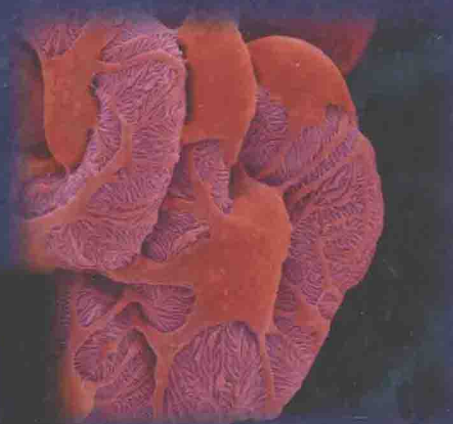
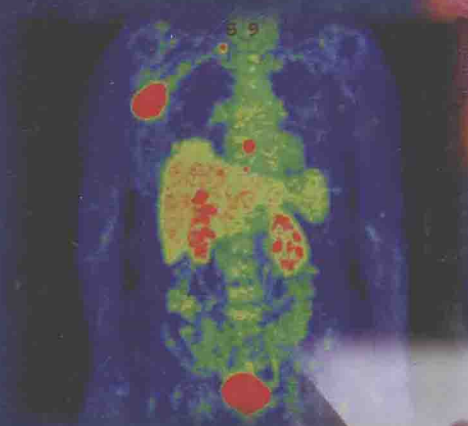
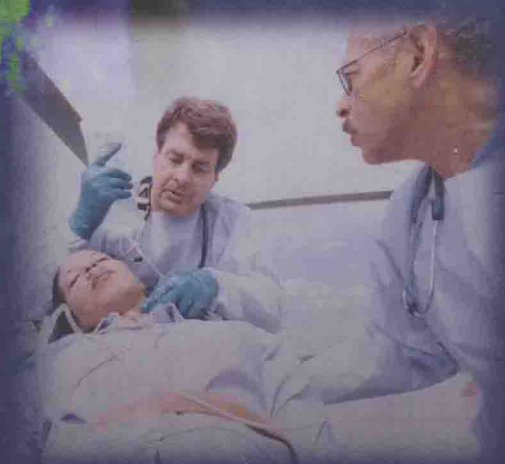
Twelfth Edition

Vander's Human Physiology

The Mechanisms of Body Function







Eric P. Widmaier

Hershel Raff

Kevin T. Strang

TWELFTH EDITION

Vander's Human Physiology

THE MECHANISMS OF BODY FUNCTION

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BOSTON UNIVERSITY

Hershel Raff
MEDICAL COLLEGE OF WISCONSIN
AURORA ST. LUKE'S MEDICAL CENTER

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VANDER'S HUMAN PHYSIOLOGY: THE MECHANISMS OF BODY FUNCTION, TWELFTH EDITION

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Meet the Authors

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HERSHEL RAFF received his Ph.D. in Environmental Physiology from the *Johns Hopkins University* in 1981 and did postdoctoral training in Endocrinology at the *University of California at San Francisco.* He is now a Professor of Medicine (Endocrinology, Metabolism, and Clinical Nutrition) and Physiology at the *Medical College of Wisconsin* and Director of the Endocrine Research Laboratory at *Aurora St. Luke's Medical Center.* At the *Medical College of Wisconsin,* he teaches physiology and pharmacology to medical and graduate students. He was an inaugural inductee into the Society of Teaching Scholars, received the Beckman Basic Science Teaching Award and the Outstanding Teacher Award, and was one of the MCW's Outstanding Medical Student Teachers for 2007–8 and 2008–9. He is also an Adjunct Professor of Biomedical Sciences at *Marquette University.* He is Associate Editor of *Advances in Physiology Education.* Dr. Raff's basic research focuses on the adaptation to low oxygen (hypoxia). His clinical interest focuses on pituitary and adrenal diseases, with a special focus on the diagnosis of Cushing's syndrome. He resides outside Milwaukee with his wife Judy and son Jonathan.

KEVIN T. STRANG received his Master's Degree in Zoology (1988) and his Ph.D. in Physiology (1994) from the *University of Wisconsin at Madison.* His research area is cellular mechanisms of contractility modulation in cardiac muscle. He teaches a large undergraduate systems physiology course as well as first-year medical physiology in the *UW-Madison School of Medicine and Public Health.* He was elected to UW-Madison's Teaching Academy and as a Fellow of the Wisconsin Initiative for Science Literacy. He is a frequent guest speaker at colleges and high schools on the physiology of alcohol consumption. He has twice been awarded the UW Medical Alumni Association's Distinguished Teaching Award for Basic Sciences, and also received the University of Wisconsin System's Underkofler/Alliant Energy Excellence in Teaching Award. Interested in teaching technology, Dr. Strang has produced numerous animations of *Vander's Human Physiology* text figures for use in teaching physiology. He lives in Madison with his children Jake and Amy.

Dedication:

TO OUR FAMILIES:

MARIA, CARRIE, AND RICK

JUDY AND JONATHAN

JAKE AND AMY

Index of Exercise Physiology

Preface

From the Authors

It is with great pleasure that we present the twelfth edition of *Vander's Human Physiology*. The cover of this edition reflects some of the major themes of the textbook: homeostasis, exercise, pathophysiology, and cellular and molecular mechanisms of body function. Research in these areas continues at a fast pace, and we have tried to reflect the excitement that this brings to the field of human physiology in the revised text. To that end, we have added new material on our modern understanding and treatment of many diseases, and have made special note wherever appropriate of recent molecular advances in human physiology. We have also expanded two new pedagogical elements that were introduced in the eleventh edition, namely, the "Physiological Inquiries" and the case studies of Chapter 19. Reviewers were unanimous that these two features of the text were excellent learning tools for students, and a clear message was received by the authors that more is better. We have added dozens of new Physiological Inquiries, roughly doubling the total number of these valuable concept checks; we have also extended them to the introductory chapters, allowing students to assess their understanding of chemical and biochemical principles introduced early in the text. Users of the book will also benefit from the extensive coverage of exercise physiology (see the special Exercise Index that follows the detailed Table of Contents), and the Index of Clinical Terms (Appendix B). This index is organized according to disease; infectious or causative agents; and the treatments, diagnostics, and therapeutic drugs used to treat disease. This is a very useful resource for instructors and students interested in the extensive medical applications of human physiology that are covered in this book.

Chapter 19, "Medical Physiology: Integration Using Clinical Cases," proved extremely popular with instructors and students. We have therefore added one more integrated case study to this chapter. This case describes a college student who is diagnosed with a type of brain tumor. The case study is notable for its integration of numerous neurological signs and symptoms and for introducing in detail the utility of magnetic resonance imaging. As with the other case studies in Chapter 19, students are asked to "Reflect and Review" the material as the case unfolds, providing them with a step-by-step interactive learning experience. This chapter was so well received that we have reorganized the other 18 chapters to include at the end of each a brief case study that is specific to the material covered in that chapter. In this way, students learn to apply material to real-life situations beginning with the material in Chapter 1. The case studies generally become more complex and integrative as the student progresses through the text and gains a deeper foundation of physiological principles.

We are always grateful to receive e-mail messages from instructors and students worldwide who are using the book and wish to offer suggestions regarding content. We continue to be indebted to the previous authors, Arthur Vander, Dorothy Luciano, and James Sherman, and to the staff at McGraw-Hill Higher Education for their support and professionalism. Finally, no textbook such as this could be written without the expert and critical eyes of our many reviewers; we are thankful to those colleagues who took time from their busy schedules to read all or a portion of a chapter (or more) and provide us with their insights and suggestions for improvements.

NEW Clinical Case Studies in Every Chapter!

CHAPTER 1 **Clinical Case Study**

Throughout this text, you will find a feature at the end of each chapter called the "Clinical Case Study." These segments reinforce what you have learned in that chapter by applying it to real-life examples of different medical conditions. The Clinical Case Studies will increase in complexity as you progress through the text and will enable you to integrate recent material from a given chapter with information learned in previous chapters. In this first Clinical Case Study, we examine a serious and potentially life-threatening condition that can occur in individuals in whom body temperature homeostasis is disrupted. All of the material presented in this Clinical Case Study will be explored in depth in subsequent chapters, as you learn the mechanisms that underlie the pathologies and compensatory responses illustrated here in brief.

A 64-year-old, fair-skinned man in good overall health spent a very hot, humid summer day gardening in his backyard. After several hours in the sun, he began to feel light-headed and confused as he knelt over his vegetable garden. Although earlier he had been perspiring profusely, his sweating had eventually stopped. Because he also felt confused and disoriented, he could not recall for how long he had not been perspiring, or even how long it had been since he had taken a drink of water. He called to his wife, who was alarmed to see that his skin had turned a pale-blue color. She asked her husband to come indoors, but he fainted as soon as he tried to stand. The wife called for an ambulance, and the man was taken to a hospital and diagnosed with a condition called heat stroke. What happened to this man that would explain his condition? How does it relate to homeostasis?

As you learned in this chapter, body temperature is a physiological function that is under homeostatic control. If body temperature decreases, heat production increases and heat loss decreases, as illustrated in Figures 1–5 and 1–6. Conversely, as in our example here, if body temperature increases, heat production decreases and heat loss increases. When our patient began gardening on a hot, humid day, his body temperature began to rise. At first, he perspired heavily. As you will learn in Chapter 16, perspiration is an important mechanism by which the body loses heat; it takes considerable heat to evaporate water from the surface of the skin, and the source of that heat is from the body. However, evaporation of water from the body is less effective in humid environments, which makes it more dangerous to exercise when it is not only hot but also humid.

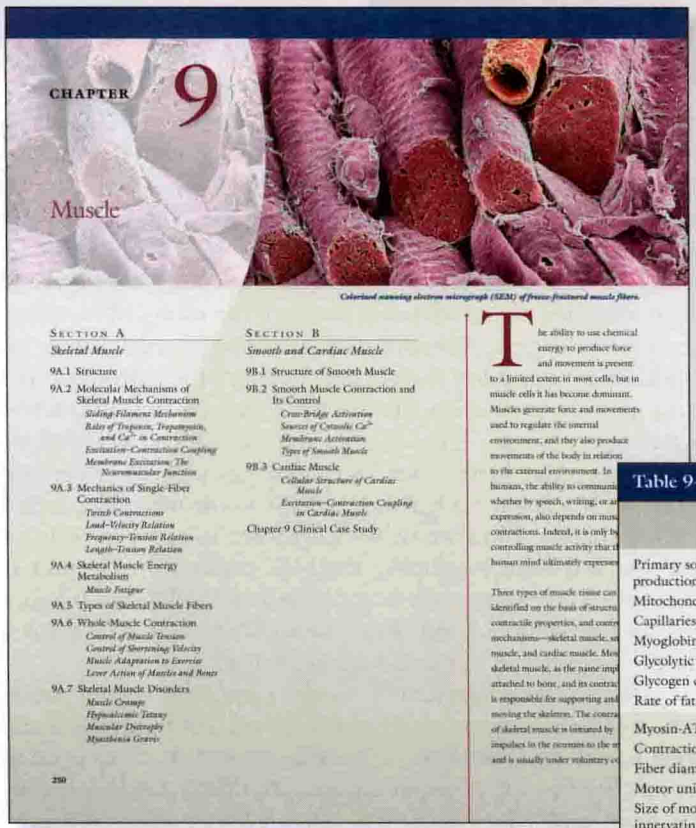
The sources of perspiration are the sweat glands, which are located beneath the skin and which secrete a salty solution through ducts to the surface of the skin. The fluid in sweat comes from the extracellular fluid compartment, which, as you have learned, consists of the plasma and interstitial fluid compartments (Figure 1–3). Consequently, the profuse sweating that initially occurred in this man caused his extracellular fluid levels to decrease. In fact, the fluid levels decreased so severely that the amount of blood available to be pumped out of his heart with each heartbeat also decreased. The relationship between fluid volume and blood pressure is an important one that you will learn about in detail in Chapter 12. Generally speaking, if extracellular fluid levels decrease, blood pressure decreases as a consequence. This explains why our patient felt light-headed, particularly when he stood up. As his blood pressure decreased, the ability of his heart to pump sufficient blood against gravity up to his brain also decreased, when brain cells are deprived of blood flow, they begin to malfunction. Standing suddenly only made matters worse. Perhaps you have occasionally experienced a little of this light-headed feeling when you have jumped out of a chair or bed and stood up too quickly. Normally, your nervous system quickly compensates for the effects of gravity on blood flowing up to the brain, as will be described in Chapters 6 and 12. In a person with decreased blood volume and pressure, however, this compensation may not happen and the person can lose consciousness. After fainting and falling, the man's head and heart were at the same horizontal level; consequently, blood could more easily reach his brain.

Another concern is that the salt concentrations in the body fluids changed. If you have ever tasted the sweat on your upper lip on a hot day, you know that it is somewhat salty. That is because sweat is derived from extracellular fluid, which as you have learned is a watery solution of ions (derived from salts, such as NaCl) and other substances. Sweat, however, is slightly more dilute than extracellular fluid because more water than ions is secreted from sweat glands. Consequently, the more heavily one perspires, the more concentrated the extracellular fluid becomes. In other words, the total amount of water and ions in the extracellular fluid decreases with perspiration, but the remaining fluid is "saltier." Heavy perspiration, therefore, not only disrupts fluid balance and blood pressure homeostasis but also has an impact on the balance of the ions in the body fluids, notably Na^+, K^+, and Cl^-. A homeostatic balance of ion concentrations in the body fluids is absolutely essential for normal heart and brain function, as you will learn in Chapters 4 and 6. As the man's ion concentrations changed, therefore, the change affected the activity of the cells of his brain.

Why did the man stop perspiring and why did his skin turn pale? To understand this, we must consider that several

(continued)

Guided Tour Through a Chapter



CHAPTER 9

Muscle

Colorized scanning electron micrograph (SEM) of freeze-fractured muscle fibers.

SECTION A
Skeletal Muscle

9A.1 Structure
9A.2 Molecular Mechanisms of Skeletal Muscle Contraction
Sliding-Filament Mechanism
Roles of Troponin, Tropomyosin, and Ca^{2+} in Contraction
Excitation–Contraction Coupling
Membrane Excitation: The Neuromuscular Junction
9A.3 Mechanics of Single-Fiber Contraction
Twitch Contractions
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9A.4 Skeletal Muscle Energy Metabolism
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9A.5 Types of Skeletal Muscle Fibers
9A.6 Whole-Muscle Contraction
Control of Muscle Tension
Control of Shortening Velocity
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Lever Action of Muscles and Bones
9A.7 Skeletal Muscle Disorders
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SECTION B
Smooth and Cardiac Muscle

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9B.2 Smooth Muscle Contraction and Its Control
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Sources of Cytosolic Ca^{2+}
Membrane Activation
Types of Smooth Muscle
9B.3 Cardiac Muscle
Cellular Structure of Cardiac Muscle
Excitation–Contraction Coupling in Cardiac Muscle
Chapter 9 Clinical Case Study

The ability to use chemical energy to produce force and movement is present to a limited extent in most cells, but in muscle cells it has become dominant. Muscles generate force and movements used to regulate the internal environment, and they also produce movements of the body in relation to the external environment. In humans, the ability to communicate whether by speech, writing, or art expression, also depends on muscle contractions. Indeed, it is only by controlling muscle activity that the human mind ultimately expresses

Three types of muscle tissue can be identified on the basis of structure, contractile properties, and control mechanisms—skeletal muscle, smooth muscle, and cardiac muscle. Most skeletal muscle, as the name implies, is attached to bone, and its contraction is responsible for supporting and moving the skeleton. The contraction of skeletal muscle is initiated by impulses in the neurons to the muscle and is usually under voluntary control

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Chapter Outline

Every chapter starts with an outline giving the reader a brief view of what is to be covered in that chapter.

Summary Tables

Summary tables are used to bring together large amounts of information that may be scattered throughout the book or to summarize small or moderate amounts of information. The tables complement the accompanying figures to provide a rapid means of reviewing the most important material in the chapter.

Table 9–3 Characteristics of the Three Types of Skeletal Muscle Fibers

	Slow-Oxidative Fibers (Type I)	Fast-Oxidative-Glycolytic Fibers (Type IIa)	Fast-Glycolytic Fibers (Type IIb)*
Primary source of ATP production	Oxidative phosphorylation	Oxidative phosphorylation	Glycolysis
Mitochondria	Many	Many	Few
Capillaries	Many	Many	Few
Myoglobin content	High (red muscle)	High (red muscle)	Low (white muscle)
Glycolytic enzyme activity	Low	Intermediate	High
Glycogen content	Low	Intermediate	High
Rate of fatigue	Slow	Intermediate	Fast
Myosin-ATPase activity	Low	High	High
Contraction velocity	Slow	Fast	Fast
Fiber diameter			
Motor unit size			
Size of motor neuron innervating fiber			

*Type IIb fibers are sometimes desi

CHAPTER 9 **Clinical Case Study**

A 17-year-old boy lay on an operating table undergoing a procedure to repair a fractured jaw. In addition to receiving the local anesthetic **lidocaine** (which blocks voltage-gated Na^+ channels and therefore action potential propagation), he was breathing **sevoflurane**, an inhaled general anesthetic that induces unconsciousness. An hour into the procedure, the anesthesiologist suddenly noticed that the patient's face was red and beads of sweat were forming on his forehead. The patient's monitors revealed that his heart rate had almost doubled since the beginning of the procedure and that there had been a significant increase in carbon dioxide levels in his exhaled breath. The oral surgeon reported that the patient's jaw muscles had gone rigid. The patient was exhibiting all of the signs of a rare but deadly condition called malignant hyperthermia, and quick action would be required to save his life.

Most patients who suffer from **malignant hyperthermia** inherit an autosomal dominant mutation of a gene found on chromosome 19. This gene encodes the ion channels involved in releasing calcium ions from the sarcoplasmic reticulum in skeletal muscle—the ryanodine receptors. Although the channels function normally under most circumstances, they malfunction when exposed to some types of inhalant anesthetics or to drugs that depolarize and block skeletal muscle neuromuscular junctions (like succinylcholine). In some cases, the malfunction occurs not on the first exposure to the triggering agent but only to a subsequent exposure.

The mechanism of malignant hyperthermia involves an excessive opening of the ryanodine receptor channel, with massive release of Ca^{2+} from the sarcoplasmic reticulum into the cytosol of skeletal muscle cells. The rate of Ca^{2+} release is so great that sarcoplasmic reticulum Ca^{2+}-ATPase pumps are unable to work fast enough to re-sequester it. The excess Ca^{2+} results in persistent activation of cross-bridge cycling and muscle contraction and also stimulates Ca^{2+}-activated proteases that degrade muscle proteins. The metabolism of ATP by muscle cells is increased enormously during an episode, with a number of consequences, some of which will be elaborated on in greater detail in later chapters:

1. ATP levels are depleted, causing cross-bridges to enter the rigor state and therefore muscle rigidity ensues.
2. Muscle cells must resort to anaerobic metabolism to produce ATP because oxygen cannot be delivered to muscles fast enough to maintain aerobic production, so patients develop lactic acidosis (acidified blood due to the build-up of lactic acid).
3. CO_2 production increases, generating carbonic acid that contributes to acidosis (see Chapter 13).
4. Muscles generate a tremendous amount of heat as a byproduct of ATP breakdown and production, producing the hyperthermia characteristic of this condition.
5. The drive to maintain homeostasis of body temperature, pH, oxygen and carbon dioxide levels triggers an increase in heart rate to support an increase in the rate of blood circulation (see Chapter 12).
6. Flushing of the skin and sweating occurs to help dissipate excess heat (see Chapter 16).

The anesthesiologist immediately halted the procedure, and then substituted 100 percent oxygen for the sevoflurane in the boy's breathing tube. Providing a high concentration of inspired oxygen increases blood oxygen to help muscles reestablish aerobic ATP production. The patient was then hyperventilated to help rid the body of excess CO_2, and ice bags were placed on his body to keep his temperature from increasing further. He was also given multiple injections of dantrolene until his condition began to improve. **Dantrolene**, a drug originally developed as a muscle relaxant, blocks the flux of Ca^{2+} through the ryanodine receptor. Since its introduction as a treatment, the mortality rate from malignant hyperthermia has decreased from greater than 70 percent to approximately 5 percent.

The boy was transferred to the intensive care unit, and his condition was monitored closely. Laboratory tests showed elevated blood H^+, K^+, Ca^{2+}, creatine kinase, and myoglobin levels, all of which are released during the rapid breakdown of muscle tissue (**rhabdomyolysis**). Among the dangers faced by such patients are malfunction of cardiac and other excitable cells, from abnormal pH and electrolyte levels, and kidney failure resulting from the overwhelming load of waste products released from damaged muscle cells. Over the next several days, the boy's condition improved and his blood chemistries returned to normal. Because the recognition and reaction by the medical team had been swift, the boy only suffered from sore muscles for the next few weeks but had no lasting damage to vital organs.

Malignant hyperthermia has a relatively low incidence, about one in 15,000 children and one in 50,000 adults. Because of its potentially lethal nature, however, it has become common practice to assess a given patient's risk of developing the condition. Although definitive proof of malignant hyperthermia can be determined by taking a muscle biopsy and assessing its response to anesthetics, the test is invasive and only available in a few labs, so it is not usually performed. Risk is more commonly assessed by taking a detailed history that includes whether the patient or a genetic relative has ever had a bad reaction to anesthesia. Even if a patient's family history is negative, however, surgical teams need to have dantrolene on hand and be prepared. Advances in our understanding of the genetic basis of this disease make it likely that a reliable genetic screening test for malignant hyperthermia will someday be available.

Clinical terms: dantrolene, lidocaine, malignant hyperthermia, rhabdomyolysis, sevoflurane

"Additional cases should be included. The best approach should be to put one of those cases at the end of each chapter with a case related to it."

Jesus A. F. Tresguerres, Medical School, University Complutense, Madrid, Spain

"I use numerous case studies in the undergraduate physiology course I teach. Students really enjoy the opportunity to utilize the information they are learning and to problem solve."

Ruth Clark, Washington University School of Medicine, Program in Physical Therapy

"I think additional case studies should definitely be added."

Elizabeth S. Tomlin, University of North Carolina at Greensboro

Clinical Case Studies—*NEW!*

The authors have drawn from their teaching and research experiences to provide students with real-life applications through clinical case studies in each chapter.

Physiological Inquiries—*EXPANDED!*

You will now find approximately twice as many critical-thinking questions based on many figures from all chapters. These concept checks were introduced in the eleventh edition and proved extremely popular with users of the textbook. They are designed to help students become more engaged in learning a concept or process depicted in the art. These questions challenge a student to analyze the content of the figure, and occasionally to recall information from previous chapters. Many of the questions also require quantitative skills.

"The physiological inquiries are great."
Jean-Pierre Dujardin, The Ohio State University

"This feature is extremely beneficial because the student has the opportunity to test their understanding of the material, by applying it to a problem."
Elizabeth S. Tomlin, University of North Carolina at Greensboro

"Absolutely, this type of "real-life" experience is excellent for the students who will be taking this level of physiology."
David S. Mallory, Marshall University

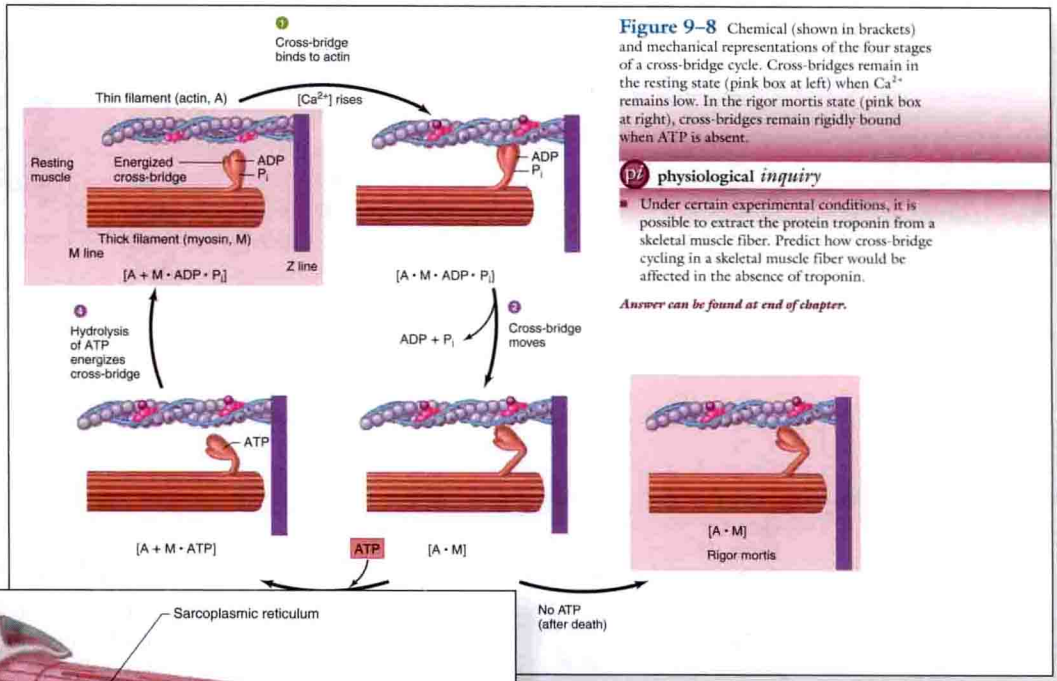


Figure 9–8 Chemical (shown in brackets) and mechanical representations of the four stages of a cross-bridge cycle. Cross-bridges remain in the resting state (pink box at left) when Ca^{2+} remains low. In the rigor mortis state (pink box at right), cross-bridges remain rigidly bound when ATP is absent.

physiological *inquiry*

- Under certain experimental conditions, it is possible to extract the protein troponin from a skeletal muscle fiber. Predict how cross-bridge cycling in a skeletal muscle fiber would be affected in the absence of troponin.

Answer can be found at end of chapter.

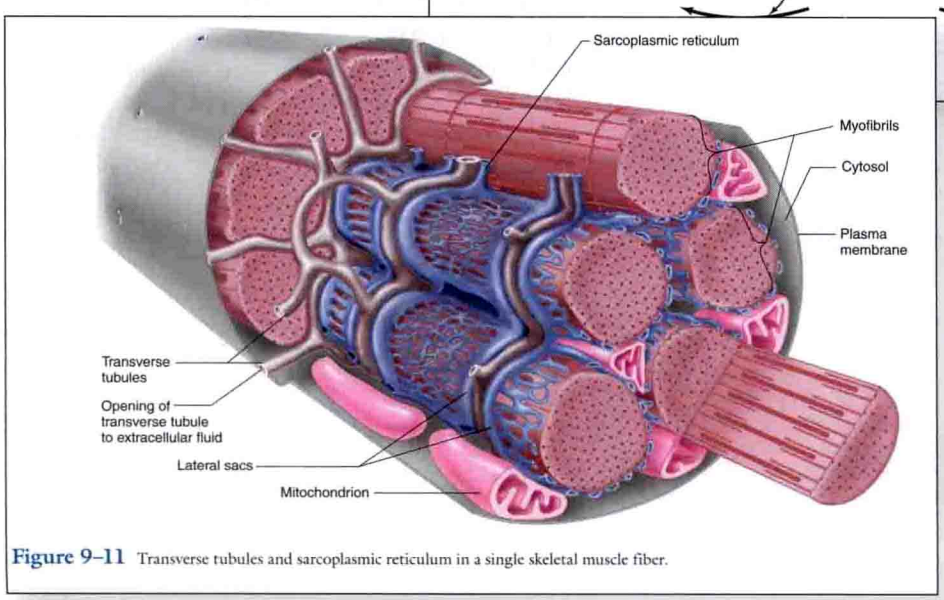


Figure 9–11 Transverse tubules and sarcoplasmic reticulum in a single skeletal muscle fiber.

Descriptive Art Style

A realistic three-dimensional perspective is included in many of the figures for greater clarity and understanding of concepts presented.

Guided Tour Through a Chapter

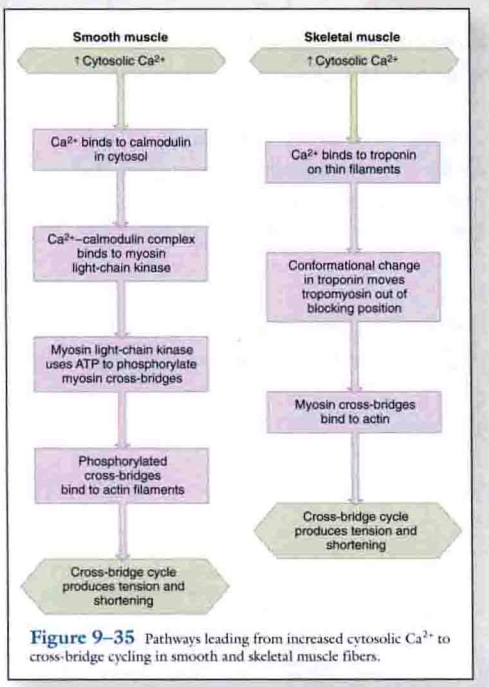


Figure 9–35 Pathways leading from increased cytosolic Ca^{2+} to cross-bridge cycling in smooth and skeletal muscle fibers.

Flow Diagrams

Long a hallmark of this book, extensive use of flow diagrams is continued in this edition. They have been updated to assist in learning.

Key to Flow Diagrams

- The beginning boxes of the diagrams are color-coded green.
- Other boxes are consistently color-coded throughout the book.
- Structures are always shown in three-dimensional form.

Multilevel Perspective

Illustrations depicting complex structures or processes combine macroscopic and microscopic views to help students see the relationships between increasingly detailed drawings.

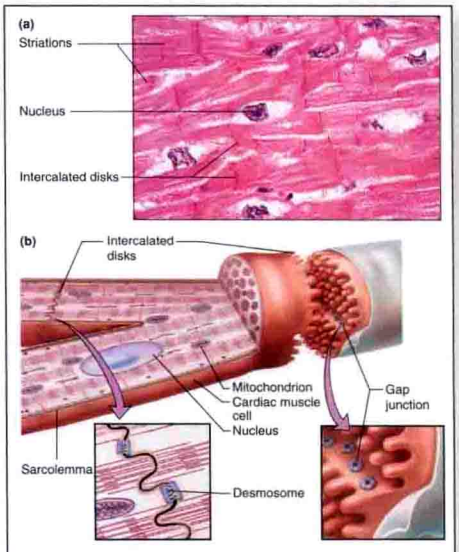


Figure 9–39 Cardiac muscle. (a) Light micrograph. (b) Cardiac muscle cells and intercalated disks.

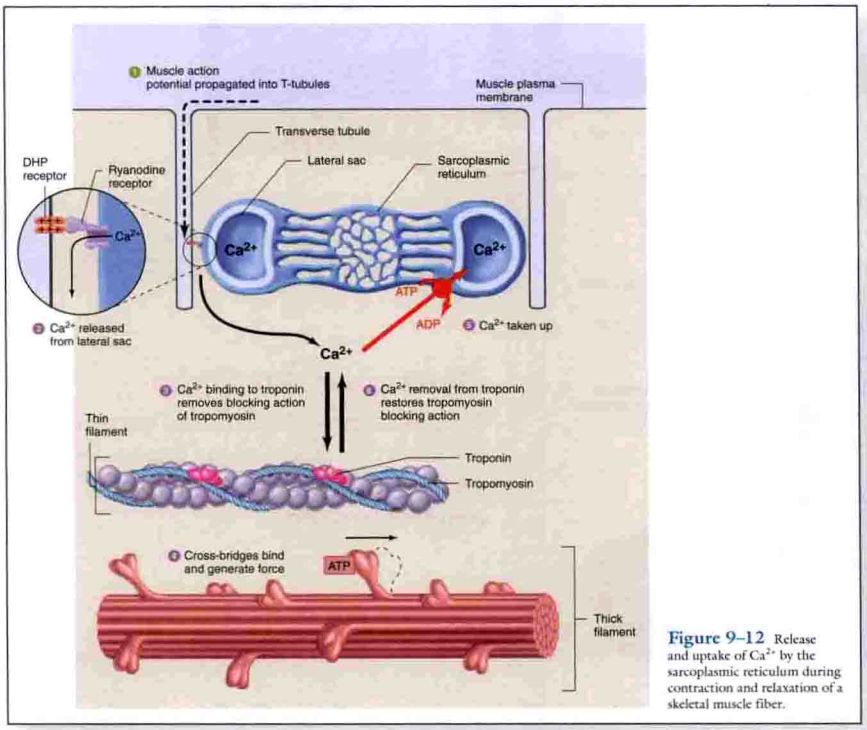


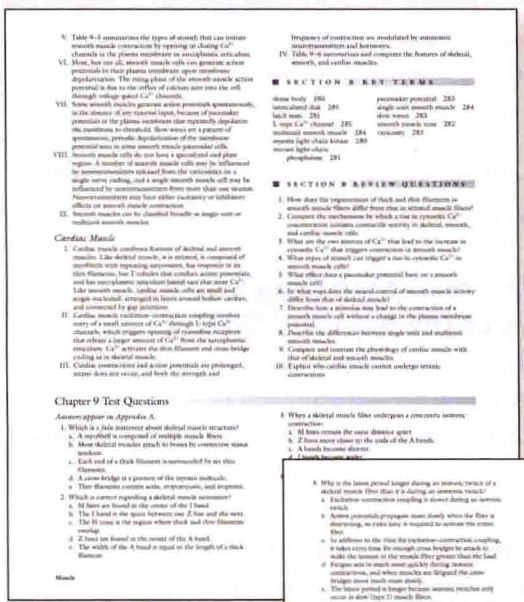
Figure 9–12 Release and uptake of Ca^{2+} by the sarcoplasmic reticulum during contraction and relaxation of a skeletal muscle fiber.

Uniform Color-Coded Illustrations

Color-coding is effectively used to promote learning. For example, there are specific colors for extracellular fluid, the intracellular fluid, muscle filaments, and transporter molecules.

End of Section

At the end of sections throughout the book you will find a summary, key terms, clinical terms, and review questions.



V. Table 9–6 summarizes the types of stimuli that can initiate smooth muscle contraction by opening or closing Ca^{2+} channels in the plasma membrane or sarcoplasmic reticulum.
VI. Most, but not all, smooth muscle cells can generate action potentials in their plasma membrane upon membrane depolarization. The rising phase of the smooth muscle action potential is due to the influx of calcium ions into the cell through voltage-gated Ca^{2+} channels.
VII. Some smooth muscles generate action potentials spontaneously, in the absence of any external input, because of pacemaker potentials in the plasma membrane that repeatedly depolarize the membrane to threshold. Slow waves are a pattern of spontaneous, periodic depolarization of the membrane potential seen in some smooth muscle pacemaker cells.
VIII. Smooth muscle cells do not have a specialized end-plate region. A number of smooth muscle cells may be influenced by neurotransmitters released from the varicosities on a single nerve axon, and a single smooth muscle cell may be influenced by neurotransmitters from more than one neuron. Neurotransmitters may have either excitatory or inhibitory effects on smooth muscle contraction.
IX. Smooth muscles can be classified broadly as single-unit or multiunit smooth muscles.

Cardiac Muscle

I. Cardiac muscle combines features of skeletal and smooth muscles. Like skeletal muscle, it is striated, is composed of myofibrils with repeating sarcomeres, has troponin in its thin filaments, has T tubules that conduct action potentials, and has sarcoplasmic reticulum limited save that store Ca^{2+}. Like smooth muscle, cardiac muscle cells are small and single-nucleated, arranged in layers around hollow cavities, and connected by gap junctions.
II. Cardiac muscle excitation–contraction coupling involves entry of a small amount of Ca^{2+} through L-type Ca^{2+} channels, which triggers opening of ryanodine receptors that release a larger amount of Ca^{2+} from the sarcoplasmic reticulum. Ca^{2+} activates the thin filament and cross-bridge cycling as in skeletal muscle.
III. Cardiac contractions and action potentials are prolonged, unique does not occur, and both the strength and frequency of contraction are modulated by autonomic neurotransmitters and hormones.
IV. Table 9–6 summarizes and compares the features of skeletal, smooth, and cardiac muscles.

■ SECTION B KEY TERMS

thone body 284
intercalated disk 285
latch bats 281
L-type Ca^{2+} channel 285
multiunit smooth muscle 284
myosin light chain kinase 280
myosin light-chain phosphatase 281
pacemaker potential 283
single-unit smooth muscle 284
slow waves 283
smooth muscle tone 282
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■ SECTION B REVIEW QUESTIONS

1. How does the organization of thick and thin filaments in smooth muscle fibers differ from that in striated muscle fibers?
2. Compare the mechanisms by which a rise in cytosolic Ca^{2+} concentration initiates contractile activity in skeletal, smooth, and cardiac muscle cells.
3. What are the two sources of Ca^{2+} that lead to the increase in cytosolic Ca^{2+} that triggers contraction in smooth muscle?
4. What types of stimuli can trigger a rise in cytosolic Ca^{2+} in smooth muscle cells?
5. What effect does a pacemaker potential have on a smooth muscle cell?
6. In what ways does the neural control of smooth muscle activity differ from that of skeletal muscle?
7. Describe how a stimulus may lead to the contraction of a smooth muscle cell without a change in the plasma membrane potential.
8. Describe the difference between single-unit and multiunit smooth muscles.
9. Compare and contrast the physiology of cardiac muscle with that of skeletal and smooth muscles.
10. Explain why cardiac muscle cannot undergo tetanic contractions.

Chapter 9 Test Questions

Answers appear in Appendix A.

1. Which is a *false* statement about skeletal muscle structure?
   a. A myofibril is composed of multiple muscle fibers.
   b. Most skeletal muscles attach to bones by connective tissue tendons.
   c. Each end of a thick filament is surrounded by six thin filaments.
   d. A cross-bridge is a portion of the myosin molecule.
   e. Thin filaments contain actin, tropomyosin, and troponin.
2. Which is correct regarding a skeletal muscle sarcomere?
   a. M lines are found in the center of the I band.
   b. The I band is the space between one Z line and the next.
   c. The H zone is the region where thick and thin filaments overlap.
   d. Z lines are found in the center of the A band.
   e. The width of the A band is equal to the length of a thick filament.

Muscle

3. When a skeletal muscle fiber undergoes a *concentric* isotonic contraction:
   a. M lines remain the same distance apart.
   b. Z lines move closer to the ends of the A bands.
   c. A bands become shorter.
   d. I bands become wider.
4. Why is the latent period longer during an isometric twitch of a skeletal muscle fiber than it is during an isotonic twitch?
   a. Excitation–contraction coupling is slower during an isometric twitch.
   b. Action potentials propagate more slowly when the fiber is shortening, so extra time is required to activate the entire fiber.
   c. In addition to the time for excitation–contraction coupling, it takes extra time for enough cross bridges to attach to make the tension in the muscle fiber greater than the load.
   d. Fatigue sets in much more quickly during isometric contractions, and when muscles are fatigued the cross bridges move much more slowly.
   e. The latent period is longer because isometric twitches only occur in slow (type I) muscle fibers.
5. When processes a *drop* in muscle fiber ATP concentration during the first few seconds of intense contraction?
   a. Because cross-bridges are pre-energized, ATP is not needed until several cross-bridge cycles have been completed.
   b. ADP is rapidly converted back to ATP by creatine phosphate.
   c. Glucose is metabolized to glucose, producing large quantities of ATP.
   d. The mitochondria immediately begin oxidative phosphorylation.
   e. Fatty acids are rapidly converted to ATP by oxidative glycolysis.
7. Which correctly characterizes a "fast-oxidative" type of skeletal muscle fiber?
   a. few mitochondria and high glycogen content
   b. low myosin ATPase rate and few surrounding capillaries
   c. low glycolytic enzyme activity and intermediate contraction velocity
   d. high myoglobin content and intermediate glycolytic enzyme activity
   e. small fiber diameter and fast onset of fatigue
8. Which is *false* regarding the structure of smooth muscle?
   a. The thin filament does not include the regulatory protein troponin.
   b. The thick and thin filaments are not organized in sarcomeres.
   c. Thick filaments are anchored to dense bodies instead of Z lines.
   d. The cells have a single nucleus.
   e. Single-unit smooth muscles have gap junctions connecting individual cells.
9. The role of myosin light-chain kinase in smooth muscle is to
   a. bind to calcium ions to initiate excitation–contraction coupling.
   b. phosphorylate cross-bridges, thus allowing them to bind with the thin filaments.
   c. split ATP to provide the energy for the power stroke of the cross-bridge cycle.
   d. dephosphorylate myosin light chains of the cross-bridge, thus releasing the muscle.
   e. pump Ca^{2+} from the cytosol back into the sarcoplasmic reticulum.
10. Single-unit smooth muscle differs from multiunit smooth muscle because
   a. single-unit muscle contraction spread is slow, and multiunit is fast.
   b. single-unit muscle has T tubules, and multiunit muscle does not.
   c. single-unit muscles are not innervated by autonomic nerves.
   d. single-unit muscle contracts when stretched, whereas multiunit muscle does not.
   e. single-unit muscle does not produce action potentials spontaneously, but multiunit muscle does.
11. Which of the following describes a similarity between cardiac and smooth muscle cells?
   a. An action potential always precedes contraction.
   b. The majority of the Ca^{2+} that activates contraction comes from the extracellular fluid.
   c. Action potentials are generated by pacemaker potentials.
   d. An extensive system of T tubules is present.
   e. Ca^{2+} release and contraction strengths are graded.

Chapter 9 Quantitative and Thought Questions

Answers appear on Appendix A.

1. Which of the following corresponds to the state of myosin (M) under resting conditions and in rigor mortis? (a. M · ATP (b) M · ADP · P_i (c) A · M · ADP · P_i (d) A + M
2. If the transverse tubules of a skeletal muscle are disconnected from the plasma membrane, will action potentials trigger a contraction? Give reasons.
3. When a small load is attached to a skeletal muscle that is then isometrically stimulated, the muscle lifts the load in an isotonic contraction over a certain distance but then stops shortening and enters a state of isometric contraction. With a heavier load, the distance shortened before entering an isometric contraction is shorter. Explain these shortening limits in terms of the length–tension relation of muscle.
4. What conditions will produce the maximum tension in a skeletal muscle fiber?

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9. The following experiments were performed on a single unit smooth muscle in the gastrointestinal tract.
   a. Stimulating the parasympathetic nerves to the muscle produced a contraction.
   b. Applying a drug that blocks the voltage-sensitive Na^+ channels in most plasma membranes led to a failure to contract upon stimulating the parasympathetic nerves.
   c. Applying a drug that binds to muscarinic receptors (Chapter 6) and, hence, blocks the action of ACh at these receptors did not prevent the muscle from contracting when the parasympathetic nerve was stimulated.

   From these observations, what might you conclude about the mechanisms by which parasympathetic nerve stimulation produces a contraction of the smooth muscle?
10. Some endocrine tumors secrete a hormone that leads to elevation of extracellular fluid Ca^{2+} concentrations. How might this affect cardiac muscle?

Chapter 9 Answers to Physiological Inquiries

Figure 9–4

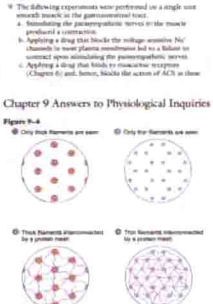

Figure 9–5 Changes in the width of the I bands and H zone would be the same, but the sarcomeres would not shift toward the fixed Z line at the right side of the diagram. They would shorten uniformly and pull both of the outer Z lines toward the center one.
Figure 9–8 As long as ATP is available, cross bridges would cycle continuously regardless of whether Ca^{2+} was present.
Figure 9–10 Tension takes longer to return to resting levels because all of the cross bridges that attached to actin when Ca^{2+} was elevated require time to complete their power stroke and detach from actin.
Figure 9–15 Na^+ current dominates when the ACh channels open because it has both a large inward diffusion gradient and, as the muscle cells resting membrane potential, a large inward electrical gradient. Although the diffusion gradient for K^+ is from the cell is large, the electrical gradient actually opposes its movement out of the cell. See Figure 6–12.
Figure 9–16 The weight in the isotonic experiment is approximately 14 mg. This can be estimated by determining the time at which the isometric load begins to move on the lower graph (approximately 12 msec), then using the upper graph to assess the amount of tension generated by the fiber at that point in time.
Figure 9–18 Peak power generation by muscle fibers occurs at intermediate loads, usually at about one third of their maximum isometric tension load. Using the arbitrary scale of 10 for the maximum velocity and load to this plot, for the points shown in this figure the power at the light load would be approximately $0.8 \times 7.6 = 2.75$. At the heavy load, it would be $1 \times 7 = 7$. At the intermediate load, the approximate power would be $3 \times 3 = 9$.
Figure 9–20 Unfused tetanic contractions will occur at between 6.7 and 28.6 stimuli per second. In order for an unfused tetanus to occur, the interval between stimuli must be less than 150 msec but greater than 35 msec. (If the interval was greater than 150 msec, twitches would not summate, and if less than 35 msec, a fused tetanus would occur.) To calculate the corresponding frequencies:
   1 stimulus/150 msec × 1000 msec/sec = 6.7 stimuli/sec
   1 stimulus/35 msec × 1000 msec/sec = 28.6 stimuli/sec
Figure 9–21 The passive tension at 160 percent of muscle length would be about 30 percent of the maximum isometric tension (see the red curve). When stimulated at that length, the active tension developed would be to additional 88 percent (see the green curve). The total tension measured would therefore be approximately 70 percent of the maximum isometric tetanic tension.
Figure 9–38 Muscle fibers containing the slow isoform of myosin contract and hydrolyze ATP relatively slowly. Their requirement for ATP can thus be satisfied by aerobic, oxidative mechanisms that, although slow, are extremely efficient (a yield of 38 ATP per glucose molecule were water and carbon dioxide as waste products—see Chapter 3). It would not be efficient for a slow fiber to produce its ATP predominately by glycolysis, a process that is extremely rapid and relatively inefficient (only 2 ATP per glucose and lactic acid as a waste product).
Figure 9–39 The force acting upward on the forearm ($F_B = 3 \times 423$) would be less than the downward acting force ($10 \times 41 = 410$), so the muscle would undergo a lengthening (eccentric) contraction and the weight would move toward the ground.
Figure 9–40 The object would move nine times farther than the biceps in the same amount of time, or 18 cm/sec.
Figure 9–41 The skeletal muscle experiments would look the same. The calcium ions for contraction in skeletal muscle come from inside the sarcoplasmic reticulum. (Note: If the ryanodine had been applied via a motor neuron, the lack of external Ca^{2+} would have prevented excitation of ACh and there would have been no action potential or contraction in the skeletal muscle cell.) Removing extracellular Ca^{2+} in the cardiac muscle experiment would eliminate both the prolonged plateau of the action potential and the contraction. Although the majority of the Ca^{2+} that activates contraction also comes from the sarcoplasmic reticulum in cardiac muscle, its release is triggered by entry of Ca^{2+} from the extracellular fluid through L-type channels during the action potential.

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Characteristic	Skeletal Muscle	Smooth Muscle		Cardiac Muscle
		Single Unit	Multiunit	
Thick and thin filaments	Yes	Yes	Yes	Yes
Sarcomeres—banding pattern	Yes	No	No	Yes
Transverse tubules	Yes	No	No	Yes
Sarcoplasmic reticulum (SR)*	++++	+	+	++
Gap junctions between cells	No	Yes	Few	Yes
Source of activating Ca^{2+}	SR	SR and extracellular	SR and extracellular	SR and extracellular
Site of Ca^{2+} regulation	Troponin	Myosin	Myosin	Troponin
Speed of contraction	Fast–slow	Very slow	Very slow	Slow
Spontaneous production of action potentials by pacemakers	No	Yes	No	Yes in a few specialized cells, but most not spontaneously active
Tone (low levels of maintained tension in the absence of external stimuli)	No	Yes	No	No
Effect of nerve stimulation	Excitation	Excitation or inhibition	Excitation or inhibition	Excitation or inhibition
Physiological effects of hormones on excitability and contraction	No	Yes	Yes	Yes
Stretch of cell produces contraction	No	Yes	No	No

*Number of plus signs (+) indicates the relative amount of sarcoplasmic reticulum present in a given muscle type.

potentials spontaneously, similar to the mechanism for smooth muscle described in Figure 9–36a. Because cardiac cells are linked via gap junctions, when an action potential is initiated by a pacemaker cell, it propagates rapidly throughout the entire heart. A single heartbeat corresponds to the initiation and conduction of a single action potential. In addition to the modulation of Ca^{2+} release and the strength of contraction, Chapter 12 will also discuss how hormones and autonomic neurotransmitters modify the frequency of cardiac pacemaker cell depolarization and, thus, vary the heart rate.

Table 9–6 summarizes and compares the properties of the different types of muscle.

■ SECTION B SUMMARY

Structure of Smooth Muscle

I. Smooth muscle cells are spindle-shaped, lack striations, have a single nucleus, and are capable of cell division. They contain actin and myosin filaments and contract by a sliding-filament mechanism.

Smooth Muscle Contraction and Its Control

I. An increase in cytosolic Ca^{2+} leads to the binding of Ca^{2+} by calmodulin. The Ca^{2+}–calmodulin complex then binds to myosin light-chain kinase, activating the enzyme, which uses ATP to phosphorylate smooth muscle myosin. Only phosphorylated myosin can bind to actin and undergo cross-bridge cycling.
II. Smooth muscle myosin has a low rate of ATP splitting, resulting in a much slower shortening velocity than in striated muscle. However, the tension produced per unit cross-sectional area is equivalent to that of skeletal muscle.
III. Two sources of the cytosolic calcium ions that initiate smooth muscle contraction are the sarcoplasmic reticulum and extracellular Ca^{2+}. The opening of Ca^{2+} channels in the smooth muscle plasma membranes and sarcoplasmic reticulum, mediated by a variety of factors, allows calcium ions to enter the cytosol.
IV. The increase in cytosolic Ca^{2+} resulting from most stimuli does not activate all the cross-bridges. Therefore, smooth muscle tension can be increased by agents that increase the concentration of cytosolic calcium ions.

End of Chapter

At the end of the chapters you will find

- Test Questions that are designed to test student comprehension of key concepts.
- Quantitative and Thought Questions that challenge the student to go beyond the memorization of facts, to solve problems and to encourage thinking about the meaning or broader significance of what has just been read.
- Answers to the Physiological Inquiries in that chapter.

Updates and Additions

In addition to updating material throughout the text to reflect cutting-edge changes in physiology and medicine, the authors:

- have added a new case study to Chapter 19, bringing the total to **four case studies** that require the student to think critically and apply what has been learned throughout the semester to novel clinical situations.
- have now incorporated shorter, chapter-specific case studies to each of the other 18 chapters. This feature, called **Clinical Case Studies**, appears at the end of each chapter; all Clinical Case Studies are based on real-life examples, and provide compelling examples of what may happen when homeostasis is disrupted.
- have roughly **doubled the number of Physiological Inquires**. This feature was introduced in the eleventh edition and was associated with key figures in chapters 4–18. Feedback from users of the text indicated that this learning tool was extremely valuable.

We believe that these additions, and those described below, make the twelfth edition of ***Vander's Human Physiology*** the most extensive, detailed, and integrative text available for students interested in learning about physiology.

Chapter 1 Homeostasis: A Framework for Human Physiology

Expanded description and illustration of cell and tissue types, particularly epithelial and connective tissue; addition of Physiological Inquiries; Clinical Case Study of an individual who develops heatstroke on a summer day.

Chapter 2 Chemical Composition of the Body

Expanded discussion of atomic structure, including *s*- and *p*-orbitals and energy shells; electronegativity and its importance for bond formation; greater tie-in of chemical and physiological principles; new art depicting multiple levels of protein structure; Clinical Case Study of a person with a mutation resulting in a change in protein structure and function.

Chapter 3 Cellular Structure, Proteins, and Metabolism

Description and new figure of the mitochondrial reticulum; new figure depicting oxidative phosphorylation and the role of ATP synthase; Clinical Case Study describing the consequence of a dietary change (grapefruit juice) on gut enzyme function and, therefore, the absorption of medication.

Chapter 4 Movement of Molecules Across Cell Membranes

Clinical Case Study of exercise-associated hyponatremia in a woman running a marathon.

Chapter 5 Control of Cells by Chemical Messengers

Improved description and illustrative depiction of G-protein structure and function; Clinical Case Study of a young person with a G-protein-related disorder (pseudohypoparathyroidism).

Chapter 6 Neuronal Signaling and the Structure of the Nervous System

Expanded discussion of neural plasticity; description of new findings on the genetic basis of Alzheimer disease; Clinical Case Study of a woman with multiple sclerosis.

Chapter 7 Sensory Physiology

New discussion of the role of transient receptor proteins (TRPs) in temperature perception; new figures explaining ON and OFF ganglion cell visual pathways and binocular visual fields; new table and description of decibel levels of common sounds and hearing loss; Clinical Case Study of a man with benign paroxysmal positional vertigo (BPPV).

Chapter 8 Consciousness, the Brain, and Behavior

Expanded discussion and new figures on EEG patterns during sleep; Clinical Case Study of a young athlete who sustains a concussion.

Chapter 9 Muscle

Expanded discussion of the role of satellite cells in muscle repair and hypertrophy; new discussion of neuromuscular blocking agents used in surgery; Clinical Case Study of a boy who develops malignant hyperthermia during a surgical procedure.

Chapter 10 Control of Body Movement

Discussion of Parkinson-disease-like condition caused by MPTP; Clinical Case Study of a gardener who contracts tetanus following a puncture wound.

Chapter 11 The Endocrine System

Expanded and improved presentation of steroid hormone synthesis and mechanism of action; functions of progesterone; clarification of differential diagnosis of hyposecretion syndromes; expanded discussion of the functions of oxytocin; increased emphasis on metabolic actions of growth hormone; control of growth hormone now depicted in two separate figures illustrating stimulatory and inhibitory pathways; Clinical Case Study of a middle aged man who develops acromegaly.

Chapter 12 Cardiovascular Physiology

Expanded discussion of the length–tension mechanism in cardiac muscle; new figure showing structural variations by region in the vascular system; in-depth discussion of possible mechanisms of primary and secondary hypertension; Clinical Case Study of a woman with pericarditis.

Chapter 13 Respiratory Physiology

Clinical Case Study of an obese man who snores and has sleep apnea.

Chapter 14 The Kidneys and Regulation of Water and Inorganic Ions

Improved presentation of the control of clearance; expanded discussion and new figure on water channels (aquaporins); Clinical Case Study of a woman with diabetic nephropathy.

Chapter 15 The Digestion and Absorption of Food

New description of incretins; additional detail and new figure on hepatic structure and function; new figures and expanded discussion on carbohydrate and protein digestion and absorption; Clinical Case Study of a college student with abdominal pain and Crohn's disease.

Chapter 16 Regulation of Organic Metabolism and Energy Balance

New discussion of incretins and their current and potential therapeutic uses; Clinical Case Study of an individual with blurry vision who is diagnosed with type 2 diabetes melllitus.

Chapter 17 Reproduction

Reorganization of introductory section on terminology and general principles; new figures on fertilization, ovulation, and implantation; Clinical Case Study of a woman with a pituitary gland tumor whose menstrual periods stop.

Chapter 18 The Immune System

"Specific" and "nonspecific" immune responses replaced with "adaptive" and "innate" immune responses; new section on pathogen-associated molecular patterns, pattern-recognition receptors, and toll-like receptors; clarification and updates of roles of B and T cells in mediating responses to pathogens; expansion of discussion of dendritic cells and regulatory T cells; addition of CD4 and CD8 proteins to relevant figures; discussion of the two families of interferons; discussion of gene therapy for SCID; Clinical Case Study of a teenage girl who develops a rash across her cheeks and nose and is later diagnosed with systemic lupus erythematosus.

Chapter 19 Medical Physiology: Integration Using Clinical Cases

A new case of a college student with nausea, flushing, sweating, and seizures.

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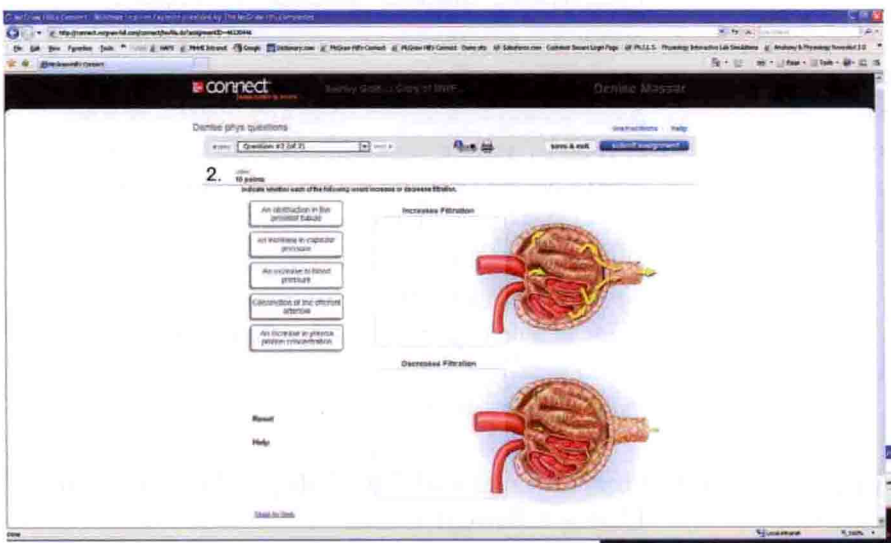

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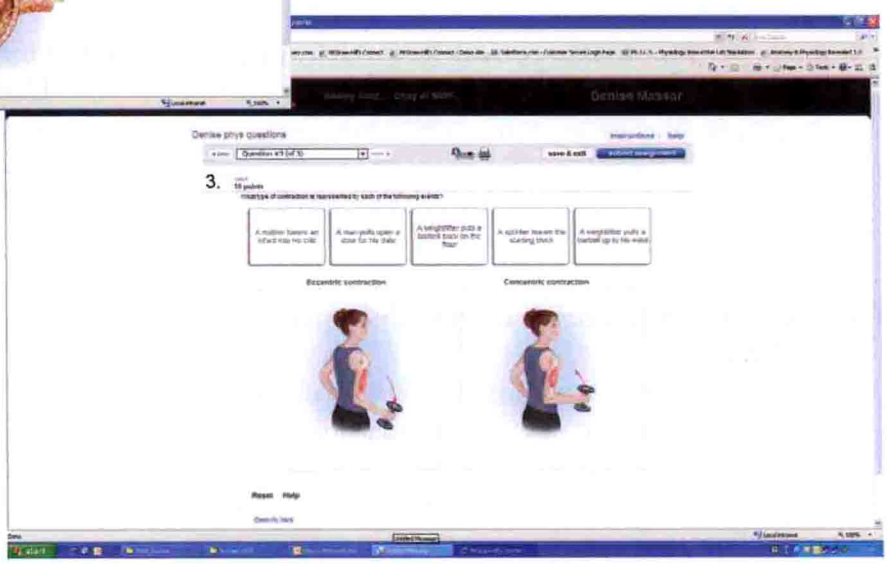

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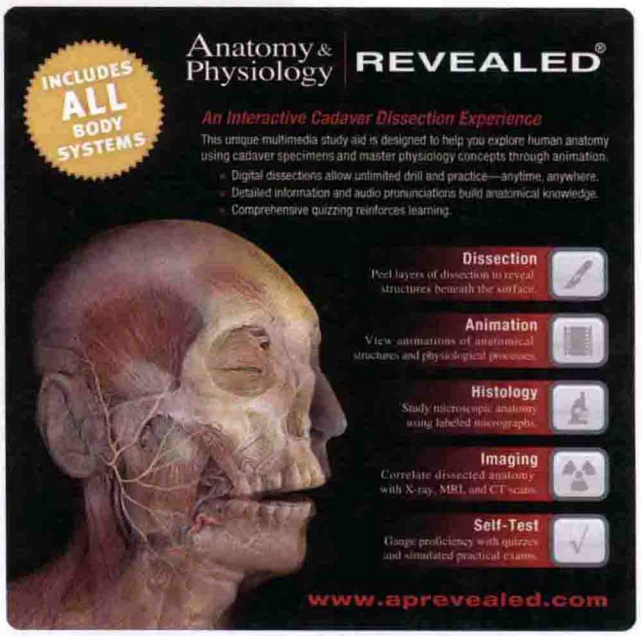

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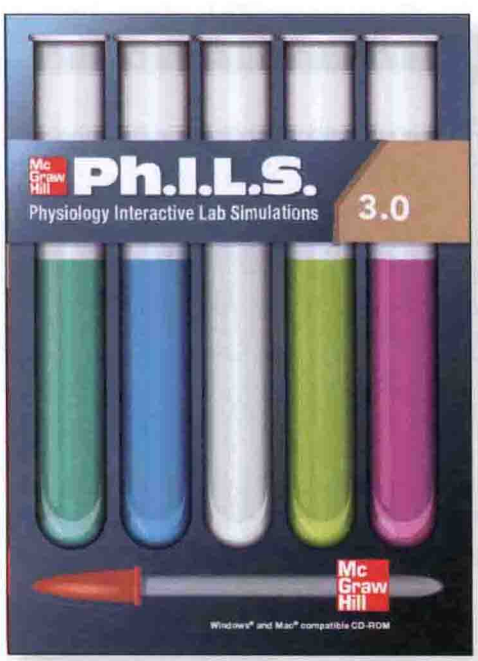

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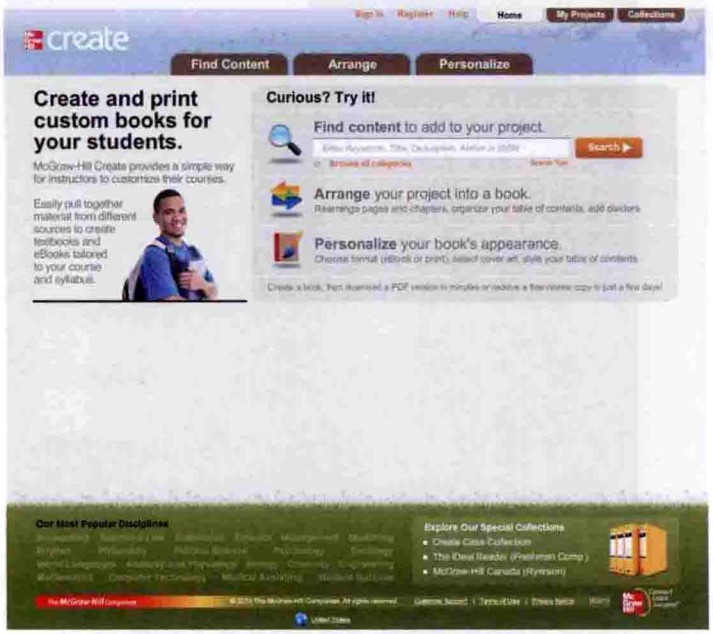

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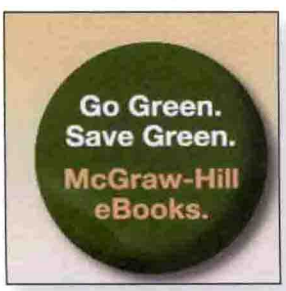

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