Emily G. Reisner | Howard M. Reisner

CROWLEY'S

AN INTRODUCTION TO HUMAN DISEASE

Pathology and Pathophysiology Correlations

ELEVENTH EDITION

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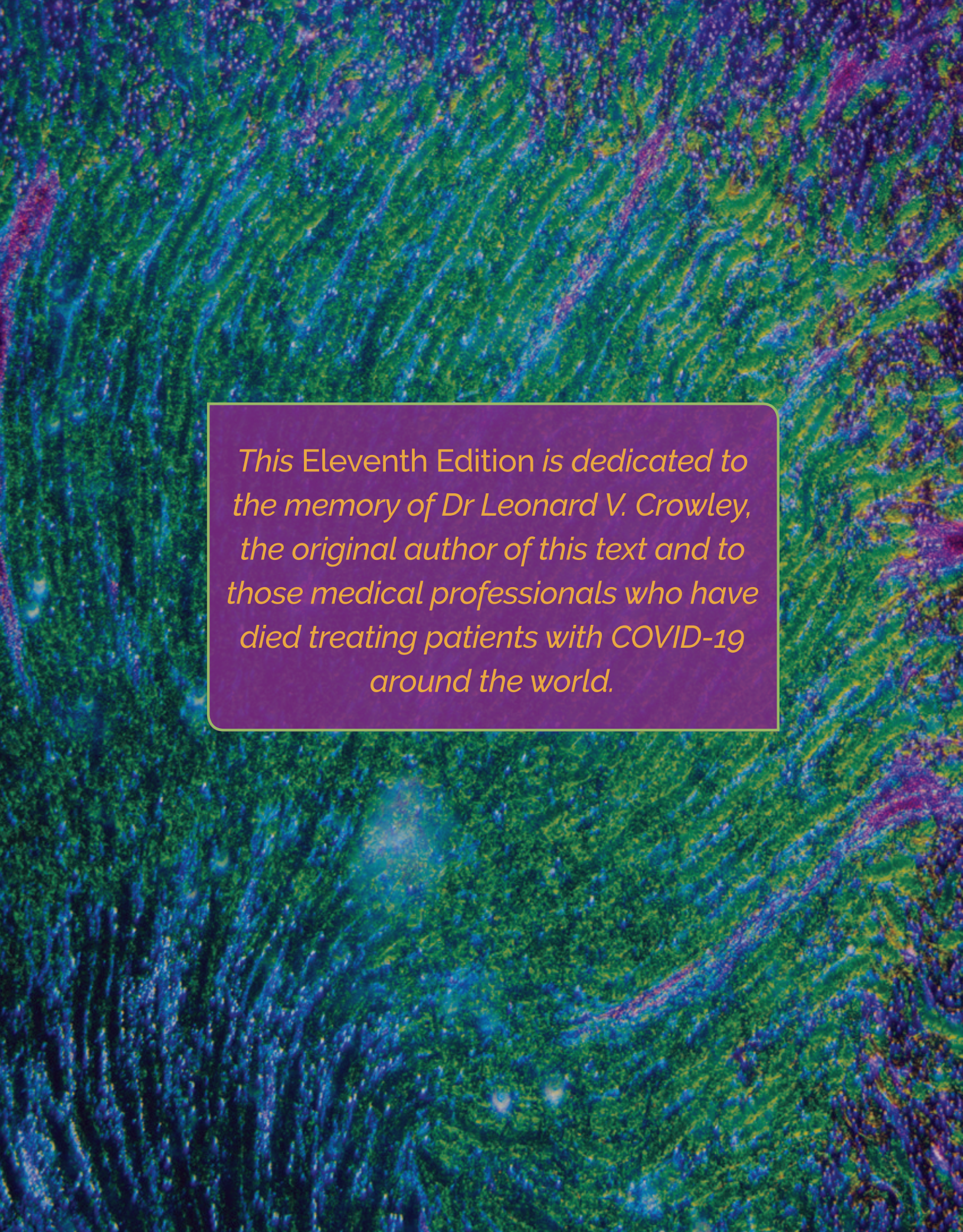

This Eleventh Edition *is dedicated to the memory of Dr Leonard V. Crowley, the original author of this text and to those medical professionals who have died treating patients with COVID-19 around the world.*

Brief Contents

Contents

Preface

In recent months, dealing with the COVID-19 pandemic has emphasized the need for everyone to be well informed about the various aspects of health care and disease. We hope this text will help fulfill that need. The book has been updated to reflect current information on the pathogenesis of infectious disease and on how changes in the genome are expressed as disease.

The *Eleventh Edition* has new content on COVID-19, Zika virus, and brain eating amoebas, plus mini podcasts to address difficult concepts such as Neoplasia, Nutrition and Obesity, Alzheimer Disease, and COVID-19. We have also added new case studies covering a variety of concepts to use for additional learning opportunities, including a four Case Study series on COVID-19.

We do hope you find this to be a valuable learning tool as well as a life-long reference.

The Audience

How did we visualize the reader of this work? The authors hope that any individual interested in the health sciences who wishes to understand the nature of disease would find the text of interest. Specifically, we hope that the text would allow a beginning student of the health sciences who has a working knowledge of biology to equip themselves with the concepts and vocabulary for more specialized areas of study in any of the health-related fields. To do this we have taken particular care to present recent information relating to the therapy and molecular diagnosis of disease.

New to This Edition

The *Eleventh Edition* includes extensive updates as described below.

Chapter 3

- Added information on molecular genetics, such as updated information on the structure of DNA in chromosomes and gene expression
- Added information on DNA technology, such as the CRISPR "gene editing" system

Chapter 4

- Added information on the Zika virus, including modes of transmission

Chapter 5

- Additional information about toll-like receptors

Chapter 7

- Updated information on immune checkpoint genes
- NEW! Section on tests using circulating tumor cells

Chapter 8

- Added information on the use of molecular technology for the study of microbiology and defining bacterial species
- Additional information on modern identification methods and tests used in identifying bacteria and organisms

Chapter 9

- NEW! Section on brain eating amoebas

Chapter 10

- Updated information of HIV prophylaxis, such as the use of the drug Truvada
- Updated information on the use of monoclonal antibodies added to passive immunization
- Added discussion of foodborne disease
- Updated information on sexually transmitted diseases, specifically in regard to HPV, syphilis, gonorrhea, and herpes

Chapter 11

- Updated treatments of acute coronary syndrome, including new antiplatelet agents and drugs such as ticagrelor
- Rewritten presentation on the use of aspirin to reduce the risk of cardiovascular disease, including the risk of bleeding

Chapter 12

- Added information on computerized tomography pulmonary angiography (CTPA) diagnosis

Chapter 14

- Added information on platelet receptor defects and tests for the presence of D-dimer

Chapter 15

- NEW! Section on vaping and its impact on vaping-induced lung injuries
- Added information on lung disorders and diseases, including both restrictive and obstructive lung disorders and pulmonary vascular disease including COVID-19
- Updated information on pulmonary fibrosis in regard to interstitial pneumonias

Chapter 16

- NEW! Section on breast cancer therapies, such as local (surgical) and systemic (chemotherapy) therapies
- NEW! Section on inflammatory lesions of the breast
- Updated information on breast examinations, including mammography and MRI imaging

Chapter 17

- Updated information on HPV vaccination
- Updated information on contraception, including oral birth control pills, the morning after pill, and the withdrawal method

Chapter 19

- Extensively reorganized.
- New information on extracellular water and body water content
- New information on regulation of plasma pH and respiratory control of pH

Chapter 21

- Added information on blood tests for liver injury and liver transplantation
- Updated information on hepatitis A and hepatitis C, including updated therapies and treatments

Chapter 22

- Updated information on cystic fibrosis therapy, such as the use of a CFTR modulator
- Updated information on diabetes and the use of a glucose pump
- Updated information on pancreatic tumors and the nature of such tumors

Chapter 23

- NEW! Section on tumors of the oropharyngeal cavity
- Added information on cancers of the head and neck, such as Boerhaave syndrome
- Updated information on tumors of the bowel, including detection and testing
- Added information on gluten sensitivity and diets, including popular fad diets such as low-carb and keto

Chapter 25

- New information on chronic traumatic encephalopathy
- NEW! Section on Zika virus, including infection and injury

Chapter 26

- Updated information on the treatment of rheumatoid arthritis
- Updated information on gene therapy, including exondys 51

About the Authors

Howard and Emily Reisner met in graduate school and hold PhDs from Case Western Reserve University in Cleveland, Ohio. Howard is Professor of Pathology emeritus at the University of North Carolina in Chapel Hill and recently retired as Professor of Pathology at the Campbell University School of Osteopathic Medicine. Emily has been a laboratory director at Duke University Medical Center and Director of Medical Writing in the pharmaceutical industry. For many years she taught medical writing for the physician's assistant program at Duke University. Both Howard and Emily are authors or editors of numerous books on pathology and have been involved in programs for teaching pathology in the Allied Health field.

Acknowledgments

The authors would like to thank the team at Jones & Bartlett Learning for their support throughout this project: Cathy Esperti, Director of Product Management; Ashley Malone, Content Strategist; Alex Schab, Senior Project Specialist; Troy Liston, Senior Media Development Editor; Benjamin Roy, Rights Specialist; and Andrea DeFronzo, Marketing Manager.

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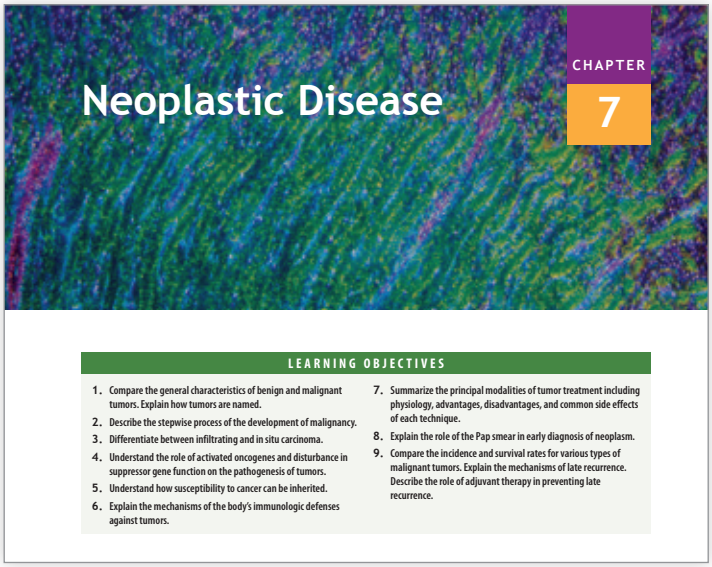
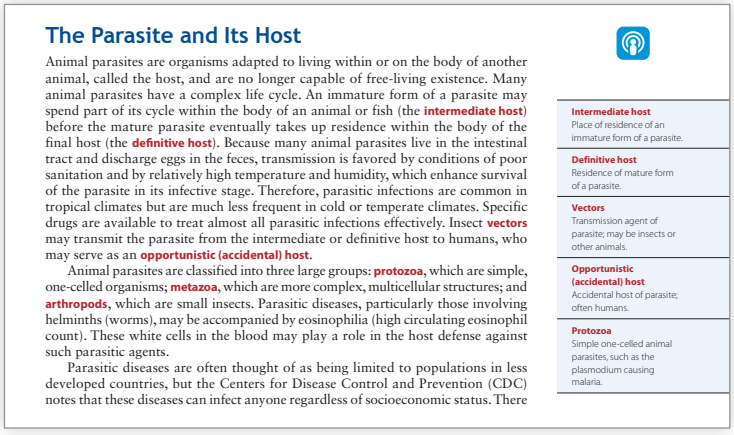
A Visual Walkthrough

Various learning features are included to enhance the usefulness of this product.



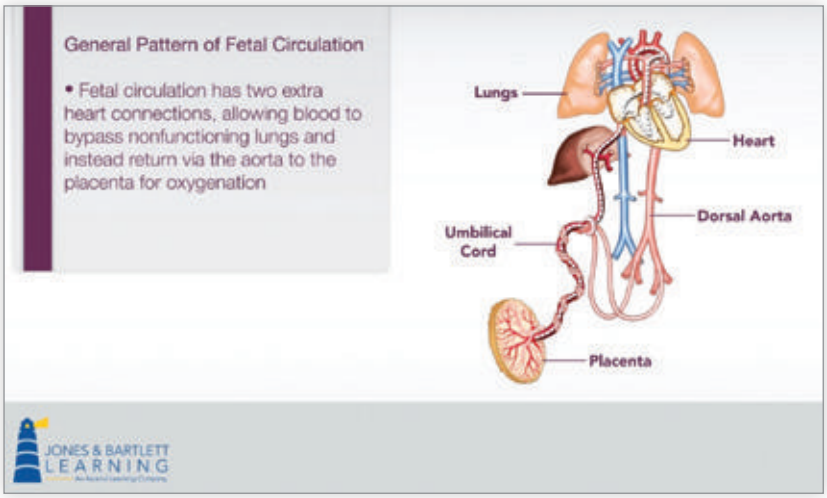
LEARNING OBJECTIVES

Learning objectives provide students with expected outcomes for each chapter as well as a checklist for measuring comprehension.



EXTENSIVE GLOSSARY

The extensive glossary proves useful to students who may not have had a course in medical terminology. It also serves as a convenient reference for students who want to quickly review a particular term. Words appearing in the glossary are set in boldface type in the text and set off in the margin for easy reference.

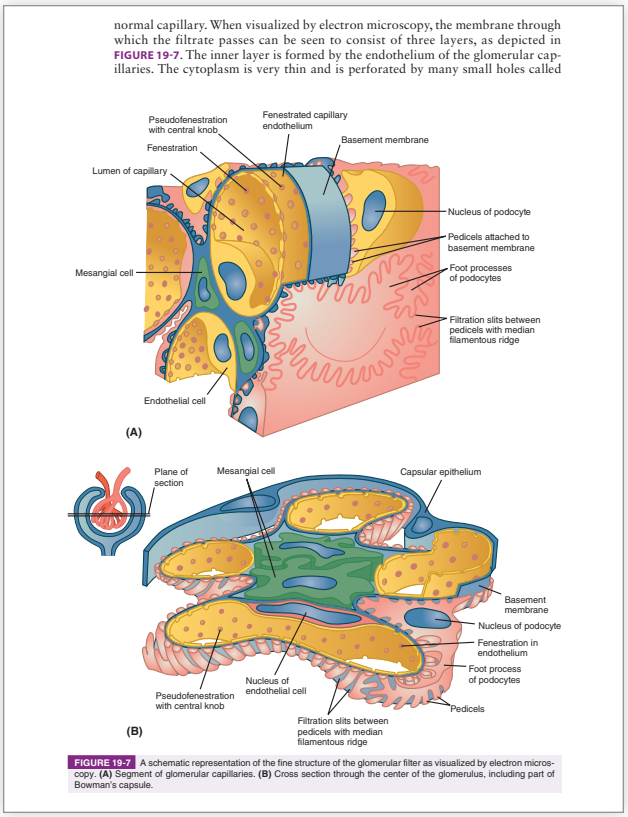


ANIMATIONS

Animations come with new, unused purchases of this text. Animations add visual clarity to key concepts and competencies.

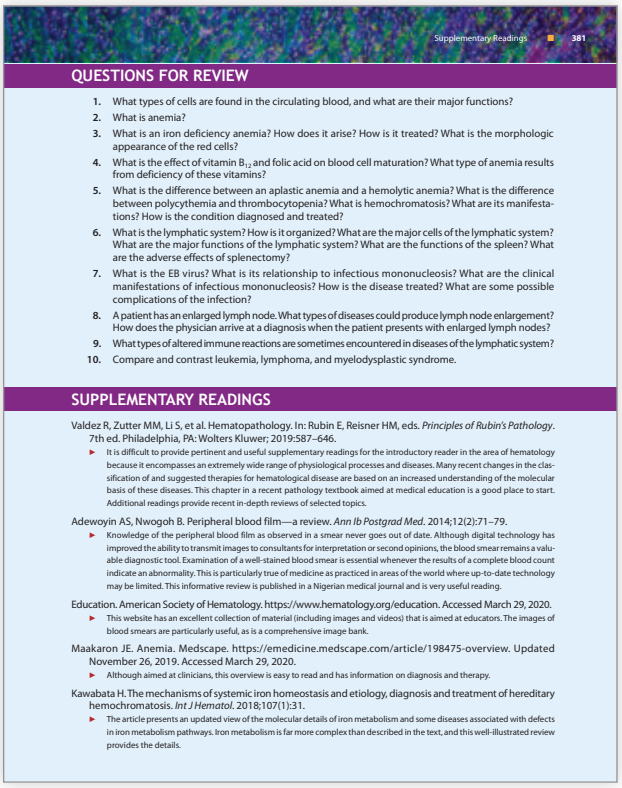
EXTENSIVE ART PROGRAM

The extensive art program, including a number of new photos and revised illustrations, has been updated and enhanced to support the new focus on the cellular and molecular roots of disease, as well as to provide additional visual support for student comprehension.



QUESTIONS FOR REVIEW

Review questions are provided for each chapter and provide students with a means to measure their learning.

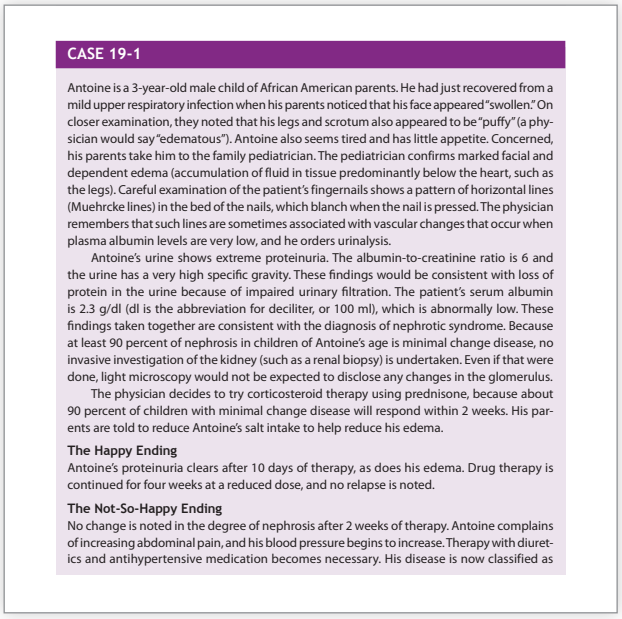


SUPPLEMENTARY READINGS

Supplementary readings were selected to provide an opportunity for the student to dig deeper. We have tried to emphasize readily available information sources that review and expand on the text, although in some cases we have suggested more research-based material that we think is of specific interest. Such papers may be a challenge to some readers, but we hope they will encourage the learner. When possible we have tried to include authoritative sources and freely available material, much of which is web-based. We hope this text will interest and encourage anyone interested in pursuing a health-related career to continue in what is an area of critical importance to our society.

CASE STUDIES

Case studies in each chapter provide an opportunity for the student to apply the concepts presented in the text to a medical setting. The cases range from common diseases likely to be encountered by the student to more uncommon conditions, both of which serve to teach specific information that expands on what is presented in the chapter. For this reason, the cases are integral to the information we hope to impart.



Case Studies

Teaching and Learning Aids

INSTRUCTOR RESOURCES INCLUDE:

- Test Bank
- Slides in PowerPoint format
- Answers to Student Workbook

STUDENT RESOURCES INCLUDE:

- Writable Workbook exercises
- Student practice activities and assessments
- NEW! **Podcasts**
  - Microscope Slides: How They are Made and Used
  - Cellular Reactions to Injury and Stress
  - Cell Death and the Body's Response
  - Chronic Inflammation and Repair
  - Neoplasia
  - Myocardial Infarct
  - The Lung
  - COVID-19
  - The Breast
  - Nutrition and Obesity
  - The Liver
  - Diabetes
  - Alzheimer Disease
- NEW! **Case Studies**
  - Acute Pancreatitis
  - Primary Ciliary Dyskinesia (PCD) Kartagener Syndrome
  - Epigenetics and Genetic Imprinting: Prader Willi and Angelman Syndromes
  - Zika Virus (ZIKV) Disease and Congenital Zika Syndrome (CZS)
  - Familial Mediterranean Fever (FMF)
  - Peanut Allergy and Anaphylaxis
  - Osteosarcoma
  - Plague
  - Neurocysticercosis
  - HPV/Oral Sex
  - Cardiac Disease (COVID 2)
  - Cytokine Storm (COVID 4)
  - Sickle Cell Disease Therapy
  - Coagulation Disorder (COVID 3)
  - Respiratory Disease (COVID 1)
  - Risk Reducing Mastectomy
  - Birth Control au Natural
  - Preimplantation Testing (Trisomy)
  - Acute Renal Injury/Acute Tabular Injury
  - Cryptorchidism
  - Hemochromatosis
  - panNET/Insulinoma/MEN1
  - Ulcerative colitis
  - Prolactinoma
  - Lewy Body Dementia
  - Myotonic Dystrophy
- **Animations**
  - Chromosomes and DNA
  - Meiosis
  - Gametogenesis
  - Phagocytosis
  - B and T Lymphocyte Formation
  - How Antibodies Work in Host Defense
  - Pathogenesis of an Allergy
  - Blood Flow in the Heart
  - Fetal Circulation
  - Following the Ovum
  - TIPS Procedure
  - Rotary Twist of Sigmoid Colon
  - Mechanisms for Antiviral Drug: Acyclovir (DNA polymerase inhibitor) – Herpes drug that treats chickenpox and Herpes Simplex Virus I lesions
  - Mechanism for Antiviral Drug: Relenza/ Tamiflu/Peramivir (Neuraminidase inhibitors) for Influenza A virus
  - Mechanism for Antiviral Drug: Protease inhibitors of HIV
  - Mechanism for Antiviral Drug: Protease inhibitor of Hepatitis C virus
  - Mechanism for Antiviral Drug: ZMapp monoclonal antibody cocktail to inhibit Ebola virus
  - Mechanism for Antiviral Drug: Integrase inhibitors to block HIV

CHAPTER 1

General Concepts of Disease: Principles of Diagnosis

LEARNING OBJECTIVES

1. Define the common terms used to describe disease including, but not limited to, lesions, symptomatic and asymptomatic disease, etiology, and pathogenesis.
2. List the major categories of human disease.
3. Outline the approach a practitioner uses to make a diagnosis and decide on a patient's treatment.
4. Describe the various types of diagnostic tests and procedures that can help the practitioner make a diagnosis.
5. Compare and contrast the different imaging techniques described.

What Is Disease?

Disease, in its broadest sense, is any compromise to the normal function of the body and the systems of which it is composed. However, it is best to consider health and illness as two extremes of a continuum. At one extreme is severe, disabling, or life-threatening illness with corresponding effects on our physical and emotional well-being. At the other extreme is ideal, perfectly good health, a state of physical and mental well-being wished for but rarely attained. Between these two extremes are many gradations of health and disease, ranging from mild or short-term illness that limits activities to some extent to moderate good health that falls short of the ideal state. The midpoint in this continuum, in which one is neither ill nor in ideal good health, is where most of us are likely to fall. Who does not suffer from an occasional cold, sprain, upset stomach, or headache? As we get older, our average position in the continuum begins to shift. Disease is no longer occasional but becomes chronic as we suffer from degenerative conditions, which are part of the inevitable process of aging.

Disease
Any disturbance of the structure or function of the body.

Symptoms
Subjective manifestations of disease.

Lesions
Any structural abnormalities or pathologic changes.

How Do We Know We Are Sick?

How do you know you are sick? This seems an obvious question. Sometimes you do know and sometimes you don't. The subjective manifestations of disease, called **symptoms**, may be related to apparent **lesions** such as structural abnormalities like

Trauma
Injury caused by a physical extrinsic agent.

Pathogens
Disease-causing microorganisms.

Inflammation
An early defensive reaction by the body to insult.

Pathologist
Person who studies the structural and functional changes in the body caused by disease.

Etiology
The cause, especially the cause of a disease.

Pathogenesis
Manner in which a disease develops.

Gross examination
Study of diseased organ with the naked eye.

Histologic examination
Study of disease using a microscope to examine tissue.

Immunological techniques
Techniques using antibody or antigen preparations, usually with chemical labels.

Laboratory medicine
Study of the composition of body fluids to diagnose disease.

Mnemonics
Aids to memory.

Idiopathic
Disease of unknown origin.

Iatrogenic
Disease resulting from a medical intervention.

Clinician
Physician having direct contact with patients.

Signs
Physical findings of disease.

Asymptomatic
Disease without symptoms.

a broken bone or a painful swelling. Often, symptoms are the result of the body's reaction to injury, which may be the result of **trauma** or infection by **pathogens**. Symptoms such as fever, muscle aches, and pain are part of the process of **inflammation**, an early defensive reaction by the body to insult (discussed in the presentation on inflammation).

A **pathologist** studies the **etiology** (cause) and **pathogenesis** (progression or "natural history") of disease by evaluating lesions at the level of organs, the tissues that compose the organs, the cells that form the tissues, and the molecules of which the cells are composed. The pathologist may observe the diseased tissue with the naked eye (**gross examination**) or with the aid of a microscope (**histologic examination**). Histologic examination may be supplemented by the use of special methods of identifying normal or abnormal tissue components using biochemical or **immunological techniques** (see Chapter 6). It is increasingly common for pathologists to study the molecules of which the tissue is composed using the techniques of molecular biology. In addition, pathologists working in the area of **laboratory medicine** study the composition of our body fluids (blood and urine, for example) to look for markers of disease.

Classifications of Disease

Pathologists interested in etiology classify diseases into several large categories. Although these categories are broad, this helps in understanding how a disease is likely to progress and how it will affect the patient. There are several alternative systems but medical students (who appreciate **mnemonics**) often use the term VINDICATE'M as a scheme:

Vascular
Infectious (or **I**nflammatory)
Neoplastic
Degenerative (or **D**eficiency)
Idiopathic (or **I**atrogenic)
Congenital
Allergic (or **A**utoimmune)
Traumatic
Endocrine (or **E**nvironmental)
Metabolic

With the exceptions of **idiopathic** (of unknown origin) and **iatrogenic** (physician caused), most of these terms will be familiar and discussed in detail in subsequent chapters. Although the VINDICATE'M scheme is useful, many diseases fit in multiple categories or fit poorly in any.

Principles of Diagnosis

The first physician to see the patient and to diagnose the disease is the **clinician** (the generalist physician, or specialist in a particular area of medicine or surgery), who is expert in detecting and evaluating the objective manifestations of disease, the **signs** or physical findings. However, a disease may cause the affected individual no discomfort or disability (an **asymptomatic** disease). Because disease is most often asymptomatic in its early stages, it may progress to the point where it causes subjective symptoms, abnormal physical findings, and is more difficult, impossible, or costly to treat. Therefore, early detection of disease, even before it is brought to the attention of the clinician, is of great importance to the public and is a major concern of the specialist in **public health** who might design **screening** systems for early diagnosis of diseases in populations.

Determination of the nature and cause of a patient's illness by a physician or other health practitioner is called a **diagnosis**. It is based on the practitioner's evaluation of the patient's history, subjective symptoms, the physical findings (signs), and the results of various laboratory tests, together with other appropriate diagnostic procedures. Many diagnostic procedures are **noninvasive** (requiring no physical invasion of the body, its openings, or cavities). A common example of such noninvasive diagnostic testing is the use of imaging technology (x-rays or ultrasound, for example). Sometimes diagnosis requires an **invasive** procedure. Such procedures may be relatively minor and have little discomfort associated with them. Common examples are drawing blood, obtaining a **Pap smear** (to collect a sample of cervical cells), or sampling fluid and cells from a surface-accessible lesion with a very fine needle (**fine-needle aspiration**). Somewhat more invasive are a variety of endoscopic procedures in which a tube (generally flexible) is passed into a body opening such as the esophagus or anus (as is done in the case of **colonoscopy**). Laparoscopic procedures involving the introduction of devices into body cavities or obtaining samples of internal organs (liver, kidney, and lungs, for example) by the use of sampling devices guided by imaging technology are yet more invasive, but much safer and potentially less costly than a surgical procedure.

The effort to reach a diagnosis may be minimal and require nothing more than evaluation of the patient's history and a physical examination, or it may require multiple diagnostic procedures and the intervention of several diagnostic specialists and extensive testing. Whatever the case, when clinicians reach a diagnosis, they can then offer a **prognosis**, an opinion concerning the eventual outcome of the disease. A course of therapy (possibly in consultation with therapeutic specialists, e.g., physical therapists) may also be instituted. The foundation for the process of obtaining a diagnosis is the history and a physical examination.

Public health
Area of medicine concerned with the health of populations.

Screening
Examining a large asymptomatic population for signs of future disease.

Diagnosis
The determination of the nature and cause of a patient's illness.

Noninvasive
Diagnostic procedure requiring no physical invasion of the body.

Invasive
Test requiring a physical invasion of the body. Also, a tumor type that infiltrates host tissue.

Pap smear
A study of cells from the cervix. Commonly used as a screening test for cancer.

Fine-needle aspiration
Sampling fluid and cells from a surface-accessible lesion.

Colonoscopy
Examination of the colon with an endoscopic procedure.

Prognosis
The probable outcome of a disease or disorder, the outlook for recovery.

Patient-centered approach
Interviewing technique empowering the patient to provide a candid and complete medical history.

THE HISTORY

The clinical history is a critical initial step in the evaluation. As is the case in any interaction between individuals, this requires the physician to establish a relationship with the patient that facilitates the accurate verbal transmission of information. This is a two-way street. The patient must feel enabled to present his or her history both fully and accurately. The physician must be able to elicit such information and accurately interpret it without prejudgment or bias (either scientific or social). This is often called a **patient-centered approach** to the history. Acquiring such interviewing skill is an early and essential part of the training of a medical student. To facilitate obtaining and recording an accurate, organized patient history, a standard approach is generally used on an initial encounter, although it may be modified on subsequent visits. This approach consists of several parts:

1. *Chief complaint*: This introduction to the history seeks to establish why the patient has sought medical attention. Most often this is elicited in the patient's own words. It may be followed up by a brief survey of any additional problems currently being experienced by the patient.
2. *History of the current illness*: The physician develops a chronological framework of the patient's illness from first symptoms to the present. This part of the history establishes the "when, where, and how" of the chief complaint—that is, the source of the symptoms experienced.
3. *Past medical history*: To establish the patient's general state of health, information about past illnesses and medical interventions, medications, allergies, immunizations, reproductive history, and participation in health maintenance programs is recorded.

3a. *The family health history*: This part of the history provides background information about potential environmental or genetic aspects pertinent to the patient's complaint, the health status of the entire living family, and historical information about deceased relatives. Family history is important in diagnosing many common chronic diseases such as diabetes and heart disease.

3b. *The psychosocial and sexual history*: The patient's education and life experiences (including personal relationships, employment, etc.), and in females the gynecological/reproductive history, may provide important information to the diagnostician. Questions are asked about potentially addictive behaviors such the use of alcohol, tobacco products, and recreational drugs.

4. *The review of systems*: This is often considered to be the center of the patient–physician encounter and consists of a body system–oriented, head-to-toe review of all presenting symptoms in an organized manner. The review may disclose additional symptoms not initially reported by the patient that are important to the diagnosis. A physician investigating the presenting symptom of back pain may elicit the additional symptom of pain on urination during the review, which suggests potential urinary tract disease. The experienced physician often will undertake this review as part of the physical examination.

THE PHYSICAL EXAMINATION

The physical examination is a system-based examination of the patient in an ordered manner. The practitioner places particular emphasis on the part of the body affected by the illness, such as the ears, throat, chest, and lungs in the case of a potential respiratory infection. However, particularly in a first encounter, all body systems are examined. For example, respiratory symptoms may be associated with a range of etiologies affecting multiple body systems (e.g., allergic diseases). Any abnormalities detected on the physical examination are correlated with the clinical history. At this point, the practitioner begins to construct a hypothesis regarding diseases or conditions that best fit with the clinical findings. Often, more than one diagnosis must be considered, and such consideration is likely to be altered by the results of laboratory and other diagnostic tests. In a **differential diagnosis**, the practitioner must consider a number of diseases that are characterized by the patient's symptoms. For example, respiratory symptoms might, based on patient history, suggest a seasonal allergy. Simple blood-based tests can aid in establishing such a diagnosis. A suggestion of renal problems in the patient could point to a serious, multisystem disease involving blood vessels (a vascular disease). Additional laboratory tests and potentially invasive procedures to sample patient tissue would be needed to support such a diagnosis.

Differential diagnosis
Consideration of the different diseases possible given the patient's symptoms.

Radiologist
Physician expert in the use and analysis of imaging techniques and results.

In difficult cases, the clinician may also obtain the opinion of a medical consultant (a physician with special training and experience in the type of medical problem presented by the patient). For a respiratory disease, a pathologist experienced in tissue-based diagnosis or a **radiologist** expert in the analysis of x-ray and other visualization data produced by physical methods might be consulted. The wise physician always maintains a probabilistic approach in constructing the diagnosis. Given the patient's history, the most likely diagnosis is considered first (a respiratory infection) followed by alternatives (a seasonal allergy) and the far less likely—but potentially life-threatening—possibilities (multisystem vascular disease). In testing the diagnostic hypothesis, the clinician uses a variety of tests and procedures and considers the usefulness of possible results of the tests in the clinical reasoning process.

Diagnostic Tests and Procedures

Today a huge number of tests and procedures are available to the physician, with more than 87,000 medical and surgical diagnoses and procedures recognized in the standard coding system used in the United States (ICD-10-PCS). One major medical center lists more than 1,300 laboratory tests that are available to its staff. How does the clinician choose from this massive array? Medical procedures carry a degree of risk, ranging from trivial to potentially serious. Diagnostic tests and procedures also vary in the amount of information they provide in relation to a potential diagnosis. For example, colonoscopy provides no information in the case of respiratory symptoms, but it may lead to a definitive diagnosis in the case of possible bleeding from the rectum. Tests and procedures differ in complexity and cost. Colonoscopy costs thousands of dollars at a major medical center, whereas determination of fecal blood (i.e., blood in stool) is trivial in cost. In a period of increased concern about the economic aspects of health care, cost must also be considered.

Choosing a Diagnostic Test

A diagnostic test can be defined in terms of a set of characteristics that help the clinician judge the usefulness of the procedure in diagnosing a specific disease. A perfect test would always be positive in a patient who has the disease in question and always negative in one who does not (see **FIGURE 1-1A**). Such a test does not exist. Instead, tests are classified by the terms *sensitivity* and *specificity*.

Sensitivity refers to the percentage of patients classified as positive by a test who *do* have the disease. Sensitivity = true positives / (true positives + false negatives). False negatives are persons who have a disease or condition that is "missed" by the test. A test with a high sensitivity will miss few people with the disease (have a low rate of **false negatives**). The obverse of sensitivity is **specificity**. Specificity = true negatives / (true negatives + false positives). False positives are persons without a disease who are misclassified as having the condition. Specificity refers to the percentage of patients without the disease who are correctly classified as negative by the test. Tests with a high specificity will have a low rate of **false positives** (see **FIGURE 1-1B**). The clinician attempts to choose a test with as high a sensitivity and specificity as possible for the diagnosis in question. Unfortunately, highly sensitive tests tend to have lower specificity (misdiagnosing people as having a disease they do not have; i.e., having a higher rate of false positives). Imagine moving the test cutoff line in Figure 1-1B. If we move the cutoff line (defining a positive test result) to the left, we decrease the number of false negatives but increase the number of false positives. The test becomes more sensitive but less specific. If the cutoff line is moved to the right, we decrease the number of false positives but increase the number of false negatives. The test becomes more specific but less sensitive. "Missing" a disease is obviously harmful, leading to a delay in therapy and potentially a more severe illness. However, a false positive result, assuming a patient has a disease he or she does not, may also lead to anxiety, discomfort, and unneeded therapy.

Sensitivity
Classification of diagnostic tests in regard to the percentage of patients with the disease who are classified as positive by the test.

False negatives
Negative test results that should be positive.

Specificity
Classification of diagnostic tests in regard to the percentage of patients without the disease who are classified as negative by the test.

False positives
Positive test results that should be negative.

Choice of test also depends on the patient population. For example, a patient in a clinic who is suspected of having a disease (based on prior clinical information) is much less likely to yield a false negative result than an individual chosen at random off the street. A physician who is considering an invasive, painful, or costly mode of therapy might choose to use a test with high specificity to exclude a false positive result. However, the case is different when choosing screening assays to be applied to a population in which the diagnostic target is a relatively uncommon but potentially serious (possibly fatal) illness where early diagnosis might effect a cure. If we choose

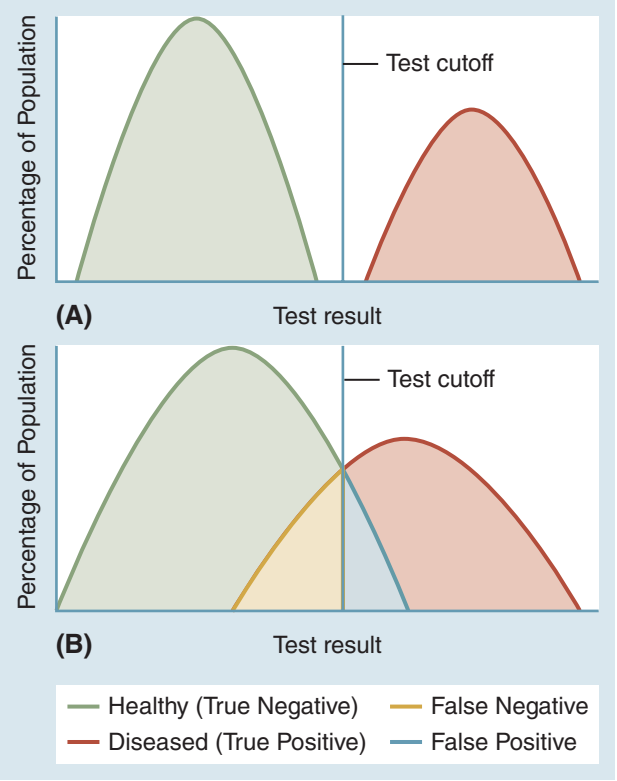


FIGURE 1-1 Sensitivity and specificity in a hypothetical clinical test. **(A)** A perfect test dealing with healthy and diseased populations where there is no overlap. **(B)** A "real-world" example demonstrating the effect of overlapping results. The test cutoff defines the result chosen to define "positive" versus "negative" results by the clinician.

a highly sensitive test (so as not to miss the uncommon affected person), the test is likely to lack specificity, increasing the number of individuals incorrectly suspected of having the disease. If there is an acceptable confirmatory test, or if the therapy is relatively harmless, such a test might be considered for use in screening. However, if the only confirmatory test (or therapy) requires a risky procedure (such as surgery), the test would be unacceptable. This is a very real problem. For example, a number of noninvasive tests have been proposed to screen for ovarian cancer because undiagnosed and untreated ovarian cancer is fatal. However, the currently available tests lack specificity and would expose an appreciable number of nonaffected women to invasive diagnostic procedures (although undoubtedly the test would lead to early diagnosis in some). So decisions in screening assay use are difficult and often lead to controversy—even among experts. The recent discussion about the utility of prostate specific antigen (PSA) as a screening test for prostate cancer is an example of how complex such decisions are (discussed in greater detail in Chapter 10).

Evidence-based medicine
Definition of treatment plan, risks, benefits, and costs based on prior rigorous investigation.

Patient-centered medicine
Practice of medicine encouraging patients to have a role in decision making.

In summary, the clinician makes a risk–benefit–cost determination in choosing diagnostic procedures. What set of tests will yield the greatest information with the least risk and cost to the patient? At times this can be a very difficult determination in which the clinician is guided by the findings of the clinical epidemiologist. Such determinations are part of **evidence-based medicine**, which seeks to define risk–benefit–cost ratios based on prior rigorous investigations. Going hand in hand with evidence-based medicine is **patient-centered medicine**, in which patients have a central role in decisions about their care. Patients are fully informed about the possible risks and benefits so that they can make informed decisions as to whether or not to consent to the procedure or ask to consider alternative approaches.

Classification of Diagnostic Tests and Procedures

Diagnostic tests and procedures can be classified into several major categories:

1. Clinical laboratory tests, including biochemical, immunological, and molecular-based tests; determination of gases in the blood; analysis of blood cells; and microbiological analysis
2. Imaging techniques including x-ray, ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET scans), and measurement of the distribution of radioisotopes (also called radionuclides)
3. Cytologic and histologic examination of cells and tissues removed from the patient
4. Endoscopy
5. Tests that measure the electrical activity in portions of the body

There is often overlap among these categories. For example, endoscopy may provide a sample that will be examined histologically or cultured in the clinical laboratory to detect an infectious agent. Some endoscopic procedures are done using radiographic guidance. Endoscopic procedures may be used to provide imaging of internal body systems. Common examples are intravaginal or intrarectal ultrasound. Another way of classifying tests is by the medical specialty responsible for providing them. Clinical laboratory medicine, a division of pathology, is responsible for a broad range of clinical laboratory tests. Anatomic pathology provides tissue- and cell-based analysis and the autopsy service. Radiology is responsible for essentially all image-based techniques but also provides a number of therapeutic procedures. Endoscopy covers a broad range of procedures that may be performed by specific medical specialists (e.g., gastroenterologists perform colonoscopy, cardiologists are responsible for a number of intravascular procedures such as placing stents to open blocked blood vessels supplying the heart). Other endoscopic procedures are performed by the surgical specialties. For example, examination of the urinary tract is the purview of urologists.

CLINICAL LABORATORY TESTS

Laboratory medicine is the area of pathology that provides and interprets diagnostic testing related to patient care. Clinical laboratory tests serve to aid not only in diagnosing disease but also in searching for occult (unrecognized) disease, establishing the severity of disease, and monitoring its progression and treatment. In laboratory medicine, basic analytical science meets medical science, and it is often the place where a new aspect of biomedicine is "translated" into patient care. Hence, analytical aspects of biochemistry, immunology, microbiology, physiology, and molecular biology are used in the clinical laboratory.

The role of the clinical laboratory and the tests it provides often are not obvious to the patient, who might simply donate several tubes of blood or a urine sample as part of a visit to the physician. However, it has been estimated that 60 to 70 percent of medical diagnoses rely on clinical tests. Almost 7 billion clinical tests are performed each year in the United States; a major medical center may perform more than 6 million tests a year. In general, such tests are a "good buy." Less than 5 percent of healthcare dollars are spent on laboratory tests.

Given the large number of available tests, it is difficult to summarize the many uses of clinical tests. **FIGURE 1-2** provides an example of a standard set of laboratory tests along with normal ranges for the results.

Patient Name: DOE, MARY **Patient MRNO: 0000012345**

Order Number: C6140101
Collection Date: 2009-06-14 at 0400

Source:
Site:

Date Completed	Test Name	Result	Flag	Units	Range
		Individual Test(s)			
2009-06-14	SODIUM	129	L	MMOL/L	135-145
2009-06-14	POTASSIUM	4.2		MMOL/L	3.5-5.0
2009-06-14	CHLORIDE	97	L	MMOL/L	98-107
2009-06-14	CO_2	25		MMOL/L	22-30
2009-06-14	UREA NITROGEN	26	H	MG/DL	7-21
2009-06-14	CREATININE	0.82		MG/DL	0.60-1.00
2009-06-14	EST. GFR (MDRD)	>= 60		mL/min/1.73m2	>=60
2009-06-14	ANION GAP	7	L	MMOL/L	9-15
2009-06-14	BUN/CREAT RATIO	32			UNDEFINED
2009-06-14	GLUCOSE, RANDOM	108		MG/DL	65-179
2009-06-14	MAGNESIUM	1.7		MG/DL	1.6-2.2
2009-06-14	PHOSPHORUS	3.5		MG/DL	2.4-4.5
		CBC+PLATELETS			
2009-06-14	CBC+PLATELETS	:			
2009-06-14	WBC	11.7	H	×10 9th/L	4.5-11.0
2009-06-14	RBC	3.80	L	×10 12th/L	4.00-5.20
2009-06-14	HGB	11.9	L	G/DL	12.0-16.0
2009-06-14	HCT	33.1	L	%	36.0-46.0
2009-06-14	MCV	87		FL	80-100
2009-06-14	MCH	31		PG	26-34
2009-06-14	MCHC	36		G/DL	31-37
2009-06-14	RDW	13.1		%	12.0-15.0
2009-06-14	MPV	7.2		FL	7.0-10.0
2009-06-14	PLATELET COUNT	247		×10 9th/L	150-440

FIGURE 1-2 Example of a laboratory report.

Courtesy of Dr. Catherine Hammett-Stabler, Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill.

Results that are "out of range" are flagged as either low or high, and it is up to the physician to determine the significance of the results. Determining the concentration of various constituents in the blood and urine is of major importance in evaluating the function of organ systems. For example, the concentration of a substance in the blood called urea is elevated if the kidneys are not functioning properly, because this constituent is normally excreted by the kidneys. The concentrations of hemoglobin and the quantity of red cells are reduced in patients with anemia. Sometimes the enzyme level in the blood is elevated because (1) enzymes are leaking from damaged cells in the diseased or injured organs (liver function tests are an example), (2) enzyme synthesis is increased as a result of disease, or (3) excretion of enzymes is impaired because disease has caused failure of normal excretory pathways.

Clinical laboratory tests also are used to evaluate the specific functions of organs. Pulmonary function tests measure the rate and efficiency with which air moves into and out of the lungs. Determinations of the concentration of oxygen and carbon dioxide in the blood also can indicate pulmonary function by evaluating how efficiently the lungs oxygenate the blood and eliminate carbon dioxide. A simple device (pulse oximeter) applied to the finger can determine the amount of oxygen carried by hemoglobin in circulating blood as another measure of pulmonary function. This is an example of a **point-of-care test**, which can be performed outside of the laboratory in the physician's office or at a patient's bedside. Of increasing importance are tests

Point-of-care test
Laboratory test that can be performed at the patient's bedside or in the physician's office.

to detect and measure concentrations of substances that are likely to be produced by tumors growing within the body. Serial analyses of these substances can be used to monitor the response of certain tumors to treatment. Microbiologic tests detect the presence of disease-producing organisms in urine, blood, bronchial secretions, and feces. These tests also can determine the responsiveness of the organisms to antibiotics. Serologic tests detect and measure the presence of antibodies as an indication of response to infectious agents and can evaluate the suitability of blood for transfusion or organs for transplantation into a patient.

IMAGING TECHNIQUES

Imaging technology enables the physician (and specifically the radiologist, the expert in obtaining and interpreting the results of imaging studies) to produce a view of the body and its organ systems previously available only to the surgeon (or to the anatomist or pathologist postmortem). Imaging technology permits anatomic investigation of the living patient, most often with little or no risk and minimal discomfort. The earliest and still an important use of imaging technology is the production of two-dimensional projected images of interior organ systems, **x-rays** or **radiographs**. However, modern computer technology now allows three-dimensional reconstruction of body systems (tomography) either using x-rays as an imaging source (**computed tomographic [CT] scans**) or using the magnetic properties of certain body constituents (most often ^{1}H in body water). To the physicist this property is called nuclear magnetic resonance; to the physician such studies are termed **magnetic resonance imaging (MRI)**. Of growing importance is the use of ultrasound to image accessible areas of the body. The technique depends on the differences in acoustical properties of tissue, so the movement and velocity of blood in vessels (Doppler ultrasound) is easily studied; images of the developing fetus can also safely be produced. The equipment for ultrasound analysis is relatively inexpensive and can easily be used outside of the hospital setting.

X-rays
X-rays are a form of electromagnetic radiation. An x-ray is a short phase equivalent to a radiograph.

Radiographs
An image taken with x-rays.

Computed tomographic (CT) scan
An x-ray technique producing detailed cross-sectional images of the body by means of x-ray tube and detectors connected to a computer. Sometimes called a CAT scan.

Magnetic resonance imaging (MRI)
A diagnostic procedure that yields computer-generated images based on the movement of hydrogen atoms in tissues subjected to a strong magnetic field.

X-Ray Examination

X-ray examinations are conducted in many ways, but the basic principle is the same. X-rays (electromagnetic radiation akin to visible light or radio waves, but much higher in energy) are produced in a vacuum tube by the impact of electrons on a tungsten target. The x-rays pass through the area of interest and are detected most commonly by a digital detecting device (formerly photographic film). X-rays are absorbed to a variable degree depending on the density of the tissue they pass through. Tissues of low density, such as the air-filled lungs, transmit most of the x-rays and appear black on the image. Tissues of high density, such as bone, absorb most of the rays and appear white on the image. Tissues of intermediate densities appear in varying shades of gray. The two-dimensional image produced is called a radiograph, or sometimes a "plain film" (**FIGURE 1-3**).

Special terminology is used for particular radiographic studies. For example, a specialized radiographic study of the breast is called a mammogram.

The lining of some internal organ systems, such as the digestive and urinary tracts, has little contrast. To aid in their examination, a nontoxic radiopaque substance (a contrast medium) designed to coat the lining (mucosa) of the organ systems may be used to outline the area of interest. For example, barium contrast media may be swallowed or given as an enema to outline portions of the gastrointestinal tract. Irregularities in the column of barium may represent constrictions in a portion of the GI tract. After the bulk of contrast material either passes through or is expelled from the tract, the remainder coats the surface of the tract and outlines details of the internal surface such as tumors, erosions, or ulcers for detection (**FIGURE 1-4**).

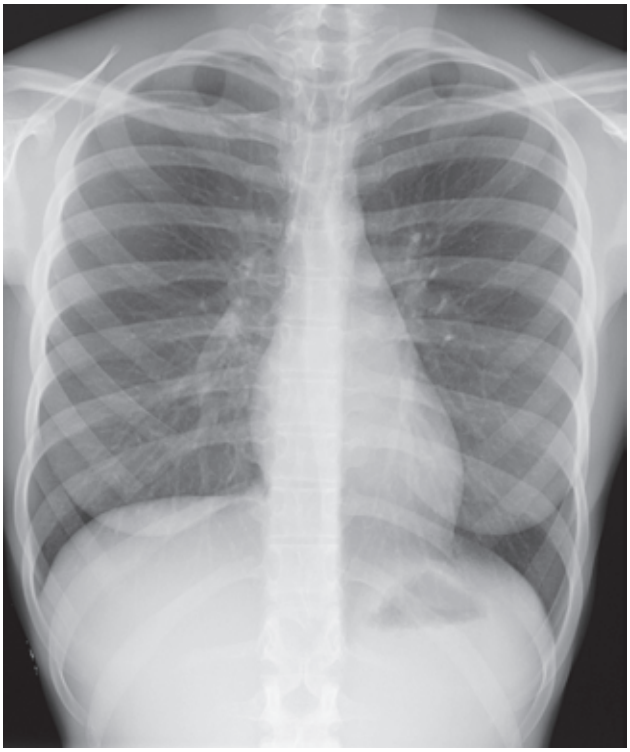


FIGURE 1-3 Chest x-ray (normal). Normal chest x-ray shows white bones and dark lung fields. The heart (*center of image*) and organs below the diaphragm (*bottom third of image*) are also white because of the density of the soft tissue through which the x-rays pass.

Courtesy of Dr. Donald Yandow, Department of Radiology, University of Wisconsin School of Medicine and Public Health.

Other soluble radiopaque substances can be injected into the circulation to aid in detecting irregularities or blockages in the vascular system and to study the renal and urinary system as the material is excreted from the kidney and passes through the bladder and remainder of the urinary tract (an intravenous pyelogram [IVP]) (**FIGURE 1-5**). The movement of contrast agents in portions of the body also can be studied in "real time" or be recorded as a movie using a technique known as fluoroscopy.

Computed Tomographic Scans

A CT scan produces a continuous series of x-ray images of the body by rotating the x-ray tube around the patient as the patient is moved past the x-ray source. The x-ray tube rotates on a toroidal (doughnut-shaped) frame linked to an array of sensitive radiation detectors that rotate around and encircle the patient, who is moving through the center of the frame. As the x-ray tube and detector array move around the patient, the radiation detectors record the amount of radiation passing through the body (**FIGURE 1-6**).

The data from the radiation detectors is fed into a computer, which reconstructs the information into a three-dimensional image composed of a series of voxels (the three-dimensional equivalent of the two-dimensional pixels on a computer monitor), each representing the x-ray density of a small volumetric area of the patient's body. Most often the image is displayed as a series of transverse cross-sections of the patient's anatomy (with the patient prone on his or her back with feet toward the viewer). However, the computer is just as capable of presenting information as a series of slices in any orientation (sagittal: head to foot dividing the body into a series

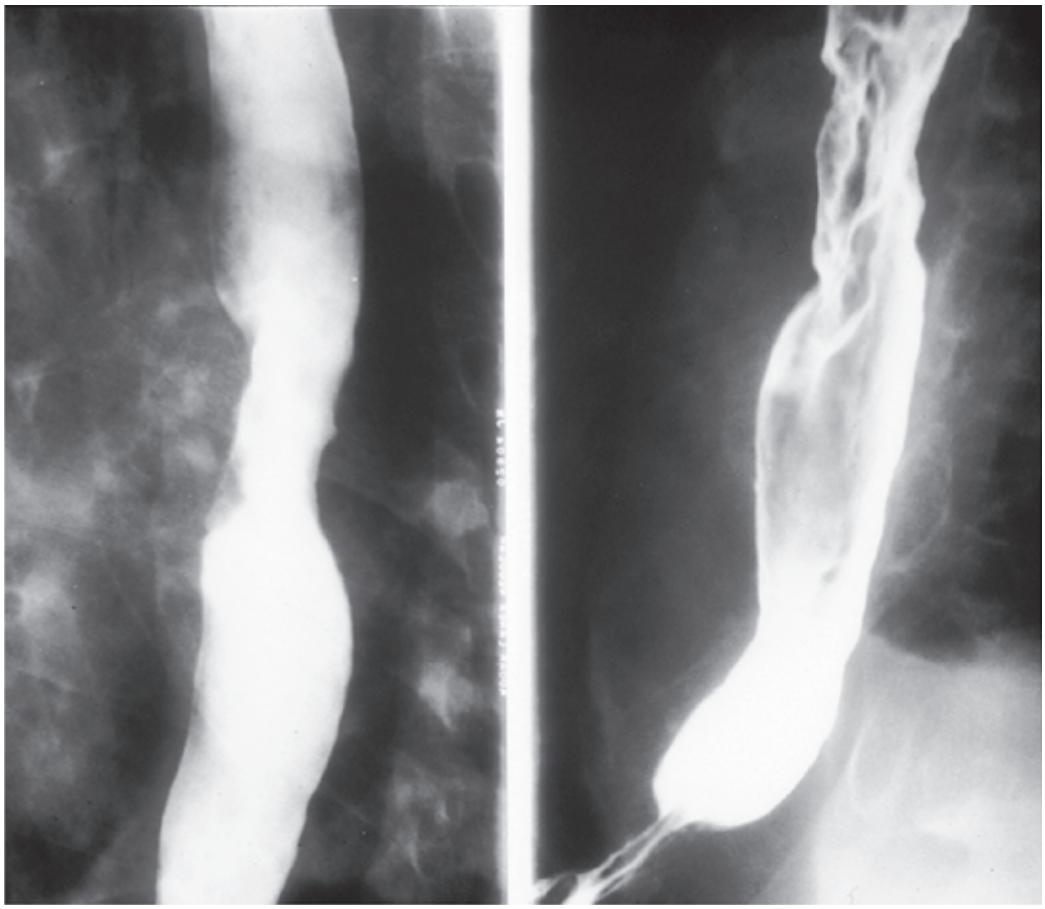


FIGURE 1-4 Barium contrast swallow study of the esophagus. X-ray of barium column in the esophagus showing narrowed area (*center of left image*) suggestive of an esophageal tumor (*left*). Following passage of the bulk of the barium, a coating of contrast medium outlines the mucosa, demonstrating irregularity and constriction as a result of esophageal cancer (*right*).

Image courtesy of Dr. David Warshauer, Department of Radiology, University of North Carolina at Chapel Hill.

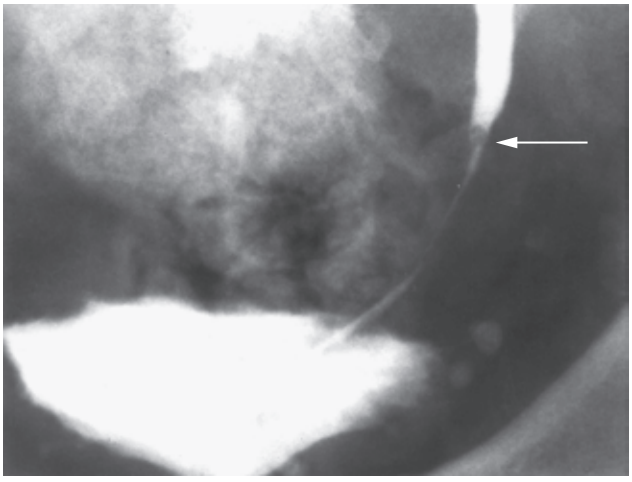


FIGURE 1-5 Intravenous pyelogram (IVP). Contrast media fills the bladder at the bottom of the image and the proximal (closer to the kidney) portion of the right ureter (*top of image*). A stone (*white arrow*) is lodged in the ureter, causing dilation of the ureter above the stone and preventing the filling of the ureter below. The dye in the bladder has come from the urine passing through the opposite ureter (*not shown*).

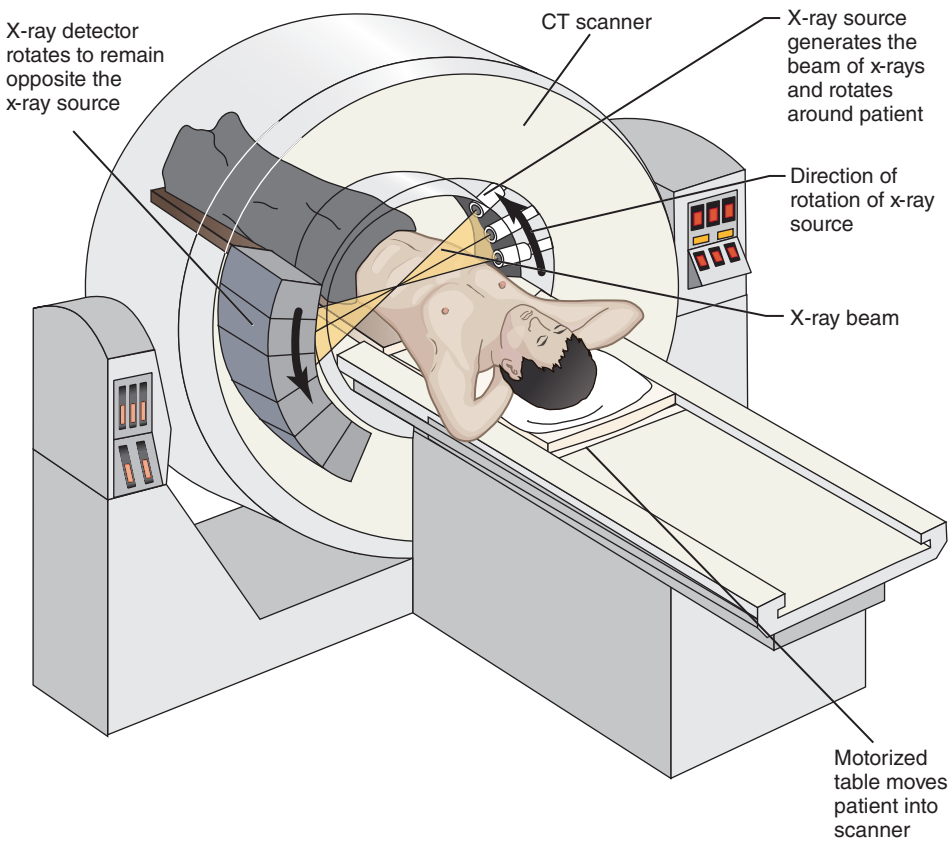


FIGURE 1-6 Computed tomographic (CT) scan. The patient lies on a table that is gradually advanced into the scanner. The x-ray tube mounted in the scanner rotates around patient, and radiation detectors also rotate so that detectors remain opposite the x-ray source. Data from radiation detectors generate computer-reconstructed images of the patient's body at multiple levels.

of left-to-right slices; coronal: head to foot dividing the body into a series of front-to-back slices). Abnormalities of internal organs that cannot be identified by means of standard x-ray examinations can often be discovered with CT scans because the geometry of an organ and the relationship of one organ to another can be seen while scanning through an entire region of the body. For example, **FIGURE 1-7** shows a lung tumor that might not have been obvious on a plain film.

Modern computational techniques allow entire organ systems to be reconstructed as three-dimensional images, which can be examined in great detail. In the technique of **virtual colonoscopy**, the surface mucosa of the entire colon can be reconstructed and "flown through" by the radiologist sitting at a computer who examines it for lesions such as polyps and other mucosal growths. The technique can substitute for endoscopy in patients for whom an invasive procedure might have additional risks (**FIGURE 1-8**).

Virtual colonoscopy
A high-resolution contrast CT image of the colon. May be substituted for colonoscopy in special cases.

Magnetic Resonance Imaging

MRI scans produce computer-constructed images of various organs and tissues somewhat like CT scans. The device consists of a strong superconducting magnet capable of developing an extremely powerful magnetic field (greater than 50,000 times that of the Earth), coils that can transmit and receive radio frequency (RF) waves, and a computer that receives impulses from the scanner and forms them into images that can be interpreted. The MRI scanner with the enclosed magnet and coils appears somewhat similar to an elongated, tubular CT scanner. The patient lies on a table that is gradually moved into the scanner, as is done in CT. The physical principles of

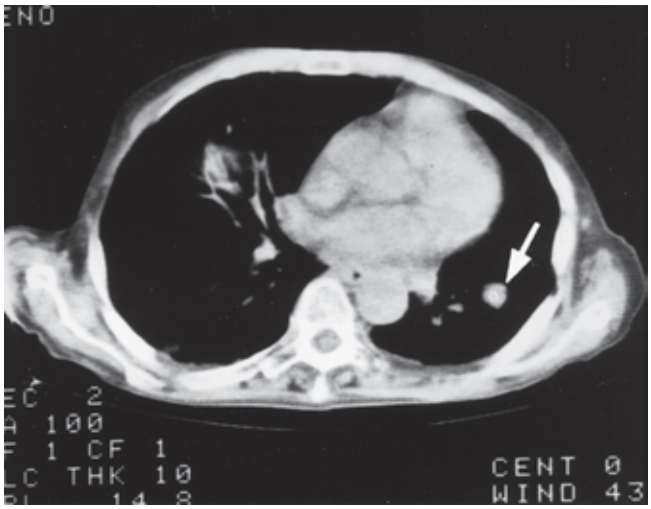


FIGURE 1-7 CT scan of chest. Mediastinum and heart appear white in the center of the scan, with less-dense lungs on either side. A lung tumor (*arrow*) appears as a white nodule in the lung.

Courtesy of Leonard V. Crowley, MD, Century College.

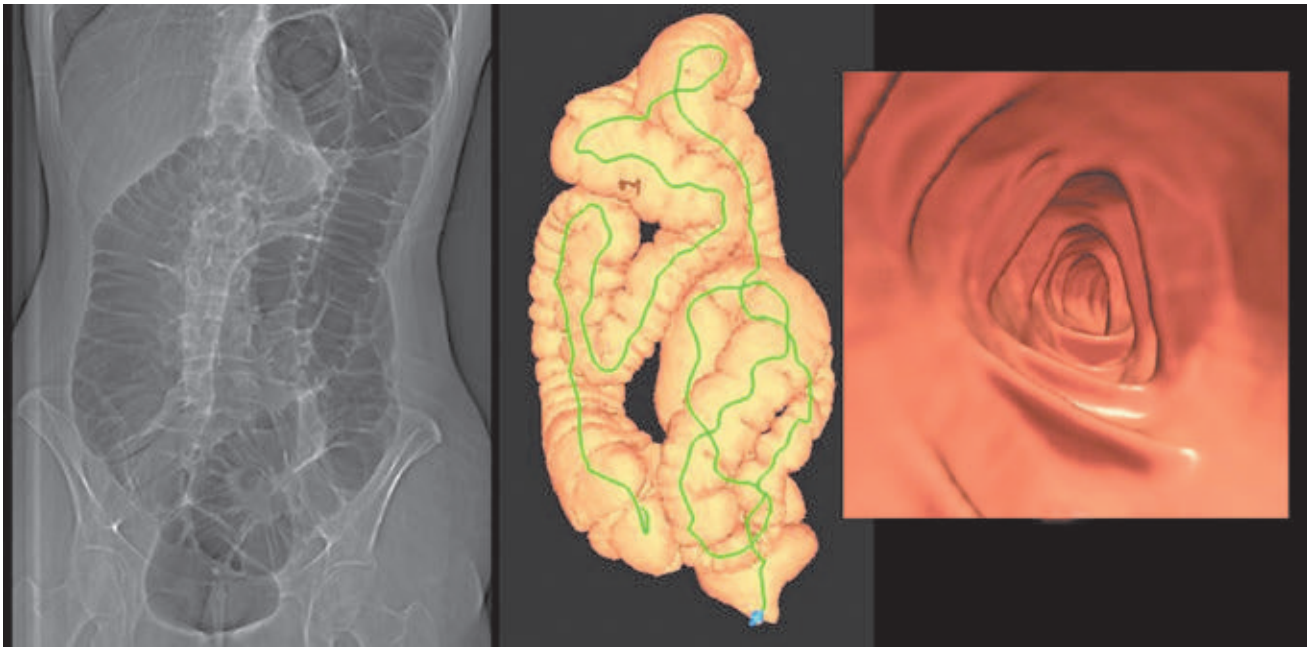


FIGURE 1-8 Virtual colonoscopy. A high-resolution contrast CT image of the colon is produced. The mucosa of the colon is highlighted by the contrast medium (*left*). A computer reconstruction of the entire colon in three dimensions is produced. The green line traces the center of the colon (*center*). The radiologist can "fly through" the colon and examine the mucosal surface of the interior (*right*).

Courtesy of Dr. David Warshauer, Department of Radiology, University of North Carolina at Chapel Hill.

MRI, however, are different from those of CT scanning. MRI scans, in contrast to the radio density used in CT, most often depend on the response of hydrogen protons (positively charged particles in the nucleus around which electrons rotate) contained within the body's water molecules. Hydrogen protons behave as if they are spinning rapidly about an axis. When subjected to a strong magnetic field, the protons become aligned in the direction of the magnetic field. After a pulse of RF waves, the protons are temporarily dislodged from their orientation. As they return to their original orientation, they emit a signal (resonance) that can be measured and used to produce

the computer-constructed images. Body tissues, which have a high water content, are a rich source of protons capable of excitation. The intensity of the signals produced is related to the varying water content (and hence hydrogen ion content) of body tissues and the strength and duration of the RF pulse plus the geometry of the applied magnetic gradient. The many combinations of RF pulse and magnetic gradients are termed MRI sequences and are chosen for particular imaging applications. For example, T2 weighted MRI is particularly useful in detecting regions in the brain and spinal cord where myelin sheaths of nerve fibers have been damaged, as in a neurologic disease called multiple sclerosis (see Chapter 25) (**FIGURE 1-9** and **FIGURE 1-10**).

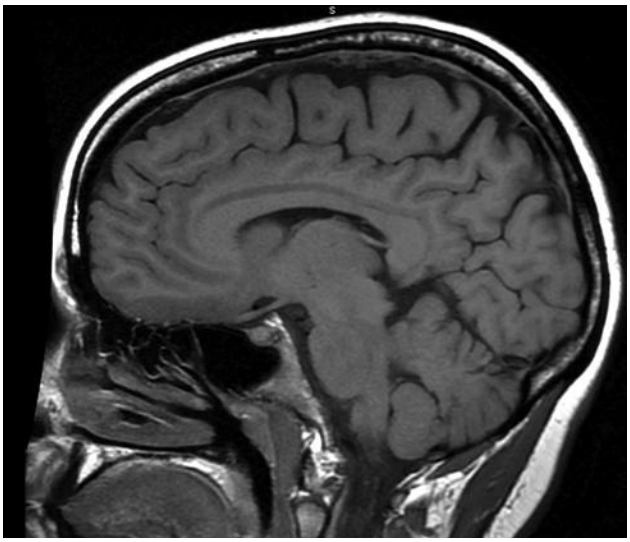


FIGURE 1-9 MRI normal brain in sagittal view. The nose is on the left. Notice how clearly the fissures and folds over the surface of the brain can be seen, as well as the distinction between the different neural elements of which the brain is composed.

Courtesy of Dr. Patrick Turski, Department of Radiology-MRI, University of Wisconsin School of Medicine and Public Health.

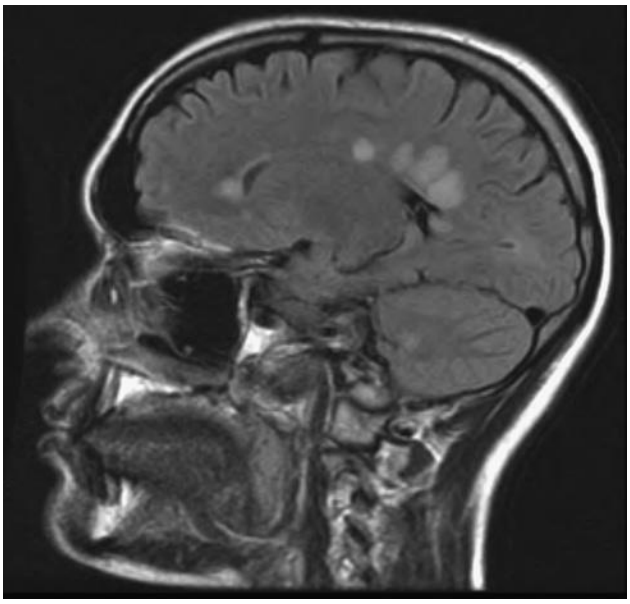


FIGURE 1-10 MRI of brain from a patient with multiple sclerosis in sagittal view (as in Figure 1-9). Multiple plaques (light areas) where neurons have lost their myelin coating are visible.

Courtesy of Dr. Patrick Turski, Department of Radiology-MRI, University of Wisconsin School of Medicine and Public Health.

Because an MRI does not use ionizing radiation, the patient does not receive radiation exposure. An MRI does expose the patient to strong magnetic and RF fields, but this appears safe provided the patient does not have implanted or embedded ferromagnetic material that might interact with the powerful magnetic field. Recent advances in the use of special contrast agents for MRI have greatly expanded the utility of the technique.

IMAGING TECHNOLOGY TO DETECT SPECIFIC MOLECULES AND PROCESSES

There is great interest in using imaging technology to detect specific chemical constituents or metabolic activity in regions of the body. For example, Alzheimer's disease, a degenerative dementia most often associated with aging, is associated with accumulation of an abnormal protein component, beta-amyloid (Aβ), in areas of the brain. Definitive diagnosis of this disease previously required obtaining brain tissue (most often postmortem) for analysis. Modern imaging technology can now detect and localize both changes in brain metabolism and the specific abnormal protein associated with Alzheimer's disease and provide early, noninvasive diagnoses. This technology depends on the ability to detect and localize radiolabeled compounds injected into the patient. The location and distribution of the radiation-emitting compounds can be mapped within the body to produce a planar (two-dimensional) image using a gamma camera or to produce tomographic (three-dimensional) images using single-photon computed tomography (SPECT), or PET technology used with positron-emitting tracers.

Radioisotope Studies Using Gamma Emitters

By using specially designed radiation detectors, the uptake location and excretion of the labeled substance can be mapped. The ability of the thyroid gland to concentrate and utilize radioactive iodine is used as a measure of thyroid function and, more importantly, can be used to detect tumors within the thyroid gland. Ventilation/perfusion (V/Q) lung scans measure the distribution of an inhaled radioactive gas (Xenon-133) to locate obstructions to the airways and combine it with a radiolabeled albumin injected into the circulation to measure pulmonary blood flow and to detect possible blood clots lodged within the lung (pulmonary emboli).

Phosphorus-containing isotopes are concentrated in the skeletal system. If there are deposits of tumor in bone, the isotopes are concentrated around the tumor deposits and can be easily identified (**FIGURE 1-11**).

Radioactive materials injected intravenously also can be used to evaluate blood flow to the heart muscle and to identify areas of damaged heart muscle. Three-dimensional tomographic techniques using SPECT or PET provide much better localization of tracers and are supplanting the use of planar gamma cameras in many radioisotope localization studies.

Positron Emission Tomography

Related to radioisotope studies using compounds labeled with gamma ray emitters is the technique of **positron emission tomography (PET scan)**. PET imaging uses a special class of radiolabel that emits positrons. Almost all positron-emitting radio tracers are very short lived and are produced at the imaging site using a cyclotron, which limits the technology to major medical centers. Positrons are subatomic particles that have the same mass as electrons but carry a positive charge. They are formed when atoms such as carbon, oxygen, or nitrogen are bombarded in a cyclotron with high-energy

Positron emission tomography (PET scan)
Imaging using positron-emitting radiolabels.

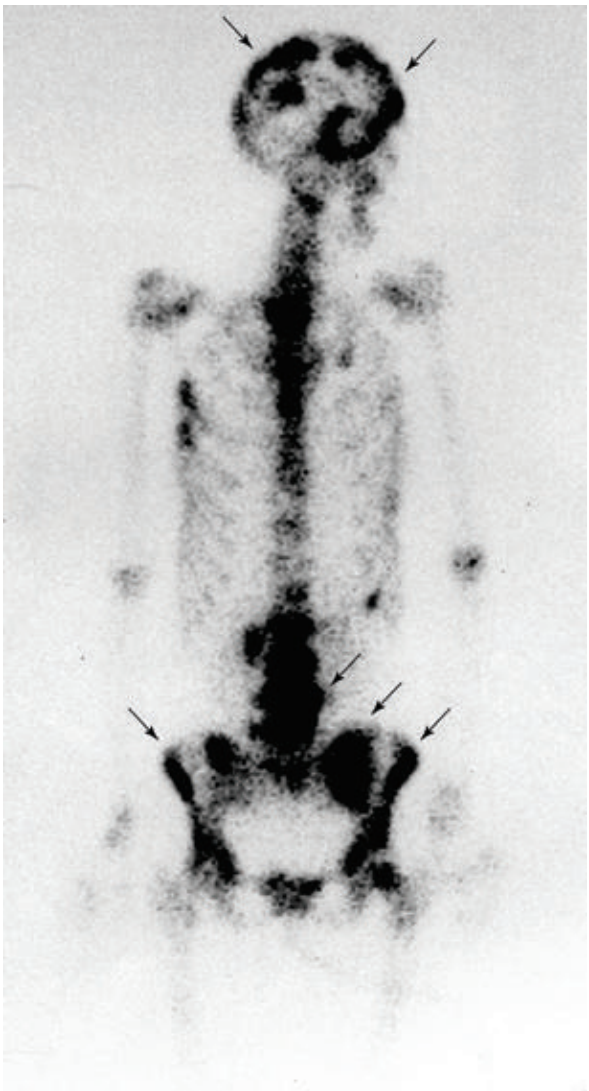


FIGURE 1-11 Radioisotope bone scan of head, chest, and pelvis. Dark areas (*arrows*) indicate the concentration of radioisotope around tumor deposits in bone.

Courtesy of Leonard V. Crowley, MD, Century College.

particles to produce a short-lived positron-emitting radio tracer. For example, one of the most commonly used positron-emitting radio tracers is fludeoxyglucose ^{18}F (^{18}F-FDG), which has a half life of under 2 hours and is made by initially bombarding oxygen isotope ^{18}O-enriched water with protons to produce the positron-emitting ^{18}F, which must be incorporated into the glucose-like molecule on site. A positron escaping from the nucleus collides with a negatively charged electron in a nearby atom, simultaneously producing two gamma rays emitted 180 degrees apart. The PET scanner registers this very weak but nearly simultaneous pair of pulses while ignoring nonpaired background radiation. The scanner uses this information to build a tomographic view of the distribution of the radio tracer. To further localize the source, the patient may also be CT scanned at the same time and the two images combined.

One of the most widely used applications of PET is to study the metabolic activity of areas of the body using ^{18}F-FDG, a compound that is metabolized like glucose in the patient. This provides information on the metabolic activities of the organ or tissue being studied, the site within an organ where the compound is being metabolized, and the blood flow to the organ being studied. One can detect and measure changes

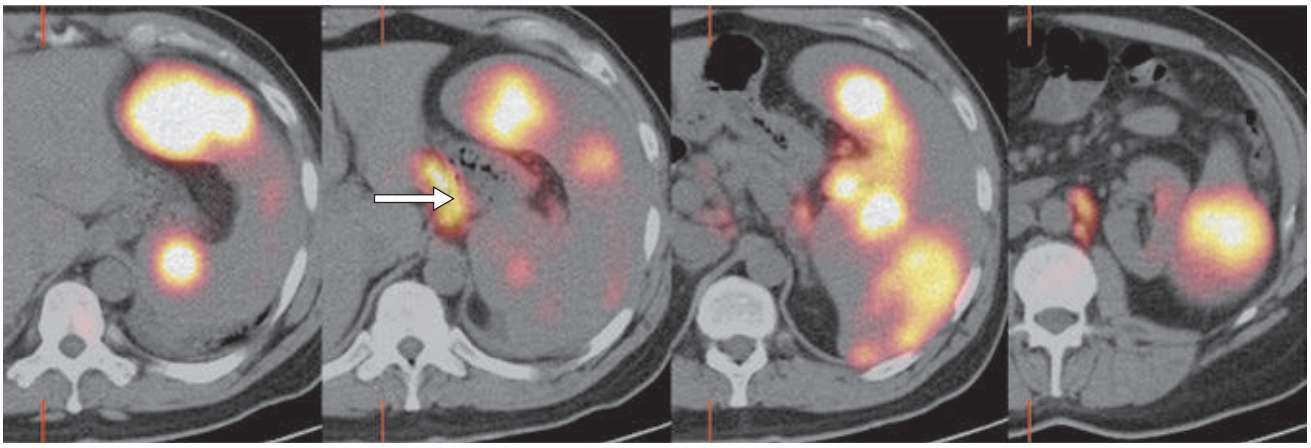


FIGURE 1-12 Combined PET scan and CT. Color represents PET scan results indicating distribution of ^{18}F-FDG metabolism in spleen (*large organ on right of images*) of a patient with lymphoma (cancer of lymphocytes). The PET scan has detected the spread of the cancer to adjacent lymph nodes (*arrow in second image*).

Image courtesy of Dr. David Warshauer, Department of Radiology, University of North Carolina at Chapel Hill.

in brain functions associated with various neurologic diseases such as strokes, brain tumors, Alzheimer's disease, Parkinson's disease, and some hereditary degenerative diseases of the nervous system. The method may also be used to evaluate changes in blood flow and metabolism in the heart muscle after a heart attack. Malignant tumors (cancer) often have higher metabolic rates than benign tumors (or normal tissue). Hence, mapping the distribution and rate of ^{18}F-FDG metabolism may be used to detect and evaluate potential occult cancers (metastases) spread within the body and to follow the effectiveness of therapy (**FIGURE 1-12**).

Even more exciting is the ability to synthesize PET radio tracers, which can bind to and localize specific abnormal molecules such as the abnormal Aβ found in Alzheimer brains.

ULTRASOUND

Unlike the imaging techniques that depend on detection of electromagnetic radiation as part of the imaging process, ultrasound is a technique for mapping the reflected echoes produced by high-frequency sound waves transmitted into the body. Echoes are reflected wherever there is a change in the density of the tissue. The reflected waves are recorded on a detector, and visual images are produced, generally on a small monitor. Unlike the complex equipment needed for CT or PET scans, ultrasound devices commonly use a single handheld transducer to produce the ultrasound and record the reflected echoes. The transducers may be moved over any external area of the body (using a water soluble gel to couple the ultrasound to the area of study) to produce a real-time image of internal organs under and within range of the acoustical beam as the transducer is moved. Although there are limits to the depth of penetration of ultrasound from the body surface (and hence to what internal areas of the body can be imaged), ultrasound transducers are small enough to be introduced into the rectum (to image the prostate in males), the vagina (for gynecological investigations in females), and the esophagus (to image abdominal organs such as the pancreas). This method is widely used to study the uterus during pregnancy because it does not require the use of potentially harmful radiation and poses no risk to the fetus (**FIGURE 1-13**).

The technique can be used to determine the position of the placenta and the fetus within the uterus; it also can identify some fetal abnormalities and detect twin

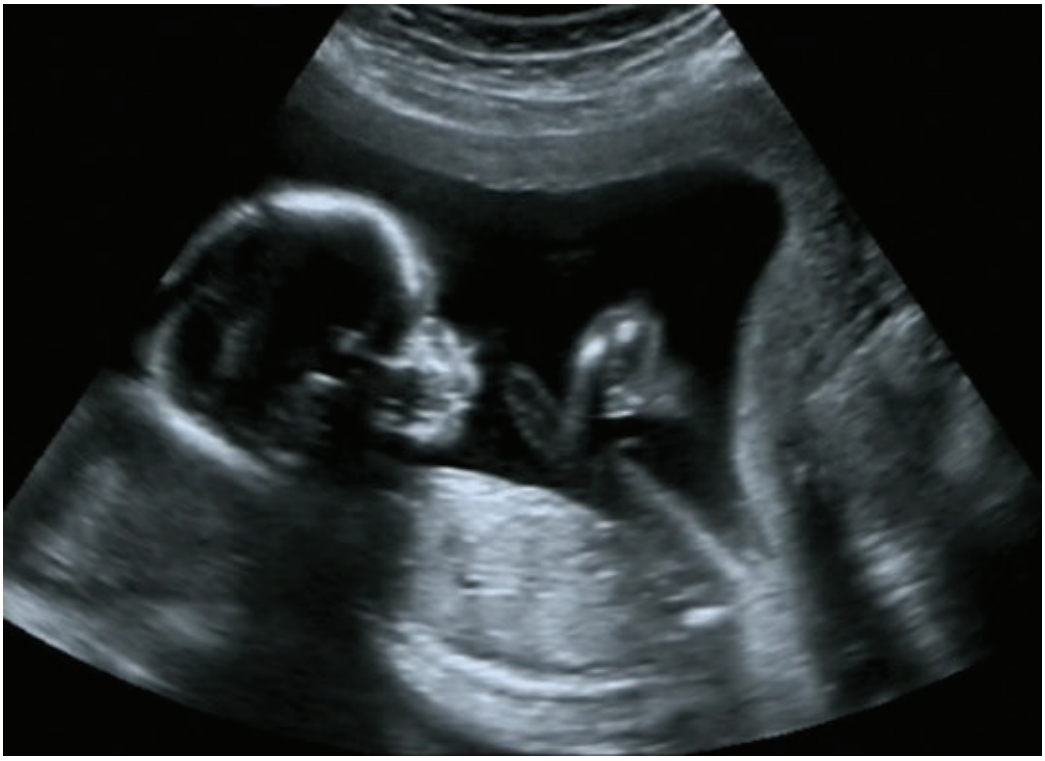


FIGURE 1-13 Ultrasound examination of a fetus at fourth months' gestation.

Echocardiogram
An examination of the cardiovascular system using ultrasound. A record obtained from an ultrasound examination of the heart and related blood vessels; used to assist in the diagnosis of cardiovascular disease.

pregnancies. Ultrasound is also often used to examine the cardiovascular system. When used for this purpose, the procedure is usually called an **echocardiogram**. An echocardiogram can detect the structure and function of the heart valves as well as determine abnormal communications between adjacent cardiac chambers. Abnormal blood flow patterns characteristic of congenital or acquired valvular heart disease or other abnormalities in cardiac function can be detected in real time as the heart beats. Doppler ultrasound can determine both the direction and velocity of blood as it moves through the heart and other organs and can detect irregularities in flow. Doppler flow images are "color coded" to show flow direction in relation to the transducer (**FIGURE 1-14**).

Ultrasound has replaced many radiology procedures because ultrasound avoids radiation, is most often not invasive (or only minimally so), and is easily performed in a doctor's office. Ultrasound devices are relatively small and inexpensive, and studies using the technology are often less expensive than those using other techniques.

CYTOLOGIC AND HISTOLOGIC EXAMINATIONS

Cytology studies the characteristics of individual cells or small groups of cells that are either shed or sampled from body organs. Such cells may be naturally cast off into body fluids and secretions or may be removed by brushes, spatulas, or similar tools. For example, the Pap (Papanicolaou) smear mentioned previously (discussed more fully in the presentations of neoplastic disease and the female reproductive system) uses such a device to obtain cells dislodged from the surface of the cervix and uterine canal to screen for cancer or early precursors to this disease. Similar approaches can be used to obtain bronchial cells and cells from the bladder. Cell samples may be obtained using very fine needles and a syringe to aspirate surface-accessible lesions. Such fine-needle aspirations (FNAs) are often painless and rapid, requiring no anesthesia.

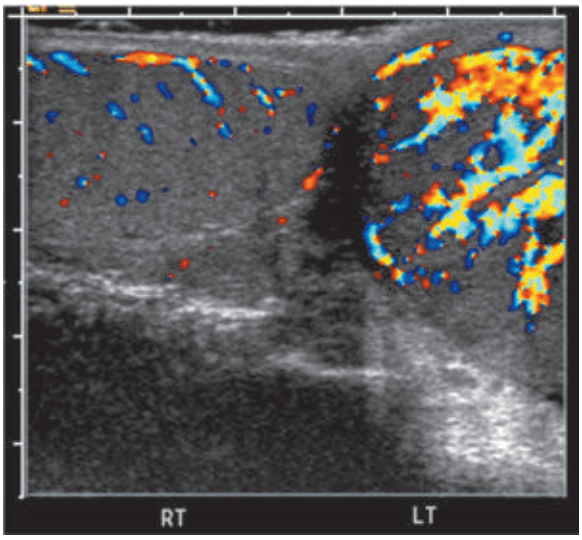


FIGURE 1-14 Doppler ultrasound examination of a testicular mass. Left testis (LT) shows an excess of blood vessels suggestive of testicular cancer. Blue indicates blood flowing toward and red indicates flow away from the transducer placed in contact with the scrotum.

Image courtesy of Dr. David Warshauer, Department of Radiology, University of North Carolina at Chapel Hill.

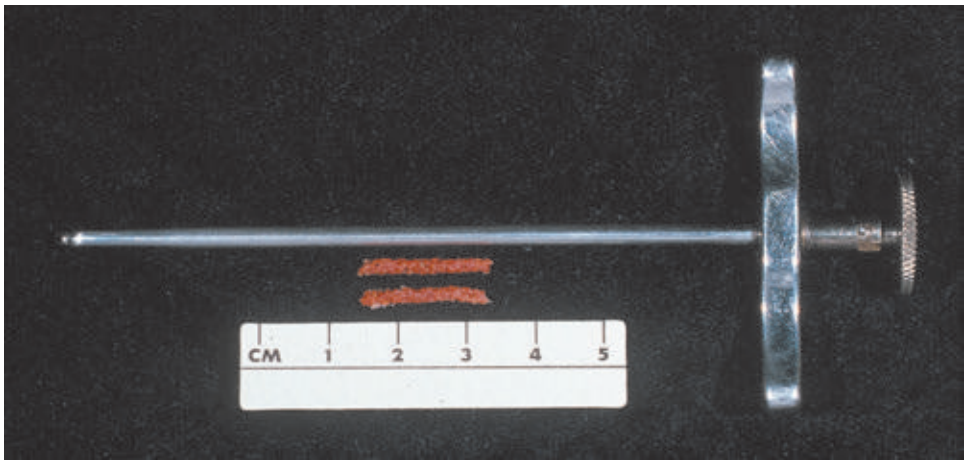


FIGURE 1-15 Two samples of bone marrow (*adjacent to scale*) obtained from a pelvic bone by means of a specially designed needle (*upper part of photograph*).

Courtesy of Leonard V. Crowley, MD, Century College.

Cytological examination of blood and bone marrow (**FIGURE 1-15**) is critical in the diagnosis of hematologic (blood-related) diseases and is often performed to diagnose neoplastic disease in blood cell precursors found in the marrow.

Bone marrow studies are carried out by hematopathologists, who use microscopes and flow cytometers that can quickly evaluate thousands of cells for multiple parameters such as size, internal contents, and surface characteristics as they flow past a series of detectors.

Histology examines the structure of organs and the tissues and groups of cells of which they are composed. The pathologist uses histopathology to recognize changes in tissue that are indicative of, or help to characterize, disease. The tissue may be obtained as part of a surgical procedure (a surgical specimen) either to confirm a diagnosis or to evaluate the adequacy of the surgical procedure, or the tissue may be

removed from the target organ for the specific purpose of histopathological examination (a **biopsy** specimen).

Samples of tissue can be obtained from any part of the body. Gastroscopes, bronchoscopes, colonoscopes, and other instruments used for endoscopic examination, for example, are constructed so that specimens for biopsy can be obtained while the internal organs are being examined. Biopsy specimens also can be taken directly from internal organs such as the liver or kidney by inserting a thin needle through the skin directly into the organ to produce a biopsy core. This is often done using ultrasound or other imaging techniques for guidance.

Biopsy
Removal of a small sample of tissue for examination and diagnosis by a pathologist.

Electrocardiogram (ECG)
A technique for measuring the serial changes in the electrical activity of the heart during the various phases of the cardiac cycle. (Often called ECG or EKG.)

Electroencephalogram (EEG)
A test that uses the electrical impulses of the body to measure activity in the brain.

Electromyogram (EMG)
A test that uses the electrical impulses of the body to measure activity in the nervous system.

Endoscopy
An examination of the interior of the body by means of various lighted tubular instruments. Method may also be used to obtain tissue samples.

Laparoscope
A long, tubular, telescope-like instrument passed through the abdominal wall to examine structures within the peritoneal cavity.

Specific treatment
Treatment of underlying cause of disease.

TESTS OF ELECTRICAL ACTIVITY

Several different tests measure the electrical impulses associated with various bodily functions and activities. These include the **electrocardiogram (ECG)**, the **electroencephalogram (EEG)**, and the **electromyogram (EMG)**. The most widely used of these tests is the ECG. Electrodes attached to the arms, legs, and chest are used to measure the serial changes in the electrical activity of the heart during the various phases of the cardiac cycle. The ECG also identifies disturbances in the heart rate or rhythm and identifies abnormal conduction of impulses through the heart. Heart muscle injury, such as occurs after a heart attack, also can be recognized by means of characteristic abnormalities in the cardiogram. The EEG measures the electrical activity of the brain by means of small electrodes attached to different areas in the scalp. Abnormalities of cerebral structure or function may cause altered brain wave patterns that are detected by this examination. The EMG measures the electrical activity of skeletal muscle during contraction and at rest. Abnormal electrical activity is often encountered in various inflammatory or degenerative diseases involving the skeletal muscles and the nerves that control them. The test is performed by inserting a needle into the muscle that is being studied. The speed at which a nerve conducts impulses also can be measured by means of electrodes taped to the surface of the skin over the nerve being tested.

ENDOSCOPY AND LAPAROSCOPY

An **endoscopy**, or endoscopic examination (*endo* = within + *skopeo* = examine), is an examination of the interior of the body by means of various types of flexible tubular instruments, all of similar design, that are named according to the part of the body they are designed to examine. These instruments have an optical system and light source and contain ports through which either sampling or therapeutic devices can be guided to the site under investigation. In addition, gas or liquid may be passed through the scope to help visualize the area studied. An instrument called a **laparoscope** is used to visualize the abdominal and pelvic organs in the procedure called *laparoscopy*. To perform a laparoscopic procedure, the peritoneal cavity is inflated first with carbon dioxide, which separates the organs so that they can be visualized more easily. Then the laparoscope is inserted through a small incision in the abdominal wall, often in or near the umbilicus. Modern laparoscopes may be used to perform surgical as well as diagnostic procedures. For example, appendectomies and gall bladder removal often are performed using laparoscopic surgical techniques (as opposed to "open" surgery).

TREATMENT

After the diagnosis has been established, a course of treatment is initiated. A **specific treatment** is used when the cause and nature of the disease are known. For example, an antibiotic may be given to a patient who has an infection that is responsive to the