GOULD'S
Pathophysiology *for the* Health Professions

SEVENTH EDITION

Karin C. VanMeter
Robert J. Hubert

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SEVENTH EDITION

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Preface

This textbook provides an introduction to pathophysiology for students in a variety of academic programs for the health professions at colleges and universities. Major disorders are described, as well as selected additional diseases, with the intention of providing information on a broad spectrum of diseases, with one or more distinguishing features for each. It is anticipated that additional information and resources pertinent to the individual's professional needs may be added to classroom presentations and assignments. We trust that students will enjoy studying these topics and proceed with enthusiasm to more detailed studies within their individual specialties.

Organization

The textbook is organized into five major sections, followed by the appendices.

Section I—Basic Concepts of Disease Processes

- An introduction to pathophysiology, including medical terminology and basic cellular changes, is provided.
- Topics such as fluid, electrolyte, and acid–base imbalances, basic pharmacology, and pain are covered.
- The core information for each topic is complemented by the inclusion of a specific disease/condition as an immediate clinical application at the end of each chapter.

Section II—Defense/Protective Mechanisms

- Topics such as inflammation and healing, infection, and immunity are covered.
- Specific areas included are a review of body defenses, healing involved in specific trauma such as burns, basic microbiology, review of the immune system components, and mechanisms.

Section III—Pathophysiology of Body Systems

- Selection of specific disorders is based on incidence and occurrence, as well as on the need to present a variety of pathophysiological processes and etiologies to the student.
- For major disorders, information is provided on pathophysiology, etiology, clinical manifestations, significant diagnostic tests, common treatment modalities, and potential complications.
- Other selected diseases are presented in less detail, but significant, unique features are highlighted.

Section IV—Factors Contributing to Pathophysiology

- Normal physiological changes related to cancer, adolescence, pregnancy, and aging, with their relevance and effect on disease processes and the treatment of the affected individual, are described.
- Specific disorders associated with cancer and the developmental stages are discussed.

Section V—Environmental Factors and Pathophysiology

- Factors such as immobility, stress, substance abuse, and environmental hazards are the major components in this section.
- Effects of the various environmental factors on the various body systems and potential complications beyond physical pathologies are discussed.
- New research and data are included, as these are areas of increasing concern with regard to pathophysiology and patient health.

Appendices—Additional Information

- Ready References include lists of anatomic terms, abbreviations and acronyms, a selection of diagnostic tests, an example of a medical history, a disease index, and a drug index.
- A glossary and a list of additional resources complete this resource.

Format and Features

The basic format as well as the straightforward, concise approach remain unchanged from the previous editions. Some material has been reorganized to improve the flow of information and facilitate comprehension. Many features related to the presentation of information in this textbook continue as before.

- Generic learning objectives are included in each chapter. Instructors may modify or add applicable objectives for a specific professional program.
- Cross-references are included, facilitating access to information.

- In the discussion of a particular disorder, the *pathophysiology* is presented *first*, because this "sets the stage," describing the basic change(s) in the body. Once the student understands the essence of the problem, he or she can easily identify the role of predisposing factors or causes and relate the resulting signs and symptoms or complications. Diagnostic tests and treatment also follow directly from the pathophysiology.
- Changes at the *cellular* level are included when significant.
- Brief *reviews* of normal anatomy and physiology are presented at the beginning of each chapter to remind students of the structures and functions that are frequently affected by pathological processes. A review of basic microbiology is incorporated into the chapter on infections. Additional review material, such as the pH scale or the location of body cavities, may be found in the Appendices.
- Numerous *illustrations*, including flow charts, schematic diagrams, and photographs, clarify and reinforce textual information, as well as offering an alternative visual learning mode, particularly when complex processes are involved. Illustrations are fully labeled, including anatomical structures and pathologic changes. Different colors may be used in a figure to distinguish between the various stages or factors in a process.
- *Tables* summarize information or offer comparisons, which are helpful to the student in selecting the more significant information and for review purposes.
- Brief reference to *diagnostic tests* and *treatment measures* promotes understanding of the changes occurring during a disease.
- *Questions* are found in boxes throughout the text to stimulate application and review of new concepts. "Apply Your Knowledge" questions are based on review of normal physiology and its application, "Think About" questions follow each small section of information, and "Study" questions are located at the end of each chapter. Questions may relate to simple, factual information, potential applications, or the integration of several concepts. These questions are helpful in alerting a student to points initially overlooked and are useful for student self-evaluation before proceeding to the next section. These features may also serve as a tool for review and test preparation. Brief answers are provided on the Evolve website.
- Brief, adaptable *case studies* with questions are incorporated at the end of many chapters and are intended to provide a basis for discussion in a tutorial, an assignment, or an alternative learning mode. It is expected that specific clinical applications may be added by instructors for each professional group.
- Chapter summaries precede the review questions in each chapter.

What's New?

- Information on specific diseases has been updated throughout.
- The specific disorders for each body system have been expanded to reflect current trends and research.
- A broader emphasis on all allied health professions has been incorporated.
- Sections and chapters have been reorganized to present the student with a building block approach: basic science and how it relates to human biology, the body's various mechanisms that respond to the disorders/diseases, the general overview of body systems and their specific disorders, other biological factors outside of the physiology of each system that contribute to instances of disorders/disease, and finally those environmental factors not directly attributed to a biological function or condition that may contribute to pathophysiology throughout a number of body systems.
- Figures have been updated with new photographs and illustrations to help in the recognition and identification of the various concepts and specific disorders.
- Tables have been updated with new information that has been made available since the previous edition.
- New boxes have been added:
  - **Technology**—presents information on newly developed tools/technologies being used to address the challenges in the specific chapter subject, with emphasis on artificial intelligence.
  - **The Bigger Picture**—in a body system chapter, a representative disorder/disease originating in that system is selected, and its effects in other body systems are listed, showing the interactions between different systems.
- Additional resources have been expanded and updated.
- Study questions and Think About questions have been reviewed and updated to cover new material in the chapter. The Apply Your Knowledge questions have replaced the Challenge questions in the previous editions.
- The Study Guide associated with this text has been updated to reflect the most recent information regarding various disorders.

Guidelines for Users

Certain guidelines were developed to facilitate the use of this textbook by students with diverse backgrounds studying in various health science programs. As well as ongoing general changes, some professional groups have developed unique practice models and language. In some disciplines, rapid changes in terminology have occurred, creating difficulty for some students. For example, current terms such as *chemical dependency* or *cognitive impairment* have many synonyms, and some of

these are included to enable students to relate to a more familiar phrase. To avoid confusion, the common, traditional terminology has been retained in this text.

- The recipient of care or service is referred to as a *patient.*
- When a disease entity refers to a group of related disorders, discussion focuses on either a typical representative of the group or on the general characteristics of the group.
- *Key terms* are listed at the beginning of the chapter. They are presented in **bold** print and defined when initially used in the chapter. Key terms are not indicated as such in subsequent chapters but may be found in the glossary at the back of the book.
- *Italics* are used to emphasize significant words.
- It is assumed that students have studied anatomy and physiology prior to commencing a pathophysiology course.
- The concise, readable style includes sufficient scientific and medical terminology to help the student acquire a professional vocabulary and appropriate communication skills. An effort has been made to avoid overwhelming the student with a highly technical approach or impeding the learning process for a student with little scientific background.
- The presence of numeric values within textual information often confuses students and detracts from the basic concepts being presented; therefore, specific numbers are included only when they promote understanding of a principle.
- Suggested diagnostic tests and treatments are not individualized or necessarily complete, but are presented generally to assist the student's application of the pathophysiology. They are also intended to provide students with an awareness of the impact of certain diseases on a client and of possible modifications in the individualized care required. Diagnostic tests increase student cognizance of the extent of data collection and sifting that may be necessary before making a diagnosis, as well as the importance of monitoring the course of a disease or the response to treatment.
- A brief introduction to pharmacology is included in Section I, and specific drugs are referred to during the discussion of certain disorders. Drugs are identified by *generic name*, followed by a trade name. Examples provided in the appropriate chapter are not recommendations but are suggested only as frequently used representatives of a drug classification. A drug index with references to the applicable chapter is located in the appendices.
- Information regarding adverse effects of drugs or other treatment is included when there may be potential problems, such as high risk for infection or special precautions required of members of the health care team.
- Every effort has been made to present current information and concepts simply but accurately. This content provides the practitioner in a health profession with the prerequisite knowledge to recognize and understand a client's problems and the limitations and implications of certain treatment measures; to reduce exacerbating factors; to participate in preventive programs; and to be an effective member of a health care team. The student will develop a knowledge base from which to seek additional information. Individual instructors may emphasize certain aspects or topics, as is most appropriate for students in a specialty area.

Resources

In the textbook:

- Selected additional resources are listed in the appendices in Ready Reference 9.
- *Reference tables* are located inside the front book cover. These comprise common normal values for blood, cerebrospinal fluid, and urine; a pH scale for body fluids; a list of blood clotting factors; and diagnostic tests.
- The chapter introducing pharmacology and therapeutics is limited in content but, combined with the brief references to treatments with individual disorders, is intended to complement the pathophysiology. This chapter also introduces a few traditional and nontraditional therapeutic modalities to facilitate the student's understanding of various therapies and of the impact of diverse treatments on the patient and on care by all members of the health care team. Also included are brief descriptions of a few selected forms of therapy, for example, physiotherapy, in hopes of clarifying the roles of different members of a health care team.
- The appendices at the back of the textbook are intended to promote effective use of study time. They include:
  - A brief review of anatomical terms describing *body cavities and planes,* with accompanying illustrations, as well as basic body movements.
  - Selected numerical conversions for temperature, weights, and volumes.
  - Lists of *anatomical terms* and combining forms, common *abbreviations,* and *acronyms*; because of the broad scope of pathophysiology, a medical dictionary is a useful adjunct for any student in the health-related professions.
  - A brief description with illustrations of common diagnostic tests such as ultrasound and magnetic resonance imaging.
  - An example of a medical history, which can be modified to fit the needs of a particular professional group.
  - A disease index, with a brief description and references to the relevant chapter.

  - A drug index identifying the principal action and references to the appropriate chapters.
  - A list of additional resources; websites consist primarily of health care groups or professional organizations that will provide accurate information and are likely to persist. Additional specific journals and websites are available for individual professions.
  - A glossary, including significant terms used to describe diseases, as well as key words.
- Accompanying this textbook and developed for it, the ancillaries available include:
  - A study guide for students, which provides learning activities such as complex test questions, matching exercises, crossword puzzles, diagrams to label, and other assignments.
  - The interactive Evolve web site, which includes self-evaluation tools and can be found at http://evolve.elsevier.com/Hubert/Goulds/.

We appreciate the time and effort of reviewers and users of this text, of sales representatives, and of the editors, who have forwarded comments regarding the first four editions. We have attempted to respond to these suggestions while recognizing that comments come from a variety of perspectives, and there is a need to respect the primary focus of this textbook, space constraints, and student concerns.

We hope that teachers and students will enjoy using this textbook, and that it will stimulate interest in the acquisition of additional knowledge in this dynamic field.

Robert J. Hubert
Karin C. VanMeter

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I will dedicate this book to my mother Theresia "Susi" Sikora, a great mother who I took care of the last five years but passed away as we were finishing the last items for the book. Without her I would not have achieved what I did – "Danke Mutti". To the same subject I would like to thank my children for their acceptance that they had a mom living between two continents and seeing me very little.

Karin C. VanMeter

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Robert J. Hubert

Contents

SECTION I

Pathophysiology: Background and Overview

CHAPTER 1

Introduction to Pathophysiology

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, the student is expected to:

1. Explain the role of pathophysiology in the diagnosis and treatment of disease.
2. Use the terminology appropriate for pathophysiology.
3. Explain the importance of a patient's medical history.
4. Describe common cellular adaptations and possible reasons for the occurrence of each.
5. Identify precancerous cellular changes.
6. List the common causes of cell damage.
7. Describe the common types of cell necrosis and possible outcomes.

KEY TERMS

anaerobic
apoptosis
autopsy
biopsy
endogenous
exogenous
gangrene
homeostasis
hypoxia
iatrogenic
idiopathic
inflammation
ischemia
lysis
lysosomal
microorganisms
microscopic
morphologic
necrosis
probability
pyroptosis

What Is Pathophysiology and Why Study It?

Pathophysiology involves the study of *functional* or physiologic changes in the body that result from disease processes. This subject builds on knowledge of the normal structure and function of the human body. Disease development and the associated changes to normal anatomy or physiology may be obvious or may be hidden with its quiet beginning at the cellular level. As such, pathophysiology includes some aspects of *pathology*, the laboratory study of cell and tissue changes associated with disease.

Understanding Health and Disease

Disease may be defined as a deviation from the *normal* structure or function of any part, organ, or system (or combination of these), or from a state of wellness. Disease is a definite pathological process with characteristic sets of signs and symptoms. The World Health Organization (WHO) includes physical, mental, and social well-being in its definition of health.

A state of health is difficult to define because the genetic differences among individuals, as well as the many variations in life experiences and environmental influences, create a variable base. The context in which health is measured is also a consideration. A person who is blind can be in good general health. Injury or surgery may create a temporary impairment in a specific area, but the person's overall health status is not altered.

Homeostasis is the maintenance of a relatively stable internal environment regardless of external changes. Disease develops when significant changes occur in the body, leading to a state in which **homeostasis** cannot be maintained without intervention. Under normal conditions homeostasis is maintained within the body with regard to factors such as blood pressure, body temperature, and fluid balance. As frequent minor changes occur in the body, the compensation mechanisms respond, and homeostasis is quickly restored. Usually the individual is not aware of these changes or the compensations taking place.

Steps to Health (Box 1.1) are recommended to prevent disease.

When one is defining "normal" limits for health indicators such as blood pressure, pulse, or laboratory data, the values used usually represent an average or a *range*. These values represent what is expected in a typical individual but are not absolutes. Among normal healthy individuals, the actual values may be adjusted for factors such as age, gender, genetics, environment, and activity level. Well-trained athletes often have a slower pulse or heart rate than the average person. Blood pressure usually increases slightly with age, even in healthy individuals. Also, small daily fluctuations in blood pressure occur as the body responds to minor changes in activity, body position, and even emotions. Therefore it is impossible to state a single normal value for blood pressure or pulse rate. It is also important to remember that any one indicator or lab value must be considered within the total assessment for the individual client.

Likewise, a discussion of a specific disease in a text presents a general description of the typical characteristics of that disease, but some differences in the clinical picture can be expected to occur in a specific individual, based on similar variables.

BOX 1.1 Seven Steps to Health

1. Be a nonsmoker and avoid secondhand smoke.
2. Eat 5 to 10 servings of vegetables and fruit a day. Choose high-fiber, lower-fat foods. If you drink alcohol, limit your intake to one to two drinks a day.
3. Be physically active on a regular basis. This will also help you to maintain a healthy body weight.
4. Protect yourself and your family from the sun.
5. Follow cancer screening guidelines.
6. Visit your doctor or dentist if you notice any change in your normal state of health.
7. Follow health and safety instructions at home and at work when using, storing, and disposing of hazardous materials.

Concept and Scope of Pathophysiology

Pathophysiology requires the use of knowledge of basic anatomy and physiology and is based on a loss of or a change in normal structure and function. Many disorders affecting a particular system or organ (e.g., the liver) display a set of common signs and symptoms directly related to that organ's normal structure and function. The interruption of the normal functioning of one organ (or tissue) will affect other organ systems as well. For example, when the liver is damaged, many clotting factors cannot be produced; therefore, excessive bleeding results. Jaundice, a yellow color in the skin, is another sign of liver disease, resulting from the liver's inability to excrete bilirubin. Also, basic pathophysiologic concepts related to the causative factors of a disease, such as the processes of inflammation or infection, are common to many diseases. Inflammation in the liver causes swelling of the tissue and stretching of the liver capsule, resulting in pain, as does inflammation of the kidneys. This cause-and-effect relationship, defined by signs and symptoms, facilitates the study of a specific disease.

To provide a comprehensive overview of disease processes, this text focuses on major diseases. Other disorders are included when appropriate to provide exposure to a broad range of diseases. The principles illustrated by these diseases can then be applied to other conditions encountered in practice. In addition, a general approach is used to describe diseases in which there may be several subtypes. For example, only one type of glomerulonephritis, a kidney disease, is described in the text—acute poststreptococcal glomerulonephritis, which represents the many forms of glomerulonephritis.

Prevention of disease has become a primary focus in health care. The known causes of and factors predisposing to specific diseases are being used in the development of more effective preventive programs, and it is important to continue efforts to detect additional significant factors and gather data to further decrease the incidence of certain diseases. The Centers for Disease Control and Prevention (CDC) in the United States have a significant role in collection of data about all types of disease and provide evidence-based recommendations for prevention. Prevention includes activities such as maintaining routine vaccination programs and encouraging participation in screening programs such as blood

BOX 1.2 Primary, Secondary, and Tertiary Prevention

Primary Prevention

The goal is to protect healthy people from developing a disease or experiencing an injury in the first place. For example:

- Education about good nutrition, the importance of regular exercise, and the dangers of tobacco, alcohol, and other drugs
- Education and legislation about proper seat belt and helmet use
- Regular exams and screening tests to monitor risk factors for illness
- Immunization against infectious disease
- Controlling potential hazards at home and in the workplace

Secondary Prevention

These interventions happen after an illness or serious risk factors have already been diagnosed. The goal is to halt or slow the progress of disease (if possible) in its earliest stages; in the case of injury, goals include limiting long-term disability and preventing reinjury. For example:

- Telling people to take daily, low-dose aspirin to prevent a first or second heart attack or stroke
- Recommending regular exams and screening tests in people with known risk factors for illness
- Providing suitably modified work for injured workers

Tertiary Prevention

This phase focuses on helping people manage complicated, long-term health problems such as diabetes, heart disease, cancer, and chronic musculoskeletal pain. The goals include preventing further physical deterioration and maximizing quality of life. For example:

- Cardiac or stroke rehabilitation programs
- Chronic pain management programs
- Patient support groups

From http://www.iwh.on.ca/wrmb/primary-secondary-and-tertiary-prevention.

pressure clinics and vision screening (Box 1.2). As more community health programs develop, and with the increase in information available on the Internet, health care workers are becoming more involved in responding to questions from many sources and have an opportunity to promote appropriate preventive measures in their communities. A sound knowledge of pathophysiology is the basis for preventive teaching in your profession.

While studying pathophysiology, the student becomes aware of the complexity of many diseases, the difficulties encountered in diagnosis and treatment, and the possible implications arising from a list of signs and symptoms or a prognosis. Sophisticated and expensive diagnostic tests are now available. The availability of these tests, however, also depends on the geographic location of individuals, including their access to large, well-equipped medical facilities. More limited resources may restrict the number of diagnostic tests available to an individual, or a long waiting period may be necessary before testing and treatment are available. When students understand the pathophysiology they can also better understand factors such as the disease manifestations, potential complications, and finally develop appropriate treatments. A solid knowledge base enables health care professionals to meet these increased demands with appropriate information.

Individuals working in health care have found that many new scientific developments have raised ethical, legal, and social issues. For example, the explosion in genetic information and related technologies has raised many ethical concerns (see Chapter 21). In relatively new areas of research such as genetics and artificial intelligence (including machine learning), discussion and resolution of the legal and ethical issues lag far behind the scientific advances. Health research is most often funded by commercial sources (up to 80%, according to some studies), and new breakthrough therapies are often announced before the start of any clinical trials. This causes increased hope and immediate demand for such treatments often as much as a decade before they become available. Understanding the research process and the time required for clinical trials of new therapies is crucial for answering questions about new therapies.

The research process in the health sciences is a lengthy three-stage process that aims to demonstrate both the safety and the effectiveness of a new therapy:

- The first stage in this process is often referred to as "basic science," in which researchers work to identify a technology that will limit or prevent the disease process. This stage is carried out in the laboratory and often requires the use of animals or cell cultures.
- The second stage involves a small number of human subjects to determine if the therapy is safe for humans.
- The third stage only takes place if the results of the previous research are positive; the majority of therapies do not make it to this point. In the third stage of research, a large number of patients with the disease or at risk for the disease are enrolled in clinical trials. These are usually *double-blind studies* in which the research subject and the person administering the treatment do not know if the subject is receiving a standard, proven therapy or the therapy being tested. The subject is identified by number only, without the particular therapy administered. All results are recorded by the subject's identification number. The principal investigator is responsible for tracking data collected in trials with many patients, often in several different health centers. The data are then analyzed to determine if the new therapy is more effective than the traditional therapy. In studies of vaccines or other preventive measures, data are collected about the occurrence of disease in both the control group and the experimental group to determine if the new measure reduces the incidence of the specific disease.

Research findings that demonstrate merit after this three-stage process are often referred to as "evidence-based research findings." The research data collected up

to this point are then passed on to regulatory bodies such as the U.S. Food and Drug Administration for review. If the therapy is deemed safe and better than the standard therapy used in the past, it will be approved for use for the specific disease identified in the research protocol.

Evidence-based research does not take into account cost, availability, or social and cultural factors that may influence use and acceptance of a therapy. These factors may be quite significant and affect the physician's or patient's acceptance of a therapy.

In rare cases, research trials in the third stage will be stopped if there is a significant difference in the mortality rate for the experimental group versus the control group. Research on the first antiretroviral agent, azidothymidine (AZT), was stopped 6 months early when the research showed a striking difference in survival rates. Those in the experimental group receiving AZT were outliving the control group in significant numbers. When the results were analyzed, trials stopped, and all patients were given the option of receiving AZT.

Once a therapy is approved for use, it may show additional potential to treat a different disease. Such use is termed "off-label" use. For the manufacturer to advertise the drug or therapy for use in different diseases, it must go through the third stage of clinical trials in patients with the new disease. An example is research using the drug thalidomide to treat malignancies such as multiple myeloma. Another recent example for "off-label" use is the use of hydroxychloroquine in the fight against SARS-CoV2 (COVID-19). The drug is approved for the treatment and prevention of malaria, and for oral therapy for rheumatoid arthritis and systemic lupus erythematosus.

THINK ABOUT 1.1

a. Describe the stages of the research process in the health sciences.
b. What is the purpose of a double-blind research trial?
c. What is a placebo, and why is it used in some studies?

Other issues may affect professional practice. Current technology provides an opportunity to prolong life through the use of various machines, many advances in surgery, and the use of organ transplants. Legal and ethical issues about fetal tissue transplants, stem cell therapies, experimental drugs or treatments, and genetic engineering continue to be difficult topics to address. In these developing areas, the primary goal is to reduce the incidence of disease and improve recovery rates. Concerns about new medical and health technologies include issues of access to therapy, costs, and relative risk versus benefits of new treatments. Questions have also been raised about the allocation of health care resources for new therapies such as heart transplants or *in vitro* fertilization (test-tube babies), which are very costly. A public health dilemma results, because a choice must be made between a high-cost treatment for one person and a low-cost treatment for many people, given the limited resources available. In many cases evidence-based research demonstrates little significant difference in outcomes for newer versus older technologies. Skill and professional training are essential in the use and interpretation of any technology. Clinical research funding is being directed to identifying treatments as well as preventive measures that are more effective on a cost-per-patient basis.

Many options other than traditional therapies are now available. Treatment by acupuncture or naturopathy may be preferred (see Chapter 3). These options may replace traditional therapies or may be used in conjunction with them. A patient may seek an alternative or complementary mode of treatment to supplement traditional care; thus, knowledge of these complementary therapies is often needed. It is also recognized that such therapies and practices should be part of a health history for any client seeking care.

Beginning the Process: A Medical History

Many individuals in the health professions will be contributing to, completing, or updating a patient's medical or health history (see Ready Reference 6 for an example). This information is essential to identify any impact health care activities might have on a patient's condition, or how a patient's illness might complicate care. The assessment includes questions on current and prior illnesses, allergies, hospitalizations, and treatment. Current health status is particularly important and should include specific difficulties and any type of therapy or drugs, prescription, nonprescription, and herbal items, including food supplements.

A basic form is usually provided for the patient to fill out, and then it is completed by the health professional asking appropriate follow-up questions to clarify the patient's current condition and identify any potential problems. Knowledge of pathophysiology is essential to developing useful questions, understanding the implications of this information, and deciding on the necessary precautions or modifications required to prevent complications. For example, a patient with severe respiratory problems or congestive heart failure would have difficulty breathing in a supine position. Reducing stress may be important for a patient with high blood pressure. Prophylactic medication may be necessary for some patients to prevent infection or excessive bleeding. In some cases, additional problems or undesirable effects of medications may be detected.

New Developments and Trends

Both students and practitioners must constantly update their information and knowledge. Developments in all areas of health care are occurring at a rapid rate,

primarily because of changes in technology. New causes of disease and more detail regarding the pathophysiology of a disorder are being uncovered, diagnostic tests are being improved, and more effective drugs are being formulated. Technology has greatly altered many aspects of health care.

Extensive research projects continue in efforts to prevent, control, or cure many disorders. For example, research indicated that most cases of cervical cancer resulted from infection by human papillomavirus. The next step involved development of a vaccine effective against the most common strains of the virus. In clinical trials, use of the vaccine showed a reduction in the number of women developing cervical cancer. This vaccine is now available to young women to prevent cervical cancer in later years. It does not provide 100% prevention, and other preventive health behaviors, such as routine screening, need to be maintained, but the number of actual cases of cervical cancer and the cost of treatment are expected to decline dramatically in the coming decades.

It is essential for the student and practitioner to continually check for new information, employing reliable, accurate resources such as professional websites, journals, or seminars. Many changes in health care are anticipated in the near future as electronic devices are more frequently used. For example, sensors implanted under the skin may measure blood glucose levels in diabetic patients or release the amount of insulin appropriate to the patient's needs. The future of health care will also include technologies such as artificial intelligence, three-dimensional (3D) printing, robotics, and nanotechnology. The increased costs associated with technologic advances then are balanced against the costs of hospitalization or chronic care.

Reports from health professionals are gathered by the WHO, the United States Public Health Service, the CDC, and state and local authorities, as well as agencies in countries around the world. These data are organized and published, leading to new research efforts, tracking new or deadly diseases, or, in some cases, signaling a warning about predisposing conditions or current treatments. Awareness of deviations from the expected outcomes is a responsibility of those working in health care. Keeping up with new discoveries may sometimes feel like information overload, but it is a critical part of professional practice (Box 1.3).

BOX 1.3 New Challenges: The Zika Virus

First discovered in 1947, Zika virus infections were for many years isolated to tropical Africa, Southeast Asia, and the Pacific Islands. In 2015, a case was confirmed in Brazil, which prompted the World Health Organization to declare the virus a public health emergency of international concern. Since identifying this new potential threat as an international concern, the U.S. Centers for Disease Control and Prevention elevated its response to the highest level available, thus expanding the research on the diagnosis, spread, and treatment/prevention of the virus. This type of timely sharing of information and support among various health agencies and organizations (including private industries) at all levels is necessary to effectively face potential epidemics in the future.

THINK ABOUT 1.2

Discuss new developments and trends affecting the health care system.

APPLY YOUR KNOWLEDGE 1.1

Using the heart and the lungs, show how you can apply your prior knowledge of anatomy and physiology to your study of pathophysiology. (Hint: Change part of the normal structure and predict the resulting loss of function.)

TECHNOLOGY 1.1

Artificial Intelligence in Health Care

Artificial intelligence (AI) has wide-ranging potential in health care, and the applications are endless. AI in the medical field relies on the analysis of huge amounts of data, followed by the interpretation of these data sets. This should help physicians to make better decisions and manage data information to effectively create personalized medical plans. In short, AI in health care is a great addition to information management for both the physician and the patient. AI is used to diagnose disease and design new drugs. Although AI in health care has a huge potential, limitations exist.

Basic Terminology of Pathophysiology

Understanding basic terminology is the essential first step in learning a new subject. Second, a review of past learning in normal anatomy and physiology, along with the associated proper names and terms, is needed in the study of pathophysiology. Selected anatomic terms may be reviewed in Ready References 1 and 2 in the appendices at the back of the text. A firm foundation in anatomy and physiology is particularly important when a disease affects several organs or systems in the body. For example, kidney disease often affects cardiovascular function through the renin, angiotensin, and aldosterone mechanisms. The significance of these effects on another system can be more easily understood and remembered when prior knowledge of normal physiology can be quickly applied to the altered function.

A disease or abnormal condition usually involves changes at the organ or system (*gross*) level, as well as at the cellular, or **microscopic**, level. Pathophysiology focuses on the effects of abnormalities at the organ level, but cellular changes are usually integral to a full understanding of these effects. Pathology laboratory studies,

which are particularly useful in establishing the *cause* of a disease, examine tissue specimens from **biopsy** procedures (excision of very small amounts of living tissue), surgical specimens, or examination after death (**autopsy**). Analysis of body fluids is another essential diagnostic tool in a pathology laboratory. As indicated, the pathophysiologic changes at a particular site also include evidence of the basic cause of disease, whether it is an infection, a neoplasm, or a genetic defect.

The Disease Process

Below are a few terms that are frequently used in the discussion of disease processes. Not all of these terms are necessarily used when describing any one disorder.

- *Diagnosis* refers to the identification of a specific disease through evaluation of signs and symptoms, laboratory tests (see front inside cover and Ready Reference 5 in the Appendix), or other tools. More than one factor is usually required to verify a diagnosis. For example, a diagnosis of diabetes mellitus could be confirmed by a blood test following consideration of the patient's signs, and a fractured leg bone is indicated by pain, swelling, and perhaps the position of the leg, but is confirmed by x-ray.
- *Etiology* concerns the causative factors in a particular disease. There may be one or several causative factors. Etiologic agents include congenital defects, inherited or genetic disorders, microorganisms such as viruses or bacteria, immunologic dysfunction, metabolic derangements, degenerative changes, malignancy, burns and other trauma, environmental factors, and nutritional deficiencies.

Etiology-Causes of Disease

When the cause of a disease is unknown, it is termed **idiopathic**. In some cases, a treatment, a procedure, or an error may cause a disease, which is then described as **iatrogenic**. Examples of iatrogenic disease are a bladder infection following catheterization, or bone marrow damage caused by a prescribed drug. In some cases, a difficult decision must be made about a treatment that involves an additional serious risk, with careful assessment of the benefits versus the risks of a specific treatment. For example, certain forms of chemotherapy and radiation used in the treatment of cancer may cause other serious complications for the patient. In these situations, the client and practitioner must make an informed choice.

- *Predisposing factors* encompass the tendencies that promote development of a disease in an individual. A predisposing factor indicates a *high risk* for the disease but not certain development. Predisposing or high-risk factors may include age, gender, inherited factors, occupational exposure, or certain dietary practices. For example, insufficient calcium intake predisposes to osteoporosis. Exposure to asbestos is known to increase the risk of developing cancer. A high dietary intake of cholesterol and saturated fats, cigarette smoking, obesity, and a sedentary lifestyle are factors that increase the risk of heart attacks. By promoting avoidance of predisposing factors, the number of individuals developing the disorder could be greatly reduced.
- A *prophylaxis* is a measure designed to preserve health (as of an individual or society) and prevent the spread of disease. Prophylactic treatment for myocardial infarction for high-risk patients is a baby aspirin daily.
- *Prevention* of disease is closely linked to etiology and predisposing factors for a specific disease. Preventive measures include vaccinations, dietary or lifestyle modifications, removal of harmful materials in the environment, and cessation of potentially harmful activities such as smoking. The health professional can provide appropriate and reliable information about activities that support the client's needs and allow him or her to make better decisions about his or her personal health.

Characteristics of Disease

In describing the characteristics of a particular disease, certain terms are standard:

- *Pathogenesis* refers to the development of the disease or the sequence of events involved in the tissue changes related to the specific disease process.
- The *onset* of a disease may be *sudden* and obvious or *acute* (e.g., gastroenteritis with vomiting, cramps, and diarrhea) or it may be *insidious*, best described as a gradual progression with only vague or very mild signs. Hepatitis may manifest quietly in this way. There may be several stages in the development of a single disease.
- An *acute* disease indicates a short-term illness that develops quickly with marked signs such as high fever or severe pain (e.g., acute appendicitis).
- A *chronic* disease is often a milder condition that develops gradually but that persists for a long time and usually causes more permanent tissue damage, such as rheumatoid arthritis. Often a chronic disease is marked by intermittent acute episodes.
- A *subclinical* state exists in some conditions in which pathologic changes occur but the patient exhibits no obvious manifestations, perhaps because of the great reserve capacity of some organs. For example, kidney damage may progress to an advanced stage of renal failure before symptoms are manifested.
- An initial *latent* or "silent" stage, in which no clinical signs are evident, characterizes some diseases. In infectious diseases this stage may be referred to as the *incubation* period, which is the time between exposure to the microorganism and the onset of signs or symptoms; it may last for a day or so or may be prolonged, perhaps for days or weeks. Often the disease agent may be communicable during this incubation period.

- The *prodromal* period comprises the time in the early development of a disease when one is aware of a change in the body but the signs are nonspecific (e.g., fatigue, loss of appetite, or headache). A sense of feeling threatened often develops in the early stage of infections. Laboratory tests are negative during the prodromal period; thus, it is difficult to confirm a diagnosis.
- The *manifestations* of a disease are the clinical evidence or effects, the signs and symptoms, of disease. These manifestations, such as redness and swelling, may be *local*, found at the site of the problem. Or signs and symptoms may be systemic, meaning they are general indicators of illness, such as fever.
- *Signs* are objective indicators of disease that are obvious to someone other than the affected individual. Signs can be either local, found at the site of the problem (such as a skin rash), or systemic, which are general indicators (such as a fever).
- *Symptoms* are subjective feelings, such as pain or nausea. Both signs and symptoms are significant in diagnosing a particular problem.
- *Lesion* is the term used to describe a specific local change in the tissue. Such a change may be microscopic, such as when liver cells are examined for pathologic change, or highly visible, such as a blister or pimple observed on the skin.
- A *syndrome* is a collection of signs and symptoms, often affecting more than one organ, that usually occur together in response to a certain condition.
- *Diagnostic tests* are laboratory tests that assist in the diagnosis of a specific disease. The appropriate tests are ordered based on the patient's manifestations and medical history, the clinical examination, and the patient's answers to specific questions. These tests may also be used for monitoring the response to treatment or the progress of the disease. Such tests may involve chemical analysis of body fluids such as blood, examination of tissues and cells from specimens (e.g., biopsies or body secretions), identification of microorganisms in body fluids or tissue specimens, or radiologic examination of the body. It is important that medical laboratories have a quality assurance program in place to ensure accurate test results. Also, it is often helpful for a patient to have any future or repeated tests done by the same laboratory to provide a more accurate comparison of results.
- *Remissions* and *exacerbations* may mark the *course* or progress of a disease. A remission is a period or condition in which the manifestations of the disease subside, either permanently or temporarily. An exacerbation is a worsening in the severity of the disease or in its signs/symptoms. Rheumatoid arthritis typically has periods of remission, when pain and swelling are minimal, alternating with acute periods, when swelling and pain are severe. An example of the exacerbation of asthma might include excessive pollen or air pollution leading to serious breathing problems.
- A *precipitating factor* is a condition that triggers an acute episode, such as a seizure in an individual with a seizure disorder. Note that a precipitating factor differs from a predisposing factor. For example, a patient may be predisposed to coronary artery disease and angina because of a high-cholesterol diet. An angina attack can be precipitated by shoveling snow on a very cold day.
- Complications are new secondary or additional problems that arise after the original disease begins. For example, following a heart attack, a person may develop congestive heart failure, a complication.
- *Therapy* or therapeutic interventions are treatment measures used to promote recovery or slow the progress of a disease. These measures may include surgery, drugs, physiotherapy, alternative therapies, or behavior modification (see Chapter 3).
- *Sequelae* are the potential unwanted outcomes of the primary condition, such as paralysis following recovery from a stroke.
- *Convalescence* or *rehabilitation* is the period of recovery and return to the normal healthy state; it may last for several days or months.

Disease Prognosis

Prognosis defines the **probability** or likelihood for recovery or other outcomes. The probability figures used in prognosis are based on average outcomes, and there may be considerable variation among affected individuals. It is important to consider the basis of the statistics used to form such conclusions. How big was the clinical group? How long was the study? It is difficult to state a prognosis for diseases that affect a small group of patients or in which outcomes vary unpredictably.

- *Morbidity* indicates the disease rates within a group; this term is sometimes used to indicate the functional impairment that certain conditions such as stroke cause within a population.
- *Mortality* figures indicate the relative number of deaths resulting from a particular disease.
- An *autopsy* or *postmortem examination* may be performed after death to determine the exact cause of death or the course of the illness and effectiveness of treatment. An autopsy is an examination of all or part of the body by a pathologist. It includes gross and microscopic examination of tissues, organs, and fluids, and can include a variety of tests depending on individual circumstances.
- *Epidemiology* is the science of tracking the pattern or occurrence of disease. Epidemiologic records include data on the transmission and distribution of diseases and are particularly important in the control of infectious diseases and environmentally related diseases. Data may be presented in graphs, in tables, or on maps to provide a visible pattern. For example,

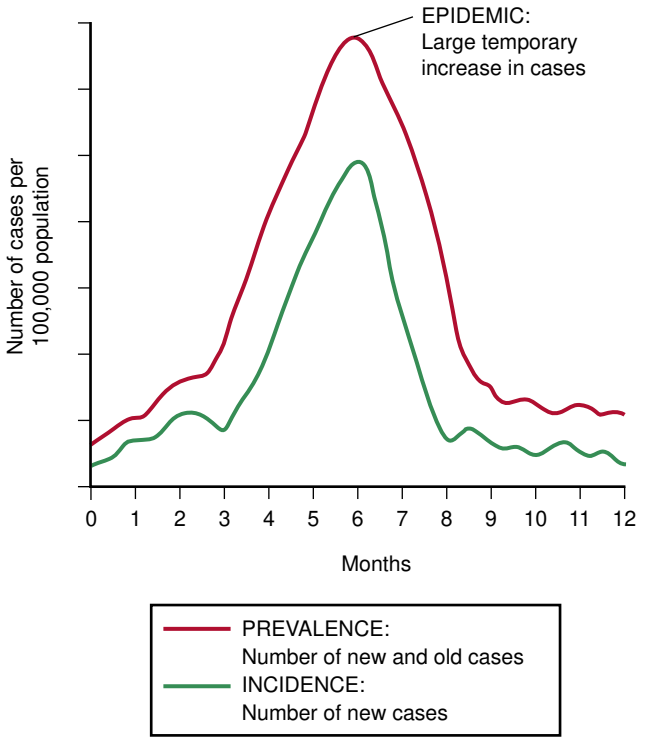


Fig. 1.1 Graph illustrating the occurrence of disease.

epidemiologic information is used to determine the components of the influenza vaccine to be administered each year based on the currently active strains and geographic movement of the influenza virus. Major data collection centers are the WHO in Ottawa, Canada and the CDC in Atlanta, Georgia. Notification and reporting of disease is required to provide data for epidemiologic studies and prevent occurrence of diseases.

- The *occurrence* of a disease is tracked by recording two factors: the *incidence* and the prevalence. The incidence of a disease indicates the number of new cases in a given population noted within a stated time period (Fig. 1.1). A significant increase or decrease in incidence of a specific disease may be analyzed to determine the responsible factors. *Prevalence* refers to the number of new and old or existing cases within a specific population and time period. Note that prevalence is always a larger figure than incidence.
- *Epidemics* occur when there are a higher than expected number of cases of an infectious disease within a given area, whereas pandemics involve higher numbers of cases in many regions of the globe (see Fig. 1.1). Influenza may occur sporadically, as well as in epidemic or *pandemic* outbreaks.
- *Communicable* diseases are infections that can be spread from one person to another. Some of these must be reported to health authorities.
- *Notifiable* or *reportable* diseases must be reported by the physician to certain designated authorities. The authority varies with the local jurisdiction. The specific diseases required to be reported may change over time. The requirement of reporting is intended to prevent further spread of the disease and maintain public health. Infections such as measles, severe acute respiratory syndrome, and human immunodeficiency virus or acquired immunodeficiency syndrome may be included in some jurisdictions.

THINK ABOUT 1.3

Rheumatoid arthritis is defined as a chronic systemic disorder with remissions and exacerbations, resulting in permanent joint damage. Describe this disease in terms of manifestations, etiology, predisposing factors, pathogenesis, and treatments.

Introduction to Cellular Changes

Cells have mechanisms by which they can adapt their growth and differentiation to altered conditions in the body. Some minor alterations, such as increases in breast and uterine tissue during pregnancy, are normal adaptations to change in the body. Tissues are frequently modified as a response to hormonal stimulation or environmental stimuli such as irritation. Frequently, such changes are reversible after the stimulus is removed. However, disease may develop when cell structure and function change and homeostasis cannot be maintained as a result. Irreversible changes in a cell signal a change in DNA structure or function. (See Fig. 21.2 for an illustration of DNA, the controlling nuclear material in a cell.) Abnormal changes are not necessarily a precursor to permanent tissue damage or the development of tumors or cancer, but it is important to determine the cause and monitor any abnormality to reduce the risk of serious consequences. Cells may be damaged or destroyed by changes in metabolic processes, reduced levels of adenosine triphosphate (ATP), altered pH in the cells, or damage to the cell membrane and receptors.

Terms Used for Common Cellular Adaptations

- *Atrophy* refers to a *decrease* in the *size* of cells, resulting in a reduced tissue mass (Fig. 1.2). Common causes include reduced use of the tissue, insufficient nutrition, decreased neurologic or hormonal stimulation, and aging. An example is the shrinkage of skeletal muscle that occurs when a limb is immobilized in a cast for several weeks.
- *Hypertrophy* refers to an *increase* in the *size* of individual cells, resulting in an enlarged tissue mass. This increase may be caused by additional work by the tissue, as demonstrated by an enlarged heart muscle resulting from increased demands (see Fig. 12.23). A common example of hypertrophy is the effect of consistent exercise on skeletal muscle, leading to an enlarged muscle mass. Excessive hormonal stimulation may also stimulate cell growth.

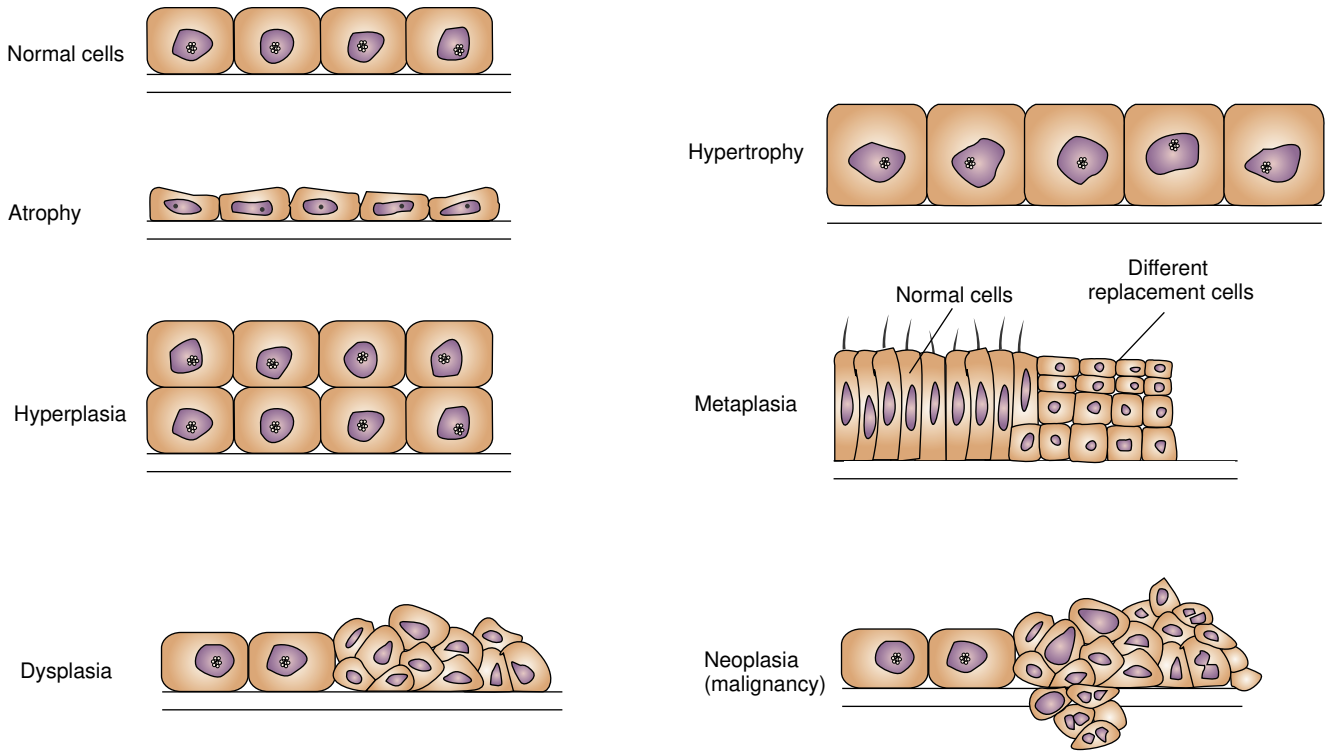


Fig. 1.2 Abnormal cellular growth patterns.

- *Hyperplasia* is defined as an increased *number* of cells resulting in an enlarged tissue mass. In some cases, hypertrophy and hyperplasia occur simultaneously, as in the uterine enlargement that occurs during pregnancy. Hyperplasia may be a compensatory mechanism to meet increased demands, or it may be pathologic when there is a hormonal imbalance. In certain instances there may be an increased risk of cancer when hyperplasia occurs.
- *Metaplasia* occurs when one mature cell type is replaced by a different mature cell type. This change may result from a deficit of vitamin A. Sometimes metaplasia may be an adaptive mechanism that provides a more resistant tissue—for instance, when stratified squamous epithelium replaces ciliated columnar epithelium in the respiratory tracts of cigarette smokers. Although the new cells present a stronger barrier, they decrease defenses for the lungs, because cilia are no longer present as a defense mechanism for the simpler squamous cells in the mucosa.
- *Dysplasia* is the term applied to tissue in which the cells vary in size and shape, large nuclei are frequently present, and the rate of mitosis is increased. This situation may result from chronic irritation infection, or it may be a precancerous change. Detection of dysplasia is the basis of routine screening tests for atypical cells such as the Pap smear (Papanicolaou test on cervical cells).
- *Anaplasia* refers to cells that are undifferentiated with variable nuclear and cell structures and numerous mitotic figures. Anaplasia is seen in most, but not all, malignant tumors and is the basis for grading the aggressiveness of a tumor.
- *Neoplasia* means "new growth," and a neoplasm is commonly called a *tumor*. Tumors are of two types: benign and malignant (see Figs. 20.1 and 20.2). Malignant neoplasms are referred to as *cancer*. Benign tumors do not necessarily become malignant. Benign tumors are usually considered less serious because they do not spread and are not life-threatening unless they are found in certain locations, such as the brain, where they can cause pressure problems. The characteristics of each tumor depend on the specific type of cell from which the tumor arises, resulting in a unique appearance and growth pattern. Neoplasms are discussed further in Chapter 20.

THINK ABOUT 1.4

Differentiate among hypertrophy, hyperplasia, anaplasia, and dysplasia.

Cell Damage and Necrosis

Apoptosis refers to programmed cell death, a normal occurrence in the body, which may increase when cell development is abnormal, cell numbers are excessive, or cells are injured or aged. Cells self-destruct, appearing to digest themselves enzymatically, and then disintegrate into vesicles called apoptotic bodies. These vesicles are quickly engulfed through phagocytic activity without eliciting an inflammatory response.

Necrosis refers to the death of one or more cells or a portion of tissue or organ as a result of irreversible damage and not a programmed cellular event.

There are many ways of injuring cells in the body, including the following:

- **Ischemia**, a decreased supply of oxygenated blood to a tissue or organ, owing to circulatory obstruction
- Physical agents, excessive heat or cold, or radiation exposure
- Mechanical damage such as pressure or tearing of tissue
- Chemical toxins
- Microorganisms such as bacteria, viruses, and parasites
- Abnormal metabolites accumulating in cells
- Nutritional deficits
- Imbalance of fluids or electrolytes

Decreased oxygen in the tissue may occur locally because of a blocked artery or systemically because of respiratory impairment. Cells with a high demand for oxygen, such as those of the brain, heart, and kidney, are quickly affected by **hypoxia** (reduced oxygen in the tissue). A severe oxygen deficit interferes with energy (ATP) production in the cell, leading to loss of the sodium pump at the cell membrane, as well as loss of other cell functions. An increase in sodium ions inside the cell leads to swelling of the cell, and eventually to rupture of the cell membrane. At the same time, in the absence of oxygen, **anaerobic** metabolism occurs in the cell, leading to a decrease in pH from buildup of lactic acid and further metabolic impairment. A deficit of other essential nutrients such as vitamins may also damage cells because normal metabolic processes cannot take place.

Another cause of cellular damage is physical injury related to thermal (heat) or mechanical pressures. These may impair blood supply to the cells or affect metabolic processes in the cells. Radiation exposure may damage cells by interfering with their blood supply or directly altering their chemical constituents, creating toxic materials inside the cells or changing DNA. Chemicals from both the environment (**exogenous**) and inside the body (**endogenous**) may damage cells, either by altering cell membrane permeability or producing other reactive chemicals, known as free radicals, which continue to damage cell components. Infectious diseases cause cell injury through the actions of **microorganisms** (living organisms too small to be seen with the naked eye) such as bacteria and viruses. Certain types of intracellular microorganisms induce a type of cell death referred to as **pyroptosis**. Pyroptosis differs from apoptosis in that pyroptosis results in the **lysis** or dissolution of the cell, releasing destructive **lysosomal** enzymes into the tissue, which cause **inflammation** (swelling, redness, and pain), as well as damage to nearby cells and reduced function (see Chapter 5). The apoptotic bodies formed through apoptosis do not cause an inflammatory response, as they are quickly engulfed through phagocytosis. Some genetic defects or inborn errors of metabolism can lead to abnormal metabolic processes. Altered metabolism leads to the accumulation of toxic intermediary compounds inside the cells, ultimately destroying them.

Cell damage usually occurs in two stages. In general, the *initial* cell damage causes an alteration in a metabolic reaction, which leads to a *loss of function* of the cell. If the factor causing the damage is removed quickly, the cell may be able to recover and return to its normal state, and the damage is said to be reversible. As the amount of damage increases, detectable **morphologic** or structural changes occur in the nucleus and the cell as well.

Cell death as a result of external damage may take on a variety of forms. Generally these involve cellular swelling and rupture if the cell membrane is affected, or accumulations of lipid inside the cell if metabolic derangements are present. If the noxious factor remains, the damage becomes irreversible, and the cell dies.

Following cell death, the nucleus of the cell disintegrates. The cells undergo **lysis** or dissolution, releasing destructive **lysosomal** enzymes into the tissue, which cause **inflammation** (swelling, redness, and pain), as well as damage to nearby cells and reduced function (see Chapter 5). If a large number of cells have died, inflammation can be extensive, causing the destruction of additional cells. The enzymes released from the dead cells can diffuse into the blood, providing helpful clues in blood tests that indicate the type of cells damaged. Diagnostic tests for specific enzymes present in the blood may determine the site and source of the problem—for example, a heart attack, in which part of the heart muscle is destroyed, which is indicated by the presence of cardiac enzymes such as creatine phosphokinase and troponin in the blood.

Necrosis is the term used when a group of cells die and cause further damage because of cellular disintegration. The process of cell death varies with the cause of the damage (Fig. 1.3):

- *Liquefaction necrosis* refers to the process by which dead cells liquefy under the influence of certain cell enzymes. This process occurs when brain tissue dies, or in certain bacterial infections in which a cavity or ulcer may develop in the infected area (Fig. 1.3B).
- *Coagulative necrosis* occurs when the cell proteins are altered or denatured (similar to the coagulation that occurs when cooking eggs), and the cells retain some form for a time after death. This process typically occurs in a myocardial infarction (heart attack) when a lack of oxygen causes cell death (Fig. 1.3A).
- *Fat necrosis* occurs when fatty tissue is broken down into fatty acids in the presence of infection or certain enzymes (Fig. 1.3C). These compounds may increase inflammation.
- *Caseous necrosis* is a form of coagulation necrosis in which a thick, yellowish, "cheesy" substance forms. Tuberculosis (TB) offers an interesting example of caseous necrosis (Fig. 1.4). When TB develops, the first

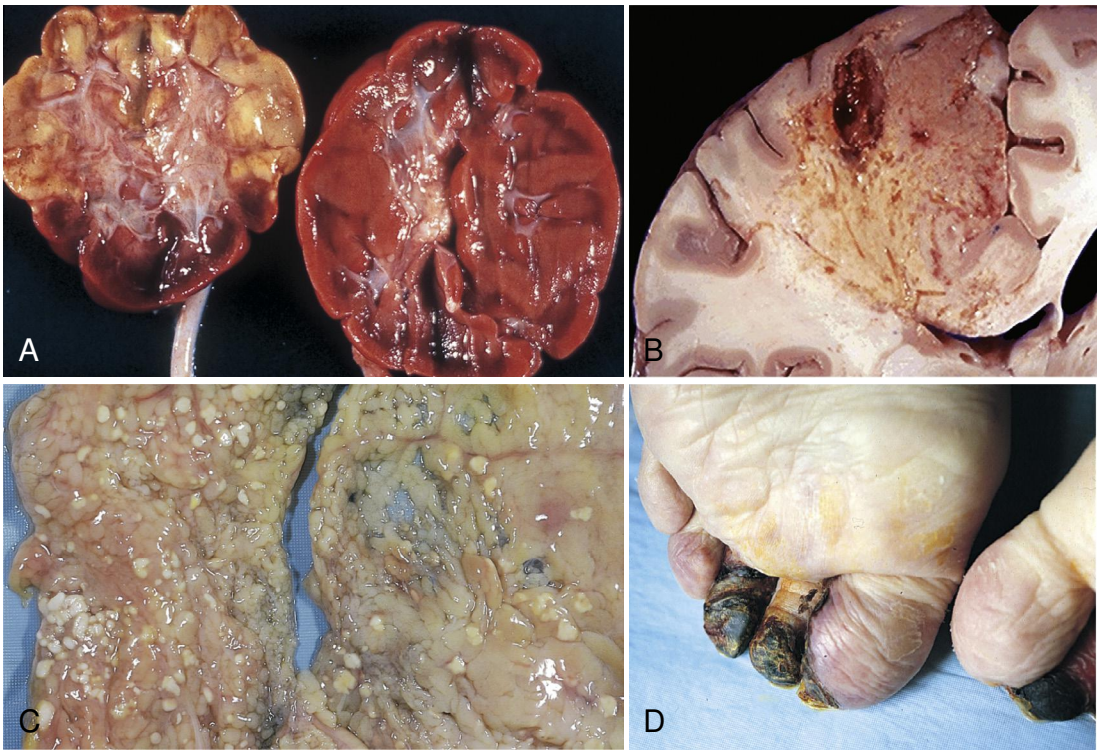


Fig. 1.3 **A,** Coagulative necrosis of the kidney caused by ischemia. The necrotic area is pale yellow, in contrast to the normal reddish-brown tissue. **B,** Liquefactive necrosis (darkened area) as a result of brain infarction. **C,** Fat necrosis in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown. **D,** Dry gangrene of the toe. (**A, D** *From Damjanov I:* Pathology for the Health Professions, *ed 3, Philadelphia, 2006, WB Saunders.* **B** *From Cotran RS, et al:* Robbins Pathologic Basis of Disease, *ed 6, Philadelphia, 1999, WB Saunders.* **C** *From Kumar V, Abbas AK, Fausto M:* Robbins and Cotran Pathologic Basis of Disease, *ed 7, Philadelphia, 2005, WB Saunders.)*

stage is characterized by development of a granuloma, a small solid mass of macrophages and lymphocytes, often covered by connective tissue, which forms in some types of chronic inflammation (see Chapter 5). With TB, caseous necrosis can be seen inside this mass. The granuloma associated with TB is called a Ghon focus or complex, and it usually heals like a scar, containing the infection. If the infection continues to develop, this area may undergo liquefaction necrosis, forming a cavity. (See Chapter 13 for more details on TB.)

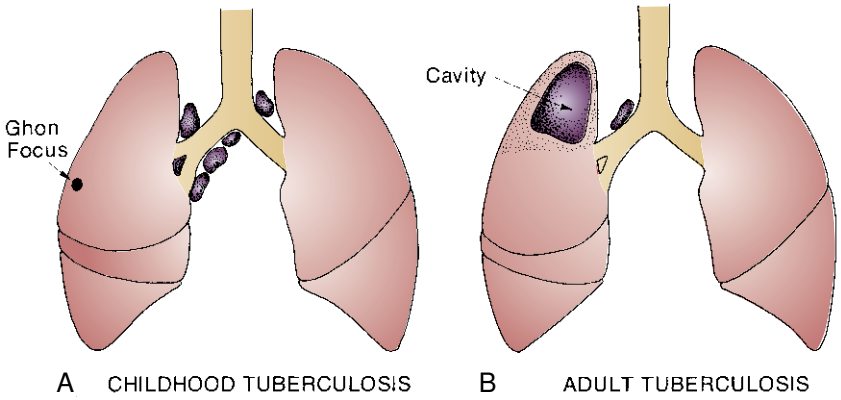
- *Infarction* is the term applied to an area of dead cells resulting from lack of oxygen (see Fig. 12.15). When a large number of cells in an area die, the functional loss can be significant. For example, when part of the heart muscle is infarcted or dies, that area can no longer contract to pump blood (see Chapter 12). After tissue dies, it is eventually replaced either by tissue regenerated from nearby similar cells or connective tissue or scar tissue that fills the gap. Myocardial or heart muscle cells do not undergo mitosis; therefore, scar tissue must replace the dead tissue.

Gangrene refers to an area of necrotic tissue, usually associated with a lack or loss of blood supply that is followed by invasion of bacteria (Fig. 1.3D). Necrotic tissue can provide a good medium for infection by microorganisms. Such an infection frequently occurs after an infarction in the intestines or in a limb in which blood supply is deficient and bacteria are normally present. Depending on its location, gangrene may be described as wet or dry. Dry gangrene is often caused by coagulative necrosis, in which the tissue dries, shrinks, and blackens. Wet gangrene is a result of liquefaction causing the tissue to become cold, swollen, and black. Gas

THINK ABOUT 1.5

Describe the different types of necrosis and identify conditions in which amputation may be necessary.

Specific types of cells die at different rates. *Brain* cells die quickly (4–5 minutes) when deprived of oxygen, whereas *heart muscle* can survive for approximately 30 minutes. Formerly, death of the body (*somatic death*) was assumed to occur when heart action and respiration ceased. Now, because cardiac and respiratory function can be maintained artificially, the diagnosis of death is more complex. Currently, *brain death* is the criterion for somatic death. A diagnosis of brain death is made following a set protocol of tests and examinations, including a lack of responses to stimuli, encephalography changes, and decreased perfusion in the brain (see Chapter 14).



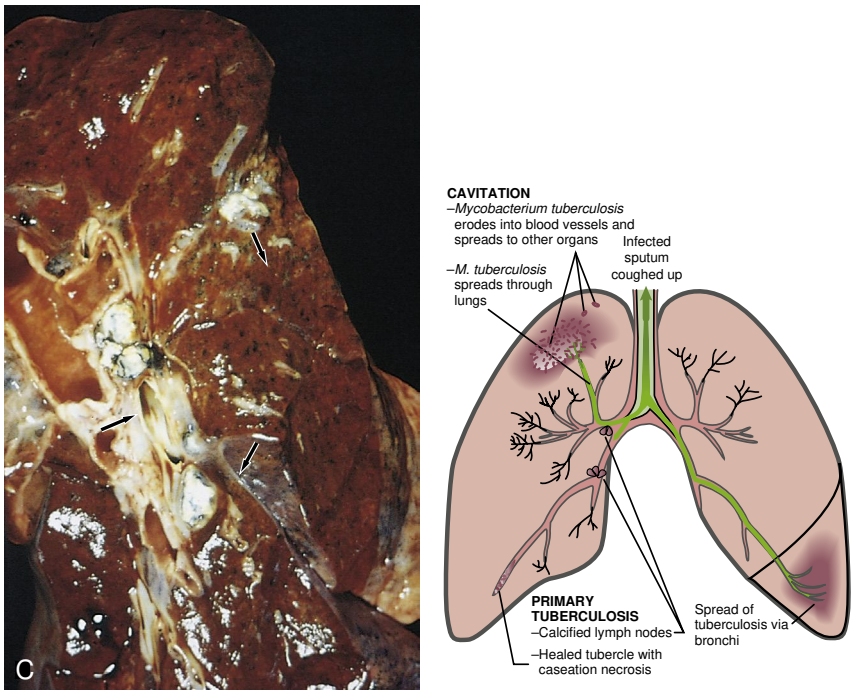


Fig. 1.4 **A, B,** Pulmonary tuberculosis. **C,** Tuberculosis in the upper lobe of the lung with areas of caseation and scar tissue (*arrows*). *(**A, B** Drawing by Margot Mackay, University of Toronto Faculty of Medicine, Department of Surgery, Division of Biomedical Communications, Toronto. Reprinted from Walter JB:* An Introduction to the Principles of Diseases, *ed 3, 1992, WB Saunders.* **C** *From Cotran RS, et al:* Robbins Pathologic Basis of Disease, *ed 6, Philadelphia, 1999, WB Saunders.)*

CASE STUDY A

Case Study 1.1

Ms. A, age 35 years, was given a Pap test during a routine medical checkup. The test showed marked dysplasia of cervical cells but no sign of infection.

1. Discuss the purposes and uses of diagnostic testing and how it applies in this scenario. (See Diagnostic Testing.)
2. Discuss how the following terms might apply to this scenario: *prognosis*, *latent stage*, *remission*, *exacerbations*, *predisposing factors*. (See Basic Terminology of Pathophysiology.)
3. Compare and contrast the various types of common cellular adaptations, focusing on dysplasia and the testing for this condition. (See Terms Used for Common Cellular Adaptations.)

gangrene is caused by the buildup of gases within tissue and further reduces blood supply. Gangrenous tissue frequently must be removed surgically (e.g., by amputation) to prevent the spread of infection to other parts of the body.

CHAPTER SUMMARY

- Disease is defined as a deviation from the individual's normal state of physical, mental, and social well-being, leading to a loss of homeostasis in the body. Pathophysiology is the study of the structural and functional changes related to disease processes.
- The effects of a specific disease depend on the organ or tissue affected and the cause of the disease (e.g., infection or malignant tumor).
- Disease prevention campaigns or screening programs for early diagnosis are based on factors such as causes, predisposing factors, and incidence of specific disease.
- Health professionals need to be aware of the new information, diagnostic tests, and therapies that are constantly emerging. The allocation of resources for health care and the ethical issues related to new technologies are concerns.
- The discussion of disease processes includes topics such as disease occurrence; diagnosis, or the

identification of a disease; etiology, or the cause of disease; pathologic changes in the tissues or organs, or signs and symptoms of disease; and prognosis, or the probable outcomes.
- Cell and tissue changes such as atrophy and hypertrophy are frequently linked to changes in demand or use of the tissue. Metaplasia often occurs as an adaptive change, replacing the normal cell with a more resistant cell. Dysplasia and anaplasia are connected to malignant changes.
- Cell damage for any reason may be reversible, causing temporary loss of function. Severe damage to a cell causes necrosis and loss of function.
- Causes of cell damage include ischemia or lack of oxygen, toxic substances, changes in pH, or microorganisms such as bacteria and viruses.

STUDY QUESTIONS

1. Choose a specific disease, prepare an appropriate list of six terms that you could use to describe this disease, and define each of the terms.
2. Define and give an example of the following:
   a. etiology
   b. incidence
   c. precipitating factor
   d. complication
   e. prognosis
   f. iatrogenic
   g. sequelae
3. Differentiate between the terms *metaplasia* and *malignant neoplasm*.
4. Describe the changes in a cell that lead to the following:
   a. loss of function
   b. necrosis
5. Define the following terms:
   a. apoptosis
   b. gangrene
6. What preventive practices can be used to reduce disease?
7. CJ is having surgery next week to remove a malignant breast tumor, following discovery of a lump in the breast and a biopsy. Her mother and aunt have had breast cancer. CJ is taking medication for high blood pressure.

   Match the significant information in the preceding description to the appropriate term: diagnosis, medical history, etiology, prognosis, benign neoplasm, iatrogenic, signs, complication, treatment, cancer, and examination of living tissue. Some terms may not be used or may be used more than once.

CHAPTER 2

Fluid, Electrolyte, and Acid-Base Imbalances

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, the student is expected to:

1. Explain the movement of water between body compartments that results in edema.
2. Describe the causes and effects of dehydration.
3. Explain the meaning of third-spacing.
4. Discuss the causes and signs of hyponatremia and hypernatremia.
5. Explain the causes and signs of hypokalemia and hyperkalemia.
6. Describe the causes and signs of hypocalcemia and hypercalcemia.
7. Describe the causes and effects of hypomagnesemia, hypophosphatemia, hypochloremia, and hyperchloremia.
8. Explain how metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis develop and their effects on the body.
9. Explain how decompensation develops and its effects on the central nervous system.
10. Explain the normal function of atrial natriuretic peptide in maintaining fluid and electrolyte balance.

KEY TERMS

aldosterone
anion
anorexia
antidiuretic hormone
ascites
atrial natriuretic peptide
capillary permeability
carpopedal spasm
cation
diffusion
diuretic
dysrhythmia
edema
electrocardiogram
extracellular
filtration
hydrogen ions
hydrostatic pressure
hypertonic/hyperosmolar
hypervolemia
hypomagnesemia
hypothalamus
hypotonic/hypoosmolar
hypovolemia
interstitial fluid
intracellular
intravascular fluid
isotonic/isoosmolar
laryngospasm
milliequivalent
nonvolatile metabolic acids
osmoreceptor
osmosis
osmotic pressure
paresthesias
skin turgor
tetany
transcellular

Fluid Imbalance

Review of Concepts and Processes

Water is a major component of the body and is found both within and outside the cells. It is essential to homeostasis, which is the maintenance of a relatively constant and favorable environment for the cells. Water is the medium within which metabolic reactions and other processes take place. It also constitutes the transportation system for the body. For example, water carries nutrients into cells and removes wastes, transports enzymes in digestive secretions, and moves blood cells around the body. Without adequate fluid, cells cannot continue to function, and death results. Fluid also facilitates the movement of body parts—for example, the joints and the lungs.

THINK ABOUT 2.1

Suggest several functions performed by water in the body and the significance of each.

Fluid Compartments

Although the body appears to be a solid object, approximately 60% of an adult's body weight consists of water, and an infant's body is about 70% water (Table 2.1). Female bodies, which contain a higher proportion of fatty tissue, have a lower percentage of water than male bodies. The elderly and the obese also have a lower proportion of water in their bodies. Individuals with less fluid reserve are more likely to be adversely affected by any fluid or electrolyte imbalance.

Fluid is divided between the **intracellular** fluid, or fluid inside the cells, and the **extracellular** compartment fluid (ECF), or fluid outside the cells. See Ready Reference 1 for a diagram showing fluid compartments of the body.

TABLE 2.1 Fluid Compartments in the Body

	Volume	Approximate Percentage of Body Weight		
	Adult Male (L)	Male (%)	Female (%)	Infant (%)
Intracellular fluid	28	40	33	40
Extracellular fluid	15	20	17	30
Plasma	(4.5)	(4)	(4)	(4)
Interstitial fluid	(10.5)	(15)	(9)	(25)
Other		(1)	(1)	(1)
Total water	43	60	50	70

Note: In elderly women, water content is reduced to approximately 45% of body weight.

ECF includes the following:

- **Intravascular fluid**, or blood
- **Interstitial fluid** (ISF), or intercellular fluid
- Cerebrospinal fluid (CSF)
- **Transcellular** fluids present in various secretions, such as those in the pericardial (heart) cavity or the synovial cavities of the joints

In an adult male, blood constitutes about 4% of body weight, and interstitial fluid about 15%; the remaining transcellular fluids amount to about 1% of total body weight. Water constantly circulates within the body and moves between various compartments. For example, CSF forms continuously from the blood and is reabsorbed back into the general circulation. A large volume of water (up to 8 L in 24 hours) is present in the digestive secretions entering the stomach and small intestine, and this fluid is reabsorbed in the colon, making up a very efficient *water-recycling* system.

THINK ABOUT 2.2

a. Which body compartment contains the most water?
b. Suggest why diarrhea may cause a fluid deficit more rapidly than coughing and sneezing with a cold.

Movement of Water

To maintain a constant level of body fluid, the amount of water entering the body should equal the amount of water leaving the body. Fluid is added to the body through the ingestion of solid food and fluids and as a product of cell metabolism (Table 2.2). Fluid is lost in the urine and feces, as well as through *insensible* (unapparent) losses through the skin (perspiration) and exhaled air.

The balance of water and electrolytes is maintained by the following:

- The *thirst* mechanism in the **hypothalamus**, the **osmoreceptor** cells of which sense the internal environment, both fluid volume and concentration, and then promote the intake of fluid when needed.
- **Antidiuretic hormone** (ADH), which controls the amount of fluid leaving the body in the urine (see Chapters 16 and 18); ADH promotes reabsorption of water into the blood from the kidney tubules.

TABLE 2.2 Sources and Losses of Water

Sources (mL)		Losses (mL)	
Liquids	1200	Urine	1400
Solid foods	1000	Feces	200
Cell metabolism	300	Insensible losses	
		Lungs	400
		Skin	500
Total	2500		2500

- The hormone **aldosterone** determines the reabsorption of both sodium ions and water from the kidney tubules; these hormones conserve more fluid when there is a fluid deficit in the body.
- The natriuretic peptide hormones: **atrial natriuretic peptide** (ANP) and **B-type natriuretic peptide** (BNP). These hormones, which are released by the cardiac muscle fibers in response to increased pressure within the cardiac chambers, stimulate the elimination of water and sodium in the urine to prevent salt-induced hypertension.

The ANP hormone is synthesized and released by the myocardial cells in the atrium of the heart. Its role in homeostasis relates to reduction of workload on the heart by regulating fluid, sodium, and potassium levels. In the kidney, ANP increases the glomerular filtration rate by altering pressure in the glomerular capillaries; it also reduces the reabsorption of sodium in the distal convoluted tubules through inhibition of ADH. Renin secretion is also reduced, and thus the renin-angiotensin system is inhibited. The result is fluid loss from the extracellular compartment and lowered blood pressure. Aldosterone secretion is also reduced, leading to retention of potassium. Research has shown that ANP is elevated in patients with congestive heart failure who have increased blood volume in the atria (see Chapter 12). Research on this peptide and its possible use in the treatment of hypertension and congestive heart failure is ongoing.

THINK ABOUT 2.3

a. Describe how excessive fluid is lost from the body during strenuous exercise on a very hot day. Explain how the body can respond to this fluid loss to maintain homeostasis.
b. What factors may limit such responses?

Fluid constantly circulates throughout the body and moves relatively freely, depending on the permeability of the membranes between compartments, by the processes of **filtration** or **osmosis** (Fig. 2.1). Water moves between the vascular compartment or blood and the interstitial compartment through the semipermeable capillary membranes, depending on the relative **hydrostatic** and **osmotic pressures** within the compartments (see Fig. 2.1). Proteins and electrolytes contribute to the osmotic pressure of a fluid, and therefore are very important in maintaining fluid volumes in various compartments. Hydrostatic pressure may be viewed as the "push" force, and osmotic pressure as the "pull" or attraction force in such fluid movements. Changes in either force will alter fluid movement and volume in the compartments.

At the arteriolar end of the capillary, the blood hydrostatic pressure (or blood pressure) exceeds the opposing interstitial hydrostatic pressure and the plasma colloid osmotic pressure of the blood, and therefore fluid moves out from (or is "pushed" out of) the capillary into the interstitial compartment. At the venous end of the capillary, the blood hydrostatic pressure is greatly decreased, and the osmotic pressure is higher, therefore fluid tends to shift (or is "pulled") back into the capillary. It is easier to remember the direction of movement if one thinks of the movement of nutrients and oxygen out of the arterial blood toward the cells and the flow of wastes and carbon dioxide from the cell back into the venous blood. Excess fluid and any protein in the interstitial compartment are returned to the circulation through the lymphatic capillaries.

APPLY YOUR KNOWLEDGE 2.1

Predict three changes that could alter normal movement of fluid in the body.

Many cells have mechanisms to control intracellular volume. A major factor in the movement of water through cell membranes is the difference in osmotic pressure between the cell and the interstitial fluids. As the relative concentrations of electrolytes in the interstitial fluid and intracellular fluid change, the osmotic pressure also changes, causing water to move across the cell membrane by osmosis. For example, if an erythrocyte is placed in a dilute hypotonic solution (low osmotic pressure), water may enter the cell, causing it to swell and malfunction.

THINK ABOUT 2.4

a. Explain how a very high hydrostatic pressure in the venous end of a capillary affects fluid shift.
b. Explain how a loss of plasma protein affects fluid shift at the capillaries.
c. Explain how a high concentration of sodium ions in the interstitial fluid affects intracellular fluid levels.

Fluid Excess: Edema

Fluid excess occurs in the extracellular compartment and may be referred to as **isotonic/isoosmolar**, **hypotonic/hypoosmolar**, or **hypertonic/hyperosmolar**, depending on the cause. The osmolarity or the concentration of

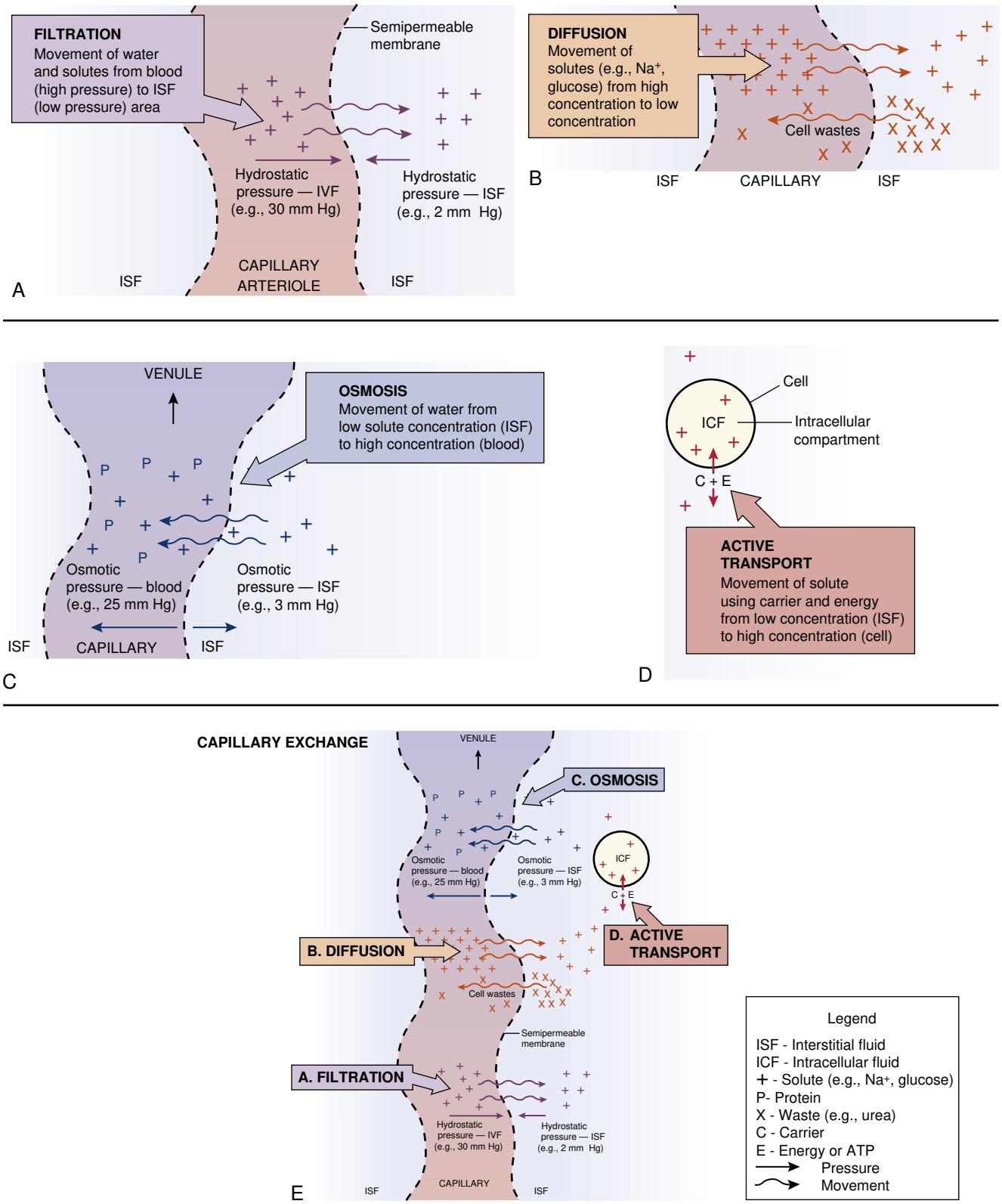


Fig. 2.1 Movement of water and electrolytes between compartments.

solute in the fluid affects fluid shifts between compartments, including the cells.

Edema refers to an excessive amount of fluid in the interstitial compartment, which causes a swelling or enlargement of the tissues. Edema may be localized in one area or generalized throughout the body. Depending on the type of tissue and the area of the body, edema may be highly visible or relatively invisible, or it may not accurately reflect the amount of fluid hidden in the area; for example, facial edema is usually visible, but edema

of the liver or a limb may not be. Edema is usually more severe in *dependent* areas of the body, where the force of gravity is greatest, such as the buttocks, ankles, or feet of a person in a wheelchair. Prolonged edema interferes with venous return, arterial circulation, and cell function in the affected area.

Causes of Edema

Edema has four general causes (Fig. 2.2):

1. The first cause is *increased capillary hydrostatic pressure* (equivalent to higher blood pressure), which prevents the return of fluid from the interstitial compartment to the venous end of the capillary or forces excessive

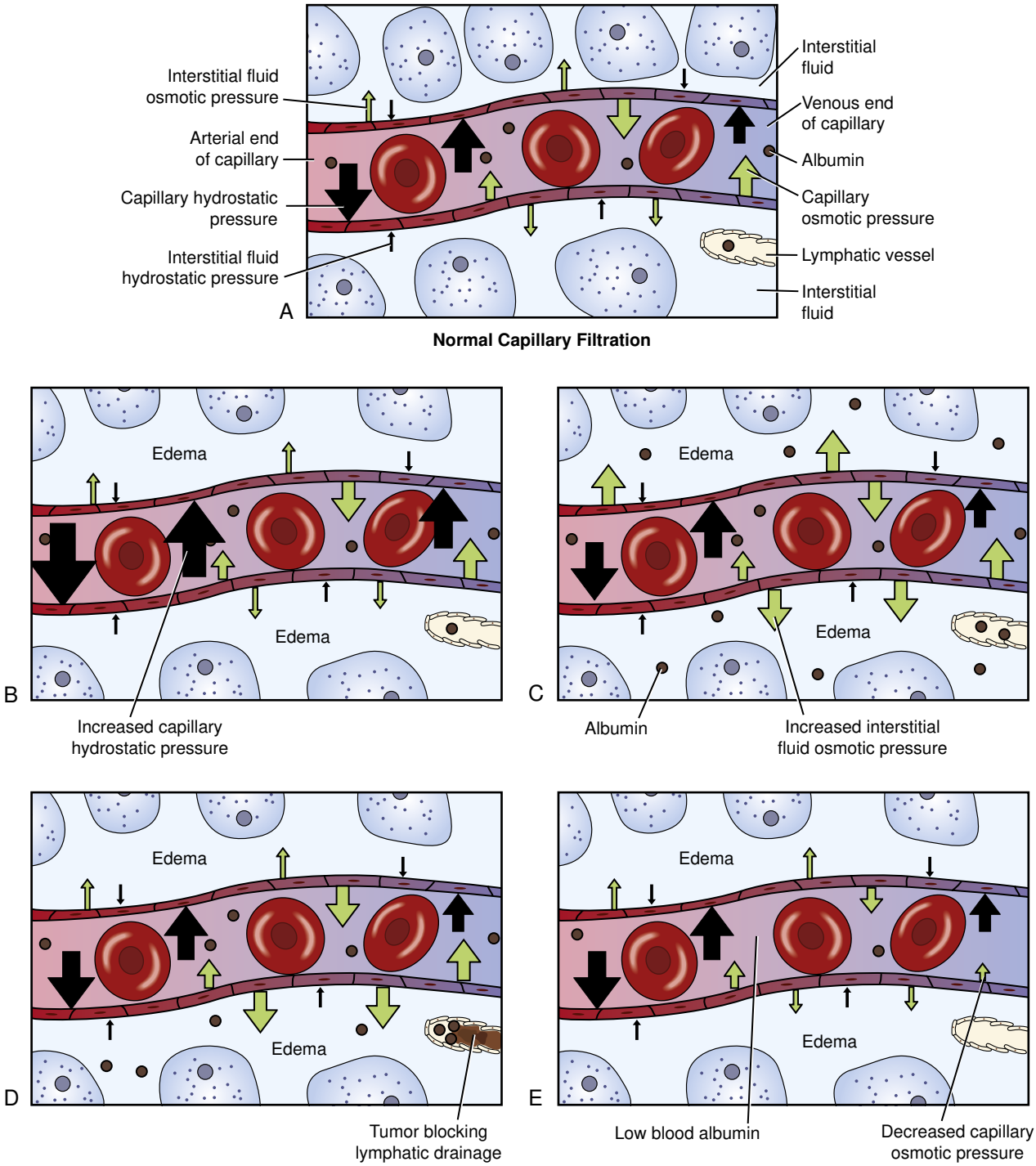


Fig. 2.2 Causes of edema. **A,** Normal capillary filtration without edema. **B,** Edema owing to increased capillary hydrostatic pressure. **C,** Edema caused by increased interstitial fluid osmotic pressure from increased capillary permeability. **D,** Edema resulting from blocked lymphatic drainage. **E,** Edema attributed to decreased capillary osmotic pressure from hypoalbuminemia. *(From Copstead-Kirkorn LC:* Pathophysiology, *ed 4, St. Louis, 2009, Saunders, Elsevier.)*

amounts of fluid out of the capillaries into the tissues. The latter is a cause of pulmonary edema, in which excessive pressure, often caused by increased blood volume, can force fluid into the alveoli, interfering with respiratory function.

Specific causes of edema related to increased hydrostatic pressure include increased blood volume (**hypervolemia**) associated with kidney failure, pregnancy, congestive heart failure, or administration of excessive fluids. In pregnancy, the enlarged uterus compresses the pelvic veins in the seated position, and when a pregnant woman must stand still for long periods of time, the pressure in the leg veins can become quite elevated, causing edema in the feet and legs. In some people with congestive heart failure, the blood cannot return easily through the veins to the heart, raising the hydrostatic pressure in the legs and abdominal organs and causing **ascites**, or fluid in the abdominal cavity.

2. Second, edema may be related to the *loss of plasma proteins*, particularly albumin, which results in a decrease in plasma osmotic pressure. Plasma proteins usually remain inside the capillary and seldom move through the semipermeable capillary membrane. The presence of fewer plasma proteins in the capillary allows more fluid to leave the capillary and less fluid to return to the venous end of the capillary.

   Protein may be lost in the urine through kidney disease, or synthesis of protein may be impaired in patients with malnutrition and malabsorption diseases or with liver disease. Protein levels may drop acutely in burn patients who have large areas of burned skin; the subsequent inflammation and loss of the skin barrier allow protein to easily leak out of the body.

   Frequently, *excessive sodium levels* in the extracellular fluid accompany the two causes just mentioned. When sodium ions are retained, they promote accumulation of fluid in the interstitial compartment by increasing the ISF osmotic pressure and decreasing the return of fluid to the blood. Blood volume and blood pressure are usually elevated as well. High sodium levels are common in patients with heart failure, high blood pressure, kidney disease, and increased aldosterone secretion.
3. Edema may result from *obstruction of the lymphatic circulation*. Such an obstruction usually causes a localized edema because excessive fluid and protein are not returned to the general circulation. This situation may develop if a tumor or infection damages a lymph node, or if lymph nodes are removed, as they may be in cancer surgery.
4. The fourth cause of edema is *increased* **capillary permeability**. This usually causes localized edema, and may result from an inflammatory response or infection (see Chapter 5). In this case, histamine and other chemical mediators released from cells following tissue injury cause increased capillary permeability and increased fluid movement into the interstitial area. Protein also leaks into the interstitial compartment, increasing the osmotic pressure in ISF and thus holding more fluid in the interstitial area. A general increase in capillary permeability can result from some bacterial toxins or large burn wounds, leading to both hypovolemia and shock.

THINK ABOUT 2.5

a. In some cases of breast cancer, many of the axillary lymph nodes are removed. Why are injections not usually done on the affected arm?
b. Explain why severe kidney disease may cause generalized edema.
c. Explain why the feet may become swollen when one sits for long periods of time, but the swelling decreases when one lies recumbent in bed.
d. Explain how protein-calorie malnutrition results in ascites.

Effects of Edema

- A local area of swelling may be visible and may be pale or red in color, depending on the cause (Table 2.3).
- *Pitting edema* occurs in the presence of excess interstitial fluid, which moves aside when firm pressure is applied by the fingers. A depression or "pit" remains after the finger is removed.

TABLE 2.3 Comparison of Signs and Symptoms of Fluid Excess (Edema) and Fluid Deficit (Dehydration)

Fluid Excess (Edema)	Fluid Deficit (Dehydration)
Localized swelling (feet, hands, periorbital area, ascites)	Sunken, soft eyes
Pale, gray, or red skin color	Decreased skin turgor, dry mucous membranes
Weight gain	Thirst, weight loss
Slow, bounding pulse, high blood pressure	Rapid, weak, thready pulse, low blood pressure, and orthostatic hypotension
Lethargy, possible seizures	Fatigue, weakness, dizziness, possible stupor
Pulmonary congestion, cough, rales	Increased body temperature
Laboratory values: Decreased hematocrit Decreased serum sodium Urine: low specific gravity, high volume	Laboratory values: Increased hematocrit Increased electrolytes (or variable) Urine: high specific gravity, low volume

Note: Signs may vary depending on the cause of the imbalance.

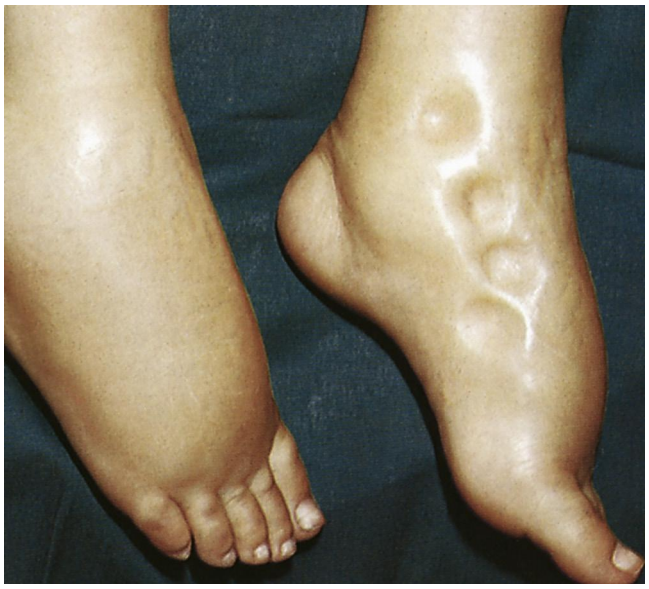


Fig. 2.3 Pitting edema. Note the finger-shaped depressions that do not rapidly refill after an examiner has exerted pressure. *(From Bloom A, Ireland J:* Color Atlas of Diabetes, *ed 2, St. Louis, 1992, Mosby.)*

- In people with generalized edema there is a significant increase in *body weight*, which may indicate a problem before there are other visible signs (Fig. 2.3).
- *Functional* impairment caused by edema may occur, for example, when it restricts range of movement of joints. Edema of the intestinal wall may interfere with digestion and absorption. Edema or accumulated fluid around the heart or lungs impairs the movement and function of these organs.
- *Pain* may occur if edema exerts pressure on the nerves locally, as with the headache that develops in patients with cerebral edema. If cerebral edema becomes severe, the pressure can impair brain function because of ischemia and can cause death. When viscera such as the kidney or liver are edematous, the capsule is stretched, causing pain.
- With sustained edema, the *arterial circulation* may be impaired. The increased interstitial pressure may restrict arterial blood flow into the area, preventing the fluid shift that carries nutrients into the cells. This can prevent normal cell function and reproduction and eventually results in tissue necrosis or the development of ulcers. This situation is evident in individuals with severe varicose veins in the legs—large, dilated veins that have a high hydrostatic pressure. Varicose veins can lead to fatigue, skin breakdown, and varicose ulcers (see Chapter 12). These ulcers do not heal easily because of the continued insufficient blood supply.
- In dental practice, it is difficult to take accurate impressions when the tissues are swollen; dentures do not fit well, and sores may develop that often are slow to heal and become infected because the blood flow is impaired to the gingival tissues.
- Edematous tissue in the skin is susceptible to tissue breakdown from pressure, abrasion, and external chemicals. Proper skin care is essential to prevent ulceration, particularly in an immobilized patient (see Chapter 25).

THINK ABOUT 2.6

a. List three signs of local edema in the knee.
b. Explain why persistent edema in a leg could cause weakness and skin breakdown.

Fluid Deficit: Dehydration

Dehydration refers to insufficient body fluid resulting from inadequate intake or excessive loss of fluids, or a combination of the two. Losses are more common and affect the extracellular compartment first. Water can shift within the extracellular compartments. For example, if fluid is lost from the digestive tract because of vomiting, water shifts from the vascular compartment into the digestive tract to replace the lost secretions. If the deficit continues, eventually fluid is lost from the cells, impairing cell function.

Fluid loss is often measured by a change in body weight; knowing the usual body weight of a person is helpful for assessing the extent of loss. As a general guide to extracellular fluid loss, a *mild* deficit is defined as a decrease of 2% in body weight, a *moderate* deficit as a 5% weight loss, and *severe* dehydration is a decrease of 8%. This figure should be adjusted for the individual's age, body size, and condition.

Dehydration is a more serious problem for infants and elderly people, who lack significant fluid reserves as well as the ability to conserve fluid quickly. Infants also experience not only greater insensible water losses through their proportionately larger body surface area but also an increased need for water, owing to their higher metabolic rate. The vascular compartment is rapidly depleted in an infant (**hypovolemia**), affecting the heart, brain, and kidneys. This is indicated by decreased urine output (number of wet diapers), increased lethargy, and dry mucosal membranes.

Water loss is often accompanied by a loss of electrolytes, and sometimes of proteins, depending on the specific cause of the loss. For example, sweating results in a loss of water and sodium chloride. Electrolyte losses can influence water balance significantly because electrolyte changes lead to osmotic pressure change between compartments. To restore balance, electrolytes, as well as fluid, must be replaced. Isotonic dehydration refers to a proportionate loss of fluid and electrolytes, hypotonic dehydration refers to a loss of more electrolytes than water, and hypertonic dehydration refers to a loss of more fluid than electrolytes. The latter two types of dehydration cause signs of electrolyte imbalance and influence the movement of water between the

intracellular and extracellular compartments (see Electrolyte Imbalances).

THINK ABOUT 2.7

a. Explain why an infant is more vulnerable than a young adult to fluid loss.
b. If more sodium is lost from the extracellular fluid compartment than water, how will fluid move between the cell and the interstitial fluid compartment? Explain the result.

Causes of Dehydration

Common causes of dehydration include the following:

- Vomiting and diarrhea, both of which result in loss of numerous electrolytes and nutrients, such as glucose, as well as water; drainage or suction of any portion of the digestive system can also result in deficits
- Excessive sweating with loss of sodium and water
- Diabetic ketoacidosis with loss of fluid, electrolytes, and glucose in the urine
- Insufficient water intake in an elderly or unconscious person
- Use of a concentrated formula in an attempt to provide more nutrition to an infant

Effects of Dehydration

Initially, dehydration involves a decrease in interstitial and intravascular fluids. These losses may produce *direct* effects such as the following:

- Dry mucous membranes in the mouth (see Table 2.3)
- Decreased **skin turgor** or elasticity (Fig. 2.4)
- Lower blood pressure, weak pulse, and a feeling of fatigue
- Increased hematocrit, indicating a higher proportion of red blood cells compared with water in the blood
- Decreasing mental function, confusion, and loss of consciousness, which develop as brain cells lose water and reduce function

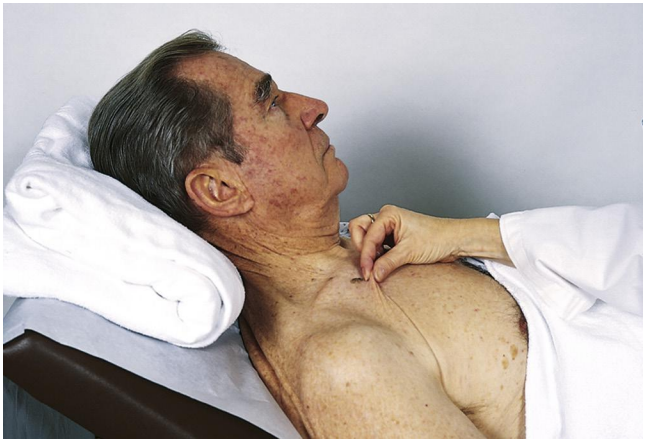


Fig. 2.4 Poor turgor is evident in severe dehydration. *(From Jarvis J:* Physical Examination and Health Assessment, *ed 7, St. Louis, 2016, Elsevier.)*

The body attempts to *compensate* for the fluid loss by doing the following:

- Increasing thirst
- Increasing the heart rate
- Constricting the cutaneous blood vessels, leading to pale and cool skin
- Producing less urine and concentrating the urine, increasing the specific gravity, as a result of renal vasoconstriction and increased secretion of ADH and aldosterone

THINK ABOUT 2.8

Describe three signs or symptoms of dehydration that are direct effects, and describe three signs that indicate the compensation that is occurring in response to dehydration.

Third-Spacing: Fluid Deficit and Fluid Excess

Third-spacing refers to a situation in which fluid shifts out of the blood into a body cavity or tissue where it is no longer available as *circulating fluid*. Examples include peritonitis, or inflammation and infection of the peritoneal membranes, and burns. The result of this shift is a fluid deficit in the vascular compartment (hypovolemia) and a fluid excess in the interstitial space. Until the basic cause is removed, fluid remains in the "third space"—in the body, but not as a functional part of the circulating fluids. Simply weighing the patient will not reflect this shift in fluid distribution. Laboratory tests such as hematocrit and electrolyte concentrations will be necessary to identify third-spacing. In the case of burns, third-spacing is evident as edema in the area of the wounds.

THINK ABOUT 2.9

Based on the information given previously on fluid excess and fluid deficit, describe three signs and symptoms of third-spacing related to a large burn area.

Electrolyte Imbalances

Sodium Imbalance

Review of Sodium

Sodium is the primary **cation** (positively charged ion) in the extracellular fluid (Table 2.4). **Diffusion** of sodium occurs between the vascular and interstitial fluids. Sodium transport across the cell membrane is controlled by the sodium-potassium pump, or active transport, resulting in sodium levels that are high in extracellular fluids and low inside the cell. Sodium is actively secreted into mucus and other body secretions. It exists in the body primarily in the form of the salts sodium chloride and sodium bicarbonate. It is ingested in food and beverages, usually in more than adequate amounts, and is lost from the body in perspiration, urine, and feces. Sodium

TABLE 2.4 Distribution of Major Electrolytes

Ions	Intracellular (mEq/L)	Blood (mEq/L)
Cations		
Sodium (Na^+)	10	142
Potassium (K^+)	160	4
Calcium (Ca^{++})	Variable	5
Magnesium (Mg^+)	35	3
Anions		
Bicarbonate (HCO_3^-)	8	27
Chloride (Cl^-)	2	103
Phosphate (HPO_4^-)	140	2

Note: There are variations in "normal" values among individuals.
The concentration of electrolytes in the plasma varies slightly from that in the interstitial fluid or other types of extracellular fluids.
The number of anions, including those present in small quantities, is equivalent to the concentration of cations in the intracellular compartment (or the plasma) so as to maintain electrical neutrality (equal negative and positive charges) in any compartment.

levels in the body are primarily controlled by the kidneys through the action of aldosterone.

Sodium is important for the maintenance of extracellular fluid volume through its effect on osmotic pressure because it makes up approximately 90% of the solute in extracellular fluid. Sodium also is essential in the conduction of nerve impulses (Fig. 2.5) and in muscle contraction.

It is important to note the relative changes of electrolytes and fluids associated with the individual's specific problem to put the actual serum value in perspective. For example, excessive sweating may result in a low serum sodium level if proportionately more sodium is lost than water, or if only water is used to replace the loss. If an individual loses more water than sodium in perspiration, the serum sodium level may be high.

Hyponatremia

Normal blood sodium levels are presented on the inside back cover of this book. Hyponatremia refers to a serum sodium concentration below 3.8 to 5 mmol/Lor 135 **milliequivalents** (mEq)/L.

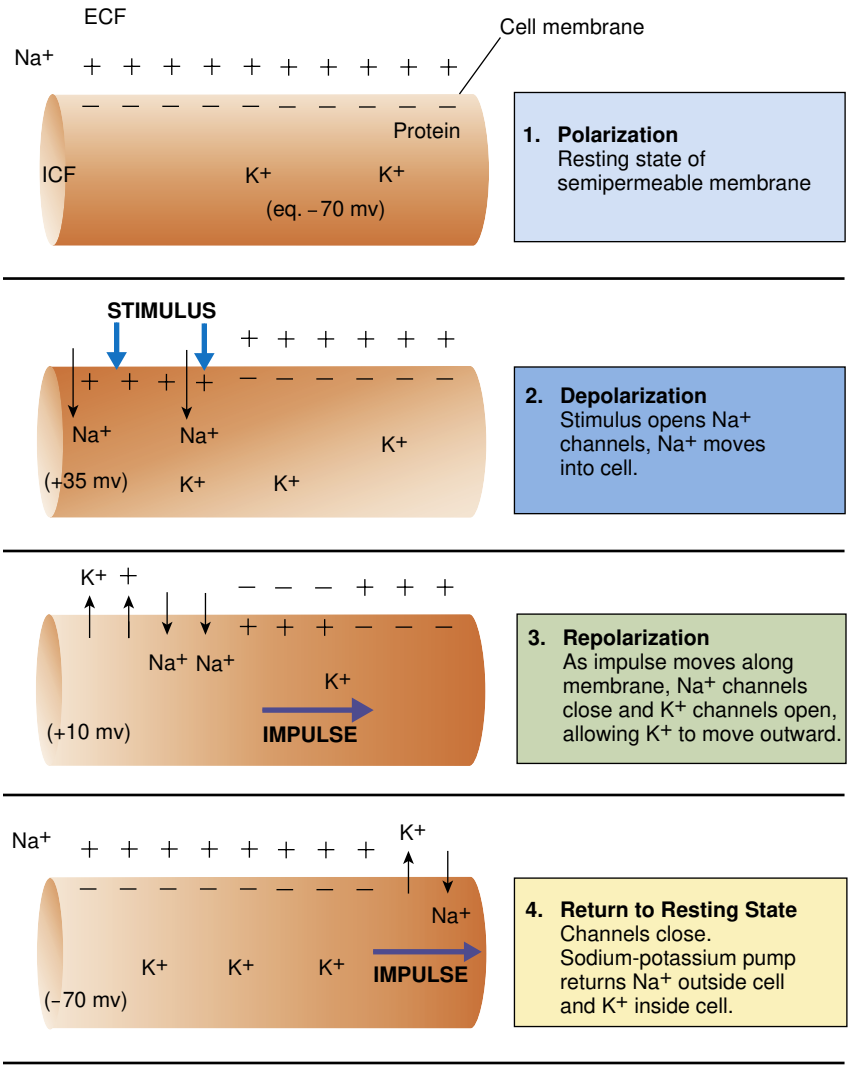


Fig. 2.5 Role of sodium and potassium ions in the conduction of an impulse. *ECF*, Extracellular compartment fluid; *Na^+*, sodium; *K^+*, potassium.

Causes of Hyponatremia

A sodium deficit can result from direct loss of sodium from the body or from an excess of water in the extracellular compartment, resulting in dilution of sodium. Common causes of low serum sodium levels include the following:

1. Losses from excessive sweating, vomiting, and diarrhea
2. Use of certain **diuretic** drugs combined with low-salt diets
3. Hormonal imbalances such as insufficient aldosterone, adrenal insufficiency, and excess ADH secretion (syndrome of inappropriate antidiuretic hormone secretion)
4. Early chronic renal failure
5. Excessive water intake

THINK ABOUT 2.10

a. A high fever is likely to cause deep, rapid respirations, excessive perspiration, and a higher metabolic rate. How would this affect the fluid and electrolyte balance in the body?
b. List several reasons why drinking a fluid containing water, glucose, and electrolytes would be better than drinking tap water after vomiting.

TABLE 2.5 Signs of Sodium Imbalance

Hyponatremia	Hypernatremia
Anorexia, nausea, cramps	Thirst; tongue and mucosa are dry and sticky
Fatigue, lethargy, muscle weakness	Weakness, lethargy, agitation
Headache, confusion, seizures	Edema
Decreased blood pressure	Elevated blood pressure

Effects of Hyponatremia

- Low sodium levels impair nerve conduction and result in fluid imbalances between the compartments. Manifestations include fatigue, muscle cramps, and abdominal discomfort or cramps with nausea and vomiting (Table 2.5).
- Decreased osmotic pressure in the extracellular compartment may cause a fluid shift into cells, resulting in hypovolemia and decreased blood pressure (Fig. 2.6).
- The brain cells may swell, causing confusion, headache, weakness, or seizures.

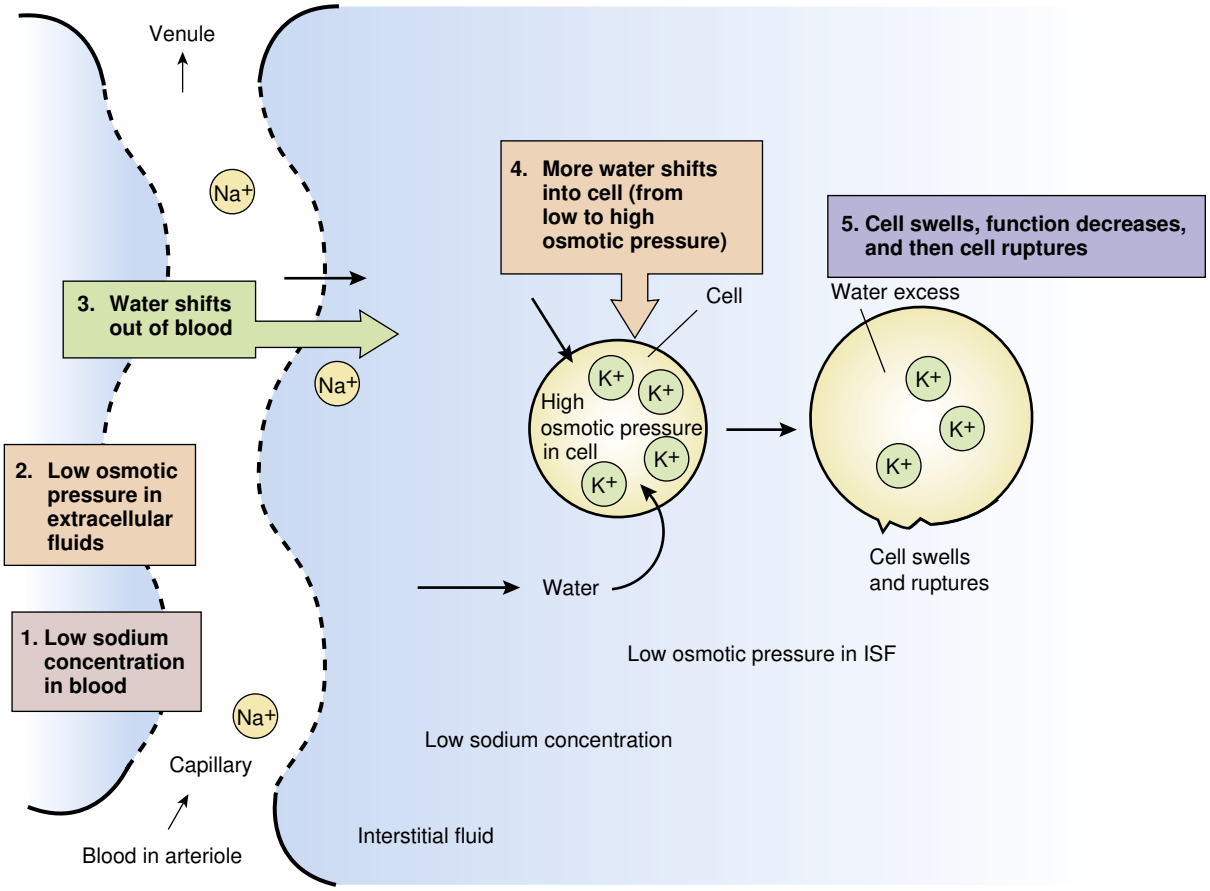


Fig. 2.6 Hyponatremia and fluid shift into cells. Na^+, Sodium; K^+, potassium.

Hypernatremia

Hypernatremia is an excessive sodium level in the blood and extracellular fluids (>145 mEq/L).

Causes of Hypernatremia

Excess sodium results from ingestion of large amounts of sodium without proportionate water intake, or from a loss of water from the body that is faster than the loss of sodium.

Specific causes include the following:

1. Insufficient ADH, which results in a large volume of dilute urine (diabetes insipidus)
2. Loss of the thirst mechanism
3. Watery diarrhea
4. Prolonged periods of rapid respiration

THINK ABOUT 2.11

Hypernatremia accompanied by an elevated hematocrit value indicates what fact about body fluids?

Effects of Hypernatremia

The major effect of hypernatremia is a fluid shift out of the cells owing to the increased osmotic pressure of interstitial or extracellular fluid; this effect is manifested by the following:

- Weakness, agitation
- Firm subcutaneous tissues (see Table 2.5)
- Increased thirst, with dry, rough mucous membranes
- Decreased urine output, because ADH is secreted

Note that the manifestations can change depending on the cause of the problem. If the cause of hypernatremia is fluid loss caused by lack of ADH, urine output is high.

THINK ABOUT 2.12

a. Compare the effects of aldosterone with those of antidiuretic hormone on serum sodium levels.
b. List the signs and symptoms common to both hyponatremia and hypernatremia, and also any signs that differentiate the two states.
c. Explain how sodium imbalances affect cardiac function.

Potassium Imbalance

Review of Potassium

Potassium is a major intracellular cation, and therefore its serum levels are very low (3.5–5 mEq/L or 3.5–5 mmol/L) compared with the intracellular concentration, which is about 160 mEq/L (see Table 2.4). It is difficult to assess total body potassium by measuring the serum level. Potassium is ingested in foods and is excreted primarily in the urine under the influence of the hormone aldosterone. Foods high in potassium include bananas, citrus fruits, tomatoes, and lentils; potassium chloride tablets may be taken as a supplement. The hormone insulin also promotes movement of potassium into cells (see Chapter 16).

Potassium levels are also influenced by the *acid-base balance* in the body; acidosis tends to shift potassium ions out of the cells into the extracellular fluids, and alkalosis tends to move more potassium into the cells (Fig. 2.7). With acidosis, many **hydrogen ions** diffuse from the blood into the interstitial fluid because of the high hydrogen ion concentration in the blood. When these hydrogen ions move into the cell, they displace potassium out of the cell to maintain electrochemical neutrality. Then the excess potassium ions in the interstitial fluid diffuse into the blood, leading to hyperkalemia. The reverse process occurs with alkalosis. Acidosis also promotes hydrogen ion excretion by the kidneys and retention of potassium in the body. Potassium assists in the regulation of intracellular fluid volume and has a role in many metabolic processes in the cell. It is also important in nerve conduction and contraction of all muscle types, determining the membrane potential (see Fig. 2.5). Most important, abnormal potassium levels, both high and low, have a significant and serious effect on the contractions of cardiac muscle, causing changes in the **electrocardiogram** (ECG) and ultimately cardiac arrest or standstill.

Hypokalemia

In hypokalemia, the serum level of potassium is less than 2 mmol/L or 3.5 mEq/L.

Causes of Hypokalemia

Low serum potassium levels may result from the following:

1. Excessive losses from the body because of diarrhea
2. Diuresis associated with certain diuretic drugs; patients with heart disease who are being treated with certain diuretic drugs such as furosemide may have to increase their intake of potassium in food or take a potassium supplement, because hypokalemia may increase the toxicity of heart medications such as digitalis
3. The presence of excessive aldosterone or glucocorticoids in the body (such as in Cushing syndrome, in which glucocorticoids have some mineralocorticoid activity that promotes the retention of sodium and the excretion of potassium)
4. Decreased dietary intake, which may occur with alcoholism, eating disorders, or starvation
5. Treatment of diabetic ketoacidosis with insulin

Effects of Hypokalemia

- Cardiac **dysrhythmias** are serious, showing typical ECG pattern changes (Fig. 2.8) that indicate prolonged repolarization, and eventually may lead to cardiac arrest (see Chapter 12).

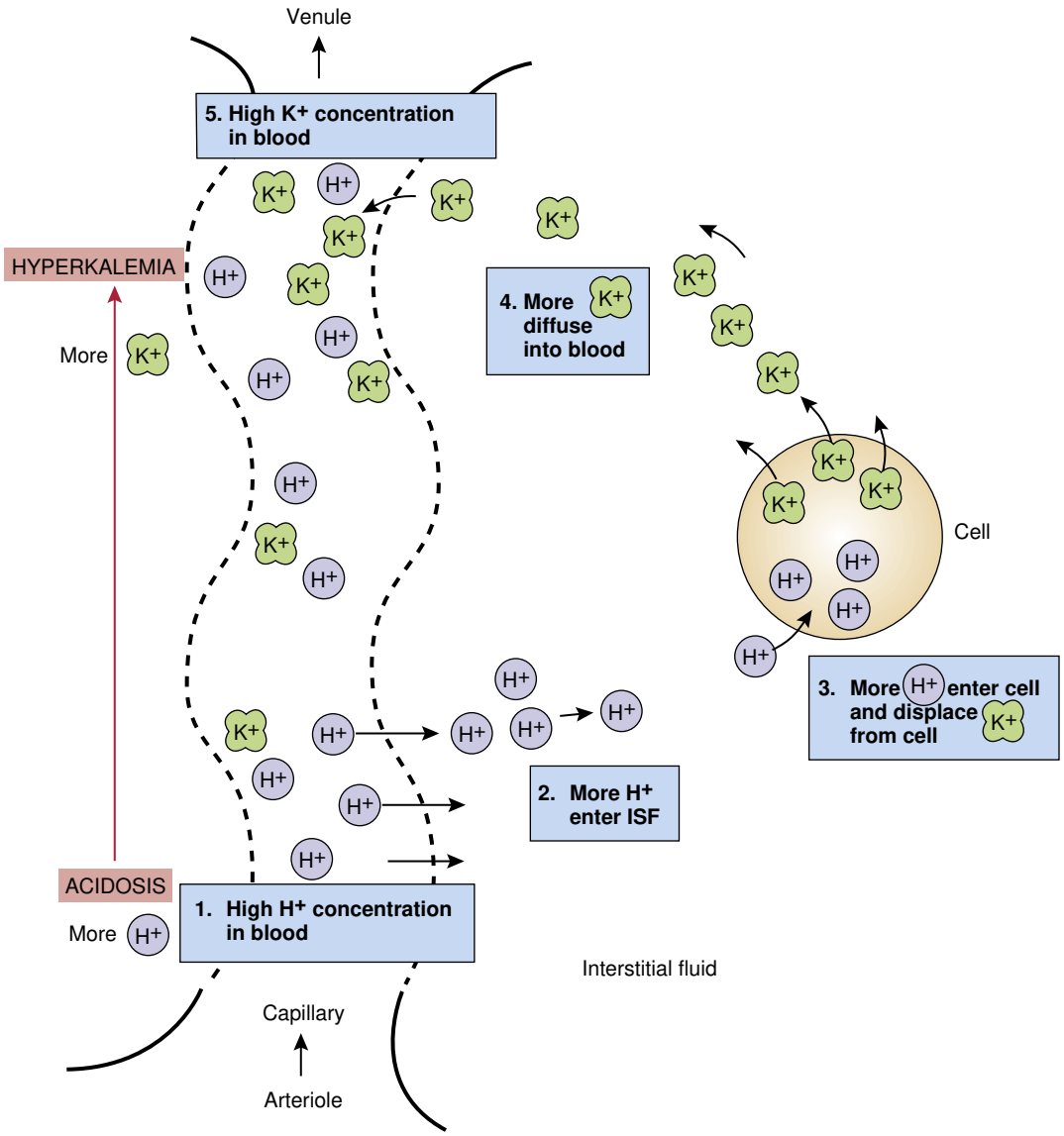


Fig. 2.7 Relationship of hydrogen and potassium ions. K^+, Potassium; H^+, hydrogen; *ISF*, interstitial fluid.

- Hypokalemia interferes with neuromuscular function, and the muscles become less responsive to stimuli, as shown by fatigue and muscle weakness commencing in the legs (Table 2.6).
- **Paresthesias** (abnormal touch sensations) such as "pins and needles" develop.
- Decreased digestive tract motility causes decreased appetite (**anorexia**) and nausea.
- In people with severe potassium deficits, the respiratory muscles become weak, leading to shallow respirations.
- In severe cases, renal function is impaired, leading to failure to concentrate the urine, and increased urine output (polyuria) results.

Hyperkalemia

In hyperkalemia, the serum level of potassium is greater than 2.6 mmol/L or 5 mEq/L.

TABLE 2.6 Signs of Potassium Imbalance

Hypokalemia	Hyperkalemia
Cardiac arrhythmias, cardiac arrest	Arrhythmias, cardiac arrest
Anorexia, nausea, constipation	Nausea, diarrhea
Fatigue, muscle twitch, weakness, leg cramps	Muscle weakness, paralysis beginning in legs
Shallow respirations, paresthesias	Paresthesias—fingers, toes, face, tongue
Postural hypotension, polyuria, and nocturia	Oliguria
Serum pH elevated—7.45 (alkalosis)	Serum pH decreased—7.35 (acidosis)

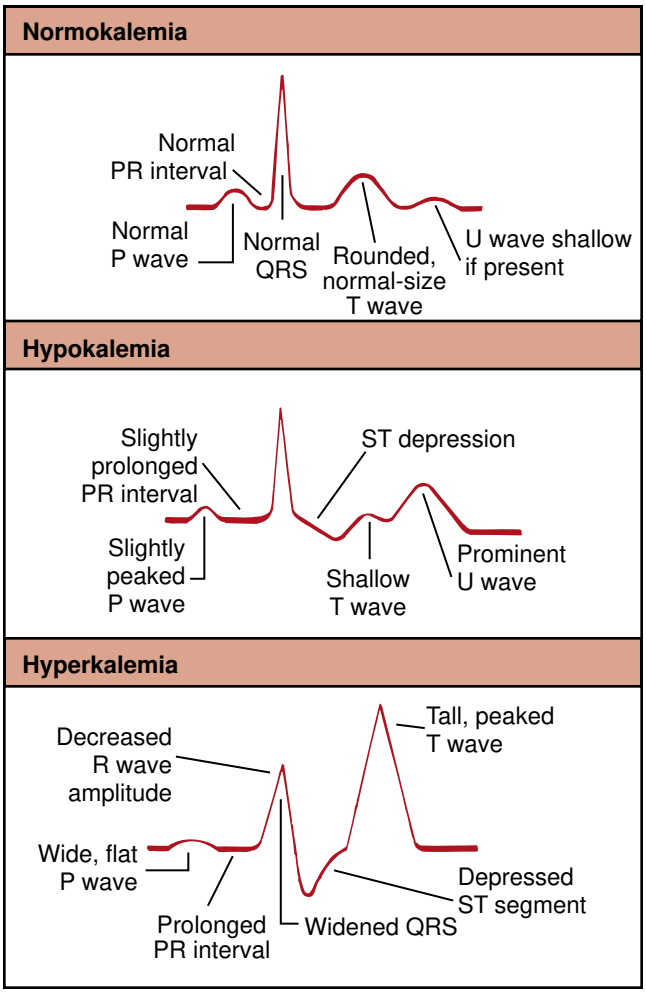


Fig. 2.8 Electrocardiogram changes with potassium imbalance. *(From McCance KL, et al:* Pathophysiology: The Biologic Basis for Disease in Adults and Children, *ed 6, St. Louis, 2010, Mosby.)*

Causes of Hyperkalemia

Causes of high serum potassium levels include the following:

1. Renal failure
2. Deficit of aldosterone
3. Use of "potassium-sparing" diuretic drugs, which prevent potassium from being excreted in adequate amounts
4. Leakage of intracellular potassium into the extracellular fluids in patients with extensive tissue damage, such as traumatic crush injuries or burns
5. Displacement of potassium from cells by prolonged or severe acidosis (see Fig. 2.7)

Effects of Hyperkalemia

- The ECG shows typical cardiac dysrhythmias (see Fig. 2.8), which may progress to cardiac arrest.
- Muscle weakness is common, progressing to paralysis as hyperkalemia advances and impairs neuromuscular activity (see Table 2.6).
- Fatigue, nausea, and paresthesias are also common.

THINK ABOUT 2.13

a. Compare the manifestations of hyponatremia and hypokalemia.
b. Why is any small change in potassium level considered a serious problem?

Calcium Imbalance

Review of Calcium

Calcium is an important extracellular cation. Calcium is ingested in food (especially milk products), stored in bone, and excreted from the body in the urine and feces. Calcium balance is controlled by parathyroid hormone (PTH) and calcitonin (see Chapter 16), but it is also influenced by vitamin D and phosphate ion levels. For example, low blood calcium levels stimulate the secretion of PTH, which (1) increases the bone resorption, causing the release of calcium and phosphate into circulation; (2) increases the formation of 1,25-dihydroxycholecalciferol in the kidneys to increase the absorption of calcium and phosphate by the intestine; and (3) decreases calcium excretion and increases phosphate excretion by the kidneys.

Vitamin D may be ingested or may be synthesized in the skin in the presence of ultraviolet rays, but then it must be activated in the kidneys. It promotes calcium movement from the bone and intestines into the blood. Most people living in northern climates have reduced vitamin D because of lack of exposure of the skin to the sun; dietary supplements are recommended to ensure adequate levels during cold weather. Sun-blocking agents with an sun protection factor greater than 15 appear to reduce vitamin D synthesis. There is also increasing evidence that vitamin D deficits may contribute to the development of multiple sclerosis and certain cancers (Box 2.1).

Calcium and phosphate ions in the extracellular fluid have a reciprocal relationship. For example, if calcium levels are high, phosphate is low. The product of calcium and phosphate concentrations should be a constant value. If levels of both calcium and phosphate rise,

BOX 2.1 Vitamin D and Cancer

Scientist at Michigan State University analyzed data from randomized controlled trials that compared participants who took vitamin D supplements with those who took a placebo for at least 3 years. The analysis used 10 trials with 79,055 participants with an average age of 68 years, 78% female. The analysis showed a 13% lower risk of dying from cancer in people who took vitamin D supplements. However, no significant association could be determined between the use of vitamin D supplements and cancer prevention. The findings were presented at the annual meeting of the American Society of Clinical Oncology in Chicago, IL in June 2019.

crystals of calcium phosphate precipitate in soft tissue. The measured or biologically active form of calcium is the ionized form, which is not attached to plasma protein or bonded to other ions such as citrate. Alkalosis can decrease the number of free calcium ions, causing hypocalcemia.

Calcium has many important functions:

- It provides the structural strength essential for bones and teeth.
- Calcium ions maintain the stability of nerve membranes, controlling the permeability and excitability needed for nerve conduction.
- Calcium ions are required for muscle contractions.
- Calcium ions are necessary for many metabolic processes and enzyme reactions, such as those involved in blood clotting.

THINK ABOUT 2.14

When nerve membranes become more permeable, is the nerve more or less easily stimulated?

Hypocalcemia

In hypocalcemia, the serum calcium level is less than 2.2 mmol/L or below 4 mEq/L.

Causes of Hypocalcemia

Causes of hypocalcemia include the following:

1. Hypoparathyroidism—decreased parathyroid hormone results in decreased intestinal calcium absorption
2. Malabsorption syndrome—resulting in decreased intestinal absorption of vitamin D or calcium
3. Deficient serum albumin
4. Increased serum pH—resulting in alkalosis

In renal failure, hypocalcemia results from retention of phosphate ion, which causes loss of calcium; also, vitamin D is not activated, thereby decreasing the intestinal absorption of calcium.

Effects of Hypocalcemia

- The increase in the permeability and excitability of nerve membranes leads to spontaneous stimulation of *skeletal muscle*. This leads to muscle twitching, **carpopedal spasm** (atypical contraction of the fingers), and hyperactive reflexes (Table 2.7). The Chvostek sign, spasm of the lip or face when the face is tapped in front of the ear, and the Trousseau sign, carpopedal spasm when a blood pressure cuff blocks circulation to the hand, both indicate low serum calcium and **tetany** (skeletal muscle spasms causing prolonged contraction and/or cramps). Severe calcium deficits may cause **laryngospasm**, which obstructs the airway. Paresthesias are common, as are abdominal cramps.
- *Heart* contractions become *weak* owing to insufficient calcium for muscle action, conduction is delayed, *arrhythmias* develop, and blood pressure drops.

TABLE 2.7 Signs of Calcium Imbalance

Hypocalcemia	Hypercalcemia
Tetany—involuntary skeletal muscle spasm, carpopedal spasm, laryngospasm	Apathy, lethargy
Tingling fingers	Anorexia, nausea, constipation
Mental confusion, irritability	Polyuria, thirst
Arrhythmias, weak heart contractions	Kidney stones
	Arrhythmias, prolonged strong cardiac contractions, increased blood pressure

Note: Effects on bone depend on the cause of the calcium imbalance.

Note that the effects of hypocalcemia on *skeletal muscle* and *cardiac muscle* differ. Skeletal muscle spasms result from the increased irritability of the nerves associated with the muscle fibers, whereas the weaker contraction of cardiac muscle (which lacks nerves) is directly related to the calcium deficit. Also, adequate calcium is stored in the skeletal muscle cells to provide for contractions, whereas contraction of cardiac muscle relies on available extracellular calcium ions passing through the calcium channels. This is the basis for action of one group of cardiac drugs.

THINK ABOUT 2.15

Explain the different effects of low serum calcium on skeletal muscle and cardiac muscle.

Hypercalcemia

In hypercalcemia, the serum calcium is greater than 5 mEq/L or greater than 2.5 mmol/L.

Causes of Hypercalcemia

Excessive serum levels of calcium frequently result from the following:

1. Uncontrolled release of calcium ions from the bones owing to neoplasms; malignant bone tumors may directly destroy the bone, and some tumors, such as bronchogenic carcinoma, may secrete PTH in excess of body needs
2. Hyperparathyroidism
3. Immobility, which may decrease stress on the bone, leading to demineralization
4. Increased intake of calcium due either to excessive vitamin D or to excess dietary calcium
5. Milk-alkali syndrome, associated with increased milk and antacid intake, which may also elevate serum calcium levels

Effects of Hypercalcemia

- High serum calcium levels depress neuromuscular activity, leading to muscle weakness, loss of muscle tone, lethargy, and stupor, often with personality changes, anorexia, and nausea (see Table 2.7).
- High calcium levels interfere with the function of ADH in the kidneys, resulting in less absorption of water and in polyuria. If hypercalcemia is severe, blood volume drops, renal function decreases, nitrogen wastes accumulate, and cardiac arrest may ensue.
- Cardiac contractions increase in strength, and dysrhythmias may develop.
- Effects on bone vary with the cause of hypercalcemia. If excess PTH is the cause, bone density will be decreased, and spontaneous (pathologic) fractures may occur, particularly in the weight-bearing areas, causing bone pain. If intake of calcium is high, PTH levels will be low, and more calcium will be stored in the bone, maintaining bone strength.
- May contribute to the formation of kidney stones in the urinary system.

THINK ABOUT 2.16

Describe the effect of each of the following conditions on serum calcium levels and on bone density: (1) hyperparathyroidism, (2) renal failure, and (3) a large intake of vitamin D.

Other Electrolytes

Magnesium

Magnesium is an intracellular ion that has a normal serum level of 0.7 to 1.1 mmol/L. About 50% of total body magnesium is stored in bone. Serum levels are linked to both potassium and calcium levels. Magnesium is found in green vegetables, and is important in many enzyme reactions, as well as in protein and DNA synthesis. Magnesium imbalances are rare.

Hypomagnesemia

Hypomagnesemia results from malabsorption or malnutrition, often associated with chronic alcoholism.

Causes of Hypomagnesemia

- Use of diuretics
- Diabetic ketoacidosis
- Hyperparathyroidism
- Hyperaldosteronism

Effects of Hypomagnesemia

- Neuromuscular hyperirritability
- Tremors or chorea (involuntary repetitive movements)
- Insomnia
- Personality changes
- Increased heart rate with arrhythmias

Hypermagnesemia

Cause of Hypermagnesemia

- Usually occurs with renal failure

Effects of Hypermagnesemia

- Depressed neuromuscular function
- Decreased reflexes
- Lethargy
- Cardiac arrhythmias

Phosphate

Phosphate ions are located primarily in the bone, but circulate in both the intracellular and extracellular fluids. The serum level is normally 0.85 to 1.45 mmol/L. Phosphate is important in a variety of circumstances:

- In bone and tooth mineralization
- In many metabolic processes, particularly those involving the cellular energy source, adenosine triphosphate
- As the phosphate buffer system for acid-base balance, and in the removal of hydrogen ions from the body through the kidneys
- As an integral part of the cell membrane
- In its reciprocal relationship with serum calcium

Causes of Hypophosphatemia

- Malabsorption syndromes
- Diarrhea
- Excessive use of antacids
- Alkalosis
- Hyperparathyroidism

Effects of Hypophosphatemia

- Tremors
- Weak reflexes (hyporeflexia)
- Paresthesias
- Confusion and stupor
- Anorexia
- Difficulty in swallowing (dysphagia)
- Blood cells function less effectively—oxygen transport decreases, and clotting and phagocytosis decrease

THINK ABOUT 2.17

Explain how serum calcium levels are affected by low phosphate levels.

Causes of Hyperphosphatemia

- Often results from renal failure. Dialysis patients often take phosphate binders with meals to control their serum phosphate levels.
- Tissue damage or cancer chemotherapy may cause the release of intracellular phosphate.

Effects of Hyperphosphatemia

- The manifestations of hyperphosphatemia are the same as those of hypocalcemia.

Chloride

Chloride ion is the major extracellular **anion**, with a normal serum level of 98 to 106 mmol/L. Chloride ions tend to follow sodium, because of the attraction between the electrical charge on the ions; therefore, high sodium levels usually lead to high chloride levels.

Chloride and bicarbonate ions, both negatively charged, can exchange places as the blood circulates through the body to assist in maintaining acid-base balance (see Acid-Base Imbalance). As bicarbonate ions are used up in binding with metabolic acids, chloride ions diffuse out of the red blood cells into the serum to maintain the same number of negative ions in the blood (Fig. 2.9). The reverse situation can also occur, when serum chloride levels decrease, and bicarbonate ions leave the erythrocytes to maintain electrical neutrality. Thus, low serum chloride leads to high serum bicarbonate, or alkalosis. This situation is referred to as a *chloride shift*.

Causes of Hypochloremia

- Associated with alkalosis in the early stages of vomiting when hydrochloric acid is lost from the stomach.
- Excessive perspiration associated with fever or strenuous labor on a hot day can lead to loss of sodium chloride, resulting in hyponatremia and hypochloremia, and ultimately dehydration.

Effects of Hypochloremia

- Nausea
- Vomiting
- Diarrhea
- Muscle twitching
- Confusion, sleepiness

Causes of Hyperchloremia

- Excessive intake of sodium chloride, orally or intravenously
- Hypernatremia attributed to other causes

Effects of Hyperchloremia

- Edema
- Weight gain

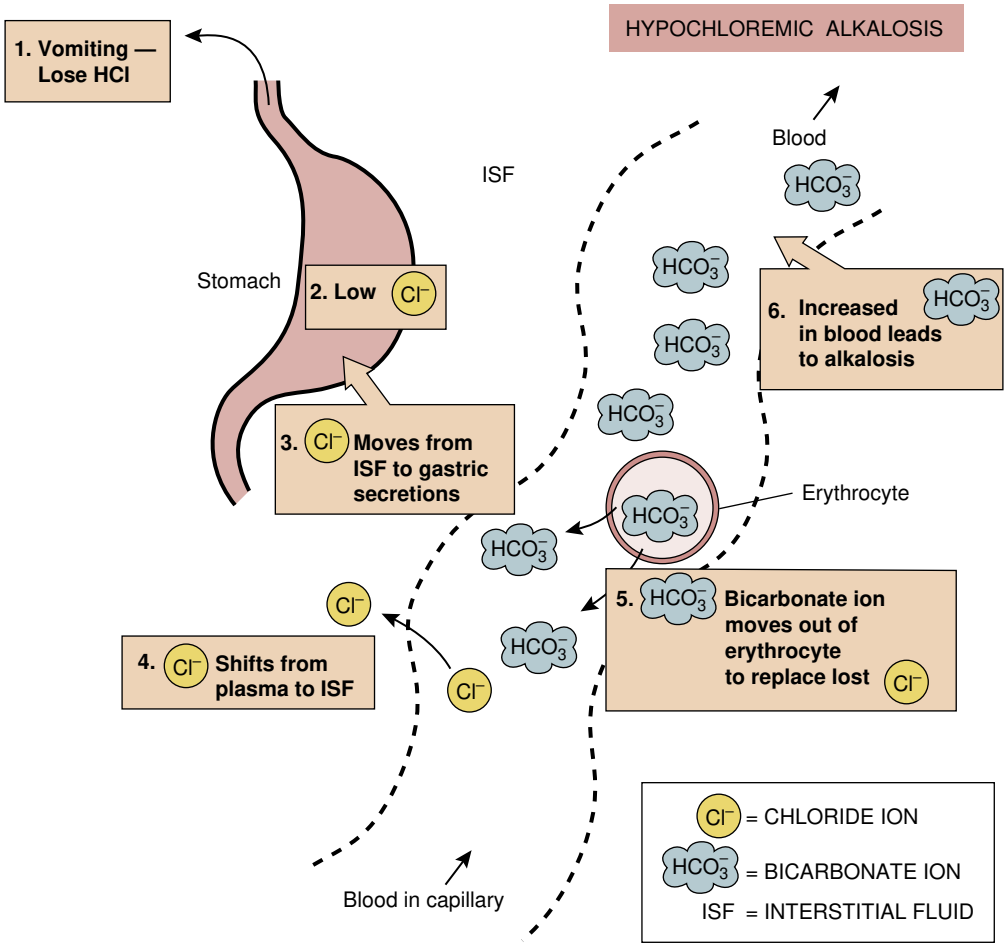


Fig. 2.9 Schematic representation of chloride-bicarbonate shift with vomiting.

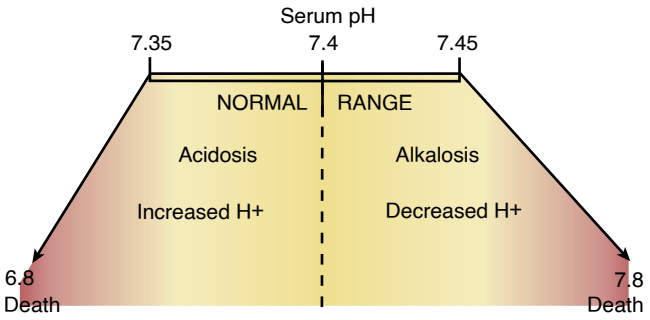


Fig. 2.10 The hydrogen ion and pH scale. H^+, Hydrogen.

THINK ABOUT 2.18

a. State one cause of hypomagnesemia.
b. State one cause of hyperphosphatemia.
c. List and describe two signs of hypophosphatemia.

Acid-Base Imbalance

Review of Concepts and Processes

Acid-base balance is essential to homeostasis, because cell enzymes can function only within a narrow pH range. *The normal serum pH range is 7.35 to 7.45*. Death usually results if serum pH is below 6.8 or above 7.8 (Fig. 2.10). For example, a pH of less than 7.35 depresses central nervous system function and decreases all cell enzyme activity.

When serum pH is less than 7.4, more hydrogen ions (H^+) are present, and acidosis results. A serum pH of greater than 7.4 is more basic, indicating alkalosis or the presence of fewer **hydrogen ions**. The body normally has a tendency toward acidosis, or a lower pH, because cell metabolism is constantly producing carbon dioxide (CO_2) or carbonic acid and **nonvolatile metabolic acids** such as lactic acid, ketoacids, sulfates, or phosphates. Lactic acid results from the *anaerobic* (without oxygen) metabolism of glucose, ketoacids result from incomplete oxidation of fatty acids, and protein metabolism may produce sulfates or phosphates.

THINK ABOUT 2.19

a. When hydrogen ions are decreased, is the pH higher or lower?
b. State the optimal range of serum pH and effects on normal cell function if serum pH is not in the optimal range.

Control of Serum pH

As the blood circulates through the body, nutrients diffuse from the blood into the cells, various metabolic processes take place in the cells using these nutrients, and metabolic wastes, including acids, diffuse from the cells into the blood (Fig. 2.11).

Three mechanisms control or compensate for pH:

1. The buffer pairs circulating in the blood respond to pH changes immediately.
2. The respiratory system can alter carbon dioxide levels (carbonic acid) in the body by changing the respiratory rate (see Chapter 13).
3. The kidneys can modify the excretion rate of acids and the production and absorption of bicarbonate ion (see Chapter 18).

Note that the lungs can change only the amount of carbon dioxide (equivalent to the amount of carbonic acid) in the body. The kidneys are slow to compensate for a change in pH, but are the most effective mechanism, because they can excrete all types of acids (volatile or gaseous and nonvolatile) and can also adjust serum bicarbonate levels.

THINK ABOUT 2.20

How does the respiratory rate change when more hydrogen ions enter the blood, and how does this change affect acid levels in the body?

Buffer Systems

To control serum pH, several buffer systems are present in the blood. A buffer is a combination of a weak acid and its alkaline salt. The components react with any acids or alkali added to the blood, neutralizing them and thereby maintaining a relatively constant pH.

The body has four major buffer pairs:

1. The sodium bicarbonate–carbonic acid system
2. The phosphate system
3. The hemoglobin system
4. The protein system

The bicarbonate system is the major extracellular fluid buffer and is used clinically to assess a patient's acid-base status. The principles of acid-base balance are discussed here using the bicarbonate pair. Specific values are not used, because the emphasis is on understanding basic concepts and recognizing trends. Laboratory tests will report the specific values and state the implications of those values.

APPLY YOUR KNOWLEDGE 2.2

Predict three ways by which control of serum pH could be impaired.

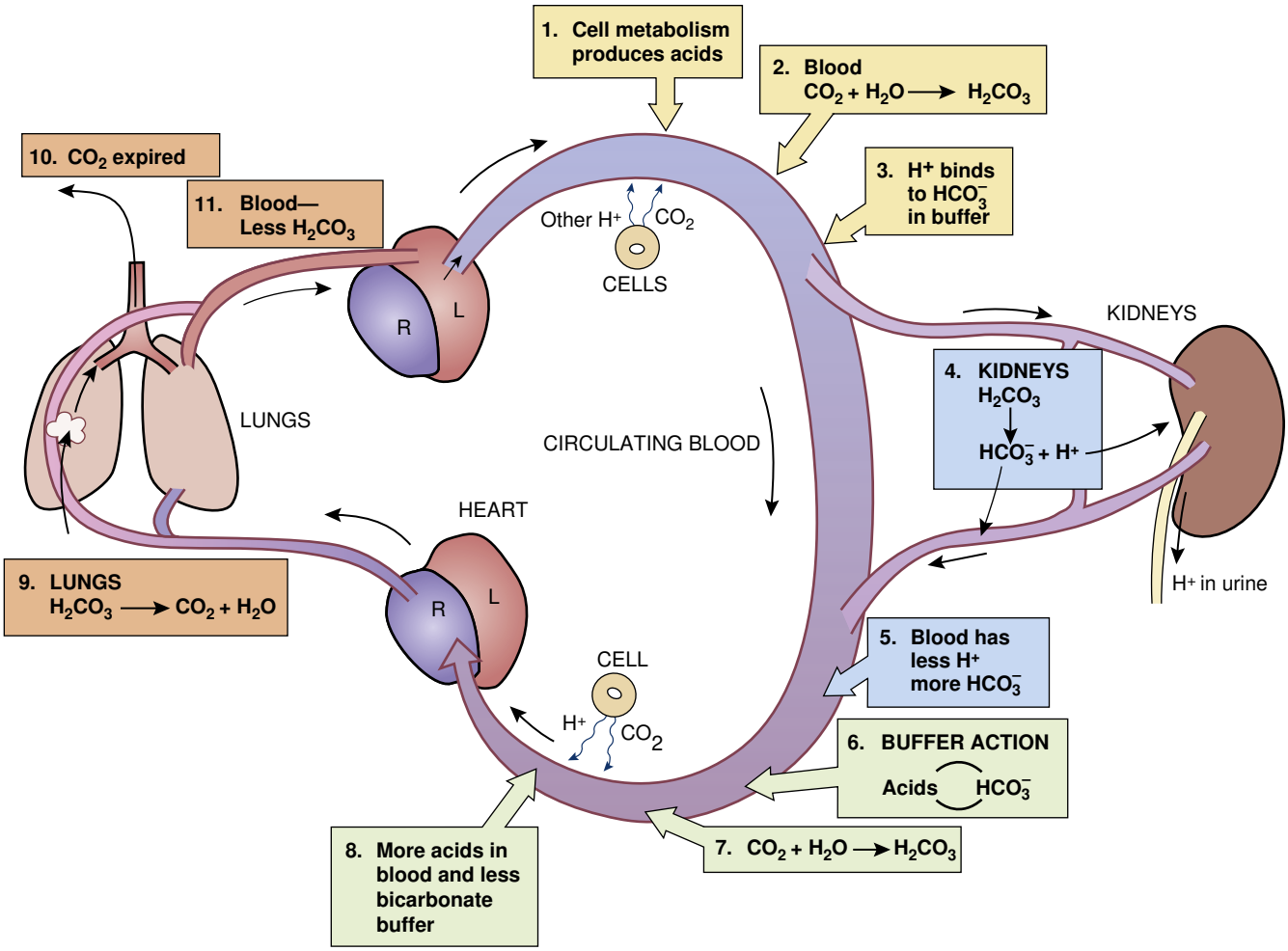


Fig. 2.11 Changes in acids, bicarbonate ion, and serum pH in circulating blood. *R*, Right; *L*, left; H^+, hydrogen; CO_2, carbon dioxide; H_2O, water; H_2CO_3, carbonic acid; HCO_3^-, bicarbonate.

Bicarbonate–Carbonic Acid Buffer System and Maintenance of Serum pH

The bicarbonate buffer system is composed of carbonic acid, which arises from the combination of carbon dioxide with water, and bicarbonate ion, which is present as sodium bicarbonate. The balance of bicarbonate ion, a *base*, and carbonic *acid* levels is controlled by the respiratory system and the kidneys (see Fig. 2.11). Cell metabolism produces carbon dioxide, which diffuses into the interstitial fluid and blood, where it reacts with water to form carbonic acid, which then dissociates immediately under the influence of the enzyme carbonic anhydrase to form three hydrogen ions and one bicarbonate ion per molecule of carbonic acid. This enzyme is present in many sites, including the lungs and the kidneys. In the *lungs*, this reaction can be reversed to form carbon dioxide, which is then expired along with water, thus reducing the total amount of carbonic acid or acid in the body. In the *kidneys*, the reaction needed to form more hydrogen ions is promoted by enzymes; the resultant hydrogen ions are excreted in the urine, and the bicarbonate ions are returned to the blood to restore the buffer levels.

To maintain serum pH within the normal range, 7.35 to 7.45, the *ratio* of bicarbonate ion to carbonic acid (or carbon dioxide) must be *20:1*. A 1:1 ratio will not maintain a pH of 7.4! The ratio is always stated with the H^+ component as 1.

As one component of the ratio changes, the other component must change *proportionately* to maintain the 20:1 ratio, and thus serum pH. For instance, if respiration is impaired, causing an increase in carbon dioxide in the blood, the kidneys must increase serum bicarbonate levels to compensate for the change. The actual concentrations are not critical, as long as the proportions are sustained. It may help to remember that the bicarbonate part or alkali part of the buffer ratio is 20, the higher figure, because more bicarbonate base is required to neutralize the acids constantly being produced by the body cells.

THINK ABOUT 2.21

If bicarbonate ion is lost from the body, how will carbonic acid levels change?

Respiratory System

When serum carbon dioxide or hydrogen ion levels increase, chemoreceptors stimulate the respiratory control center to increase the respiratory rate, thus removing more carbon dioxide or acid from the body. When alkalosis develops, the respiratory rate decreases, thus retaining more carbon dioxide and increasing acid levels in the body.

Renal System

The kidneys can also reduce the acid content of the body by exchanging hydrogen for sodium ions under the influence of aldosterone. The kidneys also provide the bicarbonate ion for the buffer pair as needed. Urine pH may range from 4.5 to 8 as the kidneys compensate for metabolic conditions and dietary intake:

lungs: carbondioxide + water ↔ carbonicacid ↔
hydrogenious + bicarbonateions: kidneys

THINK ABOUT 2.22

a. Reduced blood flow through the kidneys for a long time will have what effect on serum pH? Why?
b. How would the lungs and kidneys respond to the ingestion of large quantities of antacids?
c. How is the kidney more effective in maintaining serum pH than the lungs?

A number of laboratory tests can determine acid-base balance. These tests include arterial blood gases, base excess or deficit, or anion gap, and details about them may be found in various clinical laboratory manuals. Some normal values are listed inside the front cover of this book.

Acid-Base Imbalance

An increase in hydrogen ions or a decrease in serum pH results in acidosis, whereas alkalosis refers to an increase in serum pH or decreased hydrogen ions.

There are four basic types of acid-base imbalance (Table 2.8):

1. Respiratory acidosis, which can result from an increase in carbon dioxide levels (acid) because of respiratory problems

TABLE 2.8 Acid-Base Imbalances

	Acidosis	Alkalosis
Respiratory		
Causes	Slow shallow respirations (e.g., drugs) Respiratory congestion	Hyperventilation (anxiety, aspirin overdose)
Effect	Increased PCO_2	Decreased PCO_2
Compensation	Kidneys excrete more hydrogen ion and reabsorb more bicarbonate	Kidneys excrete less hydrogen ion and reabsorb less bicarbonate
Laboratory	Elevated PCO_2 Elevated serum bicarbonate Compensated—serum pH = 7.35 to 7.4 Decompensated—serum pH < 7.35	Low PCO_2 Low serum bicarbonate Compensated—serum pH = 7.4 to 7.45 Decompensated—serum pH > 7.45
Metabolic		
Causes	Shock Diabetic ketoacidosis Renal failure Diarrhea	Vomiting (early stage) Excessive antacid intake
Effect	Decreased serum bicarbonate ion	Increased serum bicarbonate ion
Compensation	Rapid, deep respirations Kidneys excrete more acid and increase bicarbonate absorption	Slow, shallow respirations Kidneys excrete less acid and decrease bicarbonate absorption
Laboratory	Low serum bicarbonate Low Pco_2 Compensated—serum pH = 7.35 to 7.4 Decompensated—serum pH < 7.35	Elevated serum bicarbonate Elevated Pco_2 Compensated—serum pH = 7.4 to 7.45 Decompensated—serum pH > 7.45

PCO_2, Partial pressure of carbon dioxide.

2. Metabolic acidosis, which can result from a decrease in bicarbonate ions (base) because of metabolic or renal problems
3. Respiratory alkalosis, which can result when increased respirations cause a decrease in carbon dioxide (less acid)
4. Metabolic alkalosis, which can result from the loss of hydrogen ions through the kidneys or the gastrointestinal tract

Imbalances may be acute or chronic. In some situations, combinations of imbalances may occur; for example, metabolic acidosis and respiratory alkalosis can occur simultaneously.

THINK ABOUT 2.23

Name or state the category of the imbalance resulting from each of the following: (1) increased respiratory rate, (2) renal failure, and (3) excessive intake of bicarbonate, and state the resulting change in the 20:1 ratio.

Compensation

The *cause* of the imbalance determines the first change in the ratio (Figs. 2.12–2.15). Respiratory disorders are

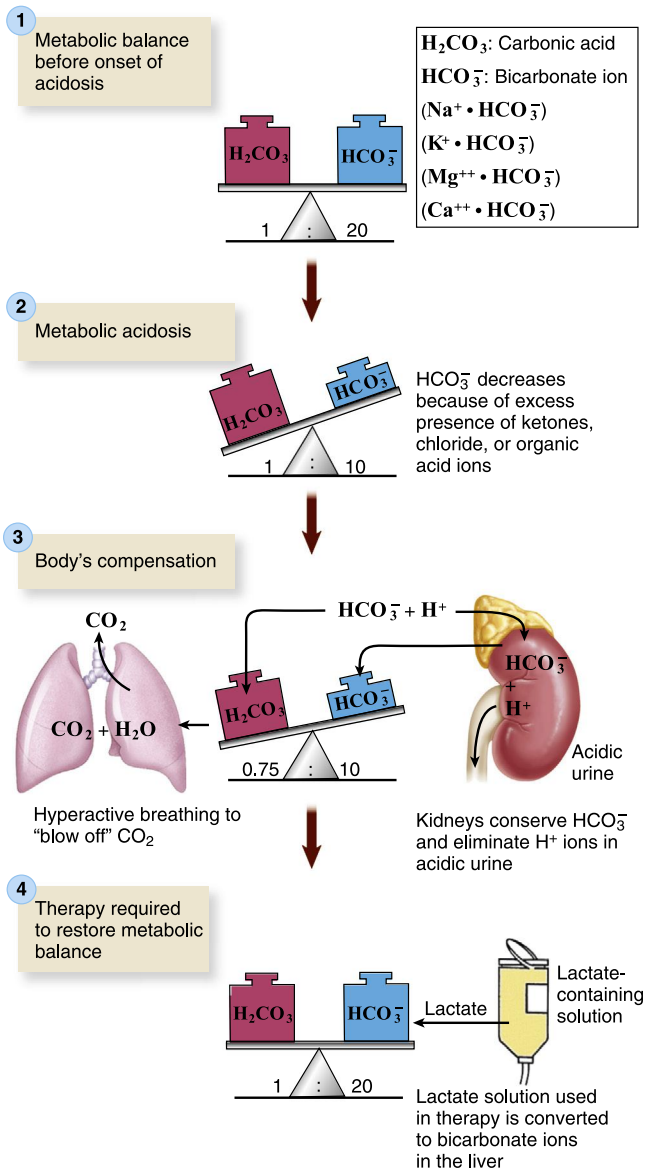


Fig. 2.12 Metabolic acidosis. CO_2, carbon dioxide; H_2CO_3, carbonic acid; HCO_3^-, bicarbonate. *(From Patton KT, Thibodeau GA:* Anatomy & Physiology, *ed 8, St. Louis, 2013, Mosby.)*

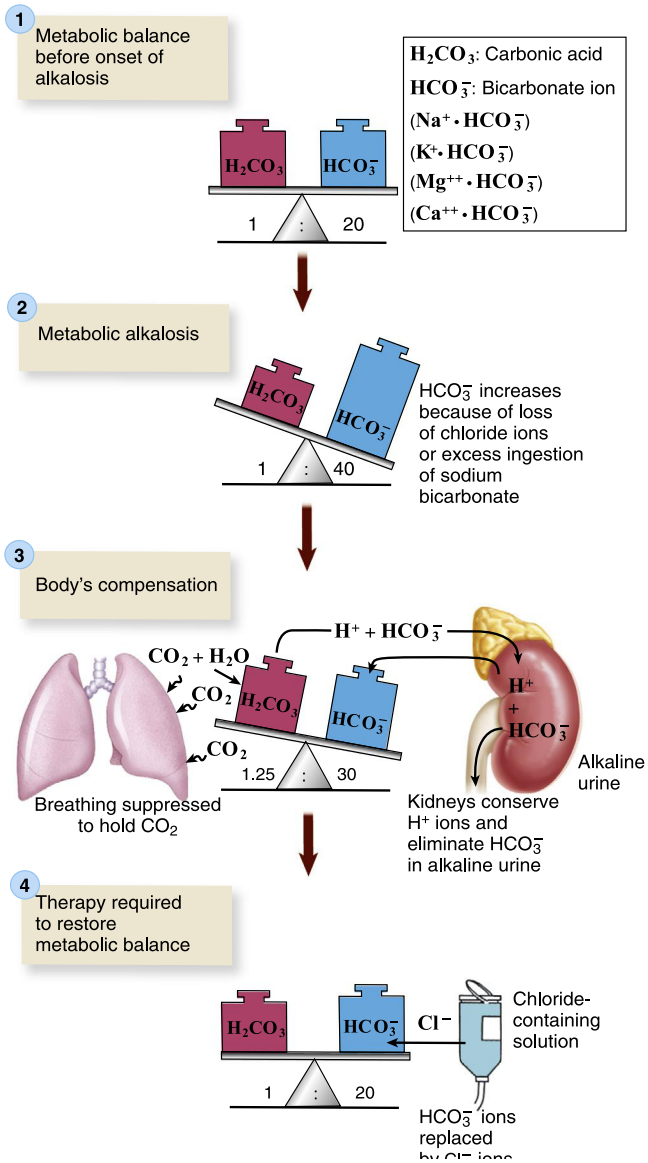


Fig. 2.13 Metabolic alkalosis. CO_2, carbon dioxide; H_2CO_3, carbonic acid; HCO_3^-, bicarbonate. *(From Patton KT, Thibodeau GA:* Anatomy & Physiology, *ed 8, St. Louis, 2013, Mosby.)*

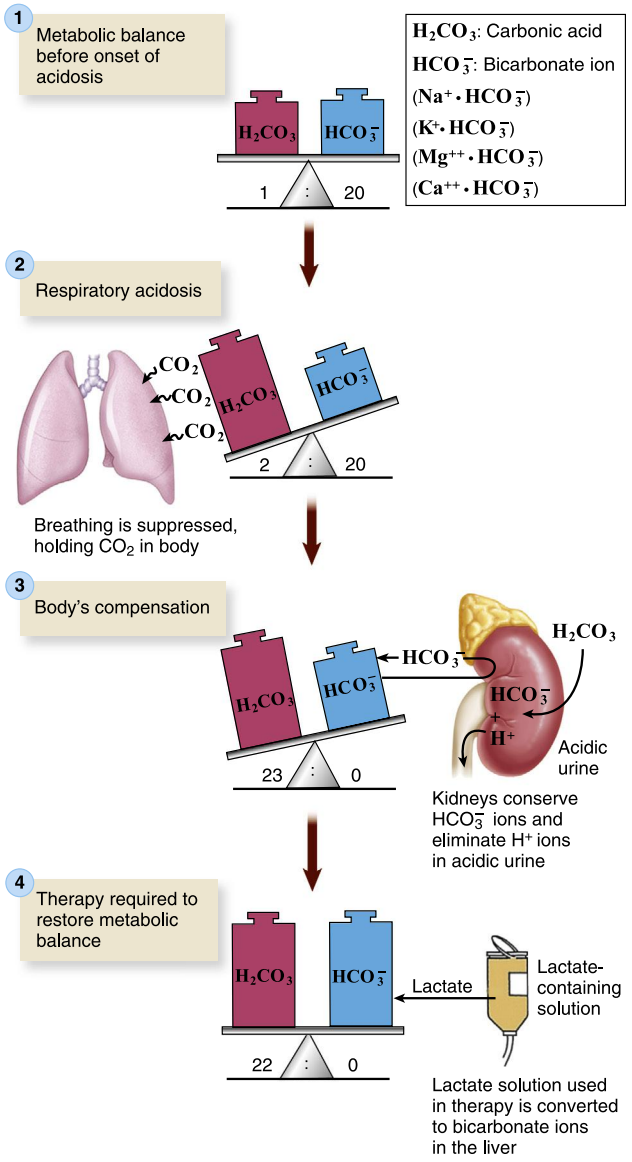


Fig. 2.14 Respiratory acidosis. CO_2, carbon dioxide; H_2CO_3, carbonic acid; HCO_3^-, bicarbonate. *(From Patton KT, Thibodeau GA:* Anatomy & Physiology, *ed 8, St. Louis, 2013, Mosby.)*

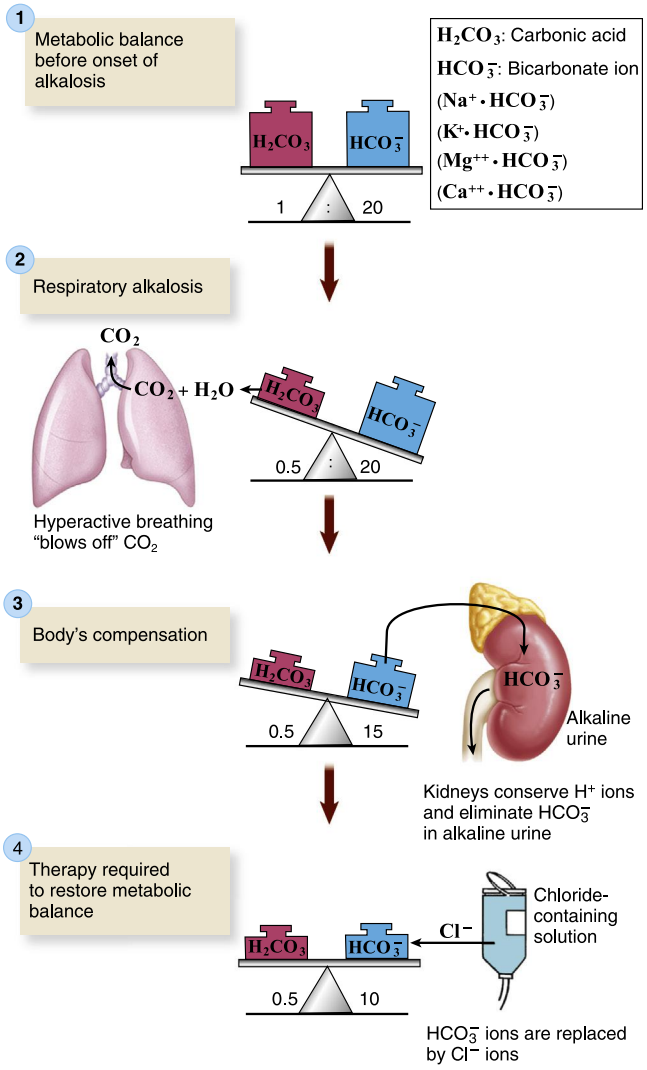


Fig. 2.15 Respiratory alkalosis. *(From Patton KT, Thibodeau GA:* Anatomy & Physiology, *ed 8, St. Louis, 2013, Mosby.)*

always represented by an initial change in carbon dioxide. All other problems are metabolic and result from an initial change in bicarbonate ions.

The *compensation* is assessed by the subsequent change in the second part of the ratio (Table 2.9) and requires function by body systems *not* involved in the cause. For example, if a patient has a respiratory disorder causing acidosis, the lungs cannot compensate effectively, but the kidneys can. As long as the ratio of bicarbonate to carbonic acid is maintained at 20:1 and serum pH is normal, the imbalance is considered to be compensated. Compensation is limited, and the patient must be monitored carefully if there is an ongoing threat to homeostasis.

Decompensation

If the kidneys and lungs cannot compensate adequately, the ratio changes, and serum pH moves out of the normal range, thus affecting cell metabolism and function. At this point, the imbalance is termed *decompensation*. Intervention is essential if homeostasis is to be regained. Examples of acid-base imbalance are given in Table 2.8.

THINK ABOUT 2.24

a. In an individual with very low blood pressure or circulatory shock, blood flow to the cells is very poor, resulting in increased lactic acid. Briefly describe the compensations that will take place.
b. What changes in the bicarbonate ratio and serum pH indicate that decompensation has occurred?

TABLE 2.9 Examples of Acidosis

Respiratory Acidosis—Individual With Emphysema Retaining CO_2		
Stage 1:	Kidneys compensate for slight increase in PCO_2 by increasing excretion of acids and production of bicarbonate.	No change in serum levels
Stage 2:	Increased retention of CO_2. Respiratory acidosis.	Elevated PCO_2
Stage 3:	Compensation. Kidneys reabsorb more bicarbonate.	Elevated serum ions. bicarbonate
Stage 4:	Compensated respiratory acidosis: Abnormal serum values indicate problem and compensation adequate to maintain ratio and normal serum pH.	Serum pH = 7.35
Stage 5:	Decompensated respiratory acidosis: Patient acquires pneumonia, and much more CO_2 is retained. Also, kidneys cannot maintain compensation. Ratio is no longer normal, CNS depression and coma ensue, and serum pH drops below the normal range.	Serum pH = 7.31
Metabolic Acidosis—Individual With Diabetic Ketoacidosis Owing to Insulin Deficit		
Stage 1:	Slight increase in production of ketoacids. Kidneys increase excretion of acids.	No change in serum values
Stage 2:	Metabolic acidosis: More ketoacids produced than kidneys can excrete quickly, and acids bind with or "use up" buffer bicarbonate.	Low serum bicarbonate
Stage 3:	Respirations become rapid and deep to remove CO_2. Kidneys compensate by excreting more acids and reabsorbing more bicarbonate but cannot keep up with the increasing ketoacids added to the blood.	Low PCO_2
Stage 4:	Compensated metabolic acidosis: Abnormal serum values indicate the problem and compensation adequate to maintain ratio and normal serum pH.	Serum pH = 7.35
Stage 5:	Decompensated metabolic acidosis: Ketoacids continue to increase in the blood at a faster rate, and the kidneys have decreased function owing to dehydration. Therefore the problem becomes more severe and compensation is inadequate. The ratio is not maintained, and serum pH drops below the normal range.	Serum pH = 7.31

PCO_2, Partial pressure of carbon dioxide; *CO_2*, carbon dioxide; *CNS*, central nervous system.

Acidosis

Causes of Acidosis

Respiratory acidosis, in which there is an increase in carbon dioxide levels, may occur under several conditions:

- Acute problems such as pneumonia, airway obstruction (aspiration or asthma), or chest injuries, and in those taking drugs such as opiates, which depress the respiratory control center
- Chronic respiratory acidosis, common in people with chronic obstructive pulmonary disease such as emphysema
- Decompensated respiratory acidosis, which may develop if the impairment becomes severe or if, for example, a patient with a chronic problem develops an additional infection

Metabolic acidosis is associated with a decrease in serum bicarbonate resulting from the following:

- Excessive loss of bicarbonate ions—for example, from diarrhea and loss of bicarbonate in the intestinal secretions.
- Increased utilization of serum bicarbonate to buffer increased acids, when large amounts of acids are produced in the body because the buffer bicarbonate binds with such acids until they can be removed by the kidneys. For example, lactic acid may accumulate if blood pressure decreases and insufficient oxygen is available to the cells, or diabetic patients may produce large amounts of ketoacid that use up bicarbonate ions (see Chapter 16).
- Renal disease or failure, in which both decreased excretion of acids and decreased production of bicarbonate ion occur (see Chapter 18). In people with renal failure, compensation by the lungs is inadequate, because the lungs can only remove carbon dioxide, not other acids, nor can they produce bicarbonate; therefore, a treatment such as dialysis is required to maintain serum pH.
- Decompensated metabolic acidosis, which may develop when an additional factor interferes with compensation. For example, a person with severe diarrhea may become so dehydrated that the kidneys receive little blood and cannot function adequately, causing decompensation. The same result is seen with cardiac arrest.

Effects of Acidosis

The direct effects of acidosis are manifested by the nervous system, in which function is impaired, leading to inadequate responses. Headache, lethargy, weakness,

and confusion develop, leading eventually to coma and death. Compensations are manifested by deep, rapid breathing (Kussmaul respirations) and secretion of urine with a low pH (e.g., 5).

Alkalosis

Alkalosis does not occur as frequently as acidosis. *Respiratory alkalosis* results from hyperventilation, usually caused by anxiety, high fever, or an overdose of aspirin. Head injuries or brain stem tumors may lead to hyperventilation. Stress-related alkalosis may develop rapidly. If the individual cannot quickly be calmed enough to hold his or her breath repeatedly, then it is best treated by rebreathing exhaled air containing excreted carbon dioxide from a paper bag placed over the face. Even if renal compensation is not impaired, it is slow to take place.

Metabolic alkalosis, in which there is an increase in serum bicarbonate ion, commonly follows loss of hydrochloric acid from the stomach either in the early stages of vomiting or with drainage from the stomach. Other potential causes are hypokalemia (see Electrolyte Imbalances) and excessive ingestion of antacids.

Effects of Alkalosis

Alkalosis increases the irritability of the nervous system, causing restlessness, muscle twitching, tingling and numbness of the fingers, and eventually tetany, seizures, and coma.

Treatment of Imbalances

The underlying cause of the imbalance must be diagnosed and treated, in addition to enacting more immediate corrective measures such as fluid/electrolyte replacement or removal.

- Deficits can be reversed by adding fluid or the particular electrolyte to the body fluids. Excess amounts of either fluid or electrolytes must be removed. For example, a fluid deficit is returned to normal by the increased intake of fluid. Excess fluid can be removed by taking diuretic drugs to increase the excretion of fluid through the kidneys.
- Caution is required when adjusting fluid levels, to ensure that electrolyte balance is maintained. For example, when adding fluid to the body, it is necessary to check electrolyte levels and perhaps add sodium or other electrolytes to achieve normal levels of all components.
- The addition of bicarbonate to the blood will reverse acidosis; levels of bicarbonate need to be monitored, because excess bicarbonate levels may occur.
- In some cases, diet may be modified to maintain better electrolyte balance.
- Other factors such as respiratory or kidney disorders and hormonal imbalances can have dramatic effects on the fluid/electrolyte balance.

THINK ABOUT 2.25

a. For each of the following situations, list the kind of acid-base imbalance likely to occur: (1) chest injury with fractured ribs, (2) infection with high fever, and (3) diarrhea.
b. Describe the effect of metabolic acidosis on respiration and on the central nervous system.
c. In an elderly person with respiratory acidosis caused by chronic respiratory congestion, why would decreased kidney function be so dangerous?
d. If serum pH decreases to 7.1 because of severe renal disease, explain the change that has occurred in the buffer pair and the effect of this change on the central nervous system.

CASE STUDY 2.1

Vomiting

Mr. K.B. is 81 years old and has had gastritis with severe vomiting for 3 days. He has a history of heart problems and is presently feeling dizzy and lethargic. His eyes appear sunken, his mouth is dry, he walks unsteadily, and he complains of muscle aching, particularly in the abdomen. He is thirsty but is unable to retain food or fluid. A neighbor has brought Mr. K.B. to the hospital, where examination shows that his blood pressure is low, and his pulse and respirations are rapid. Laboratory tests demonstrate elevated hematocrit, hypernatremia, decreased serum bicarbonate, serum pH 7.35, and urine of high specific gravity (highly concentrated).

This case study illustrates a combination of fluid, electrolyte, and acid-base imbalances. Specific laboratory values are not given so as to focus on the basic concepts. For clarity, this case study is discussed in three parts: the early stage, middle stage, and advanced stage of the imbalances. Further information about the specific problems involved is given in each part and is followed by a series of questions.

Part A: Day 1

Initially, Mr. K.B. lost water, sodium in the mucus content, and hydrogen and chloride ions in the hydrochloric acid portion of the gastric secretions.

Alkalosis develops for two reasons, the first being the direct loss of hydrogen ions, and the second being the effects of chloride ion loss. When chloride ion is lost in the gastric secretions, it is replaced by chloride from the serum (see Fig. 2.9). To maintain equal numbers of cations and anions in the serum, chloride ion and bicarbonate ion can exchanges places when needed. Therefore, more bicarbonate ions shift into the serum from storage sites in the erythrocytes to replace the lost chloride ions. More bicarbonate ions in the serum raise serum pH, and the result is *hypochloremic alkalosis*.

1. Which compartments are likely to be affected in this case by early fluid loss?
2. Explain how a loss of sodium ions contributes to dehydration.
3. Describe the early signs of dehydration in Mr. K.B.
4. What serum pH could be expected in Mr. K.B. after this early vomiting?
5. Describe the compensations for the losses of fluid and electrolytes that should be occurring in Mr. K.B.

6. Explain why Mr. K.B. may not be able to compensate for losses as well as a younger adult.

Part B: Days 2 to 3

As Mr. K.B. continues to vomit and is still unable to eat or drink any significant amounts, loss of the duodenal contents, which include intestinal, pancreatic, and biliary secretions, occurs. No digestion and absorption of any nutrients occurs.

Losses at this stage include water, sodium ions, potassium ions, and bicarbonate ions. Also, intake of glucose and other nutrients is minimal. Mr. K.B. shows elevated serum sodium levels.

7. Explain why serum sodium levels appear to be high in this case.
8. Explain how high serum sodium levels might affect the intracellular fluid.
9. Using your knowledge of normal physiology, explain how continued fluid loss is likely to affect the following:
   a. Blood volume
   b. Cell function
   c. Kidney function
10. Given Mr. K.B.'s history, why might potassium imbalance have more serious effects on him?

Part C: Day 3: Admission to the Hospital

After a prolonged period of vomiting, metabolic acidosis develops. This change results from a number of factors:

- Loss of bicarbonate ions in duodenal secretions
- Lack of nutrients leading to catabolism of stored fats and protein with production of excessive amounts of ketoacids
- Dehydration and decreased blood volume leading to decreased excretion of acids by the kidney
- Decreased blood volume leading to decreased tissue perfusion, less oxygen to cells, and increased anaerobic metabolism with increased lactic acid
- Increased muscle activity and stress leading to increased metabolic acid production

These factors lead to an increased amount of acids in the blood, which bind with bicarbonate buffer and result in decreased serum bicarbonate and decreased serum pH or metabolic acidosis.

11. List several reasons why Mr. K.B. is lethargic and weak.
21. Predict the serum level of carbon dioxide or carbonic acid in this case.
31. If Mr. K.B. continues to lose body fluid, why might serum pH decrease below 7.35?
14. If serum pH drops below 7.35, what signs would be observed in Mr. K.B.?
15. Describe the effect of acidosis on serum potassium levels.
16. Mr. K.B. will be given replacement fluid therapy. Why is it important that sodium and potassium be given as well as water?

CASE STUDY 2.2

Diarrhea

Baby C., 3 months old, has had severe watery diarrhea accompanied by fever for 24 hours. She is apathetic and responds weakly to stimulation. The condition has been diagnosed as viral gastroenteritis.

1. List the major losses resulting from diarrhea and fever.
2. List other signs or data that would provide helpful information.
3. Explain several reasons why infants become dehydrated quickly.

CHAPTER SUMMARY

Water, electrolytes, and acids are constantly moving between compartments in the body, depending on intake, output, and variations in cell metabolism. Numerous mechanisms work to maintain a constant internal environment:

- Edema, local or general, results from excess fluid in the interstitial compartment owing to increased capillary hydrostatic pressure, increased sodium ion concentration in the ECF, decreased plasma osmotic pressure related to decreased plasma proteins, obstructed lymphatic circulation, or increased capillary permeability.
- Dehydration or fluid deficit in the body may be caused by decreased intake or excessive loss of water. Infants and elderly persons exhibit the greatest risk for dehydration.
- The signs of dehydration include thirst, dry oral mucous membrane, decreased skin turgor, fatigue, decreased urine output, and low blood pressure with rapid, weak pulse.
- Third-spacing refers to the movement of fluid out of the vascular compartment into a body cavity or tissue where it cannot circulate.
- Hyponatremia impairs the conduction of nerve impulses, muscle contraction, and distribution of body fluids.
- Hypernatremia causes fluid to shift out of cells, affecting cell function.
- Both hyperkalemia and hypokalemia lead to cardiac arrhythmias and possible cardiac arrest.
- Calcium ion levels in the blood are affected by parathyroid hormone, calcitonin, vitamin D, phosphate ion levels, diet, digestive tract, and renal function.
- Hypocalcemia causes muscle twitching and tetany related to increased permeability and excitability of nerve fibers, but it also leads to weaker cardiac muscle contractions.
- Excessive parathyroid hormone leads to hypercalcemia and bone demineralization that may cause spontaneous fractures.
- Chloride and bicarbonate ions are important in acid-base balance.
- The buffer ratio of 20 parts bicarbonate ion (base) to 1 part carbonic acid is essential to maintain serum pH in the normal range of 7.35 to 7.45.
- Respiratory acidosis or alkalosis is caused by respiratory impairment increasing the partial pressure of carbon dioxide (PCO_2), or hyperventilation decreasing PCO_2, respectively. The kidneys compensate by