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Physiology
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EUGENG C. TOY, MD
The John S. Dunn Senior Academic Chief and Program Director
Obstetrics and Gynecology Residency
The Methodist Hospital, Houston
Clerkship Director and Clinical Associate Professor
Department of Obstetrics and Gynecology
University of Texas Medical School at Houston
Houston, Texas

NORMAN WEISBRODT, PhD
Professor and Interim Chairman
Department of Integrative Biology and Pharmacology
University of Texas Medical School at Houston
Houston, Texas

WILLIAM P. DUBINSKY,JR., PhD
Professor of Integrative Biology and Pharmacology
University of Texas Medical School at Houston
Houston, Texas

ROGER G. O'NEIL, PhD
Professor of Integrative Biology and Pharmacology
University of Texas Medical School at Houston
Houston, Texas

EDGAR T.WALTERS, PhD
Professor of Integrative Biology and Pharmacology
University of Texas Medical School at Houston
Houston, Texas

KONRAD P.HARMS, MD
Associate Program Director
Obstetrics and Gynecology Resic
The Methodist Hospital, Houstor
Assistant Clinical Professor
Weill Cornell College of Medicin
Houston, Texas

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二、内容上，每个分册包含几十个经典案例。基础学科强调与临床的结合，临床学科强调临床思维的培养。

三、以案例和问题导入，互动式学习，尤其适合 PBL（问题为中心的学习）和 CBL（案例为中心的学习）。

本系列书可作为医学院校双语教学或留学生教学的教材或教学辅导用书，也是医学生学习医学英语的优秀读物。在世界范围内，该系列书还是参加美国医师执照考试的必备用书。

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DEDICATION

To my outstanding obstetrics and gynecology residents who exemplify excellence and make coming to work each day a joy: Erica, Amber, Brad, Tara, Barrett, Kelli, Jennifer, Tametra, Stephen, Kristin, Tina, Lauren, Jessica, Vian, Kathryn, and Stan.

—ECT

To our many medical students over the past 25 years who have taught us so much.

—NW, WPD, RGO, ETW

To my wife, Heidi, and sons, Koen and Kort, for their many sacrifices on my behalf and their unwavering love and support.
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To my brother, Kent, for being a great role model and my best friend.

—KPH

CONTRIBUTORS

Paul G. Harms, PhD
Professor
Faculty of Reproductive Biology
Departments of Animal Science & Veterinary Integrated Biosciences
Texas A&M University
College Station, Texas
Female Reproductive Biology
Physiology of Pregnancy

Alaina Johnson
Class of 2008
University of Texas Medical School at Houston
Houston, Texas
Basal Ganglia
Electrical Activity of the Heart
Oxygen-Carbon Dioxide Transport

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Eugene C. Toy

❖ INTRODUCTION

Often, the medical student will cringe at the "drudgery" of the basic science courses and see little connection between a field such as physiology and clinical situations. Clinicians, however, often wish they knew more about the basic sciences, because it is through the science that we can begin to understand the complexities of the human body and thus have rational methods of diagnosis and treatment.

Mastering the knowledge in a discipline such as physiology is a formidable task. It is even more difficult to retain this information and to recall it when the clinical setting is encountered. To accomplish this synthesis, physiology is optimally taught in the context of medical situations, and this is reinforced later during the clinical rotations. The gulf between the basic sciences and the patient arena is wide. Perhaps one way to bridge this gulf is with carefully constructed clinical cases that ask basic science-oriented questions. In an attempt to achieve this goal, we have designed a collection of patient cases to teach physiology-related points. More important, the explanations for these cases emphasize the underlying mechanisms and relate the clinical setting to the basic science data. We explore the principles rather than emphasize rote memorization.

This book is organized for versatility: to allow the student "in a rush" to go quickly through the scenarios and check the corresponding answers and to provide more detailed information for the student who wants thought-provoking explanations. The answers are arranged from simple to complex: a summary of the pertinent points, the bare answers, a clinical correlation, an approach to the physiology topic, a comprehension test at the end for reinforcement or emphasis, and a list of references for further reading. The clinical cases are arranged by system to better reflect the organization within the basic science. Finally, to encourage thinking about mechanisms and relationships, we intentionally used open-ended questions in the cases. Nevertheless, several multiple-choice questions are included at the end of each scenario to reinforce concepts or introduce related topics.

We appreciate the good feedback from the various medical students from across the country. We have adopted many of these suggestions. In this second edition, there have been 30 cases that were substantially rewritten and 16 new figures to improve the readability and explanations. We think this second edition is an even better product.

HOW TO GET THE MOST OUT OF THIS BOOK

Each case is designed to introduce a clinically related issue and includes open-ended questions usually asking a basic science question, but at times, to break up the monotony, there will be a clinical question. The answers are organized into four different parts:

PART I

1. **Summary**
2. A **straightforward answer** is given for each open-ended question.
3. **Clinical Correlation**—A discussion of the relevant points relating the basic science to the clinical manifestations, and perhaps introducing the student to issues such as diagnosis and treatment.

PART II

An approach to the basic science concept consisting of two parts

1. **Objectives**—A listing of the two to four main principles that are critical for understanding the underlying physiology to answer the question and relate to the clinical situation.
2. **Discussion** of the physiologic principles.

PART III

Comprehension Questions—Each case includes several multiple-choice questions that reinforce the material or introduce new and related concepts. Questions about the material not found in the text are explained in the answers.

PART IV

Physiology Pearls—A listing of several important points, many clinically relevant, reiterated as a summation of the text and to allow for easy review, such as before an examination.

❖ CONTENTS

SECTION I

Applying the Basic Sciences to Clinical Medicine

Part 1. Approach to Learning Physiology

Part 2. Approach to Disease

Part 3. Approach to Reading

PART 1. APPROACH TO LEARNING PHYSIOLOGY

Physiology is best learned through a systematic approach, by understanding the cellular and macroscopic processes of the body. Rather than memorizing the individual relationships, the student should strive to learn the underlying rationale, such as: "The cell membrane allows passage of some molecules and not others based on lipid solubility, size of the molecule, concentration gradient, and electrical charge. Because the cell membrane is formed by a lipid bilayer, molecules that are lipid-soluble pass through more easily. Smaller molecules and those without an electrical charge also transfer more easily. Finally, the concentration gradient 'drives' the molecular transport, with the larger gradient providing a greater 'force'."

PART 2. APPROACH TO DISEASE

Physicians usually tackle clinical situations by taking a history (asking questions), performing a physical examination, obtaining selective laboratory and imaging tests, and then formulating a diagnosis. The synthesis of the history, physical examination, and imaging/laboratory tests is called the **clinical database.** After a diagnosis has been reached, a treatment plan usually is initiated, and the patient is followed for a clinical response. Rational understanding of disease and plans for treatment are best acquired by learning about the normal human processes on a basic science level; similarly, being aware of how disease alters the normal physiologic processes is best understood on a scientific level. Physiology also requires the ability to appreciate the normal workings of the human body, whereas pathophysiology focuses on how disease or disruption of the normal state affects the same mechanisms. The student should strive to learn the reason a disease manifests as certain symptoms or signs.

PART 3. APPROACH TO READING

There are six key questions that help stimulate the application of basic science information to the clinical setting:

1. **What is the likely mechanism for the clinical finding(s)?**
2. **What is the likely cellular response to a certain change in environment?**
3. **With the biochemical findings noted, what clinical processes are expected?**
4. **Given physiologic readings (hemodynamic, pulmonary, etc.), what is the likely disease process?**
5. **What is the likely cellular mechanism for the medication effect?**
6. **What graphic data best depict the physiologic principle?**

1. **What is the likely mechanism for the clinical finding(s)?**
   The student of physiology should try to place the understanding of the body in the context of molecular interactions, cellular adaptation, and responses by organ system. The physician must elicit data by asking questions and performing a physical examination. Through this process, the clinician forms a differential diagnosis of possible causes for the patient's symptoms. An understanding of the mechanisms by which physiological events give rise to the clinical manifestations allows for rational therapy and prognosis and directs future research. The student is advised to "think through" the mechanisms rather than memorize them. For instance, a pituitary adenoma may affect peripheral vision. Instead of memorizing this fact, the student should recall that the medial (nasal) aspects of both ocular retinas are innervated by optic nerves, which travel close to the midline and cross at the optic chiasm near the pituitary gland. Thus, an enlarging pituitary adenoma will impinge first on the nerve fibers at the optic chiasm, leading to a loss of visual acuity in the bitemporal regions, so-called bitemporal hemianopia. The clinician can screen for this by testing the patient's visual fields through testing peripheral vision on the lateral aspects.
2. **What is the likely cellular response to a certain change in environment?**
   The study of physiology must be approached on different levels. The macroscopic as well as the microscopic responses are important. When a change in the environment occurs (a stressor), individual cells adapt so that the organ adjusts, and ultimately the entire organism adapts. For instance, during an overnight fast, when serum glucose levels fall, leading to hypoglycemia, the body adapts. In the short term, the effects of insulin and glucagon on several key regulatory reactions in intermediary metabolism are directly opposed. During the fasting state, insulin levels fall and glucagon levels rise; these hormones act on glycogen synthesis or breakdown. Net production or breakdown of glycogen is dependent on the relative rates of the two reactions. These facts illustrate the hormonal responses.

   In regard to biochemical factors, often these reactions are controlled by phosphorylation-dephosphorylation cycles, and sometimes, these effects can be attributed to one common factor: in this case, cyclic adenosine monophosphate (cAMP). Glucagon activates *adenyl cyclase*, causing an increase in cellular cAMP levels and *protein kinase A* (PKA) activity. Insulin binding to its receptor, a *tyrosine kinase*, activates a signaling pathway that activates *protein kinase B* (PKB) and *protein phosphatase-1*. An example of the regulatory effects of these two hormones is the glycogen synthetic pathway. Glycogen levels are controlled by the relative rates of glycogen synthesis and glycogenolysis. *Glycogen synthase* activity is regulated by a phosphorylation-dephosphorylation cycle. In the absence of insulin, glycogen synthase is phosphorylated by a specific protein kinase. That kinase is inactivated in the presence of insulin, reducing the phosphorylation of glycogen synthase. The reaction is reinforced by an insulin-dependent activation of protein phosphatase-1 that dephosphorylates and activates glycogen synthase. Protein phosphatase-1 has multiple substrate proteins within the cell, one of which is phosphorylase. Phosphorylase catalyzes the breakdown of glycogen and is activated by phosphorylation with PKA and inactivated by dephosphorylation.

Thus, after the ingestion of a carbohydrate-containing meal, the rise in plasma insulin levels will cause an activation of glycogen synthase and an inhibition of phosphorylase. A fall in the plasma glucose reduces secretion of pancreatic insulin and stimulates secretion of glucagon. The hepatocyte responds to these changes with a decrease in protein phosphatase activity (as a result of decreased insulin levels) and an increase in PKA activity (as a result of elevated glucagon levels). The overall effect is an increase in glycogenolysis with the production of glucose.

3. **With the biochemical findings noted, what clinical processes are expected?**

   This is the converse of explaining clinical findings by reference to cellular or biochemical mechanisms. An understanding of the underlying molecular biology allows an extrapolation to the clinical findings. The student is encouraged to explore relationships between microscopic function and clinical symptoms or signs. The patient is aware only of overt manifestations such as pain, fatigue, and bleeding. Usually, substantial subclinical changes are present. The student's understanding of these relationships, as depicted below, provides opportunities to detect disease before it is clinically evident or to disrupt the disease process before it becomes advanced.

   Biochemical → Cellular → Subclinical changes → Clinical symptoms

One example is the understanding of the development of cervical cancer. It is known that human papillomavirus (HPV) is the primary oncogenic stimulus in the majority of cases of cervical intraepithelial neoplasia (CIN) and cervical cancer. HPV, particularly in the virulent subtypes, such as 16 and 18, incorporates its DNA into the host cervical epithelium cells, leading some women to develop CIN. Over years, the CIN progresses to cervical cancer; when this becomes advanced, it becomes evident by the patient's development of abnormal vaginal bleeding, lower abdominal pain, or back pain if metastasis has occurred. Awareness of this sequence of events allows for the possible development of an HPV vaccine, assays for HPV subtypes to assess the risk of CIN or cancer, and cytologic analysis of CIN when it is still asymptomatic (Pap smear), with appropriate treatment before cancer arises. The result is a 90% decrease in mortality from cervical cancer compared with the situation before the advent of the Pap smear.

4. **Given physiologic readings (hemodynamic, pulmonary, etc.), what is the likely disease process?**

The clinician's ability to interpret data relative to the physiologic and pathophysiologic processes is fundamental to rational therapy. For instance, a pulmonary artery catheter may be used to approximate the measure of a patient's left atrial pressure. In an instance of severe hypoxemia and diffuse pulmonary infiltrates on a chest radiograph, a common diagnostic dilemma is whether the patient has fluid overload and is in congestive heart failure or whether this represents acute respiratory distress syndrome (ARDS). In volume overload, the increased hydrostatic pressure drives fluid from the pulmonary capillaries into the pulmonary interstitium, leading to inefficient gas exchange between the alveoli and the capillary. The treatment for this condition would be diuresis, such as with furosemide, to remove fluid. In contrast, with ARDS, the pathophysiology is leaky capillaries, and the pulmonary capillary pressure is normal to slightly low. The therapy in this case is supportive and entails waiting for repair; diuresis may lead to hypovolemia and hypotension. In essence, the question is whether the patient is "wet" or "leaky," and the wrong therapy may be harmful. The pulmonary artery wedge pressure catheter is helpful in this case, because high pressures would suggest volume overload whereas normal-to-low pressures would suggest ARDS with leaky capillaries.

5. **What is the likely cellular mechanism for the medication effect?**

The student is best served by understanding the cellular mechanisms for not only physiologic responses but also responses to medications. For instance, an awareness of the behavior of digoxin allows one to understand its effect on the heart. Digoxin is a cardiac glycoside that acts indirectly to increase intracellular calcium. Digitalis binds to a specific site on the outside of Na^+-K^+-ATPase, reducing the activity of that enzyme. All cells express Na^+-K^+-ATPase, but they express different isoforms of the enzyme; the isoforms expressed by cardiac myocytes and vagal neurons are the most susceptible to digitalis. Inhibition of the enzyme by digitalis causes an increase in intracellular Na^+ and decreases the Na^+ concentration gradient across the plasma membrane. This Na^+ concentration provides the driving force for the Na^+-Ca^{2+} antiporter. The rate of transport of Ca^{2+} out of the cell is reduced, and this leads to an increase in intracellular Ca^{2+} and greater activation of contractile elements and an increase in the force and velocity of contraction of the heart. The electric characteristics of myocardial cells also are altered by the cardiac glycosides. The most important effect is a shortening of the action potential that produces a shortening of both atrial and ventricular refractoriness. There is also an

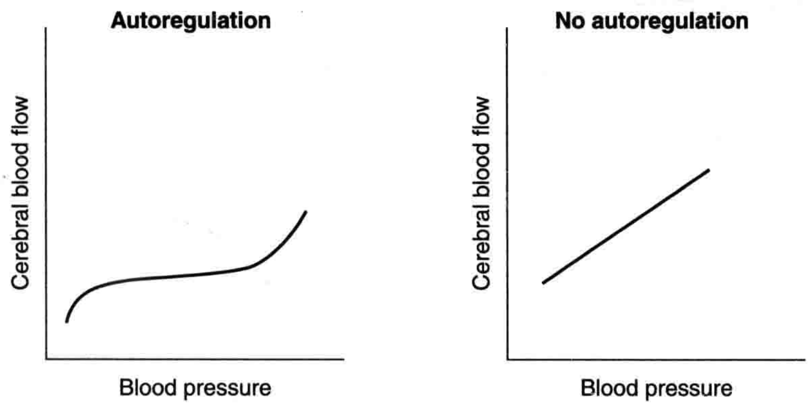

Figure I-1. Cerebral blood flow versus peripheral blood pressure.

increase in the automaticity of the heart both within the atrioventricular (AV) node and in the cardiac myocytes.

6. **What graphic data best depict the physiologic principle?**
   The basic scientist must be able to interpret data in various forms and propose explanations and theories that are then tested. Data in long lists of numbers are often inconvenient and untenable to analyze. Thus, graphic representation to allow for the determination of relationships and trends is critical. The student also should be skilled in the interpretation of graphic data and the correlation of those data to physiologic processes. For instance, the brain has a well-developed autoregulatory capacity to maintain a constant cerebral blood flow despite the fact that the systemic blood pressure is variable. In other words, with hypotension, the cerebral vessels dilate to allow for brain perfusion, whereas with hypertension, the cerebral vessels constrict. Of course, there are limits to this adaptation at the extremes of blood pressures (see Figure I-1).

PHYSIOLOGY PEARLS

- There are six key questions to stimulate the application of basic science information to the clinical arena.
- The student should strive to understand physiology from the molecular, cellular, organ, and entire organism viewpoints.
- Understanding the physiology allows for rational diagnostic and therapeutic interventions.