医学整合课程系列教材·原版影印

Integrated Physiology

整合生理学

ROBERT G. CARROLL

北京大学医学出版社

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北京大学医学出版社
Peking University Medical Press

图书在版编目（CIP）数据

整合生理学 = Elsevier's Integrated Physiology: 英文 / （美）卡罗尔（Carroll, R. G.）编. -- 北京 : 北京大学医学出版社，2014.8
ISBN 978-7-5659-0853-8

Ⅰ. ①整… Ⅱ. ①卡… Ⅲ. ①人体生理学－医学院校－教材－英文 Ⅳ. ①R33

中国版本图书馆CIP数据核字(2014)第090709号

北京市版权局著作权合同登记号：图字：01－2014－2487
Elsevier's Integrated Physiology, the first edition
Robert Carroll
ISBN-13:9780323043182
ISBN-10:0323043186

Elsevier (Singapore) Pte Ltd.
3 Killiney Road, #08-01 Winsland House I,Singapore 239519
Tel: (65) 6349-0200 Fax: (65) 6733-1817
First Published 2014
2014年初版

整合生理学

编　　写： Robert G. Carroll
出版发行： 北京大学医学出版社
电　　话： 发行部：010-82802230　图书邮购：010-82802495
地　　址：（100191）北京市海淀区学院路38号　北京大学医学部院内
网　　址： http://www.pumpress.com.cn
E-mail： booksale@bjmu.edu.cn
印　　刷： 北京圣彩虹制版印刷技术有限公司
经　　销： 新华书店
责任编辑： 冯智勇　　**责任印制：** 张京生
开　　本： 889mm×1194mm　1/16　　印张：15.5　　字数：482千字
版　　次： 2014年8月第1版　2014年8月第1次印刷
书　　号： ISBN 978-7-5659-0853-8
定　　价： 96.00元

出版说明

知识整合是当前医学教育改革的一项重要内容。目前国内基础医学各门课程的教材基本上是以学科为单位单独编写的，缺乏学科之间知识的联系。为了推动医学教育改革，借鉴国外医学教材的编写模式，北京大学医学出版社经过充分调研，引进出版了世界著名医学出版集团Elsevier公司的“Integrated”系列教材。

在编写上，该系列书最大的特色就是在保持本学科知识体系完整的同时插入大量的“整合框”。这些“整合框”出现在需要链接到其他学科相关知识的位置，每个学科都有独特的标识。例如在《病理学》的细胞损伤一节，讲述缺氧时，会插入一个“生物化学整合框”，介绍生物化学中糖酵解的知识；在感染一节，出现NK细胞的时候，会插入一个“免疫学整合框”，介绍免疫学中NK细胞的知识；在凝血一节，则是插入一个“临床医学整合框”，介绍临床上凝血的实验室评估方面的知识……这些分布在各本书中的“整合框”，把各学科之间知识点连接起来，不但方便了读者学习，更是体现了学科整合的理念。

该系列书包括：

●整合生理学　●整合病理学

●整合药理学　●整合生物化学

●整合遗传学　●整合免疫学与微生物学

该系列书可作为国内医学生整合课程教材、双语教学教材及来华留学生教材，也有利于医学教师拓展知识，方便备课；同时也是美国医师执照考试的优秀参考用书。

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Series Preface

How to Use This Book

The idea for Elsevier's Integrated Series came about at a seminar on the USMLE Step 1 exam at an American Medical Student Association (AMSA) meeting. We noticed that the discussion between faculty and students focused on how the exams were becoming increasingly integrated—with case scenarios and questions often combining two or three science disciplines. The students were clearly concerned about how they could best integrate their basic science knowledge.

One faculty member gave some interesting advice: "read through your textbook in, say, biochemistry, and every time you come across a section that mentions a concept or piece of information relating to another basic science—for example, immunology—highlight that section in the book. Then go to your immunology textbook and look up this information, and make sure you have a good understanding of it. When you have, go back to your biochemistry textbook and carry on reading."

This was a great suggestion—if only students had the time, and all of the books necessary at hand, to do it! At Elsevier we thought long and hard about a way of simplifying this process, and eventually the idea for Elsevier's Integrated Series was born.

The series centers on the concept of the *integration box*. These boxes occur throughout the text whenever a link to another basic science is relevant. They're easy to spot in the text—with their color-coded headings and logos. Each box contains a title for the integration topic and then a brief summary of the topic. The information is complete in itself—you probably won't have to go to any other sources—and you have the basic knowledge to use as a foundation if you want to expand your knowledge of the topic.

You can use this book in two ways. First, as a review book . . .

When you are using the book for review, the integration boxes will jog your memory on topics you have already covered. You'll be able to reassure yourself that you can identify the link, and you can quickly compare your knowledge of the topic with the summary in the box. The integration boxes might highlight gaps in your knowledge, and then you can use them to determine what topics you need to cover in more detail.

Second, the book can be used as a short text to have at hand while you are taking your course . . .

You may come across an integration box that deals with a topic you haven't covered yet, and this will ensure that you're one step ahead in identifying the links to other subjects (especially useful if you're working on a PBL exercise). On a simpler level, the links in the boxes to other sciences and to clinical medicine will help you see clearly the relevance of the basic science topic you are studying. You may already be confident in the subject matter of many of the integration boxes, so they will serve as helpful reminders.

At the back of the book we have included case study questions relating to each chapter so that you can test yourself as you work your way through the book.

Online Version

An online version of the book is available on our Student Consult site. Use of this site is free to anyone who has bought the printed book. Please see the inside front cover for full details on the Student Consult and how to access the electronic version of this book.

In addition to containing USMLE test questions, fully searchable text, and an image bank, the Student Consult site offers additional integration links, both to the other books in Elsevier's Integrated Series and to other key Elsevier textbooks.

Books in Elsevier's Integrated Series

The nine books in the series cover all of the basic sciences. The more books you buy in the series, the more links are made accessible across the series, both in print and online.


Anatomy and Embryology


Histology


Neuroscience


Biochemistry


Physiology


Pathology


Immunology and Microbiology


Pharmacology


Genetics

Preface

At a conference, I was asked to summarize physiology in twenty-five words or less. Here is my response: "The body consists of barriers and compartments. Life exists because the body creates and maintains gradients. Physiology is the study of movement across the barriers." Twenty-five words exactly.

This book is organized along those lines. Most chapters begin with an anatomic/histologic presentation of the system. Function does indeed follow form, and the structure provides limitations on physiology of a system. Physiology, however, is the study of anatomy in action. If anatomy is the study of the body in three dimensions, physiologic function and regulation extend the study of the body into the fourth dimension, time.

Robert G. Carroll, PhD

Editorial Review Board

In memory of my friend and mentor,
the late Dr. David F. Opdyke,
and with many thanks to my teachers
at the University of Medicine and Dentistry of New Jersey–Newark.

Contents

Physiology: The Regulation of Normal Body Function 1

CONTENTS

Life is not always about homeostasis and balance. The body must also adapt to changing requirements, such as during exercise. Now the normal resting values are physiologically inappropriate, since an increase in muscle blood flow, cardiac output, and respiratory rate are necessary to support the increased metabolic demands associated with physical activity. Physiology is the study of adaptive adjustments to new challenges.

Life is a state of constant change. The physiology of the body alters as we age. An infant is not a small adult, and the physiology of an octogenarian is different from that of an adolescent. Chapter 16 provides a concise summary of physiologic changes in each sex across the life span.

Finally, physiology makes sense. As a student, you need to look for the organizing principles in your study of the body. There are more details and variations than can be memorized. However, if you focus on the organizing principles, the details fall into a logical sequence. Look for the big picture first—it is always correct. The details and complex interactions all support the big picture.

PHYSIOLOGY

Body function requires a stable internal environment, described by Claude Bernard as the "milieu intérieur," in spite of a changing outside world. Homeostasis, a state of balance, is made possible by negative feedback control systems. Complex neural and hormonal regulatory systems provide control and integration of body functions. Physicians describe "normal" values for vital signs—blood pressure of 120/80 mm Hg, pulse of 72 beats/min, respiration rate of 14 breaths/min. These "normal" vital sign values reflect a body in homeostatic balance.

A stable milieu interior also requires a balance between intake and output. Intake and production will increase the amount of a compound in the body. Excretion and consumption will decrease the amount of a compound in the body. Body fluid and electrolyte composition is regulated about a set point, which involves both control of ingestion and control of excretion. Any changes in ingestion must be compensated by changes in excretion, or the body is out of balance.

LEVELS OF ORGANIZATION

Medical physiology applies basic principles from chemistry, physics, and biology to the study of human life. Atoms are safely in the realm of chemistry. Physiologic study begins with molecules and continues through the interaction of the organism with its environment (Fig. 1-1).

Physiology is the study of normal body function. Physiology extends to the molecular level, the study of the regulation of the synthesis of biomolecules, and to the subcellular level, details of the provision of nutrients to support mitochondrial metabolism. Physiology includes cellular function, the study of the role of membrane transport, and describes organ function, including the mechanics of pressure generation by the heart. Integrative physiology is the study of the function of the organism, including the coordinated response to digestion and absorption of the nutrients in a meal.

The components of physiology are best approached as organ systems. This approach allows all aspects of one system, e.g., the circulatory system, to be discussed, emphasizing their commonalities and coordinated function.

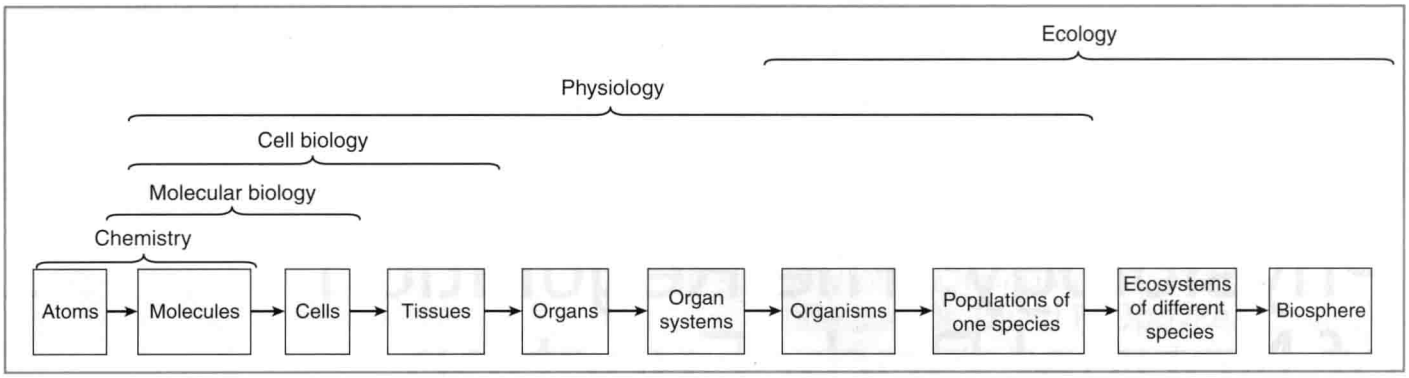


Figure 1-1. Physiology bridges the gap between chemistry and ecology. Physiology incorporates the investigational techniques from cell biology and molecular biology as well as ecology in order to better understand the function of the human body.

TABLE 1-1. Specific Examples of the Movement Theme

Process	Movement	Driving Force	Modulated by
Flow	Flow	Pressure gradient	Resistance (–)
Diffusion	Net flux	Concentration gradient	Permeability (+) Surface area (+) Distance (–)
Osmosis	Water	Particle gradient	Barrier particle permeability (–) Barrier water permeability (+)
Electrochemical	Current	Ionic gradient	Membrane permeability (+)
Capillary filtration	Flow	Combined pressure and oncotic gradient	Capillary surface area (+)
Transport	Secondary active	Ion gradient	Concentration gradient (–)

+, Modulators enhance the movement; –, modulators impede the movement.

COMMON THEMES

Common Theme 1: Movement Across Barriers

Life is characterized as a nonequilibrium steady state. The body achieves homeostatic balance—but only by expending energy derived from metabolism. Although the processes listed below appear different, they share common features. Movement results from a driving force and is opposed by some aspect of resistance (Table 1-1).

Movement against a gradient requires energy. ATP is ultimately the source of energy used to move compounds against a gradient. This is important, because after the gradients are created, the concentration gradients can serve as a source of energy for other movement (e.g., secondary active transport and osmosis).

Common Theme 2: Indicator Dilution

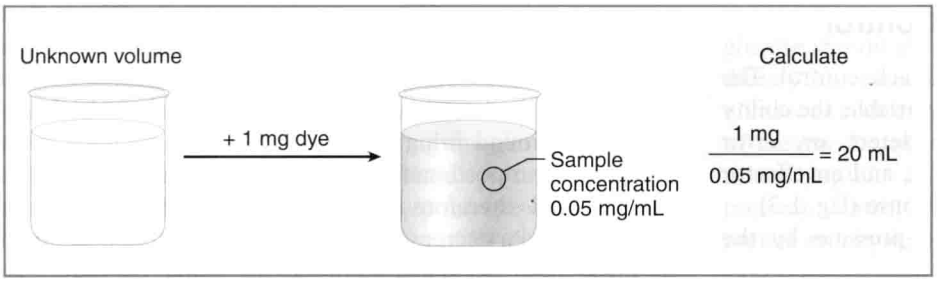
$$\text{Amount/volume} = \text{concentration}$$

or, rearranged,

$$\text{Volume} = \text{concentration/amount}$$

If any two of the above are known, the third can be calculated. This approach is used to determine a physiologic volume that cannot be directly measured. For example, plasma volume can be estimated by adding a known amount of the dye Evans blue, which binds tightly to albumin and remains mostly in the plasma space. After the dye distributes equally throughout the plasma volume, a plasma sample can be taken. The observed concentration of the sample, together with the amount of dye added, allows calculation of the plasma volume (Fig. 1-2).

There are some assumptions in this process that are rarely met, but the estimations are close enough to be clinically useful. The indicator should be distributed only in the volume of interest. There must be sufficient time for the indicator to equilibrate so that all areas of the volume have an identical concentration. For estimation of plasma volume with Evans blue, those assumptions are not met. Some albumin is lost for the plasma volume over time, so an early sampling is desirable. But some plasma spaces have slow exchange rates, and Evans blue dye requires additional time to reach those spaces. In practice, a plasma sample is drawn at 10 or 20 minutes after indicator injection, and the plasma volume is calculated with the knowledge that it is an estimate and with awareness of the limitations of the technique.



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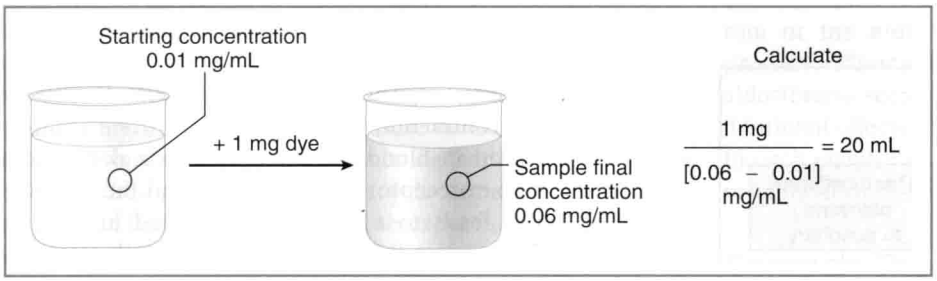

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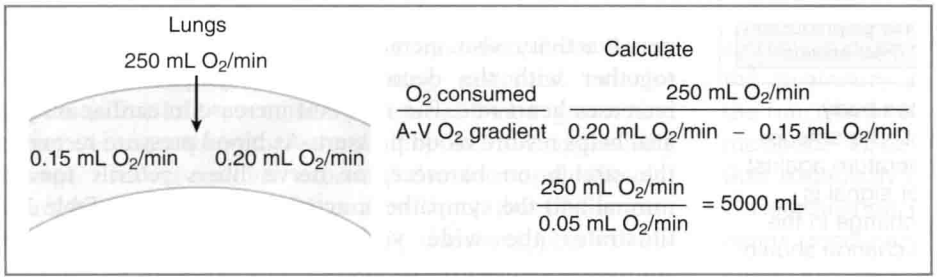

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Figure 1-2. Indicator dilution allows calculation of unknown volumes and flows. **A**, The indicator dilution technique uses addition of a known quantity of a marker, and the final concentration of that marker, to calculate the volume in which it was distributed. **B**, The procedure is the same even if some of the marker is already present in the volume. The only alteration is that the final concentration is subtracted from the starting concentration to determine the change in concentration caused by adding the marker. **C**, An equivalent procedure can be used to calculate flows. If you know the amount of $\dot{V}O_2$ absorbed across the lungs per minute, and the change in blood O_2 concentration that resulted from that absorption, you can calculate the blood flow through the lungs, or the cardiac output.

TABLE 1-2. Application of Indicator Dilution

Volume or Flow	Indicator (The Tracer)	The Change
Total body water	Iothalamate	Iothalamate concentration
Extracellular fluid volume	Inulin	Inulin concentration
RBC volume	^{51}Cr-labeled RBC	^{51}Cr-labeled RBC concentration
Residual lung volume	N_2	N_2 washout
Cardiac output	Temperature (a volume of cold saline)	Change in blood temperature over time
Cardiac output	Rate of O_2 uptake in the lungs	Change in O_2 content in blood flowing through the lungs
Glomerular filtration rate	Inulin	Inulin excretion rate
Renal blood flow	Para-aminohippuric acid	Para-aminohippuric acid excretion rate

In the best case, the only indicator in the system is the new indicator that was added. Alternatively, if the compound is already in the system, the term "change in amount" can be substituted for "amount" and "change in concentration" can be substituted for "concentration."

Change in amount/volume = change in concentration

A flow is actually a volume over time, so the indicator dilution technique can also be used to estimate flows. Instead of amount, the indicator is expressed as amount per time (Table 1-2).

Flow = amount per time/change in concentration

Common Theme 3: Feedback Control

Stability is maintained by negative feedback control. The system requires a set point for a regulated variable, the ability to monitor that variable, the ability to detect any error between the actual value and the set point, and an effector system to bring about a compensatory response (Fig. 1-3).

The acute regulation of arterial blood pressure by the arterial baroreceptors (the baroreceptor reflex) is a prototype for physiologic negative feedback control systems. Normal blood pressure is taken as the set point of the system. The sensing mechanism is a group of stretch-sensitive nerve endings in the walls of the arch of the aorta and in the walls of the carotid arteries near the carotid bifurcation. These nerve endings are always being stretched, so there is always some background firing activity. The rate of firing of these receptors is proportionate to the stretch on the blood vessels. Stretch (and therefore firing) increase as blood pressure increases, and a decrease in stretch (and therefore a decrease in firing rate) accompanies a fall in blood pressure. The afferent nerves from these receptors synapse in the cardiovascular center of the medulla, where the inputs are integrated. The efferent side of the reflex is the parasympathetic and sympathetic nervous systems (PNS and SNS), which control heart rate, myocardial contractility, and vascular smooth muscle contraction.

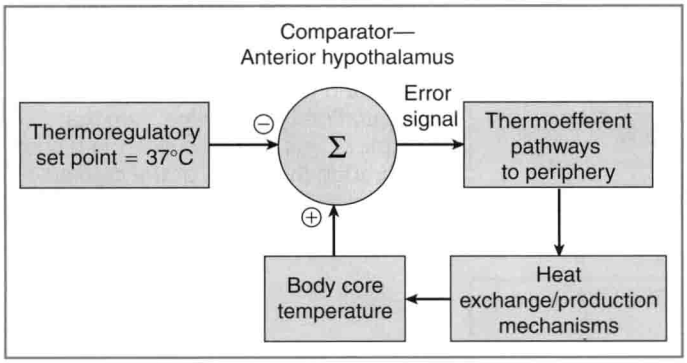


Figure 1-3. Negative feedback control matches body temperature to the thermoregulatory set point. The anterior hypothalamus compares the body core temperature against the set point. If the two do not match, an error signal is generated, which results in a compensatory change in the heat gain/heat loss balance of the body. This change should bring body core temperature back to the set point.

A sudden drop in blood pressure leads to a decrease in stretch on the baroreceptor nerve endings, and the decrease in nerve traffic leads to a medullary mediated increase in sympathetic activity and decrease in parasympathetic nerve activity. Increased sympathetic activity causes vascular smooth muscle contraction, which helps increase peripheral resistance and restore blood pressure. Increased sympathetic nerve activity also increases myocardial contractility and, together with the decrease in parasympathetic activity, increases heart rate. The resultant increase in cardiac output also helps restore blood pressure. As blood pressure recovers, the stretch on baroreceptor nerve fibers returns toward normal and the sympathetic activation diminishes. Table 1-3 illustrates the wide variety of physiologic functions controlled by negative feedback.

TABLE 1-3. Some Important Negative Feedback Control Systems

Regulated Variable	Sensed by	Response Mediated by	Effector
Arterial blood pressure	Baroreceptors	SNS and PNS	Heart, vasculature
Microcirculation blood flow	Tissue metabolites		Vascular smooth muscle, precapillary sphincter
Arterial blood CO_2	Central and peripheral chemoreceptors	CNS	Respiratory muscles
Arterial blood O_2	Peripheral chemoreceptors	CNS	Respiratory muscles
Plasma osmolarity	CNS osmoreceptors	ADH	Kidneys
Glomerular filtration rate	Macula densa	Angiotensin II	Efferent arteriole
Plasma K^+	Adrenal cortex	Aldosterone	Cells, renal tubule
Plasma glucose	Pancreas	Multiple hormones	Liver, adipose, skeletal muscle, mitochondria
Muscle stretch	Muscle spindle	Motor neuron	Muscle fibers
Gastric emptying	Small intestinal chemoreceptors	Enteric nerves, GI hormones	Pyloric tone
Body fluid volume	Cardiopulmonary volume receptors	SNS, ADH	Kidney

ADH, antidiuretic hormone; CNS, central nervous system; PNS, peripheral nervous system; SNS, sympathetic nervous system.

Positive feedback provides an unstable escalating stimulus-response cycle. Positive feedbacks are rare in human physiology. Three situations in which they do occur are oxytocin stimulation of uterine contractions during labor, the LH surge before ovulation, and Na^+ entry during the generation of an action potential. In a positive feedback system, movement away from a starting point elicits a response resulting in even more movement away from the starting point. As an example, oxytocin stimulates uterine contraction during labor and delivery. Central nervous system (CNS) oxytocin release is directly proportionate to the amount of pressure generated by the head of the baby on the opening of the uterus. So once uterine contractions begin, the opening of the uterus is stretched. Stretch elicits oxytocin release, stimulating stronger uterine contractions. Pressure on the opening of the uterus is further increased, stimulating additional oxytocin release. This positive feedback cycle continues until the pressure in the uterus is sufficient to expel the baby. Delivery stops the pressure on the uterus and removes the stimulus for further oxytocin release.

Feed-forward regulation allows an anticipatory response before a disturbance is sensed by negative feedback control systems. An excellent example is the regulation of ventilation during exercise. Respiration during sustained exercise increases five-fold even though arterial blood gases (and therefore chemoreceptor stimulation) do not appreciably change. During aerobic exercise, the increased alveolar ventilation is stimulated by outflow from the CNS motor cortex and not by the normal CO_2 chemoreceptor control system. This appears to be a finely tuned response, since the ventilatory stimulus increases as the number of motor units involved in the exercise increases. The coupling of ventilation to muscle activity allows an increased ventilation to support the increased metabolic demand without first waiting for hypoxia (or hypercapnia) to develop as a respiratory drive.

Feed-forward controls are involved in gastric acid and insulin secretion following meal ingestion and behavioral responses to a variety of stresses, such as fasting and thermoregulation. The combination of feed-forward and negative feedback controls provides the body with the flexibility to maintain homeostasis but to also adapt to a changing environment.

Common Theme 4: Redundant Control

The sophistication and complexity of physiologic control systems are quite varied. For example, Na^+ is the major extracellular cation and is controlled by multiple endocrine agents, physical forces, and appetite. In contrast, Cl^- is the major extracellular anion, but in humans, Cl^- is not under significant endocrine control.

The degree of redundant regulation can be viewed as a reflection of the importance of the variable to life. For example, a drop in plasma glucose can induce shock, but hyperglycemia is not as immediately life threatening. Consequently, there are four hormones (cortisol, glucagon, epinephrine, and growth hormone) that increase plasma glucose if glucose levels fall too low, but only one hormone (insulin) that lowers glucose should glucose levels be too high. Na^+ is an essential dietary component, and Na^+ conservation is regulated by numerous endocrine and renal mechanisms. The effectiveness of the two hormones promoting Na^+ excretion (atrial natriuretic peptide and urotensin) is limited. Arterial blood pressure control is perhaps the most redundant and includes numerous physical, endocrine, and neural mechanisms.

Disease states often provide insight into the relative importance of competing control systems. The hypertension accompanying renal artery stenosis illustrates the prominent role of the kidney in the long-term regulation of blood pressure. Plasma K^+ changes are apparent in disorders of aldosterone secretion, and plasma Na^+ changes reflect the dilutional effects of ADH regulation of renal water excretion. In each chapter of this book, emphasis is given to the more prominent or disease-related control systems.

Common Theme 5: Integration

The normal assignment of separate chapters to each organ system downplays the significant interaction among the organ systems in normal function. Provision of O_2 and nutrients by the respiratory and gastrointestinal systems is essential to the function of all cells within the body, as is the removal of metabolic waste by these systems and the kidneys. Blood flow is similarly essential to all organ function.

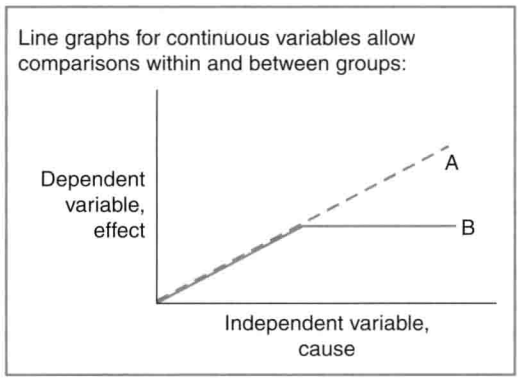
Coordination of body functions is accomplished by two major regulatory systems: the nervous system and the endocrine system. This level of regulation is superimposed on any intrinsic regulation occurring within the organ. The endocrine and nervous systems are often redundant. For example, the autonomic nervous system (ANS), angiotensin II, and adrenal catecholamines all regulate arterial pressure. In spite of the overlap, the systems usually work in concert, achieving the appropriate physiologic adjustments on organ function to counteract any environmental stress.

Common Theme 6: Graphs, Figures, and Equations

Graphs, figures, and equations condense and simplify explanations. Different graph formats communicate specific relationships. Understanding the strengths of each approach allows a reader to more quickly assimilate the important information.

Graphs

***X-Y* Graph.** The most common graph format is the x-y plot. If a graph illustrates a cause-effect relationship, the x-axis represents the independent variable (cause), and the y-axis represents the dependent variable (effect). The same graph format is used to show observations that may not be cause-effect coupled, and in this case the graph illustrates only a correlation. In physiology, time is often plotted on the x-axis, allowing the graph to illustrate a change in the y-axis variable over time (Fig. 1-4).



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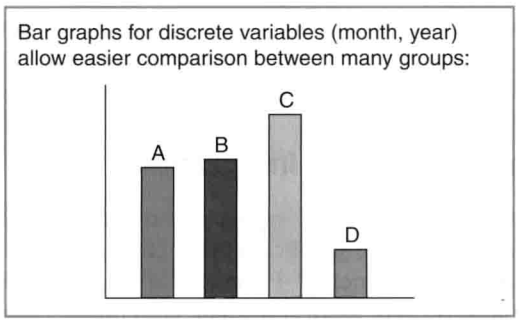

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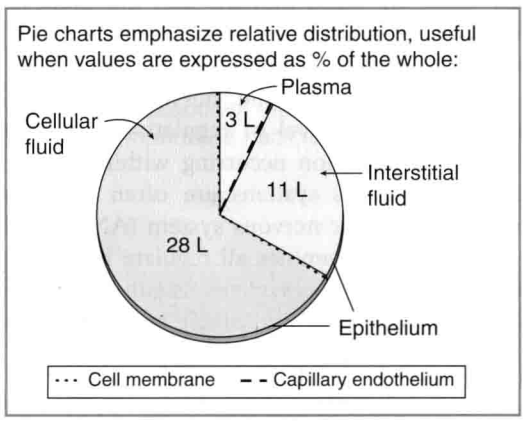

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Figure 1-4. Different graph formats convey different types of information. **A**, The *x-y* graph allows comparison of two variables. If there is a dependent variable, it is always plotted along the *y*-axis. **B**, Bar graphs are used for comparisons between many groups. **C**, Pie charts are used to emphasize distribution relative to the total amount available.

Bar Graph. A line *x-y* graph is used when both x and y numbers are continuous, such as the plot of time versus voltage on an electrocardiogram. In some measurements, the x-axis is a discrete variable (month, age, sex, treatment group), and the y-axis measures frequency. This plotting approach allows easy visual comparison among many groups.

Pie Chart. A pie chart effectively illustrates the relative distribution. It is useful to communicate proportions. Values are expressed as percentages of the whole rather than absolute values.

Equations

Variables that have a direct or inverse relationship are summarized more quickly in equations than in graphs. This approach is used for relationships that are not constant. If there are curves in the line (other than mathematical curves resulting from power, inverse, or log functions), then a line graph will have to be used.

Equations are a quick summary of direct and inverse relationships. For Fick's law of diffusion,

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

The text version saying the same thing as the equation is:

The net movement of a compound, or flux (J), is determined by the diffusion coefficient (D), the surface area available for exchange (A), the concentration gradient (Δc), and the distance over which the compound has to diffuse (Δx).

Compounds moving by diffusion always travel down the concentration gradient. By convention, the side with the higher concentration is considered first, and the side with the lower concentration is considered second. The convention uses a negative sign (–) to indicate that the flux is away from the area with the original higher concentration.

The ability of a compound to move is determined by the diffusion coefficient (D). This coefficient is characteristic of the individual compound and the barrier, and includes the molecular weight and size of the compound, its solubility, and the temperature and pressure conditions.

Flux is directly proportionate to the surface area (A) available for exchange. As the surface area participating in exchange increases, the flux of the compound also increases. As the surface area participating in the exchange decreases, the flux will decrease. If there is no surface area participating in the exchange, the flux will be zero.

Flux is directly proportionate to the concentration gradient (Δc). An increase in the concentration gradient will increase the flux of a compound, and conversely, a decrease in the concentration gradient will decrease the flux of a compound. If there is no concentration gradient, the flux will be zero.

Flux is inversely proportionate to the distance over which a compound must travel (Δx). As the distance to be traveled by the compound increases, the flux will decrease. As the distance to be traveled by the compound decreases, the flux will increase.

The explanation took 279 words to convey the information contained in the equation. Equations are a useful shorthand method and are particularly useful if the reader is aware of all the implications.

Common Theme 7: Autonomic Nervous System

The ANS is a major mechanism for neural control of physiologic functions. Discussions of ANS usually take one of three perspectives: (1) an anatomic perspective based on structure, (2) a physiologic perspective based on function, (3) a pharma-

cologic perspective based on the receptor subtypes involved. All three perspectives are valid and useful.

The anatomic perspective separates the ANS into a sympathetic and a parasympathetic branch, based in part on the origin and length of the nerves. The sympathetic nerves arise from the thoracolumbar spinal cord and have short preganglionic neurons. The preganglionic nerves synapse in the sympathetic chain, and long postganglionic nerves innervate the final target. Acetylcholine is the preganglionic nerve neurotransmitter, and norepinephrine is the postganglionic neurotransmitter, except for the sweat glands, which have a sympathetic cholinergic innervation. There is an endocrine component of the SNS. Circulating plasma norepinephrine levels come from both overflow from the sympathetic nerve terminals and from the adrenal medulla. Plasma epinephrine originates primarily from the adrenal medulla.

The parasympathetic nerves arise from the cranial and sacral portions of the spinal cord and have a long preganglionic nerve. They synapse in ganglia close to the target tissue and have short postganglionic nerves. The parasympathetic nerves use acetylcholine as the neurotransmitter for both the preganglionic and postganglionic nerves. There is not an endocrine arm to the PNS.

The physiologic perspective of the ANS is based on both homeostatic control and adaptive responses. The ANS, along with the endocrine system, regulates most body functions through a standard negative feedback process. The adaptive component of the ANS characterizes the SNS as mediating "fight or flight" and the PNS as mediating "rest and digest." This classification provides a logical structure for the diverse actions of the sympathetic and parasympathetic nerves on various target tissues.

The SNS is activated by multiple stimuli, including perceived threat, pain, hypotension, or hypoglycemia. The parasympathetic nerves are active during quiescent periods, such as after ingestion of a meal and during sleep. The specific ANS control of each organ is discussed in the appropriate chapter.

The pharmacologic division of the ANS is based on the receptor subtype activated. The SNS stimulates α- and/or β-adrenergic receptors on target tissues. The PNS stimulates nicotinic or muscarinic cholinergic receptors on the target tissues. Cells express different receptor subtypes, and the receptor subtype mediates the action of SNS or PNS on that cell.

Common Theme 8: Physiologic Research

As indicated by the volume of material contained in textbooks, much is already known about human physiology. The current understanding of body function is based on more than 3000 years of research. The presentation in this text represents the best understanding of body function. Much of the material represents models that are being tested and refined in research laboratories.

Each generation of students believes they have mastered all the physiology that it is possible to learn. They are wrong. Recent physiologic research has uncovered the mechanism of action of nitric oxide, the existence of the hormone atrial natriuretic peptide, and the nongenomic actions of steroid hormones. The sequencing of the human genome potentially has opened an entirely new clinical approach—genetic medicine. The interaction of physiology and medicine will continue. In 20 years these days may be looked upon as the "good old days" when the study of the human body was easy.

APPLICATION OF COMMON THEMES: PHYSIOLOGY OF THERMOREGULATION

The anterior hypothalamic "thermostat" adjusts heat balance to maintain body core temperature. Heat exchange is determined by convection, conduction, evaporation, and radiation. Radiation, conduction, and convection are determined by the difference between the skin temperature and the environmental temperature (*common theme 1*). Behavioral mechanisms can assist thermoregulation. The rate of heat loss depends primarily on the surface temperature of the skin, which is in turn a function of the skin's blood flow. The blood flow of the skin varies in response to changes in the body's

ANATOMY

Autonomic Nervous System

The sympathetic nerves originate in the intermediolateral horn of the spinal cord and exit at the T1 through L2 spinal cord segments. The preganglionic nerve fibers synapse in either the paravertebral sympathetic chain ganglia or the prevertebral ganglia before the postganglionic nerve fibers run to the target tissue. The parasympathetic nerves exit the CNS through cranial nerves III, VII, IX, and X and through the S2 through S4 sacral spinal cord segments. The parasympathetic preganglionic nerve fibers usually travel almost all the way to the target before making the synapse with the postganglionic fibers.

PHARMACOLOGY

Adrenergic Receptor Subtypes

There are at least two types of α-adrenergic receptors. α_1-Receptors work through IP_3 and DAG to constrict vascular and genitourinary smooth muscle and to relax GI smooth muscle. α_2-Adrenergic receptors decrease cAMP, promote platelet aggregation, decrease insulin release, and decrease norepinephrine synaptic release. There are at least three subtypes of β-adrenergic receptors, all of which increase cAMP. β_1-Receptors in the heart increase heart rate and contractility, and in the kidney release renin. β_2-Receptors relax smooth muscle and promote glycogenolysis. β_3-Adrenergic receptors in adipose promote lipolysis.

core temperature and to changes in temperature of the external environment (Box 1-1).

There are two different physiologic responses to a change in body temperature. A forced change in body temperature results when an environmental stress is sufficient to overcome the body thermoregulatory systems. Prolonged immersion in cool water would result in forced hypothermia, a drop in body core temperature. Prolonged confinement in a hot room could result in forced hyperthermia, an elevation in body core temperature. A regulated change in body temperature occurs when the hypothalamic set point is shifted (*common theme 3*). A regulated hyperthermia accompanies the release of pyrogens during an influenza infection. A regulated hypothermia follows exposure to organophosphate poisons.

A forced drop in body core temperature initiates adrenergic heat conservation (*common theme 3*). Piloerection of cutaneous hair decreases conductive heat loss. Sweating is decreased to reduce evaporative heat loss (*common theme 7*). Cutaneous adrenergic vasoconstriction decreases blood flow and therefore diminishes radiant loss of heat (*common theme 7*). These physiologic responses are augmented by behavioral responses that diminish exposure to cold, such as moving to a warmer environment or putting on additional clothes. A drop in body core temperature also stimulates heat production. Shivering and movement increase metabolic heat production. In neonates, adrenergic activity increases metabolism of neonatal brown fat. Long-term cold exposure increases thyroid hormone release and increases basal metabolic rate (*common theme 4*).

A forced increase in body core temperature initiates heat loss (*common theme 3*). A decrease in vascular sympathetic nerve activity causes an increase in cutaneous blood flow, which augments the radiant loss of heat (*common theme 7*). Sympathetic cholinergic activity increases sweating (*common theme 7*). Excessive sweating can deplete body Na^+. Aldosterone release decreases Na^+ lost in sweat in long-term heat adaptation (*common theme 5*). Increases in body core temperature also result in decreased heat production. There can be a behavioral decrease in activity, movement to a cooler environment, or removal of clothes. In the long term, basal metabolic rate can be diminished by lower thyroid hormone release (*common theme 4*).

The time course of the body thermoregulation alterations caused by influenza is shown in Figure 1-5. During the early stages of the flu, pyrogens are produced that elevate the hypothalamic thermoregulatory set point, usually to around 39°C. The body core temperature is 37°C, below the set point, generating a "too cold" error signal (*common theme 3*). The thermoregulatory balance is altered to favor heat gain mechanisms, such as shivering and reduced cutaneous blood flow, complemented by behavioral changes such as curling up in a fetal position and getting under blankets. These mechanisms persist even though body core temperature is higher than "normal." As body core temperature and set point come into balance at 39°C, there is some reduction in the heat gain mechanisms.

As the influenza infection subsides, pyrogen production ceases and the set point returns to 37°C. The hypothalamic set point is now lower than body core temperature, generating a "too hot" error signal (*common theme 3*). Heat loss mechanisms are activated, including sweating and increased cutaneous blood flow, and complemented by behavioral

Box 1-1. HEAT LOSS AND HEAT GAIN MECHANISMS

Enhance heat loss/diminish heat gain when ambient temperature is lower than body temperature

Increase cutaneous blood flow
Increase sweating (even when ambient temperature is higher than body temperature)
Remove clothing
Move to cooler environment
Decrease metabolic rate
Take sprawled posture

Diminish heat loss/enhance heat gain when ambient temperature is lower than body temperature

Decrease cutaneous blood flow
Piloerect
Huddle or take ball posture
Move to warmer environment
Increase activity and movement
Shivering
Metabolize brown adipose (infants)
Increase metabolic rate

NEUROSCIENCE

Hypothalamic Temperature Control

The preoptic area of the anterior hypothalamus is largely responsible for thermoregulatory control. The hypothalamus receives sensory information regarding temperature from central and peripheral temperature-sensitive neurons. This information is integrated in the hypothalamus, and efferent signals from the hypothalamus activate temperature regulatory mechanisms.

MICROBIOLOGY

Influenza

There are three major classes of influenza viruses: A, B, and C. Influenza A viruses are found in many different species and are subclassified based on the presence on the surface of the virus of either the hemagglutinin or the neuraminidase protein. Influenza B viruses are found almost exclusively in humans. Influenza C viruses cause only a minor respiratory infection. Small changes in the surface proteins occur each year, making it difficult to develop effective flu vaccines.