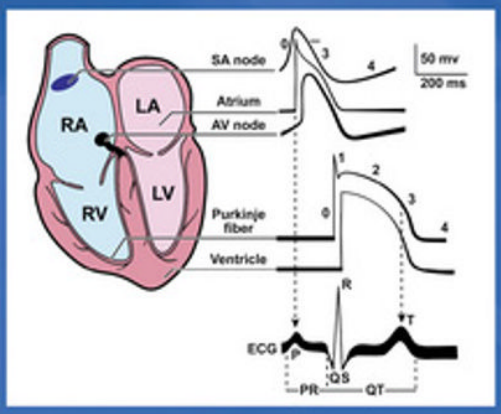
13th Edition

# DUKES' PHYSIOLOGY OF DOMESTIC ANIMALS


**Editor**
William O. Reece

**Associate Editors**
Howard H. Erickson
Jesse P. Goff
Etsuro E. Uemura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# Dukes' Physiology of Domestic Animals

This book is dedicated to my wife Shirley Ann Bruckner Reece, born 12/03/1932, died 09/29/1999.

Thanks to God for the gift of Shirley for the 46 years of our marriage and for the seven children (Mary Kay, Kathy Ann, Barbara Jean, Sara Lucinda, Anna Marie, Susan Theresa, and William Omar II) we were privileged to bring forth. Shirley was raised in Chicago, and received her BS in Foods and Nutrition at Iowa State University. We were united in marriage prior to receiving our degrees in 1954.

Shirley was a model wife and mother. At every age, she had wisdom beyond her years and was admired by all who knew her. She personified joy, received by grace through God, enjoyed life and loved Ames. Because of her example, support for my vocation, and enthusiasm for family, church, community, and the veterinary profession, I have been encouraged to continue with *Dukes' Physiology of Domestic Animals* and thereby give honor for her presence throughout much of my life.

W.O.R.

# Dukes' Physiology of Domestic Animals

## Thirteenth Edition


**Editor**

### William O. Reece DVM, PhD

University Professor Emeritus
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University, Ames, Iowa
USA

**Associate Editors**

### Howard H. Erickson DVM, PhD

Professor Emeritus of Physiology
Department of Anatomy and Physiology
College of Veterinary Medicine
Kansas State University, Manhattan, Kansas
USA

### Jesse P. Goff DVM, PhD

Professor and Anderson Chair
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University, Ames, Iowa
USA

### Etsuro E. Uemura DVM, MS, PhD

Professor
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University, Ames, Iowa
USA



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The first through twelfth editions of this volume were published by Comstock Publishing Associates, an imprint of Cornell University Press. Publication of the 13th edition has been made possible by arrangement with Cornell University Press.

*Editorial Offices*
1606 Golden Aspen Drive, Suites 103 and 104, Ames, Iowa 50010, USA
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
9600 Garsington Road, Oxford, OX4 2DQ, UK

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*Library of Congress Cataloging-in-Publication Data*

Dukes' physiology of domestic animals. – 13th edition / editor, William O. Reece ; associate editors, Howard H. Erickson, Jesse P. Goff, Etsuro E. Uemura.
p. ; cm.
Physiology of domestic animals
Preceded by Dukes' physiology of domestic animals. 12th ed. / edited by William O. Reece. Ithaca, N.Y. : Comstock Pub./Cornell University Press, 2004.
Includes bibliographical references and index.
ISBN 978-1-118-50139-9 (cloth)
I. Reece, William O., editor. II. Erickson, Howard H., 1936- , editor. III. Goff, Jesse P., editor. IV. Uemura, Etsuro E., editor. V. Title: Physiology of domestic animals.
[DNLM: 1. Animals, Domestic–physiology. 2. Physiology, Comparative. SF 768]
SF768
636.089′2–dc23
2014050190

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 9.5/12pt Minion by SPi Publisher Services, Pondicherry, India

1 2015

# Contents

# List of Contributors


### Michele Borgarelli DMV, PhD
Diplomate
European College of Veterinary Internal Medicine (Cardiology)
Associate Professor of Cardiology
Virginia-Maryland Regional College of Veterinary Medicine
Blacksburg, VA
USA
(Senior author of Chapter 39)

### Scott A. Brown VMD, PhD
Diplomate
American College of Veterinary Internal Medicine
Edward H. Gunst Professor of Small Animal Studies and Josiah Meigs Distinguished Teaching Professor
Departments of Physiology and Pharmacology and Small Animal Medicine and Surgery
College of Veterinary Medicine
University of Georgia
Athens, GA
USA
(Author of Chapter 40)

### Richard L. Engen MS, PhD
Professor Emeritus
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Coauthor of Chapter 30)

### Howard H. Erickson DVM, PhD
Emeritus Professor
Department of Anatomy and Physiology
College of Veterinary Medicine
Kansas State University
Manhattan, KS
USA
(Coauthor of Chapters 37 and 41; Editor of Section VI; volume Associate Editor)

### Robert F. Gilmour, Jr PhD
Vice President, Research and Graduate Studies
Professor of Biomedical Sciences
University of Prince Edward Island
Charlottetown, PE
Canada
(Senior author of Chapters 31 and 32)

### Jesse P. Goff DVM, PhD
Professor and Anderson Chair
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Author of Chapters 42–45, 47–50, and 51; Editor of Sections VII, VIII, and IX; volume Associate Editor)

### Patrick J. Gorden DVM
Director
Food Supply Veterinary Medicine
Veterinary Diagnostic and Production Animal Medicine
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Senior author of Chapter 54)

### Jens Häggström DVM, PhD
Diplomate
European College of Veterinary Internal Medicine (Cardiology)
Department of Clinical Sciences
Faculty of Veterinary Medicine and Animal Science
Swedish University of Agricultural Sciences
Uppsala
Sweden
(Coauthor of Chapter 39)

### Eileen M. Hasser PhD
Professor
Department of Biomedical Sciences, College of Veterinary Medicine
Department of Medical Pharmacology and Physiology
Resident Investigator, Dalton Cardiovascular Research Center
University of Missouri
Columbia, MO
USA
(Coauthor of Chapters 34 and 35; Senior author of Chapter 38)

### Cheryl M. Heesch PhD
Professor
Department of Biomedical Sciences, College of Veterinary Medicine
Resident Investigator, Dalton Cardiovascular Research Center
University of Missouri
Columbia, MO
USA
(Senior author of Chapter 35; Coauthor of Chapters 34 and 38)

### Patricia A. Johnson PhD
Professor and Chair
Department of Animal Science
College of Agriculture and Life Sciences
Cornell University
Ithaca, NY
USA
(Author of Chapter 55)

### David D. Kline PhD
Associate Professor
Department of Biomedical Sciences, College of Veterinary Medicine
Resident Investigator, Dalton Cardiovascular Research Center
University of Missouri
Columbia, MO
USA
(Senior author of Chapter 34; Coauthor of Chapters 35 and 38)

### M. Harold Laughlin PhD
Curators' Professor and Chair
Department of Biomedical Sciences, College of Veterinary Medicine
Professor
Department of Medical Pharmacology and Physiology
Investigator, Dalton Cardiovascular Research Center
University of Missouri
Columbia, MO
USA
(Coauthor of Chapters 36 and 38)

### John W. Ludders DVM
Diplomate
American College of Veterinary Anesthesia and Analgesia
Professor Emeritus
Department of Clinical Sciences
College of Veterinary Medicine
Cornell University
Ithaca, NY
USA
(Author of Chapter 26)

### Luis A. Martinez-Lemus DVM, PhD
Associate Professor
Department of Medical Pharmacology and Physiology and Dalton Cardiovascular Research Center
University of Missouri
Columbia, MO
USA
(Senior author of Chapter 36)

### N. Sydney Moïse DVM, MS
Diplomate
American College of Veterinary Internal Medicine
Professor of Medicine
Department of Clinical Sciences
College of Veterinary Medicine
Cornell University
Ithaca, NY
USA
(Coauthor of Chapter 32)

### David C. Poole PhD, DSc
Fellow, American College of Sports Medicine
Professor
Departments of Kinesiology, Anatomy and Physiology
Kansas State University
Manhattan, KS
USA
(Senior author of Chapters 37 and 41)

### William O. Reece DVM, PhD
University Professor Emeritus
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Author of Chapters 11–25, 27–29, 52, and 53; Senior author of Chapter 46; Editor of Sections II, III, IV, and V; volume Editor)

### Dean H. Riedesel DVM, PhD
Diplomate
American College of Veterinary Anesthesia and Analgesia
Professor
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Author of Chapter 33; Senior author of Chapter 30)

### Leo L. Timms PhD
Morrill Professor
Departments of Animal Science and Veterinary Diagnostics and Production Animal Medicine
Colleges of Agriculture and Veterinary Medicine
Iowa State University
Ames, IA
USA
(Coauthor of Chapter 54)

### Darrell W. Trampel DVM, PhD (Deceased)
Professor
Poultry Extension Veterinarian
Department of Veterinary Diagnostic and Production Animal Medicine
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Coauthor of Chapter 46)

### Etsuro E. Uemura DVM, PhD
Professor
Department of Biomedical Sciences
College of Veterinary Medicine
Iowa State University
Ames, IA
USA
(Author of Chapters 1–10; Editor of Section I; volume Associate Editor)

# Preface

We are pleased to continue the legacy established in 1933 by Dr H. Hugh Dukes when the lithoprinted first edition of *The Physiology of Domestic Animals* was published by Edwards Brothers, Inc., Ann Arbor, Michigan. The preface by H.H. Dukes included the following opening statement:

> This book was written mainly at Iowa State College; it was completed at Cornell University. Based on nearly fifteen years of experience in the field of animal physiology, it represents an attempt to provide students of veterinary medicine with a suitable textbook for their course in physiology. I believe also, on the basis of experience, that much of the book will be useful to students of animal husbandry. Furthermore, I venture the opinion that practitioners of veterinary medicine who wish to keep up with the trend in physiology will find the book helpful.

The first two lithoprinted editions were followed by the third revised edition in 1935 with an improved format, printed from type, by Comstock Publishing Company, Inc., Ithaca and New York. The seventh edition, the last edition authored by Dr Dukes, was published in 1955. It was the first to be published by Comstock Publishing Associates, a Division of Cornell University Press, Ithaca and London, who continued as publishers for the 8th, 9th, 10th, 11th, and 12th editions, which published in 2004.

The 8th edition was the first to be multiauthored and was begun by Dr Melvin J. Swenson as editor. Dr Swenson continued as editor for the 9th and 10th editions and coedited with Dr William O. Reece for the 11th edition. Dr Reece edited the 12th edition, the last one to be published by Cornell University Press. Publishing rights were licensed by Cornell University Press to John Wiley & Sons, Inc. for the 13th multiauthored book with William O. Reece, Editor, and Howard H. Erickson, Jesse P. Goff, and Etsuro E. Uemura, Associate Editors.

The vision of Dr Dukes for his textbook *The Physiology of Domestic Animals*, which was to provide students of veterinary medicine with a suitable textbook for their courses in physiology, and to be useful to students in animal husbandry and practitioners of veterinary medicine, has been a goal throughout all the years since the first edition and is being continued with the 13th edition.

Many features of the previous edition will be continued that include the following for each chapter.

1. The text content is preceded by an outline listing the first- and second-order headings.
2. A brief introduction.
3. A list of questions that precede each first-order heading that alert students to important information that follows. Answers to the questions will be found in the text that follows.
4. Key words are in bold color on first use.
5. Meaningful self-evaluation exercises are provided at the end of each chapter that feature important facts or concepts.
6. Answers, explanations, or solutions are provided for each self-evaluation exercise.

Conscientious use of the above features provide not only an organized study when first used, but also a quick review when needed for future use.

Our effort to identify the 13th edition as an all-new work is apparent in many ways. The chapters within several sections have a single author and their number reduced in other sections. This permits greater consistency of presentation and content overlap is minimized.

An important change was made for the renal and respiratory chapters. Previously the entire topic of each was presented in a single chapter. Now, the one single chapter has been divided into several chapters where emphasis can be focused on a single concept. This will facilitate lecture organization and selective referral.

A notable addition to this edition is the provision of full color throughout. The use of color not only enhances the attractiveness but also provides a means for contrast within the text and figures.

Other features include a downloaded version of the 13th edition available online. All figures and tables will be on PowerPoint to facilitate lecture presentations. An effort has been made to reduce pagination of the volume while at the same time providing increasing font size and space for figures and tables. Overall, the 13th edition of *Dukes' Physiology of Domestic Animals* will continue with its classic stature as a comprehensive resource, not only stressing basic physiology with application to animals, but also with updated features to assist teaching effectiveness.

William O. Reece

# Acknowledgments

We are grateful for the efforts of Erica Judisch, Commissioning Editor, Veterinary Medicine, Wiley Blackwell, Heidi Lovette, Science Editor, Cornell University Press, and Tonya Cook, Rights Manager, Cornell University Press, for successfully negotiating the transfer of rights from Cornell University Press to Wiley Blackwell. Their professionalism and patience throughout a complex process is appreciated.

Cornell University Press has been as important to the success of the book as the legacy of *The Physiology of Domestic Animals*, that began with Dr Dukes, whose publishing career was spanned at Ithaca. The continued integrity and cooperation of Cornell University Press as publisher during my tenure was always apparent. My appreciation and thanks are extended to all directors, science editors and staff throughout the years for their efforts.

A project of this complexity requires participation by many individuals. My indebtedness and thanks are extended to these very nice people.

The authors and section editors, in addition to their teaching, research, service, and administrative duties, devoted their talents to this project.

Much of my time during the preliminary phases and preparation of manuscripts involved the Veterinary Medical Library, Iowa State University. Kristi Schaaf, Director, was a friendly, knowledgeable resource for location of reference material and other information as needed. Also helpful was Lana Greve, Library Assistant.

Dr Anumantha Kanthasamy, Professor and Chair, Department of Biomedical Sciences, College of Veterinary Medicine, Iowa State University, provided office resources and services, assisted by Linda Erickson, Administrative Specialist, William Robertson, Laboratory Supervisor, and Kim Adams. Paige Behrens, Office Assistant and Iowa State University student in Graphic Design, assisted by Megan Demoss, transformed my manuscripts and all other essential items to computer documents.

Drs Howard Erickson, Jesse Goff, and Etsuro Uemura, Associate Editors for this volume, helped in the planning and its execution. Their advice, enthusiasm, and hard work have never wavered, and their innovations have provided a new freshness. In addition, Dr Howard Erickson provided faithful support and planning for the 12th edition.

Mal Rooks Hoover, Certified Medical Illustrator, College of Veterinary Medicine, Kansas State University, generously provided her expertise to enhance the effectiveness, for many of the figures, including color, that appear in the chapters authored by Dr Reece, Dr Erickson, and several other authors in the cardiovascular section. We are grateful for her effort on our behalf.

Dr Darrell Trampel sadly passed away during the production of this book. He will be greatly missed by colleagues and friends.

Nancy Turner, Senior Development Editor, Wiley Blackwell, provided timely information and guidance from the very beginning of the project. Her knowledge, experience, professionalism, and assistance in all phases were extremely helpful. This effort was continued by the expertise of Catriona Cooper, Senior Project Editor, Wiley Blackwell, in finalizing the manuscript and the associated details required for submission to the copy editor. Our thanks are extended to Nancy and Catriona on behalf of all the authors, for their patient and friendly assistance and attention to details. Extended thanks to Kathy Syplywczak, Project Manager, and Jolyon Philips, copy editor, for their expertise and attention to detail that was needed in making this edition a volume for which we can all be proud.

Above all, I thank God for this community of people and for His answer to my many prayers for this project.

William O. Reece

# Tributes to Drs H. Hugh Dukes and Melvin J. Swenson

## Veterinary educators, researchers, authors, and administrators

**Dr H. Hugh Dukes (1895–1987)**

BS, Clemson College, 1915; DVM, Iowa State College, 1918; United States Army, 1918–1920; MS, 1923, Iowa State College; Assistant Professor, Veterinary Physiology and Physiology Research, Division of Veterinary Medicine, Iowa State College, 1921–1932; Professor and Head, Department of Veterinary Physiology, New York State Veterinary College at Cornell University, 1932–1960. Author, *The Physiology of Domestic Animals*, Editions 1–7, 1933–1955.

**Dr Melvin J. Swenson (1917–2005)**

DVM, 1943, College of Veterinary Medicine, Kansas State University; United States Army Veterinary Corps, 1943–1946; MS, 1947, PhD, 1950, College of Veterinary Medicine, Iowa State University; Professor and Head, Veterinary Physiology and Pharmacology, College of Veterinary Medicine, Iowa State University, 1957–1973; Professor of Veterinary Anatomy, Physiology, and Pharmacology, College of Veterinary Medicine, Iowa State University, 1973–1987; Editor, *Dukes' Physiology of Domestic Animals*, Editions 8–11, 1970–1993.

# About the companion website

This book is accompanied by a companion website:

## www.wiley.com/go/reece/physiology

The website includes:

- Review questions and self-evaluation exercises from the book
- Powerpoints of all figures from the book for downloading
- PDFs of all tables from the book for downloading

SECTION I

# Neurophysiology

**Section Editor: Etsuro E. Uemura**

# 1 Nervous Tissue

**Etsuro E. Uemura**
Iowa State University, Ames, IA, USA



The nervous system has two categories of cells, neurons (Greek *neuron*, nerve) and neuroglia (Greek *glia*, glue). Their names reflect the fact that neurons give rise to nerves, while neuroglia are thought of as cells simply holding neurons together. Neurons and neuroglia are far more complex in their shape than cells in any other tissue. Their morphological heterogeneity reflects the functional complexity of the nervous system. Neurons and neuroglia play different roles in the nervous tissue. Neurons are specialized in information processing. Specialized contact areas called synapses mediate signals from one neuron to others. Synapses are the basis of complex neuronal networks designed for information processing. Neurons stop dividing within a few months after birth. Therefore, if nerve damage involves cell bodies in the adult animal, resulting neuronal death will permanently change the structure and functions of the affected areas. Unlike neurons, neuroglia continue to divide. This glial capacity to divide is essential for their structural and functional support of neurons. Neurons and glial cells require a chemically stable environment. Endothelial cells of the central nervous system and the choroid plexus help maintain such an environment by regulating molecules secreted into the interstitial fluid and cerebrospinal fluid (CSF).

## Division of the nervous system

1 Differentiate between the central nervous system and the peripheral nervous system.
2 What is the relationship between the autonomic and the central nervous systems?

The nervous system can be classified into three systems: the central nervous system, peripheral nervous system and autonomic nervous system. The **central nervous system (CNS)** is composed of the cerebrum, cerebellum, brainstem, and spinal cord. It is the central processing unit of the entire nervous system. All nervous tissue other than the cerebrum, brainstem, cerebellum, and spinal cord is referred to as the **peripheral nervous system (PNS)**. The PNS comprises the nerves, ganglia (spinal, cranial, sympathetic trunk, collateral, terminal), and sensory receptors. The PNS conveys (i) sensory signals about the external and internal environment of the body to the CNS and (ii) motor signals from the CNS to the peripheral effectors (skeletal muscle, cardiac muscle, smooth muscle, secretory glands). Certain neural components of the CNS and PNS regulate the visceral organs, smooth muscles (e.g., vascular, pupillary dilator, pupillary sphincter, ciliary, orbital, arrector pili), and glands (salivary, lacrimal, nasal, adrenal). These neural components of the CNS and PNS are collectively referred to as the **autonomic nervous system (ANS)**. The ANS is, in general, not under voluntary control, but rather its action is controlled by the hypothalamus. The ANS consists of many specialized neural components (e.g., nuclei, ganglia, nerves, tracts and visceral plexus). For example, the increased heart rate in the "fight or flight" response involves the hypothalamus (i.e., CNS), intermediolateral nucleus in the spinal cord (i.e., CNS), ganglia (i.e., PNS) and peripheral nerves (i.e., PNS).

## Cells of the nervous system

1 What are three different types of neurons?
2 What are the functions of an axon and a dendrite?
3 What is the axon hillock? What is its functional significance?
4 What are the structural and functional differences between myelinated and nonmyelinated axons?
5 Name the neuroglia of the CNS and PNS, and explain their functions.
6 How do Schwann cells differ from oligodendrocytes?
7 What are the bases of classifying peripheral nerve fibers?

*Dukes' Physiology of Domestic Animals*, Thirteenth Edition. Edited by William O. Reece, Howard H. Erickson, Jesse P. Goff and Etsuro E. Uemura.

Companion website: www.wiley.com/go/reece/physiology

Neurons and neuroglia are the two categories of cells of the nervous system. **Neurons** share certain universal cellular features with all other cells in the body; however, neurons have certain unique features that separate them from other cells. For example, they have distinctive cell shapes with a membrane capable of generating electrical impulses. They transfer impulses from one neuron to the next via synapses (Greek *synapsis*, a connection), the specialized contact areas between two neurons. Although transmission of impulses is a basic biological function performed by all neurons, their electrical property alone does not explain the diverse roles they play in a complex neural network. **Neuroglia** are the most abundant cells in nervous tissue (over 90%), filling essentially all the space in the nervous system not occupied by neurons and blood vessels. They provide structural, metabolic, and protective support for neurons.

## Neurons

The most obvious difference between neurons and other cells in the body lies in their great variety of shapes and sizes. Neurons have highly irregular shapes with one or more cellular processes extending from the cell body (Figure 1.1). The **neuronal cell body** (also referred to as the **soma** or **perikaryon**) contains the same organelles found in other cells. However, the rough endoplasmic reticulum and polysomes (collectively referred to as **Nissl substance**) are especially abundant in perikarya. Each neuron has a single axon. The area of the cell body where an axon originates is the **axon hillock**. The axon hillock is also referred to as the trigger zone, as action potentials are generated here. Just distal to the axon hillock is the **initial segment** of the axon.

Axons frequently branch at a distance from the cell body, forming synapses with other neurons, muscle cells, or glands. The remaining neuronal processes are **dendrites** (Greek *dendron*, tree) that resemble trees (Figure 1.1). Dendrites and perikarya are the primary receptive sites of impulses from other neurons. The number of dendrites varies depending on the type of neuron (Figure 1.2). Action potentials are generated at the axon hillock. An action potential travels along the axon at a speed that varies from 0.5 to 120 m/s. Larger axons, over 1 μm in diameter, are myelinated in both the CNS and PNS, while axons less than 1 μm in diameter are not myelinated. Myelinated axons conduct impulses much faster than nonmyelinated axons. There is a constant relationship between axon diameter, internodal length (i.e., length of each myelin sheath), and conduction velocity. Larger axons have longer internodes and faster conduction velocities. Neurons are contiguous not continuous and they communicate with each other via synapses. If a neuron is linked to more than one recipient neuron, its axon branches to make synaptic connections with all the recipient neurons. Neurons, like muscle cells, do not divide once they reach maturity. Therefore, any physical injury that leads to neuronal death will permanently change the structure and functions of the affected areas.

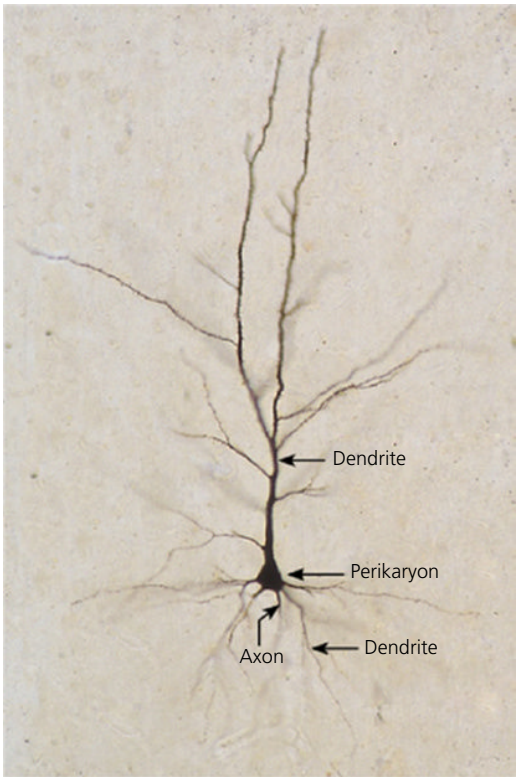



**Figure 1.1** A cortical multipolar neuron stained with the Golgi silver impregnation method showing the perikaryon, axon, and dendrites. Only one axon emerges from the perikaryon. All other neuronal processes are dendrites.

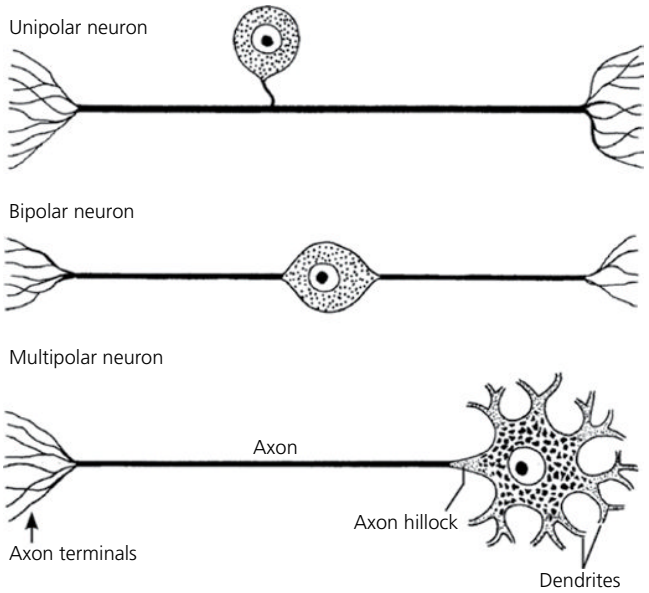



**Figure 1.2** The classification of neurons is based on the number of cell processes emerging from the cell body. Cell bodies of unipolar neurons are present in the spinal and cranial ganglia. Cell bodies of bipolar neurons are present in the retina of the eye, spiral ganglia of the auditory nerve, vestibular ganglia of the vestibular nerve, and olfactory epithelium. The majority of neurons are multipolar neurons.

The color of fresh nervous tissue reflects neuronal cell bodies and axons. Areas with a high population of perikarya (e.g., cerebral cortex) appear gray and are referred to as the **gray matter**. In contrast, areas mainly made of myelinated axons appear white because of the presence of lipid in myelin. The name **white matter** is used to indicate such areas.

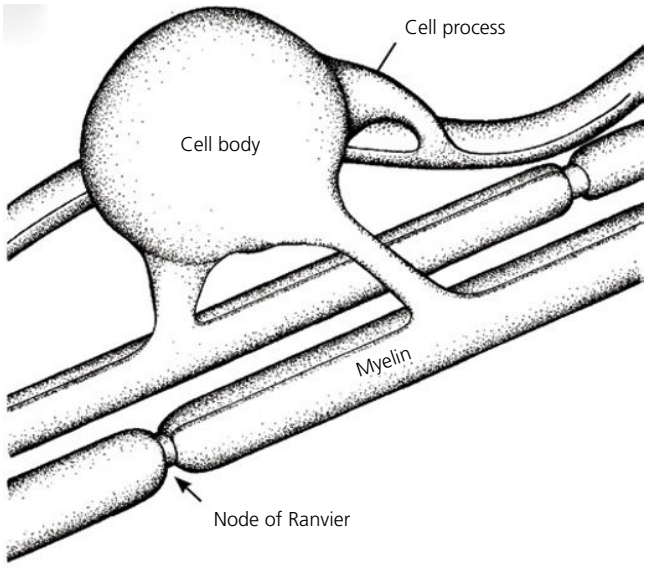
### Classification of neurons

Neurons are classified into three types (unipolar, bipolar, and multipolar) based on the number of cellular processes extending from the cell body (Figure 1.2). **Unipolar neurons** have a single stem process that bifurcates to form two processes, the peripheral and central. Unipolar neurons innervate peripheral tissues, bringing somatic and visceral sensory information to the CNS. Thus they are also referred to as primary sensory neurons. **Bipolar neurons** have two processes. Bipolar neurons are located in the retina of the eye (see Figure 7.4), spiral ganglion of the cochlea (see Figure 6.2B), vestibular ganglion of the vestibular organ (see Figure 9.1), and olfactory epithelium (see Figure 5.2). Bipolar neurons are sensory neurons. Their peripheral processes innervate sensory receptors, bringing sensory signals to the CNS. An exception to this rule is the olfactory cells. A terminal branch of the olfactory cell forms a dendritic bulb and its cilia act as receptors detecting the chemical environment in nasal air. **Multipolar neurons** are the most prevalent type. As the name "multipolar" suggests, each neuron has numerous cell processes (one axon and many dendrites). The length and arrangement of neuronal processes vary considerably.

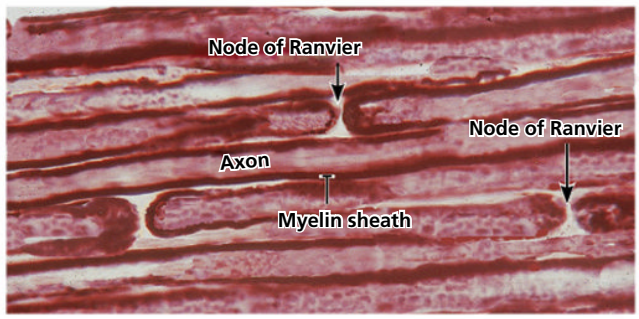
### Neuroglia

Neuroglia are generally small in size and outnumber neurons by as much as 10 : 1 to 50 : 1. Their small size is such that only their nuclei are clearly seen in routine histological preparations. The nuclei range in diameter from 3 to 10 μm, which is about the size of the smallest neurons. Unlike neurons, neuroglia have the capacity to divide. Schwann cells are the only neuroglia of the PNS. Neuroglia of the CNS are oligodendrocytes, ependymal cells, microglia, and astrocytes.

**Schwann cells** (also referred to as neurolemmocytes) support axons of the PNS, depending on the size of the axon, in two ways. Schwann cells associated with most axons over 1 μm in diameter form myelin sheaths by concentrically wrapping their plasma membrane around the axon (up to 50 or more layers) (Figure 1.3C). Schwann cells are arranged side by side along the axon. Each Schwann cell forms an **internode** of the myelin sheath of various lengths (25–1000 μm). The larger axons have longer internodes and faster conduction speed. The junction between each internode is the **node of Ranvier** (Figure 1.3B). Schwann cells are also associated with most axons less than 1 μm in diameter. Schwann cells associated with smaller axons do not form a myelin sheath, but they hold many smaller axons in their processes. **Oligodendrocytes** (Greek *oligos*, little; *dendron*, dendrite) are small neuroglia of the CNS. They are present




(A)

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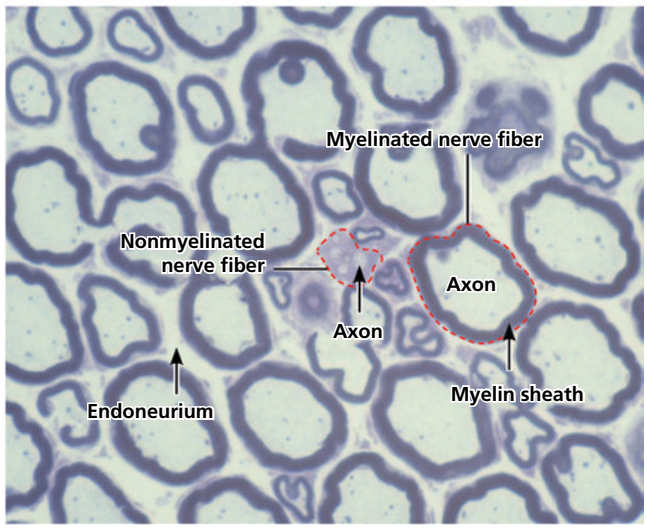


(C)

**Figure 1.3** (A) Oligodendrocytes myelinate most axons about 1 μm and over in diameter. Each oligodendrocyte contributes segments of myelin sheath (i.e., internodes) for many axons. (B) Longitudinal section of a peripheral nerve showing axons and their darkly stained myelin sheath, and nodes of Ranvier. (C) Electron micrograph of nonmyelinated and myelinated axons. Nonmyelinated axons are much smaller in size than myelinated ones. Each axon is surrounded by endoneurium.

in both the white and gray matter. Oligodendrocytes have numerous cell processes that extend to adjacent axons to form myelin sheaths (Figure 1.3A). Generally, oligodendrocytes myelinate most axons over 1 μm in diameter to speed conduction velocity (Tables 1.1 and 1.2).

**Table 1.1** Classification of peripheral nerve fibers by the letter system.

| Type | Diameter (μm) | Conduction velocity (m/s) | Function |
|---|---|---|---|
| Aα | 12–22 | 70–120 | Somatic motor, proprioception |
| Aβ | 5–12 | 30–70 | Touch, pressure |
| Aγ | 3–8 | 15–30 | Motor to muscle spindle |
| Aδ | 1–5 | 12–30 | Fast pain and temperature |
| B | 1–3 | 3–15 | Visceral motor (preganglionic) |
| C | 0.3–1.5 | 0.3–1.5 | Visceral motor (postganglionic), slow pain and temperature |

**Table 1.2** Classification of peripheral sensory nerve fibers by the numerical system.

| Type | Letter equivalent | Diameter (μm) | Origin |
|---|---|---|---|
| Ia | Aα | 12–22 | Muscle spindle (primary) |
| Ib | Aα | 10–15 | Golgi tendon organ |
| II | Aβ, Aγ | 5–12 | Muscle spindle (secondary), touch, pressure |
| III | Aδ | 1–5 | Fast pain and temperature |
| IV | C | 0.3–1.5 | Slow pain and temperature |

An axon and myelin sheath (if present) together form a **nerve fiber**. Peripheral nerve fibers vary in diameter, ranging from 0.3 to 22 μm. Nerve fibers are classified according to their fiber diameter, speed of conduction, and functions. The largest nerve fibers are classified as Aα and the smallest ones as C (Table 1.1). Since the conduction velocity reflects myelination and the axonal diameter, Aα nerve fibers that innervate the skeletal muscle are heavily myelinated and have the fastest conduction velocity. Other type A (β, γ, δ) and B nerve fibers are progressively smaller and poorly myelinated. Most nerve fibers classified as C are not myelinated and have a slow conduction velocity. A numerical system (I, II, III, IV) is used to classify sensory nerve fibers (Table 1.2). The largest sensory fibers are classified as Ia and the smallest ones as IV. Type IV sensory fibers are mostly nonmyelinated.

**Microglia** comprise 10–20% of all neuroglia. Microglia are the macrophages of the CNS and act as the first line of defense against tissue injury or infection. Once activated, microglia proliferate and assume a phagocytic role by developing into round, often large cells. They clear debris from the injured area. However, phagocytosis is not the only means of destroying foreign invaders. For example, microglia are also known to release nitric oxide, which prevents viral replication.

**Astrocytes** (Greek *astron*, star) are star-shaped cells with numerous long cell processes (Figure 1.4). However, they appear as cells with pale ovoid nuclei with routine staining. Astrocytes represent approximately 50% of the glial cell population in the CNS. They provide structural and metabolic support for neurons. For example, astrocytes seal the outer and inner surfaces of the CNS by forming the outer and

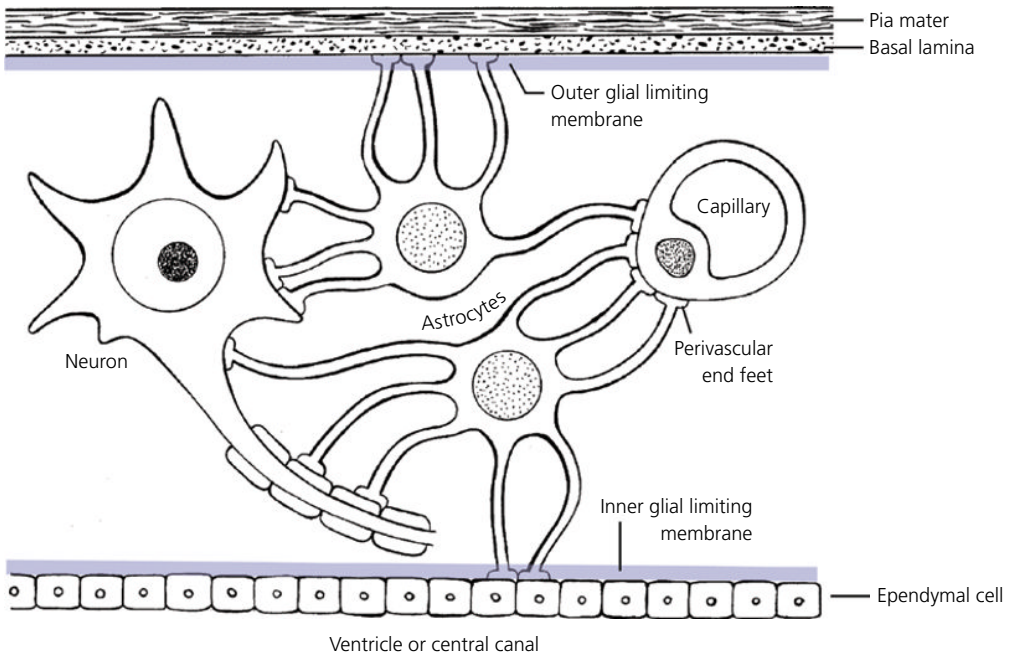


**Figure 1.4** Relationship of astrocytes to other cellular and structural components of the central nervous system. Astrocytic processes surround neurons, individual or groups of synapses, capillaries and internodal areas between myelin sheaths. They also form a plexus beneath the pia mater (outer glial limiting membrane) and ependyma (inner glial limiting membrane).

inner glial limiting membranes, respectively. Astrocytes release **neurotrophic factors** (e.g., nerve growth factor), which are important for neuronal survival. Elongation of axons and dendrites requires not only the physical presence of astrocytes, but also **extracellular adhesion molecules** (e.g., laminin, fibronectin) released from astrocytes. Astrocytic processes cover the greater part of neurons, synaptic sites, internodal areas, and capillaries. Astrocytic covering of synaptic sites and internodal areas may prevent signal interference from nearby synapses and axons.

The astrocytic processes that cover capillaries are the **perivascular end feet**. Experimental studies suggest that such close contact between astrocytes and the capillary endothelium is important for glucose transport, regulation of extracellular environment (pH, ion concentration, osmolarity), glutamate metabolism, and maintenance of the endothelial blood–brain barrier. Astrocytes maintain the optimal extracellular environment for neurons and neuroglia. For example, astrocytes are equipped with ionic channels for potassium ($K^+$), sodium ($Na^+$), chloride ($Cl^-$), bicarbonate ($HCO_3^-$) and calcium ($Ca^{2+}$). Therefore, they are capable of exchanging these ions with neighboring cells, including neurons. Excitation of neurons accompanies a marked flux of $K^+$ into the extracellular space. However, an increase in $K^+$ concentration is prevented by astrocytes, which take up $K^+$ and relocate it to areas with low neuronal activities or release it to the blood and CSF. Astrocytes also prevent the build-up of potentially neurotoxic substances. Glutamate, for example, is a neurotransmitter that excites postsynaptic neurons (see Figure 3.2B). It is also neurotoxic if accumulated beyond a certain concentration. Astrocytes prevent excess accumulation of extracellular glutamate by metabolizing glutamate into glutamine. Glutamine from astrocytes is used by neurons for synthesis of new glutamate, which is repackaged into synaptic vesicles to be used as a neurotransmitter.

Astrocytes participate in the repair process following tissue injury. Under slowly degenerative conditions, astrocytes retain their small size. Thus only special stains can observe their reactive cytoplasm and cell processes. However, typical astrocytic reactions to pathological conditions are cellular swelling and hyperplasia (Greek *hyper*, above; *plasis*, formation; a condition characterized by an increase in the number of cells). Astrocytic swelling is often induced by injuries from hypoxia (a condition where oxygen levels are below normal), trauma, and hypoglycemia (Greek *hypo*, under; *glykys*, sweet; *haima*, blood; the presence of low sugar levels in the blood). Swelling usually reflects changes in extracellular ionic concentrations (e.g., increase in $K^+$, decrease in $Na^+$ and $Cl^-$, accumulation of glutamate). Destructive lesions of the CNS, especially those caused by trauma, promote astrocytic hyperplasia. In a cerebral infarct, i.e., an area of necrosis (Greek *nekrosis*, deadness; death of tissue) resulting from insufficient blood supply, astrocytes proliferate along the edge of the necrotic area, often sealing off the lesioned area.

**Ependymal cells** (Greek *ependyma*, upper garment) cover the ventricles and central canal of the CNS (Figure 1.5). They also line the choroid plexus. The ependymal cells of the ventricles and central canal form a selective barrier between the nervous tissue and **CSF**. Junctional complexes are present between adjacent ependymal cells, enabling them to modify the CSF by secretory or absorptive processes. The choroid plexus secretes CSF (Table 1.3). However, it is not the only source of CSF. CSF is also released from the brain through (i) the ependymal lining of the ventricles and central canal and (ii) the pia–outer glial limiting membrane that covers the external surface of the CNS.

The CSF leaves the ventricular system via a small opening, the lateral aperture of the fourth ventricle, to enter the subarachnoid space. It also enters the central canal of the caudal medulla oblongata and spinal cord. The CSF in the subarachnoid

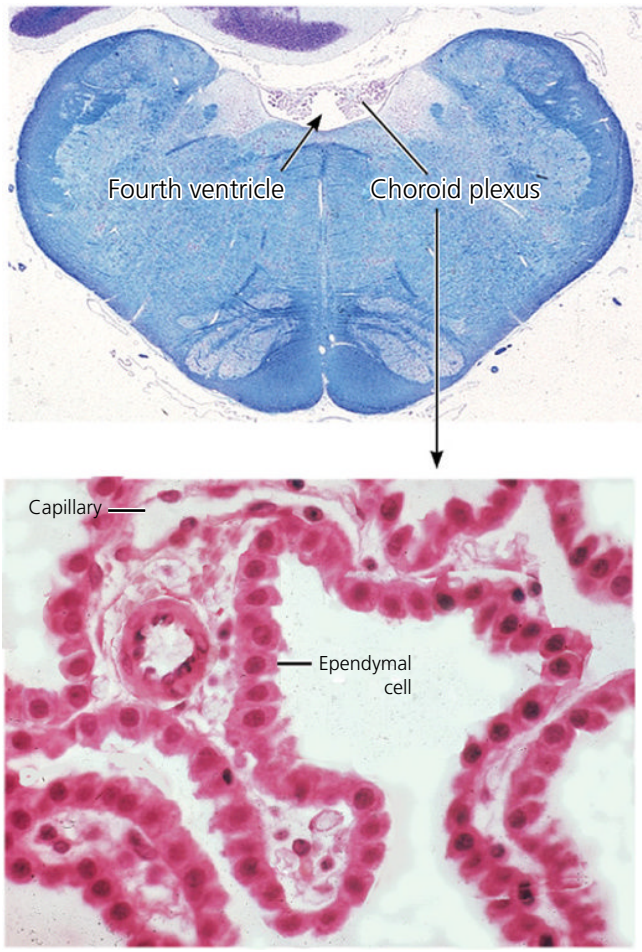


**Figure 1.5** The choroid plexus in the fourth ventricle of the medulla oblongata. The choroid plexus is composed of vascular connective tissue lined with ependymal cells on the ventricular surface.

**Table 1.3** Normal CSF values.

| |
|---|
| Color: clear |
| Cells: <5/mm$^3$ |
| Protein: <25 mg/dL |
| Glucose: 2.7–4.2 mmol/L |
| Pressure: <170 mm$H_2O$ |

space is drained into the dorsal sagittal sinus, which also receives numerous tributary veins from the cerebral hemispheres and passes blood to the maxillary, internal jugular and vertebral veins and to the vertebral venous plexuses. The CSF in the subarachnoid space of the meninges not only protects the brain and spinal cord from trauma, but also reduces the effective weight of the brain significantly by providing a buoyancy effect.

## Extracellular environment of the CNS

1 What are the blood–CSF and blood–brain barriers? Where are they located?
2 What transport mechanisms are involved in production of the CSF by the choroid plexus?
3 Explain the formation, circulation, and function of the CSF.
4 What structure represents the blood–brain barrier?
5 What transport mechanisms are involved in the blood–brain barrier?
6 List the areas of the brain where the blood–brain barrier is absent and explain the reason.

Neurons and neuroglia require a chemically stable environment. Thus, the brain receives only the essential materials from the blood and CSF. Two structures acting as gatekeepers to the brain's interior are (i) the **choroid epithelium** of the choroid plexus that acts as the blood–CSF barrier and (ii) the **capillaries** of the nervous tissue that act as the blood–brain barrier.

### Blood–CSF barrier

The choroid plexus is present in the lateral, third and fourth ventricles (Figure 1.6). It is formed by invagination of the pia mater covered with choroid epithelial cells on the surface facing the ventricle. Vasculature of the pia mater follows the choroid plexus, providing rich capillary networks. The choroid epithelial cells are modified ependymal cells (they have microvilli instead of cilia on the apical surface). The capillary endothelium of the choroid plexus has many fenestrations in its wall, allowing passage of many small molecules. In contrast, choroid epithelial cells are sealed together by a tight junction that prevents the passage of water-soluble molecules into the CSF. Tight junctions are the anatomical basis of the **blood–CSF barrier** (Figure 1.7) Thus, **choroid epithelial cells** play a key role in regulating what can enter and leave the CNS tissue, maintaining an optimal environment for neurons and neuroglia. The choroid plexus relies on carrier proteins to transport essential molecules. Carrier proteins are located on the basal surface of the choroid epithelial cells. Essential molecules are released into the ventricle through the apical surface of the choroid epithelial cells, probably by facilitated diffusion. The CSF is also important for removing waste products from the CNS. Waste products removed from the CNS are drained into the dorsal sagittal sinus via the arachnoid villi.

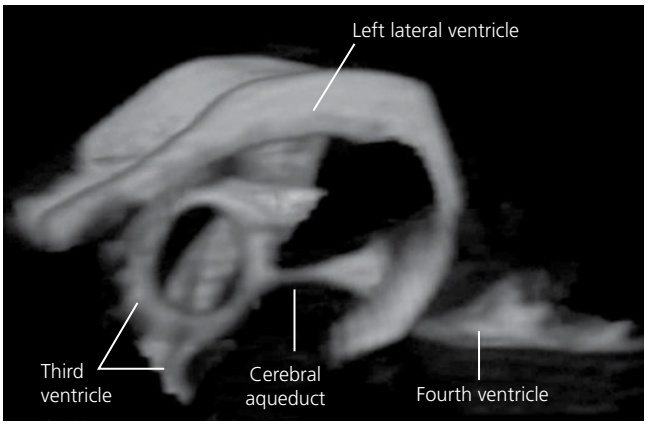


**Figure 1.6** MRI reconstruction of the ventricles of a dog showing the lateral ventricles, third ventricle, cerebral aqueduct, and fourth ventricle. Dr A. Zur Linden, Iowa State University College of Veterinary Medicine. Reproduced with permission from Dr A. Zur Linden.

**Clinical correlations**

Certain antibiotics (e.g., penicillin and most cephalosporin antibiotics) are actively removed from the CSF. Thus, the concentration of penicillin in CSF is about 1% of that in the blood. Interestingly, the choroid plexus under inflammatory conditions (e.g., meningitis) becomes leaky, resulting in a partial breakdown of the blood–CSF barrier. Consequently, the concentration of penicillin in CSF increases to 20% or more of that in the blood, preventing further bacterial growth or even killing bacteria. As inflammation subsides, the choroid plexus regains the function of the blood–CSF barrier and resumes removal of penicillin from CSF, allowing the possibility of a relapse of bacterial growth. Therefore, use of antibiotics that are not actively removed from the CSF (e.g., ceftriaxone with broad-spectrum activity against Gram-positive and Gram-negative bacteria) must be considered for treating many types of meningitis.

**Cerebrospinal fluid** is 99% water, which the choroid plexus secretes into the ventricles by creating ion gradients on both apical and basal surfaces of choroid epithelial cells (Figure 1.7). Water in the choroid epithelial cells dissociates into hydrogen ($H^+$) and hydroxyl ($OH^-$) ions. $OH^-$ combines with intracellular $CO_2$ produced by cell metabolism to form bicarbonate ions ($HCO_3^-$). At the basal surface of the cells, $H^+$ is exchanged for extracellular sodium ions ($Na^+$) from the blood. $Na^+$ is pumped out through the apical surface into the ventricles. The flux of $Na^+$ results in an excess positive charge in the ventricles. To neutralize this excess positive charge, chloride ions ($Cl^-$) and $HCO_3^-$ move into the ventricles. Water also diffuses into the ventricles to maintain osmotic balance. These processes maintain water and concentration of ions in the CSF appropriate for the brain and spinal cord. Water and ions are not the only substances that the CNS must obtain from the blood. The majority of micronutrients

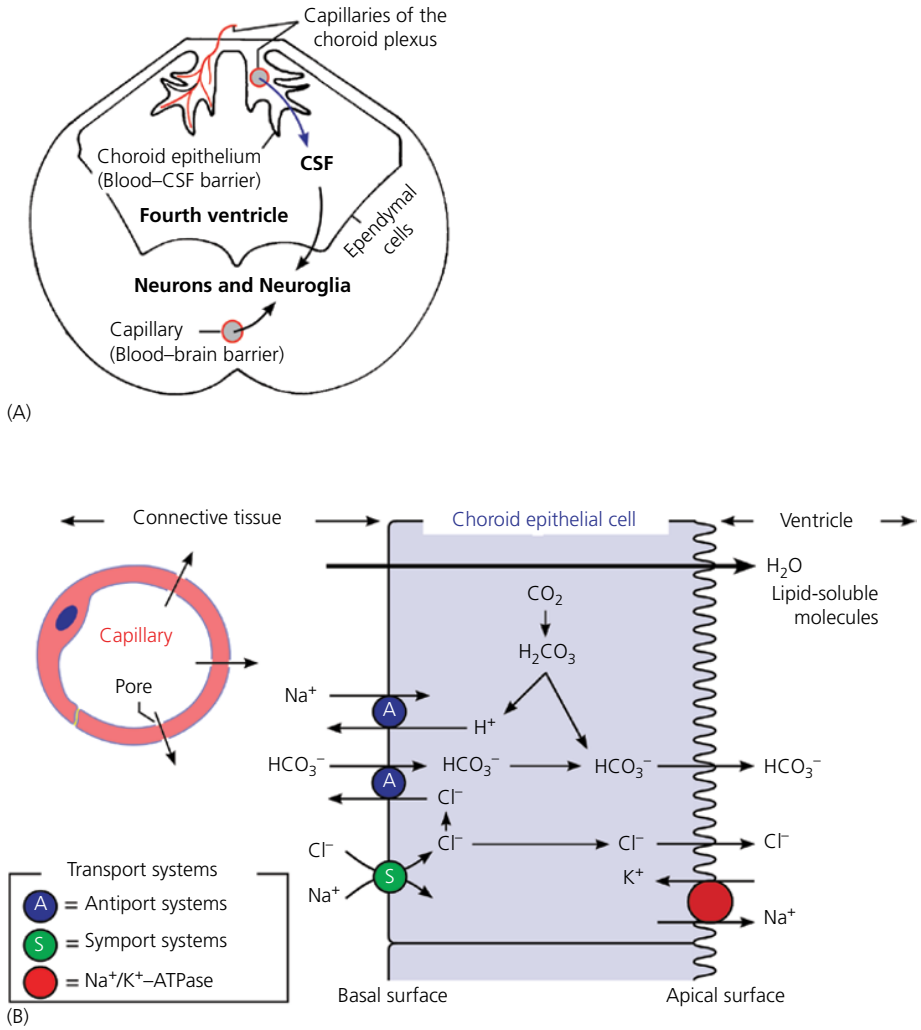


**Figure 1.7** (A) Neurons and neuroglial cells receive essential materials via two routes. Capillaries in the choroid plexus provide micronutrients, whereas interstitial capillaries provide oxygen and substances that the CNS consumes rapidly and in large amounts. The fourth ventricle is exaggerated here and not proportional to the size of the medulla oblongata. (B) The capillaries in the choroid plexus do not act as the blood–CSF barrier, as they are fenestrated (i.e., many pores) and intercellular gaps between endothelial cells are not tight as those found in capillaries of the CNS. As a result, molecules easily cross the capillary endothelial cell of the choroid plexus. The blood–CSF barrier is provided by the choroid epithelial cells, which are joined together by tight junctions. Microvilli of the choroid epithelial cells are present on the ventricular side of the epithelium. The choroid plexus produces CSF by diffusion, facilitated diffusion, and active transport systems. The choroid plexus epithelium also transports metabolites from CSF to blood (not shown).

(substances that are essential to the brain but only needed in relatively small amounts) come from the CSF. Micronutrients include vitamin $B_6$ (pyridoxine), folates (members of vitamin B-complex class) and vitamin C. In contrast, nutrients (glucose, amino acids, lactate) that the CNS requires in large amounts are delivered directly into the interstitial fluid by the capillary endothelium. This process depends on a facilitated-diffusion system.

## Blood–brain barrier

It is known that a dye such as trypan blue, injected intravenously, stains all tissues of the body except the brain and spinal cord. Animals do not show any adverse effects from this procedure. However, when the dye is injected into the ventricle, the whole brain is diffusely stained and animals suffer from neurological problems. Clearly, the central nervous tissue has some barrier against the passage of a circulating dye, and this barrier is referred to as the blood–brain barrier (Figure 1.8). The site of the blood–brain barrier was shown by use of a tracer, horseradish peroxidase (HRP). HRP injected into the ventricle easily enters the extracellular spaces of the brain by crossing the ependymal cells. Although HRP in the brain passes through the capillary basement membrane, it is prevented from crossing the capillary wall into the lumen. However, there are a few specialized areas in the brain that allow entry of dyes or HRP. These nonbarrier regions include the choroid plexus, hypophysis,