Ganong's Review of Medical Physiology

25th Edition

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Ganong's Review of Medical Physiology

TWENTY-FIFTH EDITION

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Dedication to

William Francis Ganong

William Francis ("Fran") Ganong was an outstanding scientist, educator, and writer. He was completely dedicated to the field of physiology and medical education in general. Chairman of the Department of Physiology at the University of California, San Francisco, for many years, he received numerous teaching awards and loved working with medical students.

Over the course of 40 years and some 22 editions, he was the sole author of the best selling *Review of Medical Physiology*, and a co-author of 5 editions of *Pathophysiology of Disease: An Introduction to Clinical Medicine*. He was one of the "deans" of the Lange group of authors who produced concise medical text and review books that to this day remain extraordinarily popular in print and now in digital formats. Dr. Ganong made a gigantic impact on the education of countless medical students and clinicians.

A general physiologist par excellence and a neuroendocrine physiologist by subspecialty, Fran developed and maintained a rare understanding of the entire field of physiology. This allowed him to write each new edition (every 2 years!) of the *Review of Medical Physiology* as a sole author, a feat remarked on and admired whenever the book came up for discussion among physiologists. He was an excellent writer and far ahead of his time with his objective of distilling a complex subject into a concise presentation. Like his good friend, Dr. Jack Lange, founder of the Lange series of books, Fran took great pride in the many different translations of the *Review of Medical Physiology* and was always delighted to receive a copy of the new edition in any language.

He was a model author, organized, dedicated, and enthusiastic. His book was his pride and joy and like other best-selling authors, he would work on the next edition seemingly every day, updating references, rewriting as needed, and always ready and on time when the next edition was due to the publisher. He did the same with his other book, *Pathophysiology of Disease: An Introduction to Clinical Medicine*, a book that he worked on meticulously in the years following his formal retirement and appointment as an emeritus professor at UCSF.

Fran Ganong will always have a seat at the head table of the greats of the art of medical science education and communication. He died on December 23, 2007. All of us who knew him and worked with him miss him greatly.

Key Features of the Twenty-Fifth Edition of *Ganong's Review of Medical Physiology*

A concise, up-to-date and clinically relevant review of human physiology

- Provides succinct coverage of every important topic without sacrificing comprehensiveness or readability
- Reflects the latest research and developments in the areas of chronic pain, reproductive physiology, and acid-base homeostasis
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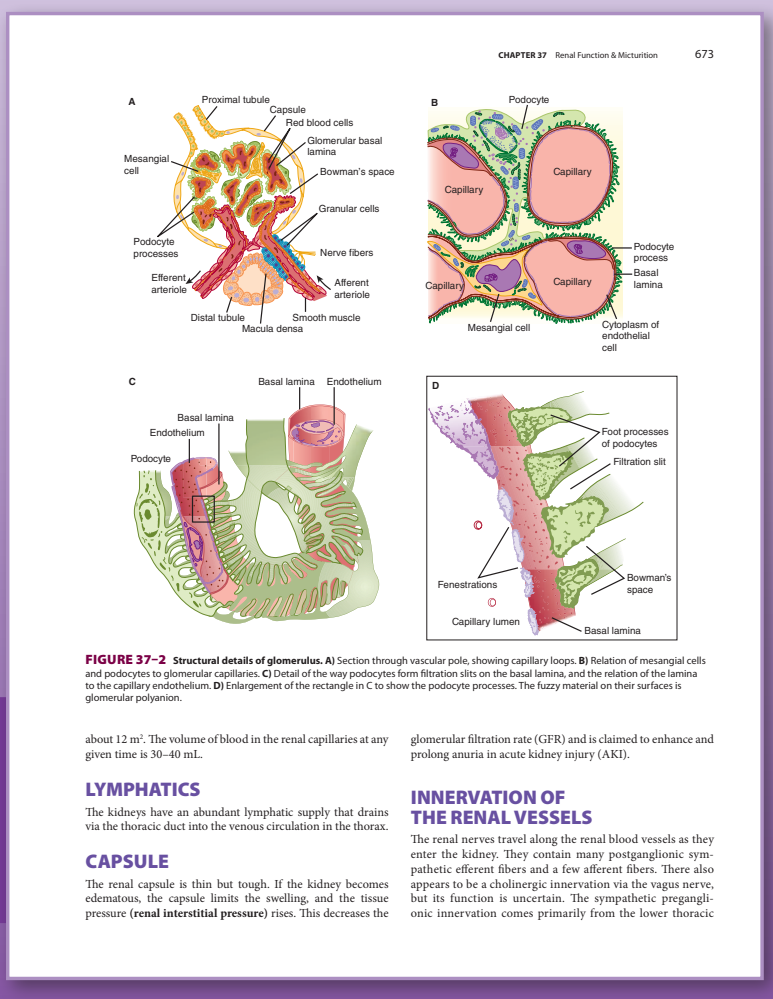

CHAPTER 37 Renal Function & Micturition 673

FIGURE 37–2 Structural details of glomerulus. A) Section through vascular pole, showing capillary loops. **B)** Relation of mesangial cells and podocytes to glomerular capillaries. **C)** Detail of the way podocytes form filtration slits on the basal lamina, and the relation of the lamina to the capillary endothelium. **D)** Enlargement of the rectangle in C to show the podocyte processes. The fuzzy material on their surfaces is glomerular polyanion.

about 12 m^2. The volume of blood in the renal capillaries at any given time is 30–40 mL.

LYMPHATICS

The kidneys have an abundant lymphatic supply that drains via the thoracic duct into the venous circulation in the thorax.

CAPSULE

The renal capsule is thin but tough. If the kidney becomes edematous, the capsule limits the swelling, and the tissue pressure **(renal interstitial pressure)** rises. This decreases the glomerular filtration rate (GFR) and is claimed to enhance and prolong anuria in acute kidney injury (AKI).

INNERVATION OF THE RENAL VESSELS

The renal nerves travel along the renal blood vessels as they enter the kidney. They contain many postganglionic sympathetic efferent fibers and a few afferent fibers. There also appears to be a cholinergic innervation via the vagus nerve, but its function is uncertain. The sympathetic preganglionic innervation comes primarily from the lower thoracic

Taste exhibits after reactions and contrast phenomena that are similar in some ways to visual after images and contrasts. Some of these are chemical "tricks," but others may be true central phenomena. A taste-modifier protein, **miraculin,** has been discovered in a plant. When applied to the tongue, this protein makes acids taste sweet.

Animals, including humans, form particularly strong aversions to novel foods if eating the food is followed by illness. The survival value of such aversions is apparent in terms of avoiding poisons.

CHAPTER SUMMARY

- Olfactory sensory neurons, supporting (sustentacular) cells, and basal stem cells are located in the olfactory epithelium within the upper portion of the nasal cavity.
- The cilia located on the dendritic knob of the olfactory sensory neuron contain odorant receptors that are coupled to G-proteins. Axons of olfactory sensory neurons contact the dendrites of mitral and tufted cells in the olfactory bulbs to form olfactory glomeruli.
- Information from the olfactory bulb travels via the lateral olfactory stria directly to the olfactory cortex, including the anterior olfactory nucleus, olfactory tubercle, piriform cortex, amygdala, and entorhinal cortex.
- Taste buds are the specialized sense organs for taste and are composed of basal stem cells and three types of taste cells (dark, light, and intermediate). The three types of taste cells may represent various stages of differentiation of developing taste cells, with the light cells being the most mature. Taste buds are located in the mucosa of the epiglottis, palate, and pharynx and in the walls of papillae of the tongue.
- There are taste receptors for sweet, sour, bitter, salt, and umami. Signal transduction mechanisms include passage through ion channels, binding to and blocking ion channels, and GPCRs requiring second messenger systems.
- The afferents from taste buds in the tongue travel via the seventh, ninth, and tenth cranial nerves to synapse in the NTS. From there, axons ascend via the ipsilateral medial lemniscus to the ventral posteromedial nucleus of the thalamus, and onto the anterior insula and frontal operculum in the ipsilateral cerebral cortex.

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. A young boy was diagnosed with congenital anosmia, a rare disorder in which an individual is born without the ability to smell. Odorant receptors are
   A. located in the olfactory bulb.
   B. located on dendrites of mitral and tufted cells.
   C. located on neurons that project directly to the olfactory cortex.
   D. located on neurons in the olfactory epithelium that project to mitral cells and from there directly to the olfactory cortex.
   E. located on sustentacular cells that project to the olfactory bulb.
2. A 37-year-old female was diagnosed with multiple sclerosis. One of the potential consequences of this disorder is diminished taste sensitivity. Taste receptors
   A. for sweet, sour, bitter, salt, and umami are spatially separated on the surface of the tongue.
   B. are synonymous with taste buds.
   C. are a type of chemoreceptor.
   D. are innervated by afferents in the facial, trigeminal, and glossopharyngeal nerves.
   E. All of the above.
3. Which of the following does *not* increase the ability to discriminate many different odors?
   A. Many different receptors
   B. Pattern of olfactory receptors activated by a given odorant
   C. Projection of different mitral cell axons to different parts of the brain
   D. High β-arrestin content in olfactory neurons
   E. Sniffing
4. As a result of an automobile accident, a 10-year-old boy suffered damage to the brain including the periamygdaloid, piriform, and entorhinal cortices. Which of the following sensory deficits is he most likely to experience?
   A. Visual disturbance
   B. Hyperosmia
   C. Auditory problems
   D. Taste and odor abnormalities
   E. No major sensory deficits
5. Which of the following are *incorrectly* paired?
   A. ENaC : Sour taste
   B. Gustducin : Bitter taste
   C. T1R3 family of GPCRs : Sweet taste
   D. Heschel sulcus : Smell
   E. Ebner glands : Taste acuity
6. A 9-year-old boy had frequent episodes of uncontrollable nose bleeds. At the advice of his clinician, he underwent surgery to correct a problem in his nasal septum. A few days after the surgery, he told his mother he could not smell the cinnamon rolls she was baking in the oven. Which of the following is true about olfactory transmission?
   A. An olfactory sensory neuron expresses a wide range of odorant receptors.
   B. Lateral inhibition within the olfactory glomeruli reduces the ability to distinguish between different types of odorant receptors.
   C. Conscious discrimination of odors is dependent on the pathway to the orbitofrontal cortex.
   D. Olfaction is closely related to gustation because odorant and gustatory receptors use the same central pathways.
   E. All of the above.
7. A 31-year-old female is a smoker who has had poor oral hygiene for most of her life. In the past few years she has noticed a reduced sensitivity to the flavors in various foods which she used to enjoy eating. Which of the following is *not* true about gustatory sensation?
   A. The sensory nerve fibers from the taste buds on the anterior two-thirds of the tongue travel in the chorda tympani branch of the facial nerve.

End-of-chapter review questions help you assess your comprehension

CLINICAL BOX 6–2

Myasthenia Gravis

Myasthenia gravis is a serious and sometimes fatal disease in which skeletal muscles are weak and tire easily. It occurs in 25 to 125 of every 1 million people worldwide and can occur at any age but seems to have a bimodal distribution, with peak occurrences in individuals in their 20s (mainly women) and 60s (mainly men). It is caused by the formation of circulating antibodies to the muscle type of **nicotinic cholinergic receptors.** These antibodies destroy some of the receptors and bind others to neighboring receptors, triggering their removal by endocytosis. Normally, the number of quanta released from the motor nerve terminal declines with successive repetitive stimuli. In myasthenia gravis, neuromuscular transmission fails at these low levels of quantal release. This leads to the major clinical feature of the disease, muscle fatigue with sustained or repeated activity. There are two major forms of the disease. In one form, the extraocular muscles are primarily affected. In the second form, there is a generalized skeletal muscle weakness. In severe cases, all muscles, including the diaphragm, can become weak and respiratory failure and death can ensue. The major structural abnormality in myasthenia gravis is the appearance of sparse, shallow, and abnormally wide or absent synaptic clefts in the motor endplate. Studies show that the postsynaptic membrane has a reduced response to acetylcholine and a 70–90% decrease in the number of receptors per endplate in affected muscles. Patients with mysathenia gravis have a greater than normal tendency to also have rheumatoid arthritis, systemic lupus erythematosus, and polymyositis. About 30% of patients with mysthenia gravis have a maternal relative with an autoimmune disorder. These associations suggest that individuals with myasthenia gravis share a genetic predisposition to autoimmune disease. The thymus may play a role in the pathogenesis of the disease by supplying helper T cells sensitized against thymic proteins that cross-react with acetylcholine receptors. In most patients, the thymus is hyperplastic; and 10–15% have a thymoma.

THERAPEUTIC HIGHLIGHTS

Muscle weakness due to myasthenia gravis improves after a period of rest or after administration of an **acetylcholinesterase inhibitor** such as **neostigmine** or **pyridostigmine.** Cholinesterase inhibitors prevent metabolism of acetylcholine and can thus compensate for the normal decline in released neurotransmitters during repeated stimulation. **Immunosuppressive drugs** (eg, **prednisone, azathioprine,** or **cyclosporine**) can suppress antibody production and have been shown to improve muscle strength in some patients with myasthenia gravis. **Thymectomy** is indicated especially if a thymoma is suspected in the development of myasthenia gravis. Even in those without thymoma, thymectomy induces remission in 35% and improves symptoms in another 45% of patients.

CLINICAL BOX 6–3

Lambert–Eaton Syndrome

In a relatively rare condition called **Lambert–Eaton myasthenic syndrome (LEMS),** muscle weakness is caused by an autoimmune attack against one of the voltage-gated Ca^{2+} channels in the nerve endings at the neuromuscular junction. This decreases the normal Ca^{2+} influx that causes acetylcholine release. The incidence of LEMS in the United States is about 1 case per 100,000 people; it is usually an adult-onset disease that appears to have a similar occurrence in men and women. Proximal muscles of the lower extremities are primarily affected, producing a waddling gait and difficulty raising the arms. Repetitive stimulation of the motor nerve facilitates accumulation of Ca^{2+} in the nerve terminal and increases acetylcholine release, leading to an increase in muscle strength. This is in contrast to myasthenia gravis in which symptoms are exacerbated by repetitive stimulation. About 40% of patients with LEMS also have cancer, especially small cell cancer of the lung. One theory is that antibodies that have been produced to attack the cancer cells may also attack Ca^{2+} channels, leading to LEMS. LEMS has also been associated with lymphosarcoma; malignant thymoma; and cancer of the breast, stomach, colon, prostate, bladder, kidney, or gallbladder. Clinical signs usually precede the diagnosis of cancer. A syndrome similar to LEMS can occur after the use of **aminoglycoside antibiotics,** which also impair Ca^{2+} channel function.

THERAPEUTIC HIGHLIGHTS

Since there is a high comorbidity with small cell lung cancer, the first treatment strategy is to determine whether the individual also has cancer and, if so, to treat that appropriately. In patients without cancer, **immunotherapy** is initiated. **Prednisone** administration, **plasmapheresis,** and **intravenous immunoglobulin** are some examples of effective therapies for LEMS. Also, the use of **aminopyridines** facilitates the release of acetylcholine in the neuromuscular junction and can improve muscle strength in LEMS patients. This class of drugs causes blockade of presynaptic K^+ channels and promote activation of voltage-gated Ca^{2+} channels. Acetylcholinesterase inhibitors can be used but often do not ameliorate the symptoms of LEMS.

Clinical cases add real-world relevance to the text

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About the Authors

KIM E. BARRETT

Kim Barrett received her PhD in biological chemistry from University College London in 1982. Following postdoctoral training at the National Institutes of Health, she joined the faculty at the University of California, San Diego, School of Medicine in 1985, rising to the rank of Professor of Medicine in 1996, and was named Distinguished Professor of Medicine in 2015. Since 2006, she has also served the University as Dean of the Graduate Division. Her research interests focus on the physiology and pathophysiology of the intestinal epithelium, and how its function is altered by commensal, probiotic, and pathogenic bacteria as well as in specific disease states, such as inflammatory bowel diseases. She has published more than 200 articles, chapters, and reviews, and has received several honors for her research accomplishments including the Bowditch and Davenport Lectureships from the American Physiological Society and the degree of Doctor of Medical Sciences, honoris causa, from Queens University, Belfast. She has been very active in scholarly editing, serving currently as the Deputy Editor-in-Chief of the *Journal of Physiology*. She is also a dedicated and award-winning instructor of medical, pharmacy, and graduate students, and has taught various topics in medical and systems physiology to these groups for more than 20 years. Her efforts as a teacher and mentor were recognized with the Bodil M. Schmidt-Nielson Distinguished Mentor and Scientist Award from the American Physiological Society (APS) in 2012, and she also served as the 86th APS President from 2013–14. Her teaching experiences led her to author a prior volume (*Gastrointestinal Physiology*, McGraw-Hill, 2005; second edition published in 2014) and she was honored to have been invited to take over the helm of Ganong in 2007 for the 23rd and subsequent editions, including this one.

SUSAN M. BARMAN

Susan Barman received her PhD in physiology from Loyola University School of Medicine in Maywood, Illinois. Afterward she went to Michigan State University (MSU) where she is currently a Professor in the Department of Pharmacology/Toxicology and the Neuroscience Program. Dr Barman has had a career-long interest in neural control of cardiorespiratory function with an emphasis on the characterization and origin of the naturally occurring discharges of sympathetic and phrenic nerves. She was a recipient of a prestigious National Institutes of Health MERIT (Method to Extend Research in Time) Award. She is also a recipient of an Outstanding University Woman Faculty Award from the MSU Faculty Professional Women's Association and an MSU College of Human Medicine Distinguished Faculty Award. She has been very active in the American Physiological Society (APS) and served as its 85th President. She has also served as a Councillor as well as Chair of the Central Nervous System Section of APS, Women in Physiology Committee and Section Advisory Committee of APS. She is also active in the Michigan Physiological Society, a chapter of the APS.

SCOTT BOITANO

Scott Boitano received his PhD in genetics and cell biology from Washington State University in Pullman, Washington, where he acquired an interest in cellular signaling. He fostered this interest at University of California, Los Angeles, where he focused his research on second messengers and cellular physiology of the lung epithelium. How the airway epithelium contributes to lung health has remained a central focus of his research at the University of Wyoming and in his current positions with the Departments of Physiology and Cellular and Molecular Medicine, the Arizona Respiratory Center and the Bio5 Collaborative Research Institute at the University of Arizona. Dr. Boitano remains an active member of the American Physiological Society and served as the Arizona Chapter's President from 2010–2012.

HEDDWEN L. BROOKS

Heddwen Brooks received her PhD from Imperial College, University of London and is a Professor in the Departments of Physiology and Pharmacology at the University of Arizona (UA). Dr Brooks is a renal physiologist and is best known for her development of microarray technology to address in vivo signaling pathways involved in the hormonal regulation of renal function. Dr Brooks' many awards include the American Physiological Society (APS) Lazaro J. Mandel Young Investigator Award, which is for an individual demonstrating outstanding promise in epithelial or renal physiology. In 2009, Dr Brooks received the APS Renal Young Investigator Award at the annual meeting of the Federation of American Societies for Experimental Biology. Dr Brooks served as Chair of the APS Renal Section (2011–2014) and currently serves as Associate Editor for the *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* and on the Editorial Board for the *American Journal of Physiology-Renal Physiology* (since 2001). Dr Brooks has served on study sections of the National Institutes of Health, the American Heart Association and recently was a member of the Nephrology Merit Review Board for the Department of Veterans' Affairs.

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Contents

Preface

FROM THE AUTHORS

Once again, we are delighted to launch a new edition of *Ganong's Review of Medical Physiology*—the 25th. The authors have attempted to maintain the highest standards of excellence, accuracy, and pedagogy developed by Fran Ganong over the 46 years during which he educated countless students worldwide with this textbook.

Recognizing the pivotal, and increasing, role for graphical material in effective medical education, our goal for this new edition was to undertake a thorough overhaul of the art program while also making important and timely updates to the text. The vast majority of the figures in this edition have been revised or are wholly new. To aid in understanding across content areas, we have used consistent coloring and diagrammatic schemes, wherever possible, to depict comparable structures, cells and organs. We have also included an increased number of cartoons and conceptual diagrams, as well as flow charts, to promote learning of the integrated material that defines physiology. Overall, we hope that the updates to the volume engage the student and make understanding and assimilation of the material a more pleasurable task.

We remain grateful to the many colleagues and students who contacted us with suggestions for clarifications and new material upon reviewing the 24th edition. This input helps us to ensure that the text is as useful as possible, although the responsibility for any errors, which are almost inevitable in a project of this scope, remains with the author team. Nevertheless, we hope that you enjoy the fruits of our labors, and the new material in the 25th Edition.

This edition is a revision of the original works of Dr. Francis Ganong.

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SECTION I

Cellular & Molecular Basis for Medical Physiology

The detailed study of physiologic system structure and function has its foundations in physical and chemical laws and the molecular and cellular makeup of each tissue and organ system. This first section provides an overview of the basic building blocks that provide the important framework for human physiology. It is important to note here that these initial sections are not meant to provide an exhaustive understanding of biophysics, biochemistry, or cellular and molecular physiology, rather they are to serve as a reminder of how the basic principles from these disciplines contribute to medical physiology discussed in later sections.

In the first part of this section, the following basic building blocks are introduced and discussed: electrolytes; carbohydrates, lipids, and fatty acids; amino acids and proteins; and nucleic acids. Students are reminded of some of the basic principles and building blocks of biophysics and biochemistry and how they fit into the physiologic environment. Examples of direct clinical applications are provided in the Clinical Boxes to help bridge the gap between building blocks, basic principles, and human physiology. These basic principles are followed up with a discussion of the generic cell and its components. It is important to realize the cell is the basic unit within the body, and it is the collection and fine-tuned interactions among and between these fundamental units that allow for proper tissue, organ, and organism function.

In the second part of this introductory section, we take a cellular approach to lay a groundwork of understanding groups of cells that interact with many of the systems discussed in future chapters. The first group of cells presented contribute to inflammatory reactions in the body. These individual players, their coordinated behavior, and the net effects of the "open system" of inflammation in the body are discussed in detail. The second group of cells discussed are responsible for the excitatory responses in human physiology and include both neuronal and muscle cells. A fundamental understanding of the inner workings of these cells, and how they are controlled by their neighboring cells helps the student to understand their eventual integration into individual systems discussed in later sections.

In the end, this first section serves as an introduction, refresher, and quick source of material to best understand systems physiology presented in the later sections. For detailed understanding of any of the chapters within this section, several excellent and current textbooks that provide more in depth reviews of principles of biochemistry, biophysics, cell physiology, muscle and neuronal physiology are provided as resources at the end of each individual chapter. Students who are intrigued by the overview provided in this first section are encouraged to visit these texts for a more thorough understanding of these basic principles.

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General Principles & Energy Production in Medical Physiology

CHAPTER 1

OBJECTIVES

After studying this chapter, you should be able to:

- Define units used in measuring physiologic properties.
- Define pH and buffering.
- Understand electrolytes and define diffusion, osmosis, and tonicity.
- Define and explain the significance of resting membrane potential.
- Understand in general terms the basic building blocks of the cell: nucleotides, amino acids, carbohydrates, and fatty acids.
- Understand higher-order structures of the basic building blocks: DNA, RNA, proteins, and lipids.
- Understand the basic contributions of the basic building blocks to cell structure, function, and energy balance.

INTRODUCTION

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms progressed, various cell groups organized into tissues and organs have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include a gastrointestinal system to digest and absorb food; a respiratory system to take up O_2 and eliminate CO_2; a urinary system to remove wastes; a cardiovascular system to distribute nutrients, O_2, and the products of metabolism; a reproductive system to perpetuate the species; and nervous and endocrine systems to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole. This first chapter focuses on a review of basic biophysical and biochemical principles and the introduction of the molecular building blocks that contribute to cellular physiology.

GENERAL PRINCIPLES

THE BODY AS ORGANIZED "SOLUTIONS"

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an "internal sea" of **extracellular fluid (ECF)** enclosed within the integument of the animal. From this fluid, the cells take up O_2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present-day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

In animals with a closed vascular system, the ECF is divided into the **interstitial fluid,** the circulating **blood plasma,** and **the lymph fluid that bridges these two domains.** The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the **total blood volume.** The interstitial fluid is that part of the ECF that is outside the vascular and lymph systems, bathing the cells. About one-third of the **total body water** is extracellular; the remaining two-thirds is intracellular **(intracellular fluid).** Inappropriate compartmentalization of the body fluids can result in edema (Clinical Box 1–1). In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat.

CLINICAL BOX 1–1

Edema

Edema is the build up of body fluids within tissues. The increased fluid is related to an increased leak from the blood and/or reduced removal by the lymph system. Edema is often observed in the feet, ankles, and legs, but can happen in many areas of the body in response to disease, including those of the heart, lung, liver, kidney, or thyroid.

THERAPEUTIC HIGHLIGHTS

The best treatment for edema includes reversing the underlying disorder. Thus, proper diagnosis of the cause of edema is the primary first step in therapy. More general treatments include restricting dietary sodium to minimize fluid retention and using appropriate diuretic therapy.

The remaining 60% is water. The distribution of this water is shown in Figure 1–1A.

The intracellular component of the body water accounts for about 40% of body weight and the extracellular component for about 20%. Approximately 25% of the extracellular component is in the vascular system (plasma = 5% of body weight) and 75% outside the blood vessels (interstitial fluid = 15% of body weight). The total blood volume is about 8% of body weight. Flow between these compartments is tightly regulated.

UNITS FOR MEASURING CONCENTRATION OF SOLUTES

In considering the effects of various physiologically important substances and the interactions between them, the number of molecules, electrical charges, or particles of a substance per unit volume of a particular body fluid are often more meaningful than simply the weight of the substance per unit volume. For this reason, physiologic concentrations are frequently expressed in moles, equivalents, or osmoles.

Moles

A mole is the gram-molecular weight of a substance, that is, the molecular weight of the substance in grams. Each mole (mol) consists of 6×10^{23} molecules. The millimole (mmol) is 1/1000 of a mole, and the micromole (μmol) is 1/1,000,000 of a mole. Thus, 1 mol of NaCl = 23 g + 35.5 g = 58.5 g and 1 mmol = 58.5 mg. The mole is the standard unit for expressing the amount of substances in the SI unit system.

The molecular weight of a substance is the ratio of the mass of one molecule of the substance to the mass of one-twelfth the mass of an atom of carbon-12. Because molecular weight is a ratio, it is dimensionless. The dalton (Da) is a unit of mass equal to one-twelfth the mass of an atom of carbon-12. The kilodalton (kDa = 1000 Da) is a useful unit for expressing the molecular mass of proteins. Thus, for example, one can speak of a 64-kDa protein or state that the molecular mass of the protein is 64,000 Da. However, because molecular weight is a dimensionless ratio, it is incorrect to say that the molecular weight of the protein is 64 kDa.

Equivalents

The concept of electrical equivalence is important in physiology because many of the solutes in the body are in the form of charged particles. One equivalent (Eq) is 1 mol of an ionized substance divided by its valence. One mole of NaCl dissociates into 1 Eq of Na^+ and 1 Eq of Cl^-. One equivalent of Na^+ = 23 g, but 1 Eq of Ca^{2+} = 40 g/2 = 20 g. The milliequivalent (mEq) is 1/1000 of 1 Eq.

Electrical equivalence is not necessarily the same as chemical equivalence. A gram equivalent is the weight of a substance that is chemically equivalent to 8.0 g of oxygen. The normality (N) of a solution is the number of gram equivalents in 1 L. A 1 N solution of hydrochloric acid contains both H^+ (1.0 g) and Cl^- (35.5 g) equivalents, = (1.0 g + 35.5 g)/L = 36.5 g/L.

WATER, ELECTROLYTES, & ACID/BASE

The water molecule (H_2O) is an ideal solvent for physiologic reactions. H_2O has a **dipole moment** where oxygen slightly pulls away electrons from the hydrogen atoms and creates a charge separation that makes the molecule **polar.** This allows water to dissolve a variety of charged atoms and molecules. It also allows the H_2O molecule to interact with other H_2O molecules via hydrogen bonding. The resulting hydrogen bond network in water allows for several key properties relevant to physiology: (1) water has a high surface tension, (2) water has a high heat of vaporization and heat capacity, and (3) water has a high dielectric constant. In layman's terms, H_2O is an excellent biologic fluid that serves as a solute; it provides optimal heat transfer and conduction of current.

Electrolytes (eg, NaCl) are molecules that dissociate in water to their cation (Na^+) and anion (Cl^-) equivalents. Because of the net charge on water molecules, these electrolytes tend not to reassociate in water. There are many important electrolytes in physiology, notably Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and HCO_3^-. It is important to note that electrolytes and other charged compounds (eg, proteins) are unevenly distributed in the body fluids (Figure 1–1B). These separations play an important role in physiology.

pH & BUFFERING

The maintenance of a stable hydrogen ion concentration ($[H^+]$) in body fluids is essential to life. The **pH** of a solution is defined as the logarithm to the base 10 of the reciprocal of

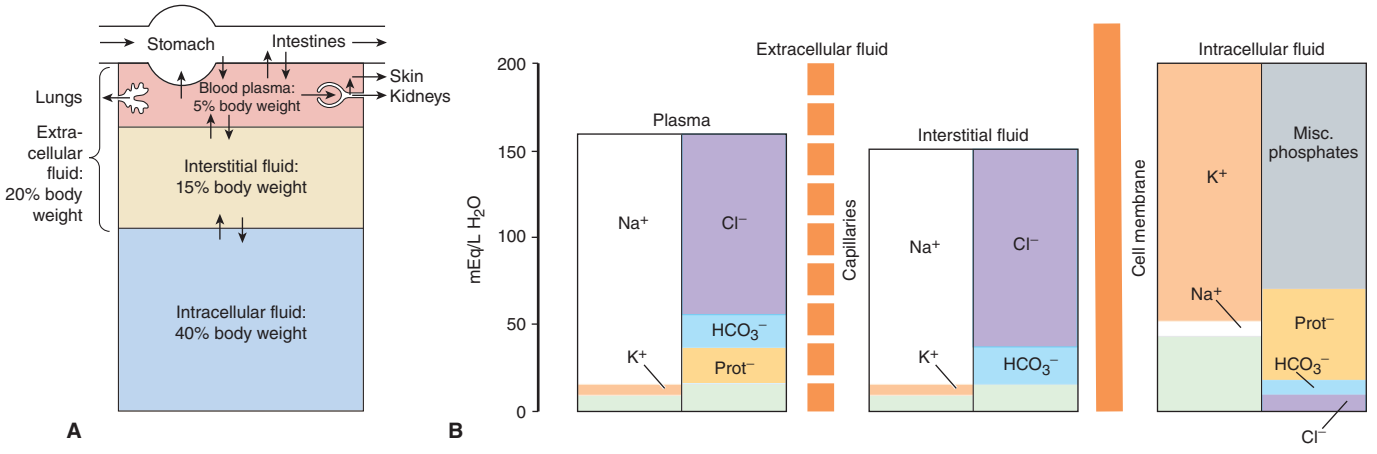

FIGURE 1–1 Organization of body fluids and electrolytes into compartments. A) Body fluids can be divided into intracellular and extracellular fluid compartments (ICF and ECF, respectively). Their contribution to percentage body weight (based on a healthy young adult male; slight variations exist with age and gender) emphasizes the dominance of fluid makeup of the body. Transcellular fluids, which constitute a very small percentage of total body fluids, are not shown. Arrows represent fluid movement between compartments. **B)** Electrolytes and proteins are unequally distributed among the body fluids. This uneven distribution is crucial to physiology. $Prot^-$, protein, which tends to have a negative charge at physiologic pH.

the H^+, that is, the negative logarithm of the $[H^+]$. The pH of water at 25°C, in which H^+ and OH^- ions are present in equal numbers, is 7.0 (Figure 1–2). For each pH unit less than 7.0, the $[H^+]$ is increased 10-fold; for each pH unit above 7.0, it is decreased 10-fold. In the plasma of healthy individuals, pH is slightly alkaline, maintained in the narrow range of 7.35–7.45 (Clinical Box 1–2). Conversely, gastric fluid pH can be quite acidic (on the order of 3.0) and pancreatic secretions can be quite alkaline (on the order of 8.0). Enzymatic activity and protein structure are frequently sensitive to pH; in any given body or cellular compartment, pH is maintained to allow for maximal enzyme/protein efficiency.

Molecules that act as H^+ donors in solution are considered acids, while those that tend to remove H^+ from solutions are considered bases. Strong acids (eg, HCl) or bases (eg, NaOH) dissociate completely in water and thus can most

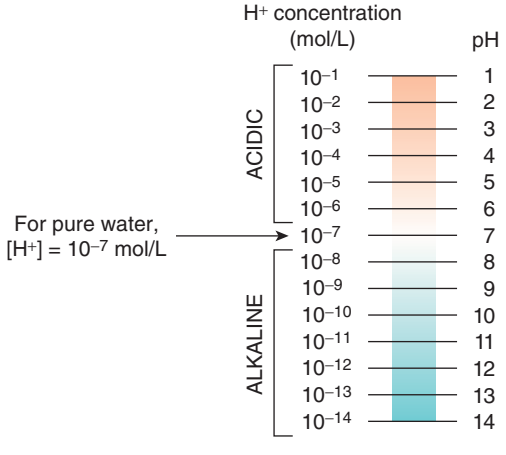

FIGURE 1–2 Proton concentration and pH. Relative proton (H^+) concentrations for solutions on a pH scale are shown.

CLINICAL BOX 1–2

Acid–Base Disorders

Excesses of acid (acidosis) or base (alkalosis) exist when the blood is outside the normal pH range (7.35–7.45). Such changes impair the delivery of O_2 to and removal of CO_2 from tissues. There are a variety of conditions and diseases that can interfere with pH control in the body and cause blood pH to fall outside of healthy limits. Acid–base disorders that result from respiration to alter CO_2 concentration are called respiratory acidosis and respiratory alkalosis. Nonrespiratory disorders that affect HCO_3^- concentration are referred to as metabolic acidosis and metabolic alkalosis. Metabolic acidosis or alkalosis can be caused by electrolyte disturbances, severe vomiting or diarrhea, ingestion of certain drugs and toxins, kidney disease, and diseases that affect normal metabolism (eg, diabetes).

THERAPEUTIC HIGHLIGHTS

Proper treatments for acid–base disorders are dependent on correctly identifying the underlying causal process(es). This is especially true when mixed disorders are encountered. Treatment of respiratory acidosis should be initially targeted at restoring ventilation, whereas treatment for respiratory alkalosis is focused on the reversal of the root cause. Bicarbonate is typically used as a treatment for acute metabolic acidosis. An adequate amount of a chloride salt can restore acid–base balance to normal over a matter of days for patients with a chloride-responsive metabolic alkalosis whereas chloride-resistant metabolic alkalosis requires treatment of the underlying disease.

change the [H^+] in solution. In physiologic compounds, most acids or bases are considered "weak," that is, they contribute or remove relatively few H^+ from solution. Body pH is stabilized by the **buffering capacity** of the body fluids. A **buffer** is a substance that has the ability to bind or release H^+ in solution, thus keeping the pH of the solution relatively constant despite the addition of considerable quantities of acid or base. Of course there are a number of buffers at work in biologic fluids at any given time. All buffer pairs in a homogenous solution are in equilibrium with the same [H^+]; this is known as the **isohydric principle.** One outcome of this principle is that by assaying a single buffer system, we can understand a great deal about all of the biologic buffers in that system.

When acids are placed into solution, there is dissociation of some of the component acid (HA) into its proton (H^+) and free acid (A^-). This is frequently written as an equation:

$$HA \leftrightharpoons H^+ + A^-$$

According to the laws of mass action, a relationship for the dissociation can be defined mathematically as:

$$K_a = [H^+][A^-]/[HA]$$

where K_a is a constant, and the brackets represent concentrations of the individual species. In layman's terms, the product of the proton concentration ([H^+]) times the free acid concentration ([A^-]) divided by the bound acid concentration ([HA]) is a defined constant (K). This can be rearranged to read:

$$[H^+] = K_a\,[HA]/[A^-]$$

If the logarithm of each side is taken:

$$\log[H^+] = \log K_a + \log[HA]/[A^-]$$

Both sides can be multiplied by –1 to yield:

$$-\log[H^+] = -\log K_a + \log[A^-]/[HA]$$

This can be written in a more conventional form known as the **Henderson-Hasselbalch equation:**

$$pH = pK_a + \log[A^-]/[HA]$$

This relatively simple equation is quite powerful. One thing that can be discerned right away is that the buffering capacity of a particular weak acid is best when the pK_a of that acid is equal to the pH of the solution, or when:

$$[A^-] = [HA],\ pH = pK_a$$

Similar equations can be set up for weak bases. An important buffer in the body is carbonic acid. Carbonic acid is a weak acid, and thus is only partly dissociated into H^+ and HCO_3^-:

$$H_2CO_3 \leftrightharpoons H^+ + HCO_3^-$$

If H^+ is added to a solution of carbonic acid, the equilibrium shifts to the left and most of the added H^+ is removed from solution. If OH^- is added, H^+ and OH^- combine, taking H^+ out of solution. However, the decrease is countered by more dissociation of H_2CO_3, and the decline in H^+ concentration is minimized. A unique feature of HCO_3^- is the linkage between its buffering ability and the ability for the lungs to remove CO_2 from the body. Other important biologic buffers include phosphates and proteins.

DIFFUSION

Diffusion is the process by which a gas or a substance in a solution expands, because of the motion of its particles, to fill all the available volume. The particles (molecules or atoms) of a substance dissolved in a solvent are in continuous random movement. A given particle is equally likely to move into or out of an area in which it is present in high concentration. However, because there are more particles in the area of high concentration, the total number of particles moving to areas of lower concentration is greater; that is, there is a **net flux** of solute particles from areas of high concentration to areas of low concentration. The time required for equilibrium by diffusion is proportional to the square of the diffusion distance. The magnitude of the diffusing tendency from one region to another is directly proportional to the cross-sectional area across which diffusion is taking place and the **concentration gradient,** or **chemical gradient,** which is the difference in concentration of the diffusing substance divided by the thickness of the boundary **(Fick's law of diffusion).** Thus,

$$J = -DA\frac{\Delta c}{\Delta x}$$

where J is the net rate of diffusion, D is the diffusion coefficient, A is the area, and $\Delta c/\Delta x$ is the concentration gradient. The minus sign indicates the direction of diffusion. When considering movement of molecules from a higher to a lower concentration, $\Delta c/\Delta x$ is negative, so multiplying by –DA gives a positive value. The permeabilities of the boundaries across which diffusion occurs in the body vary, but diffusion is still a major force affecting the distribution of water and solutes.

OSMOSIS

When a substance is dissolved in water, the concentration of water molecules in the solution is less than that in pure water, because the addition of solute to water results in a solution that occupies a greater volume than does the water alone. If the solution is placed on one side of a membrane that is permeable to water but not to the solute, and an equal volume of water is placed on the other, water molecules diffuse down their concentration (chemical) gradient into the solution (Figure 1–3). This process—the diffusion of **solvent** molecules into a region in which there is a higher concentration of a **solute** to which the membrane is impermeable—is called **osmosis.**

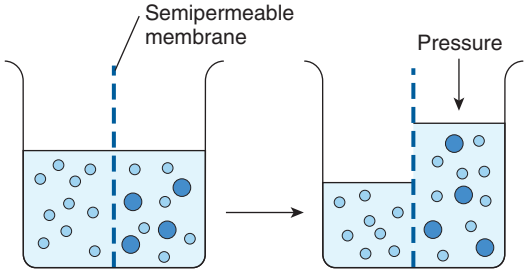

FIGURE 1–3 Diagrammatic representation of osmosis. Water molecules are represented by small open circles, and solute molecules by large solid circles. In the diagram on the left, water is placed on one side of a membrane permeable to water but not to solute, and an equal volume of a solution of the solute is placed on the other. Water molecules move down their concentration (chemical) gradient into the solution, and, as shown in the diagram on the right, the volume of the solution increases. As indicated by the arrow on the right, the osmotic pressure is the pressure that would have to be applied to prevent the movement of the water molecules.

It is an important factor in physiologic processes. The tendency for movement of solvent molecules to a region of greater solute concentration can be prevented by applying pressure to the more concentrated solution. The pressure necessary to prevent solvent migration is the **osmotic pressure** of the solution.

Osmotic pressure—like vapor pressure lowering, freezing-point depression, and boiling-point elevation—depends on the number rather than the type of particles in a solution; that is, it is a fundamental colligative property of solutions. In an **ideal solution,** osmotic pressure (P) is related to temperature and volume in the same way as the pressure of a gas:

$$P = \frac{nRT}{V}$$

where n is the number of particles, R is the gas constant, T is the absolute temperature, and V is the volume. If T is held constant, it is clear that the osmotic pressure is proportional to the number of particles in solution per unit volume of solution. For this reason, the concentration of osmotically active particles is usually expressed in **osmoles.** One osmole (Osm) equals the gram-molecular weight of a substance divided by the number of freely moving particles that each molecule liberates in solution. For biologic solutions, the milliosmole (mOsm; 1/1000 of 1 Osm) is more commonly used.

If a solute is a nonionizing compound such as glucose, the osmotic pressure is a function of the number of glucose molecules present. If the solute ionizes and forms an ideal solution, each ion is an osmotically active particle. For example, NaCl would dissociate into Na^+ and Cl^- ions, so that each mole in solution would supply 2 Osm. One mole of Na_2SO_4 would dissociate into Na^+, Na^+, and SO_4^{2-} supplying 3 Osm. However, the body fluids are not ideal solutions, and although the dissociation of strong electrolytes is complete, the number of particles free to exert an osmotic effect is reduced owing to interactions between the ions. Thus, it is actually the effective concentration **(activity)** in the body fluids rather than the number of equivalents of an electrolyte in solution that determines its osmotic capacity. This is why, for example, 1 mmol of NaCl per liter in the body fluids contributes somewhat less than 2 mOsm of osmotically active particles per liter. The more concentrated the solution, the greater the deviation from an ideal solution.

The osmolal concentration of a substance in a fluid is measured by the degree to which it depresses the freezing point, with 1 mol of an ideal solution depressing the freezing point by 1.86°C. The number of milliosmoles per liter in a solution equals the freezing point depression divided by 0.00186. The **osmolarity** is the number of osmoles per liter of solution (eg, plasma), whereas the **osmolality** is the number of osmoles per kilogram of solvent. Therefore, osmolarity is affected by the volume of the various solutes in the solution and the temperature, while the osmolality is not. Osmotically active substances in the body are dissolved in water, and the density of water is 1, so osmolal concentrations can be expressed as osmoles per liter (Osm/L) of water. In this book, osmolal (rather than osmolar) concentrations are considered, and osmolality is expressed in milliosmoles per liter (of water).

Note that although a homogeneous solution contains osmotically active particles and can be said to have an osmotic pressure, it can exert an osmotic pressure only when it is in contact with another solution across a membrane permeable to the solvent but not to the solute.

OSMOLAL CONCENTRATION OF PLASMA: TONICITY

The freezing point of normal human plasma averages –0.54°C, which corresponds to an osmolal concentration in plasma of 290 mOsm/L. This is equivalent to an osmotic pressure against pure water of 7.3 atmospheres (atm). The osmolality might be expected to be higher than this, because the sum of all the cation and anion equivalents in plasma is over 300 mOsm/L. It is not this high because plasma is not an ideal solution and ionic interactions reduce the number of particles free to exert an osmotic effect. Except when there has been insufficient time after a sudden change in composition for equilibrium to occur, all fluid compartments of the body are in (or nearly in) osmotic equilibrium. The term **tonicity** is used to describe the osmolality of a solution relative to plasma. Solutions that have the same osmolality as plasma are said to be **isotonic;** those with greater osmolality are **hypertonic;** and those with lesser osmolality are **hypotonic.** All solutions that are initially isosmotic with plasma (ie, that have the same actual osmotic pressure or freezing-point depression as plasma) would remain isotonic if it were not for the fact that some solutes diffuse into cells and others are metabolized. Thus, a 0.9% saline solution remains isotonic because there is no net movement of the osmotically active particles in the solution into cells and the particles are not metabolized. On the other hand, a 5% glucose solution is isotonic when initially infused intravenously, but

CLINICAL BOX 1–3

Plasma Osmolality & Disease

Unlike plant cells, which have rigid walls, animal cell membranes are flexible. Therefore, animal cells swell when exposed to extracellular hypotonicity and shrink when exposed to extracellular hypertonicity. Cells contain ion channels and pumps that can be activated to offset moderate changes in osmolality; however, these can be overwhelmed under certain pathologies. Hyperosmolality can cause coma (hyperosmolar coma). Because of the predominant role of the major solutes and the deviation of plasma from an ideal solution, one can ordinarily approximate the plasma osmolality within a few mOsm/L by using the following formula, in which the constants convert the clinical units to millimoles of solute per liter:

$$\text{Osmolarity (mOsm/L)} = 2[Na^+]\ \text{(mEq/L)} + 0.055[\text{Glucose}]\ \text{(mg/dL)} + 0.36[\text{BUN}]\ \text{(mg/dL)}$$

BUN is the blood urea nitrogen. The formula is also useful in calling attention to abnormally high concentrations of other solutes. An observed plasma osmolality (measured by freezing-point depression) that greatly exceeds the value predicted by this formula probably indicates the presence of a foreign substance such as ethanol, mannitol (sometimes injected to shrink swollen cells osmotically), or poisons such as ethylene glycol (component of antifreeze) or methanol (alternative automotive fuel).

glucose is metabolized, so the net effect is that of infusing a hypotonic solution.

It is important to note the relative contributions of the various plasma components to the total osmolal concentration of plasma. All but about 20 of the 290 mOsm in each liter of normal plasma are contributed by Na^+ and its accompanying anions, principally Cl^- and HCO_3^-. Other cations and anions make a relatively small contribution. Although the concentration of the plasma proteins is large when expressed in grams per liter, they normally contribute less than 2 mOsm/L because of their very high molecular weights. The major nonelectrolytes of plasma are glucose and urea, which in the steady state are in equilibrium with cells. Their contributions to osmolality are normally about 5 mOsm/L each but can become quite large in hyperglycemia or uremia. The total plasma osmolality is important in assessing dehydration, overhydration, and other fluid and electrolyte abnormalities (Clinical Box 1–3).

NONIONIC DIFFUSION

Some weak acids and bases are quite soluble in cell membranes in the undissociated form, whereas they cannot cross membranes in the charged (ie, dissociated) form. Consequently, if molecules of the undissociated substance diffuse from one side of the membrane to the other and then dissociate, there is appreciable net movement of the undissociated substance from one side of the membrane to the other. This phenomenon is called **nonionic diffusion.**

DONNAN EFFECT

When an ion on one side of a membrane cannot diffuse through the membrane, the distribution of other ions to which the membrane is permeable is affected in a predictable way. For example, the negative charge of a nondiffusible anion hinders diffusion of the diffusible cations and favors diffusion of the diffusible anions. Consider the following situation,

X	m	Y
K^+	|	K^+
Cl^-	|	Cl^-
$Prot^-$	|	

in which the membrane (m) between compartments X and Y is impermeable to charged proteins ($Prot^-$) but freely permeable to K^+ and Cl^-. Assume that the concentrations of the anions and of the cations on the two sides are initially equal. Cl^- diffuses down its concentration gradient from Y to X, and some K^+ moves with the negatively charged Cl^- because of its opposite charge. Therefore,

$$[K^+_X] > [K^+_Y]$$

Furthermore,

$$[K^+_X] + [Cl_X] + [Prot^-_X] > [K^+_Y] + [Cl^-_Y]$$

that is, more osmotically active particles are on side X than on side Y.

Donnan and Gibbs showed that in the presence of a nondiffusible ion, the diffusible ions distribute themselves so that at equilibrium their concentration ratios are equal:

$$\frac{[K^+_X]}{[K^+_Y]} = \frac{[Cl^-_Y]}{[Cl^-_X]}$$

Cross-multiplying,

$$[K^+_X][Cl^-_X] = [K^+_Y][Cl^-_Y]$$

This is the **Gibbs–Donnan equation.** It holds for any pair of cations and anions of the same valence.

The Donnan effect on the distribution of ions has three effects in the body introduced here and discussed below. First, because of charged proteins ($Prot^-$) in cells, there are more osmotically active particles in cells than in interstitial fluid, and because animal cells have flexible walls, osmosis would make them swell and eventually rupture if it were not for **Na, K ATPase** pumping ions back out of cells. Thus, normal

cell volume and pressure depend on Na, K ATPase. Second, because at equilibrium the distribution of permeant ions across the membrane (m in the example used here) is asymmetric, an electrical difference exists across the membrane whose magnitude can be determined by the **Nernst equation** (see below). In the example used here, side X will be negative relative to side Y. The charges line up along the membrane, with the concentration gradient for Cl^- exactly balanced by the oppositely directed electrical gradient, and the same holds true for K^+. Third, because there are more proteins in plasma than in interstitial fluid, there is a Donnan effect on ion movement across the capillary wall.

FORCES ACTING ON IONS

The forces acting across the cell membrane on each ion can be analyzed mathematically. Chloride ions (Cl^-) are present in higher concentration in the ECF than in the cell interior, and they tend to diffuse along this **concentration gradient** into the cell. The interior of the cell is negative relative to the exterior, and chloride ions are pushed out of the cell along this **electrical gradient.** An equilibrium is reached between Cl^- influx and Cl^- efflux. The membrane potential at which this equilibrium exists is the **equilibrium potential.** Its magnitude can be calculated from the Nernst equation, as follows:

$$E_{Cl} = \frac{RT}{FZ_{Cl}} \ln \frac{[Cl_o^-]}{[Cl_i^-]}$$

where

E_{Cl} = equilibrium potential for Cl^-
R = gas constant
T = absolute temperature
F = the Faraday number (number of coulombs per mole of charge)
Z_{Cl} = valence of Cl^- (–1)
$[Cl_o^-]$ = Cl^- concentration outside the cell
$[Cl_i^-]$ = Cl^- concentration inside the cell

Converting from the natural log to the base 10 log and replacing some of the constants with numeric values holding temperature at 37°C, the equation becomes:

$$E_{Cl} = 61.5 \log \frac{[Cl_i^-]}{[Cl_o^-]} \text{ at } 37°C$$

Note that in converting to the simplified expression the concentration ratio is reversed because the –1 valence of Cl^- has been removed from the expression.

The equilibrium potential for Cl^- (E_{Cl}) in the mammalian spinal neuron, calculated from the standard values listed in Table 1–1, is –70 mV, a value identical to the typical measured resting membrane potential of –70 mV. Therefore, no forces other than those represented by the chemical and electrical gradients need be invoked to explain the distribution of Cl^- across the membrane.

TABLE 1–1 Concentration of some ions inside and outside mammalian spinal motor neurons.

Ion	Concentration (mmol/L of H_2O)		Equilibrium Potential (mV)
	Inside Cell	Outside Cell	
Na^+	15.0	150.0	+60
K^+	150.0	5.5	–90
Cl^-	9.0	125.0	–70

Resting membrane potential = –70 mV

A similar equilibrium potential can be calculated for K^+ (E_K; again, at 37°C):

$$E_K = \frac{RT}{FZ_k} \ln \frac{[K_o^+]}{[K_i^+]} = 61.5 \log \frac{[K_o^+]}{[K_i^+]} \qquad \text{(at 37°C)}$$

where

E_K = equilibrium potential for K^+
Z_K = valence of K^+ (+1)
$[K_o^+]$ = K^+ concentration outside the cell
$[K_i^+]$ = K^+ concentration inside the cell R, T, and F as above

In this case, the concentration gradient is outward and the electrical gradient inward. In mammalian spinal motor neurons E_K is –90 mV (Table 1–1). Because the resting membrane potential is –70 mV, there is somewhat more K^+ in the neurons that can be accounted for by the electrical and chemical gradients.

The situation for Na^+ in the mammalian spinal motor neuron is quite different from that for K^+ or Cl^-. The direction of the chemical gradient for Na^+ is inward, to the area where it is in lesser concentration, and the electrical gradient is in the same direction. E_{Na} is +60 mV (Table 1–1). Because neither E_K nor E_{Na} is equal to the membrane potential, one would expect the cell to gradually gain Na^+ and lose K^+ if only passive electrical and chemical forces were acting across the membrane. However, the intracellular concentration of Na^+ and K^+ remain constant because selective permeability and because of the action of the Na, K ATPase that actively transports Na^+ out of the cell and K^+ into the cell (against their respective electrochemical gradients).

GENESIS OF THE MEMBRANE POTENTIAL

The distribution of ions across the cell membrane and the nature of this membrane provide the explanation for the membrane potential. The concentration gradient for K^+ facilitates its movement out of the cell via K^+ channels, but its electrical gradient is in the opposite (inward) direction. Consequently, an equilibrium is reached in which the tendency of K^+ to move out of the cell is balanced by its tendency to move into the cell, and at that equilibrium there is a slight excess of cations on the outside and anions on the inside. This condition is maintained