. Acute migratory polyarthritis in children and young adults beginning shortly after a streptococcal infection suggests ARF. Typically, there is swelling, heat, redness, tenderness, pain, and limitation of motion of two or more joints, most commonly the knees, ankles, elbows, wrists, hips, and small joints of the feet. According to the modified Jones criteria, the presence of two major criteria, or one major and two minor criteria, of those listed in the following, is considered diagnostic of ARF.
A. Major manifestations
1. Carditis
a. Significant murmurs
b. Cardiomegaly
c. Pericarditis
2. Polyarthritis
3. Chorea
4. Erythema marginatum
5. Subcutaneous nodules
B. Minor manifestations
1. Clinical
a. History of previous ARF or evidence of rheumatic heart disease
b. Arthralgias
c. Fever (>38°C)
2. Laboratory
a. Elevated sedimentation rate and positive C-reactive protein test
b. Electrocardiographic changes, chiefly prolongation of the P-R interval
c. Supporting evidence of streptococcal infection
3. Laboratory
a. Positive throat culture
b. Positive antibody test (ASO titer)
4. Scarlet fever

II. Although RA usually begins insidiously, it may begin as an acute polyarthritis. Favoring RA are the presence of prolonged morning stiffness and symmetric involvement of the small joints of the hands and feet. The need for a hot bath or shower in the morning in order to "get going" is also a helpful diagnostic finding, especially if this information is volunteered by the patient.

III. SLE may present as an acute polyarthritis. The American College of Rheumatology has proposed criteria for making the diagnosis of SLE. The presence,

serially or simultaneously, of four or more manifestations strongly supports the diagnosis of SLE and militates against the presence of another CTD. The manifestations are listed in Table 8-1.

IV. Seronegative spondyloarthropathies, such as psoriatic arthritis, Reiter's syndrome, and enteropathic arthropathy, may begin as an acute polyarthritis. The distinguishing features are discussed in the following.

V. Gonococcal arthritis is usually a febrile illness beginning 1 to 2 weeks after a gonorrheal infection with evidence of a migratory polyarthritis. Eventually, the infection localizes to one or more joints. Signs of joint inflammation and tenosynovitis may be observed. Macular, hemorrhagic, vesicular, or pustular skin lesions are often seen. Culture of the synovial fluid is positive in less than 50% of cases and is not necessary for the diagnosis. A good therapeutic response to penicillin but not to salicylates strongly supports the diagnosis in an appropriate clinical setting, even when bacteriologic studies are negative.

VI. Infectious arthritis of other origin may present a similar picture. Joint involvement is by local extension or hematogenous spread. If proper sterile procedure is utilized, it is exceedingly unusual to inoculate a joint during arthrocentesis.

VII. Gout and pseudogout may show up in acute polyarticular form, but this is rare. The diagnosis depends on the demonstration of urate or calcium pyrophosphate dihydrate crystals, respectively, in the synovial fluid.

VIII. Foreign protein reactions, including serum sickness, may look like an acute polyarthritis. Clues to the correct diagnosis are a history of drug or horse serum administration and the presence of urticaria.

IX. Palindromic rheumatism is an acute migratory polyarthritis in which the pattern of onset of the inflammation mimics the pattern of resolution.

Chronic Polyarthritis

I. A progressive, symmetric polyarthritis with fusiform swelling of the joints, muscle atrophy, and, eventually, deformities is characteristic of RA. There is a predilection for involvement of the PIP and MCP joints of the fingers, the MTP joints of the feet, and the toes, wrists, knees, elbows, shoulders, and hips. Stiffness after inactivity, especially in the morning on arising, is a characteristic symptom. Subcutaneous nodules, when present, are virtually pathognomonic. The outcome of a test for RF is positive in 70% to 80% of cases.

II. A chronic rheumatoid arthropathy may occur in other CTD, especially in SLE. Recurrent or persistent small joint inflammation in the absence of deformity or radiographic erosions also suggests SLE. Ankylosis and contractures are uncommon. An overlap syndrome, labeled MCTD, incorporates clinical features of SLE, scleroderma, and polymyositis. The articular manifestations resemble those seen in SLE, with arthritis or arthralgias in over 90% of patients. Marked swelling of the hands, particularly the fingers, leads to a sausagelike appearance. Raynaud's phenomenon, a low incidence of renal involvement, and a good response to steroid therapy further characterize this entity.

III. Polyarthritis may occur in the seronegative spondyloarthropathies. In these diseases, joint involvement tends to be asymmetric and progression to deformity is less common than in RA. Interphalangeal synovitis of the toes ("sausage toes") is a feature of Reiter's syndrome, psoriatic arthritis, and the peripheral arthritis of AS. Spondylitis and sacroiliitis are commonly observed in the HLA group of diseases. Tests for RF are usually negative. There is a link between HLA-B27 and the seronegative spondyloarthropathies.

A. Reiter's disease is characterized by a combination of urethritis, iritis or conjunctivitis, arthritis, and often diarrhea, balanitis, and keratodermia blennorrhagica. Heel pain in a young man should suggest this diagnosis. Spinal involvement similar to that of AS may occur; asymmetric sacroiliac involvement is the rule in Reiter's disease. Reiter's syndrome has clearly been associated with HIV infection. The articular symptoms in most cases occur after the onset of apparent HIV infection. The knees are most commonly involved, and urethritis and conjunctivitis are frequently absent.

Table 8-1. Criteria for the classification of systemic lupus erythematosus[a]

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR* Pericarditis—documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation not performed *OR* Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance) *OR* Psychosis—in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia—with reticulocytosis *OR* Leukopenia—less than 4000/μL total on two or more occasions *OR* Lymphopenia—less than 1,500/μL in the absence of offending drugs *OR* Thrombocytopenia—less than 100,000/μL in the absence of offending drugs
Immunologic disorder	Positive LE cell preparations *OR* Anti-DNA: antibody to native DNA in abnormal titer *OR* Anti-Sm: presence of antibody to Sm nuclear antigen *OR* False-positive serologic test for syphilis known to be positive for at least 8 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

[a] The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
Source: From the *Primer on the Rheumatic Diseases*, 10th edition, copyright 1993. For more information, please call the Arthritis Foundation's information line 1-800-283-7800. Used by permission of the Arthritis Foundation.

B. Psoriatic arthritis may mimic RA. Involvement of the DIP joints, typical changes in the nails, cutaneous psoriasis, and a positive family history are clues to the diagnosis.
C. AS with peripheral arthritis is not often mistaken for RA when the spinal involvement dominates the clinical picture, but it may begin with peripheral joint signs.
D. Enteropathic arthritis (e.g., arthritis associated with regional enteritis and ulcerative colitis) may simulate the polyarthritis of RA. The joint symptoms may precede the GI disease.

IV. Although chronic gouty arthritis may mimic RA, advanced deforming arthritic changes owing to gout are uncommon. A long history of acute episodic arthritis with remissions between attacks can usually be obtained. Hyperuricemia, the demonstration of urate crystals in the synovial fluid, specific x-ray changes, response to colchicine, and biopsy of a gouty tophus have confirmatory value.
V. Osteoarthritis is a polyarticular disease, with symptoms usually related to involvement of the knees, hips, vertebral column, and hands. Heberden's nodes are bony protuberances of the DIP joints of the fingers, often associated with flexion and angulation of the distal phalanges. Local pain, tenderness, and some warmth may be present. Tender, knobby enlargement of the PIP joints (Bouchard's nodes) is not uncommon and may cause confusion with RA. Degenerative changes in the knees are often manifested by pain, joint swelling, crepitus, and deformity. Slight increase in skin temperature over the joint is a common finding. Involvement of the spine and hips is discussed later in this chapter.
VI. The joint swelling present in cases of hypertrophic osteoarthropathy may be mistaken for a polyarthritis of other origin. The presence of clubbing and an association with chronic pulmonary disease, bronchogenic carcinoma, cyanotic congenital heart disease, cirrhosis, or enteropathic disease usually make the diagnosis apparent. The presence of periosteal proliferation on radiography is confirmatory.

Acute and Chronic Monarthritis

I. Acute monarticular arthritis in a male involving the MTP joint of the great toe, instep, heel, ankle, knee, wrist, hand, or elbow, with complete recovery between attacks, is virtually pathognomonic of gout. The diagnosis is established by the demonstration of urate crystals in the synovial fluid or a therapeutic response to adequate doses of colchicine. Hyperuricemia is usually but not always present. Tophi are found in advanced cases.
II. Acute monarticular arthritis may also be caused by pseudogout (chondrocalcinosis). The diagnosis depends on finding calcium pyrophosphate dihydrate crystals in aspirated synovial fluid and on the presence of calcium deposits in the menisci or the articular cartilages.
III. Trauma frequently affects only one joint. Because the trauma is usually severe, the diagnosis is generally evident from the history.
IV. Pyogenic, tuberculous, or gonococcal arthritis is commonly monarticular, and evidence of antecedent or concomitant infection is not difficult to obtain. Cytologic and bacteriologic studies of the synovial fluid establish the etiologic diagnosis.
V. Although several joints are usually affected in osteoarthritis, involvement of a single weight-bearing joint, such as the knee or hip, may dominate the clinical picture. Further details may be found elsewhere in this chapter.
VI. RA and especially JRA may be monarticular at the onset of the disease. Local signs of inflammation are commonly observed. The diagnosis may become apparent only after a prolonged period of observation. Infectious arthritis and other causes of monarthritis must be excluded.
VII. Neuropathic arthropathy (Charcot's joint) is characterized by joint hypermobility, effusion, and disproportionately little pain in association with a primary neurologic disorder such as tabes dorsalis, diabetic neuropathy, or syringomyelia.
VIII. Pigmented villonodular synovitis, synovial chondromatosis, and chondrosarcoma are less common causes of monarthritis.

IX. The typical pattern of arthritis in Lyme disease is intermittent monoarticular or pauciarticular (4 joints) synovitis of large joints, especially the knees. Approximately 10% of cases develop chronic arthritis with cartilage damage and erosions.

Diagnostic Procedures in Arthritis

Synovial Fluid Analysis

Synovial fluid analysis should include the following: white cell count, differential count, crystal identification, gram and acid-fast stains, and culture. The pertinent findings on examination of joint fluid are summarized in Tables 8-2 and 8-3. Table 8-4 contains information concerning commonly used laboratory tests in the diagnosis of arthritis.

Suggested Workup for Acute Arthritis

I. CBC
II. Urinalysis
III. ESR (Westergren)
IV. Biochemical screening
V. Test for RF by nephelometry
VI. ANA, including titer
VII. HB_sAg
VIII. HLA-B27, if compatible with spondyloarthritis
IX. Exclusion of infectious process clinically, and if necessary, by cytologic study and culture of synovial fluid
X. Synovial fluid analysis to rule out crystalline arthropathy when appropriate; culture of cervix, rectum, throat, and skin lesions when indicated
XI. Radiographs of involved and contralateral joints
XII. Chest films to rule out sarcoid arthritis
XIII. Electrocardiogram
XIV. Antispirochetal (Lyme) antibodies

Suggested Workup for Chronic Arthritis

I. CBC
II. Urinalysis
III. ESR (Westergren)
IV. Biochemical screening
V. Liver profile
VI. Test for RF, including titer
VII. ANA, including titer
VIII. HLA-B27, if compatible with spondyloarthritis
IX. Serologic test for syphilis
X. Thyroid function tests, if appropriate
XI. Radiographs of involved and contralateral joints
XII. Chest films
XIII. Electrocardiogram
XIV. Synovial fluid analysis
XV. Special procedures, when appropriate
  A. Complete ANA profile
  B. Immunoglobulins
  C. Serum complement
  D. Creatinine clearance
  E. Coagulation screening
  F. Esophageal motility studies
  G. Contrast studies of the GI tract
  H. Biopsy of subcutaneous nodules, tophi, or synovium
  I. Electromyogram
  J. Technetium bone scan
XVI. Antispirochetal (Lyme) antibodies
XVII. HIV antibody assay

(*text continues on page 293*)

Table 8-2. Examination of joint fluid

Measure	Normal	Group I (noninflammatory)	Group II (inflammatory)	Group III (septic)
Volume (mL) (knee)	<3.5	Often >3.5	Often >3.5	Often >3.5
Clarity	Transparent	Transparent	Translucent-opaque	Opaque
Color	Clear	Yellow	Yellow to opalescent	Yellow to green
Viscosity	High	High	Low	Variable
WBC/□L	<200	200–2000	200–100,000	>100,000[a]
Polymorphonuclear leukocytes (%)	<25%	<25%	50% or more	75% or more[a]
Culture	Negative	Negative	Negative	Often positive

[a] Lower with infections caused by partially treated or low-virulence organisms.
From *Primer on the rheumatic diseases*, 10th ed. Arthritis Foundation, 1993, with permission. For more information, please call the Arthritis Foundation's information line, 1-800-283-7800.

Table 8-3. Differential diagnosis by joint fluid groups

Group I (noninflammatory)	Group II (inflammatory)	Group III (septic)	Hemorrhagic
Degenerative joint disease	Rheumatoid arthritis	Bacterial infections	Hemophilia or other hemorrhagic diathesis
Trauma[a]	Acute crystal-induced synovitis (gout and pseudogout)		Trauma with or without fracture
Osteochondritis dissecans	Reiter's syndrome		Neuropathic arthropathy
Osteochromatosis	Ankylosing spondylitis		Pigmented villonodular synovitis
Neuropathic arthropathy[a]	Psoriatic arthritis		Synovioma
Subsiding or early inflammation	Arthritis accompanying ulcerative colitis and regional enteritis		Hemangiomas and other benign neoplasms
Hypertrophic osteoarthropathy[b]	Rheumatic fever[b]		
Pigmented villonodular synovitis[a]	Systemic lupus erythematosus[b]		
	Progressive systemic sclerosis (scleroderma)[b]		

[a] May be hemorrhagic
[b] Groups I or II
From *Primer on the rheumatic diseases*, *JAMA* 1973;224;661–812, American Medical Association, with permission.

Table 8-4. Diagnostic procedures in arthritis

Test	Purpose	Results and interpretation
CBC	Routine	Anemia common in RA, connective tissue diseases, rheumatoid variants Leukocytosis in infectious arthritis, juvenile RA, crystalline arthropathy, occasionally RA; eosinophilia rare in RA Leukopenia common in SLE; also occurs in Felty's syndrome Thrombocytopenia occurs in SLE
ESR (Westergren method)	Routine	Nonspecific sign of inflammatory disease May parallel severity of RA When normal, favors noninflammatory joint disease Strikingly elevated in polymyalgia rheumatica Normal values in increase with age
Urinalysis	Routine	Proteinuria in nephropathy of SLE, polyarteritis nodosa, scleroderma, gout Pyuria in gonorrhea, Reiter's syndrome Cylindruria and RBC casts in SLE nephritis
RF	Diagnosis of RA	Nonspecific test, not absolutely pathognomonic of RA. It may be positive in 5% to 10% of normal individuals above the age of 50 years and in 20% to 30% of cases of SLE. A positive rheumatoid factor may also be seen in chronic bacterial infections; viral illnesses; chronic inflammatory diseases, such as sarcoidosis and interstitial lung disease; cryoglobulinemia; and diseases associated with hypergammaglobulinemia.
ANA	Diagnosis of SLE, MCTD	ANA more sensitive than LE cell phenomenon but less specific for the diagnosis of SLE. What constitutes a significant titer and the importance of the pattern of ANA varies with different laboratories and the techniques of performing the test. ANA rarely if ever absent in SLE but frequently positive in low titer in other CTD and in 5% of "healthy" elderly individuals High titer of speckled ANA seen in MCTD
Antibody to RNP	Diagnosis of MCTD	Positive in very high percentage of MCTD May be positive in SLE
Antibody to native DNA	Diagnosis of SLE	High titer strongly suggestive of SLE May be positive in some patients with RA Anti-Sm antibody is a test of purpose. Diagnosis of SLE results in interpretation of the most specific test for SLE but present in only up to 30% of patients with lupus
Cytoplasmic neutrophil Cytoplasmic antibodies (C-ANCA)	Diagnosis of active Wegener's granulomatosis and systemic vasculitis	
C3 and C4 complement components	Diagnosis of SLE	Useful in determining disease activity of SLE
Anti-Ro (SS-A)	Diagnosis of primary Sjögren's syndrome	Present in 70% of patients with primary Sjögren's and 30% of patients with SLE
Anti-La (SS-B)	Detection of primary Sjögren's syndrome	Present in 60% of patients with primary Sjögren's and 10–15% of patients with SLE
Anticentromere antibody	Diagnosis of CREST syndrome	Present in 60–90% of patients with CREST syndrome and 10–15% of patients with PSS
Anti-SCL–70	Diagnosis of PSS	Highly specific for systemic sclerosis, but present in only 10–20% of patients
Antihistone antibodies	Detection of drug-induced SLE	Antihistone is found in 90–95% of patients with drug-induced LE.
HLA-B27 (histocompatibility antigen)	Detection of occult axial arthropathy	Positive in 85–95% of patients with AS and Reiter's syndrome May be positive in enteropathic and psoriatic arthropathy with spinal involvement
Anti-DNA	Reflects activity of SLE	Serial determinations of value in monitoring efficacy of therapy in SLE
Skin biopsy for immunofluorescence	Diagnosis of SLE	Immunoglobulins at dermal-epidermal junction in sun-protected areas in 50–60% of patients with SLE
HB_sAG	Detection of hepatitis B infection	Present in arthritis of type B viral hepatitis Positive in some patients with PAN
Liver profile	Diagnosis of arthritis associated with liver disease	Abnormal in acute viral hepatitis, chronic active hepatitis, primary biliary cirrhosis, sarcoidosis
T_4 and T_3 resin uptake, TSH	Diagnosis of hypothyroidism	Performed to rule out hypothyroidism, which may produce rheumatoid-like arthropathy and a carpal tunnel syndrome

continued

Table 8-4. *Continued.*

Test	Purpose	Results and interpretation
CPK, SGOT, aldolase	Diagnosis of polymyositis	One or all elevated in polymyositis CPK often elevated in myopathy of hypothyroidism Enzymes normal in polymyalgia rheumatica and other connective tissue diseases
Serum calcium, phosphorus, alkaline phosphatase	Detection of arthritis associated with intrinsic bone disease	Hypercalcemia, hypophosphatemia, and elevated alkaline phosphatase in hyperparathyroidism
Borella burgdorferi antibodies	Detection of infection with the Lyme spirochete	Hypercalcemia, often present in sarcoidosis, metastatic malignancy Alkaline phosphatase increased in osteomalacia Elevated IgM titers peak 4–6 weeks after infectious IgG titers stay elevated in chronic cases; false positives occur in other autoimmune diseases (SLE, RA) and other spirochetal infections (syphilis, relapsing fever)
Serum protein electrophoresis, immunoglobulins	Detection of hyperglobulinemia and dysproteinemias	Hyperglobulinemia seen in sarcoidosis, enteropathic arthroplasty, lymphomas, other malignancies, and advanced stages of some connective tissue diseases Diffuse hypergammaglobulinemia in chronic infection, liver disease, SLE and RA Monoclonal gammopathy in myeloma, macroglobulinemia, some cases of primary amyloidosis or carcinoma, and some normal elderly persons
Serum uric acid	Detection of hyperuricemia	Cases of hyperuricemia Asymptomatic, genetic Gout (primary or secondary) Drugs (e.g., salicylates, diuretics) Hematologic disorders (e.g., polycythemia, leukemia, hemolytic anemias) Renal disease Hypertension Hereditary disorders (e.g., Lesch-Nyhan syndrome) Endocrine disorders

Myalgia

Kenneth P. Glassman and Herbert Kaplan

Myalgia is poorly localized aching in a muscle or group of muscles. Although any of the diseases that primarily affect the joints may also cause muscle pain, this discussion is limited to patients with muscle pain and minimal or no articular involvement. The presence of muscle pain does not discern between an inflammatory and a noninflammatory condition.

Etiology

Myalgia may be secondary to rheumatic or nonrheumatic conditions. The causes are listed in order of decreasing frequency within each group (Tables 8-5 and 8-6).

I. Rheumatic disorders
   A. Fibromyalgia and psychogenic rheumatism. Both conditions are diagnosed by exclusion. A consideration of whether they are the same condition or separate entities is beyond the scope of this discussion.
   B. Tendinitis and peritendinitis
   C. Connective tissue diseases
   D. Ankylosing spondylitis
   E. Polymyalgia rheumatica
   F. Sarcoidosis
II. Nonrheumatic disorders
   A. Infectious diseases (viremia, bacteremia, HIV, parasitic)
   B. Disease of the spinal column (intervertebral disk protrusion, spondylolisthesis, osteoporosis of the spine)
   C. Peripheral nerve entrapment syndromes (e.g., carpal tunnel syndrome)
   D. Neoplasms, including hypertrophic osteoarthropathy
   E. Endocrine disorders (hypothyroidism, hyperparathyroidism, acromegaly, osteomalacia)
   F. Peripheral neuritis, including diabetic neuropathy, pernicious anemia
   G. Drug-induced myalgia
      1. Steroid-induced pseudorheumatism
      2. Hypokalemia secondary to diuretics
      3. SLE syndrome secondary to anticonvulsants, hydralazine, procainamide, isoniazid, antibiotics
      4. Chloroquine
      5. Lipid-lowering agents (e.g., lovastatin)
      6. Zidovudine
      7. D-penicillamine
   H. Reflex sympathetic dystrophy (shoulder-hand syndrome)
   I. Alcoholism, acute and chronic
   J. Parkinson's disease
   K. Paget's disease of bone
   L. Postgastrectomy (subtotal)
   M. Neuromuscular disorders

Diagnostic Approach

History

I. Mode of onset
   A. An insidious onset and gradual course are typical of most of the etiologic entities. A sudden onset is reported in the majority of patients with polymyalgia rheumatica and those with occult or overt infections.
   B. Acute muscle pain, often associated with muscle swelling during the course of an alcoholic bout, is seen in alcoholic myopathy.
II. Area of involvement
   A. The more localized and symmetric the area of discomfort, the more likely it is that the diagnosis is fibromyalgia.

Table 8-5. Clinical features of the most common causes of myalgia

Cause	History	Physical examination	Laboratory data
Fibromyalgia	Symmetric, reproducible, relatively localized muscular aching with or without morning stiffness; occurs predominantly in women	Reproducible, localized muscle tender points	Negative
Psychogenic rheumatism	Pain described in bizarre terms (tearing, pulsating); role of emotions vigorously denied	Nonreproducible tender points; histrionic reaction to light palpation	Negative
Tendinitis, peritendinitis, capsulitis (especially shoulder)	Acute or insidious onset, often associated with trauma or excessive use of muscle involved	Local tenderness over tendon insertion and contiguous muscle; periarticular tenderness; limited motion common	Negative
Rheumatoid arthritis	Muscular symptoms may precede articular symptoms; often severe pain and stiffness	Usually significant synovitis in the peripheral joints; subcutaneous nodules; muscle wasting if severe	ESR elevated; RF positive; minimal inflammation on muscle biopsy
Polymyalgia rheumatica	Typically, elderly woman with relatively acute onset of aching and stiffness of the proximal muscles and pelvic and shoulder girdles	Painful and tender proximal muscles without true weakness; minimal synovitis; possible temporal artery tenderness	Striking elevation of ESR; other tests negative
Dermatomyositis, SLE, scleroderma, MCTD, inclusion body myositis (IMB)	Usually insidious onset, except in dermatomyositis; insidious onset of painless weakness	Abnormal muscle consistency, wasting, weakness; skin induration in scleroderma; rash in SLE and dermatomyositis	Abnormal SGOT, CPK, aldolase in dermatomyositis; positive anti-PM1 in dermatomyositis; positive ANA in SLE; positive RNP in MCTD; soft tissue calcification in scleroderma and dermatomyositis; abnormal esophageal motility may be present in all; muscle biopsy abnormal in dermatomyositis; EMG abnormal; abnormal CPK; abnormal EMG and muscle biopsy

Table 8-6. The American College of Rheumatology 1990 criteria for classification of fibromyalgia[a]

History of widespread pain
Definition: Pain is considered widespread when all the following are present—pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back) must be present. In this definition, shoulder and buttock pain is considered pain for each involved side. "Low back" pain is considered lower segment pain.

Pain in 11 of 18 tender point sites on digital palpation
Definition: On digital palpation, pain must be present in at least 11 of the following 18 tender point sites:
Occiput—bilateral, at the suboccipital muscle insertions
Low cervical—bilateral, at the anterior aspects of the intertransverse spaces at C5–7
Trapezius—bilateral, at the midpoint of the upper border
Supraspinatus—bilateral, at origins, above the scapular spine near the medial border
Second rib—bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral epicondyle—bilateral, 2 cm distal to the epicondyles
Gluteal—bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
Greater trochanter—bilateral, posterior to the trochanteric prominence
Knee—bilateral, at the medial fat proximal to the joint line
Digital palpation should be performed with an approximate force of 4 kg.
For a tender point to be considered "positive," the subject must state that the palpation was painful. "Tender" is not to be considered "painful."

[a] For classification purposes, patients are said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.
From *Arthritis and Rheumatism* 1990;33:160–172, with permission.

B. Specific localization over a tendon is helpful, as in bicipital tendinitis, de Quervain's disease, or the carpal tunnel syndrome.
C. Involvement of the muscles of the neck, the pelvic and pectoral girdles, and the thighs and upper arms occurs in polymyalgia rheumatica. The muscles below the elbows and knees are not affected in this condition.
D. Concomitant arthritis in an adjacent or distant joint suggests one of the connective tissue diseases. However, CTD may be present with myalgia unassociated with articular involvement.
E. Episodic or continuous aching in the low back region or shoulder girdle occurring in a young man, with or without sciatic radiation and improved by activity and NSAIDs, suggests AS.
F. Pain in the muscles of the pelvic girdle and thighs may occur in Paget's disease.

III. A history of use of any of the drugs listed in the preceding as etiologic agents suggests drug-induced myalgia.

IV. Response or lack of response to therapy
A. Antiinflammatory drugs (salicylates, steroids, indomethacin, phenylbutazone, and other NSAIDs) may give some relief in both rheumatic and nonrheumatic conditions. Hence, the response of these agents is of little diagnostic value, although dramatic relief of low back pain with indomethacin or phenylbutazone suggests AS.
B. Failure to respond to antiinflammatory analgesic treatment should suggest fibromyalgia, psychogenic rheumatism, peripheral neuritis, nerve entrapment, reflex neurovascular dystrophy, endocrinopathy, Parkinson's disease, or nonmuscular causes of pain and myositis.

System Review
In the system review, areas of inquiry specifically applicable to the evaluation of myalgia are listed in the following.

I. Weight loss, malaise, anorexia, and fever suggest neoplasia (with or without associated dermatomyositis), granulomatous disease (sarcoidosis, tuberculosis), infection, or giant cell arteritis.
II. The well-known but nonspecific symptoms of hypothyroidism suggest the myopathy associated with this disease.
III. Recurrent and severe headaches, especially in the temporal region, a history of tender spots over the scalp, claudication of the jaw, and unilateral or bilateral blurring or loss of vision suggest temporal arteritis associated with polymyalgia rheumatica.
IV. Neuropsychiatric evaluation during the history-taking process is most important in evaluating a patient with myalgia. Overemphasis by the patient of a "strong family history of arthritis," multitudinous complaints, strong denial of any emotional problems, grimacing, and autopalpation during the teary-eyed recitation of symptoms all may be clues to psychogenic rheumatism.

Physical Examination
General Examination
The abnormalities noted in the section Peripheral Joint Arthritis should also be sought in evaluating the patient who has myalgia. Abnormalities of the general physical examination that are specifically pertinent to the patient with myalgia are as follows:

I. Lethargy, a husky voice, dry skin and hair, edema, and delayed tendon reflex relaxation suggest hypothyroidism. The well-known facies and bone structure of acromegaly should suggest the myopathy associated with this disease.
II. The motor, sensory, and reflex changes caused by nerve root compression in the cervical or lumbar area may be observed in patients in whom myalgia is secondary to intervertebral disc protrusion. Pain or tingling in the forearm or hand, or both, while tapping over the median nerve at the wrist (Tinel's sign) suggests carpal tunnel syndrome. Median nerve compression at the wrist may cause aching proximal to the wrist and extending to the shoulder. A masklike facies, a pill-rolling tremor, and rigidity suggest Parkinson's disease.
III. An erythematous, indurated rash over the "shawl" distribution of the shoulders, face, and extremities may be seen in dermatomyositis. Indurated skin is observed in scleroderma. Symptoms and signs of SLE, dermatomyositis, and scleroderma are seen in MCTD.
IV. Hepatosplenomegaly, spider angiomata, and clubbed fingers, with or without other physical findings of alcoholism, suggest alcoholic myopathy.
V. A shiny skin with swollen fingers, atrophic skin, and hyperhidrosis of palms is seen in the shoulder-hand syndrome.
VI. Temporal artery thickening or tenderness and bruits over carotid or other peripheral arteries may be found in some cases of polymyalgia rheumatica.

Musculoskeletal Examination
Many of the disease entities causing myalgia may show abnormalities of the musculoskeletal system, as described in the section Peripheral Joint Arthritis. Examination of the muscles may reveal various abnormalities.

I. Moderate to exquisite tenderness in many muscle groups without anatomic localization, normal muscle tone, absence of muscle atrophy, and maintenance of a normal range of motion are characteristic of psychogenic rheumatism.
II. Striking proximal muscle stiffness without weakness, normal muscle consistency, and marked periarticular tenderness in the proximal musculature of the shoulder and pectoral girdle in a patient over 55 (female to male ratio 5 : 1) suggest PMR.

III. Proximal muscle weakness that is symmetric and diffuse, often with induration and muscle tenderness, with or without an associated skin rash, occurs in polymyositis and dermatomyositis. Inclusion body myositis (IBM) presents with insidious onset of painless asymmetric proximal and distal weakness.
IV. Severe low back pain, with or without percussion tenderness over one or more vertebrae, suggests osteoporosis with possible compression fracture, myeloma, or metastatic bone disease.

Laboratory Studies
The diagnostic survey outlined in the section Peripheral Joint Arthritis is applicable to the patient with myalgia.

I. Normal findings on a battery of tests do not rule out organic disease but strongly favor fibromyalgia or psychogenic rheumatism.
II. An ESR (Westergren) greater than 50 mm/hour with no other abnormality suggests polymyalgia rheumatica.
III. One or more serum enzymes (SGOT, CPK, aldolase) are commonly elevated in polymyositis and dermatomyositis, and the EMG may be abnormal.
IV. Decreased thyroid function occurs in hypothyroidism, but the only abnormality may be an elevation of TSH.
V. Hypokalemia is usually diuretic-induced.
VI. Hypercalcemia may be associated with the myopathy of hyperparathyroidism, sarcoidosis, myeloma, and metastatic carcinoma.
VII. Hyperuricemia is commonly associated with the myopathy of lymphoma, leukemia, sarcoidosis, hyperparathyroidism, and hypothyroidism.
VIII. The serum alkaline phosphatase level is usually elevated in Paget's disease of the bone, metastatic carcinoma, sarcoidosis, hyperparathyroidism, and osteomalacia.
IX. The ANA is likely to be positive in CTD and the drug-induced SLE syndrome. Antihistone antibodies are present in drug-induced SLE.
X. The postprandial blood sugar or glucose tolerance test is abnormal in the occasional patient with diabetes who exhibits diabetic amyotrophy before other abnormalities of this disease are manifested.
XI. A characteristic triad of abnormalities is seen in the electromyogram in polymyositis: spontaneous fibrillations with positive, saw-toothed (spike) potentials, complex polyphasic or short-duration potentials on voluntary contraction, and salvos of repetitive high-frequency action potentials.
XII. Temporal artery biopsy and arteriograms may be abnormal in polymyalgia rheumatica.
XIII. Muscle biopsy may show inflammatory changes in polymyositis. Muscle tissue studied with histochemical techniques shows abnormalities in patients with polymyalgia rheumatica and rheumatoid arthritis.
XIV. HIV antibody testing in the clinically appropriate context can reveal the presence of an HIV-induced polymyositis.

Radiologic Findings
In a patient with myalgia, the following roentgenographic abnormalities should be sought:

I. Hilar adenopathy or pulmonary parenchymal abnormalities would suggest sarcoidosis, neoplasm, or CTD.
II. Subcutaneous calcifications may be seen in scleroderma and dermatomyositis. Calcification about the shoulder joint is common objective evidence for tendinitis in this area.
III. Subtle changes of sclerosis of the sacroiliac joints, squaring of the vertebrae, and spinal ligamentous calcification occur in ankylosing spondylitis. In the spine, intervertebral disc space narrowing, spondylolisthesis, osteoporosis, and foraminal encroachment secondary to osteoarthritis are capable of causing muscle pain.
IV. Radionuclide joint scans may show inflammation before changes are visible in conventional roentgenograms.

Painful Shoulder

Robert C. Jacobs

Shoulder pain is the symptom that causes most patients with shoulder disorders to seek medical attention. The pain may arise from the joint structures or the periarticular tissues, or both. It is also important to be aware that the shoulder is a common site of pain referral from cervical, intrathoracic, and diaphragmatic lesions. Contrary to popular belief, nonarticular disorders of the shoulder, not arthritis, cause the vast majority of painful shoulders. Fractures and dislocations are not considered in this discussion.

Etiology

Omitting fractures and dislocations, approximately 80% to 90% of cases of shoulder disability are caused by one of the following conditions: acute and chronic tendinitis and bursitis (often calcific), bicipital tenosynovitis, adhesive capsulitis, and lesions of the musculotendinous cuff. The more common causes of shoulder pain and disability are listed in Table 8-7.

Table 8-7. Common causes of shoulder pain and disability

I. Intrinsic lesions
  A. Periarticular disorders
    1. Calcific tendinitis
    2. Adhesive capsulitis
    3. Bicipital tendinitis
    4. Lesions of the musculotendinous cuff
  B. Articular disorders
    1. Inflammatory lesions
      a. Connective tissue diseases
      b. Rheumatoid variants
      c. Crystalline arthropathies
    2. Osteoarthritis
    3. Neuropathic arthropathy
    4. Traumatic arthritis
    5. Infectious arthritis
    6. Neoplasms
II. Extrinsic lesions
  1. Neurologic disorders
    a. Central nervous system (e.g., cervical disks, herpes zoster)
    b. Peripheral nervous system (e.g., neuropathy)
  2. Neurovascular syndromes
    a. Thoracic outlet syndromes
      (1) Cervical and first rib syndromes, scalenus anterior syndrome
      (2) Costoclavicular syndrome
      (3) Hyperabduction syndrome
    b. Reflex neurovascular syndromes
      (1) Shoulder-hand syndrome
      (2) Sudeck's atrophy
  3. Vascular syndromes
    a. Arterial (e.g., arterial occlusion, Raynaud's phenomenon)
    b. Venous (e.g., venous occlusion, thrombophlebitis)
    c. Lymphatic (e.g., lymphangitis, lymphedema)
  4. Psychogenic disorders
  5. Viscerogenic disorders (referred pain)
  6. Idiopathic disorders (e.g., fibrositic syndromes, myalgias, arthralgias, neuralgias)

Clinical Features

Calcific Tendinitis and Bursitis

Pain, tenderness, and limited motion of the shoulder are characteristic findings in calcific tendinitis. The condition may be acute, subacute, or chronic. On examination, there is tenderness below the tip of the acromion, especially pronounced in acute cases. X-ray films of the shoulder show calcific deposits in the vicinity of the affected tendon.

Bicipital Tenosynovitis

Bicipital tenosynovitis is a common cause of shoulder pain. The onset is acute or insidious. The pain usually radiates along the course of the bicipital tendon, and muscle tenderness over the tendon in the bicipital groove is characteristic. Shoulder motion is generally limited, particularly in abduction and internal rotation. Yergason's sign (the production of pain on resisted supination of the forearm while the elbow is flexed at 90 degrees) is usually positive. X-ray findings are negative. When the condition is chronic, the shoulder may become "frozen."

Adhesive Capsulitis

The onset of adhesive capsulitis is acute or insidious. It is often precipitated by trauma or strain but probably has varied causes. In some instances, it represents the end stage of other conditions. The clinical manifestations include localized pain, diffuse periarticular tenderness, and often a profound reduction in shoulder mobility that may eventually result in complete limitation of glenohumeral motion (frozen shoulder). X-ray findings are negative except for demineralization of the humerus in long-standing cases.

Lesions of the Musculotendinous Cuff

The rotator cuff is able to withstand mild to moderate injury with little effect unless the tendons are already diseased as a result of degenerative changes. The supraspinatus tendon is the one most frequently affected. Partial or complete rupture of this tendon is usually precipitated by a fall with the shoulder abducted. The injury is followed by pain, limited motion of the shoulder, and especially, an inability to initiate abduction. Tenderness over the tip of the shoulder and a sulcus at the site of rupture may be noted. Assisted abduction may cause pain when the acromial process impinges on the damaged tendon. Once the arm is elevated to 90 degrees or more, the glenohumeral joint can usually be held in abduction with little or no pain. Radiographs may reveal elevation of the humeral head, concavity of the acromial process, and cystic changes in the bone. An arthrogram may demonstrate leakage of dye through the rotator cuff.

Neurovascular Syndromes

I. Reflex neurovascular dystrophy (the shoulder-hand syndrome). The shoulder-hand syndrome is a symptom complex characterized by painful disability of the shoulder in association with painful swelling of the hand. The latter may precede, accompany, or follow the former. Vasomotor disturbances (vasospasm or vasodilatation) are common. The condition may terminate with permanent dystrophic changes and contractures of the hand and fingers. The syndrome may be unilateral or bilateral. Provocative or associated conditions include myocardial infarction, cervical osteoarthritis, trauma, hemiplegia, and other disorders. Approximately 25% of cases are idiopathic. Mottled or diffuse osteoporosis of the humeral head and wrist is a characteristic x-ray finding.

II. Other neurovascular syndromes. The distinctive features of the costoclavicular, hyperabduction, and the scalenus anterior and cervical rib syndromes and their differential diagnosis from the shoulder-hand syndrome are summarized in Table 8-8. (See the section The Thoracic Outlet Syndrome and Chapter 10 for additional information.)

Fibromyopathies

See Myalgia.

Table 8-8. Neurovascular syndromes of the shoulder girdle[a]

Syndrome	History	Pulse	Diagnostic test
Costoclavicular syndrome	Symptoms associated with shoulder being forced downward and backward for long periods	Reduced in abnormal shoulder position	Downward and backward bracing of the shoulder reproduces symptoms and signs
Hyperabduction syndromes (costoclavicular syndrome)	Hyperabduction in sleep or at work for long periods	Reduced in hyperabduction (also blood pressure and oscillometry)	Hyperabduction; reproduction of symptoms and signs
Scalenus anterior, cervical rib, and first rib syndromes	No special postural features	Reduced in resting position or brought on by Adson maneuver	Adson maneuver may reproduce musculoskeletal, neuritic, and vascular signs; tender point at scalenus area
Shoulder-hand syndrome (reflex neurovascular dystrophy)	Trauma, intrathoracic disease, or idiopathic; no special postural features	Sometimes reduced	Stellate ganglion block produces transient or prolonged relief

[a] Symptoms common to some or all in each disorder: pain of shoulder, and arm or hand, or both; numbness, paresthesias of fingers; swelling of hand(s), fingers; discoloration of hand(s); Raynaud's phenomenon; weakness of hand(s); supraclavicular bruit possible in compression disorders.
From Friedman HH, Argyros TG, Steinbrocker O. Neurovascular syndromes of the shoulder girdle and upper extremity—the compression disorders and the shoulder-hand syndrome. *Postgrad Med J* 1959;35:397, with permission.

Diagnostic Approach

History

I. The history is of little diagnostic assistance. Inquiry should be made concerning previous involvement or the presence of systemic disease.
II. A history of minor trauma or strain is commonly elicited in musculotendinous lesions. Tendon rupture is suggested by a sudden onset of pain and inability to abduct the shoulder precipitated by a fall or a sudden strain in abduction.
III. The diagnosis of a shoulder-hand syndrome should be entertained in patients who have sustained a myocardial infarct, stroke, or trauma to the distal portion of the upper extremity (e.g., Colles' fracture). Cervical radicular syndromes, thoracotomy, and pulmonary disease (e.g., tuberculosis) are also predisposing factors.
IV. Analysis of the shoulder pain may be helpful in ruling out pain referred from other localities. Diaphragmatic lesions (e.g., pleurisy) commonly cause pain in the distribution of the trapezius muscle, and disease of the biliary tract, in the right scapular area. Cardiac pain is rarely localized to the shoulder; a retrosternal component is usually present. On the other hand, pain caused by intrinsic disease of the shoulder is almost always felt in the deltoid region. Vague, poorly localized pain, unassociated with limited mobility and unaffected by activity, should arouse suspicion of a fibrositic-psychogenic origin.

Physical Examination

I. Careful examination of all four articulations (glenohumeral, acromioclavicular, scapuloclavicular, and scapulohumeral) is indicated and may help to differentiate between intrinsic and extrinsic disease of the shoulder. The range of motion of the shoulder should be recorded. Localized tenderness suggests tendinitis or a fibrositic syndrome. Diffuse tenderness suggests a more extensive process. A frozen shoulder implies adhesive capsulitis.
II. Signs of joint inflammation and effusion suggest one of the following: crystalline-induced arthropathy, infectious arthritis or a connective tissue disease, tumor, or degenerative change.
III. Popping, snapping, and crepitation on movement are common abnormalities but are nonspecific. Moreover, they may occur in the absence of disease.
IV. Limited or painful motion of the neck suggests disease of the cervical spine.
V. Neurovascular abnormalities—shoulder and extremity pain, numbness, paresthesias, swelling of the hand and fingers, and dystrophic changes—suggest a thoracic outlet syndrome or reflex neurovascular dystrophy. The maneuvers employed to diagnose the neurovascular compression syndromes are listed in Table 8-8.

X-Ray Examination

I. All patients with shoulder disability should have roentgenograms of the shoulder taken in both internal and external rotation.
II. Cervical spine films are important in evaluating cervical radicular syndromes associated with shoulder discomfort. Chest films are indicated for the assessment of thoracic outlet and neurovascular syndromes.

Other Procedures

I. In the presence of effusion, the joint fluid should be aspirated and examined for white cell count, cytologic features, and the presence of crystals. Smears and cultures are indicated when infection is suspected.
II. Plethysmography, nerve conduction studies, and angiography may be useful in evaluating thoracic outlet syndromes.
III. Contrast arthrography is often of material assistance in the diagnosis of rotator cuff tears.
IV. MRI may be used to assess the shoulder impingement syndrome, including rotator cuff tears.

Painful Hip

Joseph C. Tyor

Definition

This discussion is limited to conditions, exclusive of fractures and dislocations, that may cause hip pain in adults.

Etiology and Clinical Features

I. Intrinsic causes
   A. Periarticular disorders
      1. Muscle rupture. A history of trauma is usual. Tenderness at the site of rupture, hematoma formation, and deformity of the muscle are usually noted. Some degree of limitation of the hip may be present.
      2. Bursitis
         a. Trochanteric bursitis commonly causes pain in the thigh and along the posterolateral region of the hip. Direct manual pressure over the greater trochanter usually reproduces the pain. Pain may be noted on external rotation of the hip.
         b. Ischiatic bursitis causes pain and tenderness over the ischial tuberosities. Straight leg raising may be painful and limited.
         c. Iliopectineal bursitis is associated with tenderness over the superior and anterior aspect of the joint capsule, under the psoas muscle, and in Scarpa's triangle. Hip extension may be limited.
         d. Obturator bursitis causes painful internal rotation of the hip.

B. Articular disorders
1. Connective tissue diseases. Rheumatoid arthritis, scleroderma, polymyositis, systemic lupus erythematosus, and polyarteritis nodosa rarely cause involvement of the hip joint alone. Usually, other joints are also affected.
2. Rheumatoid variants. Ankylosing spondylitis, Reiter's syndrome, enteropathic arthropathy, and psoriasis may involve the hip joints and lead to permanent articular damage. Usually, joint involvement is not limited to the hip. Early rheumatoid arthritis can affect only the hip joint.
3. Crystalline arthropathies
   a. Gouty arthritis of the hip is quite rare.
   b. Pseudogout may cause acute arthritis of the hip. The presence of crystals of calcium pyrophosphate in the joint fluid is diagnostic.
4. Neuropathic arthropathy. Neuropathic arthropathy owing to tabes dorsalis, diabetic neuropathy, or other neurologic disorders may affect the hip. It is characterized by effusion, undue mobility and instability of the hip, and disproportionately little pain. Some authorities have suggested that neuropathic hip disease may also result from repeated intraarticular injections of steroids.
5. Osteoarthritis of the hip. Degenerative arthritis of the hip is usually a disease of older individuals, more common in men, and more often unilateral than bilateral. It may be primary or secondary to long-standing mechanical malalignment of the hip owing to congenital dislocation of the hip, Calvé-Perthes disease, slipped capital femoral epiphysis, or trauma (leg fracture, dislocation). The onset is insidious. The chief symptoms are pain, stiffness, and a limp on walking. The pain is usually located in the groin but may be felt along the medial aspect of the thigh. It is commonly referred to the buttock or knee. Initially, the pain is present on standing or walking and relieved by rest. Over a period of time, however, the pain tends to persist in the sitting position or recumbency. Backache from mechanical strain is a common accompaniment. On physical examination, the lower extremity is often found to be everted, with the hip in a flexed and adducted position. Hip motion is limited in all directions, especially on internal rotation and adduction. In early stages the radiograph may show only narrowing of the joint space. Sclerosis often follows along with osteophyte formation and the development of cysts.
6. Tumors of the hip. Tumors of the hip, including benign cysts, giant cell tumors, osteogenic or synovial sarcomas, and metastatic carcinomas are uncommon causes of hip pain.
7. Infectious arthritis
   a. Septic arthritis is usually hematogenous in origin and caused by staphylococci, streptococci, or less commonly, other organisms. Fever and other systemic symptoms are present. Pain may be located in the hip but is commonly referred to the knee. The thigh is flexed, adducted, and internally rotated. Motion is markedly limited. Local signs of inflammation and bulging of the joint capsule are noted commonly. Joint aspiration is essential for early diagnosis and proper treatment. The synovial fluid should be cultured and cytologic studies performed. If a septic arthritis is suspected, it becomes imperative that a diagnosis be established urgently. The radiograph is often negative and joint destruction may occur very rapidly. Hip joints that have had surgery or prior injury are more susceptible to infection.
   b. Tuberculosis of the hip joint is usually associated with pulmonary or visceral tuberculosis. It is more common in adolescents than adults. A history of preceding trauma is often obtained. The onset is insidious. Nocturnal and rest pain are common. Pain in the knee and thigh, a limp, muscle spasm, fullness in the groin, tenderness over the hip, and limited motion of the hip are usually noted. The diagnosis should be suspected in any tuberculous individual with chronic monarticular arthritis involving the hip. Confirmation by culture of the joint fluid or biopsy is indicated.
8. Aseptic necrosis of the femoral head. Aseptic or avascular necrosis of the femoral head refers to the changes that occur in the bone after interruption of its blood supply by trauma or disease. Avascular necrosis may occur in the osteochondroses, following fracture of the neck of the femur or dislocation of the hip, in sickle cell anemia or other hemoglobinopathies, or in caisson disease. Avascular necrosis is seen in individuals previously treated with steroids, especially with high doses and long intervals. The condition is painful. The diagnosis is made radiologically.
9. Bleeding disorders. Hemarthrosis occurs in the vast majority of patients with hemophilia and may lead to permanent joint drainage and deformity.

II. Extrinsic causes. Pain may be referred to the hip in degenerative disease of the lumbar spine, pelvic disease, and vascular insufficiency in the lower extremities. Pain in the hip is not commonly of psychogenic origin.

Diagnostic Approach

I. In the history, the type of onset and course of the disease may be of some help. Trauma may itself result in hip pain or may predispose to subsequent development of osteoarthritic changes. A history of conditions such as congenital dislocation of the hip, slipped capital femoral epiphysis, and Calvé-Perthes disease may be important in revealing the underlying cause in osteoarthritis of the hip.
II. The location of the pain, its relationship to weight bearing or walking, and its constancy may provide clues to the severity of the hip joint involvement. Pain at rest and nocturnal pain suggest inflammatory or neoplastic disease.
III. Evidence of systemic disease suggests that hip involvement may be secondary to the primary disorder. Infection, tuberculosis, connective tissue disease, and the rheumatoid variants should be ruled out. Usually this can be accomplished on clinical grounds alone.
IV. Examination of the hip joint should include observation for the presence of an abnormal gait, limp, or deformity. Palpation of the joint and periarticular structures may help to localize the source of difficulty. The range of motion of the hip and the length of the extremity should be measured.
V. Routine laboratory studies should include CBC, urinalysis, and sedimentation rate. In the presence of effusion, the synovial fluid should be aspirated. When an infectious etiologic agent is under consideration, appropriate cultures and cytologic studies are indicated. Examination for urate and calcium pyrophosphate crystals should be performed if crystalline arthropathy is suspected.
VI. X-ray examination is essential for the proper evaluation of hip pain. An AP roentgenogram of the pelvis, including both hips, and a lateral view of the hip should be taken. Salient features of the more common abnormalities causing hip pain are listed in the following.
   A. Rheumatoid arthritis and rheumatoid variants. Early, there is juxtaarticular demineralization of the bone, which is followed by narrowing of the joint space, the appearance of marginal erosions, pseudocyst formation, and eventually bone ankylosis. Protrusio acetabuli may occur occasionally in rheumatoid arthritis.
   B. Osteoarthritis. Reduction of the joint space without osteoporosis is an early finding. Later, spur formation is found at the acetabular margins and around the head of the femur. Sclerosis of the subchondral bone and cyst formation eventually appear. The head of the femur tends to drift laterally and become flattened.
   C. Pseudogout. Roentgenograms show calcification of the articular cartilage and acetabular labra. The calcification is indistinguishable from that produced by degenerative joint disease.
   D. Neuropathic arthropathy. The radiologic picture is that of degenerative arthritis "gone wild," with acetabular erosions, irregularity of the joint space,

marked osteophyte formation, bone destruction, the presence of fragmented bone in the joint space, and ossification of the soft tissues.

E. Infectious arthritis. In septic arthritis, the earliest finding is narrowing of the joint space. Later, destruction of the articular margin and adjacent bone occurs. Eventually, hypertrophic changes and bony ankylosis may occur. Tuberculous arthritis may show little change early in the course of the disease. Later, demineralization without narrowing of the joint space appears. This is followed by destructive changes at the joint margins and contiguous bone. Joint destruction may eventually become quite extensive. Sinus tract formation is often present in advanced cases.

F. Avascular necrosis of the femoral head. Initially there is separation of the subchondral bone from the articular margin and apparent condensation of the separated fragment within the femoral head, leaving a crescentic lucent area between the two. Over a period of time, intermingled areas of increased and decreased bone density are formed.

G. Magnetic resonance imaging (MRI) can help resolve causes of hip pain that are not identified by the usual radiograph. MRI evaluation is quite helpful in early avascular necrosis, osteomyelitis, soft-tissue abnormalities, injuries, and congenital malformations.

Painful Knee

Arnold Heller

Knee pain is a common complaint in office practice. The etiologic diagnosis is often elusive and imprecise. It is frequently difficult to determine whether the cause is primarily intraarticular, periarticular, or referred in origin.

Etiology and Clinical Features

The causative factors fall into three main categories:

I. Training or competition injuries
II. Anatomic factors (leg length discrepancy, quadriceps insufficiency, severe foot pronation), bowleg, or knock knee deformities owing to epiphyseal disturbances
III. Axial or patellar malalignment. Lateral patellar subluxation is most common.

Intrinsic Causes

Periarticular Disorders

I. Musculotendinous pain. A history of overt or occult trauma is usual. Knee injuries account for 40% of the overuse injuries seen in runners. The most common form is a musculotendinous patellofemoral pain syndrome resulting from stress or strain of the fibers that stabilize the patella.

Local tenderness at the superior or inferior pole of the patella is common. Tenderness at the insertional sites of the hamstrings at the head of the fibula or posteromedial proximal tibia may be found. Excessively tight hamstrings in children and adults can cause vague knee and calf pain with inability of the patient to take a full stride in running. Tenderness at the lateral compartment of the knee can occur with popliteus tendinitis. Occasionally the strain may be so severe that rupture of the quadriceps from the patella occurs. A palpable defect with incomplete active extension occurs. Rupture of the patellar tendon from the patella more commonly affects the younger athlete.

II. Bursitis and tendinitis

A. Pes anserinus bursitis commonly causes pain and tendinitis at the proximal anteromedial aspect of the tibial metaphysis. Direct local pressure with active or passive external rotation of the tibia on the femur usually reproduces the pain. Resisting forced active internal rotation may also reproduce the pain.

B. Infrapatellar bursitis causes pain, tenderness, and swelling in the patellar tendon. The tendon itself may be enlarged or the infrapatellar fat pad may seem larger on one side. Knee effusion is usually absent.

C. Prepatellar bursitis is usually associated with a painless effusion in the anterior prepatellar region between the skin and the patella (housemaid's knee). If this region is hot and painful, a pyogenic bursitis must be suspected.

D. Tensor fascia lata tendinitis is associated with tenderness over the distal anterolateral aspect of the proximal tibia, often extending to the insertion site at the tibia (Gerdy's tubercle). Localized pain at the lateral femoral condyle may occur. Pain is noted lateral to the knee on resisting external rotation of the tibia on the femur and also on active abduction of the hip.

E. Osgood-Schlatter disease is a disorder of heterotopic bone formation in an area of tendinitis involving the portion of the proximal tibial epiphysis that forms the patellar tendon attachment to the tibial tubercle. It is characterized by swelling and pain that is made worse by strenuous running or jumping activities and relieved by rest. It occurs in the 10- to 15-year-old age group. It is a self-limiting condition with cessation of symptoms occurring when fusion of the proximal tibial epiphysis takes place. Fragmentation of the tibial tubercle can occur normally with the formation of more than one ossification center. This is not necessarily associated with Osgood-Schlatter disease.

Intraarticular Disorders

I. Inflammatory disorders

A. Connective tissue diseases. The knee joint is commonly affected in rheumatoid arthritis. Bilateral involvement is common. Monarticular arthritis is more common in juvenile rheumatoid arthritis. Scleroderma, polymyositis, systemic lupus erythematosus, and polyarteritis nodosa rarely cause involvement of the knee joint alone.

B. Axial arthropathies. Ankylosing spondylitis, Reiter's syndrome, enteropathic arthropathies, and psoriatic arthritis can cause monarticular involvement of the knee joint.

C. Crystalline arthropathies

1. Pseudogout is a common cause of inflammatory arthritis of the knee, especially when superimposed on preexisting degenerative arthritis. The presence of calcium pyrophosphate crystals in the synovial fluid is diagnostic. A warm, swollen knee joint is a common finding and must be differentiated from pyogenic arthritis.

2. Acute primary gouty arthritis of the knee does occasionally occur. Secondary gouty arthritis is the more common cause of inflammatory urate synovitis of the knee. This is more common in patients taking diuretics.

D. Pyogenic arthritis is usually hematogenous in origin and most commonly owing to staphylococci. The knee is the joint most likely to be infected by nongonococcal organisms. Gram-negative organisms such as *E. coli*, *Proteus*, and *Hemophilus influenzae* account for most of the remaining cases. Pyogenic arthritis is characterized by an acute onset of a hot, red, swollen knee. Fever and general malaise may be present. Painful restriction of motion is present. The classic signs of inflammation may be modified or absent in the patient who cannot mount a strong immune defense. Gram-negative organisms are more typically responsible in this type of patient. An indolent infection may be present for months and may be mistaken for nonpyogenic inflammatory arthritis or recurrent crystalline synovitis. Gonococcal arthritis is unusual as an isolated cause of monarticular arthritis of the knee. Joint aspiration is essential for prompt diagnosis and treatment. X-ray abnormalities may not appear for 7 to 10 days. Cartilage destruction can begin within 24 hours. Arthroscopic drainage and partial synovectomy for debridement and culture may be necessary.

II. Noninflammatory disorders

A. Degenerative arthritis of the knee is usually a disease of older individuals, more often unilateral than bilateral. Medial compartment deterioration

associated with varus deformity is more common than lateral compartment deterioration with valgus deformity. Both can cause loss of full extension and flexion. Degenerative arthritis may be secondary to occult traumatic disorders and mechanical malalignment. Degenerative arthritis develops slowly over many years. The chief symptoms are pain, stiffness, and weight-bearing discomfort. A limp may be present. The pain may be localized or involve the entire joint. In tibiofemoral compartmental arthritis, a bowleg (varus) or knock-knee (valgus) deformity may develop, depending on which side is more severely involved. The pain is usually relieved by rest. Crepitation or grating can be palpated on flexion-extension maneuvers and aggravated by rotation of the tibia on the femur, both in internal and external rotation, stressing the individual compartment causing pain (McMurray maneuver). If effusion is present, it is usually of a cool type unless an acute calcium pyrophosphate synovitis is present.

B. Patellofemoral arthritis. Symptomatic chondromalacia or patellofemoral arthritis is characterized by aching, crepitation, or patellofemoral stiffness that is aggravated by stair walking, squatting, and sustained running. It may cause stiffness and aching following prolonged driving or sitting. It is less severe when walking on level ground. Painless, cool effusions may occur. Cartilage fibrillation present on the medial facet of the patella is thought to be nonprogressive. Lesions involving the lateral side of the patella are more likely to be symptomatic and progressive. Patellofemoral crepitation on flexion or extension is present in many asymptomatic adults. Skyline patellar radiographic views are necessary to define clearly the severity of degeneration at the patellofemoral joint as well as the degree of subluxation.

C. Meniscus injuries. The most common meniscal injury is a tear. The usual history is that of an acute injury involving rotational stress of the flexed knee. Joint line tenderness and blockage of motion appear to be the most reliable physical signs. Knee effusion may be present. Rotatory stress tests to determine the side of the lesion are usually reliable. Radiograms should be obtained to rule out other causes of knee pain and mechanical locking. True locking may also be caused by loose bodies or major flap tears of articular cartilage, or bucket handle meniscus tears.

D. Acute ligamentous injuries are characterized by acute trauma associated with painful restriction of motion, effusion, and instability. A thorough history and physical examination are essential. The anterior cruciate ligament may rupture in a noncontact situation owing to external rotation of the femur on a fixed tibia. The patient often states that he heard and felt a pop in his knee and may complain of posterolateral knee pain, which represents the rupture of the anterior cruciate ligament at the femur. This may be mistaken for a strain of the lateral head of the gastrocnemius muscle. The most important finding on physical examination during the first 24 hours is a large tense effusion that on aspiration is grossly bloody. Anterior cruciate ligament tears are the most common cause of tense hemarthroses (75%). Acute lateral dislocations of the patella and osteochondral fractures are less common. An isolated tear of the meniscus seldom produces a tense hemarthrosis. A first- or second-degree sprain (incomplete tears) of the medial collateral ligament does not lead to a tense hemarthrosis unless the athlete continues to play and aggravates the injury. Third-degree tears (complete) of the medial or lateral collateral ligament may not be accompanied by a tense hemarthrosis, because blood escapes into the soft tissues. The most reliable clinical indicator of anterior cruciate ligament injury is the anterior drawer test performed with the knee held in 20 to 30 degrees of flexion (Lachman's test). If hamstring spasm is present, this test may be negated. Examination under general anesthesia may be necessary with arthroscopy. Stress tests in valgus and varus of the collateral ligaments should be done in 30 degrees of flexion. Ruptures of the posterior cruciate ligament with instability can be perceived by flexing the knee to 90 degrees and appreciating a posterior sag of the tibia on the femur.

E. Patellar dislocation and malalignment syndromes. Acute lateral dislocations or subluxations are associated with a history of an acutely painful episode with medial parapatellar tenderness and decreased range of motion, with rather acute apprehension on gentle lateral motion of the patella. Swelling may not be present. Radiograms in patients with recurrent lateral dislocations of the patella may demonstrate loose bodies or avulsion fragments along the medial border of the patella. Pseudolocking or giving way may be reported as occurring in the extended position (not in the flexed position of true locking that occurs with a displaced meniscus). Medial joint line tenderness owing to patellar retinacular injury may lead to erroneous diagnosis of meniscal injury.

F. Fractures. A history of trauma followed by pain, local tenderness with or without deformity, or effusion may be present. Radiographic studies are imperative for establishing the diagnosis. Radiograms may not reveal the fracture for a period of several weeks. A detailed discussion of fractures is beyond the scope of this text.

G. Neuropathic arthropathy. Neuropathic arthropathy owing to tabes dorsalis, diabetic neuropathy, or other neurologic disorders may affect the knee. It is characterized by effusion, relatively painless mobility, and instability of the knee, with disproportionately little pain relative to the degree of destruction visualized radiographically.

H. Osteochondritis dissecans is a disorder most commonly of the medial femoral condyle of the knee and less commonly of the lateral femoral condyle or the patella. In a child, the symptoms are usually intermittent, nonspecific, and present over a long period of time. There are no special physical findings that allow the diagnosis to be made easily. The tunnel and lateral radiographic views are essential to diagnosis. Both knees should be radiographed because as many as 30% of patients have been reported to have bilateral involvement. In the adult, spontaneous osteonecrosis is a similar condition that develops in the juxtaarticular region of the medial femoral condyle and often leads to rapid degeneration of the medial compartment of the knee.

I. Bleeding disorders. Hemarthrosis involving the knee joint occurs in patients with hemophilia and may lead to severe destruction of articular cartilage with instability and deformity.

J. Tumors of the knee. Benign tumors, including benign cysts, giant cell tumors, osteosarcomas or synovial sarcomas, and metastatic carcinomas, are uncommon causes of knee pain. Pigmented villonodular synovitis may require arthroscopy and biopsy for diagnosis.

K. Tuberculosis of the knee, primarily an osseous disease seen in adults, spreads secondarily to the adjacent joint. Destruction of cartilage occurs rather late in the course of the disease. A caseating, granulomatous synovitis is produced.

Extrinsic Causes

Pain may be referred to the knee in degenerative diseases of the lumbar spine, especially anteriorly in the distribution of the femoral nerve and medially in the distribution of the obturator nerve along the inner thigh. Vascular insufficiency and pelvic disorders may be causes of referred pain to the knee. Disorders of the hip joint commonly radiate to the inner aspect of the knee. Radiograms may reveal slipped epiphysis of the femoral head or avascular necrosis of the femoral head in children.

Diagnostic Approach

Initial Evaluation

I. The initial investigation of every patient with knee pain should include a complete history and physical examination. The type of onset and course of the pain may be of some help. Trauma itself may result in knee pain or may predispose to subsequent development of degenerative arthritic changes. A prior history of traumatic effusion following twisting injuries may be important. If a warm effusion is present, one should seek an obvious source of recent or concurrent infection.

II. Evidence of systemic disease, especially if associated with polyarthritis and symmetric joint involvement, suggests inflammatory arthritis owing to connective tissue disease.

III. The location of the pain in relationship to transfer activities, weight bearing, walking, and more strenuous activities such as running may provide clues to the severity and location of the involvement. Nocturnal pain and pain at rest suggest the possibility of inflammatory or neoplastic disease.

IV. Examination of the knee joint should include observation, auscultation, palpation, and measurements of the range of motion. This should be performed with the patient supine, sitting, standing, and ambulating. Thigh and calf circumferences should be measured equidistant from a joint line reference to reveal disuse atrophy. Palpation of the joint during various movements and rotatory stress tests may be helpful in localizing the diseased area. Measurements of the alignment angle of the patella during the excursions of flexion and extension are helpful in ruling out painful subluxation of the patella.

V. When pyogenic arthritis is suspected, the joint should be aspirated. Synovial fluid should be submitted for cell count and differential, Gram stain, and aerobic and anaerobic culture and sensitivity. Examination for urate and calcium pyrophosphate crystals under polarized light microscopy should be performed. In an infected joint, the white cell count is unlikely to be under 25,000. Blood cultures should be performed if hematogenous pyogenic arthritis is suspected.

VI. Radiographic examinations are essential for the proper evaluation of knee pain. Comparative, symmetric, AP, lateral, tunnel, oblique, and skyline patellar views may be of great value. Weight-bearing AP and tunnel radiograms are essential to assess fully the articular cartilage space narrowing that is present with early degenerative arthritis. Single leg weight-bearing and manual stress techniques in varus and valgus sometimes may be indicated to evaluate further medial and lateral compartmental narrowing, degeneration, and stability.

VII. Knee arthrography is a safe procedure that may provide a definitive diagnosis; it is especially helpful in midbody, and posterior horn tears in the medial meniscus. It is less accurate in evaluating the lateral meniscus. Arthrography is also useful in extrameniscal lesions, such as popliteal cysts. Flexing the knee 90 degrees may significantly improve accuracy of diagnosis of a popliteal (Baker's) cyst. Tears of the medial collateral ligament can be evaluated arthrographically within 48 hours of the injury. Tears of the deep fibers of the medial ligament attached to the joint capsule allow contrast material to escape from the joint.

If the articular cartilage overlying a lesion of osteochondritis dissecans is present, it is likely to be stable. If air or contrast media surround the fragment, it is likely to be a loose body.

Irregularities, thinning, or loss of articular cartilage to subchondral bone is seen in various stages of degenerative arthritis.

VIII. An experienced arthroscopist can examine the interior of a knee joint and derive as much or more information about the state of the joint as can be gained from arthrotomy or arthrography alone. This can be performed without risking the morbidity often associated with arthrotomy. The condition of the synovial lining, articular cartilage, menisci, synovium-covered fat pads, and cruciate ligaments can be assessed. Loose bodies can be visualized, and the functional status of the patellofemoral joint can be determined. Degenerative changes in the patellofemoral joint with or without lateral patellar subluxation can be appreciated. Suprapatellar plicae (congenital folds), which may cause symptoms of internal derangement, can be demonstrated. Knee arthroscopy has been useful in the evaluation of adhesive capsulitis, rheumatoid arthritis, foreign bodies, pigmented villonodular synovitis, and synovial tumors.

IX. A bone scan is unnecessary for making a diagnosis in most cases. It can, however, aid in establishing cases of early osteomyelitis before bone changes are present and revealing early cases of "spontaneous" osteonecrosis of the tibia before the appearance of a radiolucent area. Radionuclide scintigraphy in osteoarthritis reveals low values on both sides of the joint (tibial-femoral), whereas in osteonecrosis, high values are found on the femoral side of the joint.

X. MRI should not be used indiscriminately but may be helpful in screening patients with suspected internal derangement of the knee, especially tears of the anterior cruciate ligament and menisci. MRI is a useful tool in the diagnosis of less common disorders, including popliteal cysts, pigmented villonodular synovitis, and synovial osteochondromatosis. It is very useful in the detection and staging of bone and soft tissue tumors around the knee. It is a reasonable alternative to nuclear medicine bone scanning in patients with persistent obscure bone pain despite normal conventional radiographs. Stress fractures, subchondral contusions, and avascular necrosis can be diagnosed.

Potential pitfalls in the interpretation of an MRI can be caused by volume-averaging artifacts owing to the concavity of the outer margin of the meniscus and by structures with low signal intensity: the lateral inferior geniculate artery, veins, the transverse ligament, and the popliteus tendon. MRI is very sensitive to intrameniscal degeneration, but it does not replace arthroscopy for diagnostic accuracy. Knee arthrography is a much less accurate method for diagnosing meniscus tears than arthroscopy or MRI.

XI. Doppler ultrasound is a good technique for differentiation of a ruptured or "leaking" popliteal cyst as a cause of superficial thrombophlebitis versus deep vein thrombosis.

Low Back Pain

Mark Malyak

Low back pain is a common symptom, occurring in up to 80% of individuals at some time during their lives (Table 8-9). Although low back pain is usually acute and self-limited, it may become a chronic problem in a sizable proportion of patients, resulting in long-term and occasionally lifelong pain and disability. The causes of low back pain are vast and often difficult to pinpoint in the individual patient. Although usually noninflammatory and mechanical in origin, the critical aspect of the evaluation of the patient with low back pain is to assess for those disorders with potentially dire consequences, particularly cauda equina syndrome, infection, and neoplasia.

I. Etiology

Noninflammatory Disorders

This large group of disorders is responsible for the majority of cases of low back pain. It is a heterogeneous collection of syndromes and includes disorders of the soft tissues, intervertebral discs, synovial-lined facet joints, and bone.

A. Low Back Strain

This disorder may be owing either to an acute injury or chronic, repetitive stress to the soft tissues of the lower back (muscles, ligaments, tendons) resulting in localized low back pain. The pain is often unilateral and is usually worsened with activity and improved with rest. Standing and lumbar flexion exacerbate the pain. The constitutional symptoms of fever and weight loss are absent. Low back strain is usually an acute, self-limited syndrome, but may, in some cases, become a recurrent acute disorder, or a chronic and disabling problem.

Physical Examination Local spasm and tenderness of paravertebral musculature are common. The neurologic examination is normal.

Laboratory Tests Laboratory evaluation, including assessment for systemic inflammation with ESR, is normal.

Imagining Plain radiographs are normal.

B. Acute Herniated Intervertebral Disc

This disorder is a common cause of low back pain, although less frequent than low back strain. More than 95% of disc herniations occur at the L4-L5 or L5-S1 levels. L2-L3 and L3-L4 herniations occur infrequently. Disc herniation often occurs in a posterolateral location, which may result in unilateral

(*text continues on page 312*)

Table 8-9. Differential diagnosis of selected lower back pain syndromes

Clinical features	Lumbar root entrapment syndromes	Lumbosacral facet syndrome	Lumbar claudication syndrome owing to spinal stenosis
Pain	Painful radicular paresthesias conforming to one or two dermatomes (unilateral more common than bilateral)	Painful radicular paresthesias involving part of the L-5 dermatome (unilateral more than bilateral)	Bilateral lower extremity paresthesias, including numbness, involving two or more dermatomes (unilateral unusual)
	Pain less when sitting than standing, and usually least when lying down. With a free fragment of nucleus pulposus, back pain may clear entirely, but no relief results from recumbency.	Pain less when standing than sitting, but unable to maintain any position for a long period of time including recumbency. A "restless" type of pain, and patients often resort to movement to obtain relief.	Pain or painful numbness clears promptly (within 2–5 minutes) when sitting down or bending forward at the waist. Pain is precipitated and aggravated by walking or standing.
Onset and course	Onset is often insidious, but commonly follows major load-bearing injury to the lumbar spine	Onset almost always can be pinpointed and results from a combination of flexion and twisting of the low back region.	Onset insidious, course progressive; claudication occurs at progressively shorter distances; length of time that can be tolerated in standing position decreases.
Cauda equina syndrome	Rare	Never	Occurs ultimately, but usually only after the claudication becomes severe
Physical findings	S-1 root Mechanical: SLR and LS positive Reflex: Decreased or absent ankle jerk Motor: Decreased strength of gastrocnemius Sensory: Decreased sensation on lateral aspect of foot L-5 Root Mechanical: SLR and LS positive Reflex: No deficit Motor: Decreased strength of extensor hallucis longus, peronei, and tibialis anticus Sensory: Decreased sensation on dorsum of foot L-4 root Mechanical: SLR or femoral stretch test may be positive, but negative tests do not exclude L-4 involvement Reflex: Decreased or absent knee jerk Motor: Decreased strength of quadriceps Sensory: Decreased anterior thigh and medial aspect of leg	Mechanical: 1. Focal tenderness over lumbosacral facet joint 2. Pain referred to this joint by the ipsilateral knee-chest position 3. Although SLR may be positive at the same degree of hip flexion produced by the knee-chest position, the LS should be negative Reflex: No deficit Motor: No deficit Sensory: No deficit	Mechanical: 1. SLR is negative 2. LS is negative in the knee-chest position Reflex: No deficit Motor: No deficit Sensory: No deficit Reflex, motor, and sensory changes occur if the cauda equina syndrome is present

SLR, straight leg raising; LS, Lasègue's sign. Courtesy of Henry G. Fieger, Jr.

Vũ Minh Hồng

nerve root impingement of the root exiting from the next caudal intervertebral foramen. Thus, L5-S1 disc herniation may impinge the S1 nerve root, and L4-L5 herniation may result in L5 root impingement. An unusual but extremely dangerous consequence of a large and posterior disc herniation is cauda equina syndrome, and is discussed later in detail.

This disorder usually results in severe, often unilateral, low back pain with radiation of discomfort into a lower extremity owing to nerve root impingement, often occurring acutely and occasionally preceded by similar episodes. The low back pain is often sharp, with the leg discomfort, or sciatica, variously described as sharp, aching, or paresthetic.

The back pain is frequently worsened with lumbar flexion and sitting, and improved with standing. Fever and weight loss are absent.

Physical Examination The straight leg raising test often results in exacerbation of lower extremity pain with radiation below the knee; exacerbation of low back pain alone is not considered a positive test. The neurologic examination often detects objective evidence of nerve root impingement. S1 root impingement may result in depressed ankle deep tendon reflex, weakness of the foot and toe plantar flexors, and hypoesthesia of the lateral and plantar surfaces of the foot. L5 root impingement is not associated with an abnormal deep tendon reflex, but the foot and toe dorsiflexors are often weak, and hypoesthesia is present in the lateral leg and dorsomedial aspect of the foot. L4 root impingement results in a depressed knee reflex, weakness of the knee extensors, and hypoesthesia of the medial aspect of the leg.

Laboratory Tests Laboratory tests are normal.

Imaging Imaging with plain radiographs are often normal, but MRI and CT-myelography demonstrate the disc herniation and root impingement.

C. Osteoarthritis

This disorder is a very common cause of chronic low back pain. Osteoarthritis may affect the intervertebral discs, the synovial-lined facet joints, or both, and is sometimes referred to as spondylosis. Osteoarthritis of the lumbar spine is usually a primary disorder, probably a consequence of genetic, traumatic, biochemical, and biomechanical processes. Occasionally, osteophyte formation as a consequence of osteoarthritis will impinge on the spinal canal or intervertebral foramina, leading to a variety of neural impingement syndromes.

In distinction to acute low back strain and acute disc herniation, this disorder is usually bilateral and arises gradually. Lumbar spine osteoarthritis is age-related, and thus is more common in the older individual. The pain is often localized to the lower back initially, but may eventually result in lower extremity pain and paresthesia if neural impingement occurs. The low back pain is often worsened with activity and improved with rest, as is typical of noninflammatory disorders. Fever and weight loss are absent.

Physical Examination The neurologic examination may be abnormal if neural impingement is present.

Laboratory Tests Laboratory tests are normal.

Imaging Plain radiographs reveal decreased disc height with osteophyte formation and facet joint degeneration, depending on the location of the osteoarthritis. It is important to remember that radiographic osteoarthritis is an extremely common finding in the elderly individual; therefore, its presence in the patient with low back pain does not necessarily exclude other, potentially more dangerous causes of low back pain.

D. Spinal Stenosis

Spinal stenosis is usually a consequence of lumbar osteoarthritis and refers to encroachment of the spinal canal owing to osteophyte formation, leading to impingement of the nerve roots that comprise the cauda equina. A common manifestation is pseudoclaudication, in which a patient experiences bilateral lower extremity pain on standing (walking is not usually necessary), with relief on sitting or forward flexion. The flexed lumbar spine expands the spinal canal, relieving neural impingement.

Physical Examination The presence of normal lower extremity arterial pulses helps support the diagnosis of lumbar stenosis in the setting of symptoms of pseudoclaudication. Neurologic examination often reveals objective evidence of nerve root impingement at multiple levels.

Laboratory Tests Laboratory tests are normal.

Imaging MRI and CT-myelography are the most helpful imaging techniques in delineating the location and degree of stenosis and neural impingement.

E. Cauda Equina Syndrome

This disorder, like spinal stenosis, is a manifestation of noninflammatory disorders that may cause low back pain. The most common cause is a large central intervertebral disc herniation. Epidural abscesses and neoplasms are occasionally responsible. This disorder is distinguished from spinal stenosis by extent of impingement of the spinal canal and acuity of onset. It classically results in low back pain, lower extremity motor weakness, bowel and bladder incontinence, and saddle anesthesia. This disorder constitutes a surgical emergency, and surgical decompression is usually preformed immediately on diagnosis in an attempt to prevent irreversible injury to the impinged nerve roots.

F. Spondylolysis and Spondylolisthesis

Spondylolysis is a structural abnormality of a vertebra in which there is a defect in the pars interarticularis, the region that lies between the superior and inferior articular processes. The cause of spondylolysis is not clear, but a combination of congenital abnormality with consequential traumatic or degenerative disease may be responsible. Spondylolisthesis refers to forward subluxation of the superior vertebrae as a consequence of spondylolysis. Spondylolysis, with or without spondylolisthesis, is associated with low back pain.

G. Osteoporosis and Fragility Fractures

Osteoporosis is a common disorder characterized by decreased bone density. Although many causes exist, the untreated postmenopausal state is probably the most common. Osteoporosis itself is asymptomatic and results in clinical expression only as a consequence of fracture. A common site of fracture is the vertebral body, and an acute fracture, often as a consequence of trivial or even unrecognized trauma, results in severe localized back pain. The pain, although severe, is usually self-limited. Additionally, the fracture rarely results in neural impingement and thus the neurologic examination is usually normal. The vertebral body fractures often are wedge-shaped compressed in the anterior position; additive fractures may thus result in kyphosis, particularly in the thoracic and cervical regions.

II. Seronegative Spondyloarthropathies

These disorders are inflammatory in origin, in distinction to the above noninflammatory causes of low back pain, and are considered to have an autoimmune basis. They are associated with the class I major histocompatibility complex HLA-B27.

A. Ankylosing Spondylitis

Ankylosing spondylitis (AS) may be considered the prototypic HLA-B27 associated seronegative spondyloarthropathy. It is a chronic disorder that typically begins in young adulthood and occurs more commonly in men (male to female ratio 3:1). The predominant joints involved are the sacroiliac (SI) joints, with frequent involvement of the discs and facet joints of the spine, and occasional inflammatory synovitis of the peripheral joints. Enthesopathy, or inflammation of the insertions of tendons and ligaments, may also occur, resulting in disorders such as Achilles tendinitis and plantar fasciitis. Finally, extramusculoskeletal involvement may occur, resulting in anterior uveitis and cardiopulmonary disorders. Because this is a systemic inflammatory disorder, the constitutional symptoms of fatigue, weight loss, and low-grade fever may be present.

AS has a number of features that distinguish it from the more common mechanical, noninflammatory causes of low back pain. AS occurs prior to age 40 years, whereas mechanical pain may occur at any age. The onset of AS

is typically insidious, whereas many mechanical causes result in abruptly severe pain. The duration of AS is chronic and patients often complain of months or years of pain prior to first presenting to the physician. Exercise usually improves the low back pain of AS and exacerbates mechanical pain. AS, as is typical of inflammatory arthropathies, results in prolonged morning stiffness (60 minutes), whereas mechanical low back pain is associated with stiffness lasting less than 30 minutes after prolonged inactivity, or gelling.

Physical Examination The physical examination is helpful in detecting the presence of inflammation of the SI joints, a universal feature of AS absent in the noninflammatory disorders. Pelvic compression is performed with the patient lying on his or her side, with the examiner applying downward pressure on the iliac crest. Sacroiliitis is associated with induced SI joint region tenderness. A Gaenslen test is performed with the patient supine holding one knee to his or her chest to stabilize the pelvis. The other leg is then passively extended at the hip over the side of the table, resulting in ipsilateral SI joint region pain if sacroiliitis is present. A Patrick test, or Faber test, is performed with the patient supine. The ankle is placed on the contralateral straight leg, and the ipsilateral knee is then passively pressed by the examiner, resulting in acronymic flexion, abduction, and external rotation of the hip. SI joint tenderness is elicited if sacroiliitis is present. Other maneuvers may elicit limitation of motion of the lumbar spine owing to lumbar ankylosis from AS. The Schober test is performed by marking a 10-cm vertical distance on the lumbar spine, with the caudal point at the level of the superior posterior iliac spines. Forward flexion normally results in an increase of the line to at least 15 cm. This test is neither as specific nor as sensitive as the tests of SI joint involvement, and may be positive in a number of nonmechanical disorders. Chest expansion may also be abnormal in AS because of involvement of the costochondral joints. This should be measured at the fourth intercostal joint, and should demonstrate at least a 5-cm increase.

Laboratory Tests Elevation of the ESR and anemia of chronic inflammation may be present. HLA-B27 serotype is present in approximately 95% of Caucasian patients with AS.

Imaging Radiographic evaluation is critical is the diagnosis of AS. Radiographic sacroiliitis is universally present in AS and its absence should make the diagnosis suspect. Radiographic features include narrowing or "pseudowidening," irregularity, erosions, and eventual fusion of the SI joints. In early unusual cases where the plain films are normal, MRI will demonstrate the inflammatory changes. If the spine is involved, syndesmophytes, calcifications of the annulus fibrosa of the discs, may be present. Other features include squaring of the vertebrae resulting in loss of the normal concavity of the vertebral body.

B. Other

The other common seronegative spondyloarthropathies are Reiter's syndrome (or reactive arthritis), enteropathic arthritis (associated with Crohn's disease and ulcerative arthritis), and psoriatic arthritis. Each of these have their unique features, and may be associated with inflammatory sacroiliitis and spondylitis in a fashion similar to AS.

III. Infectious Disorders

Infectious disorders may result in acute and chronic low back pain through a variety of mechanisms. Focal infection of the spine may be caused by osteomyelitis, intervertebral disc space infection, and septic sacroiliitis. Herpes zoster may cause severe pain in a dermatomal distribution and may be difficult to diagnosis prior to onset of the classic rash. Meningitis may of course cause back pain, but additional features usually aid in the diagnosis. Finally, viral syndromes and other systemic infections may cause low back pain in a nonspecific fashion.

A. Vertebral Osteomyelitis

A variety of microorganisms may result in vertebral osteomyelitis, usually entering the bone via hematogenous spread from an extraosseous primary source, including the genitourinary tract, endocarditis, soft-tissue infection, and infected intravenous catheters. *S. aureus* and *E. coli* are common causes in the adult patient. Certain populations of patients including children, patients with sickle cell disease, HIV-infected individuals, and intravenous drug abusers are susceptible to unique and characteristic infections. Finally, chronic forms of vertebral osteomyelitis may occur in the setting of mycobacterial or fungal infection.

Low back pain is common if the lumbar vertebrae are infected, often occurring in an acute or subacute fashion. The constitutional symptoms of fatigue, low-grade fever, and weight loss are often but not always present, and their absence may result in delayed diagnosis. If the infection spreads beyond the bone into the epidural space, forming an epidural abscess, symptoms of neural impingement may be present.

Physical Examination Fever may be present but is not universal. Percussion over the involved bone results in tenderness. Paravertebral muscle spasm and decreased range of motion of the lumbar spine, both very nonspecific findings and often present in the noninflammatory disorders, may be present. Objective evidence of neural impingement may be present in the setting of epidural abscess.

Laboratory Tests The ESR is usually, but not always, elevated. Blood cultures are positive in up to 50% of patients with osteomyelitis owing to acute bacterial infection. PPD is often positive in mycobacterial osteomyelitis. Direct aspiration or biopsy of involved bone will reveal the organism, but may not be necessary in the setting of positive blood cultures.

Imaging Irregularity and erosions of the endplate of a vertebral body followed by invasion into the intervertebral disc resulting in disc space narrowing, and finally invasion of the adjacent end plate, are the classic plain film findings of vertebral osteomyelitis. Imaging with MRI may demonstrate extraosseous infection, including epidural abscess.

B. Intervertebral Disc Space Infection

Intervertebral disc space infection, or discitis, is rare in adults and is not further discussed here.

C. Sacroiliac Joint Septic Arthritis

This is an unusual site for septic arthritis. Unilateral sacroiliac pain and tenderness, with erosive and destructive findings on plain films, are characteristic findings.

IV. Neoplasms

A variety of benign and malignant primary neoplasms may originate within the structures of the lumbar spine leading to low back pain. More commonly, neoplastic causes of low back pain arise through metastasis to the lumbar spine from distant, primary sites. Metastatic carcinoma, lymphoma, and myeloma are the usual causes of lumbar metastases.

In general, low back pain owing to neoplasia is constant, unrelieved with rest, and worsened with recumbency or at night. If the neoplasm results in neural impingement, the characteristic symptoms may be present. The plain radiographs may reveal one or multiple destructive lytic or blastic lesions within the bone; the disc spaces are often spared in distinction to infectious disorders. Further evaluation with MRI or CT is usually performed, and biopsy is necessary if the diagnosis remains elusive.

V. Intraabdominal and Intrapelvic Disorders

A variety of disorders within the abdomen and pelvis may result in radiation to the lumbar region. Occasionally, the back pain may predominate, delaying the diagnosis. This is particularly true with abdominal aortic aneurysm, where the only symptom may be low back pain in up to 20% of affected individuals.

VI. Psychologic Disorders

A number of psychologic disorders, including depression, anxiety, and malingering, may be associated with low back pain. Of course, organic causes need to be excluded prior to attributing the low back pain to a psychologic origin.

VII. Other Rare Causes

The preceding list discusses the common in addition to the life-threatening causes of low back pain. The other, more unusual causes of low back pain are beyond

the scope of this book, but can be accessed in general rheumatology and orthopedic texts.

Diagnostic Approach

Initial Evaluation

The critical aspect of the initial evaluation of patients with low back pain is assessment for potentially life-threatening or crippling disorders, particularly cauda equina syndrome, infection, and neoplasia, in addition to serious visceral disorders that may cause radiated pain, such as ruptured abdominal aortic aneurysm. These patients of course require immediate and specific treatment. Those patients who do not fall into these categories may be treated conservatively, and only those who fail conservative therapy require more specific assessment and treatment.

History

I. Symptoms of intraabdominal and intrapelvic pathology should be sought as possible explanations of low back pain. The possibility of abdominal aortic aneurysm should always be considered. This is a particularly critical problem in that an aortic aneurysm, with or without rupture, may manifest subjectively only as low back pain, in addition to the fact that this may be a rapidly fatal disorder requiring immediate surgical intervention.

II. Symptoms of cauda equina syndrome, including low back pain associated with lower extremity weakness, bowel and bladder incontinence, and saddle anesthesia should be sought.

III. Low back pain associated with fever and/or weight loss suggests an inflammatory disorder, including neoplasia and infection (Table 8-9). These constitutional symptoms, though, may be present in other inflammatory disorders, particularly the seronegative spondyloarthropathies.

IV. A history of low back pain initiated by acute injury or overuse suggests low back strain, herniated disc, or fracture. Absence of definite trauma or overuse, though, does not exclude these possibilities.

V. The low back pain should be analyzed with respect to its chronology, character, and response to previous treatment. The character of pain refers to its severity, localization, radiation, and duration, and the effects of aggravating (cough, sneezing, straining) and alleviating (rest, exercise, activity, drugs) factors.

A. Low back pain with sciatica is caused most commonly by disc herniation. The pain is characteristically aggravated by cough, sneezing, straining, bending, or lifting.

B. In the elderly, lumbar nerve root impingement may be caused not only by osteoarthritis and disc herniation, but also neoplasia and infection.

C. Continuous, severe low back pain that is worse at night and is not relieved by analgesics should arouse suspicion of neoplasia, including metastatic carcinoma, multiple myeloma, lymphoma, and abdominal or retroperitoneal malignancy.

D. In young adults, particularly men, continuous, aching low back pain and sacroiliac region pain suggests ankylosing spondylitis and other seronegative spondyloarthropathies.

Physical Examination

I. The evaluation of patients with low back pain should include an abdominal, pelvic, and rectal examination to assess for intraabdominal and intrapelvic pathology resulting in referred low back pain.

II. A general examination of the peripheral musculoskeletal system is also required to assess for peripheral manifestations of the seronegative spondyloarthropathies and osteoarthritis. Primary arthritis in the hip may occasionally cause low back pain.

III. A neurologic examination is also necessary to assess for evidence of impingement of the spinal cord, cauda equina, and nerve roots. Straight leg raising may be positive in nerve root impingement.

IV. The physical examination of the low back includes assessment of the spinal joints, sacroiliac joints, and the adjacent soft tissues. The examination includes inspection, palpation, range of motion, and observation of gait.

A. Focal tenderness on palpation or percussion over a spinal process or adjacent processes suggests focal skeletal pathology, including fracture, infection, and neoplasia.

B. Reduction of chest expansion suggests seronegative spondyloarthropathy.

C. A "step-off" may be palpated in patients with significant spondylolisthesis.

D. Paraspinal spasm is a nonspecific finding and may result in limitation of motion of the lumbar spine.

E. Specific tests for sacroiliitis are discussed in the preceding.

Psychologic Examination

It is helpful to recognize and evaluate emotional factors in patients with low back pain. Nonorganic physical signs include superficial or nonanatomic distribution of tenderness, distracted straight leg raising, overreaction during the examination, ill-defined weakness, and sensory changes that do not follow a root or nerve distribution.

Imaging Studies

Although mandatory in acute low back pain that may be a consequence of cauda equina syndrome, infection, and neoplasia, imaging as part of the initial evaluation may not be necessary in the vast majority of patients with acute low pain that is assessed as low back strain or other benign processes.

Plain Radiographs

These are the routine anteroposterior, lateral, and coned-down lateral views of the lateral spine. These studies are warranted in evaluation of patients with possible dangerous acute low back pain (cauda equina syndrome, infection, and neoplasm) and in patients with chronic low back pain. These studies may not be necessary in the initial evaluation of acute low back pain of presumed benign origin in that they are neither sensitive nor specific for the usual nondangerous causes. Radiographic findings of osteoarthritis of the discs and facet joints are very common in the normal population. Thus, their presence does not necessarily explain the cause in the patient with low back pain.

MRI and CT-Myelography

These studies are considered fairly equivalent when more sophisticated imaging is required. They are equivalent in the diagnosis of disc disease and lumbar stenosis. MRI is superior in imaging the soft tissues and exposes the patient to less radiation. CT-myelography is superior in imaging the bony structures. Plain CT of the lumbar spine, bone scan, and discography are used less frequently and provide less information than MRI and CT-myelography.

Laboratory Studies

As with imaging studies, laboratory studies may not be necessary in patients with presumed benign acute low back pain. If neoplasm or infection is suspected, assessment for systemic inflammation with ESR, in addition to CBC and studies of renal and hepatic function, are necessary. Serum calcium and phosphorus levels, in addition to laboratory assessment for multiple myeloma, may also be warranted.

Electrodiagnostic studies (nerve conduction velocity and electromyography) occasionally may be useful in determining the location and extent of neural impingement.

Subsequent Evaluation

This is necessary in the patient with chronic low back pain of presumed benign cause who does not respond to a trial of conservative therapy. The specific laboratory and imaging studies depend on the absence or presence of lower extremity symptoms and risk factors for a serious underlying etiology. Consultation with neurology, spine surgery, and psychiatry may be necessary.

Neck Pain and Selected Cervical Syndromes

Walter G. Briney

The human cervical spine is quite susceptible to disease and trauma in that it is interposed between the head and the relatively immobile thoracic spine. The cervical spine offers little protection to the vital structures it encloses, including the lower medulla oblongata, spinal cord, vertebral and spinal arteries, and spinal and sympathetic nerves. For effective use of the senses of sight and hearing, the neck must have a wide range of motion. About 85% of this movement occurs at the atlas-axis-skull complex. In addition to the marked mobility of the cervical spine, 32 cervical joints with synovial lining are present and can be involved in inflammatory processes.

Clinical Characteristics of Neck Pain

The cause of neck pain may be easier to determine if the character, location, and time of day when pain occurs is considered. Bone pain is dull, deep, and constant. Fracture pain is sharp and severe. Muscle pain is cramping in nature. Night pain is seen with Paget's disease, osteomyelitis, and osteoid osteoma (a benign tumor). Pain that increases with coughing suggests a cervical radiculopathy or increased intracranial pressure. Paresthesias in the head, face, or tongue are seen with involvement of the upper three cervical nerve roots. Occipital headaches are common with cervical spine disease of many causes but especially with cervical spondylosis. Unrelenting pain not affected by rest or exercise suggests malignant disease, occult infection, or psychological problems.

Etiology and Clinical Features of Neck Pain

I. Acute neck pain. This usually results from a relatively sudden insult to the cervical spine and the structures it encloses.
   A. Acute torticollis. This is the most common cause of neck pain in adolescents and young adults. Unilateral pain occurs with limitation of one rotational movement. The neck is fixed in side flexion owing to awkward neck position of several hours.
   B. Cervical muscle strain. A history of trauma, such as flexion-extension (whiplash) neck injury, is usually present.
   C. Cervical disk herniation with nerve root compression. This is relatively uncommon. It is attended by severe neck and arm pain with voluntary immobilization of the neck (see Cervical Radiculopathies, Chapter 10).
   D. Osteomyelitis. This disease is usually caused by *Staphylococcus aureus* and is seen in patients with underlying diseases that make them more susceptible to infection and with the use of corticosteroids or immunosuppressive drugs. Patients with AIDS and IV drug abusers are candidates for opportunistic infections, and appropriate cultures are indicated.
   E. Osteoporosis and vertebral collapse. These conditions occur less commonly in the cervical than in the dorsal and lumbar regions.
   F. Pathologic fracture (tumor)
   G. Meningitis. Neck pain, occipital headache, marked nuchal rigidity, altered sensorium, and fever usually occur.
   H. Subarachnoid hemorrhage. The symptoms may be similar to those produced by meningitis. The onset is usually acute and the headache severe. Change in sensorium may be rapid. This is a life-threatening emergency and immediate neurosurgical consultation is mandatory.
II. Chronic neck pain
   A. Cervical spondylosis. This is the most common cause of neck pain in middle and old age. Chronic disk degeneration followed by osteophytes and degenerative joint disease in facet joints and the joints of Luschka results in a triad of painful stiff neck, pain in the arm and hand, and the later development of spasticity in the legs. The onset is gradual with a slowly progressive course.
   B. Cervical disk herniation (see Cervical Radiculopathies, Chapter 10).
   C. Ankylosing spondylitis (see Low Back Pain, this chapter).

   D. Chronic infection in the vertebrae and discs. Tuberculosis and fungal diseases should be considered diagnostic possibilities.
   E. Primary and metastatic tumors. Neck pain and neurologic impairment are common presenting problems. MRI is usually diagnostic, and bone scans may be helpful. See comments in the preceding regarding tumor pain.
   F. Fibromyalgia, psychogenic rheumatism, and myofascial pain. These conditions are common causes of neck, upper back, and shoulder pain. They are seen frequently in those who work in a sitting position with the neck chronically flexed, especially if they are emotionally labile and unhappy with their life situations. Fibromyalgia and psychogenic rheumatism are discussed elsewhere in this chapter and in the section on Anxiety in Chapter 1.
   G. Rheumatoid arthritis of the cervical spine. This disease is usually associated with evidence of extensive rheumatoid arthritis elsewhere. Subluxation of C1-C2 is the most serious complication of rheumatoid arthritis and can be life threatening. High neck and occipital pain occur and may be aggravated by coughing or sudden movements. Paresthesias in the arms, electric shock sensations down the back, paresthesias in the legs, spastic paraplegia or quadriplegia, urinary retention, loss of bladder control, and loss of deep tendon reflexes may be seen. Vertebral artery compression and "drop" attacks have also been reported (Table 8-8).

Cervical Syndromes Not Associated with Pain

I. Vertebral artery compression. Osteophytes from the intervertebral disc or zygapophyseal joints are common causes. Posterior subluxation of vertebrae with a scissoring action may also cause this condition. Turning the head to the opposite side or extension of the neck while looking upward may decrease vertebral artery blood flow, causing dizziness, unsteadiness of gait, paresthesias of the lips or face, visual disturbances, and "drop" attacks.
II. Cervical spondylosis. Osteophytes from the discs and zygapophyseal joints may compress the spinal cord. Hypertrophy of the ligamentum flavum is a frequently associated finding. A spastic, ataxic gait, loss of bladder and bowel control, and other neurologic abnormalities may result. Extension of the neck may aggravate the clinical findings.

Diagnostic Approach

I. Examination of the cervical spine. Scoliosis and kyphosis are easily recognized. Palpation may reveal local areas of tenderness, and crepitus may be found with rotation. Motion should be observed with forward flexion, backward extension, rotation to the left and right, and lateral bending of the head to the left and right. Spasm may also be noted, particularly over the trapezius muscles. Palpate the carotid pulses and thyroid gland and examine for adenopathy. Occipital tenderness may indicate occipital neuralgia.
II. Radiographic studies
   A. Cervical spine radiographs should be obtained with AP, oblique, lateral flexion, and extension views. Straightening of the spine may be seen because of muscle spasm. The oblique views can demonstrate osteophyte encroachment of the neural foramina. Lateral flexion views should be examined for possible C1-C2 subluxation of rheumatoid involvement of the spine. Narrowed intervertebral disks, hypertrophic spurring, and cervical instability may be present. Osteoporosis and vertebral collapse can be observed. The destructive lesions of tumor or infection may be identified. If ankylosing spondylitis is suspected, radiographs of the pelvis should be obtained for examination of the sacroiliac joints.
   B. Tomograms are extremely helpful in outlining structures that are not well visualized on routine radiographic studies.
   C. Bone scans should be ordered in all cases of obscure neck pain and are especially helpful in identifying metastatic tumor and osteomyelitis.
   D. CT scanning, with or without myelographic dye, may be indicated when there is physical or other x-ray evidence of a mass lesion (e.g., tumor, herniated

disc, hypertrophic spurring). The use of myelographic material is an invasive procedure, and neurologic consultation is recommended before proceeding to this. In addition, sagittal, coronal, or oblique views cannot be directly acquired. Magnetic resonance imaging, although more costly, may be a good choice before myelography is performed.

E. Magnetic resonance imaging is noninvasive and affords no radiation exposure. The bony architecture of the cervical spine, structure of the cord, and surrounding structures are all visualized with excellent detail. Sagittal, oblique, and axial images may be obtained. MRI is applicable in the evaluation of degenerative disc disease, infection, trauma, and neoplasia involving osseous structures, soft tissues, and the cord.

III. Lumbar puncture

A. Examination of the spinal fluid may be performed at the time of myelography. If increased intracranial pressure is suspected, as may occur with subarachnoid hemorrhage, a small needle should be used and only a small amount of fluid be withdrawn.

B. Diagnostic tests

1. Cell count and differential count. The presence of red blood cells suggests subarachnoid bleeding. Increased numbers (several thousand or more) of granulocytes indicate bacterial meningitis.
2. A low spinal fluid glucose with a normal blood glucose value suggests bacterial infection.
3. Modest elevation of the spinal fluid protein is frequently seen with cervical disc disease.
4. Gram stains, India ink preparations, and cultures should be performed if infection is suspected.

IV. Electromyography with nerve conduction velocities of the upper extremities may be helpful in demonstrating nerve root compression in cervical disc disease. Electromyography of the lower extremities is helpful occasionally in cervical spondylosis with spinal cord compression.

V. Additional laboratory tests may be of benefit (see Low Back Pain).

A. Elevation of the sedimentation rate may indicate infection or inflammatory arthritis.

B. If ankylosing spondylitis is suspected, obtain an HLA-B27 test, which is positive in about 95% of cases. The test is also frequently positive in spondyloarthropathies owing to other causes (see HLA-B27 under Low Back Pain). X-ray confirmation is necessary to confirm this disease, as only 2% to 10% of patients who test positive for HLA-B27 develop AS or another spondyloarthropathy.

VI. Needle biopsy under fluoroscopic control. This procedure is seldom carried out in diseases of the cervical spine because of the risk of damage to adjacent structures. However, occasionally it may be valuable in detecting tumors or infection.

9. ENDOCRINE AND METABOLIC PROBLEMS

Hyperglycemia

Walter A. Huttner

Definition

Hyperglycemia is the presence of elevated blood glucose levels in fasting or postprandial specimens.

The criteria listed in the following for the diagnosis of normal glucose levels, diabetes mellitus, impaired glucose, and gestational diabetes are based on recommendations from the Expert Committee of ADA, 1997.

Blood Glucose Determinations

I. Glucose determinations performed on plasma or serum are preferable to those performed on whole blood. Plasma or serum methods are not dependent on the hematocrit value and are more suitable for use in autoanalyzers. Plasma and serum glucose levels, which are about equal, are approximately 15% higher than those obtained from whole blood.

II. Venous blood is customarily used for glucose determinations, although capillary blood may be more convenient in children. In the fasting state, venous and capillary glucose levels are comparable, but the values tend to be higher in capillary than in venous blood for at least 2 hours after eating.

III. Glucose determinations by true glucose methods (e.g., glucose oxidase) are preferred because their use avoids the spuriously elevated values produced by hemolysis, uremia, or other sugars such as fructose or galactose.

IV. Home glucose monitoring is performed on capillary whole blood. This has become an important aspect of glucose control in diabetes. The determinations are performed by various monitoring devices.

The Oral Glucose Tolerance Test

I. Prior to the test, the patient should be on a diet containing at least 150 g/day of carbohydrate for 3 days. Standardized conditions should prevail so that they may be reproduced if desired. The test should be given only to patients who are otherwise healthy, ambulatory, and free from any complicating acute or chronic illness that might impair carbohydrate tolerance. They should not be taking drugs that elevate blood glucose or interfere with the laboratory determination of glucose.

II. The oral glucose tolerance test (OGTT) should be performed in the morning after a fast of at least 10 hours but no more than 16 hours, although water is permitted during this period. The patient should be seated and should not smoke throughout the test.

III. The dose of glucose administered should be 75 g (1.75 g/kg ideal body weight)—100 g when testing for gestational diabetes. After a fasting blood sample is drawn, glucose is administered in a flavored drink. Zero time is the beginning of the drink. Blood samples are customarily drawn after 1/2 hour, 1 hour, 2 hours, and 3 hours.

IV. The standard OGTT is a 3-hour procedure. If reactive hypoglycemia is suspected, the test should be suspended until the glucose levels begin to rise. Urinary sugar determinations are no longer considered significant, but a qualitative glucose determination on the total urine collection during the test period may be worthwhile.

Criteria for Normal Glucose Tolerance in Nonpregnant Adults
Fasting values are plasma glucose <110; 2 hours postglucose <140 mg/dL.

I. Fasting values
   A. Venous plasma <115 mg/100 mL
   B. Venous whole blood <100 mg/100 mL
   C. Capillary whole blood <100 mg/100 mL
II. Values between ½ hour and 1½ hours
   A. Venous plasma <200 mg/100 mL
   B. Venous whole blood <180 mg/100 mL
   C. Capillary whole blood <200 mg/100 mL
III. Two-hour values
   A. Venous plasma <140 mg/100 mL
   B. Venous whole blood <120 mg/100 mL
   C. Capillary whole blood <140 mg/100 mL
IV. Glucose values above these concentrations but below the levels found in diabetes or impaired glucose tolerance should be considered nondiagnostic for these conditions.

Criteria for the Diagnosis of Diabetes Mellitus
Fasting plasma glucose is >126; 2 hours plasma glucose <200 using 75 g of glucose.

Nonpregnant Adults
Any one of the following criteria is considered diagnostic of diabetes.

I. The presence of classic symptoms of diabetes such as polyuria, polydipsia, rapid weight loss, and ketonuria, associated with gross elevation of blood glucose concentrations
II. Elevated fasting glucose concentrations on more than one occasion
   A. Venous plasma ≥ 140 mg/100 mL
   B. Venous whole blood ≥ 120 mg/100 mL
   C. Capillary whole blood ≥ 120 mg/100 mL

If the fasting glucose values meet these criteria, *an OGTT is not required.*

III. Fasting glucose concentrations that are below those diagnostic of diabetes and that are associated with elevation of *both* the 2-hour sample and another sample drawn during the time between the administration of glucose and the 2-hour specimen
   A. Venous plasma ≥ 250 mg/100 mL
   B. Venous whole blood ≥ 180 mg/100 mL
   C. Capillary whole blood ≥ 200 mg/100 mL

Children
I. The presence of classic symptoms of diabetes together with a random plasma glucose above 200 mg/100 mL or the criteria listed in the following. In asymptomatic individuals, both an elevated fasting glucose and an elevated glucose concentration on more than one occasion during the OGTT.
II. Both the 2-hour specimen and another sample drawn between the administration of the glucose dose (1.75 g/kg ideal body weight [maximum 75 mg]) and the 2-hour sample
III. Criteria for elevated fasting, 2-hour, and intervening values are the same as those listed for nonpregnant adults

Gestational Diabetes
I. Screening test
   A. The test should be administered between the 24th and 28th weeks of pregnancy to women who have not previously been identified as having glucose intolerance.

   B. Fifty grams of glucose are administered orally without regard to the time of day or the time of the previous meal.
   C. A plasma glucose level taken 1 hour later equal to or greater than 140 mg/100 mL indicates the need for a conventional glucose tolerance test.
II. Diagnostic test
   A. Prior to the test, the patient should be on an unrestricted diet containing at least 150 g/day of carbohydrate for 3 days.
   B. The test should be performed after an overnight fast of 8 to 14 hours.
   C. Venous plasma glucose determinations should be performed in the fasting state and at 1 hour, 2 hours, and 3 hours after the administration of 100 g of glucose. The patient should remain seated and not smoke during the test.
   D. Two or more of the following plasma glucose levels must be met or exceeded for a positive diagnosis: fasting, 105 mg/100 mL; 1 hour, 190 mg/100 mL; 2 hours, 165 mg/100 mL; 3 hours, 145 mg/100 mL.

Criteria for Impaired Glucose Tolerance
The fasting level is >110 and <126; 2 hours after glucose >140 and <200.

In adults, three criteria must be met: (a) The fasting glucose concentration must be below the value that is diagnostic of diabetes, (b) the glucose concentration 2 hours after glucose administration must be between normal and diabetic values, and (c) a value between the ½-hour and 2-hour samples must be unequivocally elevated.

In children, two criteria must be fulfilled: (a) The fasting glucose concentration must be below diabetic levels, and (b) the glucose concentration 2 hours after the oral glucose challenge must be elevated to between normal and diabetic values.

Miscellaneous Considerations

The Effects of Age on the Oral Glucose Tolerance Test
Glucose tolerance appears to decrease with age. Approximately 50% of patients over the age of 60 years have abnormal glucose tolerance test results, but only a minority of these individuals eventually develop frank diabetes mellitus. An approximately equal number will be normal on retesting. Because of impaired glucose tolerance with aging, some authorities add 10 mg/100 mL to each of the maximum normal values (whole blood glucose) for each decade above the age of 50 years. Other authorities feel that with adequate dietary preparation, the effect of age on the OGTT is insignificant. Still other investigators feel that a 3-hour whole blood value of 110 mg/100 mL or greater is the most reliable criterion for the diagnosis of diabetes in elderly persons.

Nondiabetic Causes of Abnormal Glucose Tolerance
I. Fasting hyperglycemia, otherwise unexplained, is virtually diagnostic of diabetes mellitus, especially in a patient with a family history of diabetes. The same holds true for an OGTT that is clearly abnormal. However, the final decision depends on the exclusion of nondiabetic causes of impaired glucose tolerance.
II. The major nondiabetic causes of an abnormal OGTT are as follows:
   A. Inadequate dietary preparation
   B. Hepatocellular disease
   C. Chronic disease and prolonged physical inactivity (bed rest)
   D. Malnutrition and starvation
   E. Potassium depletion owing to diuretics, primary aldosteronism, renal disease, or alcoholism
   F. Stress secondary to strokes, myocardial infarction, surgery, and febrile illnesses
   G. Endocrinopathies, such as acromegaly, Cushing's syndrome or disease, adrenocortical hyperfunction, prolonged steroid therapy, islet cell tumors (insulinomas, glucagonomas), pheochromocytoma, and thyrotoxicosis
   H. Chronic renal disease and uremia
   I. Alimentary hyperglycemia following gastric surgery
   J. Drugs (e.g., steroids, diuretics, oral contraceptives, nicotinic acid)
III. An abnormal OGTT found in any of the previously mentioned conditions should be considered nondiabetic until proved otherwise, provided the fasting blood

sugar is normal. Patients with these disorders should be retested with an oral OGTT after recovery has taken place and normal physical activity has been resumed. Adequate dietary preparation prior to the test is most important. The intravenous OGTT is helpful in differentiating between alimentary hyperglycemia and diabetes mellitus.

Effect of Drugs on the Oral Glucose Tolerance Test
Drugs may raise or lower blood sugar values. Drugs that can affect glucose tolerance include steroids, some oral contraceptives, diuretics, nicotinic acid, salicylates administered in large doses, alcohol, propranolol, and monoamine oxidase inhibitors (MAOIs). As a general rule, a normal OGTT found in patients on any of these medications can be considered valid.

Diagnosis of Diabetes in the Presence of Conditions That May Impair Glucose Tolerance
There are six conditions, listed in the following, in which, although the fasting blood sugar is normal, the OGTT is abnormal. It is often difficult and sometimes impossible to determine whether the glucose intolerance is a reflection of the underlying disorder or is the result of coexisting diabetes mellitus.

I. Obesity. An abnormal OGTT in an obese individual should be considered prima facie evidence of diabetes and treated accordingly.
II. Pregnancy. The criteria for the diagnosis of gestational diabetes are listed in the preceding.
III. Hyperlipoproteinemia. Familial hyperlipoproteinemia, including types III, IV, and V in the Frederickson classification, is often associated with abnormal glucose tolerance. Until more is known, patients with hyperlipoproteinemia and glucose intolerance should be treated the same as other diabetics with standard regimens, including weight reduction and carbohydrate restriction.
IV. Degenerative vascular disease. Strokes, intracerebral hemorrhages, and heart attacks are commonly associated with transitory hyperglycemia. Unless the diagnosis of diabetes is unequivocal, a final decision as to whether or not such patients are diabetic should be postponed until complete recovery has taken place and normal physical activity has been resumed.
V. Chronic liver disease. Hepatocellular disease may produce an abnormal OGTT, but fasting hyperglycemia is a rare occurrence. Usually, the glucose intolerance disappears when the liver function returns to normal. There is no available test that distinguishes between hepatic and diabetic glucose tolerance curves.
VI. Gout and hyperuricemia. A much higher incidence of glucose tolerance abnormality is found in gouty and hyperuricemic individuals than in the general population. The usual criteria for the diagnosis of diabetes are applicable.

Intravenous Glucose Tolerance Test
The intravenous GTT is primarily a research tool. It has no demonstrable clinical advantage over the oral test. Its major usefulness is in differentiating between diabetes and alimentary hyperglycemia secondary to gastric surgery.

Hypoglycemia

Walter A. Huttner

Definition
Hypoglycemia is a symptom complex associated with abnormally low blood glucose levels. Plasma glucose values below 50 mg/100 mL are usually diagnostic of hypoglycemia in the presence of typical symptoms. For blood glucose determinations and the preparation and precautions in performing the oral glucose tolerance test, see the preceding section, Hyperglycemia. For the diagnosis of hypoglycemic states, the standard 3-hour oral GTT is extended to a 5-hour period.

Symptoms
The occurrence of hypoglycemic symptoms is related to both the rapidity and the severity of the decline in the blood glucose level. Symptoms that accompany a rapid fall in the concentration of blood glucose include a sensation of "not feeling well," shakiness, sweating, palpitation, restlessness, anxiety, hunger, nausea, and vomiting. Loss of consciousness and even coma may occur. These symptoms, which are largely owing to catecholamine release, are alleviated promptly by correction of the hypoglycemia. The symptoms are usually different when the fall in glucose levels is slow and prolonged or severe. Neuroglycopenic symptoms, such as headache, restlessness, reduction in spontaneous conversation and activity, mental confusion, prolonged sleep, stupor, coma, and hypothermia or fever, may occur. Sensory and motor disturbances and bizarre behavior may also be noted.

Etiology
The causes of hypoglycemia can be divided into three major groups: reactive, fasting, and factitious hypoglycemia. The two types of hypoglycemia found most commonly in practice are reactive functional hypoglycemia and reactive hypoglycemia secondary to diabetes mellitus. The distinction between fasting and reactive hypoglycemia is important clinically because fasting hypoglycemia is not a feature of either reactive functional hypoglycemia or reactive hypoglycemia secondary to diabetes mellitus.

I. Reactive hypoglycemia
   A. Reactive functional hypoglycemia, which seems to be unusually common in individuals with emotional problems, is characterized by transient postprandial hypoglycemia that occurs 2 to 4 hours after the ingestion of food containing carbohydrate. The symptoms are predominantly those of hyperepinephrinemia, brought about by the rapid decline in the blood sugar concentration. The symptoms usually subside spontaneously within half an hour after their onset. Reactive functional hypoglycemia does not predispose to the subsequent development of diabetes.
   B. Reactive hypoglycemia secondary to diabetes mellitus. Reactive hypoglycemia secondary to mild diabetes mellitus is the second most common type of hypoglycemia found in adults. Low blood sugar values accompanied by symptoms of hyperepinephrinemia typically occur 3 to 5 hours after meals. A family history of diabetes is commonly obtained.
   C. Alimentary hypoglycemia. Alimentary hypoglycemia is found in approximately 5% to 10% of patients who have had partial to complete gastrectomies or gastroenterostomies. However, it sometimes occurs in individuals who have not had gastric surgery. The rapid gastric emptying time leads, sequentially, to accelerated absorption of glucose, hyperglycemia, and hypoglycemia. Symptoms usually occur 2 to 3 hours after meals, corresponding to the time when blood glucose levels are low.
   D. Hereditary fructose intolerance. Patients with familial fructose intolerance may have postprandial reactive hypoglycemia following the ingestion of fructose-containing foods. Because the disease occurs primarily in children and is seldom found in adults, it is not discussed here. The diagnosis is established by the use of an oral fructose tolerance test.
II. Fasting hypoglycemia
   A. Pancreatic islet cell disease. The symptoms of hypoglycemia due to islet cell tumors (insulinomas) are produced by the excessive secretion of insulin. Approximately 85% of these tumors are benign and 15% malignant. They occur most frequently between the ages of 35 and 55 years. Insulinomas may be solitary or multiple and may be either macroscopic or microscopic in size. Multiple islet cell tumors are sometimes associated with multiple endocrine adenomatosis and peptic ulceration (Zollinger-Ellison syndrome)

Hypoglycemic symptoms usually develop insidiously, but with the passage of time hypoglycemic episodes tend to increase in frequency and severity. Most attacks occur in the early morning or later afternoon hours. They are often precipitated by fasting and physical activity. Neuroglycopenic symptoms predominate over those caused by epinephrine release. Whipple's triad, consisting of symptoms of hypoglycemia, low blood sugar levels, and relief with administration of glucose, is suggestive of organic hypoglycemia but is not specific for hyperinsulinism due to islet cell disease.

B. Glucagon deficiency. This is an extremely rare cause of hypoglycemia. The failure of plasma glucose and glucagon to rise following an arginine infusion is diagnostic of this condition.

C. Extrapancreatic tumors. Severe fasting hypoglycemia may occur in the presence of such tumors as mesotheliomas, fibromas, fibrosarcomas, or leiomyosarcomas, particularly when they are large. The neoplasms are usually found in the pelvis, retroperitoneum, or thorax. The diagnosis is usually based on the association of hypoglycemia with easily identified abdominal or thoracic masses.

D. Liver disease. Glycogen storage disease and galactosemia are examples of congenital anomalies that may be associated with hypoglycemia. Hypoglycemia may also occur in severe, diffuse liver disease (e.g., fulminating hepatitis, hepatic necrosis owing to toxic agents, cholangitis, cirrhosis) and in some patients with hepatomas.

E. Leucine sensitivity. Leucine-induced hypoglycemia is an extremely rare disorder in adults but is a not uncommon cause of fasting hypoglycemia in children below the age of 4 years. The administration of leucine may produce hypoglycemia in patients with islet cell tumors or in those on sulfonylureas.

F. Alcohol-induced hypoglycemia. Ethanol-induced hypoglycemia occurs most frequently in alcoholics who are eating little or no food. Occasionally, following a 2- to 3-day fast, the ingestion of alcohol may produce hypoglycemia in a young, healthy person. Patients with hypopituitarism or adrenocortical insufficiency exhibit increased sensitivity to the hypoglycemic effects of alcohol. Ethanol-induced hypoglycemia is promptly corrected by the administration of glucose.

G. Malnutrition. Hypoglycemia is relatively common in children with kwashiorkor, but in adults, even severe protein depletion and malnutrition rarely lead to hypoglycemia.

H. Endocrine disorders. Fasting hypoglycemia may occur in patients with hypopituitarism or Addison's disease, but it is a relatively uncommon finding in these disorders. The endocrine cause of the hypoglycemia is usually apparent from the clinical picture.

III. Factitious hypoglycemia. This is the most common cause of hypoglycemia in adults. Hypoglycemia may be induced by ingestion of salicylates in large amounts, MAOIs, barbiturates, and other drugs. It may be precipitated in diabetics receiving insulin, when the dose of insulin is too high, when physical activity is excessive, or when food intake is inadequate or delayed. Sulfonylureas may induce hypoglycemia, especially in the presence of renal failure or the use of alcoholic beverages. Insulin has sometimes been used by medical personnel, diabetics, and the relatives of patients, with malingering, suicidal, or homicidal intent. However, insulin overdose is most commonly accidental.

Diagnostic Approach to Reactive Hypoglycemia

I. The most effective method for documenting true hypoglycemia is to teach the patient to perform self glucose monitoring. Using this procedure, the patient can determine the glucose levels during attacks and bring these to the attention of the physician.

II. A 5-hour oral GTT is the mainstay of the diagnostic approach to suspected reactive hypoglycemia.

A. In reactive functional hypoglycemia, the fasting blood sugar level is normal. The curve is not remarkable except for the occurrence of abnormally low plasma glucose values (50 mg/100 mL or less) between the second and fourth hours of the test.

B. In reactive hypoglycemia secondary to mild diabetes mellitus, the glucose tolerance curve generally shows a normal or slightly elevated fasting blood sugar level, hyperglycemia at the peak value and at 2 hours, and low plasma glucose levels (50 mg/100 mL or less) during the third to fifth hours.

C. In alimentary hypoglycemia, the oral GTT reveals a normal fasting glucose level, peak hyperglycemia at ½ to 1 hour, normal glucose concentration at 2 hours, and hypoglycemia shortly thereafter.

III. Because the intravenous GTT is normal in alimentary hypoglycemia but abnormal in diabetes mellitus, it is useful in differentiating between the two.

IV. Once an oral GTT has been performed, when fasting hypoglycemia has to be ruled out, the procedures outlined in Diagnostic Approach to Fasting Hypoglycemia should be followed.

Diagnostic Approach to Fasting Hypoglycemia

In addition to the oral 5-hour GTT, the following procedures are recommended in the evaluation of patients with suspected fasting hypoglycemia:

I. Determine, on at least two or three occasions, the plasma glucose and insulin levels after an overnight fast. Plasma glucose values of 50 mg/100 mL or less together with plasma insulin levels exceeding 40 ?U/mL occurring in association with hypoglycemia symptoms are considered virtually diagnostic of insulinoma.

II. If the plasma glucose and insulin levels are not diagnostic, the overnight fast should be prolonged for 4 hours and the plasma glucose and insulin determinations repeated. If the results still prove to be inconclusive, the fast should be extended for an additional 48 to 72 hours, with only black coffee permitted. During this time, multiple plasma glucose determinations should be obtained. These are usually performed at 6-hour intervals or whenever symptoms appear. As soon as low glucose levels and symptoms of hypoglycemia are induced, the test is terminated. Otherwise, at the conclusion of the 3-day period, the patient is exercised and a blood sample is drawn thereafter.

III. In patients with islet cell tumors, the plasma glucose concentration normally falls below 50 mg/100 mL at some time during the fast. Hypoglycemia of this severity is uncommon in patients who do not have disease of the islet cells. Exercise is a valuable adjunct in the evaluation of hypoglycemia because it produces a further drop in plasma glucose concentration in patients with insulinomas or other conditions associated with fasting hypoglycemia and a rise in plasma glucose levels in patients with reactive hypoglycemia.

IV. The measurement of plasma insulin levels in conjunction with plasma glucose concentrations is extremely valuable in the diagnosis of islet cell disease. Elevated plasma levels in connection with low fasting plasma glucose levels confirm the diagnosis of insulinoma. However, not all patients with islet cell tumors show fasting hyperinsulinemia. Moreover, normal fasting plasma insulin levels not only do not exclude the diagnosis but may actually support it if they occur in association with low plasma glucose concentrations. During the fast, a fall of plasma glucose to hypoglycemic levels while the plasma insulin remains unchanged or rises is also a significant finding. High fasting plasma insulin levels are not always pathognomonic of insulinoma because they may sometimes occur in obese persons without fasting hyperglycemia, in children with idiopathic hypoglycemia, and, rarely, in patients with nonpancreatic neoplasms. It has also been reported that assay of fasting plasma proinsulin levels may be helpful in the diagnosis of islet cell disease, particularly when fasting plasma insulin levels are not elevated.

V. Tests that induce the secretion of insulin are useful in confirming the diagnosis of islet cell tumors and in the differential diagnosis of hypoglycemia. The procedures used most commonly are the intravenous tolbutamide, leucine, and glucagon tests, in which serial determinations of plasma glucose and insulin are performed following the administration of the test substance. Details of the test

procedures and information concerning their interpretation can be found in standard textbooks. These provocative tests for insulin secretion are abnormal in a high percentage of patients with insulinomas. However, false-positive and false-negative results may occur with any of them. All three tests should be employed in suspected islet cell disease because an abnormal response may be obtained with one test but not with another. False-positive results may occur with the tolbutamide test in patients with nonpancreatic causes of hypoglycemia, uremia, or malnutrition, but not in patients with reactive hypoglycemia. With the leucine test, false-positive results may occur in individuals on the sulfonylureas. In children, the leucine test does not differentiate between insulinoma and the so-called idiopathic hypoglycemia of children. It is the writer's opinion that the glucagon test may prove to be the most reliable provocative test for insulin secretion.

VI. Once the diagnosis of islet cell tumor is made on the basis of the foregoing tests, an abdominal CT scan should be performed to help localize the tumor. It is often positive if the islet cell tumor is of significant size. Sometimes, MRI may more clearly delineate the soft-tissue mass. A CT scan of the head and serum calcium and phosphorus determinations are indicated to rule out multiple endocrine adenomatosis. If carcinoma is suspected, a liver scan should be performed to rule out metastatic disease.

VII. Extrapancreatic neoplasms merit consideration as possible causes of hypoglycemia after islet cell tumor has been ruled out, particularly in elderly individuals. Radiologic examinations, such as chest and abdominal films, intravenous pyelography, contrast studies of the gastrointestinal (GI) tract, CT scan, and MRI, are useful diagnostic studies for this purpose.

VIII. If glucagon deficiency is suspected, an arginine test should be performed. The failure of plasma glucagon and glucose to rise following the administration of arginine by infusion is diagnostic of glucagon deficiency.

IX. If pituitary and adrenal hypofunction are suspected causes of hypoglycemia, appropriate laboratory studies to confirm the diagnosis are indicated.

X. The relationship of diffuse liver disease to hypoglycemia is usually apparent from the clinical picture. Liver function tests show abnormalities. Hepatic hypoglycemia is easily corrected by the administration of glucose. Glucagon should be avoided because it may fail to cause hyperglycemia in the presence of severely impaired gluconeogenic reserve.

XI. The diagnosis of alcohol hypoglycemia is supported by a fall in plasma glucose levels following an infusion of ethanol.

XII. When factitious hypoglycemia owing to malingering is suspected, the following procedures merit consideration:
   A. Serum insulin antibody levels. The presence of such antibodies is proof of the administration of insulin.
   B. Sulfonylurea blood levels
   C. Examination of the urine for tolbutamide excretion products
   D. Leucine sensitivity test, which produces elevated insulin levels in patients with hypoglycemia owing to sulfonylurea compounds
   E. In patients with hypoglycemia and hyperinsulinism, measurement of the serum C-peptide level can determine whether the insulin in the circulation is endogenously secreted or administered exogenously. If the C-peptide level is low in the presence of high concentrations of circulating insulin, it can be assumed that the insulin is exogenous in origin. On the other hand, if the C-peptide levels are elevated, the implication is that the insulin is secreted endogenously, possibly by an insulinoma.

XIII. Many investigators rely heavily on encephalographic changes for the diagnosis of questionable cases of hypoglycemia. The disappearance of alpha waves when blood sugar values are low and their reappearance after correction of the hypoglycemia are regarded as specific evidence, provided hyperventilation and severe anoxia are ruled out. The test is considered to be especially valuable in the diagnosis of organic hypoglycemia.

Failure to Mature

Janet E. Schemmel

Definition and Etiology

Failure to mature or the failure to develop secondary sex characteristics is a relatively common disorder. It is frequently, but not always, associated with delayed growth. The condition has many causes. This discussion is limited to boys; the problem as related to females is considered in the following section, Amenorrhea. The age of presentation varies, often depending on the family history and the patient's identification with his peers. Usually, the patient is seen between the ages of 12 and 17 years; within the last decade, at a slightly younger age. The various abnormalities that can occur are listed in the following.

I. Failure to mature, with growth retardation or failure
   A. Delayed puberty (constitutional retardation)—most common; commonly familial; cause unknown
   B. Pituitary-hypothalamic disease
      1. Idiopathic hypopituitarism (with isolated or multiple tropic hormone losses)
      2. Pituitary tumor, nonsecreting, with multiple tropic hormone losses
      3. Pituitary tumor, secreting, as in Cushing's disease
      4. Suprasellar or parasellar tumor
      5. Infiltrative disease of the hypothalamus (e.g., sarcoidosis)
      6. Vascular abnormalities (e.g., internal carotid aneurysm)
   C. Hypothyroidism, juvenile, with or without goiter
   D. Chronic systemic disease (e.g., congenital heart disease, pulmonary disease, steroid treatment for asthmatic and dermatologic patients, chronic renal disease)
   E. Cushing's syndrome
   F. Cryptorchidism
   G. Testicular failure
      1. Infection
      2. Trauma
   H. Anorchism and testicular dysgenesis

II. Failure to mature, without growth retardation
   A. Hypogonadotropic hypogonadism, including isolated LRH deficiency (Kallmann's syndrome)
   B. Klinefelter's syndrome and associated syndromes

III. Delayed puberty secondary to other disease states and syndromes (e.g., myotonia dystrophica, and the obesity, mental retardation, and polydactylism or syndactylism seen in the Laurence-Moon-Biedl syndrome). Deprivational dwarfism is beyond the scope of this text.

Symptoms

Multiple symptoms may occur. They are usually related to the underlying cause and to the state of growth of the patient.

I. Failure to mature with growth retardation
   A. Immature genitalia
   B. Lack of beard
   C. Delay in growth
   D. Considered younger than chronologic age by peers and adults
   E. Immature voice
   F. In patients with pituitary or hypothalamic disorders (or both), additional symptoms may be present: (a) headaches, (b) visual complaints, (c) polydipsia and polyuria, (d) easy fatigability or episodic weakness, or both, and (e) failure to tan.

G. In addition to the general symptoms, patients with hypothyroidism may have (a) somnolence, (b) poor concentration, (c) cold intolerance, (d) constipation and obstipation, (e) mass in neck, (f) hearing defects, and (g) joint pain, especially hip pain.
H. Patients with systemic disease frequently have symptoms of their underlying disease. Cushing's disease or syndrome, uncommon at this age, is discussed in the sections Amenorrhea and Obesity.

II. Failure to mature without growth retardation. Patients without growth retardation may have few complaints except those of delayed maturity. Patients with hypogonadotropic hypogonadism (Kallmann's syndrome) may complain of inability to smell.

Signs

Failure to Mature with Growth Retardation

I. Below height and weight for chronologic age
II. Immature facies for chronologic age
III. Immature voice and larynx for chronologic age
IV. Paucity or absence of axillary or pubic hair
V. Absence of any pubertal breast tenderness or tissue
VI. Span and upper and lower segment heights that are compatible with normal prepubertal dimensions, although occasionally a eunuchoidal habitus may be seen
VII. Tanning may be absent, or the skin may be pale, yellowish, or dry
VIII. Blood pressure may be variable, depending on the underlying disease
IX. Genitalia are prepubertal, compatible with the patient's somatic age; the testes may be inguinal or impalpable
X. In patients with pituitary disorders, additional findings may be noted:
   A. Changing visual acuity and visual field defects
   B. Cranial bruit
   C. Pale, yellowish, or dry skin when multiple tropic hormones are lost
XI. Patients with chronic disease frequently demonstrate findings of the underlying disease (e.g., hepatosplenomegaly). The findings in Cushing's disease and syndrome are discussed in the sections Amenorrhea and Obesity.

Failure to Mature without Growth Retardation

I. Normal height or taller than predicted on the basis of the family height history
II. Commonly, increased span, with the lower segment height greater than the upper segment height
III. Absent or small scrotal testes and a small phallus
IV. Gynecomastia
V. Sparsity or absence of beard and axillary and pubic hair
VI. Obesity (not uncommon)
VII. Hyposmia or anosmia, which may be present in hypothalamic hypogonadotropic hypogonadism (Kallmann's syndrome)

Diagnostic Approach

Initial Evaluation

Initial studies should be carried out to help clarify the diagnosis, determine the need for further investigation, and determine proper treatment. These studies should include the following tests:

I. Hemoglobin and hematocrit values
II. White blood cell (WBC) and differential counts
III. Platelet count
IV. Sedimentation rate
V. TSH; free T_3 or T_4; T_3 RIA
VI. Biochemical profile
VII. Serum calcium, phosphorus, and alkaline phosphatase (usually included in profile)
VIII. Plasma FSH, LH, and testosterone; growth hormone; IGF-I

IX. Radiographs; chest, skull, and AP; hands and wrists, for bone age
X. Chromosomal karyotype in selected cases
XI. Twenty-four-hour urine collection for 17-ketogenic steroids or 17-hydroxycorticoids and creatinine; alternatively, a 7:00 AM serum cortisol and plasma ACTH

Patients with idiopathic delayed puberty usually have normal findings except for a delayed bone age that correlates with height, facial maturity, and genital development. Plasma gonadotropins may be low or absent. The span is usually prepubertal, occasionally eunuchoidal. A family history of delayed puberty supports this diagnosis.

In contrast, patients with pituitary disease may demonstrate the following findings: low or absent growth hormone; normal or low-normal thyroid function, reduced 17-ketogenic steroids or 17-hydroxycorticoids, and 17-ketosteroids, low cortisol and ACTH levels, and reduced gonadotropins. Skull radiographs are usually abnormal if a pituitary tumor is present. Enlargement of the sella turcica, with or without intracranial calcification, is a common finding. In idiopathic hypopituitarism, the sella turcica is usually normal. The blood urea nitrogen (BUN) and plasma glucose are frequently low. The serum phosphorus and alkaline phosphatase are reduced. Slight anemia may be present. Bone age is delayed. The body proportions and span are prepubertal.

Subsequent Evaluation

Further evaluation should include the following tests to determine tropic hormone losses:

I. Measurement of ACTH, cortisol, and compound S or measurement of 17-ketogenic steroids or 17-hydroxycorticoids before and after metyrapone administration
II. Plasma TSH. TRH infusion with measurement of TSH may be helpful in separating hypothalamic from pituitary disease.
III. Fasting growth hormone. A number of tests are used to evaluate growth hormone deficiency. These include the following:
   A. Growth hormone drawn 2 hours after the patient goes to sleep
   B. Growth hormone measurement after 15 minutes of exercise
   C. Pharmacologic tests
      1. Clonidine (ambulatory setting)
      2. L-dopa (ambulatory setting)
      3. Arginine (ambulatory setting)
      4. Glucagon (ambulatory setting)
      5. Insulin tolerance test. This test should be done in the hospital observation unit with the physician in attendance. A rise to 7 ng/mL is probably a normal growth hormone level. After provocative testing, multiple tests may be necessary, because more than 20% of normal children may show no response after one pharmacologic test.
      6. IGF-I (insulin growth factor I). A normal IGF-I level suggests the absence of growth hormone deficiency. Unfortunately, IGF-I levels may be normal in a small percentage of patients with growth hormone deficiency. For details about performing these tests, see the section Amenorrhea.
         Growth hormone is elevated in Lévi-Lorain–type dwarfism. IGF-I levels are usually low.
IV. Further radiologic investigation, including cranial CT scan, MRI, or both

If the diagnosis of primary hypothyroidism is established, tests for thyroid antibodies are indicated; a positive result suggests Hashimoto's struma. If a goiter is present and hearing is abnormal, other members of the family should be examined for familial goiter. A perchlorate test may be indicated in the presence of a goiter when the RAI uptake is elevated (see the section Thyroid Enlargement). Other tests to determine thyroxin-synthesizing defects are not yet available. It should be remembered that patients with juvenile hypothyroidism frequently have normal to accelerated puberty in the presence of delayed growth.

Ordinarily, the history, physical findings, and initial laboratory tests suggest the presence of an underlying chronic disease as the cause of the patient's failure to mature.

Electrocardiogram, pulmonary function tests, liver function tests, long bone radiographs, skin tests, urinary electrolyte excretion, and other tests should be carried out when applicable.

V. Serial growth hormone measurements before and after provocative testing may be necessary to prove growth hormone deficiency. At present, growth response to growth hormone administration may be the only conclusive way to diagnose growth hormone deficiency.
VI. Growth hormone releasing factor (GHRF). GHRF testing is not a sensitive method for diagnosing growth hormone deficiency because of variability in response.

Hypogonadotropic hypogonadism may occur as an isolated abnormality or in association with other conditions, such as palatal abnormalities and anosmia. The initial workup usually discloses a eunuchoidal or normal habitus, prepubertal scrotal testes, negative plasma gonadotropins, and delayed bone age.

Further investigation for tropic hormone losses should include the following:

VII. Metyrapone test with measurement of ACTH, cortisol, compound S, and/or 17-ketogenic steroids or 17-hydroxycorticoids before and after administration of the drug
VIII. Growth hormone measurements before and after the oral administration of L-dopa, and arginine infusion or insulin-induced hypoglycemia, or both
IX. TSH, TRH infusion with measurement of TSH may be indicated
X. Careful testing of the sense of smell
XII. Testicular biopsy is not necessary. Follow-up study may be indicated in selected patients because tropic hormone losses theoretically may occur at a later date. More common than hypogonadotropic hypogonadism is Klinefelter's syndrome (and its variants). These patients frequently are eunuchoidal and usually have small testes. Gynecomastia may be present. Bone age is delayed, and plasma gonadotropins are elevated. Karyotype determination is necessary to confirm the diagnosis.

Amenorrhea

Janet E. Schemmel

Definition

Amenorrhea is the failure of menstruation to occur in a woman of menstrual age. It is considered primary if menstruation has never occurred, and secondary if menses have ceased in a woman who has menstruated previously. The normal menarche is variable but generally occurs between 12 and 15 years of age in this country. A somewhat wider age range of 9 to 17 years has been reported for other countries. In recent years, the age of onset of menstruation appears to be lower than formerly. In the United States the average age of menarche is 12.8 years.

Primary Amenorrhea

Etiology

The causes of primary amenorrhea are many and varied. Occasionally, the past or family history provides clues to the diagnosis, particularly in the presence of chronic disease or a familial disorder. Primary amenorrhea is commonly associated with delayed growth. The most frequent causes are listed in the following.

I. Delayed puberty of unknown cause
II. Ovarian dysgenesis (agenesis, dysplasia)
III. Pituitary-hypothalamic disease, associated with idiopathic onset, tumors, infiltrative disease, vascular anomalies
IV. Testicular feminization syndrome

V. Cushing's syndrome or disease occurring at puberty
VI. Juvenile hypothyroidism
VII. Systemic disease (e.g., chronic renal disease, cystic fibrosis, congenital heart disease)
VIII. Cervical or uterine abnormalities
IX. Other endocrine disorders, including congenital or acquired adrenal hyperplasia, pseudohermaphroditism, true hermaphroditism, and ambiguous sexual differentiation
X. Ovarian failure (e.g., autoimmune oophoritis, chemotherapy)

Symptoms

I. Delayed puberty of unknown cause and ovarian dysgenesis are probably the two most common causes of primary amenorrhea. Delayed growth usually accompanies these conditions. Patients with systemic disease and Cushing's syndrome or disease may also have retardation in growth.
II. The usual symptoms encountered in patients with primary amenorrhea are (a) amenorrhea, in association with absent or delayed development of breast tissue and absence or paucity of pubic and axillary hair; (b) retardation in growth; and (c) a younger appearance than expected for the patient's chronologic age.
III. When primary amenorrhea is owing to pituitary-hypothalamic disorders, additional symptoms related to its underlying cause or to the loss of specific tropic hormones may occur, such as (a) headaches, (b) visual disturbances, (c) polydipsia, (d) polyuria, (e) easy fatigability or episodic weakness, or both, and (f) failure of the skin to tan.
IV. Patients with hypogonadotropic hypogonadism and testicular feminization may complain only of amenorrhea.
V. The symptoms found in young patients with Cushing's syndrome or disease are similar to those encountered in adults. The usual symptoms are (a) obesity that is not owing to excessive food intake and that is chiefly truncal in distribution, (b) easy fatigability and weakness, (c) irritability and difficulty in concentrating, (d) skin problems such as acne and easy bruisability, and (e) growth retardation.
VI. Patients with underlying chronic disease frequently have symptoms related to the basic disorder. Delayed growth often coexists.
VII. Patients with congenital adrenal hyperplasia owing to a 21-hydroxylase defect are usually diagnosed shortly after birth because of the presence of pseudohermaphroditism or adrenal insufficiency, or both. However, when acquired, this rare anomaly may manifest itself primarily with amenorrhea and, sometimes, with mild hirsutism but without any delay in growth. Other rare causes of congenital adrenal hyperplasia are the 11-hydroxylase and 17-hydroxylase deficiencies, both of which may be associated with systemic hypertension. However, significant growth problems are not encountered in these disorders.
VIII. Patients with ambiguous sexual differentiation may have fewer symptoms other than amenorrhea and delayed growth.

Physical Findings

Primary Amenorrhea with Associated Growth Retardation

I. Delayed height and weight for chronologic age
II. Immature facies for chronologic age
III. Immature voice and larynx for chronologic age
IV. Paucity or absence of axillary and pubic hair
V. Minimal or absent breast development
VI. An arm span and upper and lower segment heights that are more compatible with normal prepubertal than postpubertal dimensions
VII. Normotension, but occasionally systolic hypertension
VIII. Skin changes, consisting of absence of tanning or a dry skin that is pale and yellowish
IX. Abnormalities that are suggestive of ovarian dysgenesis: strabismus, webbing of the neck, increased carrying angle of the arms, pedal edema, pes cavus, shortened metacarpals, and a high-arched palate

X. External genitalia that are normal but prepubertal in appearance
XI. Findings suggestive of chronic underlying disease, such as chest deformities, heart murmurs, and hepatomegaly
XII. Diminished visual acuity, visual field defects, cranial bruits, and a pale yellow or dry skin in some patients with pituitary disorders

Primary Amenorrhea without Associated Growth Retardation
This group of patients includes those with sexual ambiguity, some cases of ovarian dysgenesis, the testicular feminization syndrome, hypogonadotropic hypogonadism (including Kallmann's syndrome), some patients with congenital (11-hydroxylase or 17-hydroxylase deficiency) or acquired (21-hydroxylase deficiency) adrenal hyperplasia, and some patients with chronic systemic illness. Cases with these disorders may show the following features:

I. Immature but otherwise normal facies for the chronologic age
II. Immature voice and larynx for the chronologic age, although the larynx is sometimes enlarged and the voice low-pitched
III. Paucity or absence of axillary and pubic hair except in patients with acquired adrenal hyperplasia, who may show hirsutism
IV. Variable breast development—minimal to absent, or normal in the testicular feminization syndrome
V. Normal arm span and upper and lower segment heights, or greater than normal arm spans and lower segment height
VI. External genitalia showing normal prepubertal development, clitoral hypertrophy, ambiguity, a vaginal dimple, or urethral abnormalities
VII. Absent uterus (Rokitansky syndrome)
VIII. Anosmia (Kallmann's syndrome)

Diagnostic Approach
Initial Workup
I. Careful measurement of the arm span, total height, and upper and lower segment heights
II. Skull films to determine the size of the sella turcica and to search for other abnormalities (e.g., intracranial calcification)
III. AP radiographs of the wrists and hands to evaluate bone age
IV. Chest films to detect bony abnormalities and to determine the heart size
V. Chromosomal karyotype
VI. TSH; free T_4
VII. A 24-hour urine collection for 17-ketogenic steroids or 17-hydroxycorticoids, 17-ketosteroids, and creatinine
VIII. Serum electrolytes, BUN, creatinine, calcium, phosphorus, and alkaline phosphatase (biochemical profile)
IX. Plasma FSH and LH determinations
X. Fasting serum growth hormone, IGF-I, and prolactin determinations
XI. Pelvic examination. Rectal examination may be substituted if necessary

Patients with primary amenorrhea owing to delayed puberty, ovarian dysgenesis, pituitary-hypothalamic disease, or hypothyroidism show evidence of delayed bone maturation. The arm span and the upper and lower segment heights are prepubertal in character. Normal skull films generally exclude pituitary tumors. Thyroid function studies may be normal in each of these conditions. However, they may be borderline or low in pituitary disorders and, occasionally, in ovarian dysgenesis. TSH is always elevated in hypothyroidism. Plasma FSH and LH are absent or low in hypopituitarism and delayed puberty but are elevated in patients with ovarian dysgenesis and ovarian failure.

Serum electrolyte, BUN, creatinine levels, and biochemical profile are normal unless a systemic disease or hypothyroidism is present. The BUN may be less than 10 mg/100 mL in patients with pituitary disease. It may be slightly elevated in some patients with hypothyroidism. The serum calcium is usually normal unless chronic disease is present. Elevated serum phosphorus and alkaline phosphatase values suggest that body growth is occurring. Such a finding is helpful because the results of growth hormone assays often are not reported until several weeks after specimens were collected and submitted for analysis. On pelvic examination, the genitalia are usually prepubertal in size, but the uterus may be absent or impalpable in ovarian dysgenesis. Uterine or vaginal anomalies may be present.

Subsequent Workup in Primary Amenorrhea with Delayed Growth
The diagnosis of delayed puberty is suggested when the biochemical profile, serum electrolytes, BUN and creatinine, growth hormone assay, thyroid function tests, and excretion of 17-ketogenic steroids and 17-ketosteroids are normal, plasma FSH and LH are low, bone maturation is retarded, and serum phosphorus and alkaline phosphatase are elevated.

Ovarian dysgenesis should be suspected if the skull films are negative, the fasting growth hormone level is normal, bone age is delayed, and plasma FSH and LH are elevated. The karyotype is usually XO, but a mosaic pattern may occur with or without other obvious extragenital abnormalities. Because diabetes mellitus is common in ovarian dysgenesis, serial random plasma glucose determinations should be performed on all patients with this disorder. Thyroid antibodies are commonly present in patients with this anomaly. Hypothyroidism is common.

A pituitary tumor should be suspected when skull films reveal an abnormality of the sella turcica or show suprasellar calcification. Confirmatory findings of hypopituitarism include delayed bone growth, low or absent plasma FSH and LH, absent growth hormone, low or normal thyroid function, normal or low BUN, and a normal or reduced serum alkaline phosphatase and phosphorus. To establish the diagnosis of pituitary hypofunction, additional studies are indicated.

I. Plasma TSH before and after the administration of TRH to differentiate pituitary from hypothalamic disease
II. Metyrapone test
III. Growth hormone stimulation tests. Growth hormone (GH) is measured before and 60 and 90 minutes after ingestion.
   A. Clonidine. After an overnight fast, 4 μg/kg clonidine is administered by mouth
   B. L-Dopa. After an overnight fast, 125 to 250 mg L-dopa is administered. Growth hormone is measured before and 60 and 90 minutes after ingestion. Propranolol given on 2 consecutive days prior to the test improves the response. Nausea limits the usefulness of this test.
   C. Insulin tolerance test to measure the release of growth hormone and plasma cortisol with insulin-induced hypoglycemia. Prior to the test, a fasting blood sample is drawn for glucose determination, growth hormone assay, and plasma cortisol. Regular insulin is then injected intravenously in a dose of 0.05 to 0.10 U/kg of body weight. Blood samples are collected at 15, 30, 45, and 60 minutes after the injection for glucose determinations. Samples at 30 and 60 minutes are also used for growth hormone assay and plasma cortisol. Normally, insulin-induced hypoglycemia causes a rise in growth hormone levels to at least 20 ng at 60 minutes and a threefold rise in the plasma cortisol level. Because the insulin tolerance test is a potentially dangerous procedure, a physician should be in attendance at all times.
   D. Arginine infusion test. Arginine is not readily available. The test is performed as follows: A growth hormone level is obtained, following which 30 g of arginine diluted in 100 mL of sterile water is infused over a 30-minute period. In children, the dose of arginine is 0.5 mg/kg of body weight up to a maximum of 30 g. The growth hormone level is measured at 30-minute intervals for a period of 2 hours after the completion of the infusion. The plasma growth hormone level should rise at least 7 ng/mL. This test is sometimes combined with intravenous insulin.

Response to both arginine and L-dopa does not occur invariably. (Failure of the growth hormone levels to rise has been observed in over 25% of adults above the age of 50 years.)

IGF-I levels, if measured, may parallel the growth hormone levels. GHRF testing is not a sensitive method for elucidating growth hormone deficiency because of variable responses.

IV. GH. Response to growth hormone-releasing hormone if GH response to insulin induced hypoglycemia is blunted.
V. Plasma FSH and LH. Measurements before and after LHRH administration may be indicated.
VI. Visual acuity and visual field tests
VII. Radiologic studies, such as sellar tomography, cranial CT scan or MRI, and arteriography, depending on the circumstances
VIII. Patients with suspected hypothyroidism should have a TSH assay and thyroid antibody determinations
IX. Patients with Cushing's syndrome or disease show elevated 17-ketogenic steroids or 17-hydroxycorticoids on initial workup.

Further investigation should include urinary steroid excretions before and after the administration of dexamethasone, metyrapone, or ACTH (see the section Obesity). Plasma cortisol and ACTH may be useful.

X. Patients with chronic systemic disease may show abnormalities in the initial workup that are primarily related to the underlying disorder. Usually, bone maturation is delayed and plasma FSH and LH may be lower than expected for the chronologic age. Additional studies to elucidate the diagnosis are advisable.
XI. If the FSH and LH are elevated and the karyotype is XX, ovarian failure owing to autoimmune oophoritis may be suspected.

Subsequent Workup in Primary Amenorrhea without Delayed Growth

I. Patients with suspected hypogonadotropic hypogonadism should have workups similar to those performed on patients with hypopituitarism because other tropic hormones may be deficient either initially or at a later date. Those with anosmia have luteinizing hormone deficiency. Luteinizing releasing hormone administration in these individuals is followed by a rise in LH.
II. Patients with the testicular feminization syndrome have normal breast development together with abnormalities of the external genitalia, and usually normal excretion of testosterone, 17-ketogenic steroids, and 17-ketosteroids. Because the mode of inheritance is consistent with either an X-linked recessive or a sex-limited autosomal dominant trait, other members of the family should be studied.
III. The diagnosis of ambiguous sexual differentiation is suggested by abnormality of the external genitalia and pelvic examination findings. Karyotype should be determined. Intravenous pyelography, cystography, vaginography, and urethroscopy are indicated to further elucidate the renal and uterovaginal abnormalities commonly seen in true hermaphroditism or pseudohermaphroditism. Pelvic ultrasound and CT scan are helpful as screening studies.
IV. Patients with the common type of congenital adrenal hyperplasia (21-hydroxylase deficiency) rarely have amenorrhea because they are usually diagnosed at a much earlier age. The acquired form of the disease may occur without any associated abnormality of growth. The urinary excretion of pregnanetriol is elevated in these patients with increased excretion of 17-ketogenic steroids. Elevation of the plasma 17-hydroxyprogesterone level is confirmatory.
V. Congenital adrenal hyperplasia caused by 11-hydroxylase deficiency is a rare cause of amenorrhea. This syndrome is associated with excessive production of 11-desoxycorticosterone and ultimately with the development of hypertension. The external genitalia are abnormal. The urinary excretion of aldosterone and 17-hydroxycorticoids is reduced.
VI. Another variant of congenital adrenal hyperplasia, the 17-hydroxylase deficiency syndrome, is also associated with amenorrhea and hypertension. The external genitalia are underdeveloped. The urinary excretion of corticosterone and desoxycorticosterone is elevated, and that of aldosterone and 17-hydroxycorticoids is reduced.
VII. Pelvic exploration may be indicated in ambiguous sexual differentiation once congenital or acquired adrenal hyperplasia has been ruled out by appropriate testing.
VIII. If autoimmune oophoritis is suspected, antinuclear antibodies and antiovarian antibodies should be measured.

Secondary Amenorrhea

Patients with secondary amenorrhea may have an abrupt cessation of menses, or the amenorrhea may be preceded by a period of oligomenorrhea. Investigation is usually warranted after 4 to 6 menstrual periods have been missed. Pregnancy is an obvious cause and should be excluded before proceeding with further investigations.

Etiology

I. Polycystic ovary syndrome—probably the most common cause in patients in their teens or early twenties
II. Pituitary-hypothalamic disease
  A. Tumors
    1. Pituitary, nonsecretory
    2. Pituitary, secretory
      a. Acromegaly
      b. Prolactin-secreting
      c. Cushing's disease
    3. Suprasellar, parasellar and, rarely, intrasellar
  B. Hypopituitarism
    1. Idiopathic (Simmonds' disease)
    2. Infarction (Sheehan's syndrome)
  C. Infiltrative disease (e.g., sarcoidosis)
  D. Internal carotid aneurysm and other vascular anomalies
  E. Prolactin secretion in the absence of radiologic evidence of tumor (idiopathic and drug-induced)
  F. Postpubertal hypogonadotropic hypogonadism
  G. Cushing's disease
  H. Empty sella syndrome
III. Adrenal disease
  A. Cushing's syndrome
    1. Tumor
    2. Carcinoma
  B. Adrenal tumors with virilization
  C. Addison's disease
IV. Ovarian disease
  A. Ovarian failure
    1. Premature menopause (before the age of 40 years), usually idiopathic. It also may occur in polyendocrine autoimmune syndromes.
    2. Acquired anatomic lesions, including tumors, carcinoma, and infection
    3. Normal menopause
  B. Autoimmune oophoritis
V. Chronic systemic disease (e.g., kidney, liver, lung)
VI. Anorexia nervosa or bulimia, or both
VII. Drug-induced: contraceptives, spironolactone, chemotherapy
VIII. Intrauterine adhesions (Asherman's syndrome)
IX. Idiopathic, including exercise-induced
X. Radiation therapy

Symptoms

The symptoms in secondary amenorrhea are quite variable. The more common ones are listed in the following:

I. Amenorrhea, either abrupt in onset or preceded by a period of oligomenorrhea. Galactorrhea may or may not be present.
II. Changes in body weight
   A. Weight loss, which may be marked, occurs in anorexia nervosa, panhypopituitarism, Addison's disease, some tumors and carcinomas, and idiopathic amenorrhea.
   B. Weight gain may be noted in patients with polycystic ovaries, Cushing's syndrome or disease, adrenal and ovarian tumors, acromegaly, prolactin-secreting tumors, and idiopathic amenorrhea.
III. Weakness and fatigability, which are most prominent in Cushing's disease, panhypopituitarism, Addison's disease, ovarian and adrenal malignancies, and chronic systemic illness.
IV. A variety of specific or nonspecific symptoms related to the cause of the amenorrhea. Thus, symptoms of hypopituitarism, hyperadrenocorticism, adrenal insufficiency, or hypothyroidism may be reported by the patient.
V. Increase in body and facial hair noted by patients with polycystic ovaries
VI. Hot flushes in ovarian failure

Physical Findings
There are no physical signs that are specifically related to secondary amenorrhea. The findings, if any, are those of the primary disorder.

Diagnostic Approach
Clinical Features
I. Weight loss without skin changes suggests anorexia nervosa, acquired anatomic lesions, systemic disease, infiltrative hypothalamic lesions
II. Weight loss in a patient with a pale, thin, sallow, yellowish skin suggests possible hypopituitarism
III. Weight loss with hyperpigmentation and increased numbers of freckles and moles is commonly seen in Addison's disease.
IV. Weight gain, with or without skin changes, may be observed in acromegalic patients, many of whom have increased numbers of papillomata and moles as well as a slight increase in body hair.
V. Weight gain, in association with plethora, acne, and striae, is common in Cushing's syndrome or disease.
VI. Weight gain, in association with lactation, suggests a prolactin-secreting tumor and hypothyroidism.
VII. The association of obesity with mild hirsutism is often noted in patients with the polycystic ovary syndrome.
VIII. Hirsutism of mild to severe degree may accompany ovarian or adrenal disease.
IX. Patients with postpubertal hypogonadism and premature ovarian failure rarely demonstrate any significant change in body weight.
X. A history of excessive exercise may clarify the cause.

Initial Workup
The following preliminary studies are recommended in the workup of patients with secondary amenorrhea:

I. CBC and platelet count
II. Sedimentation rate
III. Chest and skull films
IV. Plasma FSH, LH, and prolactin, fasting growth hormone, IGF-I
V. Urinary 17-ketogenic steroids or 17-hydroxycorticoids, 17-ketosteroids, and creatinine
VI. TSH, free T_4, or thyroid profile
VII. Careful pelvic examination to establish the size of the uterus and ovaries and to detect the presence of infection or masses. (A single index of maturation is usually not helpful.)

Subsequent Workup
I. If the skull films are abnormal, additional studies, cranial CT scan or MRI, and arteriography may be indicated.
II. If acromegaly is suspected, appropriate bone radiographs should be performed. A glucose tolerance test, including simultaneous determinations of the glucose and growth hormone levels, should also be performed.
III. Pituitary function studies are indicated in the presence of lactation. If the prolactin level is elevated, a pituitary tumor may be suspected. When the prolactin level is 200 ng/mL or greater, a pituitary tumor is likely in the absence of drug therapy.
   Lower levels of prolactin may sometimes occur in the presence of a pituitary tumor and in primary hypothyroidism.
IV. Appropriate diagnostic studies are warranted whenever systemic disease is suspected.

Adrenocortical Hyperfunction

Janet E. Schemmel

Excessive production of adrenocortical hormones produces distinctive clinical syndromes. The recognized syndromes include Cushing's syndrome, caused by hypercortisolemia; virilization of women and children, related to excessive secretion of 17-ketosteroids or testosterone or both; feminization of men or children, owing to the overproduction of estrogen; and hypertension with hypokalemia, which results from increased secretion of aldosterone. Aldosteronism is discussed in the section Arterial Hypertension (Chapter 3). The virilization and feminization syndromes are beyond the scope of this text. This section will be confined to a discussion of the syndrome of glucocorticoid excess.

Cushing's Syndrome

Etiology
I. ACTH-dependent hyperadrenocorticism (70% of cases)
   A. Cushing's disease. This condition is most probably owing to hypothalamic dysfunction. Excessive secretion of pituitary ACTH leads to adrenocortical hyperplasia and hypercortisolemia. Pituitary tumors are responsible for most cases.
   B. Nonpituitary tumors (the ectopic ACTH syndrome). ACTH is secreted and leads to adrenocortical hyperplasia and hypercortisolemia. The most common causes are oat cell carcinoma of the lung, pancreatic carcinoma, thymoma, and bronchial adenoma and carcinoid. Other tumors may also cause this syndrome.
II. ACTH-independent hyperadrenocorticism
   A. Iatrogenic. This is the most common cause of Cushing's syndrome. It is the result of the prolonged and often excessive administration of cortisol, cortisone, or their derivatives.
   B. Adrenal adenomas. There is autonomous secretion of excessive quantities of cortisol with suppression of ACTH production.
   C. Adrenal carcinoma. Autonomous hypersecretion of cortisol and other steroids occurs. ACTH secretion is suppressed.
   D. Primary pigmented nodular adrenal dysplasia (PPNAD) Micronodular adrenal disease. This is a disease of the young. It may be sporadic or familial.
   E. Macronodular adrenal hyperplasia
   F. Other syndromes (e.g., Carney complex, McCune–Albright syndrome)

Clinical Manifestations
Most of the more common clinical features are listed in the following:

I. Truncal obesity
II. Moon facies

III. Plethora
IV. Increased fragility of the skin with ecchymoses and striae
V. Muscle atrophy
VI. Easy fatigability and weakness
VII. Mild acne
VIII. Hirsutism (virilization suggests adrenal carcinoma)
IX. Amenorrhea
X. Nephrolithiasis
XI. Hypertension
XII. Leukocytosis with lymphopenia and eosinopenia; erythrocytosis
XIII. Glucose intolerance
XIV. Osteoporosis

Patients with the ectopic ACTH syndrome ordinarily have few of the manifestations outlined in the preceding. Weight loss rather than weight gain is the rule. Weakness, fatigability, and muscle atrophy are usually profound. Anemia and hypokalemia occur commonly. Cutaneous pigmentation is often pronounced.

Diagnosis

Confirmation of the clinical diagnosis of Cushing's syndrome is based on the following criteria:

I. Increased urinary excretion of free cortisol or its metabolites, measured as 17-hydroxycorticosteroids (17-OHS) or 17-ketogenic steroids (17-KGS), or both. Urinary free cortisol levels of 250 g/day is diagnostic of Cushing's syndrome.
II. Loss of the normal diurnal variation in plasma cortisol levels; both the AM and PM values are usually elevated. Sampling between 6 AM and 8 AM and 10 PM and 12 AM is recommended.
III. Failure of cortisol secretion to be suppressed by low-dose dexamethasone testing

Etiologic Diagnosis of Cushing's Syndrome

Once the diagnosis of Cushing's syndrome is established, its etiology must be determined. For this purpose, a variety of laboratory tests and diagnostic procedures are employed (Table 9-1).

I. Iatrogenic hyperadrenocorticism is usually evidenced by a history of prolonged, excessive administration of corticosteroids.
II. Measurement of plasma ACTH levels may distinguish between the ectopic ACTH syndrome, in which the levels are usually high, and adrenocortical tumors, in which the levels are low. The ACTH levels may be normal or increased in Cushing's disease.
III. Cortisol levels not only show a loss of the normal diurnal variation but are elevated as well.
IV. Corticotropin-releasing hormone (CRH) dexamethasone suppression test. After 48 hours of low-dose dexamethasone, CRH is infused and plasma cortisol is measured 15 minutes thereafter. A cortisol level greater than 1.4 ug/dL confirms Cushing's syndrome.
V. Low- and high-dose dexamethasone suppression tests are valuable aids to diagnosis.
   A. In normal and obese individuals, cortisol levels are suppressed with low dosage of dexamethasone.
   B. High-dose testing ordinarily suppresses cortisol levels in patients with Cushing's disease.
   C. Cortisol levels usually are not suppressed with high dosage of dexamethasone in patients with the ectopic ACTH syndrome or adrenocortical adenoma and carcinoma.
VI. Metyrapone testing is useful in differentiating adrenal tumors from adrenal hyperplasia. The response to metyrapone is impaired in adrenal tumors but is normal in adrenal hyperplasia.

Table 9-1. Etiologic diagnosis of Cushing's syndrome by evaluation of pituitary-advanced function

Test	Normal	Cushing's disease			Adrenal adenoma	Adrenal carcinoma	Iatrogenic
		Hypothalamic	Pituitary tumor	Ectopic ACTH syndrome			
Plasma Cortisol level	N		I	I	I	I	Variable; depends on method and steroid used
Diurnal Cortisol	Higher in AM than PM		None	None	None	None	Not applicable
Plasma ACTH	N	N or I	N or I	N or I[a]	D	D	D
Urinary excretion control	N		I	I	I	I	Variable; depends on steriod used
17-OSH, 17-KGS, free cortisol 17-KS	N		I	I	L	Usually markedly I	Variable; depends on steroid used; usually D
Response to high-dose dexamethasone	S		S	NS	Usually NS	NS	S
Response to metyrapone	N		N to IR	D to NR	NR	NR	NR
Response to ACTH stimulation	N		N to IR	N to slightly IR	D	Usually NR	Variable or slightly IR

[a] Inferior petrosal sampling of ACTH, if available, differentiates ectopic ACTH syndrome from pituitary tumor.
D, decreased; I, increased; IR, increased response; L, low; N, normal; NR, no response; NS, no suppression; S, suppression.

VII. Exogenous ACTH stimulation may cause an exaggerated response in adrenal hyperplasia, a variable response in adrenal adenomas, and no response in adrenal carcinoma.

Diagnostic Approach
A gamut of procedures is available for the investigation of Cushing's syndrome. Not all of the tests are indicated in every case. Selectivity in the choice of diagnostic procedures depends on the circumstances and the judgment of the physician. Repetition of some tests is often necessary.

I. As a first step, it is necessary to confirm the clinical diagnosis by the laboratory tests outlined in the preceding section, Diagnosis.
II. Once the diagnosis is confirmed, the cause can usually be ascertained by use of the following tests, as dictated by the circumstances (Table 9-1).
   A. Plasma cortisol and ACTH levels
   B. Response to suppression by dexamethasone testing
III. Routine studies are advisable to evaluate the systemic effects of hypercortisolemia.
   A. CBC and platelet count
   B. Urinalysis
   C. Biochemical screening
   D. Serum electrolytes
   E. Random postprandial glucose determinations
   F. Radiologic studies
      1. Chest radiographs
      2. Lumbar spine and other films may be indicated, particularly if osteoporosis is suspected.
   F. Electrocardiogram
IV. Special procedures if a pituitary tumor is suspected
   A. Pituitary MRI
   B. Visual fields may be indicated.
V. CT scan of the adrenals is indicated if an adrenal cause of Cushing's syndrome has been demonstrated from biochemical studies. If the CT is negative, a thorough search for an ectopic source of ACTH should be made, including CT or MRI (or both) of the chest. Adrenal adenomas are usually 3 cm or less in diameter; carcinomas are usually larger than 6 cm.
VI. Corticotropin-releasing factor (CRF) administration. Patients with primary ACTH secreting adenomas usually respond to intravenous CRH with an increase in ACTH levels. Patients with an ectopic ACTH source usually do not respond to CRH administration.
VII. Inferior petrosal sinus sampling. Although this technique is not widely available, petrosal sinus and peripheral measurement of ACTH before and after administration of CRF clarifies the diagnosis of pituitary as opposed to ectopic ACTH syndrome. Further, this study frequently can localize the pituitary tumor to the right or left side of the pituitary gland, which is especially useful because the MRI is often normal. Petrosal sinus sampling should be carried out only after establishing the diagnosis of ACTH-dependent Cushing's syndrome.

Adrenocortical Hypofunction (Insufficiency)

Janet E. Schemmel

Definition and Etiology
Adrenocortical insufficiency is a symptom complex that results from deficiency of adrenocortical hormones. It may be primary, as in Addison's disease, or secondary, as in hypopituitarism. The onset may be acute or insidious.

I. Primary adrenocortical insufficiency. The term *Addison's disease* refers to primary adrenocortical insufficiency. The course of the disease may be chronic or acute, or an acute phase may be superimposed on a chronic state. Primary atrophy (idiopathic adrenal insufficiency), tuberculosis, and fungal infections are common causes. Adrenal hemorrhage (owing to anticoagulants or idiopathic in origin), AIDS, surgical removal of the adrenal glands, drugs (e.g., OP-DDD, amino-glutethimide), medication (e.g., ketoconazole), congenital adrenal hyperplasia, and metastatic carcinoma may also produce primary adrenocortical insufficiency. In present-day medical practice, adrenal suppression from prolonged steroid therapy is probably the most commonly diagnosed cause.

   Idiopathic adrenal insufficiency (Addison's disease) may be associated with a multiplicity of other diseases, including diabetes mellitus, Hashimoto's thyroiditis, thyrotoxicosis (Graves' disease), mucocutaneous candidiasis, hypoparathyroidism, primary ovarian failure, and pernicious anemia. An autoimmune mechanism has been postulated. Polyglandular autoimmune syndromes, Type I and Type II (PGA I and PGA II, respectively), are associated with adrenal insufficiency and may be familial.
II. Secondary adrenocortical insufficiency. Adrenocortical insufficiency may also be secondary to hypopituitarism from pituitary or hypothalamic disease. Destruction of pituitary or hypothalamic tissue may be caused by infarction, granulomatous disease (e.g., sarcoidosis, tuberculosis), chromophobe adenoma, suprasellar meningioma, craniopharyngioma, or aneurysm.

Symptoms
The onset of adrenocortical insufficiency is usually insidious but it can be acute. The spectrum of symptoms in both primary and secondary adrenocortical insufficiency is variable. The following symptoms may be described by the patient: (a) asthenia, weakness, and lethargy; (b) weight loss; (c) easy fatigability, especially in the afternoon; (d) dizziness and syncope; (e) anorexia, nausea, vomiting, and diarrhea; (f) nervousness, irritability, and apathy; and (g) nonspecific complaints such as myalgias, loss of libido, or heat and cold intolerance.

Primary Adrenocortical Insufficiency
Any of the aforementioned symptoms can occur in primary adrenal disease, but chronic weakness, fatigue, weight loss, and GI symptoms are the most frequent complaints. Changes in the color of the skin or increased numbers of moles and freckles are sometimes noted by the patient or his or her friends. Salt craving and increased salt intake are also common symptoms.

Other conditions may be associated if the patient has PGA I or PGA II. PGA I patients may have mucocutaneous candidiasis and those with PGA II, autoimmune thyroid disease and diabetes mellitus. Further discussion is beyond the scope of this text.

Secondary Adrenocortical Insufficiency
In addition to many of the symptoms noted in the preceding, patients with hypopituitarism may have local symptoms related to its underlying cause and systemic symptoms resulting from specific tropic hormone deficiencies, as follows: (a) impairment of vision or visual field defects; (b) headaches (frontal, vertical, temporoparietal, or varying combinations of these locations); (c) failure to tan after exposure to sunlight; (d) mental confusion and somnolence; (e) loss of libido, amenorrhea, or impotence; (f) loss of body hair and decreased beard growth; (g) growth failure in children; and (h) polydipsia and polyuria. Salt craving does not occur.

Acute Adrenocortical Insufficiency
Adrenal crisis is characterized by headaches, malaise, restlessness, vomiting, abdominal pain, hyperpyrexia, and shock, which may progress to coma and death. Acute adrenal insufficiency may occur under the following circumstances: (a) failure of the patient with adrenocortical insufficiency to take the prescribed replacement therapy; (b) following acute illness, stress, anesthesia, or surgery in patients with decreased adrenocortical reserve; (c) failure to increase the dosage of steroids in patients with Addison's disease complicated by acute disease or other stressful situations; (d) abrupt withdrawal of adrenocortical hormones in steroid-treated individuals; (e) following

injury to the adrenals by trauma, thrombosis, or hemorrhage; (f) after bilateral adrenalectomy; and (g) overwhelming sepsis, with or without hemorrhagic phenomena.

Physical Findings

Primary Adrenocortical Insufficiency

The physical findings may be normal, but patients with symptoms of weakness, lethargy, and weight loss usually exhibit changes in the pigmentation of the skin. Sometimes this is the only abnormality detectable on examination. The skin changes observed include hyperpigmentation or tanning of both the exposed and unexposed parts of the body (especially prominent over pressure areas), increased numbers of freckles, and sometimes vitiligo. Brownish blue discoloration of the lips and gums and other mucous membranes may be present. The blood pressure may be normal, although postural hypotension is more common. The heart size is often reduced. Manifestations of PGA I or II may be present.

Secondary Adrenocortical Insufficiency

The physical findings may be normal, although the examination may provide evidence suggestive not only of adrenocortical insufficiency but also of hypothyroidism and hypogonadism. Changes in visual acuity or visual field defects may be demonstrable. In the preadolescent age group, growth failure and delayed puberty are frequent findings. The skin of the exposed portions of the body may be pale.

Diagnostic Approach

Primary Adrenocortical Insufficiency

I. A simple procedure called the rapid ACTH test or Cortrosyn (tetracosactin) test is useful for initial screening. The plasma cortisol level is determined from a blood sample drawn between 7 AM and 9 AM. Cortrosyn (0.25 mg) is then injected intramuscularly. Plasma cortisol levels are then obtained 30 and 45 minutes after the injection. In normal subjects, plasma cortisol levels rise by at least 7 g/100 mL in 30 minutes or the total value exceeds 18 g/100 mL. Usually there is at least a twofold rise above the control value to 20 g/100 mL or above. The plasma cortisol value at 45 minutes should approximate that in the 30-minute sample. A normal response excludes primary adrenocortical failure.

II. If the Cortrosyn test elicits an abnormal response, additional tests may be performed.
   A. CBC and urinalysis
   B. Biochemical profile or screen
   C. Skin tests for tuberculosis and fungal diseases
   D. Chest films, which may show a small heart
   E. A KUB film to demonstrate adrenal calcification, which suggests tuberculosis or fungal disease. Idiopathic adrenal insufficiency is associated with small adrenal glands on CT scanning of the adrenals. Enlarged glands are consistent with metastatic or granulomatous disease.
   F. Skull films to exclude pituitary lesions
   G. Antithyroglobulin antibodies, which if present suggest an autoimmune basis for the adrenal disease.
   H. TSH and free T_4
   I. Adrenal antibodies

III. The most specific and sensitive test for adrenocortical insufficiency is the intravenous ACTH test. On the day before the test, a 24-hour urine collection is made, and the quantities of 17-ketogenic steroids or 17-hydroxycorticoids and creatinine excreted are determined. Subsequently, on 3 consecutive days, 25 units of ACTH in 1000 mL of 5% dextrose in normal saline or 0.45 normal saline are infused intravenously over a period of exactly 8 hours. Daily 24-hour urine specimens are collected for 17-ketogenic steroids or 17-hydroxycorticoids and creatinine. A rise in steroid excretion of less than 100% of the control value is diagnostic of adrenocortical insufficiency. Normally, a threefold or greater excretion occurs on the first day of the test, with a further increase on the second day and maximum excretion on the third day. The urinary creatinine determinations are made to check on the reliability of the urine collections.

An equally specific and shorter test for adrenocortical insufficiency is the 48-hour ACTH test. Cortrosyn in a dose of 0.5 mg dissolved in glucose and water is infused every 12 hours for a continuous 48-hour period, during which time urines are collected for 17-ketogenic steroids or 17-hydroxysteroids and creatinine, as in the 3-day ACTH test. Normally there is at least a twofold increase in the baseline values following the 2-day infusion. Depot Cortrosyn is not yet available.

IV. If PGA I or II is suspected, additional studies may be necessary. HLA typing may be indicated.

V. ACTH levels are markedly elevated.

VI. Plasma renin levels are considerably elevated and aldosterone levels are usually markedly decreased, if aldosterone deficiency coexists with hydrocortisone deficiency.

VII. CT of the adrenals if adrenal hemorrhage is suspected

Secondary Adrenocortical Insufficiency

I. Patients with secondary adrenocortical insufficiency generally require a more extensive workup than those with primary disease, not only for the purpose of determining the cause but also to ascertain which tropic hormones are deficient.

II. The tests listed in the following are recommended for this type of comprehensive survey.
   A. CBC and urinalysis
   B. Biochemical profile or screen
   C. Skull films
   D. Chest films
   E. Visual acuity, including visual fields, if appropriate
   F. TSH and free T_4
   G. TSH by RIA. If the TSH is low, TRH infusion with measurement of TSH both before and after the infusion may be carried out to detect pituitary or hypothalamic dysfunction.
   H. Fasting serum growth hormone and prolactin determination.
   I. Inslin tolerance test with growth hormone determinations may be indicated. The L-dopa or arginine infusion test may be substituted in selected cases.
   J. Plasma FSH, LH, testosterone, and plasma estradiol in selected cases. LHRF (luteinizing hormone releasing factor) can facilitate the investigation of patients with low FSH and LH values. A 100-μg bolus of synthetic LHRF is given intravenously with blood samples collected before, and at 20 and 60 minutes after the injection. Normally, there is at least a threefold rise in FSH and LH above the baseline levels. If the 20-minute or 60-minute values for both FSH and LH are above normal, the response is regarded as exaggerated. When the 60-minute levels are the same as or greater than those found at the 20-minute interval, the response is considered to be delayed. A delayed response in the FSH level is seen in most normal women. The LHRF infusion test can also be performed with blood samples taken 20 and 30 minutes after the injection.
   K. Metyrapone test. This test is carried out by collecting 24-hour urine specimens for 17-ketogenic steroids or 17-hydroxycorticoids and creatinine on the day before and the day following the administration of metyrapone. The drug is given orally in a dosage of 750 mg every 4 hours for six doses. A normal response is characterized by an increase of 2.8 times or greater in steroid excretion on the day after the test compared to the control value.

   The metyrapone test can also be carried out as an overnight procedure. Plasma cortisol, 11-deoxycortisol, or ACTH levels (or all three) are measured at 8:00 A.M. on the day before the test. At midnight, 2 g of metyrapone is administered. At 8:00 A.M. the following morning, plasma cortisol, 11-deoxycortisol, or ACTH levels (or all three) are determined. A normal response is a rise in the 11-deoxycortisol level above 10 μg/100 ml.

L. Plasma ACTH; CRH infusion if act H is low.
M. Vasopressin assay. The determination is best made after a period of water deprivation. Vasopressin acts on the pituitary gland as a corticotropin-releasing hormone. Measurement of plasma cortisol levels following the administration of vasopressin has been used to differentiate between pituitary and hypothalamic disease. This test has not achieved wide popularity at present.

III. MRI of the pituitary gland and hypothalmic area is indicated.
IV. If surgical intervention is necessary before the appropriate laboratory studies can be completed blood samples should be drawn for the following tests: CBC; urinalysis; electrolytes; BUN; creatinine: free T_3 and TSH; plasma cortisol; fasting growth hormone; plasma FSH and LH; ACTH; prolactin; testosterone and IGF-I.

Obesity

Janet E. Schemmel

Definition

Obesity may be defined as an excess quantity of body fat. The diagnosis of obesity is usually based on statistics given in life insurance tables. A patient is considered overweight if his or her weight is 20 pounds greater than the norm established for his or her age, sex, height, and body build. However, the tables should be considered only as an approximate clinical guide. More precisely, obesity may be defined by a body mass index of more than 30 (weight in kg divided by height in square meters). This value correlates well with skin fold measurements greater than 30 mm in women and 23 mm in men. Fat normally constitutes 15% to 20% of the total body weight. The degree and interpretation of obesity relate to cultural values.

Etiology

Obesity is most commonly caused by overeating, but it may be associated with the conditions listed in the following. Although this list is not all-inclusive, it encompasses the more common and several unusual syndromes reported.

I. Diabetes
II. Pregnancy
III. Use of contraceptives
IV. Genetic influences
V. Hypothalamic injuries or abnormalities (e.g., Prader–Willi syndrome)
VI. Hyperlipemic states
VII. Miscellaneous diseases
  A. Cushing's syndrome or disease
  B. Acromegaly
  C. Islet cell tumor
  D. Hypothyroidism
  E. Polycystic ovary syndrome
  F. Laurence–Moon–Biedl syndrome—obesity, hypogonadism, polydactylism
  G. Pseudohypoparathyroidism—hypocalcemia, obesity, bone abnormalities
  H. Babinski–Fröhlich syndrome—hyperphagia and hypogonadism owing to hypothalamic lesions
  I. Abnormal thermogenesis (causal relationship not well established)

Symptoms

Most obese patients are otherwise asymptomatic. When obesity is marked, easy fatigability, exertional dyspnea, depression, anxiety, and somnolence are likely to occur. Many of the symptoms attributed to obesity actually result from an underlying or associated disorder rather than from the obesity itself. The more common symptoms encountered in obese individuals are listed in the following:

I. Easy fatigability
II. Depression with anxiety
III. Malaise
IV. Weakness, hunger, fatigue, and dyspepsia—common in pregnancy
V. Symptoms of reactive hypoglycemia—weakness, hunger, palpitation, and sweating—often seen in obese adult-onset diabetics about 3 to 5 hours after meals
VI. Excessive hunger—not uncommon in patients with adult-onset diabetes mellitus, islet cell tumors, the Babinski–Fröhlich syndrome, pregnant women, women taking oral contraceptives, and hypothalamic disorders
VII. Excessive weight gain in spite of a normal or reduced caloric intake, frequent in Cushing's disease or syndrome
VIII. Weight gain not caused by overeating, often in association with loss of libido, headaches, increased hair growth, and enlargement of the hands and feet—common in acromegaly
IX. Muscle cramps, numbness of the hands, feet, and face, seizures, and obesity—suggestive of pseudohypoparathyroidism

Signs

Some physical findings are produced by obesity per se, but most of the signs encountered in obese individuals are primarily related to the underlying disease.

I. Obesity that is generalized in distribution is typical of exogenous obesity. However, truncal accentuation (presumably genetic) is frequently observed.
II. Pink striae are commonly distributed over the axillae, breasts, abdomen, flanks, thighs, and buttocks, particularly in young women if the weight gain has been rapid. Usually, the pink color tends to fade and eventually disappear, leaving the striae shiny and white.
III. The blood pressure is usually normal, unless systemic hypertension owing to another cause coexists or the blood pressure cuff is ill-fitting.
IV. Intertrigo is quite common in the folds below the breasts and in the inguinal regions.
V. Ankle edema is occasionally noted.
VI. Plethora involving the cheeks and neck is not unusual.
VII. When obesity is massive, tachypnea may be evident.
VIII. The presence of a thyroidectomy scar, typical changes in the skin, and a delayed return of deep tendon reflexes suggest hypothyroidism.
IX. Purpura, moon facies, truncal obesity, plethora, and weakness are common in Cushing's syndrome or disease.
X. Xanthomata, xanthelasma, and arcus senilis suggest hyperlipoproteinemic abnormalities.
XI. Brachydactylia, a round facies, a stocky build, and tetany are found in patients with pseudohypoparathyroidism.
XII. Excessive growth of the hands, feet, and jaw are typical of acromegaly.
XIII. Hypogonadism may occur in the hypothalamic obesity syndromes.
XIV. Hirsutism may occur in the polycystic ovary syndrome and in acromegaly.

Diagnostic Approach

Initial Evaluation

I. CBC and platelet count
II. Urinalysis
III. Glucose tolerance testing
  A. Several normal 2-hour postprandial glucose level tests may be adequate in most cases to exclude diabetes mellitus.
  B. A 5-hour glucose tolerance test may be indicated in patients with symptoms of reactive hypoglycemia to document the hypoglycemia.
IV. Fasting triglycerides
V. Thyroid function tests (TSH, free T_4 or T_4 and $_{T3}$ RIA)
VI. Biochemical profile or screen

VII. Serum uric acid, primarily to obtain a baseline value, because hyperuricemia often occurs with restricted caloric intake and after weight loss
VIII. Chest films
IX. Electrocardiogram
X. Psychiatric consultation is especially valuable in planning treatment and estimating prognosis in patients with serious weight problems.

As a rule, the aforementioned laboratory tests are normal in patients with exogenous obesity who have not been on diuretic therapy or on a dietary regimen. However, serum triglyceride levels frequently are elevated, particularly when obesity is marked.

Subsequent Evaluation
Additional workup, as follows, is indicated in patients in whom the symptoms, signs, or initial laboratory studies suggest the possibility of an associated disorder or systemic disease.

I. Fasting total lipids and lipoprotein electrophoresis when the serum triglyceride or cholesterol levels are markedly elevated, or if the glucose levels are abnormal.
II. Pulmonary function studies and arterial blood gases, if somnolence or exertional dyspnea is present. Sleep study may be necessary.
III. Thyroid antibodies, when thyroid dysfunction is suspected
IV. Random IGF II measurement if acromegaly is suspected
V. Growth hormone measured in association with a glucose tolerance test, if acromegaly is being considered. Growth hormone levels are measured while fasting, and at 1- and 2-hour intervals after glucose administration.
VI. Cranial MRI, CT, and arteriography when acromegaly, Cushing's disease, or infiltrative pituitary-hypothalamic disease is suspected
VII. Fasting insulin and fasting blood sugar determinations. Both of these parameters should be measured serially during a 72-hour fast if hyperinsulinism is suspected. Insulin levels may also be helpful in the evaluation of patients who exhibit symptoms of reactive hypoglycemia during glucose tolerance tests.
VIII. If truncal adiposity, weakness, plethora, and other symptoms or signs suggest concomitant Cushing's disease or syndrome, an overnight dexamethasone suppression test should be performed in the following manner. A plasma cortisol level is obtained in a blood sample drawn at 8 AM on the day of the test. Dexamethasone (1.0 mg) is given at midnight. The plasma cortisol level is determined on a sample drawn at 8 AM the next morning. Normally, the administration of dexamethasone causes a reduction in the plasma cortisol level to 5 to 7 g/100 mL or less. If the plasma cortisol level is not suppressed by this maneuver or if Cushing's disease or syndrome is suspected, further evaluation of adrenal function is necessary. The following procedure is recommended: Daily 24-hour urine specimens for 17-ketogenic steroids and creatinine are collected before and during the test period. After an adequate collection of baseline urine (two specimens) has been obtained, dexamethasone is given orally (0.5 mg every 6 hours for a 2- to 3-day period, followed by 2.0 mg every 6 hours for an additional 2- to 3-day period). Normally, steroid excretion is reduced to at least 50% of the control values by the second day of dexamethasone administration. In patients with adrenocortical hyperplasia, suppression of steroid excretion is ordinarily apparent by the fourth to sixth day of dexamethasone therapy. Steroid excretion is usually not suppressed in patients with neoplasms of the adrenal cortex. When the test results are equivocal, the study can be repeated. The metyrapone and ACTH stimulation tests are important adjuncts that are helpful in differentiating between adrenal hyperplasia, tumor, and carcinoma. ACTH assay should be carried out. The specimens may be collected before and after dexamethasone suppression and may give helpful adjunctive information. Urinary free cortisol measurements may be substituted for 17-ketogenic steroid determinations.
IX. Measurement of testosterone, androstenedione and dehydroandrostenedione, and plasma FSH and LH may be helpful in those cases in which the polycystic ovary syndrome is suspected. Pelvic ultrasound and CT scanning may be indicated.

X. In the future, lepton measurements may be helpful in the elucidation of causes of obesity.

Thyroid Enlargement

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Definition
Enlargement of the thyroid gland is referred to as goiter. A goiter may be congenital or acquired, endemic or sporadic. Throughout the world, regions exist in which goiter is endemic. In such areas, the incidence of thyrotoxicosis, thyroiditis, and thyroid malignancy is increased. Malignancy of the thyroid gland occurs frequently in individuals who have received radiation therapy to the head, neck, or face during infancy and childhood.

Etiology
Enlargement of the thyroid gland may be owing to many causes. Various classifications of goiter, based on the palpatory findings, the histologic examination, the state of thyroid function, or the results of laboratory tests, have been proposed. The more common causes of goiter are as follows:

I. Diffuse goiter
  A. Euthyroid
    1. Endemic or sporadic diffuse goiter; colloid goiter
    2. Drug-induced goiter
    3. Abnormality of hormone synthesis
    4. Thyroiditis
      a. Acute
      b. Subacute
      c. Chronic
      d. Hashimoto's struma
      e. Postpartum thyroiditis; silent thyroiditis
  B. Hypothyroid
    1. Cretinism
    2. Juvenile hypothyroidism
    3. Thyroiditis and Hashimoto's struma
    4. Drug-induced goiter
    5. Abnormality of hormone synthesis
  C. Hyperthyroid
    1. Graves' disease
    2. Subacute thyroiditis
II. Multinodular goiter: endemic or sporadic
  A. Nontoxic
  B. Toxic
III. Solitary nodular goiter
  A. Nontoxic
    1. Benign
    2. Malignant
  B. Toxic

Symptoms
I. Many patients with goiters are asymptomatic. The mass in the neck may be the presenting complaint, having been discovered by the patient or brought to his attention by a relative or friend. At other times, the goiter is found by a physician during the course of a routine physical examination.
II. Absence of symptoms is common in patients with endemic or sporadic goiter, drug-induced goiter, multinodular goiter, solitary nodular goiter, early hyperthyroidism, and Hashimoto's struma.

III. The presence or absence of systemic symptoms may provide a clue to the state of thyroid function or the presence of coexisting disease.
IV. Fatigue, lethargy, a 10- to 20-pound weight gain, intolerance to cold, dry skin, myalgia, and arthralgia suggest hypothyroidism. This may be the result of inadequate or abnormal thyroid hormone synthesis, thyroiditis, multinodular goiter, or drug-induced goiter.
V. Weakness, weight loss, heat intolerance, palpitation, and exophthalmos suggest hyperthyroidism.
VI. Pain in the thyroid during deglutition, or radiation of pain to the ear or jaw, may be indicative of subacute thyroiditis, cancer, or hemorrhage or other degenerative changes in an adenoma or cyst.
VII. Dyspnea may occur when large thyroids encroach on the trachea or bronchus.
VIII. Dysphagia suggests esophageal obstruction owing to chronic thyroiditis or carcinoma but may occur whenever the gland is massively enlarged.
IX. Symptoms of systemic illness, such as rheumatoid arthritis or nontuberculous Addison's disease, should raise the possibility of associated Hashimoto's struma.
X. Growth retardation in infants and children is common in hypothyroidism. Precocious puberty may also occur infrequently.
XI. A history of x-ray therapy to the thymus, pharynx, or face during infancy or childhood should suggest the possibility of thyroid carcinoma or multiple nodularity.

Signs

I. The findings on general examination depend largely on the status of thyroid function. Every patient with a goiter should be examined for clinical evidence of hyperthyroidism or hypothyroidism. If the patient is euthyroid, the findings are usually limited to the neck area.
II. A diffusely and symmetrically enlarged thyroid that is smooth or lobulated is found in neonatal and childhood goiters, endemic or sporadic goiters, thyroiditis, and Graves' disease. The gland is usually soft in colloid goiter and firm in hyperthyroidism. In Hashimoto's thyroiditis, the gland tends to be firm and lumpy. Stony hard glands are usually indicative of malignancy or Riedel's struma. The presence of a vascular thrill or bruit over the thyroid gland suggests hyperthyroidism.
III. Multinodular enlargement of the thyroid gland may be observed in toxic or nontoxic endemic or sporadic goiters and, occasionally, in carcinoma or chronic thyroiditis.
IV. The occurrence of a solitary nodular goiter suggests toxic or nontoxic adenoma, carcinoma, or a cyst.
V. The presence of cervical lymphadenopathy suggests carcinoma but may occur in thyroiditis.
VI. Evidence of tracheal or esophageal obstruction, or both, may occur in carcinoma, retrosternal goiter, or Hashimoto's struma, or whenever the gland is massively enlarged.
VII. Fixation of the gland is typical of carcinoma but occurs occasionally in thyroiditis.
VIII. Hoarseness owing to compression of the recurrent laryngeal nerve suggests a malignant neoplasm of the thyroid, although hoarseness may occur in Hashimoto's struma.

Diagnostic Approach

Clinical Features

I. The duration of a goiter, the age, sex, and geographic origin of the patient, the family history, evidence of previous irradiation to the pharynx, thymus, or face, or prior exposure to goitrogenic agents may provide important clues to the cause of thyroid enlargement.
II. The nodularity of the thyroid gland is of diagnostic significance. Multinodular goiters are most often nontoxic and are rarely malignant. Solitary nodular goiters occur much more frequently in women than men, but the incidence of carcinoma is higher in men than women and is greatest below the age of 40 years. Functioning nodules are more likely to be benign than are nonfunctioning nodules. Solitary nodules may be toxic or nontoxic. Nodularity of the thyroid gland in a patient of either sex with a history of head or neck irradiation is suggestive of carcinoma.
III. When signs of hyperthyroidism are present, the thyroid gland is usually diffusely enlarged, although it is sometimes nodular or lobulated. Hyperthyroidism rarely coexists with malignancy.

Laboratory Studies

I. CBC and platelet count. Leukopenia and a relative lymphocytosis are common in thyrotoxicosis.
II. Thyroid function tests. A number of accurate thyroid tests are available. Commonly, the so-called thyroid profile includes a T_4, a T_3 uptake, and a sensitive TSH.
   A. Recommended principal screening tests for thyroid disease should include a sensitive TSH and a free T4.
      1. An elevated TSH and a decreased free T_4 confirm primary hypothyroidism.
      2. A suppressed TSH to 0.1 mIU/mL and an increased free T_4 confirm the diagnosis of hyperthyroidism.
   B. Other tests may be indicated to clarify a variety of clinical disorders.
      1. T_3 by RIA in certain cases of suspected hyperthyroidism
      2. Thyrotropin (TRH) test. If secondary hypothyroidism is suspected because of a low TSH in conjunction with a normal or low T_4, TRH can be injected intravenously. TSH is measured before and 30 and 60 minutes after the administration of TRH. A threefold rise is expected. If no increase occurs, a pituitary or hypothalamic cause of hypothyroidism is suspected.
      3. Screening of sick hospitalized patients requires careful scrutiny of the thyroid tests. The free T_4 may be the most reliable test. Serial tests of TSH and free T_4 may be indicated.
III. Thyroid antibodies. Increased serum levels of antithyroglobulin antibodies and antimicrosomal antibodies may occur in Hashimoto's thyroiditis, as well as in simple goiter, thyrotoxicosis, and malignancy. Usually, the incidence of positive tests and the antibody titer are higher in Hashimoto's struma than in the other conditions. Positive tests may be considered specific for Hashimoto's struma in the appropriate patient.
IV. Ultrasonography is useful in differentiating between thyroid cysts and solid nodules and in delineating the size of the thyroid gland.
V. Thyroxin-binding globulin determination may be indicated when thyroid function tests do not correlate with the clinical picture, when hepatitis or nephrosis is present, when there is an uncertain history of previous drug therapy (e.g., diphenylhydantoin, estrogens), or if the diagnosis of primary thyroxin-binding globulin deficiency is suspected.
VI. RAI uptake. This test is usually carried out at 2 or 6 and 24 hours after the administration of ^{123}I or ^{131}I. An abnormally low level may occur in hypothyroidism, iodine contamination, and acute and subacute thyroiditis. An elevated value may be seen in iodine deficiency, certain types of thyroid hormone synthesis abnormalities, hyperthyroidism (both diffuse and nodular types), and Hashimoto's struma. It may be normal in thyroiditis, multinodular goiter, toxic nodular goiter, and T_3 thyrotoxicosis.
VII. Thyroid scan with ^{123}I is usually not necessary in the hyperthyroid patient with diffuse thyroid enlargement and exophthalmos. However, a scan may be helpful in differentiating between toxic and nontoxic nodular goiter. It is particularly valuable when the iodine uptake is within the normal range. Under such circumstances, the demonstration of a single area of intense uptake is significant. In the case of nontoxic solitary nodules, radioisotope scanning may be helpful in management of the patient. Thyroid scanning is recommended for all patients who have had x-ray therapy to the head and neck during infancy and childhood.

VIII. Needle aspiration of the thyroid gland with cytologic studies is indicated to differentiate among thyroiditis, carcinoma, and colloid goiter. Conventional surgical biopsy is also employed for diagnostic purposes in selected cases.
IX. An elevated T_3 by RIA confirms the diagnosis of T_3 thyrotoxicosis in a patient with symptoms of hyperthyroidism and a normal free T_4.

Further Investigations

I. Serum calcium and phosphorus levels are occasionally abnormal in both hyperthyroidism and hypothyroidism. The serum alkaline phosphatase is frequently elevated in thyrotoxicosis.
II. TRH stimulation test. This test can be used to confirm the diagnosis of autonomous thyroid nodules. TSH may be suppressed before and after TRH administration even when T_4 and T_3 measurements are normal. This test replaces the Cytomel suppression test used previously.
III. Perchlorate study. This test is indicated if an organification defect is suspected. A tracer dose of RAI is given. After a suitable interval, 500 mg of potassium perchlorate is administered by mouth. Normally, because of the rapid organic binding of the iodide, no thyroid loss of ^{131}I occurs. However, when organification is impaired, the potassium perchlorate causes a partial or complete discharge of ^{131}I from the thyroid gland within a 30-minute period. This test is also useful in the occasional case of Hashimoto's struma in which the RAI uptake is elevated.
IV. Thyroid stimulating immunoglobulins. Measurement of immunoglobulins may be helpful in confirming neonatal Graves' disease, in the differential diagnosis of exophthalmos, and sometimes in predicting spontaneous remission or cure of Graves' disease.
V. Indirect laryngoscopy is indicated in dysphonic patients to exclude intrinsic lesions of the larynx.
VI. Investigation of other family members is indicated when familial disease is suspected.
VII. Hearing and taste tests should be carried out in children with thyroid enlargement in whom either multinodular goiter or Pendred's syndrome (familial goiter with deafness) is suspected.
VIII. Other tests of thyroid function, the determination of iodinated products in serum, and chromatography of thyroid hormone precursors are either research procedures or as yet not readily available clinically.
IX. Despite the number of available tests, the cause of a goiter is not always easily determined. In such cases, thyroid hormone suppression treatment over a 6-month period may be indicated with further evaluation at the completion of the therapy.

Hypercalcemia

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Definition

Hypercalcemia is said to exist when the serum calcium is 10.5 mg/100 mL or greater. This figure may vary slightly depending on the normal values of the method as established by the individual laboratory. The determination is automated. Commonly used examples are the Paramax machine using the cresol phthalein complex method and the Beckman CXR equipment. Hypercalcemia is emerging as an even more complex diagnostic problem than it was in the past. With automation of laboratory procedures, biochemical screenings or profiles are often performed routinely, both in the physician's office and the hospital. The serum calcium is generally included in these screenings, and elevations are often seen in asymptomatic patients. Elevations of the serum calcium level are found in about 1% of routine biochemical screens.

Etiology

Multiple causes for hypercalcemia have been elucidated; therefore, the diagnosis may be difficult. Sometimes the diagnosis can be established only by observation of the patient over a period of time. The various known causes of hypercalcemia include the following conditions:

I. Malignancy—probably most common in hospitalized patients
   A. Carcinoma
   B. Multiple myeloma
   C. Leukemia; lymphoma
   D. Nonendocrine, parathyroid hormone-secreting carcinoma (e.g., lung, kidney, ovary, colon, cervix, pancreas), ectopic hyperparathyroidism
II. Primary hyperparathyroidism (0.1%)
   A. Tumor
   B. Hyperplasia
   C. Carcinoma
III. Drug-induced hypercalcemia, including the thiazides and spironolactone—increasingly common
IV. Vitamin D intoxication
V. Milk-alkali syndrome
VI. Multiple endocrine neoplasia, I and II; Zollinger–Ellison syndrome
VII. Benign familial hypercalcemia (familial hypocalciuric hypercalcemia)
VIII. Others
   A. Hypothyroidism and hyperthyroidism
   B. Adrenal insufficiency
   C. Sarcoidosis and other granulomatous diseases
   D. Acromegaly
   E. Immobilization
   F. Idiopathic hypercalcemia of infancy (William's syndrome)
   G. Vitamin A intoxication
   H. Pheochromocytoma

Symptoms

It is obvious from the many possible causes of hypercalcemia that a variety of symptoms may occur. Frequently, an asymptomatic patient is found to have an elevated serum calcium on routine biochemical screening. As a general rule, patients with slightly elevated serum calciums usually have fewer symptoms than those with higher values. Usually, most patients with serum calcium levels below 11 mg/100 mL are relatively asymptomatic, whereas most patients with serum calcium levels above 12 mg/100 mL are symptomatic. The following symptoms may occur.

I. None—particularly common at this time
II. Nocturia—perhaps the earliest symptom
III. Polydipsia, polyuria—both early symptoms
IV. Easy fatigability
V. Irritability, difficulty in concentrating, depression, confusion
VI. Constipation, obstipation
VII. Urinary tract stones and urinary tract infections—may antedate other modes of presentation by a number of years
VIII. High blood pressure—may antedate other symptoms by a number of years
IX. Muscle weakness, generalized or involving the shoulders and hips
X. Anorexia, nausea, vomiting, abdominal pain, peptic disease
XI. Weight loss
XII. Joint pain
XIII. Deep pain (e.g., arms, legs, back)
XIV. Instability when walking
XV. Headache
XVI. Difficulty in focusing the eyes

Signs

The physical examination may yield no abnormalities, particularly if hypercalcemia has been of short duration or if the serum calcium is 11 mg/100 mL or less. In patients

with malignancy, marked weight loss may occur. Physical findings in hypercalcemia may include the following:

I. Elevated systolic blood pressure with or without elevated diastolic pressure. This is a common finding.
II. Rarely, a parathyroid tumor may be palpable and then usually is more than 4 g in weight. (Most palpable anterior neck masses are of thyroid origin.)
III. Bone or muscle tenderness on pressure
IV. Proximal or generalized muscle weakness
V. Disequilibration
VI. Emotional lability, mental confusion, depression
VII. Weight loss, varying from 10 to 30 pounds, although none may be noted
VIII. Reflexes may be normal or reduced; hypotonia may be present.
IX. Skin lesions, such as purpura, ecchymosis, and petechia may be present.
X. An enlarged liver or spleen may be palpable; lymphadenopathy may be present.
XI. Recurring, intermittent urticaria
XII. Somnolence, coma
XIII. Band keratopathy on slit-lamp examination of the eyes. This is an uncommon finding.

Diagnostic Approach

Initial Workup

In view of the paucity of signs that may be present, the workup may be particularly difficult. The purpose of the initial study is to establish a diagnosis, or, failing that, to reduce the number of diagnostic possibilities. Patients with marked hypercalcemia (serum calcium ≥ 13 mg/100 mL) should be treated immediately in order to reduce the serum calcium level. Once this has been accomplished, diagnostic studies may be performed at a later and more appropriate time. The following initial studies are recommended.

I. Serial determinations of serum calcium and phosphorus to establish that hypercalcemia is present. These should be obtained while the patient is not on excessive intake of phosphate because this ion may reduce the serum calcium levels.
II. A careful review of all of the patient's medications and diet. All drugs that are not essential or that are known to influence serum calcium levels (e.g., calcium, vitamin D, thiazides, and spironolactone) should be withheld.
III. Hemoglobin and hematocrit determinations
IV. WBC and differential counts
V. Platelet count
VI. Biochemical profile or screen
VII. Serum protein electrophoresis in selected cases
VIII. Urine protein electrophoresis in selected cases
IX. Serum immunoglobulins in selected cases
X. Sedimentation rate (Westergren) in selected cases
XI. Parathyroid hormone assay (PTH). A number of commercial assays are available. Intact PTH by the immunoradiometric method (IRMA) differentiates the hypercalcemia of primary hyperparathyroidism from the hypercalcemia of malignancy and renal disease.
XII. Parathyroid hormone-related protein. This measurement is now available and is useful in patients with hypercalcemia secondary to a variety of malignancies.
XIII. 24-hour urine for calcium, phosphorus, and creatinine determinations
XIV. Radiographs—chest (PA and lateral), lumbar spine, skull, and other films may be indicated.

If continuous hypercalcemia and associated hypophosphatemia are documented, the most likely diagnosis is primary or ectopic hyperparathyroidism, myeloma, or sarcoidosis. However, if normal phosphate levels are found, the diagnosis remains uncertain. If the drug history indicates the use of medications known to influence serum calcium, the drugs should be withdrawn and the patient reevaluated for hypercalcemia after approximately 4 to 6 weeks.

Patients with hypercalcemia may demonstrate slight anemia. Profound anemia is usually seen only in patients with leukemia, myeloma, malignancy, and secondary renal disease. The WBC, differential, and platelet counts may not be helpful except in leukemia and occasionally in myeloma. The erythrocyte sedimentation rate is frequently normal in primary hyperparathyroidism but may be elevated in malignancy, leukemia, and myeloma. It may also be elevated in patients with vitamin D intoxication and, presumably, in patients with parathyroid hormone-secreting nonendocrine tumors. The serum sodium and potassium levels may be normal or reduced in primary hyperparathyroidism. The serum chloride is frequently, but not always, elevated in this disease. In patients with adrenal crisis, the serum sodium and chloride may be normal or reduced in association with elevated calcium and phosphorus levels. Elevation of the BUN and serum creatinine can be expected if hypercalcemia has been present for a long period of time or if the serum calcium is over 12 mg/100 mL. Obtaining the BUN and creatinine is helpful in determining the duration of the disease, the selection of additional tests, the appropriate treatment, and the prognosis of the renal disease that may be present.

The serum alkaline phosphatase may be normal in the presence of hypercalcemia. Elevation of this enzyme suggests the bone disease of hyperparathyroidism. However, patients with malignancy of any type may have high alkaline phosphatase levels. Measurement of the serum enzyme gamma glutamyl transpeptidase (GGT), or fractionation of the alkaline phosphatase levels, or both, can usually clarify whether an elevated alkaline phosphatase is of bony or hepatic origin.

Routine protein electrophoresis is useful in excluding sarcoidosis and multiple myeloma. Urine protein electrophoresis should also be performed to identify the rare patient who may have an abnormal protein in the urine that is not detectable by serum protein electrophoresis. Immunoglobulins are determined for the same reason.

A 24-hour urine collection (with the patient on a normal phosphate intake) for calcium, phosphorus, and creatinine determinations may be useful. Hypercalciuria and hyperphosphaturia are commonly seen in primary or ectopic hyperparathyroidism. However, they may also occur in vitamin D overdose, myeloma, and sarcoidosis. The 24-hour urine calcium level is usually less than 150 mg in benign familial hypercalcemia.

X-ray studies may provide the following information:

I. Chest films may disclose the presence of a hilar or peripheral lung lesion. The distal portions of the clavicles should be examined for subperiosteal resorption.
II. Lumbar spine films may reveal osteoporosis or the lytic lesions of multiple myeloma, or both. In addition, nephrolithiasis and urinary tract stones may be visualized.
III. Hand films may be normal, demonstrate subperiosteal resorption, or reveal osteoporosis. Subperiosteal resorption of bone is pathognomonic of hyperparathyroidism. Its absence, however, is not helpful in clarifying the diagnosis. At present, osteoporosis is perhaps the most common radiologic finding in hyperparathyroidism.
IV. Skull films may demonstrate osteoporosis or the presence of a pituitary tumor, or both. Occasionally, intracranial calcification suggestive of sarcoidosis can be identified.

Subsequent Workup

I. Abdominal CT scan may be indicated if malignancy is suspected. Bone marrow biopsy is indicated if myeloma, leukemia, or lymphoma is suspected from preliminary studies.
II. Other tests
   A. Vitamin D. 1,25(OH) Vitamin D may be elevated in lymphomas, vitamin D intoxication, and granulomatous diseases (e.g., sarcoidosis).
   B. Serum magnesium is usually normal or decreased in primary hyperparathyroidism.

III. Localization techniques
   A. A number of tests have been utilized to localize parathyroid tumors. These include cervical CT scan, cervical ultrasonography, and a number of isotopic scans. Unfortunately, none of these radiologic tests have been particularly useful, probably because parathyroid tumors are usually small.
   B. A barium swallow may show extrinsic pressure at the site of the tumor.
   C. Measurement of the intact molecule of PTH in multiple venous samples from the neck obtained by venous catheterization is useful in localizing parathyroid tumors. This procedure is recommended for patients who have had previously negative surgical exploration of the neck.

Comments

At present, there is no practical or widely available method for differentiating hyperparathyroidism owing to an adenoma from that caused by hyperplasia or parathyroid carcinoma. The latter condition, however, is rare.

If hyperparathyroidism is considered the most probable cause of hypercalcemia, other associated endocrine abnormalities should be considered. These include pituitary tumor, islet cell tumors, pheochromocytoma, and medullary carcinoma of the thyroid. Acromegaly is sometimes associated with hypercalcemia and may occur in the presence of multiple endocrine neoplasia. Even if other endocrine syndromes are not found in hypercalcemic patients with hyperparathyroidism, repeated examinations for this purpose over a period of years are advisable because of the frequency with which this association occurs. Also, because hyperparathyroidism may be familial, other members of the family should be evaluated.

Occasionally, a diagnosis cannot be made using any of the aforementioned procedures. Under such circumstances, the case should be followed and laboratory studies repeated at appropriate intervals.

Hypocalcemia

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Definition

Hypocalcemia exists when the total serum calcium value is less than 8.5 mg/100 mL as determined by the autoanalyzer using the Gitelman modification of the Kessler and Wolfman colorimetric method. This value may vary depending on the normal values of the method as established by the individual laboratory.

Approximately 50% of calcium in blood is bound mainly to albumin and globulins. The ionized calcium concentration is 5 mg/dL and this fraction is biologically active. Concurrent measurement of albumin is indicated in order to interpret total serum calcium. When hypocalcemia is present in acute illness or when hypoalbuminemia is present, ionized calcium should be measured.

Etiology

The most common cause of hypocalcemia is surgically induced hypoparathyroidism. Therefore, if a thyroidectomy scar is present, the diagnosis is usually obvious. A history of antecedent illness, past GI surgery, or known underlying renal disease may elucidate the cause in other cases. The various causes of hypocalcemia include the following conditions.

I. Hypoparathyroidism
   A. Surgically induced, partial or complete—most common
   B. Idiopathic
   C. Transient hypoparathyroidism of infancy (newborn)—usually partial
   D. Bioinactive parathyroid hormone (PTH)
II. Reduction in serum albumin
   A. Malabsorption states
   B. Short bowel syndrome

   C. Chronic liver disease and liver failure
   D. Nephrotic syndrome
   E. Malnutrition
III. Pancreatitis
IV. Renal disease
   A. Renal tubular dysfunction
   B. Acute tubular necrosis
   C. Chronic renal failure
V. Rickets and osteomalacia
VI. Pseudohypoparathyroidism, types I and II
VII. Hypoparathyroidism in association with other disease states, which may be familial
   A. Addison's disease
   B. Pernicious anemia
   C. Candidiasis
VIII. Medullary carcinoma of the thyroid, sporadic, familial, or in men
IX. Hyperphosphatemia
X. Other vitamin D-related disorders

Symptoms

Symptoms of hypocalcemia usually occur when the total serum calcium value is below 7.5 mg/100 mL, but they sometimes occur at higher levels when there has been a rapid decrease in the serum calcium concentration. The symptoms are generally those of neuromuscular irritability. Patients with chronic renal disease have such symptoms infrequently because of coexisting metabolic acidosis. Patients with primary GI disease may have remarkably few symptoms, complaining chiefly of weakness, weight loss, diarrhea, increased number of stools, and abdominal cramping. Children and adults with pseudohypoparathyroidism often complain of weight problems. Patients with rickets or osteomalacia may have bone pain or problems related to the growth of bone. Hypocalcemic individuals may be asymptomatic or exhibit one or more of the following symptoms:

I. Numbness and tingling of the face, hands, and feet
II. Muscle cramps in the arms, hands, abdomen, legs, and feet
III. Increased number of stools or diarrhea
IV. Headaches, usually frontal; irritability, anxiety
V. Difficulty in breathing, particularly noisy breathing during exercise or sleep
VI. Seizures, which are common; in infants this may be the only complaint
VII. Decreased vision
VIII. Nail growth abnormalities and infections; delay in "cutting" teeth
IX. Dry skin, often infected
X. Weight problems
   A. Weight loss in association with chronic systemic disease
   B. Difficulty in losing weight in pseudohypoparathyroidism
XI. Bone growth abnormalities or pain (in rickets and osteomalacia)

Signs

Physical signs may help to clarify the underlying disease. Signs of neuromuscular irritability occur most often. It should be remembered that even when a patient has previously undergone thyroidectomy, other signs may suggest a coexisting disease. The following findings may be noted on physical examination:

I. None
II. Thyroidectomy scar
III. Dry skin
IV. Abnormal or infected nails; delayed dentition
V. Cataracts
VI. Chvostek's sign

VII. Trousseau's sign
VIII. Crowing noises during sleep
IX. Seizure disorder—may be the only finding in infants
X. Hypotension—infrequently seen
XI. Coma—rare, but does occur
XII. Bone pain or bone abnormalities, including abnormal growth, bowing, and brachydactylia—findings that suggest rickets, osteomalacia, or pseudohypoparathyroidism
XIII. Goiter, if present, may suggest medullary carcinoma of the thyroid, chronic thyroiditis, or Graves' disease
XIV. Other findings suggestive of underlying chronic disease (e.g., hepatomegaly, edema, surgical abdominal scars)

Diagnostic Approach

Initial Investigation

As mentioned previously, the most common cause of hypocalcemia is surgically induced hypoparathyroidism. The demonstration of hypocalcemia, hyperphosphatemia, and normal serum alkaline phosphatase, BUN, and serum albumin in a patient with a thyroidectomy scar is virtually diagnostic of hypoparathyroidism. The initial workup should include the following tests:

I. Several determinations of serum calcium and phosphorus
II. BUN, creatinine
III. Serum albumin and globulin
IV. Hemoglobin and hematocrit determinations
V. WBC and differential counts
VI. Platelet count
VII. Urinalysis
VIII. Electrolytes, including magnesium
IX. Thyroid function tests, if the patient is not on replacement therapy

Subsequent Investigation

I. If hypoparathyroidism has been documented by the initial investigation, the following studies may be indicated:
   A. Slit-lamp examination of the eye for cataracts
   B. Skull films for evaluation of calcification
   C. EEG to evaluate seizure activity
   D. Routine chest radiographs
   E. Routine ECG (may show Q-T interval increase)
   F. PTH determination. PTH is usually low. A high level suggests bioinactive PTH, pseudohypoparathyroidism, rickets, or osteomalacia.
II. Because many patients with hypocalcemia caused by hypoparathyroidism have an increased number of stools, it may be difficult to know whether primary GI disease coexists. In these patients, the following tests may be helpful:
   A. Serum carotene—usually within normal limits
   B. D-Xylose absorption test—usually within normal limits, but may be reduced
   C. Seventy-two-hour stool fat—usually abnormal, with a high fat content, resembling that seen in steatorrhea of GI origin

   Following therapy and restitution of the serum calcium level to normal, a 72-hour stool fat determination can be repeated. It should be normal if the hypocalcemia is secondary to hypoparathyroidism.
III. Further investigation is indicated if the patient is thought to have another underlying disease or if no previous thyroid surgery has been performed. In addition to the aforementioned tests, the following tests may be warranted if symptoms and signs suggest other disease states.
   A. Liver function tests
   B. Creatinine clearance, urine pH, urine electrolyte excretion, urine amino acid chromatography, and ammonium chloride loading in patients with renal dysfunction from varying causes

Hyperlipidemia

Fred H. Katz

Definition

The central role of elevated cholesterol level in the cause of coronary and peripheral artery disease has long been securely established. Furthermore, more detailed analyses of the constituents of plasma lipids over the past three to four decades have put a finer focus on the molecular basis of atherosclerosis. Hyperlipidemia is defined as an excess concentration of lipids in plasma or serum. Because fats are practically insoluble in plasma water, they must circulate in the bloodstream bound to soluble proteins known as lipoproteins. Therefore, the terms *hyperlipidemia* and *hyperlipoproteinemia* are used synonymously. Clinical laboratories, however, usually do not measure the lipoproteins but only the lipids, mainly cholesterol and triglyceride. Thus, hyperlipidemia is elevation of either serum cholesterol or triglyceride level, or both. The more recent elucidation of the central role of reduced HDL cholesterol in the pathogenesis of atherosclerosis has broadened the definition of hyperlipidemia to include alterations in the relationship of the various lipid fractions to each other.

Laboratory Diagnosis

I. Standing serum test. Even before sending a sample of serum to the laboratory, the clinician can detect certain hyperlipidemias by visual inspection of the plasma or serum. When serum triglyceride exceeds 300 mg/dL (normal range is up to 175 mg/dL), the serum has an opalescent or cloudy appearance. Furthermore, the large fat-containing globules, chylomicrons, form a characteristic layer of "cream" on top of such a "milky" serum, especially when the specimen is allowed to settle in a refrigerator overnight. Thus, the hyperlipidemias with elevated triglycerides and those with circulating chylomicrons, usually absent from the circulation in the postadsorptive (fasting) state, can be diagnosed clinically by inspection of the serum. Elevation of serum cholesterol (normal levels are 150 to 250 mg/dL) does not alter the gross appearance of serum. Most clinical laboratories measure serum cholesterol, triglyceride, and HDL cholesterol.
II. Lipoprotein electrophoresis. This is an old-fashioned technique not frequently needed clinically anymore. It involves staining electrophoretically separated serum proteins for lipids. Chylomicrons do not travel from the origin. Lipoproteins rich in triglycerides and known as *very low-density lipoproteins* (VLDL) travel next on the electrophoretic strip and are also known as *prebeta lipoproteins*. Next come *beta-lipoproteins*, because they travel with the beta globulins. These are the richest in cholesterol and are known as *low-density lipoproteins* (LDL). Lipoproteins richest in phospholipids travel fastest from the electrophoretic origin and are known as *alpha-lipoproteins*. It is here that the HDL or *high-density lipoproteins* are found.
III. Ultracentrifugation. This technique of separating lipoproteins is not used clinically. However, this is the technique with which the relative densities of the various classes of lipoproteins was determined, and from which their names derive.
IV. HDL cholesterol. HDL cholesterol is the cholesterol associated with *high-density lipoproteins*. HDL cholesterol is now routinely measured in the laboratory by simple differential solubility. The non-HDL lipoproteins are precipitated by the addition of phosphotungstic acid and magnesium sulfate. After centrifugation, the supernatant contains the HDL, and its content of cholesterol can then be measured.
V. VLDL and LDL cholesterol. The concentration of VLDL cholesterol can be calculated by dividing the triglyceride concentration in mg/dL by 5. This calculation is invalid if the triglyceride level exceeds 400 mg/dL. The LDL cholesterol can then be calculated by subtracting the levels of HDL cholesterol and VLDL cholesterol from the value of the total serum cholesterol.
VI. Apolipoproteins. Apolipoproteins play their important roles in lipid transport by activating or inhibiting enzymes involved in lipid metabolism, binding lipoproteins to cell surface lipoprotein receptors or both. Specific immunoassay

measurements of these protein moieties of lipoproteins can now be obtained, although their clinical usefulness is not yet proven. Apolipoproteins A, with their subclasses AI and AII, are the major structural proteins of HDL and appear to be crucial to its function of reverse transport of cholesterol out of atheromatous deposits in arteries. Apo-B 100 (apolipoprotein B) performs similar functions for LDL and VLDL. These measurements are useful in genetic studies of families and other groups with lipid-related vascular disease. Their genetic loci on the human chromosomes have also been determined.

VII. Cholesterol/HDL to cholesterol ratio. This ratio has proven to be very effective in gauging the risk of present or future coronary artery disease. Table 9-2 summarizes this relationship for the two sexes. The National Cholesterol Education Panel (NCEP), on the other hand, has recommended that the absolute level of LDL-cholesterol be used to determine this risk. They advise that efforts be made to keep LDL-cholesterol below 160 mg/dL to minimize the risk in individuals without any evidence of coronary disease. The NCEP goes on to recommend that the level be kept below 130 mg/dL in individuals with known previous coronary events or with any two of the following risk factors: male gender, family history of premature coronary disease, cigarette smoking, hypertension, diabetes mellitus, HDL-cholesterol under 35 mg/dL, severe obesity, or proven cerebrovascular or peripheral vascular disease.

Lipoprotein Metabolism

The major carrier of plasma cholesterol is the LDL, which carries approximately two-thirds, with HDL as the other important carrier. The major triglyceride-carrying lipoproteins are the chylomicrons and the VLDLs. In the circulation, the chylomicrons, bringing absorbed fats from the GI tract, and VLDLs, originating in the liver, are hydrolyzed by lipoprotein lipase that resides on endothelial cells, producing remnant particles that are endocyted by the liver. The remnant particles not removed by the liver lose their remaining triglycerides, phospholipids, and apolipoprotein E through the action of hepatic lipase, resulting in the cholesterol-rich lipoprotein that contains apolipoprotein B-100, the LDL. LDL delivers cholesterol to all nucleated cells via endocytosis by the LDL receptor that recognizes apolipoprotein B-100 as the ligand for this uptake. Approximately 70% of the LDL is eventually removed by the liver. The remaining lipoprotein, HDL, is synthesized from precursors in the liver, intestine, and circulation. HDL, as mentioned, is believed to participate in reverse cholesterol transport. It acquires cholesterol in the tissues and esterifies it. The cholesterol esters are then transferred either directly by HDL to the liver or indirectly by transfer to other lipoproteins. This cholesterol can then be secreted directly into the bile or can be converted to bile acids.

Clinical Features

Most cases of hyperlipidemia are diagnosed by laboratory screening, which is now widely available. An increase in sedentary lifestyles and resultant obesity has seemed to increase the incidence of hyperlipidemias.

Table 9-2. Risk of coronary heart disease according to ratio of total cholesterol to HDL cholesterol

	Ratio	
Risk of heart disease	Men	Women
Low risk	Under 4.2	Under 3.8
Average risk	4.3–7.3	3.9–5.7
Moderate risk	7.4–11.5	5.8–9.1
High risk	Over 11.5	Over 9.2

An early system of classifying the hyperlipidemias, dating from the middle of the last century, was the Frederickson typing, Types I through V:

Type I features chylomicron elevation due to deficient lipoprotein lipase. It is fairly rare.

Type IIa or hyperbetalipoproteinemia features high total and LDL-cholesterol. It is relatively common.

Type IIb, also fairly common, combines Type IIa with elevated VLDL and its triglyceride. It is also called combined hyperlipidemia.

Type III, uncommon, features carbohydrate-induced hypertriglyceridemia with hypercholesterolemia. Remnants circulate in large amounts.

Type IV, the most common, has high triglycerides and VLDL without cholesterol elevation.

Type V, mixed endogenous and exogenous hyperlipidemia, is like a combination of Types I and IV, and is rare.

For patients who do not fit into the common syndromes listed in the preceding or the genetic disorders described in the following, measurements of cholesterol, triglyceride, and HDL-cholesterol usually suffice to make a diagnosis of hyperlipidemia. High levels of the cholesterol:HDL ratio, associated with abnormally high levels of LDL-cholesterol, are seen in a large number of patients with hyperlipidemia. The most commonly associated clinical states are: obesity, lack of exercise, hypertension, diabetes, smoking, and coronary artery disease. Individuals with very high triglycerides but normal or high cholesterol:HDL ratios may have a similar clinical profile.

Common Genetic Disorders of Lipid Metabolism

Familial Hypertriglyceridemia with Hypoalphalipoproteinemia

This common autosomal dominant disorder is characterized by plasma triglyceride levels above 250 mg/dL and HDL cholesterol below 35 mg/dL. These patients have overproduction of VLDL triglyceride but not of apo B-100 as well as hypercatabolism of HDL apo A-I. These patients may also have delayed triglyceride clearing after a meal and can be detected by a casual serum triglyceride measured in the nonfasting state. They have normal levels of LDL cholesterol and do not have xanthomas. This disorder is observed in about 15% of coronary heart disease cases before the age of 60 and is present in about 1% to 2% of the general population. Patients with this disorder are frequently overweight, hypertensive, and diabetic and may have elevated uric acid levels.

Familial Combined Hyperlipidemia with Hypoalphalipoproteinemia

Also transmitted as an autosomal dominant trait, this common disorder is characterized by either hypertriglyceridemia (250 mg/dL) or hypercholesterolemia (240 mg/dL, with LDL cholesterol 160 mg/dL) or both, coupled with HDL cholesterol levels below 35 mg/dL. This condition is seen in about 15% of coronary heart disease patients under age 60 and is present in about 1% of the population. These patients have overproduction of VLDL apo B-100 but not of VLDL triglyceride. They have delayed triglyceride clearance and enhanced HDL apo A-I catabolism. They may have xanthomas and xanthelasmas. They are also frequently overweight, diabetic, and hypertensive and may have elevated uric acid levels, resulting in kidney stones.

Familial Hypoalphalipoproteinemia

This common autosomal dominant disorder is characterized by isolated HDL cholesterol deficiency below the tenth percentile (i.e., 30 mg/dL in men and 35 mg/dL in women), with normal levels of plasma triglycerides and LDL cholesterol. This disorder has been associated with decreased HDL apo A-I production. These patients do not have xanthomas. This disorder is found in 5% to 10% of patients with coronary heart disease prior to the age of 60, and is present in about 0.5% of the general population.

Familial Hypercholesterolemia

This autosomal dominant disorder is associated with a marked increase in plasma LDL cholesterol and reduction in HDL cholesterol. There is a defect in the configuration or

function of the plasma membrane receptors for LDL cholesterol lipoproteins, preventing their clearance from the plasma. This results in their excessive arterial deposition. Heterozygotes suffer from a considerable increase in coronary heart disease. The homozygous form results in a malignant form of coronary heart disease very early in life. These patients may have xanthomas.

Secondary Types of Hyperlipidemia

Obesity caused by overeating can be etiologic in types of hyperlipidemia in which triglyceride levels are elevated. Although triglyceride elevation has been thought to be a far smaller risk factor for vascular occlusive disease than cholesterol or LDL cholesterol elevation, it has been found to be frequently combined with elevation of LDL cholesterol. Indeed, in the first two familial syndromes mentioned, hypertriglyceridemia has been shown to be an excellent predictor for coronary heart disease. Poorly controlled diabetes, especially the maturity-onset type, frequently causes hypertriglyceridemia and resulting vascular disease. Alcohol abuse can have the same effect and is often the cause of acute pancreatitis. Among the drugs that can cause hypertriglyceridemia are glucocorticoids and estrogens, as in oral contraceptives.

Hypercholesterolemia is sometimes a clue that hypothyroidism or possibly a nephrotic syndrome may be present. Appropriate diagnostic measures should be undertaken.

Conclusion

Hyperlipidemia can be diagnosed clinically by obtaining a family history and by obtaining three measurements in the laboratory: cholesterol, triglyceride, and HDL cholesterol.

10. NEUROLOGIC PROBLEMS

Coma

Sidney Duman and Stanley H. Ginsburg

Definition

Coma, stupor, and lethargy are altered states of consciousness. *Coma* may be defined as "unarousable unresponsiveness" to stimulation. *Stupor,* like coma, represents a state of marked unresponsiveness, but arousal is possible by stimulation. *Lethargy,* which represents lesser impairment of consciousness, is characterized by dullness, decreased mental alertness, some mental confusion, and especially by excessive drowsiness. However, responsiveness to auditory or physical stimuli is retained. Altered states of consciousness should be distinguished from other mental disturbances such as delirium and dementia. *Delirium* is an acute confusional state characterized by clouding of the sensorium, decreased alertness, irritability, agitation, sensory misinterpretations, and often, hallucinations. Delirium is usually associated with metabolic or toxic encephalopathy as well as multifocal cerebral disease. *Dementia* is a state of mental deterioration characterized by failing memory and loss of intellectual and cognitive functions usually owing to chronic and often progressive brain disease of multiple etiologies.

Etiology

Metabolic abnormalities, alcoholism, drug overdose, and trauma are the most common causes of coma encountered in hospital emergency rooms.

The etiology of coma is listed in Table 10-1. It is important to bear in mind that more than one cause may be responsible for coma in any given patient.

Based on the anatomic location of the lesion and the mechanisms by which neurologic diseases produce coma, the causes of coma can be classified into four major groups:

I. Supratentorial lesions (epidural hematoma, subdural hematoma, cerebral hemorrhage, pituitary apoplexy, cerebral infarction, tumor, abscess, and closed head injury)
II. Infratentorial lesions (brainstem or cerebellar infarction, hemorrhage, tumor, abscess, and brainstem demyelination)
III. Metabolic and diffuse brain disorders (hypoxia; ischemia; hypoglycemia; endogenous and exogenous toxins; nutritional deficiencies; infection; head injury; postictal states; metabolic and electrolyte disorders, including endocrine conditions; and temperature regulation problems)
IV. Psychiatric disorders. In Plum and Posner's series of "comas of unknown etiology," approximately 65% were owing to diffuse or metabolic brain dysfunction, including intoxications, and 33% were owing to supratentorial and infratentorial lesions. There were only a few cases of psychiatric disorders. "Drug poisons" accounted for 30% of the 500 patients.

Clinical Features

I. *Supratentorial lesions* are characterized by the following:
   A. Premonitory symptoms, such as headaches or seizures
   B. Focal hemispheric symptoms or signs: sensory or motor disturbances, aphasia, visual field defects
   C. Signs of bilateral hemispheric dysfunction: decorticate posturing
   D. Absence of signs of infratentorial involvement, except terminally
   E. When progressive, signs of transtentorial herniation
      1. Uncal herniation
         a. Ipsilateral dilated and eventually fixed pupil with oculomotor nerve paralysis

Table 10-1. Etiology of coma

I. Craniocerebral trauma
  A. Subdural hematoma
  B. Epidural hematoma
  C. Concussion
  D. Contusion
II. Metabolic encephalopathy
  A. Exogenous
    1. Alcoholism
    2. Drug overdose
    3. Poisoning
  B. Endogenous
    1. Endocrine
      a. Diabetes (ketoacidosis, lactic acidosis, nonketotic hyperosmolar hyperglycemia coma, hypoglycemia)
      b. Hyperpituitarism and hypopituitarism
      c. Hyperthyroidism and hypothyroidism
      d. Hyperadrenocorticism and hypoadrenocorticism
      e. Hyperparathyroidism and hypoparathyroidism
    2. Nonendocrine
      a. Renal failure
      b. Hepatic failure
      c. Respiratory failure
      d. Vitamin deficiency (e.g., thiamine, vitamin B12)
      e. Other systemic illnesses
    3. Fluid, acid-base, and electrolyte disorders
      a. Hypernatremia and hyponatremia
      b. Hyperkalemia and hypokalemia
      c. Hypercalcemia and hypocalcemia
      d. Hypermagnesemia and hypomagnesemia
      e. Hyperosmolarity and hypoosmolarity
      f. Acidosis (metabolic and respiratory)
      g. Alkalosis (metabolic and respiratory)
      h. Water intoxication
III. Cerebral vascular disease
  A. Intracerebral hemorrhage
  B. Subarachnoid hemorrhage
  C. Hypertensive encephalopathy
  D. Cerebrovascular ischemia from any cause
  E. Occlusion of a major cerebral artery
  F. Hyperviscosity encephalopathy
  G. Eclampsia
  H. Systemic vasculitis and coagulopathies owing to immune disorders
IV. Infection
  A. Meningitis
  B. Encephalitis
  C. Cerebritis or abscess
  D. Systemic infections and septicemia
V. Neoplasms and other space-occupying lesions
VI. Miscellaneous
  A. Psychiatric (hysteria, depression, catatonia)
  B. Syncope
  C. Seizures and postictal states

    b. Progressive impairment of the level of consciousness
    c. Hemiparesis, which may be ipsilateral
  2. Central herniation
    a. Progressive impairment of the level of consciousness
    b. Evidence of respiratory dysfunction: sighing, yawning, Cheyne-Stokes respiration
    c. Preservation of pupillary light responses and oculovestibular reflexes until increasing brainstem dysfunction occurs
    d. Bilateral rigidity and spasticity with extensor plantar reflexes

II. The onset of coma in acute *infratentorial lesions* is usually more rapid than in supratentorial lesions. Premonitory symptoms frequently include occipital headache, nausea and vomiting, ataxia, dysarthria, and diplopia. The specific findings depend on the site of the lesion.
  A. Midbrain—upper pons
    1. Fixed, nonreactive pupils that are usually in midposition (about 5 to 6 mm in size)
    2. Nuclear ophthalmoplegia
    3. Signs of long motor tract involvement, including decerebrate rigidity
    4. Central neurogenic hyperventilation (deep, rapid breathing)
  B. Pons
    1. Constricted, nonreactive pupils
    2. Altered or absent oculovestibular reflexes
    3. Signs of long motor tract involvement
    4. Apneustic breathing (prolonged inspiration followed by an expiratory pause) or sometimes Biot's respiration
  C. Lower pons—medulla
    1. Miotic nonreactive pupils that dilate terminally
    2. Absence of oculovestibular reflexes
    3. Flaccid quadriplegia
    4. Ataxic (irregular) breathing culminating in respiratory arrest
  D. Cerebellum
    1. Signs of cerebellar involvement may precede the onset of coma
    1. Signs of progressive brainstem dysfunction, as outlined in the preceding, ultimately occur

III. Depending on the cause, the signs of *metabolic encephalopathy* are quite variable. The findings include:
  A. Respiratory abnormalities such as hyperventilation or hypoventilation
  B. Preservation of pupillary light reflexes. However, certain drugs (e.g., atropine, glutethimide) may cause alterations in pupillary light reflexes
  C. Random eye movements, but not persistent ocular deviations
  D. Disorders of motor tone, strength, and reflexes
  E. Tremor, asterixis, multifocal myoclonic jerks, and seizures

IV. *Psychogenic coma* is rare. The condition is characterized by the following:
  A. Absence of signs of structural disease of the brain
  B. A normal response to ice water caloric testing, which often has the added advantage of waking up the patient

Diagnostic Approach

I. Coma is a medical emergency. No time should be wasted. It is often necessary to perform the physical examination while obtaining the history.

II. Life-sustaining measures have precedence over diagnostic procedures. Quickly evaluate the status of the respiratory and cardiovascular systems. Check to see that the patient has an adequate airway, is not hypotensive or in shock, and is not bleeding. Institute appropriate therapy if any of these abnormalities is detected.

III. Insert a large-bore intravenous catheter or needle and immediately draw a blood sample for laboratory tests. Because hypoglycemia and thiamine deficiency can mimic many intoxications, all patients with stupor or coma of unknown etiology

should be given 50 mL of 50% glucose and 50 mg of thiamine intravenously. Lethargic, stuporous, or comatose patients with pinpoint pupils and hypoventilation should also receive naloxone, 0.4 to 1.2 mg intravenously, because of the possibility of narcotic overdose.

IV. The history is vital in the diagnosis of altered states of consciousness. It is usually necessary to obtain the requisite information from relatives, friends, or bystanders. Do not permit anyone with information about the patient to leave until the diagnosis is established, or until it becomes clear that additional information will no longer be helpful. Salient points to be checked in the history include the following:
   A. The presenting symptom or symptoms
   B. The rapidity of onset, whether sudden or gradual
   C. The evolution of the clinical picture
   D. The state of the patient's health prior to the onset of coma
   E. The patient's access to drugs or poisons
   F. Conditions that commonly cause coma
      1. Trauma
      2. Epilepsy
      3. Drug abuse
      4. Cardiovascular disease
      5. Pulmonary disease
      6. Cerebrovascular disease
      7. Metabolic disorders
      8. Infections
      9. Neoplasms

V. The initial examination should be as thorough as the patient's condition permits. Examine the patient's personal effects for cards or medical identification tags that may reveal any other existing conditions. After a preliminary observation of the patient, systematically check the following:
   A. Vital signs (temperature, respiratory and heart rates, and blood pressure)
      1. Temperature
         a. Fever may suggest infection
         b. Hyperthermia of any cause
         c. Hypothermia may be indicative of alcoholic or barbiturate intoxication, myxedema, hypopituitarism, peripheral circulatory collapse, or exposure
      2. Heart rate
         a. A slow heart rate may suggest heart block. If combined with periodic breathing and hypertension, consider increased intracranial pressure.
         b. Marked tachycardia (?140/min) may suggest an ectopic paroxysmal tachyarrhythmia.
      3. Blood pressure
         a. Hypotension is commonly found in barbiturate or alcoholic intoxication, hemorrhage, shock, and other conditions.
         b. Hypertension may be a manifestation of hypertensive encephalopathy as well as increased intracranial pressure of any etiology.
      4. Respiratory rate
         a. Slow breathing may indicate intoxication or myxedema.
         b. Rapid breathing is common in a variety of conditions.
      5. Respiratory pattern
         a. Cheyne-Stokes respiration implies bilateral hemispheric dysfunction with the brainstem intact. It may be the first sign of transtentorial herniation. It may occur in metabolic disorders and congestive failure.
         b. Central neurogenic hyperventilation (deep rapid breathing) usually indicates involvement of the brainstem between the midbrain and pons.
         c. Apneustic respiration (prolonged inspiration followed by an expiratory pause) signifies a pontine lesion.

         d. Ataxic (irregular) breathing is usually a terminal event and implicates a medullary lesion.
         e. Coma with hyperventilation is frequently seen in metabolic encephalopathy associated with either metabolic acidosis or respiratory alkalosis.
   B. Skin
      1. Look for cyanosis, rashes, bruises
      2. Check the skin turgor.
      3. Note whether the skin is dry or moist.
   C. Body orifices
      1. Bleeding from the ears or nose suggests cranial trauma.
      2. Bleeding from other orifices suggests a bleeding disorder or hemorrhage as the cause of coma.
   D. Odor of the breath
      1. The odor of alcohol is characteristic.
      2. A fruity odor is observed in diabetes ketoacidosis.
      3. A musty odor generally signifies hepatic coma.
      4. A uriniferous odor is found in uremia.
   E. Central nervous system
      1. Posture in bed
         a. Decorticate rigidity, characterized by flexion of the arms and extension of the legs, signifies bilateral hemispheric dysfunction with the brainstem intact.
         b. Decerebrate rigidity, in which the arms, legs, and head are in an extended position, implies bilateral involvement of the upper brainstem or lesions deep in the hemispheres.
      2. Meningeal signs
         a. Resistance of the neck limited to active flexion or extension is a sign of meningeal irritation, which may be owing to meningitis or subarachnoid hemorrhage.
         b. Positive Kernig's or Brudzinski's signs
         c. Restriction of movement of the neck in all directions may occur in generalized rigidity or disease of the cervical spine.
      3. Level of consciousness
         a. Reduced awareness, but with appropriate responses to auditory or physical stimulation, indicates lethargy.
         b. Limited responsiveness to noxious stimulation is found in stupor.
         c. Complete absence of responsiveness to stimulation is diagnostic of coma.
      4. Cranial nerves. Localization of a lesion may be assisted by detecting involvement of specific cranial nerves.
      5. Eye movements
         a. In comatose patients without involvement of the neural pathways influencing ocular movements, the eyes are usually directed straight ahead or display slow, roving movements.
         b. Sustained involuntary conjugate deviation of the eyes toward the unaffected side of the body suggests a hemispheric lesion; toward the paralyzed side, a pontine lesion.
         c. Absence of oculocephalic (doll's eye movements) and corneal reflexes indicates pontine dysfunction.
         d. Oculovestibular reflexes, demonstrable by testing, may be lost in brainstem lesions.
      6. Pupils
         a. Reactive pupils indicate that the midbrain is intact.
         b. Reactive pupils in association with absent oculocephalic and corneal reflexes generally signify a metabolic encephalopathy or drug overdose.
         c. Pinpoint pupils may be owing to drugs such as opiates or pilocarpine, or to pontine dysfunction.

d. Dilated fixed pupils may occur with severe midbrain lesions or in response to such drugs as atropine.
e. A unilateral fixed, dilated pupil with oculomotor nerve paralysis occurs in uncal herniation.

7. Fundi
   a. Papilledema is a sign of increased intracranial pressure.
   b. The presence of specific types of retinopathy may suggest an etiologic diagnosis.
8. Sensory system. Sensory loss may be suspected if the patient exhibits variations in responsiveness to noxious stimuli.
9. Motor system
   a. Hemiplegia, hyperreflexia, and an extensor plantar response implicate a structural lesion of the brain as the cause of coma.
   b. Hyporeflexia without paralysis and with preservation of normal plantar responses suggests a metabolic cause or drug ingestion.
10. Movements
   a. Yawning, swallowing movements, and licking of the lips suggest preservation of brainstem function.
   b. Multifocal myoclonic jerks are typical of metabolic or anoxic encephalopathy.
   c. Multifocal seizures may occur in metabolic encephalopathies such as uremia.
   d. Jacksonian seizures preceding the onset of coma suggest a cortical lesion.
   e. Tremors and asterixis are prominent manifestations of metabolic brain disease.
   f. Laboratory procedures. Unless the diagnosis is obvious from the history and physical examination, the following procedures should be obtained in *coma of unknown etiology:*
      (1) CBC and platelet count
      (2) Urinalysis
      (3) Prothrombin and partial thromboplastin times
      (4) Toxicology screen
      (5) Arterial blood gases and pH
      (6) Serum electrolytes
      (7) Biochemical screening
      (8) Chest films
      (9) Lumbar puncture (may be advisable provided there are no contraindications, such as infection at the site of lumbar puncture, suspected mass lesion, and papilledema)
      (10) Cardiac rhythm monitoring
      (11) Computed tomography is indicated if a structural intracranial lesion is suspected. An MRI or MRA scan may add further information.
   g. Repeated observation and examination of the patient at frequent intervals are essential to ensure appropriate management.
   h. Supportive measures having been previously instituted, specific therapy is begun once the cause of the coma is determined.

Delirium

Sidney Duman and Stanley H. Ginsburg

Definition

Delirium is an acute confusional state characterized by clouding of the sensorium, irritability, restlessness, agitation, and abnormal mental phenomena, such as illusions, delusions, and hallucinations. It is usually of relatively brief duration. Delirium and stupor may alternate in the same patient.

Etiology

I. Delirium is most common in toxic and metabolic aberrations.
   A. Use and abuse of various cerebroactive drugs (e.g., acute atropine intoxication)
   B. Withdrawal from various cerebroactive drugs (e.g., alcohol, barbiturates)
   C. Metabolic disturbances, such as uremia, liver failure, hyponatremia, hypoxemia
   D. Fever
   E. Postictal states
   F. Head trauma
II. Delirium is unusual in primary cerebral disease but may occur in encephalitis and other multifocal brain disorders.
III. Underlying brain disease of various etiologies (e.g., senility, various structural brain lesions) often allows for the development of delirium with relatively minor metabolic disturbances.

Clinical Features

Varying degrees of confusion, agitation, restlessness, and emotional lability are seen. Attention is poor and perception is altered. Delusions, illusions, and hallucinations (usually visual) are common. These symptoms may fluctuate considerably, with swings from intense agitation to stupor, depending on environmental stimuli, use of sedative agents, or the advent of exhaustion. During periods of stupor, especially when drug-induced, hypotension and its attendant complications may occur. Cerebral hypoxia may result and further complicate the picture.

Delirium tremens is a striking example of an acute delirium. It is characterized by profound confusion, agitation, sleeplessness with delusions, and vivid hallucinations. Increased autonomic activity prevails (e.g., fever, tachycardia). Delirium tremens occurs in the chronic alcoholic in whom, for whatever reason, alcohol is withdrawn. Symptoms, initially consisting of irritability, restlessness, tremulousness, poor appetite, and insomnia, typically begin 2 to 3 days after withdrawal. Frightening dreams may occur. These symptoms then lead to the full-blown picture outlined in the preceding. The patient also becomes increasingly tremulous, and autonomic hyperfunction occurs. Convulsive seizures may occur. Improvement may be rapid, with the entire illness lasting only several days. However, death may occur in as many as 15% to 20% of cases.

Differential Diagnosis

I. The distinction between acute delirium and psychiatric disorders such as manic or catatonic excitement can be difficult. Table 10-2 lists the diagnostic criteria for delirium.
   A. The behavior may be identical, although in psychiatric disorders lethargy and confusion are less prominent.
   B. Absence of localizing neurologic signs is not unusual in either.
   C. Longitudinal observation usually helps to resolve the question.
   D. The EEG may be helpful in distinguishing acute delirium from behavioral disorders. It tends to be abnormally slow in hepatic failure, encephalitis, and other organic conditions, and abnormally fast in drug withdrawal states. A normal EEG, however, does not rule out organic delirium.
II. Delirium must also be distinguished from dementia. Delirium is characterized by an acute onset. It is not caused by central nervous system disease, but it is associated with prominent autonomic nervous system symptoms, fragmented thoughts, and a labile course. On the other hand, in dementia the onset is insidious.

The etiology is of central nervous system origin. Autonomic nervous system symptoms are absent. Impoverished thoughts and a relatively stable course are characteristic features.

Diagnostic Approach

I. Careful history and physical examination are indicated, with special reference to drug (and alcohol) habits, withdrawal from medications, head trauma, and evidence of neurological disease.

Table 10-2. Diagnostic criteria for delirium

I. Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to shift attention appropriately to new external stimuli (e.g., perseverates in answering a previous question)
II. Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech
III. At least two of the following:
   A. Reduced level of consciousness (e.g., difficulty keeping awake during examination)
   B. Perceptual disturbances: misinterpretations, illusions, or hallucinations
   C. Disturbance of sleep-wake cycle with insomnia or daytime sleepiness
   D. Increased or decreased psychomotor activity
   E. Disorientation in time, place, or person
   F. Memory impairment (e.g., inability to learn new material, such as the names of several unrelated objects after 5 minutes, or to remember past events, such as history of current episode of illness)
IV. Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day
V. Either:
   A. Evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance *OR*
   B. In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder (e.g., manic episode accounting for agitation and sleep disturbance)

From *Diagnostic and statistical manual of mental disorders*, 3rd ed. Washington, DC: American Psychiatric Association, 1987, with permission.

II. An EEG is often helpful.
III. A detailed search for metabolic derangements (including anemia and biochemical disturbances, such as uremia, hepatic dysfunction, and impairment of oxygenation) and toxins should be instituted.
IV. A CT or MRI scan of the head is usually worthwhile.

Dementia

H. Harold Friedman

Definition

Dementia is a state of mental deterioration characterized by failing memory and loss of intellectual and cognitive functions.

Etiology

Dementia may be associated with clinical and laboratory evidence of medical disease. It may also occur in neurologic diseases, either as the only evidence of a neurologic disorder or accompanied by other neurologic signs related to the primary neurologic illness.

Presenile and senile dementia are most commonly caused by Alzheimer's disease. It is now generally accepted that Alzheimer's disease (formerly considered presenile dementia) and senile dementia are the same disease. It is estimated that it is the cause of 65% of cases of presenile and senile dementia. Vascular disease is probably the cause in only about 10% to 15% of such cases.

The various causes of dementia are listed in Table 10-3.

Table 10-3. Causes of dementing diseases of the brain

Dementia associated with medical disease
Hypothyroidism
Cushing's syndrome
Nutritional deficiency states (pellagra, vitamin B_{12} deficiency, Wernicke-Korsakoff's syndrome)
Hepatolenticular degeneration (familial and acquired)
Chronic meningoencephalitis (general paresis, meningovascular syphilis)
Drug intoxication (brominism and chronic barbiturism)
Dementia associated with neurologic disease
Other neurologic signs invariably present
Huntington's chorea
Schilder's disease
Lipid storage disease (e.g., amaurotic familial idiocy)
Jakob-Creutzfeldt disease
Myoclonic epilepsy
Spastic paraplegia
Other neurologic signs commonly present
Vascular disease (thrombotic and embolic)
Brain tumor
Brain abscess
Cerebral trauma
Communicating (low-pressure) or obstructive hydrocephalus
Dementia as the sole evidence of neurologic disease
Alzheimer's disease
Diffuse Lewy body disease
Multiple system degeneration
Pick's disease

From Adams RD, Victor M. *Principles of neurology*. New York: McGraw-Hill, 1977:275, with permission.

Characteristics of Dementia (Table 10-4)

I. Lack of orientation to time, place, and person
II. Poor memory for past and recent events. Immediate recall also defective.
III. Inability to perform simple calculations
IV. Difficulty or inability to think in abstract fashion
V. Difficulty with language
   A. Impaired fluency of speech and writing
   B. Difficulty in following simple oral or written commands
   C. Impaired ability to read and understand written or printed material
   D. Difficulty in writing or copying
VI. Visual agnosia (the ability to see but not recognize objects)
VII. Apraxia (the loss of purposive movement without paralysis). Table 10-4 lists diagnostic criteria for dementia.

Clinical Features of Dementing Disorders

Dementia is sometimes misdiagnosed as a primary psychologic disturbance (especially, reactive depression). Usually the conditions can be differentiated without too much difficulty. Psychogenic disorders are almost invariably associated with a positive psychiatric history; not so with dementing diseases. In psychological disorders, the onset is usually acute with rapid evolution of the symptomatology. The loss of cognitive functions is generally not severe and tends to remain static. Vegetative signs occur commonly, and there is usually improvement with appropriate therapy. On the other hand, the onset of dementia tends to be insidious and the course subacute but progressive.

Table 10-4. Diagnostic criteria for dementia

I. Demonstrable evidence of impairment in short- and long-term memory. Impairment in short-term memory (inability to learn new information) may be indicated by inability to remember three objects after 5 minutes. Long-term memory impairment (inability to remember information that was known in the past) may be indicated by inability to remember past personal information (e.g., what happened yesterday, birthplace, occupation) or facts of common knowledge (e.g., past presidents, well-known dates).
II. At least one of the following:
   A. Impairment in abstract thinking, as indicated by inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks.
   B. Impaired judgment, as indicated by inability to make reasonable plans to deal with interpersonal, family, and job-related problems and issues
   C. Other disturbances of higher cortical function, such as aphasia (disorder of language), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact sensory function), and "constructional difficulty" (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs)
   D. Personality change, such as alteration or accentuation of premorbid traits
III. The disturbance in I and II significantly interferes with work or usual social activities or relationships with others.
IV. Not occurring exclusively during the course of delirium
V. Either
   A. There is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance.
   B. In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder (e.g., major depression accounting for cognitive impairment).

Criteria for severity of dementia:
Mild: Although work or social activities are significantly impaired, the capacity for independent living remains, with adequate personal hygiene and relatively intact judgment.
Moderate: Independent living is hazardous, and some degree of supervision is necessary.
Severe: Activities of daily living are so impaired that continual supervision is required (e.g., unable to maintain minimal personal hygiene; largely incoherent or mute).

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Cognitive functions tend to decline steadily, vegetative signs are often absent, and there is little or no response to medications.

It is impossible to describe the clinical features of all the many possible causes of dementia in a text of this size. Listed in the following are some of the more common and important causes of dementia.

Medical Disorders
It is usually possible to exclude medical causes such as *hypothyroidism* and *Cushing's syndrome* on clinical grounds and with simple laboratory tests. *Pellagra* is characterized by dermatitis, pigmentation of the skin, glossitis, stomatitis, and diarrhea, all correctable by the administration of niacin. Patients with *Wernicke–Korsakoff psychosis* classically exhibit retrograde and antegrade amnesia with lesser impairment of cognitive functions. Confabulation may be present. *Vitamin B_{12} deficiency* is almost invariably associated with megaloblastic anemia and not infrequently with subacute combined degeneration of the cord. *Liver disorders* are usually recognized by clinical examination and laboratory tests.

Neurologic Disorders
Vascular Dementia
Arteriosclerotic dementia is the result of multiple cerebral infarctions. There is often a history of hypertension, diabetes, and vascular disease involving other organs. The course is often episodic. Focal neurologic signs, such as bilateral pyramidal tract signs, pseudobulbar palsy, cerebellar signs, and hemiparesis, may be present. CT scans of the head typically reveal areas of infarction.

Brain Tumor
Frontal lobe tumors may occur without localizing signs, but there may be abnormal frontal lobe reflexes (snout, suck, grasp). In other areas, there are usually focal neurologic abnormalities. If obstructive hydrocephalus occurs, dementia may appear. Headaches are a common feature of metastatic tumors to the brain. Seizures, hemiplegia, and visual and psychic disturbances may also occur. Subtle changes in mental status may be clues to metastatic disease.

Subdural Hematoma
There may or may not be a history of trauma. The course is variable; it may be acute or prolonged over a period of weeks or months. Headache is generally present. A CT scan usually leads to diagnosis.

Normal-Pressure Hydrocephalus
This condition is usually idiopathic, but it may follow trauma, meningitis, or subarachnoid hemorrhage. The disease may be rapidly progressive. Psychomotor slowing, ataxia, and urinary incontinence are characteristic features. The CT cranial scan shows enlargement of the ventricles without cerebral atrophy.

Jakob–Creutzfeldt Disease
This disease has a rapid course, usually terminating in death in a matter of months. Upper motor neuron signs, myoclonus, basal ganglia signs, and EEG changes are features of this disorder.

Alzheimer's Disease
The onset is usually insidious and the course is usually progressive over a period of years. It may be familial. Its only manifestation is presenile or senile dementia. There are no associated neurologic signs. A cranial CT scan reveals ventricular enlargement and diffuse cortical atrophy.

Pick's Disease
The clinical picture is exactly like that of Alzheimer's disease. However, the temporal and frontal lobes are affected to a greater degree than the remainder of the brain.

Diagnostic Approach
History and Physical Examination
I. Obtain a careful history from both the patient and the patient's family. Observations by family members are particularly important because abnormalities unknown to the patient may have been noted.
II. Check the family history; Alzheimer's disease is often familial.
III. Make inquiries about symptoms or illnesses that might establish a medical cause for the dementia.
IV. Careful physical and neurologic examinations are indicated in all cases.
V. Differentiate between dementia and delirium.

Mental Status Examination
Evaluation of the mental status is mandatory. The mental status can often be defined by using simple tests at the bedside or in the physician's office. The patient's educational level and prior intellectual capabilities must be considered in evaluating the results.

I. Orientation
   A. Determine if the patient is aware of the time, date, month, and year.
   B. Check whether the patient is cognizant of where he or she is and of his or her surroundings.
II. Memory
   A. Can the patient recall remote events (e.g., dates of graduation from school, date of marriage, names of the last two presidents)?
   B. Can the patient recall recent events (e.g., newspaper stories, items eaten at his last meal, activities within the past day or so)?
   C. What is the patient's capacity for immediate recall? Name three common objects (e.g., hat, car, pencil). Can the patient name them 5 minutes later?
III. General information. Can the patient discuss current events, weather conditions, common geography (e.g., names of major cities, states, rivers), important dates in history?
IV. Calculations
   A. Ask the patient to count backward by 7, starting with 100.
   B. Give the patient a simple problem. For example, if I purchase four apples at 9 cents each, how much change should I receive from $1.00?
V. Abstraction. Can the patient think in abstract terms?
   A. Ask the patient to describe how a ball and an orange are alike.
   B. Ask the patient to tell the difference between a child and a dwarf.
VI. Naming. Ask the patient to name such objects as a pencil, book, knife, table, and coin.
VII. Apraxia. Ask the patient to lock an imaginary door with an imaginary key or to use an imaginary pair of scissors.
VIII. Language
   A. Ask the patient to read a paragraph in a newspaper. Is it read accurately? Is it comprehended?
   B. Ask the patient to write a sentence of his or her choosing. Dictate one for the patient to write.
   C. Ask the patient to follow a simple command or commands (e.g., "Take a pencil and place it on a desk").
   D. Ask the patient to draw or copy a simple object, such as a cube.
   E. Ask the patient to repeat, "No ifs, ands, or buts."
   F. Ask the patient to complete and interpret a proverb (e.g., "A new broom sweeps . . .," or "A rolling stone gathers no. . . .").
IX. Standardized testing by "mini mental status examination."

Additional Studies
If the mental status evaluation is indicative of dementia, further workup is indicated. It is not necessary to perform a sophisticated battery of psychological tests to evaluate the mental status, except under unusual conditions.

Depending on the circumstances and clinical information, some or all of the following procedures should be performed.

I. CBC
II. Urinalysis
III. Biochemical screening (including liver function tests)
IV. Serum vitamin B12 level
V. Serum electrolytes
VI. Arterial blood gases
VII. Thyroid function tests (T_4; T_3 resin uptake or T_3 RIA, or both; TSH)
VIII. Drug levels (when appropriate)
IX. Serologic tests for syphilis

X. Chest films
XI. Electroencephalogram
XII. Lumbar puncture
XIII. Cranial CT or MRI scan
XIV. HIV antibodies if AIDS is suspected

Headaches and Facial Pain

Sidney Duman and Stanley H. Ginsburg

Headache
Headache is a symptom, not a disease.

Diagnostic Approach
History
I. Age, sex, occupation
   A. Migraine headaches are more frequent in teenagers and young adults, with a higher occurrence in women. Migraine may occur in later years coincident with the development of systemic hypertension.
   B. Cluster headaches occur almost exclusively in men.
   C. Cranial arteritis occurs more frequently in late middle age and in elderly persons.
   D. Exposure to occupational toxins (e.g., carbon monoxide, lead, nitrates) may predispose to headache.
II. Duration
   A. Tension headaches often have symptoms of long duration.
   B. Headaches owing to expanding intracranial disease are usually of short duration. It should be mentioned that patients with chronic subdural hematoma may give no history of head trauma (often the injury is forgotten).
   C. Headaches owing to meningeal causes (e.g., spontaneous subarachnoid hemorrhage, acute meningitis) are usually acute in onset.
   D. Posttrauma headache, although of variable duration, tends to be self-limiting. Undue prolongation of symptoms suggests nonorganic factors.
   E. Migraine headaches usually recur over a long period of time, with symptom-free intervals between attacks.
III. Location of headache
   A. As a general rule, localized headache is of greater significance than diffuse headache.
   B. Tension headaches are typically generalized, bandlike, or bioccipital.
   C. Classic migraine, now termed *migraine with aura,* is often unilateral and frequently more prominent anteriorly. Although the side of involvement may alternate, one side tends to be affected more frequently.
   D. Common migraine, now termed *migraine without aura,* is frequently bilateral.
   E. The cluster variety of migraine is invariably limited to the same side of the head in any given attack. It is usually periorbital.
   F. Headache early in the course of expanding intracranial lesions is often appreciated at the site of the expanding mass. When there is a progressive increase in intracranial pressure, the headache may become generalized.
   G. The headache of acute subarachnoid hemorrhage is not only sudden in onset but usually is generalized, with predominant occipital localization.
   H. Headache owing to meningitis is often predominantly occipital.
   I. Cranial arteritis is initially manifested by localized temporal headache.
IV. Quality of the pain
   A. Tension headaches are pressing, squeezing, tight, or heavy.
   B. Migraine headaches are usually throbbing or pounding and photophobia and phonophobia frequently occur.
   C. The headache associated with an expanding intracranial lesion is usually relatively mild.

D. In acute subarachnoid hemorrhage, the pain tends to be explosive and intense. Unruptured intracranial aneurysms are usually not associated with pain. Cerebral infarction is commonly painless.

V. Prodromal symptoms
A. Migraine headaches are commonly preceded by such systemic complaints as euphoria, anorexia, or nausea.
B. Migraine headaches are often preceded by such neurologic symptoms as scintillating scotomata, transient hemianopias, hemimotor or hemisensory disturbances, and dysphasia.

VI. Associated symptoms
A. Tension headaches are often associated with other psychophysiologic disturbances.
B. Migraine headaches may be accompanied by all of the prodromal symptoms listed in the preceding. On occasion, transitory blindness or paresis of eye movements may occur.
C. Cluster headaches are typically associated with ipsilateral lacrimation, conjunctival injection, rhinorrhea, and facial flushing. Focal cerebral symptoms or signs are absent.
D. In the case of intracranial mass lesions, the associated symptomatology is often more prominent than the headache. The symptoms that occur depend on the anatomic location of the lesion. Some intracerebral lesions (e.g., tumors, arteriovenous malformations) may exhibit seizures, whereas extracerebral masses (e.g., chronic subdural hematoma) are less likely to be accompanied by seizures.
E. Cranial arteritis is often associated with systemic symptoms, including fever, anorexia, and rheumatic symptoms (polymyalgia rheumatica). Focal cerebral symptoms may be related to intracranial arterial occlusion. Ocular involvement is frequent.

VII. Precipitating and aggravating factors
A. Tension headaches and vascular headaches are commonly induced or aggravated by emotional factors.
B. Factors such as alcohol, hypoxia, systemic hypertension, and hormonal changes (e.g., menses, oral contraceptives, pregnancy) may affect the frequency of vascular headaches.
C. The headache of intraventricular and posterior fossa tumors may be accentuated by changes in head position, coughing, and the Valsalva maneuver.

VIII. Frequency, duration, and diurnal variation of headaches
A. Tension headaches are often persistent and may worsen as the day progresses.
B. The frequency of migraine headaches is variable and unpredictable. Although the usual duration is from 6 to 36 hours, they may persist for days. Migraine headaches frequently begin in sleep but may occur at any time of the day.
C. Cluster headaches usually occur repetitively over a period of weeks or months. Often there are one or two attacks daily. The headaches are typically nocturnal and of brief duration (30 minutes to a few hours). The peak incidence is in the spring and fall.
D. Expanding intracranial lesions exhibit no specific pattern.
E. The headache of acute spontaneous subarachnoid hemorrhage is persistent.

IX. Family history
A. There is usually a strong family history of migraine in patients with this type of headache. Cluster headaches are not familial.
B. Some brain tumors, especially the phakomatoses, may be reported in the family history.

Physical Examination

I. General physical examination
A. A flushed face, lacrimation, and unilateral rhinorrhea may be noted in cluster headaches.
B. Facial hemangiomas and neurofibromatosis may be observed in the phakomatoses.

C. Systemic signs of disease, such as fever, weight loss, and anemia, may be seen in the following conditions:
1. Infectious disease
2. Specific infections of the central nervous system
3. Metastatic disease to the brain or meninges, or both
4. Cranial arteritis

II. Neurologic examination
A. No neurologic abnormalities are noted in patients with tension headaches.
B. A small percentage of patients with migraine may exhibit permanent residual neurologic evidence of cerebral ischemia. Most patients, however, show no neurologic abnormalities.
C. Horner's syndrome is sometimes seen during a migraine headache, but it is rarely permanent.
D. With any expanding intracranial lesion, localizing signs are the rule. The findings depend on the location of the lesion.
1. Chronic subdural hematomas may not have localizing or lateralizing physical signs.
2. Midline neoplasms may have no localizing neurologic signs.
3. Confusion and obtundation may be the only positive findings in chronic subdural hematomas and in midline intracranial lesions.
E. Papilledema is observed in intracranial lesions producing increased intracranial pressure, but it may also be seen in benign intracranial hypertension (pseudotumor cerebri).
F. Bruits may be audible over the eyes or cranium in vascular malformations of the brain.
G. Signs of meningeal irritation are noted in lesions affecting the meninges.

Diagnostic Studies

I. If the history does not suggest significant neurologic disease and the clinical examination reveals nothing remarkable, no further investigation is warranted.
II. If either the history or the examination suggests organic disease, additional studies are indicated. These should include an electroencephalogram, CT or MRI scan, and mapping of the visual fields. Angiography may be needed.
III. Lumbar puncture may be indicated in suspected subarachnoid hemorrhage, encephalitis, or meningitis. It may also be of value in the investigation of other neurologic diseases producing headache. A spinal tap is contraindicated in the presence of increased intracranial pressure, with an occasional specific exception (e.g., bacterial meningitis with associated papilledema or pseudotumor cerebri).
IV. The need for other studies is ordinarily suggested by the history and physical examination (e.g., sedimentation rate and biopsy in suspected cranial arteritis, various diagnostic x-ray studies to rule out primary neoplasm metastatic to the brain).

Facial Pain

Neuralgia

Neuralgia may be defined as recurrent, usually brief, paroxysmal, intense, lancinating pain of unknown cause, localized to the distribution of a specific nerve, and not associated with objective evidence of nerve dysfunction.

I. Trigeminal neuralgia (tic douloureux)
A. Trigeminal neuralgia may involve one or more of the sensory divisions of the trigeminal nerve.
B. The condition usually occurs in older people. Its occurrence in patients under 35 years of age is rare and should suggest the possibility of multiple sclerosis.
C. The frequency of episodes of pain is variable. Pain may occur many times each day or may occur infrequently. Various stimuli, such as talking, eating, exposure to cold, and local pressure, may trigger paroxysms of pain.
D. The presence of signs of dysfunction of the fifth cranial nerve in association with neuralgia should suggest the possibility of such entities as multiple sclerosis or tumors of the nerve.

E. The diagnosis is based entirely on the history and the absence of neurologic, radiologic, and laboratory abnormalities.

II. Glossopharyngeal neuralgia
   A. This condition is found much less frequently than trigeminal neuralgia.
   B. The pain is generally referred to the throat or ear.
   C. The frequency of attacks is variable.
   D. The pain is often triggered by swallowing, talking, or contact with pharyngeal structures.
   E. Occasionally, glossopharyngeal neuralgia is accompanied by syncope owing to associated vagal stimulation.

III. Postherpetic facial pain (postherpetic neuralgia)
   A. Postherpetic neuralgia involving any of the divisions of the trigeminal nerve may follow herpes zoster.
   B. The pain differs from typical neuralgic pain in its tendency to be more constant, its nonparoxysmal quality, and its failure to be triggered by stimuli that ordinarily aggravate conventional neuralgic pain.
   C. Objective sensory loss is usually present, and the skin of the affected area is sensitive to touch.

Atypical Facial Pain

I. The term *atypical facial pain* refers to pain that does not conform to the anatomic distribution of a nerve.
II. The pain is quite variable in character, frequency, and duration.
III. Some authorities think that it may represent a form of migraine.
IV. No abnormalities are noted on physical examination. Laboratory and x-ray findings are also negative.

Other Facial Pains

Many facial pains are related to local disease affecting the teeth, nose, paranasal sinuses, mouth, eyes, ears, temporomandibular joints, and other structures. Careful examination supplemented by appropriate x-ray studies usually establishes the diagnosis in these disorders.

Syncope

H. Harold Friedman

Definition

Syncope, or fainting, is a brief period of unconsciousness caused by reversible disturbances in cerebral function. The most common mechanism is a decrease in cerebral blood flow owing to diminished cardiac output, arterial hypotension, or cerebral arterial obstruction. Altered patterns of central nervous system activity or impairment of cerebral metabolism by systemic disorders may be contributory mechanisms in some instances.

Etiology

I. Vasovagal or vasodepressor syncope (simple faint)
   A. This is the most common form of syncope, accounting for more than 50% of cases. Its primary mechanism is a fall in blood pressure. The symptoms and signs of the faint result from vasodepressor and vagal responses usually initiated by pain, fear, or anxiety. Contributory factors include excessive intake of food or alcohol, close quarters, and excessive heat.
   B. Fainting occurs *only* when the patient is sitting or standing.
   C. Vasodepressor syncope occurs typically in young people. Fainting that begins in middle age or later in life is usually owing to other causes.
   D. The clinical picture is well known. The faint is almost always preceded by prodromal symptoms, such as a feeling of warmth, nausea, abdominal stress, yawning, or belching. The premonitory symptoms are followed by weakness, lightheadedness or faintness, pallor, sweatiness, coldness of the hands and feet, and eventually, loss of consciousness. During the premonitory phase, the heart rate is rapid, but when the systolic pressure falls to a critical level of 55 or 60 mm Hg, the heart rate slows (instead of accelerating) and the radial pulse usually becomes weak. Consciousness is rapidly regained with recumbency. However, symptoms may recur for a brief period after the faint if the patient tries to sit up or stand.

II. Cardiac syncope
   A. Syncope may result from lesions or structural abnormalities of the heart and from cardiac arrhythmias. A decreased cardiac output is the fundamental mechanism of this type of syncope.
   B. On the left side of the heart, the most common causes of cardiac syncope are aortic stenosis, idiopathic hypertrophic subaortic stenosis, malfunction or thrombosis of a prosthetic mitral or aortic valve, left atrial myxoma, and a ball-valve thrombus.
   C. Right-sided lesions that may be responsible for syncope include Eisenmenger's syndrome, the tetralogy of Fallot, primary pulmonary hypertension, pulmonary embolism, and pulmonary stenosis.
   D. Certain congenital or familial syndromes characterized by prolongation of the Q-T interval may be associated with syncope owing to ventricular dysrhythmias.
   E. Fainting is a common occurrence in organic heart disease. The relationship to exertion may have diagnostic significance.
      1. Severe aortic stenosis, *on exertion* (effort syncope)
      2. Primary pulmonary hypertension, *on exertion*
      3. Idiopathic hypertrophic subaortic stenosis, *after exertion*
   F. Syncope may occur when the heart is beating too fast or too slow, or, obviously, when it is not beating at all. Heart block and cardiac arrhythmias are the most common causes.
   G. *Heart block,* whether complete or incomplete, may be permanent or intermittent. Unconsciousness usually occurs when the block is complete and the idioventricular pacemaker fails to initiate impulses. However, syncope is not uncommon in second-degree atrioventricular block when the ventricular response is slow. The term *Adams-Stokes attack* refers to syncope occurring in association with heart block. The mechanism is ventricular tachyarrhythmia or asystole.
   H. Fainting may occur at the onset and during paroxysmal tachycardias because of the sudden fall in cardiac output. The arrhythmias that may produce syncope are supraventricular tachycardia, ventricular tachycardias, and torsades de pointes. It may also occur at the termination of a paroxysm with asystole from overdrive suppression.
   I. Syncope may be the result of *sinus arrest* or *sinoatrial block* and is common in the *sick sinus syndrome.* Marked sinus bradycardia, especially in elderly persons, may sometimes produce syncope.
   J. *Pacemaker malfunction* may sometimes produce syncope.
   K. Common underlying causes of cardiac arrhythmias associated with syncope include: sinus node dysfunction, the WPW syndrome, the LGL syndrome, cardiomyopathy, mitral valve prolapse, long Q-T interval syndromes, drugs, and metabolic disturbances.

III. Vascular syncope
   A. Vascular syncope may be divided into three categories: orthostatic, cerebrovascular, and miscellaneous.

IV. Orthostatic hypotensive syncope
   A. Orthostatic syncope occurs *only* in the upright position (sitting or standing). The faint occurs *without* warning; its mechanism is a precipitous drop in blood pressure.
   B. Orthostatic syncope may occur *physiologically* in some individuals after prolonged standing or on assumption of an upright position after a long period of recumbency.

C. Orthostatic syncope may occur after *venous pooling or volume depletion* as a result of factors such as hemorrhage and sodium depletion. It may also occur following the use of drugs such as diuretics, guanethidine, L-dopa, carbidopa, phenothiazines, tricyclic antidepressants, MAOIs, and prazosin.
D. Orthostatic syncope may be owing to *neurologic disease or disease with neurologic complications,* such as diabetic neuropathy, and tabes dorsalis. The mechanism appears to be a loss of normal sympathetic compensatory mechanisms.
E. *Idiopathic orthostatic hypotension* and the Shy-Drager syndrome may be associated with syncope. The causes of these syndromes are unknown. They are often associated with impotence, anhidrosis, and parkinsonian-like symptoms.

V. Cerebrovascular syncope
A. Cerebrovascular disease is one of the less common causes of syncope. It is usually the result of a reduction in cerebral blood flow owing to atherosclerotic narrowing of vessels, thrombosis, or embolism.
B. Cerebrovascular syncope is a common feature of vertebrobasilar arterial insufficiency. It may occur in the subclavian steal syndrome and the aortic arch syndrome. Unilateral carotid artery insufficiency usually does not cause fainting unless the contralateral artery is compressed. Cerebral arterial obstructive disease may make a patient more susceptible to syncope form other causes.

VI. Miscellaneous causes of syncope
A. The *carotid sinus syndrome* is an uncommon cause of syncope. The vasodepressor type is characterized by a drop in blood pressure without a change in heart rate; the cardioinhibitory type, by cardiac standstill; and the cerebral type, by a loss of consciousness without a change in either pulse rate or blood pressure. The diagnosis should be suspected when fainting is induced by turning the head, looking upward, or wearing tight collars.
B. *Glossopharyngeal neuralgia* is characterized by paroxysmal pain in the throat, bradycardia, hypotension, and syncope.
C. *Micturition syncope* is not unusual in elderly men. It is usually nocturnal. Syncope occurs during or immediately after urination.
D. *Cough syncope* is a faint preceded by a violent coughing spell. It usually occurs in overweight men with chronic obstructive pulmonary disease.
E. *Hysterical fainting* occurs in neurotic young people, more often in women. The faint characteristically takes place in the presence of other people. Usually there are no premonitory symptoms. The vital signs are unchanged at the time of the syncope episode. Although the fainting is usually involuntary, some individuals can produce a faint at will. Beyond early adult life the diagnosis of hysterical fainting is unlikely, and other causes of the fainting should be sought.
F. Syncope may occur during *hypoglycemic episodes.* The diagnosis is established by the clinical picture and low blood sugar values. Injection of glucose intravenously usually leads to a prompt return of consciousness. Although hypoglycemia may be spontaneous, the vast majority of cases occur in diabetics who are receiving insulin or oral hypoglycemic medications.
G. *Hyperventilation* may cause syncope. Paresthesias, numbness, lightheadedness, coldness, and at times, tetany are the associated telltale signs of hyperventilation.
H. Rarely, syncope may occur in the absence of heart disease as a result of reflex cardiac asystole (*vasovagal syncope*).

VII. Combined causes of syncope
A. In many cases, particularly in elderly persons, several factors may be responsible for syncope.
B. Such conditions as arrhythmias, volume depletion, decreased cardiac output, and decreased peripheral resistance in combination may result in syncopal episodes.
C. In some cases, especially in elderly persons, in spite of thorough investigation, no apparent cause for syncope can be found.

Diagnostic Approach

As a first step, conditions such as coma, dizziness and vertigo, seizures, and other neurologic symptoms should be excluded.

History

I. Check for systemic conditions that predispose to volume depletion and venous pooling, or for drugs that have these effects (e.g., nitrates, beta-blockers, nifedipine, prazosin, quinidine, M-dopa, and verapamil).
II. The age of the patient may be significant. Vasodepressor syncope and hysterical fainting are rare beyond early adult life. Syncope that begins during or after middle age is usually owing to other causes.
III. Inquire into the circumstances of the attack.
A. Symptoms
1. Fainting preceded by pain, fear, or anxiety suggests a vasovagal origin.
2. Premonitory symptoms (e.g., weakness, sweating, pallor) are commonly present in vasodepressor and hypoglycemic syncope.
3. Associated symptoms of numbness, paresthesias, and coldness of the extremities suggest the diagnosis of hyperventilation.
4. Syncope preceded by prolonged standing is probably orthostatic.
5. Absence of warning symptoms is typical of cardiac or orthostatic syncope.
B. Effect of posture
1. In vasovagal syncope, the patient is always upright at the time of the faint.
2. In orthostatic hypotensive syncope, fainting occurs after prolonged standing or on a shift from recumbency to the erect position; it never occurs in recumbency.
3. Fainting in the upright position with little or no warning is indicative of cardiac or orthostatic syncope.
4. Syncope in recumbency is almost always cardiac.
C. Sleep. Syncope while the patient is asleep (manifested by inability to arouse the patient) suggests the cause may be cardiac, hypoglycemic, or epileptic.
D. Meals. Syncope in the fasting state or long after a meal requires investigation for hypoglycemia.
E. Relationship to exercise. Effort syncope is often owing to aortic stenosis or primary pulmonary hypertension; posteffort syncope, to idiopathic hypertrophic subaortic stenosis.
F. Duration of syncope. Syncope lasts but a few seconds, except in aortic stenosis, hypoglycemia, and hysteria, when it may be of longer duration.
G. Other factors
1. Nocturnal fainting in men in relationship to the act of urination suggests micturition syncope.
2. Fainting following a coughing episode is characteristic of cough syncope.
3. Fainting that occurs in relationship to head and neck movements or the wearing of tight collars may be indicative of carotid sinus syncope.
4. Fainting in diabetics receiving insulin or hypoglycemic medications suggests hypoglycemia.
5. Syncope associated with palpitation suggests a cardiac arrhythmia.

IV. Obtain a record, if available, of the blood pressure, heart rate, and associated findings during the attack. Hypotension with a slow rate suggests vasodepressor syncope. Marked bradycardia with normal or elevated pressure implicates atrioventricular block or sinoatrial node dysfunction. Marked hypotension with a normal or rapid heart rate suggests orthostatic syncope. The presence of bifascicular, trifascicular, or bilateral bundle branch block in the electrocardiogram suggests AV block as a possible cause of syncope. Electrocardiographic monitoring may be useful in the diagnosis of syncope owing to cardiac arrhythmias.
V. Check for a history of organic heart disease, neurologic disease, diabetes, anemia, or cerebrovascular disease, all of which may predispose to syncope.

Physical Examination and Special Studies

I. Look for diseases or disorders (listed in the preceding paragraph) that predispose to syncope.

II. Listen for carotid bruits, and examine the patient for other evidence of cerebrovascular disease.
III. Search for signs of organic heart disease, particularly for such conditions as aortic and mitral valve disease, primary pulmonary hypertension, and the tetralogy of Fallot.
IV. When cardiac arrhythmia is suspected, record an electrocardiogram, and, if necessary, monitor the patient continuously.
V. Determine the heart rate and blood pressure with the patient recumbent and after the patient has been standing still for at least 1 minute. Because there is normally little change in these parameters on change of position, a significant fall in blood pressure implicates postural hypotension. Orthostatic hypotension is also demonstrable on a tilt table.
VI. Have the patient hyperventilate for a 2-minute period while seated, to see if the symptoms of hyperventilation are similar to those of spontaneous attacks.
VII. When carotid sinus syncope is suspected, massage first the right and then the left carotid bulb with the patient seated. Observe the patient for changes in clinical status, heart rate, and blood pressure. Carotid massage should be employed with great caution in elderly persons and is contraindicated in cerebrovascular and some cardiac disorders.
VIII. When spontaneous hypoglycemia is suspected, blood sugar determinations and 5-hour glucose tolerance tests may be indicated.
IX. Specialized procedures may be necessary for the diagnosis of cardiovascular lesions: ambulatory monitoring (preferably with loop recorders), determination of systolic time intervals, exercise testing, signal-averaged electrocardiography, echocardiography, angiography, cardiac catheterization, radioisotopic studies, upright tilt testing, and electrophysiologic studies.

Signal-averaged electrocardiography may be useful in identifying patients at risk for ventricular tachycardia as a cause of syncope. It is most valuable in patients with coronary artery disease.

Upright tilt-table testing may provide a means for the diagnosis of neurally mediated syncopes. It has been claimed that this procedure provides the diagnosis in 50% to 75% of cases. It should be noted that there is no universally accepted protocol for head-up tilt-table testing.

Electrophysiologic studies are an important part of the workup in some patients with syncope of unexplained cause. The best candidates for electrophysiologic studies are patients with organic heart disease and unexplained syncope. Electrophysiologic testing may have significant limitations, however, both in diagnosis and in the interpretation of the results.

Table 10-5. Differential diagnosis of syncope and seizures

Parameter	Syncope	Seizures
Onset	Gradual in vasodepressor type; often sudden in other types	Sudden
Warning symptoms	Usual in vasodepressor; absent in other types	Aura common
Duration of unconsciousness	Brief	Prolonged except in absence seizures
Position at onset	Usually erect or on change to erect; rarely recumbent	Any
Convulsions	Rare	Common
Incoherence, tongue biting	Rare	Common
Postictal symptoms (headache, drowsiness, confusion)	Usually absent	Usually present

X. Diagnostic evaluation of cerebrovascular syncope may require ophthalmodynamometry, Doppler flow studies, skull films, and angiography.

Differential Diagnosis

I. *Coma* is differentiated from syncope by the prolonged duration of the state of unconsciousness.
II. *Dizziness and vertigo* are not associated with unconsciousness and are characterized by a subjective sensation of motion.
III. The differential diagnosis of *seizures* and *syncope* is summarized in Table 10-5.

Epilepsy (Seizures)

Sidney Duman and Stanley H. Ginsburg

Definition

Epilepsy is a paroxysmal disorder of the central nervous system, sudden in onset, usually recurrent, and characterized by one or more of the following manifestations:

I. Unconsciousness
II. Localized or generalized tonic spasms or clonic muscle contractions, or both
III. Sensory disturbances
IV. Psychic disturbances

The disorder may be classified into two major categories: (a) idiopathic (*generalized seizures without focal onset*, as termed by the International Classification of Seizures), and (b) symptomatic (*partial seizures*, according to the International Classification).

Idiopathic Epilepsy

Idiopathic epilepsy refers to seizures not directly attributable to demonstrable organic brain disease. The condition usually begins in the first two decades of life and may last well into adult life. A hereditary factor may be present. Idiopathic epilepsy may be manifested as grand mal or petit mal seizures.

Clinical Features

Major Motor Seizures (Grand Mal)

Grand mal seizures are characterized by sudden loss of consciousness, often preceded by a cry, following which the patient falls. Various injuries may occur. Usually a tonic phase, consisting of generalized muscle rigidity, precedes a clonic phase of generalized muscle activity. During this period, the patient may be incontinent of either urine or feces, and he may lacerate his tongue or buccal mucous membranes. Frothing at the mouth may occur. During the tonic phase, respirations often cease and cyanosis may occur. After cessation of the convulsive activity, flaccidity supervenes, but unresponsiveness may persist for a variable period of time. On awakening, the patient often is sleepy and confused. The patient may complain of headache or sore muscles. The postictal symptoms may persist for several hours to several days. The duration of an individual convulsion is variable, lasting from less than a minute to 30 minutes or longer. The frequency of seizures is also extremely variable. They may happen at any time of the night or day. Convulsions may occur only during sleep in some patients.

Minor Motor Seizures (Petit Mal)

I. The petit mal triad consists of the following:
   A. Myoclonic jerks, which are brief, sudden, involuntary muscle contractions
   B. Akinetic seizures, in which there is a transitory loss of motor tone sufficient to cause falling without associated clonic muscle activity. Consciousness may be lost briefly.
   C. Brief absences or loss of contact with the environment without a loss of muscle tone
II. Classic petit mal is characterized by a blank or vacant expression and momentary cessation of motor activity without loss of muscle tone.

III. Petit mal seizures are not followed by a postictal state. Consciousness returns promptly. Voluntary motor activity may resume immediately. Petit mal episodes often occur with great frequency. As many as 50 or more attacks in a day may occur. The onset of true petit mal epilepsy is invariably in childhood.
IV. Patients with idiopathic epilepsy often have both major and minor seizures. Although petit mal seizures usually cease spontaneously before the age of 20 years, they occasionally persist into adult life. Idiopathic grand mal seizures, however, frequently continue in adult life.

Physical Examination
Examination of the patient with idiopathic epilepsy demonstrates no localizing neurologic abnormalities. Following a grand mal seizure, bilateral extensor plantar reflexes are often present.

Symptomatic Epilepsy
The term *symptomatic epilepsy* refers to seizures attributable to demonstrable organic brain disease. The anatomic localization of the lesion determines the clinical features of the seizure. Symptomatic epilepsy may begin at any age. The various manifestations of symptomatic epilepsy are described in the following.

Clinical Features
Generalized Convulsions
The generalized convulsions encountered in symptomatic epilepsy do not differ from the grand mal seizures of idiopathic epilepsy. Unlike the latter, they may be preceded by an aura. The nature of the aura depends on the focus of origin of the seizures. For example, the aura may be a sensation such as unpleasant odor or paresthesia in a limb. The aura should be regarded as the initial manifestation of the seizure, although it sometimes represents the entire seizure. In some instances, seizures are manifested by unconsciousness without associated involuntary motor activity. It is worth noting that a generalized convulsion may follow any variety of symptomatic epilepsy.

Temporal Lobe Epilepsy (Partial Seizures with Complex Symptomatology)
I. *Absences* found in symptomatic epilepsy are of themselves clinically indistinguishable from those of petit mal epilepsy. However, associated temporal lobe phenomena (e.g., lip smacking) assist in identifying their origin.
II. *Automatisms* ("psychomotor epilepsy") may be defined as repetitive automatic behavior patterns.
III. *Dreamy states*, or feelings of familiarity (*déjà vu*) or unfamiliarity (*jamais vu*) and forced or compulsive thinking
IV. *Auditory, vertiginous, olfactory, or gustatory hallucinations*
V. *Abdominal sensations*, usually unpleasant or peculiar epigastric feelings that not uncommonly seem to radiate to the head
VI. *Visual hallucinations* are well formed in temporal lobe disturbances but tend to be ill-defined in more posteriorly situated (occipital lobe) lesions.

Focal Motor and Sensory Epilepsy (Partial Seizures with Elementary Symptomatology)
Focal motor seizures originate in the precentral cortex and are characterized by tonic or clonic muscle activity limited to one extremity, one side of the body, or one side of the face. Focal sensory seizures are similarly localized sensory phenomena that have their origin in the postcentral cortex.

I. Jacksonian seizures are motor or sensory phenomena that spread peripherally in accordance with the anatomic cortical location of the lesion.
II. Epilepsia partialis continua are continuous focal motor seizures of exceptionally prolonged duration, sometimes lasting for months.

Adversive Seizures
Adversive seizures are of frontal lobe origin. They result in deviation of the head and eyes, and occasionally the body, to the side opposite the lesion. These are a form of partial seizures with elementary symptomatology.

Unclassified Seizures
I. Reflex epilepsy. Reflex epilepsy refers to seizures precipitated by some form of external stimulation. Examples are photic stimulation, reading (reading epilepsy), and music (musicogenic epilepsy).
II. Tonic postural seizures. This type of epilepsy refers to the paroxysmal occurrence of generalized muscle rigidity, often with opisthotonos. The limb posture may resemble that observed in decerebrate rigidity. Such seizures are presumed to originate in the brainstem.
III. Infantile massive spasms. This uncommonly occurring syndrome of varied causes is characterized by frequent, abrupt, myoclonic, and akinetic seizures. It is often accompanied by mental retardation and a typical electroencephalographic pattern (hypsarrhythmia).
IV. Juvenile myoclonic epilepsy (Unverricht's syndrome). This is a rare familial disorder, beginning in childhood, that is manifested by generalized convulsive and myoclonic seizures and progressive intellectual deterioration. So-called Lafora's bodies are a characteristic pathologic finding in the brain.

Postictal Symptoms
In addition to the general postictal symptoms just noted, patients with symptomatic epilepsy may experience focal neurologic symptoms representing dysfunction of that portion of the brain responsible for the seizure. Dysphasia following a generalized convulsion is an example of this type of symptom. The occurrence of such a localized symptom makes it possible to deduce that the seizure is focal in origin, arising from the dominant hemisphere.

Physical Examination
Examination may demonstrate localizing neurologic abnormalities that may be transient (e.g., Todd's postictal paralysis) or permanent. The presence of localizing signs implies a focal lesion and thus rules out the diagnosis of idiopathic epilepsy.

Etiology
The occurrence of symptomatic epilepsy implies a focal lesion in the brain but does not specify its cause. Search for a lesion amenable to specific therapy is imperative. The types of lesions responsible for symptomatic epilepsy are listed in the following.

I. Localized structural lesions
   A. Static—local brain atrophy
   B. Progressive—neoplasms, abscesses, vascular malformations
   C. Vascular
      1. Thrombotic cerebral infarction seizures uncommon
      2. Embolic cerebral infarction and intracerebral hemorrhage—seizures somewhat more common
      3. Cortical vein thrombosis—seizures frequent
   D. Various other encephalopathic disorders, such as HIV encephalopathy
II. Diffuse structural lesions
   A. Infections (e.g., encephalitis)
   B. Metabolic (e.g., uremia, hypoxia, hyponatremia, hypothyroidism)
   C. Degenerative (e.g., Tay-Sachs disease)
III. Cerebral trauma. Seizures may occur in cerebral trauma, especially in penetrating brain injuries.
IV. Febrile seizures. Seizures may be caused by fever alone in children from 6 months to 3 years of age. Seizures owing to focal brain lesions may sometimes be triggered by fever.

Diagnostic Approach to Epilepsy
I. All patients with epilepsy should have an EEG and usually a CT or MRI scan of the head, as well as determinations of the fasting blood sugar, serum calcium, electrolytes, and BUN or creatinine. An isotope brain scan may also be helpful.

II. All patients with the onset of seizures in adult life should have a CT scan or MRI. Children with seizures and suspected structural brain diseases should also have cerebral imaging.
III. Ambulatory EEG monitoring may be useful.

Status Epilepticus

Status epilepticus refers to the failure of a patient to recover from one seizure before the next attack occurs. Vigorous attempts to terminate the seizures are mandatory, because death may occur. Petit mal status epilepticus and partial status epilepticus occur occasionally.

Dizziness and Vertigo

Sidney Duman and Stanley H. Ginsburg

Definitions

Vertigo is a subjective sensation of movement. The patient may feel either that he or she is revolving in space or that objects in the environment are moving around him or her. *Dizziness* is the term most commonly used by patients to describe vertigo. However, because this term may have a different meaning to different individuals, the patient should be asked to describe the symptoms in detail. It will then become apparent whether the patient is suffering from vertigo or other symptoms such as giddiness, lightheadedness, faintness or a sensation of "passing out," a feeling of fullness in the head, swaying or swimming sensations, or visual disturbances (e.g., diplopia).

Clinical Features of Nonvertiginous Dizziness

I. The etiology is varied. Psychogenic, cerebrovascular, neurologic, arthritic, otologic, or visual disturbances may play a role, separately, or in various combinations.
II. Nonvertiginous dizziness is easily distinguished from true vertigo by the absence of the sensation of rotary movement of either the patient or his or her environment.

Evaluation of Dizziness

I. Clues to the causes of dizziness may be obtained from the history. Specific inquiry should be made concerning the following:
   A. Symptoms of anxiety, hyperventilation, or both
   B. Cerebrovascular disease, especially vertebrobasilar insufficiency
   C. Cardiovascular disease, with special reference to rhythm disturbances, the sick sinus syndrome, and orthostatic hypotension
   D. Neurologic disease, particularly with reference to the neuropathies
   E. Cervical osteoarthritis and spondylosis
   F. Visual disturbances, especially cataracts
   G. Medications
   H. Precipitating factors—change of position, effort, cough, anemia
II. In the general physical examination, special attention should be paid to the following:
   A. The blood pressure in both arms during recumbency and standing
   B. Disorders of cardiac rhythm
   C. Auscultation of the neck for bruits
   D. The effect of carotid sinus massage
   E. Relationship of symptoms to neck movements
   F. Attempted reproduction of the symptoms by hyperventilation
   G. Visual disturbances
   H. Neurologic examination, including, if indicated, the procedures elaborated in the following in the workup for vertigo
III. Routine laboratory studies such as CBC, urinalysis, biochemical screening, serologic study, and an ECG are probably indicated in most patients.
IV. Dizziness owing to postural change is especially common in middle-aged and elderly patients. It is probably related to unstable vasomotor reflexes, cerebrovascular disease, cervical spondylosis, or any combination of these. The occurrence of transient giddiness accompanied by dimming of vision and spots before the eyes following an abrupt change from a recumbent or sitting position to an erect one is typical.
V. Psychogenic dizziness is more frequently encountered in younger, tense, and anxious individuals who often exhibit symptoms of hyperventilation.
VI. Disturbances in cardiac rhythm as a cause of dizziness may not be apparent from the history, examination, or random ECG. Electrocardiographic monitoring may be necessary to establish the diagnosis.
VII. Miscellaneous but less common causes of dizziness are the sensory neuropathies, autonomic nervous system dysfunction, orthostatic hypotension, poor vision, and vestibular disturbances.
VIII. Any of the conditions that can cause syncope may also be responsible for dizziness.

Clinical Features of Vertigo

Vertigo may result from lesions of the labyrinth, the eighth cranial nerve, the brainstem, or the cerebral cortex.

Labyrinthine Vertigo

Labyrinthine vertigo is generally sudden in onset and of variable duration (several days to several weeks). The vertigo is often aggravated by changes in position. Recurrence is frequent.

Acute Labyrinthine Vertigo

Attacks of acute labyrinthitis are usually self-limiting. The vertigo is not associated with hearing loss, tinnitus, or symptoms of brainstem dysfunction. However, nausea and vomiting occur frequently. Aside from nystagmus and dysequilibrium of gait, no abnormalities are detectable on neurologic examination. It is worth noting, however, that vertical nystagmus is indicative of brainstem rather than labyrinthine disease.

Chronic Labyrinthine Vertigo (Ménière's Syndrome)

Chronic labyrinthitis is characterized by recurrent, acute, usually brief episodes of vertigo associated with tinnitus, hearing loss, nausea, and vomiting. The tinnitus and hearing loss may persist between attacks. No signs of brainstem dysfunction are noted on examination.

Toxic Labyrinthine Vertigo

Many drugs, such as aspirin and ethacrynic acid, may affect labyrinthine and cochlear function and thereby produce vertigo.

Traumatic Labyrinthine Vertigo

Vertigo may result from relatively mild to severe cranial trauma (e.g., temporal bone fracture). Resolution of the vertigo usually occurs spontaneously.

Labyrinthine Ischemia

The acute vertigo sometimes found in elderly persons or in patients with cerebrovascular disease may be the result of interruption of the blood supply to the labyrinth (via the auditory artery). The clinical picture may be similar to or indistinguishable from that which occurs in acute labyrinthitis or brainstem ischemia, but usually there are differences (see the section Brainstem Lesions).

Benign Positional Vertigo

Benign positional vertigo of the peripheral type is characterized by brief (10 seconds or less) vertigo and nystagmus that appear within seconds of a change in head position, using Bárány's test, and are fatigable. There is no hearing loss, and caloric testing is normal. Positional vertigo and nystagmus of central origin, on the other hand, begin immediately, may last longer, and are not fatigable. Lesions of central origin are likely to be associated with physical signs of central nervous system dysfunction.

Acoustic Nerve Lesions
Patients with eighth nerve or cerebellopontine angle tumors often complain of dizziness, when in fact they mean imbalance or unsteadiness of gait. True vertigo is rare. Involvement of adjacent structures, such as the trigeminal and facial nerves, in association with unilateral ataxia, are clues to the diagnosis of such lesions.

Brainstem Lesions
Vertigo is a common symptom of acute or chronic brainstem dysfunction owing, most commonly, to ischemic disease. It may also result from demyelinating diseases, inflammatory and toxic disorders, or, unusually, from destructive intramedullary lesions (e.g., neoplasms, vascular malformations, syringobulbia). The presence or absence of physical signs of brainstem dysfunction permits the differentiation between vertigo owing to lesions of the brainstem and labyrinthine disturbances, respectively.

Cerebral Cortex Lesions
Vertigo may in rare instances be the manifestation of a temporal lobe cortical discharge (temporal lobe seizure).

Diagnostic Approach
History and Physical Examination
It is usually possible to determine the anatomic location of the lesion causing vertigo from the history and examination.

I. Labyrinthine vertigo, which is most common, is characterized by nystagmus and disequilibrium of gait and the absence of other neurologic abnormalities.
II. Acoustic nerve lesions are characterized by evidence of both auditory dysfunction (deafness and tinnitus) and vestibular abnormality (nystagmus and ataxia), as well as by the presence of "neighborhood" neurologic signs.
III. Brainstem lesions are characterized by (a) horizontal or vertical nystagmus, or both, (b) evidence of eye muscle dysfunction or involvement of other cranial nerve nuclei, and (c) abnormalities of long tract motor, sensory, or cerebellar pathways.
IV. Cerebral cortical lesions (temporal lobe seizures) are rare causes of vertigo.
V. Ischemic labyrinthine disease can usually be differentiated from ischemic brainstem disease by the absence of the neurologic abnormalities described in the preceding.

Caloric and Audiometric Testing
These procedures are valuable in suggesting labyrinthine rather than cerebral cortex or brainstem lesions as the cause of vertigo. Electronystagmography (ENG), a more sophisticated type of caloric investigation, is employed in some medical centers in place of conventional caloric testing. Brainstem evoked potentials may confirm a CNS origin of vertigo.

Imaging Procedures
I. MRI scans of the posterior fossa are helpful.
II. Cervical spine radiographs may be useful in demonstrating vertebral foraminal encroachment, which sometimes causes obstruction of the arterial blood flow to the brainstem and the peripheral auditory apparatus.
III. ENG may be useful.

Electroencephalogram (EEG)
The EEG may be of help in the identification of irritable cortical foci producing temporal lobe seizures.

Lumbar Puncture
Examination of the spinal fluid is occasionally helpful diagnostically. For example, the protein concentration is typically elevated in acoustic neurinomas. Abnormal protein electrophoretic patterns and oligoclonal bands may be observed in the demyelinating diseases.

Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) Scans
These procedures are of great assistance in the diagnosis of mass intracranial lesions. The outline of the internal auditory canals may also be visualized.

Contrast Angiography or Contrast Cisternography
Contrast studies may be necessary for the demonstration of specific intracranial lesions.

Weakness of Neuromuscular Origin

Sidney Duman and Stanley H. Ginsburg

Weakness is one of the most common complaints presented to the physician. This section deals only with weakness produced by neuroanatomic or neurophysiologic lesions. Other causes of weakness are considered elsewhere in this book. Because weakness of neuromuscular origin is manifested by objective evidence of reduced muscle strength, manual testing of muscle function is an important early step in the evaluation of weakness.

Etiology
The various neuromuscular causes of weakness and paralysis can be divided into five major groups:

I. Disease of the upper motor neurons (the long motor pathways of the brain and spinal cord, consisting of the corticobulbar and corticospinal pathways)
II. Disease of the lower motor neurons (the anterior horn cells of the spinal cord and the motor nuclei of the brainstem)
III. Disease of the nerve roots and the peripheral nerves
IV. Disease of the myoneural junction
V. Disease of skeletal muscle

Table 10-6 lists the more common causes of these anatomic lesions.

Clinical Features
Upper Motor Neuron Disease
Chronic Lesions
I. The weakness is located below the anatomic level of the lesion.
II. Unilateral lesions situated above the pyramidal decussation in the medulla produce weakness on the contralateral side, whereas those situated below this level produce ipsilateral weakness.
III. The weakness is in "elective distribution"; that is, in patients who are not completely paralyzed, the pattern of involvement is selective.
   A. In the upper extremity, the muscles that produce abduction, external rotation, and extension of the joints are primarily affected. The antagonistic muscle groups are usually less severely involved.
   B. In the lower extremity, the muscles responsible for flexion and internal rotation of the articulations are the ones that are primarily involved. However, with respect to the ankle, it is the dorsiflexors that are weakened and the plantar flexors that are relatively spared.
   C. The demonstration of weakness in elective distribution is virtually diagnostic of disease of the long motor tracts.
IV. Spasticity of the involved extremities is seen commonly.
V. The deep tendon reflexes are increased and the superficial reflexes are lost on the affected side.
VI. Pathologic reflexes, such as the Babinski sign, are noted frequently.

Acute Lesions
I. The onset of weakness is sudden.
II. An elective pattern of weakness is observed, as with chronic lesions.
III. Flaccidity or hypotonia is commonly present during the acute phase.

Table 10-6. Common causes of neuromuscular weakness and paralysis

Anatomic site of involvement	Location	Disease state
Upper motor neurons (long motor pathways)	Brain	Infarction Hemorrhage Neoplasm Infection
	Brainstem	Infarction Motor neuron disease (progressive pseudobulbar palsy) Neoplasm
	Spinal cord	Demyelinating diseases Neoplasm Primary lateral sclerosis
Lower motor neurons	Brainstem	Progressive bulbar palsy Syringobulbia Poliomyelitis
	Spinal cord	Progressive primary muscular atrophy Syringomyelia Poliomyelitis
Nerve roots and peripheral nerves	Nerve roots	Intervertebral disk herniation Metabolic radiculopathies (e.g., diabetic neuropathy) HIV
	Peripheral nerves	Metabolic disorders Inflammatory disorders Trauma HIV
Myoneural junction		Myasthenia gravis Botulism
Muscle		Polymyositis Muscular dystrophies HIV

IV. The deep tendon reflexes may be depressed or absent.

Comments

I. Weakness with any of the aforementioned characteristics indicates disease of the central nervous system but does not imply a specific cause. All disease processes involving the long motor pathway produce similar findings.
II. Lesions of the extrapyramidal tracts (e.g., parkinsonism) or cerebellar pathways may also present as complaints of weakness but without objective evidence of decreased muscle strength.

Pseudobulbar Palsy

Bilaterally situated corticobulbar lesions, regardless of cause, may produce the syndrome referred to as pseudobulbar palsy. It is characterized by dysphagia, dysarthria associated with clumsy movements of a spastic tongue, loss of emotional control with frequent outbursts of crying or laughter, exaggerated jaw and pharyngeal reflexes, and the appearance of sucking and snout reflexes.

Lower Motor Neuron Disease

I. The motor involvement is segmental in distribution.
II. The affected musculature is flaccid and ultimately becomes atrophic.

III. Fasciculations of the involved muscles are typically observed.
IV. Depression or loss of tendon reflexes occurs in the involved segments.
V. Sensory abnormalities do not occur.
VI. Lesions of the motor nuclei of the brainstem produce the syndrome of bulbar palsy. The clinical picture is similar to that of pseudobulbar palsy. However, as with other lower motor neuron lesions, the muscles innervated by the motor nuclei of the brainstem (e.g., the tongue) become weak, flaccid, and atrophic, and usually show fasciculations. The jaw jerk and gag reflex are diminished or absent. Loss of emotional control is not a feature of bulbar palsy.

Disease of the Nerve Roots and Peripheral Nerves

Monoradiculopathies and Mononeuropathies

I. Weakness is limited to those muscles innervated by the affected nerve roots or nerves.
II. The weakness produced by these lesions is similar to that found in disease of the lower motor neurons.
   A. Hypotonia is commonly present, and the deep tendon reflexes are depressed or absent.
   B. Although atrophy often occurs, it is less prominent than that noted with involvement of the anterior horn cells.
   C. Fasciculations are a rare occurrence in lesions of the nerve roots or peripheral nerves.

Polyneuropathies

I. The quality of the muscle weakness and the associated phenomena, such as hypotonia and depressed reflexes, is similar to that seen with anterior horn cell disease or lesions of the nerve roots or peripheral nerves.
II. The distinguishing feature of the polyneuropathies is the more widespread distribution of the weakness. It tends to be bilateral, symmetric, and more prominent in the distal than in the proximal portions of the affected extremities. The legs are more likely to be involved than the arms.
III. Sensory changes may or may not accompany the weakness caused by peripheral nerve lesions.

Disease of the Myoneural Junction

Diseases of the myoneural junction resemble the myopathies more than the neuropathies. As a general rule, muscle weakness is more prominent proximally than distally, sensory changes do not occur, and there are no significant early reflex changes.

Myasthenia gravis is a disease of the myoneural junction with very specific clinical characteristics, as listed in the following.

I. There is undue fatigability of the musculature. The weakness of the muscles is greatest after physical exercise and at the end of the day. Following rest, there is improvement in the muscle strength.
II. Although weakness may be generalized, there is a predilection for involvement of the muscles supplied by the nuclei of the brainstem as well as the proximal limb musculature. Involvement of the ocular muscles is especially frequent.
III. Improvement of muscle strength following the administration of anticholinesterase drugs (neostigmine or edrophonium) is typical and virtually diagnostic.
IV. In advanced cases, the muscle weakness may be permanent and may fail to respond either to rest or to drugs.
V. A progressive diminution in the muscle response to repetitive electric nerve stimulation is typical and often diagnostic.
VI. Myasthenic features may occur in patients with myopathy owing to various malignancies (Eaton-Lambert syndrome). Electrodiagnostic studies may help in differentiating this condition from myasthenia gravis. In the Eaton-Lambert syndrome, repetitive electric nerve stimulation at slow frequencies produces a decreased response, but at higher frequencies there is an augmentation of muscle potentials.

Disease of Skeletal Muscle (Myopathies)

I. Muscle weakness is usually symmetrically distributed but tends to affect the proximal musculature more than the distal musculatures.
II. Sensation is unimpaired.
III. The deep tendon reflexes are preserved.
IV. Muscle atrophy is not an early feature.

Diagnostic Approach

I. In the patient with bona fide muscular weakness, it is usually possible to determine clinically whether the lesion is located in the upper motor neurons, the lower motor neurons, the nerve roots or peripheral nerves, the myoneural junction, or the muscles.
II. In the case of suspected intracranial lesions, it may be advisable to obtain CT or MRI scan. When spinal cord involvement is suspected, appropriate radiographs of the spine (cervical, dorsal, or lumbar) are indicated. CT, MRI, or myelography may be necessary. Systemic laboratory studies that may assist in establishing the cause are also warranted.
III. In the case of peripheral lesions, the following routine studies are advisable: CBC, sedimentation rate, muscle enzyme levels, serum protein electrophoresis, immunoglobulins, ANA, B_{12}, thyroid function studies, serologic test for syphilis, and HIV testing. Under some circumstances, investigation for porphyria or heavy-metal poisoning may be indicated.
IV. The edrophonium and neostigmine tests and electrodiagnostic tests are the procedures of choice for the diagnosis of myasthenia gravis.
V. Electromyography is useful in evaluating suspected lesions affecting the anterior horn cells, muscle, and peripheral nerves.
VI. In myopathies, muscle biopsy (with examination of the tissue under both light and electron microscopy) and histochemical studies may be helpful.
VII. Evoked potentials (visual, brainstem, and somatosensory) are of diagnostic value, especially in multiple sclerosis.

Selected Neurogenic Pain Syndromes

Sidney Duman and Stanley H. Ginsburg

Central Nervous System Pain

Pain arising from disease of the central nervous system is an infrequently diagnosed occurrence clinically. The anatomic structures from which such pain most commonly originates are the thalamus and spinal cord. The causes of painful central lesions are varied.

Pain of central origin is typically constant, intractable, burning in quality, and agonizing. Exacerbations of more severe pain often occur spontaneously or in response to minimal cutaneous stimulation. The associated neurologic findings depend on the anatomic site of the lesion.

The thalamic syndrome is a classic example of central pain that is cerebral in origin. It is characterized by severe, intractable pain as well as by contralateral hemiparesis and hemihypesthesia, both of which may become permanent. Any lesions of the thalamic structures (e.g., infarction, neoplasm) may produce the thalamic syndrome.

Central pain originating in the spinal cord results from trauma or disease affecting the spinothalamic pathways (e.g., cord injuries, multiple sclerosis). The precise nature of the associated neurologic abnormalities depends on the anatomic site of the lesion.

In the case of cerebral disease, CT scan of the head and an electroencephalogram should be obtained. When the spinal cord appears to be involved, lumbar puncture may be indicated. In addition, spinal imaging, such as CT, MRI, or CT and myelography, may be needed.

Painful Upper Extremity

Cervical Radiculopathies

History

The patient usually complains of neck pain that radiates in dermatomal distribution. Suprascapular pain on the affected side is also common. Dysesthesias in the distribution of the involved nerve root may be noted. Both the pain and the dysesthesias are frequently aggravated by neck movements and the Valsalva maneuver. The nerve roots most commonly involved are C7 and C6. Involvement of C5 and C8 occurs less frequently.

Physical Findings

Tenderness in the cervical and paracervical regions is common. Motor and sensory changes, as well as decreased or absent reflexes, are usually noted. The types of abnormalities that occur are listed in Table 10-7.

Etiology

Of the variety of causes, the most common causes are nerve root compression from foraminal encroachment by bony spurs or intervertebral disc herniation. Less frequent causes are inflammatory masses or neoplasms.

Diagnostic Approach

The level of the lesion can usually be determined clinically. Cervical spine films, including AP, lateral, and oblique views, should be obtained. Other diagnostic studies that may be helpful are EMG, MRI, and CT myelogram. In some instances, the correct diagnosis can only be established at the time of surgery.

Brachial Plexus Neuropathy

I. Brachial plexus neuropathy may be idiopathic, or it may follow infectious diseases or inoculations.
II. An acute onset with severe pain, usually located around the shoulder and upper arm, is typical.
III. Muscle weakness usually develops eventually. It has a predilection for the proximal musculature of the arm, but any of the muscles of the upper extremity may be involved. The deltoid, infraspinatus, and supraspinatus muscles are most commonly affected; the trapezius and serratus anterior muscles, somewhat less often.
IV. Involvement of the phrenic nerve may cause diaphragmatic paralysis.
V. Physical examination (see the preceding) reveals weakness and often atrophy of the affected musculature. Sensory changes may occur but are less prominent than the motor abnormalities.
VI. Spontaneous recovery, which is often complete, generally takes place over a period of several months or years. The recovery time tends to be longer when the distal portion of the limbs is the major site of involvement.

Table 10-7. Neurologic signs in the cervical radiculopathies

Type of abnormality	Nerve root affected				
	C5	C6	C7	C8	T1
Major sensory abnormality (hypalgesia)	Lateral arm	Lateral forearm and thumb	Middle finger	Little finger	Medial forearm
Major motor abnormality (weakness)	Biceps, supraspinatus, infraspinatus, deltoid	Brachioradialis	Triceps	Wrist and finger flexors	Intrinsic hand muscles
Reflex changes (decreased or absent reflexes)	Biceps	Brachioradialis	Triceps	None	Finger flexors

Other Brachial Plexus Lesions
Direct (penetrating injuries) and indirect (torsion, pressure) trauma accounts for about 50% of brachial plexus lesions. Pain is usually caused by the musculoskeletal injury rather than by damage to the plexus. Tumors involving the brachial plexus are usually quite painful. Most often these are metastatic (e.g., Pancoast's tumor). In addition to the motor and sensory deficits, Horner's syndrome is a not uncommon finding.

The Thoracic Outlet Syndrome

I. The thoracic outlet syndrome comprises a number of conditions in which the neurovascular bundle is subjected to pressure at the thoracic outlet. The subclavian and axillary vessels as well as the brachial plexus may be compressed.
II. Pain and paresthesias, usually in C8 and T1 distribution, are the most common symptoms. However, sensory disturbances may affect other parts of the extremity. Numbness and clumsiness are also frequent complaints. Ischemic symptoms are present in some cases, but muscle weakness is less common. Positional and postural changes may initiate or aggravate the symptoms.
III. Objective signs of neurologic dysfunction are absent in most cases, but motor weakness and sensory disturbances in C8 and T1 distribution are observed occasionally.
IV. The reproduction of the pain and paresthesias and the diminution or obliteration of the pulse by various maneuvers are considered to have diagnostic significance. The reader is referred to the sections Chest Pain, Chapter 3, and Painful Shoulder, Chapter 8, for additional information.
V. Plethysmography, nerve conduction studies, and angiography may be helpful diagnostically.

Peripheral Nerve Lesions
Ulnar Neuropathy
Paresthesias involving the little finger and the ulnar side of the ring finger are frequent complaints of ulnar neuropathy. Objective sensory changes occur in similar distribution. Pain is relatively slight. Weakness and atrophy of the intrinsic muscles of the hand, such as the interossei and the two lateral lumbricals, may be noted. Electrodiagnostic studies may be helpful.

Median Neuropathy (Carpal Tunnel Syndrome)

I. Pain and paresthesias are the most prominent symptoms of the carpal tunnel syndrome. Although these sensations are generally referred to the area of distribution of the median nerve, many patients also complain of discomfort of the forearm. The symptoms are frequently aggravated by inactivity. Nocturnal pain is often quite severe and may awaken the patient.
II. The syndrome may occur unilaterally or bilaterally. It tends to occur most frequently in individuals whose occupations require repeated wrist movements (e.g., typists). Median neuropathies are also prevalent in such diseases as rheumatoid arthritis, myxedema, and acromegaly.
III. Examination usually discloses tenderness over the transverse carpal ligament. Percussion at this site may reproduce the discomfort (Tinel's sign). Wrist movements may act in a similar fashion. Sensory loss may occur over the palmar surface of the first three fingers, the radial half of the ring finger, and the medial portion of the hand. Weakness, with or without atrophy, of the short abductor of the thumb and the opponens pollicis is commonly observed.
IV. Electrodiagnostic studies may be helpful.

Painful Lower Extremity

Lumbosacral Radiculopathies
History
The patient typically complains of low back and gluteal pain that radiates to the lower extremity. The distribution of the pain in the lower extremity depends on the nerve root affected. Involvement of the lower nerve roots (L5 and S1) is generally manifested by pain that radiates along the posterior and lateral aspects of the thigh and leg. Lesions of the upper lumbar nerve roots usually produce pain that radiates more anteriorly, especially to the thigh. The pain is characteristically aggravated by back movements and the Valsalva maneuver.

Table 10-8. Neurologic signs in the lumbosacral radiculopathies

Type of abnormality	Nerve root affected		
	L4	L5	S1
Major sensory abnormality (hypalgesia)	Medial calf	Lateral calf, dorsomedial aspect of foot and great toe	Posterior calf; sometimes, lateral aspect of the foot
Major motor abnormality (weakness)	Quadriceps and iliopsoas; sometimes, adductors of the thigh	Extensors of the toes and ankle	May have weakness of the hamstrings and gastrocnemius
Reflex changes (decreased or absent)	Knee jerk	None	Ankle jerk

Physical Findings
Motor and sensory changes as well as decreased or absent reflexes are usually noted. The types of abnormalities encountered are summarized in Table 10-8.

Etiology

I. Intervertebral disc herniation is the most common cause. The S1 and L5 nerve roots are most frequently affected, although L4 involvement also occurs. Additional information about herniated intervertebral discs may be found in the section Low Back Pain, Chapter 8.
II. Diabetic radiculopathy is also a common cause. The L4 root is most frequently involved in this condition.
III. Primary and metastatic neoplasms may also cause radiculopathies.

Diagnostic Approach
Usually, a fairly accurate diagnosis can be established from the history and physical examination. Lumbosacral spine films should be obtained. EMG, MRI scanning, and myelography may also be helpful diagnostically.

Meralgia Paresthetica (Lateral Femoral Cutaneous Neuropathy)
Meralgia paresthetica is the term applied to the syndrome of entrapment of the lateral femoral cutaneous nerve at the lateral aspect of the inguinal ligament. The primary symptom is a burning, superficial type of discomfort located in the anterior and lateral aspects of the thigh. Complaints of itching and "numbness" may also be noted. Examination usually reveals hypalgesia of the involved area of the thigh. There are no motor or reflex changes.

Spinal Fluid Findings in Disease

Sidney Duman and Stanley H. Ginsburg

The spinal fluid findings in the more common neurologic abnormalities are shown in Table 10-9.

Bibliography

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Table 10-9. Spinal fluid findings in disease

Disease	Initial pressure (mm CSF)	Appearance	Cells (per cubic mm)	Protein (mg/100 mL)	Culture	Sugar (mg/100 mL)	Chlorides	Comments
Normal	70–150	Clear, colorless	0–5; monos	15–45		40–80		
Infections of the central nervous system								
Tuberculous meningitis	Often ↑	Opalescent, faintly yellow; fibrin clot	50–300; monos	60–700	Positive for acid-fast bacilli	<20	Diminished	Polys in acute phase
Fungal and yeast meningitis	Often ↑	Opalescent	30–500; monos	100–700	Positive (smear may demonstrate fungi)	<30	Diminished	Positive India ink prep in cryptococcosis
Acute purulent meningitis	Often ↑	Turbid	Few to 20,000; chiefly polys	100–1000	Positive (smear often positive)	<20	Often N	Early, or in partially treated forms, cell count may be low
Acute anterior poliomyelitis	N	Clear, colorless	50–250; chiefly monos	40–200	Negative	N	N	In preparalytic stage, polys may exceed 80%
Viral meningitis and encephalitis	N (rarely elevated)	Clear, colorless	Few–350; chiefly monos	40–100	Negative	N	N	Polymorphonuclear reaction early; virus cultures may be positive
Brain abscess	Maybe ↑	Clear, colorless; may be xanthochromic	Few to 100; monos predominate	40–140	Negative	N	N	
Landry-Guillain-Barré disease	N	Clear, colorless	N	50–1000	Negative	N	N	Similar changes in various other polyneuropathies (e.g., diabetes)
Acute syphilitic meningitis	N to slightly ↑	Clear to slightly opalescent	300–2000; monos	50–400	Negative	N	N	Serologic tests nearly always positive
Meningovascular syphilis	N	Clear, colorless	10–50; monos	50–100	Negative	N	N	Serologic tests positive in 60%
Parenchymatous syphilis	N	Clear, colorless	10–40; monos	50–100	Negative	N	N	Serologic tests positive in practically all untreated paretics; usually negative in tabes
Miscellaneous conditions								
"Bloody tap"	N	Blood-tinged; *supernatant fluid colorless*	RBC; WBC ratio similar to peripheral blood	Slightly ↑ (depends on amount of blood introduced)	Negative	N	N	Progressively less bloody in consecutive tubes
Early subarachnoid hemorrhage	Elevated	Bloody; faintly yellow supernatant	Many RBCs	50–4000	Negative	N	N	

continued

Table 10-9. *Continued.*

Disease	Initial pressure (mm CSF)	Appearance	Cells (per cubic mm)	Protein (mg/100 mL)	Culture	Sugar (mg/100 mL)	Chlorides	Comments
Late subarachnoid hemorrhage	Elevated	Slightly bloody; supernatant deep yellow	Fewer RBCs; WBCs ↑ owing to aseptic meningitis	100–800	Negative	May be depressed	N	RBCs disappear in about 2 weeks; xanthochromia may persist for several weeks
Spinal cord tumor (with "block")	Low	Deep yellow; may coagulate	5–50; monos	Up to 6000	Negative	N	N	No rise of pressure on jugular compression
Brain tumor	May be ↑	Clear or yellow	Usually normal; may have few monos	N–150	Negative	N	N	Occasionally cytologic examination reveals tumor cells
Meningeal carcinomatosis (carcinomatous meningitis)	May be ↑	Clear to turbid	20–300 (may be mixture of malignant and inflammatory cells)	60–200	Negative	Often depressed	N	Cytologic examination often reveals tumor cells
Multiple sclerosis	N	Clear, colorless	5–50; monos	N–80	Negative	N	N	Gammagobulin fraction may be ↑; oligoclonal bands may be present; myelin basic protein is elevated
Cerebral infarction	N (occasionally elevated)	Clear	Usually normal; occasionally a few monos (RBCs frequent in embolic infarction)	N–80	Negative	N	N	Pleocytosis when infarct is in proximity to ventricle or subarachnoid space
Cerebral hemorrhage	Often ↑	Blood-tinged (sometimes grossly bloody)	RBCs; varying number WBCs, especially late	50–200	Negative	N	N	

↑, increased; Monos, mononuclear leukocytes; N, normal; Polys, polymorphonuclear leukocytes.
From Grinker RR, Bucy PC, Sahs AL. *Neurology*, 6th ed. Springfield, IL: Charles C Thomas, 1966.

Appendix. NORMAL VALUES OF STANDARD LABORATORY AND FUNCTION TESTS

Alimentary Tract Function Tests

Gastric secretion	
Volume	
Fasting	20–100 mL/h
Nocturnal	<800 mL/10 h
Acid output (mean ± standard deviation)	
Basal (BAO)	
Male	3.7 ± 2.1 mEq/h
Female	2.2 ± 1.7 mEq/h
Stimulated after betazole (Histalog), 0.5 mg/kg or pentagastrin 6 μg/kg subcutaneous (PAO)	
Male	23 ± 7 mEq/h
Female	18 ± 5 mEq/h
BAO/PAO ratio	<0.5
Gastrin, serum	<150 pg/mL
Gastrin, serum following stimulation with intravenous secretin 2 U/kg	Increases of 110 pg/mL or 100% of basal level 1, 2, 5, 7, 10, 15, or 30 min after secretin indicate Z-E syndrome gastrinoma)
Intestinal absorption	
Stool fat on diet containing 80–100 g fat/day (72- to 96-h collection)	<8 g/24 h
D-Xylose absorption (25 g D-xylose administered orally after overnight fast)	
5-h urine collection after D-xylose	>5 g
1- or 2-h serum level after D-xylose	>25 mg/dL
Triolein breath test (5 μgCi ^{14}C-triolein administered in 30 mL Lipomul; breath collected hourly for 6 h for measurement of breath $^{14}CO_2$)	>3.5% of dose/h
Lactose absorption (50 g lactose administered after overnight fast; baseline and 1-, 2-, and 3-h serum samples obtained; alternatively, breath hydrogen can be measured in expired air 90–120 min after lactose administered)	>25 mg/dL increase in serum glucose >(20 PPM H_2 in expired air
Schilling test (see Hematologic Normal Values)	
Pancreatic secretion	
Secretin test (2 units secretin/kg body weight, intravenously; duodenal fluid collected for four periods of 20 min thereafter)	
Volume	>1.5 mL/kg/80 min
Bicarbonate output	>16 mEq/80 min
Bicarbonate concentration	>80 mEq/L
Bentiromide (*N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid) test (500 mg administered after overnight fast followed by oral hydration and collection of a 6-h urine sample)	>50% urinary recovery of ingested PABA/6 h

Cardiovascular Function Tests
Cardiac index

$$L/min/m^2 = \frac{C.O.}{\text{body surface area (BSA)}}$$

Normal = 2.8–4.2
Cardiac output
C.O. = heart rate × stroke volume
Cardiac output (Fick principle)

$$C.O.\ (L/min) = \frac{O_2 \text{ consumption (mL } O_2/min)}{\text{AV } O_2 \text{ difference (mL } O_2/L)}$$

where
O_2 consumption (basal state estimate) = 3 mL O_2/min/kg body weight
AV O_2 difference = arterial O_2 content – venous O_2 content (mL O_2/L)
O_2 content (vol %) = Hb (g/dL) × 1.39 (mL O_2/g Hb) × % saturation
O_2 content (mL O_2/L) = vol % × 10
Therefore

$$C.O.\ (L/min) = \frac{3\ (mL/min) \times \text{weight (kg)}}{(SaO_2 - SvO_2)(1.39) \times Hb\ (g/dL) \times 10}$$

Mean arterial pressure

From Stein JH, ed. *Internal Medicine*, 3rd ed. Boston: Little, Brown. 1990, with permission.

Cardiovascular Normal Values

Table A-1. Normal pressures in the heart and great vessels[a]

Pressures	Average (mm Hg)	Range (mm Hg)
Right atrium		
Mean	2.8	1–5
a wave	5.6	2.5–7.0
z point	2.9	1.5–5.0
c wave	3.8	1.5–6.0
x wave	1.7	0–5
v wave	4.6	2.0–7.5
y wave	2.4	0–6
Right ventricle		
Peak systolic	25	17–32
End diastolic	4	1–7
Pulmonary artery		
Mean	15	9–19
Peak systolic	25	17–32
End diastolic	9	4–13
Pulmonary artery wedge		
Mean	9	4.5–13.0
Left atrium		
Mean	7.9	2–12
a wave	10.4	4–16
z point	7.6	1–13
v wave	12.8	6–21

continued

Table A-1. *Continued.*

Pressures	Average (mm Hg)	Range (mm Hg)
Left ventricle		
Peak systolic	130	90–140
End diastolic	8.7	5–12
Brachial artery		
Mean	85	70–105
Peak systolic	130	90–140
End diastolic	70	60–90

[a] Reference elevation = 10 cm above the spine of the recumbent subject.

Mean arterial pressure = diastolic pressure + ⅓ (systolic pressure – diastolic pressure)

Resistance can be expressed in absolute resistance units (ARU) of dyne-sec-cm^{-5} or hybrid resistance units (HRU) of mm Hg/L/min; ARU = 80 × HRU

Systemic vascular resistance (SVR)

$$SVR = \frac{SA - RA}{C.O.} \text{(Normal = 1130 dyne-sec-cm}^{-5} \pm 178)$$

Pulmonary arteriolar resistance (PAR)

$$PAR = \frac{PA - LA}{C.O.} \text{(Normal = 67 dyne-sec-cm}^{-5} \pm 23)$$

Total pulmonary resistance (TPR)

$$TPR = \frac{PA}{C.O.} \text{(Normal = 205 dyne-sec-cm}^{-5} \pm 51)$$

Total systemic resistance (TSR)

$$TSR = \frac{SA}{C.O.}$$

where

RA = mean right atrial pressure

PA = mean pulmonary artery pressure

LA = mean left atrial pressure

SA = mean systemic arterial pressure

C.O. = cardiac output

Cerebrospinal Fluid Normal Values

Bilirubin	0
Cells	0–5/mm^3, all lymphocytes
Chloride	110–129 mEq/L
Glucose	48–86 mg/dL or ≥60% of serum glucose
pH	7.34–7.43
Pressure	7–20 cm water

Protein, lumbar	15–45 mg/dL
Albumin	58%
α1-globulins	9%
α2-globulins	8%
β-globulins	10%
γ-globulins	10(5–12)%
Protein, cisternal	15–25 mg/dL
Protein, ventricular	5–15 mg/dL

Endocrinologic Normal Values

Hormone and Metabolite Normal Values

Adrenocorticotropin (ACTH), serum	15–70 pg/mL	
Aldosterone (mean ± standard deviation)		
Serum		
210 mEq/day sodium diet		
Supine	48 ± 29 pg/mL	
Upright (2h)	65 ± 23 pg/mL	
110 mEq/day sodium diet		
Supine	107 ± 45 pg/mL	
Upright (2h)	532 ± 228 pg/mL	
Urine	5–19 μg/24 h	
Calcitonin, serum	None detectable	
Catecholamines, free urinary	<110 μg/24 h	
Chorionic gonadotropin, serum		
Pregnancy		
First month	10–10,000 mIU/mL	
Second and third months	10,000–100,000 mIU/mL	
Second trimester	10,000–30,000 mIU/mL	
Third trimester	5,000–15,000 mIU/mL	
Nonpregnant	0	
Cortisol		
Serum		
8 AM	5–25 μg/dL	
8 PM	<10 μg/dL	
Cosyntropin stimulation (30–90 min after 0.25 mg cosyntropin intramuscularly or intravenously)	>10 μg/dL rise over baseline	
Overnight suppression (8 AM serum cortisol after 1 mg dexamethasone orally at 11 PM)	≤5 μg/dL	
Urine	20–70 μg/24 h	
C-peptide, serum	0.28–0.63 pmol/mL	
11-Deoxycortisol, serum		
Basal	0–1.4 μg/dL	
Metyrapone stimulation (30 mg/kg orally 8 h prior to level)	>7.5 μg/dL	
Estrogens, urine (increased during pregnancy; decreased after menopause)	*Male*	*Female*
Total	4–25 μg/24 h	5–100 μg/24 h
Estriol	1–11 μg/24 h	0–65 μg/24 h
Estradiol	0–6 μg/24 h	0–14 μg/24 h
Estrone	3–8 μg/24 h	4–31μg/24 h
Etiocholanolone, serum	<1.2 μg/dL	
Follicle-stimulating hormone, serum		
Male	6–18 mIU/mL	
Female		
Follicular phase	5–20 mIU/mL	

Peak midcycle	12–30 mIU/mL
Luteal phase	5–15 mIU/mL
Postmenopausal	>50 mIU/mL
Free thyroxine index, serum	1–4 ng/dL
Gastrin, serum (fasting)	60–200 pg/mL
Growth hormone, serum	
Adult, fasting	<5 ng/mL
Glucose load (100 g orally)	<5 ng/mL
Levodopa stimulation (500 mg orally in a fasting state)	>5 ng/mL rise over baseline within 2 h
17-Hydroxycorticosteroids, urine	
Male	2–12 mg/24 h
Female	2–8 mg/24 h
5′-Hydroxyindoleacetic acid (5′-HIAA), urine	2–9 mg/24 h
Insulin, plasma	
Fasting	6–26 (μU/mL
Hypoglycemia (serum glucose <5 mg/dL)	<5 (μU/mL
17-Ketosteroids, urine	
Under 8 years old	0–2 mg/24 h
Adolescent	0–18 mg/24 h
Adult	
Male	8–18 mg/24 h
Female	5–15 mg/24 h
Luteinizing hormone, serum	
Male	6–18 mIU/mL
Female	
Basal	5–22 mIU/mL
Ovulation	30–250 mIU/mL
Metanephrines, urine	<1.3 mg/24 h
plasma	150–450 pg/mL
Norepinephrine, urine	<100 μg/24 h
Parathyroid hormone, serum	150–300 pg/mL
C-terminal	150–350 pg/mL
N-terminal	230–650 pg/mL
Pregnanediol, urine	
Female	
Follicular phase	<1.5 mg/24 h
Luteal phase	2.0–4.2 mg/24 h
Postmenopausal	0.2–1.0 mg/24 h
Male	<1.5 mg/24 h
Progesterone, plasma	
Female	
Follicular phase	0–5.3 ng/mL
Luteal phase	0–21 ng/mL
Postmenopausal	<2 ng/mL
Male	<2 ng/mL
Prolactin, serum	
Nonpregnant	
Day	5–10 ng/mL
Night	20–40 ng/mL
Pregnant	150–200 ng/mL
Radioactive iodine (^{131}I) uptake (RAIU)	5%–25% at 24 h (varies with iodine intake)
Renin activity, plasma (mean ± standard deviation)	
Normal diet	
Supine	1.1 ± 0.8 ng/mL/h
Upright	1.9 ± 1.7 ng/mL/h
Low-sodium diet	

Supine	2.7 ± 1.8 ng/mL/h
Upright	6.6 ± 2.5 ng/mL/h
Diuretics and low-sodium diet	10.0 ± 3.7 ng/mL/h
Testosterone, total plasma	
Bound	
Adolescent male	>100 ng/dL
Adult male	300–1100 ng/dL
Female	25–90 ng/dL
Unbound	
Adult male	3–24 ng/dL
Female	0.09–1.30 ng/dL
Thyroid-stimulating hormone, serum	<10 μU/mL
Thyroxine (T_4) serum	
Total	4.5–11.5 μg/dL
Free	0.8–2.4 ng/dL
Thyroxine-binding globulin capacity, serum	15–25 μg T_4/dL
Thyroxine index, free	1–4 ng/dL
Tri-iodothyronine (T_3), serum	70–190 ng/dL
T_3 resin uptake	25%–45%
Vanillylmandelic acid (VMA), urine	1–8 mg/24 h

Endocrine Function Tests

Adrenal gland	
Glucocorticoid suppression: overnight dexamethasone suppression test (8 AM serum cortisol after 1 mg dexamethasone orally at 11 PM)	≤5 μg/dL
Glucocorticoid stimulation: cosyntropin stimulation test (serum cortisol 30–90 min after 0.25 mg cosyntropin intramuscularly or intravenously)	>10 μg/mL more than baseline serum cortisol
Metyrapone test, single dose (8 AM serum deoxycortisol after 30 mg/kg metyrapone orally at midnight)	<7.5 μg/dL
Aldosterone suppression: sodium depletion test (urine aldosterone collected on day 3 of 200 mEq/day sodium diet)	<20 μg/24 h
Pancreas	
Glucose tolerance test[a] (serum glucose after 100 g glucose orally)	
60 min after ingestion	<180 mg/dL
90 min after ingestion	<160 mg/dL
120 min after ingestion	<125 mg/dL
Pituitary gland	
Adrenocorticotropic hormone (ACTH) stimulation. See Adrenal gland, Metyrapone test	
Growth hormone stimulation: insulin tolerance test (serum growth hormone after 0.1 U/kg regular insulin intravenously after an overnight fast to induce a 50% fall in serum glucose concentration or symptomatic hypoglycemia)	>5 ng/mL rise over baseline
Levodopa test (serum growth hormone after 0.5 g L-dopa orally while fasting)	>5 ng/mL rise over baseline within 2 h
Growth hormone suppression: glucose tolerance test (serum growth hormone after 100 g glucose orally after 8-h fast)	<5 ng/mL within 2 h
Luteinizing hormone (LH) stimulation: gonadotropin-releasing hormone (GnRH) test (serum LH after 100 μg GnRH intravenously or intramuscularly) fourfold to sixfold rise over baseline	
Thyroid-stimulating hormone (TSH) stimulation: thyrotropin-releasing hormone (TRH) stimulation test (serum TSH after 400 μg TRH intravenously)	>Twofold rise over baseline within 2 h
Thyroid gland	
Radioactive iodine uptake (RAIU) suppression test (RAIU on day 7 after 25 μg tri-iodothyronine orally four times daily)	<10%–<50% baseline
Thyrotropin-releasing hormone (TRH) stimulation test. See Pituitary gland, TSH stimulation	

Hematologic Normal Values

Acid hemolysis test (Ham)	No hemolysis
Carboxyhemoglobin	
Nonsmoker	<1%
Smoker	2.1%–4.2%
Cold hemolysis test (Donath-Landsteiner)	No hemolysis
Complete blood count (see Table A-3)	
Erythrocyte life span	
Normal	120 days
^{51}Cr-labeled half-life	28 days

[a]Add 10 mg/dL for each decade over 50 years of age.

Table A-2. Differential cell count of bone marrow

Myeloid cells	
Neutrophilic series	
Myeloblasts	0.3%–5.0%
Promyelocytes	1%–8%
Myelocytes	5%–19%
Metamyelocytes	9%–24%
Bands	9%–15%
Segmented cells	7%–30%
Eosinophil precursors	0.5%–3.0%
Eosinophils	0.5%–4.0%
Basophilic series	0.2%–0.7%
Erythroid cells	
Pronormoblasts	1%–8%
Basophilic normoblasts	
Polychromatophilic normoblasts	7%–32%
Orthochromatic normoblasts	
Megakaryocytes	0.1%
Lymphoreticular cells	
Lymphocytes	3%–17%
Plasma cells	0%–2%
Reticulum cells	0.1%–2.0%
Monocytes	0.5%–5.0%

continued

Table A-2. *Continued.*

Myeloid/erythroid ratio	0.6/2.7	
Erythropoietin by radioimmunoassay	9–33 mU/dL	
Ferritin, serum		
Male	15–200 μg/L	
Female	12–150 μg/L	
Folate, RBC	120–670 ng/mL	
Fragility, osmotic		
Hemolysis begins	0.45%–0.38%	
Hemolysis completed	0.33%–0.30%	
Haptoglobin, serum	100–300 mg/dL	
Hemoglobin		
Hemoglobin A_{1c}	0%–5% total	
Hemoglobin A_2 by column	2%–3% of total	
Hemoglobin, fetal	<1% of total	
Hemoglobin, plasma	0%–5% of total	
Hemoglobin, serum	2–3 mg/mL	
Iron, serum		
Male	75–175 μg/dL	
Female	65–165 μg/dL	
Iron-binding capacity, total serum (TIBC)	250–450 μg/dL	
Iron turnover rate (plasma)	20–42 mg/24 h	
Leukocyte alkaline phosphatase (LAP) score	30–150	
Methemoglobin	<1.8%	
Osmotic fragility		
Hemolysis begins	0.45–0.38 NaCl	
Hemolysis completed	0.33–0.30 NaCl	
Reticulocytes		
Male	4.6–6.2	
Female	4.2–5.4	
Schilling test (urinary excretion of radiolabeled vitamin B_{12} after "flushing" intramuscular injection of B_{12})	6%–30% of oral dose within 24 h	
Sedimentation rate	*Male*	*Female*
Wintrobe	0–5 mm/h	0–15 mm/H
Westergren	0–15 mm/h	0–20 mm/h
Transferrin saturation, serum	20%–50%	
Volume	*Male*	*Female*
Blood	52–83 mL/kg	50–75 mL/kg
Plasma	25–43 mL/kg	28–45 mL/kg
Red cell	20–36 mL/kg	19–31 mL/kg
Coagulation Normal Values		
Template bleeding time	3.5–7.5 min	
Clot retraction, qualitative	Apparent in 30–60 min; complete in 24 h, usually in 6 h	
Coagulation time (Lee-White)		
Glass tubes	5–15 min	
Siliconized tubes	20–60 min	
Euglobulin lysis time	120–240 min	
Factors II, V, VII, VIII, IX, X, XI, or XII	100% or 1.0 U/mL	
Fibrin degradation products	<10 μg/mL or titer ≤1.4	
Fibrinogen	200–400 mg/mL	
Partial thromboplastin time, activated	20–40 s	
Prothrombin time (PT)	11–14 s	
Thrombin time	10–15 s	
Whole blood clot lysis time	>24 h	

Table A-3. Complete blood count

Parameter	*Male*	*Female*
Hematocrit (%)	40–52	38–48
Hemoglobin (g/dL)	13.5–18.0	12–16
Erythrocyte count ($\times 10^{12}$ cells/L)	4.6–6.2	4.2–5.4
Reticulocyte count (%)	0.6–2.6	0.4–2.4
MCV (fL)	82–98	82–98
MCH (pg)	27–32	27–32
MCHC (g/dL)	32–36	32–36
WBC ($\times 10^9$ cells/L)	4.5–11.0	4.5–11.0
Segmented neutrophils	1.8–7.7	1.8–7.7
Average (%)	40–60	40–60
Band (cells)	0–0.3	0–0.3
Average (%)	0–3	0–3
Eosinophils (cells $\times 10^9$/L)	0–0.5	0–0.5
Average (%)	0–5	0–5
Basophils (cells $\times 10^9$/L)	0–0.2	0–0.2
Average (%)	0–1	0–1
Lymphocytes (cells $\times 10^9$/L)	1.0–4.8	1.0–4.8
Average (%)	20–45	20–45
Monocytes (cells $\times 10^9$/L)	0–0.8	0–0.8
Average (%)	2–6	2–6
Platelet count (cells $\times 10^9$/L)	150–350	150–350

Pulmonary Function Tests

Abbreviations
P_B = barometric pressure (mm Hg)
F_{IO_2} = inspired oxygen fraction (0.21 = room air)
P_{aCO_2} = partial pressure of carbon dioxide in arterial blood (mm Hg)
P_{ACO_2} = partial pressure of carbon dioxide in alveolar gas (mm Hg)
P_{aO_2} = partial pressure of oxygen in arterial blood (mm Hg)
P_{AO_2} = partial pressure of oxygen in alveolar gas (mm Hg)
Alveolar-arterial oxygen gradient (F_{IO_2} = 0.21)
P(A – a) in adolescents = <10 mm Hg
adults <40 years = 10 mm Hg
>40 years = 10–15 mm Hg
Alveolar oxygen partial pressure (sea level, F_{IO_2}, = 0.21)
$P_{AO_2} = 150 - (1.2 \times P_{aCO_2})$
Blood gases (F_{IO_2} = 0.21)

	Arterial	*Alveolar*
P_{O_2}	80–105 mm Hg	90–115 mm Hg
P_{CO_2}	38–44 mm Hg	38–44 mm Hg
pH	7.35–7.45	

Spirometric volumes and lung volumes are size-dependent.
Typical normal values for adults are provided.

Lung volumes	*Male*	*Female*
Total lung capacity (TLC)	6–7 L	5–6 L
Functional residual capacity (FRC)	2–3 L	2–3 L
Residual values (RV)	1–2 L	1–2 L
Measures of air flow		
Forced vital capacity (FVC)	4.0 L	3.0 L
One second forced vital capacity (FEV_1)	>3.0 L	>2.0 L
Pulmonary resistance (RL)	<3.0 cm H_2O/sec/L	

Airway resistance (Raw)	<2.5 cm H_2O/sec/L
Other	
Pulmonary compliance (C_L)	0.2 L/cm H_2O
Diffusing capacity (D_{LCO})	25 mL CO/min/mm Hg

Renal Function Tests

Anion gap
$Na^+ - HCO_3^- + Cl^- = 10 \pm 2$ mEq/L
Osmolality
Osmolality (serum) = 2 Na (mEq/L) + BUN (mg/dL)/2.8 + glucose (mg/dL)/18
Bicarbonate deficit
HCO_3^- = body weight (kg) × 0.4 (desired HCO_3^- – observed HCO_3^-)
Glomerular filtration rate
$GFR = U_{cr} \times V/P_{cr}$
= 130 ± 20 mL/min in males
= 120 ± 15 mL/min in females
$\cong U_{cr}/P_{cr} \times 70$
where
U_{cr} = urine creatinine (mg/dL)
P_{cr} = plasma creatinine (mg/dL)
V = urine volume/24 h (mL/min)
Renal plasma flow
$RPF = U_{pah} \times V/P_{pah}$
= 700 ± 130 mL/min in males
= 600 ± 100 mL/min in females
where
U_{pah} = urine para-aminohippuric acid (mg/dL)
V = urine volume/24 h (mL/min)
P_{pah} = plasma para-aminohippuric acid (mg/dL)

Serum Normal Values

Acetoacetate	0.3–2.0 mg/dL
Acid phosphatase	0–0.8 U/mL
Acid phosphatase, prostatic	2.5–12.0 IU/L
Albumin	3.0–5.5 g/dL
Aldolase	1–6 IU/L
Alkaline phosphatase	
15–20 years	40–200 IU/L
20–101 years	35–125 IU/L
Alpha-1 antitrypsin	200–500 mg/dL
Ammonia	11–35 μmol/dL
Amylase, serum	2–20 U/L
Anion gap	8–12 mEq/L (mmol/L)
Ascorbic acid	0.4–1.5 mg/dL
Bilirubin	
Total	0.2–1.2 mg/dL
Direct	0–0.4 mg/dL
Bromsulphalein (BSP)	Normal retention: 0%–5% at 45 min
Calcium, serum	8.7–10.6 mg/dL
Carbon dioxide, total	18–30 mEq/L (mmol/L)

Carcinoembryonic antigen, serum	<2.5 μg/L
Carotene (carotenoids)	50–300 μg/dL
C3 complement	55–120 mg/dL
C4 complement	14–51 mg/dL
Ceruloplasmin	15–60 mg/dL
Chloride, serum	95–105 mEq/L (mmol/L)
Cholesterol, total	
12–19 years	120–230 mg/dL
20–29 years	120–240 mg/dL
30–39 years	140–270 mg/dL
40–49 years	150–310 mg/dL
50–59 years	160–330 mg/dL
Copper	100–200 μg/dL
Creatine phosphokinase, total	20–200 IU/L
Creatinine phosphokinase, isoenzymes	
MM fraction	94%–95%
MB fraction	0%–5%
BB fraction	0%–2%
Normal values in	
Heart	80% MM, 20% MB
Brain	100% BB
Skeletal muscle	95% MM, 2% MB
Creatinine, serum	
Female adult	0.5–1.3 mg/dL
Male adult	0.7–1.5 mg/dL
Delta-aminolevulinic acid (ALA)	<200 μg/dL
α-Fetoprotein, serum	<40 μg/L
Folate, serum	1.9–14.0 ng/mL
Gamma glutamyl transpeptidase	
Male	12–38 IU/L
Female	9–31 IU/L
Gastrin	60–200 pg/mL
Glucose, serum	70–120 mg/dL
Glucose 6-phosphate dehydrogenase	5–10 IU/g Hb
G6PD screen, qualitative	Negative
Haptoglobin	100–300 mg/dL
Hemoglobin A_2	0%–4% of total Hb
Hemoglobin F	0%–2% of total Hb
Immunoglobulin, quantitation	
IgG	700–1500 mg/dL
IgA	70–400 mg/dL
IgM	
Male	30–250 mg/dL
Female	30–300 mg/dL
IgD	0–40 mg/dL
Insulin, fasting	6–26 μU/mL
Iron binding capacity	250–400 μg/dL
Iron, total, serum	40–150 μg/dL
Lactic acid	0.6–1.8 mEq/L
LDH, serum	20–220 IU/L
LDH isoenzymes	
LDH_1	20%–34%
LDH_2	28%–41%
LDH_3	15%–125%
LDH_4	3%–12%
LDH_5	6%–15%
Leucine aminopeptidase (LAP)	30–55 IU/L
Lipase	4–24 IU/dL

Magnesium, serum	1.5–2.5 mEq/L
5′-Nucleotidase	0.3–3.2 Bodansky units
Osmolality, serum	278–305 mOsm/kg serum water
Phenolsulfonphthalein (PSP)	>25% excreted within 15 min after injection of 1 mL dye
Phenylalanine	3 mg/dL
Phosphorus, inorganic, serum	2.0–4.3 mg/dL
Potassium, plasma	3.1–4.3 mEq/L
Potassium, serum	3.5–5.2 mEq/L
Protein, total, serum	
2–55 years	5.0–8.0 g/dL
55–101 years	6.0–8.3 g/dL
Protein electrophoresis, serum	
Albumin	3.5–5.2 g/dL
Alpha-1	0.6–1.0 g/dL
Alpha-2	0.6–1.0 g/dL
Beta	0.6–1.2 g/dL
Gamma	0.7–1.5 g/dL
SGOT	5–40 IU/L
Sodium, serum	135–145 mEq/L
Sulfate	0.5–1.5 mg/dL
T_3 uptake	24%–45%
T_4	4.5–11.5 μg/dL
Triglycerides	
2–29 years	10–140 mg/dL
30–39 years	20–150 mg/dL
40–49 years	20–160 mg/dL
50–59 years	20–190 mg/dL
60–101 years	20–200 mg/dL
Urea nitrogen, serum	
2–65 years	5–22 mg/dL
65–101 years	
Male	10–38 mg/dL
Female	8–26 mg/dL
Uric acid	
10–59 years	
Male	2.5–9.0 mg/dL
Female	2.0–8.0 mg/dL
60–101 years	
Male	2.5–9.0 mg/dL
Female	2.5–9.0 mg/dL
Viscosity	1.4–1.8 (serum compared to H_2O)
Vitamin A	0.15–0.60 μg/mL
Vitamin B^{12}	200–850 pg/mL

Stool Normal Values

Bulk	
Wet weight	<197 g/24 h
Dry weight	<66.4 g/24 h
Coproporphyrin	12–832 mg/24 h
Fat (on a diet containing 30 g fat/day)	<7.2 g/24 h or <30% of dry weight
Nitrogen	<2.2 g/24 h
Urobilinogen	40–280 mg/24 h
Water	Approximately 65%

Synovial Fluid Normal Values

Cells	<200 cells/mm³
Polymorphonuclear cells	<25%
Crystals	None
Fibrin clot	None
Glucose	Same as serum
Hyaluronic acid	2.45–3.97 g/L
pH	7.31–7.64
Protein	<2.5 g/dL
Albumin	63%
α1-Globulins	7%
α2-Globulins	7%
β-Globulins	9%
γ-Globulins	14%
Relative viscosity	>300
Uric acid	Same as serum

Urine Normal Values

Acidity, titratable	20–40 mEq/24 h
Ammonia	30–50 mEq/24 h
Amylase	36–260 Somogyi U/h
Bence Jones protein	None detected
Bilirubin	None detected
Calcium	
Unrestricted diet	<300 mg/24 h (men) <250 mg/24 h (women)
Low-calcium diet (200 mg/day for 3 days)	<150 mg/24 h
Chloride	120–240 mEq/24 h (varies with dietary intake)
Copper	0–32 μg/24 h
Creatine	
Male	0–40 mg/24 h
Female	0–100 mg/24 h
Creatinine	1.0–1.6 g/24 h or 15–25 mg/kg body weight/24 h
Cysteine, qualitative	Negative
Delta-aminolevulinic acid	1.3–7.0 mg/24 h

Toxicology

Table A-4. Serum values for drugs and toxic substances

Substance	Therapeutic range	Toxic range
Acetaminophen	10–20 mg/L	>150 mg/L 4 h after ingestion
Alcohol	0 300–450 mg/dL: stupor >400 mg/dL: coma → death	150–300 mg/dL: confusion
Amphetamine	0	

continued

Table A-4. *Continued.*

Substance	Therapeutic range	Toxic range
Amobarbital	7–15 μg/mL	
Bromide	20–120 mg/dL	>150 mg/dL
Carbamazepine	6–10 μg/mL	
Clonazepam	0.02–0.10 μg/mL	
Digitoxin	5–40 ng/mL	
Digoxin	0.5–2.0 ng/mL	>2.0 ng/mL
Diphenylhydantoin	10–20 μg/mL	
Ethosuximide	40–100 μg/mL	
Glutethimide	1–7 μg/mL	
Lead	<40 μg/dL; occupational <80 μg/dL	
Lithium	0.5–1.5 mEq/L	2.0 mEq/L
Meprobamate	10–20 μg/mL	30–70 μg/mL: coma
Methanol	0	
Pentobarbital	4–6 μg/mL	
Phenobarbital	5–30 μg/mL	>40 μg/mL
Primidone	4–12 μg/mL	
Procainamide	4–6 μg/mL	
Propranolol	100–300 ng/mL	
Quinidine	3–5 μg/mL	>8 μg/mL
Salicylate	20–25 mg/dL	30 mg/dL
Secobarbital	3–5 μg/mL	
Theophylline	10–20 μg/mL	
Valproic acid	<100 μg/mL	

Glucose	
Qualitative	None detected
Quantitative	16–300 mg/24 h
Hemoglobin	None detected
Homogentisic acid	None detected
Iron	40–140 μg/24 h
Lead	0–120 μg/24 h
Myoglobin	None detected
Osmolality	50–1200 mOsm/L
pH	4.6–8.0
Phenylpyruvic acid, qualitative	None detected
Phosphorus	0.8–2.0 g/24 h
Porphobilinogen	
Qualitative	None detected
Quantitative	0–2.4 mg/24 h
Porphyrins	
Coproporphyrin	50–250 μg/24 h
Uroporphyrin	10–30 μg/24 h
Potassium	25–100 mEq/24 h
Protein	
Qualitative	None detected
Quantitative	10–150 mg/24 h
Sodium	130–260 mEq/24 h (varies with dietary sodium intake)
Specific gravity	1.003–1.030
Uric acid	80–976 mg/24 h
Urobilinogen	0.05–3.5 mg/24 h; <1.0 Ehrlich U/2 h

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