CECIL MEDICINE, 24TH EDITION
Edited by Lee Goldman and Andrew I. Schafer

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281: Crystal Deposition Diseases  
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282: Fibromyalgia and Chronic Fatigue Syndrome  
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283: Systemic Diseases in which Arthritis is a Feature  
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Editor: Schafer, Andrew

284: Multifocal Fibrosclerosis  
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Editor: Schafer, Andrew

285: Surgical Treatment of Joint Diseases  
C. Ronald Mackenzie; Edwin Su  
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287: Principles of Anti-Infective Therapy
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   James Leggett
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290: Approach to the Patient with Healthcare-associated Infections
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291: Approach to the Patient with Suspected Enteric Infection
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292: Approach to the Patient with Urinary Tract Infection
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321: Whooping Cough and Other Bordetella Infections

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Editor: Schafer, Andrew

324: Granuloma Inguinale (Donovanosis)  
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325: Mycoplasma Infections  
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327: Treponema Infection (Syphilis)  
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Editor: Schafer, Andrew

329: Lyme Disease  
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331: Leptospirosis  
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333: The Nontuberculous Mycobacteria  
*Steven Holland*  
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335: Rickettsia Infections
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   Stuart Levin
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   Itzhak Brook
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338: Nocardiosis
   Frederick Southwick
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339: Systemic Antifungal Agents
   David A. Stevens
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340: Histoplasmosis
   Carol Kauffman
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341: Coccidioidomycosis
   John N. Galgiani
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349: Pneumocystis Penumonia  
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350: Mycetoma  
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351: Dematiaceous Fungal Infections  
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352: Antiparasitic Therapy  
*Richard Pearson*  
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353: Malaria  
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354: African Trypanosomiasis (Sleeping Sickness)  
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355: American Trypanosomiasis (Chagas' Disease)  
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359: Giardiasis
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363: Schistosomiasis (Bilharziasis)
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364: Liver, Intestinal, and Lung Fluke Infections
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405: Headaches and Other Head Pain
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407: Spine, Disc, Spinal Cord and Spinal Root Disease
   Richard, L Barbano
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408: Regional Cerebral Dysfunction
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409: Alzheimer's Disease and Other Dementias
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420: Meningitis: Bacterial, Viral, and Other
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422: Acute Viral Encephalitis
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   Barbara Koppel
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   Jeanine Wiener-Kronish; Lee Fleisher  
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445: Principles of Therapy  
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446: Eczema, Photosensitivity, and papulosquamous (including fungal) Diseases and Figurate Erythemas  
   Henry Lim  
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  Madeleine Duvic
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449: Infections, Hyper- and Hypopigmentation, Regional Dermatology, and Distinctive Lesions in Black Skin
  Jean Bologna
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450: Diseases of Hair and Nails
  Antonella Tosti
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APPENDIX: LABORATORY REFERENCE INTERVALS AND VALUES

Appendix: Reference Intervals and Laboratory Values
  Ronald J. Elin
  Editor: Goldman, Lee
APPROACH TO MEDICINE

Medicine is a profession that incorporates science and the scientific method with the art of being a physician. The art of tending to the sick is as old as humanity itself. Even in modern times, the art of caring and comforting, guided by millennia of common sense as well as a more recent, systematic approach to medical ethics (Chapter 2), remains the cornerstone of medicine. Without these humanistic qualities, the application of the modern science of medicine is suboptimal, ineffective, or even detrimental.

The caregivers of ancient times and premodern cultures tried a variety of interventions to help the afflicted. Some of their potions contained what are now known to be active ingredients that form the basis for proven medications (Chapter 40); others (Chapter 38) have persisted into the present day despite a lack of convincing evidence. Modern medicine should not dismiss the possibility that these unproven approaches may be helpful; instead, it should adopt a guiding principle that all interventions, whether traditional or newly developed, can be tested vigorously, with the expectation that any beneficial effects can be explored further to determine their scientific basis.

When compared with its long and generally distinguished history of caring and comforting, the scientific basis of medicine is remarkably recent. Other than an understanding of human anatomy and the later description, albeit in more detail in this text, are relatively recent evolutionary branches. The term "medical knowledge" was perhaps exemplified best by hospitals and hospital care. Although hospitals provided caring that all but well-to-do people might not be able to obtain elsewhere, there is little if any evidence that hospitals improved health outcomes. The term "hospitalism" referred not to expertise in hospital care but rather to the aggregate of iatrogenic afflictions that were induced by the hospital stay itself.

The essential humanistic qualities of caring and comforting can achieve full benefit only if they are coupled with an understanding of how medical science can and should be applied to patients with known or suspected diseases. Without this knowledge, caring may be inappropriate or misleading, and caring may be ineffective or counterproductive if it inhibits a sick person from obtaining appropriate, scientific medical care. Goldman's Cecil Textbook of Medicine focuses on the discipline of internal medicine, from which neurology and dermatology, which are also covered in substantial detail in this text, are relatively recent evolutionary branches. The term "internal medicine," which is often misunderstood by the lay public, was developed in 19th century Germany. Inneren medizin was to be distinguished from clinical medicine because it emphasized the physiology and chemistry of disease, not just the patterns or progression of clinical manifestations. Goldman's Cecil Textbook of Medicine follows this tradition by showing how pathophysiologic abnormalities cause symptoms and signs and by emphasizing how therapies can modify the underlying pathophysiologic and improve the patient's well-being.

Modern medicine has moved rapidly past organ physiology to an increasingly detailed understanding of cellular, subcellular, and genetic mechanisms. For example, the understanding of microbial pathogenesis and many inflammatory diseases (Chapter 264) is now guided by a detailed understanding of the human immune system and its response to foreign antigens ( Chapters 44 to 48).

Health, disease, and an individual's interaction with the environment are also substantially determined by genetics. In addition to many conditions that may be determined by a single gene (Chapter 40), medical science increasingly understands the complex interactions that underlie multigenic traits (Chapter 41). In the not-so-distant future, the decoding of the human genome holds the promise that personalized health care can be targeted according to an individual's genetic profile, in terms of screening and pre-symptomatic disease management, as well as in terms of specific medications and their adjusted dosing schedules. Currently, knowledge of the structure and physical forms of proteins helps explain abnormalities as diverse as sickle cell anemia (Chapter 166) and prion-related diseases (Chapter 424). Proteomics, which is the normal and abnormal protein expression of genes, also holds extraordinary promise for developing drug targets for more specific and effective therapies.

Concurrent with these advances in fundamental human biology has been a dramatic shift in methods for evaluating the application of scientific advances to the individual patient and to populations. The randomized controlled trial, sometimes with thousands of patients at multiple institutions, has replaced anecdote as the preferred method for measuring the benefits and optimal uses of diagnostic and therapeutic interventions (Chapter 9). As studies progress from those that show biologic effect, to those that elucidate dosing schedules and toxicity, and finally to those that assess true clinical benefit, the metrics of measuring outcome has also improved from subjective impressions of physicians or patients to reliable and valid measures of morbidity, quality of life, functional status, and other patient-oriented outcomes (Chapter 10). These marked improvements in the scientific methodology of clinical investigation have expedited extraordinary changes in clinical practice, such as recanalization therapy for acute myocardial infarction (Chapter 73), and have shown that reliance on intermediate outcomes, such as a reduction in asymptomatic ventricular arrhythmias with certain drugs, may unexpectedly increase rather than decrease mortality. Just as physicians in the 21st century must understand advances in fundamental biology, similar understanding of the fundamentals of clinical study design it as applies to diagnostic and therapeutic interventions is needed. An understanding of human genetics will also help stratify and refine the approach to clinical trials by helping researchers select fewer patients with a more homogeneous disease pattern to study the efficacy of an intervention.

This explosion in medical knowledge has led to increasing specialization and sub specialization, defined initially by organ system and more recently by locus of principal activity (inpatient vs. outpatient), reliance on manual skills (proceduralist vs. nonproceduralist), or participation in research. Nevertheless, it is becoming increasingly clear that the same fundamental molecular and genetic mechanisms are broadly applicable across all organ systems and that the scientific methodologies of randomized trials and careful clinical observation span all aspects of medicine.

The advent of modern approaches to managing data now provides the rationale for the use of health information technology. Computerized health records, oftentimes shared with patients in a portable format, can avoid duplication of tests and assure that care is coordinated among the patient's various health care providers.

APPROACH TO THE PATIENT

Patients commonly have complaints (symptoms). These symptoms may or may not be accompanied by abnormalities on examination (signs) or on laboratory testing. Conversely, asymptomatic patients may have signs or laboratory abnormalities, and laboratory abnormalities can occur in the absence of symptoms or signs.

Symptoms and signs commonly define syndromes, which may be the common final pathway of a wide range of pathophysiologic alterations. The fundamental basis of internal medicine is that diagnosis should elucidate the pathophysiologic explanation for symptoms and signs so that therapy may improve the underlying abnormality, not just attempt to suppress the abnormal symptoms or signs.

When patients seek care from physicians, they may have manifestations or exacerbations of known conditions, or they may have symptoms and signs that suggest malfunction of a particular organ system. Sometimes the pattern of symptoms and signs is highly suggestive or even pathognomonic for a particular disease process. In these situations, in which the physician is focusing on a particular disease, Goldman’s Cecil Textbook of Medicine provides scholarly yet practical approaches to the epidemiology, pathobiology, clinical manifestations, diagnosis, treatment, prevention, and prognosis of entities such as acute myocardial infarction (Chapter 73), chronic obstructive lung disease (Chapter 88), obstructive uropathy (Chapter 125), inflammatory bowel disease (Chapter 143), gallstones (Chapter 158), rheumatoid arthritis (Chapter 272), hypothyroidism (Chapter 233), tuberculosis (Chapter 332), and virtually any known medical condition in adults.

Many patients, however, have undiagnosed symptoms, signs, or laboratory abnormalities that cannot be immediately ascribed to a particular disease or cause. Whether the initial manifestation is chest pain (Chapter 50), diarrhea (Chapter 37), headache (Chapter 128), neck pain (Chapter 407), or a variety of more than 100 common symptoms, signs, or laboratory abnormalities, Goldman’s Cecil Textbook of Medicine provides tables, figures, and entire chapters to guide the approach to diagnosis and therapy (see E-Table 1-1 or table on inside back cover). By virtue of this dual approach to known disease as well as to undiagnosed abnormalities, this textbook, similar to the modern practice of medicine, applies directly to patients regardless of their mode of manifestation or degree of previous evaluation.

The patient-physician interaction proceeds through many phases of clinical reasoning and decision making. The interaction begins with an elucidation of complaints or concerns, followed by inquiries or evaluations to address these concerns in increasingly precise ways. The process commonly requires a careful history or physical examination, ordering of diagnostic tests, integration of clinical findings with test results, understanding of the risks and benefits of the possible courses of action, and careful consultation with the patient and family to develop future plans. Physicians can increasingly call on a growing literature of evidence-based medicine to guide the process so that benefit is maximized while respecting individual variations in different patients. Throughout Goldman’s Cecil Textbook of Medicine, the best current evidence is highlighted with specific grade A references that can be accessed directly in the electronic version.

The increasing availability of evidence from randomized trials to guide the approach to diagnosis and therapy should not be equated with “cookbook” medicine. Evidence and the guidelines that are derived from it emphasize proven approaches for patients with specific characteristics. Substantial clinical judgment is required to determine whether the evidence and guidelines apply to individual patients and to recognize the occasional exceptions. Even more judgment is required in the many situations in which evidence is absent or inconclusive. Evidence must also be tempered by patients’ preferences, although a physician’s responsibility to emphasize evidence when presenting alternative options to the patient. The adherence of a patient to a specific regimen is likely to be enhanced if the patient also understands the rationale and evidence behind the recommended option.

To care for a patient as an individual, the physician must understand the patient as a person. This fundamental precept of doctoring includes an understanding of the patient’s social situation, family issues, financial concerns, and preferences for different types of care and outcomes, ranging from maximum prolongation of life to the relief of pain and suffering (Chapters 2 and 3). If the physician does not appreciate and address these issues, the science of medicine cannot be applied appropriately, and even the most knowledgeable physician will fail to achieve the desired outcomes.

Even as physicians become increasingly aware of new discoveries, patients can obtain their own information from a variety of sources, some of which are difficult to control or provide reliability. The increasing availability of alternative therapies (Chapter 38) is an example of patients’ frequent dissatisfaction with prescribed medical therapy. Physicians should keep an open mind regarding unproven options but must advise their patients carefully if such options may carry any degree of potential risk, including the risk that they may be relied on to substitute for proven approaches. It is crucial for the physician to have an open dialogue with the patient and family regarding the full range of options that either may consider.

The physician does not exist in a vacuum, but rather as part of a complicated and extensive system of medical care and public health. In premodern times and even today in some developing countries, basic hygiene, clean water, and adequate nutrition have been the most important ways to promote health and reduce disease. In developed countries, adoption of healthy lifestyles, including better diet (Chapter 220) and appropriate exercise (Chapter 15), is the cornerstone to reducing the epidemics of obesity (Chapter 227), coronary disease (Chapter 70), and diabetes (Chapter 237). Public health interventions to provide immunizations (Chapter 17) and reduce injuries (Chapter 16) and the use of tobacco (Chapter 31), illicit drugs (Chapter 33), and excess alcohol (Chapter 32) can collectively produce more health benefits than nearly any other imaginable health intervention.

**APPRAOCH TO THE MEDICAL PROFESSION**

In a profession, practitioners put the welfare of clients or patients above their own welfare. Professionals have a duty that may be thought of as a contract with society. The American Board of Internal Medicine and the European Federation of Internal Medicine have jointly proposed that medical professionalism should emphasize three fundamental principles: the primacy of patient welfare, patient autonomy, and social justice. As modern medicine brings a plethora of diagnostic and therapeutic options, the interactions of the physician with the patient and society become more complex and potentially fraught with ethical dilemmas (Chapter 2). To help provide a moral compass that is not only grounded in tradition but also adaptable to modern times, the primacy of patient welfare emphasizes the fundamental principle of a profession. The physician’s altruism, which begets the patient’s trust, must be out of respect for the patient’s autonomy, the patient’s rights, and the social justice that is based on the physician’s sense of fair dealing. The increasing availability of evidence from randomized trials to guide the approach to diagnosis and therapy should not be equated with “cookbook” medicine. Evidence and the guidelines that are derived from it emphasize proven approaches for patients with specific characteristics. Substantial clinical judgment is required to determine whether the evidence and guidelines apply to individual patients and to recognize the occasional exceptions. Even more judgment is required in the many situations in which evidence is absent or inconclusive. Evidence must also be tempered by patients’ preferences, although a physician’s responsibility to emphasize evidence when presenting alternative options to the patient. The adherence of a patient to a specific regimen is likely to be enhanced if the patient also understands the rationale and evidence behind the recommended option.

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### TABLE 1-1 PROFESSIONAL RESPONSIBILITIES

<table>
<thead>
<tr>
<th>Commitment to:</th>
<th>Professional competence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honesty with patients</td>
<td>Patient confidentiality</td>
</tr>
<tr>
<td>Maintaining appropriate relations with patients</td>
<td>Improving the quality of care</td>
</tr>
<tr>
<td>Improving access to care</td>
<td>Just distribution of finite resources</td>
</tr>
<tr>
<td>Scientific knowledge</td>
<td>Maintaining trust by managing conflicts of interest</td>
</tr>
<tr>
<td>Professional responsibilities</td>
<td></td>
</tr>
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or even making someone uninsurable. The ethical approach to medicine (Chapter 2), genetics, and genetic counseling (Chapter 39) provides means to protect against this adverse effect of scientific progress. In this new environment, the physician often has a dual responsibility: to the health care system as an expert who helps create standards, measures of outcome, clinical guidelines, and mechanisms to ensure high-quality, cost-effective care and to individual patients who entrust their well-being to that physician to promote their best interests within the reasonable limits of the system. A health insurance system that emphasizes cost-effective care, that gives physicians and health care providers responsibility for the health of a population and the resources required to achieve these goals, that must exist in a competitive environment in which patients can choose alternatives if they are not satisfied with their care, and that places increasing emphasis on health education and prevention can have many positive effects. In this environment, however, physicians must beware of overt and subtle pressures that could entice them to underserve patients and abrogate their professional responsibilities by putting personal financial reward ahead of their patients’ welfare. The physician’s responsibility to represent the patient’s best interests and avoid financial conflicts by doing too little in the newer systems of capitated care provides different specific challenges but an analogous moral dilemma to the historical American system in which the physician could be rewarded financially for doing too much. In the current health care environment, all physicians and trainees must redouble their commitment to professionalism. At the same time, the challenge to the individual physician to retain and expand the scientific knowledge base and process the vast array of new information is daunting. In this spirit of a profession based on science and caring, Goldman’s Cecil Textbook of Medicine seeks to be a comprehensive approach to modern internal medicine.

SUGGESTED READINGS


Access the complete reference list online at http://www.expertconsult.com
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<td>Suspected lung cancer</td>
<td>201</td>
<td>Figure 201-4</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>52</td>
<td>Tables 52-2 to 52-5</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; ECG = electrocardiogram; PT = prothrombin time; PTT = partial thromboplastin time.
ADDITIONAL SUGGESTED READINGS


Patients with cardiovascular disease may present with a wide range of symptoms and signs, each of which may be caused by noncardiovascular conditions. Conversely, patients with substantial cardiovascular disease may be asymptomatic. Because cardiovascular disease is a leading cause of death in the United States and other developed countries, it is crucial that patients be evaluated carefully to detect early cardiovascular disease, that symptoms or signs of cardiovascular disease be evaluated in detail, and that appropriate therapy be instituted. Improvements in diagnosis, therapy, and prevention have contributed to a 70% or so decline in age-adjusted cardiovascular death rates in the United States since the 1960s. However, the absolute number of deaths from cardiovascular disease in the United States has not declined proportionately because of the increase in the population older than 40 years as well as the aging of the population in general.

In evaluating a patient with known or suspected heart disease, the physician must determine whether a potentially life-threatening condition exists. In these situations, the evaluation must focus on the specific issue at hand and be accompanied by the rapid performance of appropriately directed additional tests. Examples of potentially life-threatening conditions include acute myocardial infarction (Chapter 73), unstable angina (Chapter 72), suspected aortic dissection (Chapter 78), pulmonary edema (Chapter 59), and pulmonary embolism (Chapter 98).

Using the History to Detect Cardiovascular Symptoms

Patients may complain spontaneously of a variety of cardiovascular symptoms (Table 50-1), but sometimes these symptoms are elicited only by obtaining a careful, complete medical history. In patients with known or suspected cardiovascular disease, questions about cardiovascular symptoms are key components of the history of present illness; in other patients, these issues are a fundamental part of the review of systems.

Chest Pain

Chest discomfort or pain is the cardinal manifestation of myocardial ischemia resulting from coronary artery disease or any condition that causes myocardial ischemia by an imbalance of myocardial oxygen demand compared with myocardial oxygen supply (Chapter 71). New, acute, often ongoing pain may indicate an acute myocardial infarction, unstable angina, or aortic dissection; a pulmonary cause, such as acute pulmonary embolism or pleural irritation; a musculoskeletal condition of the chest wall, thorax, or shoulder; or a gastrointestinal abnormality, such as esophageal reflux or spasm, peptic ulcer disease, or cholecystitis (Table 50-2). The chest discomfort of myocardial infarction commonly occurs without an immediate or obvious precipitating clinical cause and builds in intensity for at least several minutes; the sensation can range from annoying discomfort to severe pain (Chapter 73). Although a variety of adjectives may be used by patients to describe the sensation, physicians must be suspicious of any discomfort, especially if it radiates to the neck, shoulder, or arms. The probability of an acute myocardial infarction can be estimated by integrating information from the history, physical examination, and electrocardiogram (Fig. 50-1). The chest discomfort of unstable angina is clinically indistinguishable from that of myocardial infarction except that the former may be precipitated more clearly by activity and may be more rapidly responsive to antianginal therapy (Chapter 72). Aortic dissection (Chapter 78) classically presents with the sudden onset of severe pain in the chest and radiating to the back; the location of the pain often provides clues to the location of the dissection. Ascending aortic dissections commonly present with chest discomfort radiating to the back, whereas dissections of the descending aorta commonly present with back pain radiating to the abdomen. The presence of back pain or a history of hypertension or other predisposing factors, such as Marfan syndrome, should prompt a careful assessment of peripheral pulses to determine whether the great vessels are affected by the dissection and of the chest radiograph to evaluate the size of the aorta. If this initial evaluation is suggestive, further testing with transesophageal echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) is indicated. The pain of pericarditis (Chapter 77) may simulate that of an acute myocardial infarction, may be primarily pleuritic, or may be continuous; a key physical finding is a pericardial rub. The pain of pulmonary embolism (Chapter 98) is commonly pleuritic in nature and is associated with dyspnea; hemoptysis also may be present. Pulmonary hypertension (Chapter 68) of any cause may be associated with chest discomfort with exertion; it commonly is associated with severe dyspnea and often is associated with cough.

Recurrent, episodic chest discomfort may be noted with angina pectoris and with many cardiac and noncardiac causes (Chapter 71). A variety of stress tests (Table 50-3) can be used to provoke reversible myocardial ischemia in susceptible individuals and to help determine whether ischemia is the pathophysiologic explanation for the chest discomfort (Chapter 71).

Dyspnea

Dyspnea, which is an uncomfortable awareness of breathing, is commonly due to cardiovascular or pulmonary disease. A systematic approach (see Fig. 83-3 in Chapter 83) with selected tests nearly always reveals the cause. Acute dyspnea can be caused by myocardial ischemia, heart failure, severe hypertension, pericardial tamponade, pulmonary embolism, pneumothorax, upper airway obstruction, acute bronchitis or pneumonia, or some drug overdoses (e.g., hydantoins). Subacute or chronic dyspnea is also a common presenting or accompanying symptom in patients with pulmonary disease (Chapter 83). Dyspnea also can be caused by severe anemia (Chapter 161) and can be confused with the fatigue that often is noted in patients with systemic and neurologic diseases (Chapters 264 and 403).

In heart failure, dyspnea typically is noted as a hunger for air and a need or an urge to breathe. The feeling that breathing requires increased work or effort is more typical of airway obstruction or neuromuscular disease. A feeling of chest tightness or constriction during breathing is typical of bronchoconstriction, which is commonly caused by obstructive airway disease (Chapters 87 and 88) but also may be seen in pulmonary edema. A feeling of heavy breathing, a feeling of rapid breathing, or a need to breathe more is classically associated with deconditioning.

In cardiovascular conditions, chronic dyspnea usually is caused by increases in pulmonary venous pressure as a result of left ventricular failure (Chapters 58 and 59) or valvular heart disease (Chapter 75). Orthopnea, which is an exacerbation of dyspnea when the patient is recumbent, is due to increased work of breathing because of either increased venous return to the pulmonary vasculature or loss of gravitational assistance in diaphragmatic effort. Paroxysmal nocturnal dyspnea is severe dyspnea that awakens a patient at night and forces the assumption of a sitting or standing position to achieve gravitational redistribution of fluid.

Palpitations

Palpitations (Chapter 62) describe a subjective sensation of an irregular or abnormal heartbeat. Palpitations may be caused by any arrhythmia (Chapters 64 and 65) with or without important underlying structural heart disease. Palpitations should be defined in terms of the duration and frequency of the episodes; the precipitating and related factors; and any associated symptoms of chest pain, dyspnea, lightheadedness, or syncope. It is crucial to use the history to determine whether the palpitations are caused by an irregular or a regular heartbeat. The feeling associated with a premature atrial or ventricular contraction, often described as a “skipped beat” or a “flip-flopping of the heart,” must be distinguished from the irregularly irregular rhythm of atrial fibrillation and the rapid but regular rhythm of supraventricular tachycardia. Associated symptoms of chest pain, dyspnea, lightheadedness, dizziness, or diaphoresis suggest an important effect on cardiac output and mandate further evaluation. In general, evaluation begins with ambulatory electrocardiography (ECG) (Table 50-4), which is indicated in patients who have palpitations in the presence of structural heart disease or substantial accompanying symptoms. Depending on the series, 9 to 43% of patients have important underlying heart disease. In such patients, more detailed evaluation is warranted (See Fig. 62-1).
TABLE 50-1 CARDINAL SYMPTOMS OF CARDIOVASCULAR DISEASE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>Quality</th>
<th>Duration</th>
<th>Aggravating or Relieving Factors</th>
<th>Associated Symptoms or Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain or discomfort</td>
<td>Retrosternal region, radiates to neck, jaw, epigastrium, shoulder, or arms (left common)</td>
<td>Pressure, burning, squeezing, heaviness, indigestion</td>
<td>&lt;2-10 min</td>
<td>Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal’s) angina may be unrelated to activity, often early morning</td>
<td>S, or murmur of papillary muscle dysfunction during pain</td>
</tr>
<tr>
<td>Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, wheezing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations, dizziness, syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough, hemoptysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremities with exertion (claudication)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


TABLE 50-2 CAUSES OF CHEST PAIN

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>Quality</th>
<th>Duration</th>
<th>Aggravating or Relieving Factors</th>
<th>Associated Symptoms or Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>Retrosternal region; radiates to neck, jaw, epigastrium, shoulder, or arms (left common)</td>
<td>Pressure, burning, squeezing, heaviness, indigestion</td>
<td>&lt;2-10 min</td>
<td>Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal’s) angina may be unrelated to activity, often early morning</td>
<td>S, or murmur of papillary muscle dysfunction during pain</td>
</tr>
<tr>
<td>Rest or unstable angina</td>
<td>Same as angina but may be more severe</td>
<td>Usually &lt;20 min</td>
<td>Same as angina, with decreasing tolerance for exertion or at rest</td>
<td>Similar to stable angina but may be pronounced; transient heart failure can occur</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Substernal and may radiate like angina</td>
<td>Heaviness, pressure, burning, constriction</td>
<td>≥30 min but variable</td>
<td>Unrelieved by rest or nitroglycerin</td>
<td>Shortness of breath, sweating, weakness, nausea, vomiting</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Usually begins over sternum or toward cardiac apex and may radiate to neck or left shoulder; often more localized than the pain of myocardial ischemia</td>
<td>Sharp, stabbing, knifelike</td>
<td>Lasts many hours to days; may wax and wane</td>
<td>Aggravated by deep breathing, rotating chest, or supine position; relieved by sitting up and leaning forward</td>
<td>Pericardial friction rub</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Anterior chest; may radiate to back</td>
<td>Excruciating, tearing, knifelike</td>
<td>Sudden onset, unrelenting</td>
<td>Usually occurs in setting of hypertension or predisposition, such as Marfan syndrome</td>
<td>Murmur of aortic insufficiency, pulse or blood pressure asymmetry; neurologic deficit</td>
</tr>
<tr>
<td>Pulmonary embolism (chest pain often not present)</td>
<td>Substernal or over region of pulmonary infarction</td>
<td>Pleuritic (with pulmonary infarction) or angina-like</td>
<td>Sudden onset; minutes to &lt;1 hr</td>
<td>May be aggravated by breathing</td>
<td>Dyspnea, tachypnea, tachycardia; hypertension, signs of acute right ventricular failure, and pulmonary hypertension with large emboli; rales, pleural rub, hemoptysis with pulmonary infarction</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Substernal</td>
<td>Pressure; oppressive</td>
<td>Similar to angina</td>
<td>Aggravated by effort</td>
<td>Pain usually associated with dyspnea; signs of pulmonary hypertension</td>
</tr>
<tr>
<td>Pneumonia with pleurisy</td>
<td>Localized over involved area</td>
<td>Pleuritic, localized</td>
<td>Brief or prolonged</td>
<td>Painful breathing</td>
<td>Dyspnea, cough, fever, dull to percussion, bronchial breath sounds, rales, occasional pleural rub</td>
</tr>
<tr>
<td>Spontaneous pneumothorax</td>
<td>Unilateral</td>
<td>Sharp, well localized</td>
<td>Sudden onset, lasts many hours</td>
<td>Painful breathing</td>
<td>Dyspnea; hyperresonance and decreased breath and voice sounds over involved lung</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
<td>Variable</td>
<td>Aching</td>
<td>Short or long duration</td>
<td>Aggravated by movement; history of muscle exertion or injury</td>
<td>Tender to pressure or movement</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Dermatomal in distribution</td>
<td>Burning, itching</td>
<td>Prolonged</td>
<td>None</td>
<td>Vesicular rash appears in area of discomfort</td>
</tr>
<tr>
<td>Esophageal reflux</td>
<td>Substernal, epigastric</td>
<td>Burning, visceral discomfort</td>
<td>10-60 min</td>
<td>Aggravated by large meal, postprandial recumbency; relief with antacid</td>
<td>Water brash</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Epigastric, substernal</td>
<td>Visceral burning, achings</td>
<td>Prolonged</td>
<td>Relief with food, antacid</td>
<td></td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>Epigastric, right upper quadrant</td>
<td>Visceral</td>
<td>Prolonged</td>
<td>May be unprovoked or follow meals</td>
<td>Right upper quadrant tenderness may be present</td>
</tr>
<tr>
<td>Anxiety states</td>
<td>Often localized over precordium</td>
<td>Variable; location often moves from place to place</td>
<td>Varies; often fleeting</td>
<td>Situational</td>
<td>Sighing respirations, often chest wall tenderness</td>
</tr>
</tbody>
</table>


**TABLE 50-3 COMMON EXERCISE TEST PROTOCOLS**

<table>
<thead>
<tr>
<th>PROTOCOL</th>
<th>STAGE</th>
<th>DURATION (min)</th>
<th>GRADE (%)</th>
<th>RATE (mph)</th>
<th>METABOLIC EQUIVALENTS AT COMPLETION</th>
<th>FUNCTIONAL CLASS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Bruce protocol†</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1.7</td>
<td>2.5</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>1.7</td>
<td>5</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>12</td>
<td>2.5</td>
<td>7</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3</td>
<td>14</td>
<td>3.4</td>
<td>10</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3</td>
<td>16</td>
<td>4.2</td>
<td>13</td>
<td>I</td>
</tr>
<tr>
<td>Naughton protocol‡</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3.5</td>
<td>2</td>
<td>3</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>10.5</td>
<td>2</td>
<td>5</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
<td>14</td>
<td>2</td>
<td>6</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2</td>
<td>17.5</td>
<td>2</td>
<td>7</td>
<td>I</td>
</tr>
</tbody>
</table>

†Ramp protocols in which the workload is gradually increased on the basis of the patient’s estimated functional capacity to achieve maximal effort in approximately 10 minutes are also useful.
‡Commonly used in ambulatory patients.  
††Commonly used in patients with recent myocardial infarction, unstable angina, or other conditions that are expected to limit exercise.  
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syncope. When the history, physical examination, and ECG do not provide helpful diagnostic information that points toward a specific cause of syncope, it is imperative that patients with heart disease or an abnormal ECG be tested with continuous ambulatory ECG monitoring to diagnose a possible arrhythmia (see Fig. 62-1 in Chapter 62); in selected patients, formal electrophysiologic testing may be indicated (Chapter 62). In patients with no evident heart disease, tilt testing (Chapter 62) can help detect reflex-mediated vasomotor instability.

Other Symptoms
Nonproductive cough (Chapter 83), especially a persistent cough (see Fig. 83-1 in Chapter 83), can be an early manifestation of elevated pulmonary venous pressure and otherwise unsuspected heart failure. Fatigue and weakness are common accompaniments of advanced cardiac disease and reflect an inability to perform normal activities. A variety of approaches have been used to classify the severity of cardiac limitations, ranging from class I (little or no limitation) to class IV (severe limitation) (Table 50-5).

CHAPTER 50  APPROACH TO THE PATIENT WITH POSSIBLE CARDIOVASCULAR DISEASE

(Chapter 83) is a classic presenting finding in patients with pulmonary embolism, but it is also common in patients with mitral stenosis, pulmonary edema, pulmonary infections, and malignant neoplasms (see Table 83-5 in Chapter 83). **Claudication,** which is pain in the extremities with exercise, should alert the physician to possible peripheral arterial disease (Chapters 79 and 80).

**Complete Medical History**
The complete medical history should include a thorough review of systems, family history, social history, and past medical history (Chapter 14). The review of systems may reveal other symptoms that suggest a systemic disease as the cause of any cardiovascular problems. The family history should focus on premature atherosclerosis or evidence of familial abnormalities, such as may be found with various causes of the long QT syndrome (Chapter 65) or hypertrophic cardiomyopathy (Chapter 60).

The social history should include specific questioning about cigarette smoking, alcohol intake, and use of illicit drugs. The past medical history may reveal prior conditions or medications that suggest systemic diseases, ranging from chronic obstructive pulmonary disease, which may explain a complaint of dyspnea, to hemochromatosis, which may be a cause of restrictive cardiomyopathy. A careful history to inquire about recent dental work or other procedures is crucial if bacterial endocarditis is part of the differential diagnosis.

**PHYSICAL EXAMINATION FOR DETECTION OF SIGNS OF CARDIOVASCULAR DISEASE**
The cardiovascular physical examination, which is a subset of the complete physical examination, provides important clues to the diagnosis of asymptomatic and symptomatic cardiac disease and may reveal cardiovascular manifestations of noncardiovascular diseases. The cardiovascular physical examination begins with careful measurement of the pulse and blood pressure (Chapter 7). If aortic dissection (Chapter 78) is a consideration, blood pressure should be measured in both arms and, preferably, in at least one leg. When coarctation of the aorta is suspected (Chapter 69), blood pressure must be measured in at least one leg and in the arms. Discrepancies in blood pressure between the two arms also can be caused by atherosclerotic disease of the great vessels. Pulsus paradoxus, which is more than the usual 10 mm Hg drop in systolic blood pressure during inspiration, is typical of pericardial tamponade (Chapter 77).

**General Appearance**
The respiratory rate may be increased in patients with heart failure. Patients with pulmonary edema are usually markedly tachypneic and may have labored breathing. Patients with advanced heart failure may have Cheyne-Stokes respirations.

Systemic diseases, such as hyperthyroidism (Chapter 233), hypothyroidism (Chapter 233), rheumatoid arthritis (Chapter 272), scleroderma (Chapter 275), and hemochromatosis (Chapter 219), may be suspected from the patient’s general appearance. Marfan syndrome (Chapter 268), Turner’s syndrome (Chapter 243), Down syndrome (Chapter 40), and a variety of congenital anomalies also may be readily apparent.

**Ophthalmologic Examination**
Examination of the fundi may show diabetic (see Fig. 431-15 in Chapter 431) or hypertensive retinopathy (see Fig. 67-11 in Chapter 67) or Roth’s spots (see Fig. 431-17 in Chapter 431) typical of infectious endocarditis. Beading of the retinal arteries is typical of severe hypercholesterolemia. Osteogenesis imperfecta, which is associated with blue sclerae, also is associated with aortic dilation and mitral valve prolapse. Retinal artery occlusion (see Fig. 431-20 in Chapter 431) may be caused by an embolus from clot in the left atrium or left ventricle, a left atrial myxoma, or atherolectotic debris from the great vessels. Hyperthyroidism may present with exophthalmos and typical stare (see Fig. 431-14 in Chapter 431), whereas myotic dystrophy, which is associated with atrioventricular block and arrhythmia, often is associated with ptosis and an expressionless face (see Fig. 429-2 in Chapter 429).

**Jugular Veins**
The external jugular veins help in assessment of mean right atrial pressure, which normally varies between 5 and 10 cm H2O; the height (in centimeters) of the central venous pressure is measured by adding 5 cm to the height of the observed jugular venous distention above the sternal angle of Louis (Fig. 50-2). The normal jugular venous pulse, best seen in the internal jugular vein (and not seen in the external jugular vein unless insufficiency of the jugular venous valves is present), includes an a wave, caused by right atrial contraction; a c wave, reflecting right atrial pressure; an x descent; a y descent, which corresponds to isovolumetric right ventricular contraction and is more marked in the presence of tricuspid insufficiency; and a y descent, which occurs as the tricuspid valve opens and ventricular filling begins (Fig. 50-3). Abnormalities of the jugular venous pressure (Fig. 50-4) and arterial pulse are useful in detecting conditions such as heart failure, pericardial disease, tricuspid valve disease, and pulmonary hypertension (Table 50-6).

**Carotid Pulse**
The carotid pulse should be examined in terms of its volume and contour. The carotid pulse (Fig. 50-5) may be increased in frequency and may be more intense than normal in patients with a higher stroke volume secondary to aortic regurgitation, arteriovenous fistula, hyperthyroidism, fever, or anemia. In aortic regurgitation or arteriovenous fistula, the pulse may have a bisferi- nous quality. The carotid upstroke is delayed in patients with valvular aortic stenosis (Chapter 75) and has a normal contour but diminished amplitude in any cause of reduced stroke volume.

**Cardiac Inspection and Palpation**
Inspection of the precordium may reveal the hyperinflation of obstructive lung disease or unilateral asymmetry of the left side of the chest because of right ventricular hypertrophy before puberty. Palpation may be performed with the patient either supine or in the left lateral decubitus position; the latter position moves the left ventricular apex closer to the chest wall and increases the ability to palpate the point of maximal impulse and other phenomena. Low-frequency phenomena, such as systolic heaves or lifts from the left ventricle (at the cardiac apex) or right ventricle (parasternal in the third...
or fourth intercostal space), are felt best with the heel of the palm. With the patient in the left lateral decubitus position, this technique also may allow palpation of an S1 gallop in cases of advanced heart failure or an S3 gallop in cases of poor left ventricular distensibility during diastole. The left ventricular apex is more diffuse and sometimes may be frankly dyskinetic in patients with advanced heart disease. The distal palm is best for feeling thrills, which are the tactile equivalent of cardiac murmurs. By definition, a thrill denotes a murmur of grade 4/6 or louder. Higher-frequency events may be felt best with the fingertips; examples include the opening snap of mitral stenosis or murmurs of grade 4/6 or louder. Higher-frequency events may be felt best with the fingertips; examples include the opening snap of mitral stenosis or murmurs of grade 4/6 or louder. Higher-frequency events may be felt best with the fingertips; examples include the opening snap of mitral stenosis or murmurs of grade 4/6 or louder.

**Auscultation**

The first heart sound (Fig. 50-6), which is largely produced by closure of the mitral valve, is described as a “lub” or “lub-dub.” It is the first wave with or without elevation of mean systemic venous pressure (echo-Doppler or cardiac catheterization recommended). A prominent y wave with or without elevation of mean systemic venous pressure has been termed a “dicrotic notch” in cases of advanced heart failure or an S4 gallop in cases of advanced heart failure. The second heart sound is caused primarily by closure of the aortic valve, but closure of the pulmonary valve is also commonly audible. In normal individuals, the louder aortic closure sound occurs first, followed by pulmonic closure. With expiration, the two sounds are virtually superimposed. With inspiration, by comparison, the increased stroke volume of the right ventricle commonly leads to a discernible splitting of the second sound. This splitting may be fixed in patients with an atrial septal defect (Chapter 69) or right bundle branch block. The split may be paradoxical in patients with left bundle branch block or other causes of delayed left ventricular emptying. The aortic component of the second sound is increased in intensity in the presence of mitral valve stenosis and intact valve leaflet movement and less audible in patients with poor closure due to mitral regurgitation (Chapter 75).

**TABLE 50-6 ABNORMALITIES OF VENOUS PRESSURE AND PULSE AND THEIR CLINICAL SIGNIFICANCE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive hepatoid reflex</td>
<td>Suspect heart failure, particularly left ventricular systolic dysfunction (echocardiography recommended)</td>
</tr>
<tr>
<td>Elevated systemic venous pressure without obvious x or y descent, quiet precordium, and pulus paradoxus</td>
<td>Suspect cardiac tamponade (echocardiography recommended)</td>
</tr>
<tr>
<td>Elevated systemic venous pressure with a sharp y descent, Kussmaul’s sign, and quiet precordium</td>
<td>Suspect constrictive pericarditis (cardiac catherization and MRI or CT recommended)</td>
</tr>
<tr>
<td>Elevated systemic venous pressure with a sharp brief y descent, Kussmaul’s sign, and evidence of pulmonary hypertension and tricuspid regurgitation</td>
<td>Suspect restrictive cardiomyopathy (cardiac catheterization and MRI or CT recommended)</td>
</tr>
<tr>
<td>A prominent x wave with or without elevation of mean systemic venous pressure</td>
<td>Exclude tricuspid stenosis, right ventricular hypertrophy due to pulmonary stenosis, and pulmonary hypertension (echo-Doppler or cardiac catheterization to determine etiology)</td>
</tr>
<tr>
<td>A prominent y wave with a sharp y descent</td>
<td>Suspect tricuspid regurgitation (echo-Doppler or cardiac catheterization to determine etiology)</td>
</tr>
</tbody>
</table>

**FIGURE 50-4** Normal jugular venous pulse. ECG = electrocardiogram; JUG = jugular ven-tr; LSB = left sternal border; phono = phonocardiogram; S1 = first heart sound; S2 = second heart sound.

**FIGURE 50-5** Schematic diagrams of the configurational changes in the carotid pulse and their differential diagnosis. Heart sounds also are illustrated. A, Normal. B, Anacrotic pulse with slow initial upstroke. The peak is close to the second heart sound. These features suggest fixed left ventricular outflow obstruction, such as valvular aortic stenosis. C, Pulus bisferiens, with pericussion and tidal waves occurring during systole. This type of carotid pulse contour is observed most frequently in patients with hemodynamically significant aortic regurgitation or combined aortic stenosis and regurgitation with dominant regurgitation. It rarely is observed in patients with mitral valve prolapse or in normal individuals. D, Pulus bisferiens in hypertrophic obstructive cardiomyopathy. This finding rarely is appreciated at the bedside by palpation. E, Dicrotic pulse results from an accentuated dicrotic wave and tends to occur in sepsis, severe heart failure, hypolemic shock, and cardiac tamponade and after aortic valve replacement. A2 = aortic component of the second heart sound; P2 = pulmonary component of the second heart sound; S1 = first heart sound; S2 = atrial sounds. (From Chatterjee K. Bedside evaluation of the heart: the physical examination. In: Chatterjee K, Chetlin MD, Karliner J, et al, eds. Cardiology: An Illustrated Text/Reference. Philadelphia: JB Lippincott; 1991:3.11-3.51.)

of systemic hypertension and decreased in intensity in patients with aortic stenosis. The pulmonic second sound is increased in the presence of pulmo-

card hypertrophy.

Early systolic ejection sounds are related to forceful opening of the aortic or pulmonic valve. These sounds are common in congenital aortic stenosis, with a mobile valve; in hypertension, with forceful opening of the aortic valve; and in healthy young individuals, especially when cardiac output is increased. Midsystolic or late systolic clicks are caused most commonly by mitral valve prolapse (Chapter 75). Clicks are relatively high-frequency sounds that are heard best with the diaphragm of the stethoscope.

An S₁ corresponds to rapid ventricular filling during early diastole. It may occur in normal children and young adults, especially if stroke volume is increased. After about 40 years of age, however, an S₁ should be considered abnormal; it is caused by conditions that increase the volume of ventricular filling during early diastole (e.g., mitral regurgitation) or that increase pressure in early diastole (e.g., advanced heart failure). A left ventricular S₂ gallop is heard best at the apex, whereas the right ventricular S₂ gallop is heard best at the fourth intercostal space at the left parasternal border; both are heard best with the bell of the stethoscope. An S₃ is heard rarely in young individuals but is common in adults older than 40 or 50 years because of reduced ventricular compliance during atrial contraction; it is a nearly ubiquitous finding in patients with hypertension, heart failure, or ischemic heart disease. The opening snap of mitral and, less commonly, tricuspid stenosis (Chapter 75) occurs at the beginning of mechanical diastole, before the onset of the rapid phase of ventricular filling. An opening snap is high pitched and is heard best with the diaphragm; this differential frequency should help distinguish

an opening snap from an S₃ on physical examination. An opening snap commonly can be distinguished from a loud pulmonic component of the second heart sound by the differential location (mitral opening snap at the apex, tricuspid opening snap at the left third or fourth intercostal space, pulmonic second sound at the left second intercostal space) and by the longer interval between S₃ and the opening snap.

Heart murmurs may be classified as systolic, diastolic, or continuous (Table 50-7). Murmurs are graded by intensity on a scale of 1 to 6. Grade 1 is faint and appreciated only by careful auscultation; grade 2, readily audible; grade 3, moderately loud; grade 4, loud and audible with a palpable thrill; grade 5, loud and audible with the stethoscope only partially placed on the chest; and grade 6, loud enough to be heard without the stethoscope on the chest. Systolic ejection murmurs usually peak in early to mid systole when left ventricular ejection is maximal; examples include fixed valvular, supraval-

vular, or infravalvular aortic stenosis and pulmonic stenosis. The murmur of hypertrophic obstructive cardiomyopathy has a similar ejection quality, although its peak may be later in systole when dynamic obstruction is maximal (Chapter 60). Pan systolic murmurs are characteristic of mitral or tricuspid regurgitation or with a left-to-right shunt from conditions such as a ventricular septal defect (left ventricle to right ventricle). A late systolic murmur is characteristic of mitral valve prolapse (Chapter 75) or ischemic papillary muscle dysfunction. Ejection quality murmurs also may be heard in patients with normal valves but increased flow, such as occurs with marked anemia, fever, or bradycardia secondary to congenital complete heart block; they also may be heard across a valve that is downstream from increased flow because of an intracardiac shunt. Maneuvers such as inspiration, expiration, standing, squatting, and hand gripping can be especially useful in the differentia-

tional diagnosis of a murmur; however, echocardiography commonly is required to make a definitive diagnosis of cause and severity (Table 50-8).

High-frequency, early diastolic murmurs are typical of aortic regurgitation and pulmonic regurgitation from a variety of causes. The murmurs of mitral and tricuspid stenosis begin in early to mid diastole and tend to diminish in intensity later in diastole in the absence of effective atrial contraction, but they tend to increase in intensity in later diastole if effective atrial contraction is present.

Continuous murmurs may be caused by any abnormality that is associated with a pressure gradient in systole and diastole. Examples include a patent ductus arteriosus, ruptured sinus of Valsalva aneurysm, arteriovenous fistula (of the coronary artery, pulmonary artery, or thoracic artery), and a mammary souffle. In some situations, murmurs of two coexistent conditions (e.g., aortic stenosis and regurgitation; atrial septal defect with a large shunt and resulting flow murmurs of relative mitral and pulmonic stenosis) may mimic a continu-

ous murmur.

Abdomen

The most common cause of hepatomegaly in patients with heart disease is hepatic engorgement from elevated right-sided pressures associated with right ventricular failure of any cause. Hepatojugular reflux is elicited by pressing on the liver and showing an increase in the jugular venous pressure; it indicates advanced right ventricular failure or obstruction to right ventricular filling. Evaluation of the abdomen also may reveal an enlarged liver caused by a systemic disease, such as hemochromatosis (Chapter 219) or sarcoidosis (Chapter 95), which also may affect the heart. In more severe cases, spleno-

megaly and ascites also may be noted. Large, palpable, polycystic kidneys (Chapter 129) commonly are associated with hypertension. A systolic bruit suggestive of renal artery stenosis (Chapter 127) or an enlarged abdominal aorta (Chapter 78) is a clue of atherosclerosis.

Extremities

Extremities should be evaluated for peripheral pulses, edema, cyanosis, and clubbing. Diminished peripheral pulses suggest peripheral arterial disease (Chapters 79 and 80). Delayed pulses in the legs are consistent with coarcta-

tion of the aorta and are seen after aortic dissection. Edema (Fig. 50-7) is a cardinal manifestation of right-sided heart failure. When it is caused by heart failure, pericardial disease, or pulmonary hyper-

tension, the edema is usually symmetrical and progresses upward from the ankles; each of these causes of cardiac edema commonly is associated with jugular venous distention and often with hepatic congestion. Unilateral edema suggests thrombophlebitis or proximal venous or lymphatic obstruction (Fig. 50-8). Edema in the absence of evidence of right-sided or left-sided heart failure suggests renal disease, hypoalbuminemia, myxedema, or other noncardiac causes. Among unselected patients with bilateral edema, about
40% have an underlying cardiac disease, about 40% have an elevated pulmonary blood pressure, about 20% have bilateral venous disease, about 20% have renal disease, and about 25% have idiopathic edema.

Cyanosis (Fig. 50-9) is a bluish discoloration caused by reduced hemoglobin exceeding about 5 g/dL in the capillary bed. Central cyanosis is seen in patients with poor oxygen saturation resulting from a reduced inspired oxygen concentration or inability to oxygenate the blood in the lungs (e.g., as a result of advanced pulmonary disease, pulmonary edema, pulmonary arteriovenous fistula, or right-to-left shunting); it also may be seen in patients with marked erythrocytosis. Methemoglobinemia (Chapter 161) also can present with cyanosis. Peripheral cyanosis may be caused by reduced blood flow to the extremities secondary to vasoconstriction, heart failure, or shock. Clubbing (Fig. 50-10), which is loss of the normal concave configuration of the nail as it emerges from the distal phalanx, is seen in patients with pulmonary abnormalities such as lung cancer (Chapter 197) and in patients with cyanotic congenital heart disease (Chapter 69).

Examination of the Skin
Examination of the skin may reveal bronze pigmentation typical of hemochromatosis (Chapter 219); jaundice (see Fig. 149-2 in Chapter 149) characteristic of severe right-sided heart failure or hemochromatosis; or capillary hemangiomas typical of Osler-Weber-Rendu disease (see Fig. 176-2 in Chapter 176), which also is associated with pulmonary arteriovenous fistulas and cyanosis. Infectious endocarditis may be associated with Osler’s nodes (see Fig. 76-2 in Chapter 76), Janeway’s lesions, or splinter hematomas (see Fig. 176-2 in Chapter 176). Xanthomas (Fig. 50-12) are subcutaneous deposits of cholesterol seen on the extensor surfaces of the extremities or on the palms and digital creases; they are found in patients with severe hypercholesterolemia.

Laboratory Studies
All patients with known or suspected cardiac disease should have an ECG and chest radiograph. The ECG (Chapter 54) helps identify rate, rhythm,
### CHAPTER 50  APPROACH TO THE PATIENT WITH POSSIBLE CARDIOVASCULAR DISEASE

#### TABLE 50-8  SENSITIVITY AND SPECIFICITY OF BEDSIDE MANEUVERS IN THE IDENTIFICATION OF SYSTOLIC MURMURS

<table>
<thead>
<tr>
<th>MANEUVER</th>
<th>RESPONSE</th>
<th>MURMUR</th>
<th>SENSITIVITY (%)</th>
<th>SPECIFICITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory</td>
<td>↑</td>
<td>RS</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>Expiratory</td>
<td>↓</td>
<td>RS</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td>↑</td>
<td>HC</td>
<td>65</td>
<td>96</td>
</tr>
<tr>
<td>Squat to stand</td>
<td>↑</td>
<td>HC</td>
<td>95</td>
<td>84</td>
</tr>
<tr>
<td>Stand to squat</td>
<td>↓</td>
<td>HC</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>Leg elevation</td>
<td>↓</td>
<td>HC</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>Handgrip</td>
<td>↓</td>
<td>HC</td>
<td>85</td>
<td>75</td>
</tr>
<tr>
<td>Handgrip</td>
<td>↑</td>
<td>MR and VSD</td>
<td>68</td>
<td>92</td>
</tr>
</tbody>
</table>

HC = hypertrophic cardiomyopathy; MR = mitral regurgitation; RS = right sided; VSD = ventricular septal defect.


#### FIGURE 50-7  Pitting edema in a patient with cardiac failure. A depression (“pit”) remains in the edema for some minutes after firm fingertip pressure is applied. *(From Forbes CD, Jackson WD. Color Atlas and Text of Clinical Medicine. 3rd ed. London: Mosby; 2003.)*

#### FIGURE 50-8  Diagnostic approach to patients with edema. CHF = congestive heart failure; DVT = deep venous thrombosis; MRI = magnetic resonance imaging; R/O = rule out; TSH = thyroid-stimulating hormone; WBC = white blood cell count. *(From Chertow G. Approach to the patient with edema. In: Braunwald E, Goldman L, eds. Primary Cardiology. 2nd ed. Philadelphia: WB Saunders; 2003.)*

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conduction abnormalities, and possible myocardial ischemia. The chest radiograph (Chapter 53) yields important information on chamber enlargement, pulmonary vasculature, and the great vessels.

Blood testing in patients with known or suspected cardiac disease should be targeted to the conditions in question. In general, a complete blood cell count, thyroid indices, and lipid levels are part of the standard evaluation.

Echocardiography (Chapter 55) is the most useful test to analyze valvular and ventricular function. By use of Doppler flow methods, stenotic and regurgitant lesions can be quantified. Hand-held ultrasonography performed by generalists can improve the assessment of left ventricular function, cardiomegaly, and pericardial effusion. Transesophageal echocardiography is the preferred method to evaluate possible aortic dissection and to identify clot in the cardiac chambers. Radionuclide studies (Chapter 56) can measure left ventricular function, assess myocardial ischemia, and determine whether ischemic myocardium is viable. CT can detect coronary calcium, which is a risk factor for symptomatic coronary disease (Chapter 56). In the setting of acute chest pain, multislice CT is effective in diagnosing coronary disease, but it currently cannot adequately determine the physiologic significance of ventricular or supraventricular wide-complex tachycardia, and it is crucial for guiding a wide array of new invasive electrophysiologic therapies (Chapter 66).

**SUMMARY**

The history, physical examination, and laboratory evaluation should help the physician establish the cause of any cardiovascular problem; identify and quantify any anatomic abnormalities; determine the physiologic status of the valves, myocardium, and conduction system; determine functional capacity; estimate prognosis; and provide primary or secondary prevention. Key preventive strategies, including diet modification, recognition and treatment of hyperlipidemia, cessation of cigarette smoking, and adequate physical exercise, should be part of the approach to every patient, with or without heart disease.


**SUGGESTED READINGS**


Access the complete reference list online at [http://www.expertconsult.com](http://www.expertconsult.com)
ADDITIONAL SUGGESTED READINGS


INTRODUCTION TO MICROBIAL DISEASE: HOST-PATHOGEN INTERACTIONS

W. MICHAEL SCHELD

Infectious diseases have profoundly influenced the course of human history. The “black death” (caused by Yersinia pestis) changed the social structure of medieval Europe, in the process eliminating approximately a third of the population. The outcomes of military campaigns have been altered by outbreaks of diseases such as dysentery and typhus. Examples include Napoleon’s retreat from Russia, after typhus did more damage to his army than the opposition forces did; the decision by the French to sell the Louisiana Territory after French soldiers died from yellow fever in Cuba and the Gulf Coast; and the introduction of smallpox to the nonexistent immune population of the New World by Europeans, thus facilitating the “conquest” and the dawn of the colonial age. Malaria influenced the geographic and racial pattern and distribution of hemoglobin S and erythrocyte antigens in Africa. The development of Plasmodium falciparum is inhibited by the presence of hemoglobin S, and Duffy-negative erythrocytes are resistant to infection with Plasmodium vivax. Thus, populations with these erythrocyte factors are found in areas where malaria is common.

Infections are a major cause of morbidity and mortality in the world. Of the approximately 53 million deaths worldwide in 2009, at least a third were due to infectious diseases. In the United States, pneumonia is the fifth leading cause of death overall and the most common cause of death related to infectious and parasitic diseases. The outcomes of military campaigns have been altered by outbreaks of diseases such as dysentery and typhus. Examples include Napoleon’s retreat from Russia, after typhus did more damage to his army than the opposition forces did; the decision by the French to sell the Louisiana Territory after French soldiers died from yellow fever in Cuba and the Gulf Coast; and the introduction of smallpox to the nonexistent immune population of the New World by Europeans, thus facilitating the “conquest” and the dawn of the colonial age. Malaria influenced the geographic and racial pattern and distribution of hemoglobin S and erythrocyte antigens in Africa. The development of Plasmodium falciparum is inhibited by the presence of hemoglobin S, and Duffy-negative erythrocytes are resistant to infection with Plasmodium vivax. Thus, populations with these erythrocyte factors are found in areas where malaria is common.

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Host reaction to infection may result in illness. For example, previous infection with *Campylobacter jejuni* is responsible for about 40% of cases of Guillain-Barré syndrome. The mechanism is thought to be the production of antibodies against *C. jejuni* lipopolysaccharides that cross-react with gangliosides in peripheral nerves. Similarly, much of the damage resulting from meningitis is due to the host’s response to invading bacterial pathogens.

With some exceptions, infectious diseases are often treatable and curable. Thus, it is important to make an accurate etiologic diagnosis and institute appropriate therapy promptly. In acute infections such as pneumonia, meningitis, or sepsis, rapid institution of therapy may be life-saving; thus, a presumptive etiologic diagnosis should be established before a definitive diagnosis. This presumptive diagnosis is based on the history, physical examination, epidemiology of illness in the community, and rapid techniques such as microscopic examination of appropriate Gram-stained specimens. Antimicrobial therapy can then be instituted for the presumptive etiologic agents, but it must be reevaluated as more definitive diagnostic information becomes available.

Thus, it is well as the understanding of infectious diseases is a dynamic process. A number of factors or themes of current interest contribute to this conclusion, including the following:

**EMERGING INFECTIONS.** The most obvious is AIDS, but recent examples with a major impact on the public health in the United States include community-associated methicillin-resistant *S. aureus*, a hypervirulent strain of *Clostridium difficile*, and the 2009 H1N1 influenza. More than 300 new, emerging infectious diseases have been described in the last 70 years, approximately 60% are zoonoses associated with geographic “hotspots.” Their emergence is driven largely by ecologic, socioeconomic, and environmental factors.

**GENOMICS AND OTHER “OMICs.”** The exact sequence of the genome of more than 2000 microbes relevant to humans has been determined. This new information, in concert with genomic information from multicellular organisms such as the *Anopheles* mosquito, offers significant promise for the development of new therapies and vaccines. Careful analysis of the genomes of pathogens will continue to yield important information about the pathogenesis of infection. For example, genome sequencing of group A streptococci, collected over time with relevant robust clinical information, has detected the acquisition of new determinants (often by prophage) responsible for increased virulence and resulting in toxic shock syndrome, necrotizing fasciitis, or both. Proteomics, transcriptomics, metabolomics, and virulomics have transformed research on infectious diseases and promise significant improvements in diagnostics and therapeutics in the future.

**GENETIC FACTORS ALTERING SUSCEPTIBILITY TO INFECTION AND THE RESPONSE TO INFECTIOUS DISEASES.** This field promises new and significant information relevant to the wide variety of responses to infectious diseases in humans. For example, an overvigorous response, with generation of tumor necrosis factor-α, may accentuate the development of cerebral complications in falciparum malaria. Analysis of single-nucleotide polymorphisms of the human genome will lead to an enhanced understanding of two fundamental issues in infectious diseases: why invasive, overt disease develops in only a small fraction of individuals colonized with a given microbe, and why infections are more severe in some people than in others. Variants in genes that encode molecules that mediate attachment, pathogen recognition, inflammatory cytokine response, and innate and adaptive immunity are being identified at an astonishing rate.

**INNATE IMMUNITY.** This is the most active field in immunology. The identification of pattern recognition receptors (e.g., Toll-like receptors [TLRs] and NOD-like receptors) that recognize pathogen-associated molecular patterns, as well as endogenous substances reflecting tissue injury (e.g., alarmins), has revolutionized our understanding of the early host response to infection. Agonists or antagonists of TLRs have already entered clinical trials as adjuvant therapies (e.g., editoran for sepsis) or to improve the immunogenicity of vaccines. The other area that has exploded recently is the study of antimicrobial peptides (e.g., defensins, cathedcins, histatins, galectins) and their role in the early response to infectious disorders.

**ANTIMICROBIAL RESISTANCE.** The development of new antimicrobial agents has slowed despite the burgeoning problem of antimicrobial resistance. This disconnect has been the focus of meetings among the pharmaceutical industry, the Infectious Diseases Society of America, the Food and Drug Administration, and others. Multiresistant pneumococci, vancomycin resistance in *S. aureus*, vancomycin-resistant enterococci, and, perhaps most important, multidrug-resistant gram-negative bacilli (MDR-GNB) are just a few examples. Some MDR-GNB are susceptible to only a few agents of “last resort,” such as colistin or tigecycline; others are truly untreatable (Chapter 313). Unfortunately, new agents active against these strains are years, if not decades, away from introduction.

**THE ROLE OF INFECTIOUS AGENTS IN CHRONIC DISEASES.** Many so-called idiopathic diseases may in fact have an infectious basis. Conditions for which there is some evidence (but not conclusive proof) of an infectious basis include diabetes, atherosclerosis, acute leukemia, collagen vascular diseases, and inflammatory bowel disease. Detection of “uncultivable” microorganisms by newer techniques, such as 16S RNA analysis, may uncover agents responsible for “noninfectious” diseases or suggest a role in conditions that are considered infectious but in which the pathogen or pathogens are controversial (e.g., bacterial vaginosis). In addition, we know that hepatitis C virus, human papillomavirus, and *Helicobacter pylori* cause human cancers. In addition, changes in our own microbiome may lead to disease. Alterations in the gut microbiome are associated with obesity. Another recent example comes from experiments with mice lacking TLRs. These mice develop hyperphagia and hallmark features of the metabolic syndrome, including hyperlipidemia, hypertension, insulin resistance, and increased adiposity, associated with an altered gut microbiome. Further, transfer of this changed microbiota into germ-free wild-type mice induces most features of the metabolic syndrome in the recipients.

**SUGGESTED READINGS**


Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science. 2010;328:228-231. The salient findings of these experiments are discussed in the text.