# ANNUAL REVIEW OF PHYSIOLOGY

VOLUME 63, 2001

## SECTIONS

*Perspectives*
Joseph F. Hoffman, Editor
*Special Topic: Intermediary Metabolism*
Joseph F. Hoffman, Editor
*Gastrointestinal Physiology*
Luis Reuss, Section Editor
*Endocrinology*
Jean D. Wilson, Section Editor
*Cell Physiology*
Paul De Weer, Section Editor
*Comparative Physiology*
George N. Somero, Section Editor
*Cardiovascular Physiology*
Jeffrey Robbins, Section Editor
*Respiratory Physiology*
Carole R. Mendelson, Section Editor
*Renal and Electrolyte Physiology*
Steven C. Hebert, Section Editor
*Special Topic: Circadian Rhythms*
Amita Sehgal, Special Topic Editor
*Neurophysiology*
Richard W. Tsien, Section Editor

# ANNUAL REVIEW OF PHYSIOLOGY

VOLUME 63, 2001

JOSEPH F. HOFFMAN, *Editor*
Yale University School of Medicine

PAUL De WEER, *Associate Editor*
University of Pennsylvania School of Medicine

www.AnnualReviews.org science@AnnualReviews.org 650-493-4400

ANNUAL REVIEWS
4139 El Camino Way • P.O. BOX 10139 • Palo Alto, California 94303-0139

ANNUAL REVIEWS
Palo Alto, California, USA



*International Standard Serial Number: 0066-4278*
*International Standard Book Number: 0-8243-0363-6*
*Library of Congress Catalog Card Number: 39-15404*



TYPESET BY TECHBOOKS, FAIRFAX, VA
PRINTED AND BOUND IN THE UNITED STATES OF AMERICA

# Annual Review of Physiology

Production Editor: SANDRA H. COOPERMAN
Bibliographic Quality Control: MARY A. GLASS
Color Graphics Coordinator: EMÉ O. AKPABIO
Online Quality Control: NOËL J. THOMAS
Subject Indexer: KYRA KITTS

# PREFACE

Readers of the *Annual Review of Physiology* should be apprised that our board of editors is always concerned about the extent of our coverage and responsibilities concerning our field. We are aware of the changing character of different areas, not just the novel advances and new accomplishments, but also the development and application of new approaches leading to better understanding of cellular and systemic processes. We attempt to bridge the reductionist insights into molecular mechanisms with their integrated counterparts in the whole organisms. Taken together, we hope that the subjects reviewed in each edition reflect these various aspects, recognizing that the themes covered in each section change yearly. We continue to encourage our readers to send comments and suggestions concerning topics and/or blind spots in our coverage. We can be reached at our web site, www.Annual Reviews.org.

This year's volume contains, in addition to the articles in the various sections, our prefatory chapter written by Alexander Leaf and two special topics. The purpose of including special topics is to bring to the attention of our readership developments in related fields that lie outside our normal coverage. The first special topic, edited by Amita Sehgal, concerns an in-depth survey of circadian rhythms with special emphasis on molecular aspects. The second topic, written by Robert Shulman and Douglas Rothman, considers new aspects of intermediary metabolism, with implications for systems physiology, and utilizes concepts derived from metabolic control analysis.

Joseph F. Hoffman
Editor

# OTHER REVIEWS OF INTEREST TO PHYSIOLOGISTS

From the ***Annual Review of Biochemistry***, Volume 69 (2000):

*Two-Component Signal Transduction*, Ann M Stock, Victoria L Robinson, and Paul N Goudreau

*Apoptosis Signaling*, Andreas Strasser, Liam O'Connor, and Vishva M Dixit

*Protein Tyrosine Kinase Structure and Function*, Stevan R Hubbard and Jeffrey H Till

*Platelet-Activating Factor and Related Lipid Mediators*, Stephen M Prescott, Guy A Zimmerman, Diana M Stafforini, and Thomas M McIntyre

*Mediator of Transcriptional Regulation*, Lawrence C Myers and Roger D Kornberg

*GTPase-Activating Proteins for Heterotrimeric G Proteins: Regulators of G Protein Signaling (RGS) and RGS-Like Proteins*, Elliott M Ross and Thomas M Wilkie

*Swinging Arms and Swinging Domains in Multifunctional Enzymes: Catalytic Machines for Multistep Reactions*, Richard N Perham

From the ***Annual Review of Cell and Developmental Biology***, Volume 16 (2000):

*Molecular Regulation of Adipogenesis*, Evan D Rosen and Bruce Spiegelman

*Epithelial M Cells: Differentiation and Function*, Jean-Pierre Kraehenbuhl and Marian R Neutra

*The Role of Orphan Nuclear Receptors in the Regulation of Cholesterol Homeostasis*, Joyce J Repa and David J Mangelsdorf

*Structure and Regulation of Voltage-Gated $Ca^{2+}$ Channels*, William Catterall

*Secretory Protein Trafficking and Organelle Dynamics in Living Cells*, Jennifer Lippincott-Schwartz, Theresa Roberts, and Koret Hirschberg

From the ***Annual Review of Medicine***, Volume 52 (2001):

*Molecular Genetics and Pathogenesis of Autosomal Dominated Polycystic Kidney Disease*, MA Arnaout

*Novel Platelet Inhibitors*, Joel S Bennett

*Effects of Neuropeptides and Leptin on Nutrient Partitioning: Dysregulation in Obesity*, Bernard Jeanrenaud and Françoise Rohner-Jeanrenaud

From the ***Annual Review of Neuroscience***, Volume 24 (2001)

*Localization and Globalization in Conscious Vision*, S Zeki

*Protein Synthesis at Synaptic Sites on Dendrites*, Steward Schuman and E Schuman

*Neuropeptides and the Integration of Motor Responses to Dehydration*, AG Watts

*The Vanilloid Receptor: A Molecular Gateway to the Pain Pathway*, M Caterina and D Julius

*Viktor Hamburger and Rita Levi-Montalcini: The Path to the Discovery of Nerve Growth Factor*, WM Cowan

From the ***Annual Review of Nutrition***, Volume 20 (2000):

*The Behavioral Determinants of Exercise: Implications for Physical Activity Interventions*, Nancy E Sherwood and Robert W Jeffrey

*Leptin—Much More than a Satiety Signal*, Ruth BS Harris

*Regulation of Metabolism and Body Fat Mass by Leptin*, Clifton A Baile, Mary Anne Della-Fera, and Roy J Martin

*Iron Transport*, Marianne Wessling-Resnick

*Intestinal Transport During Fasting and Malnutrition*, Ronaldo P Ferraris and Hannah V Carey

*Cellular Copper Transport and Metabolism*, Edward D Harris

*The Extracellular $Ca^{2+}$-Sensing Receptor (CAR): Central Mediator of Systemic Calcium Homeostasis*, Edward M Brown

*The Health Benefits of Wine*, J Bruce German and Rosemary L Walzem

*Iron Regulatory Proteins and the Molecular Control of Mammalian Iron Metabolism*, Richard S Eisenstein

From the ***Annual Review of Pharmacology and Toxicology***, Volume 41 (2001):

*Genetic Variations and Polymorphisms of G Protein–Coupled Receptors: Functional and Therapeutic Implications*, Brinda K Rana, Testuo Shiina, and Paul A Insel

*Lysophospholipid Receptors*, Nobuyuki Fukushima, Isao Ishii, James JA Contos, Joshua A Weiner, and Jerold M Chun

*Molecular Approach to Adenosine Receptors: Receptor-Mediated Mechanisms of Tissue Protection*, Joel Linden

*Compartmentation of G Protein–Coupled Signaling Pathways in Cardiac Myocytes*, Susan F Steinberg and Laurence L Brunton

*Physiological Functions of Cyclic ADP-Ribose and NAADP as Calcium Messengers*, Hon Cheung Lee

*Regulation and Role of Adenylyl Cyclase Isoforms*, Jacques Hanoune and Nicole Defer

*Novel Effects of Nitric Oxide*, Karen L Davis, Emil Martin, Illarion V Turko, and Ferid Murad

*$Ca^{2+}$/CaM-Dependent Kinases: From Activation to Function*, Sara S Hook and Anthony R Means

*Anesthetics and Ion Channels: Molecular Models and Sites of Action*, Tomohiro Yamakura, Edward Bertaccini, James R Trudell, and R Adron Harris

*Molecular Targets of Lithium Action*, Christopher J Phiel and Peter Klein

ANNUAL REVIEWS is a nonprofit scientific publisher established to promote the advancement of the sciences. Beginning in 1932 with the *Annual Review of Biochemistry*, the Company has pursued as its principal function the publication of high-quality, reasonably priced *Annual Review* volumes. The volumes are organized by Editors and Editorial Committees who invite qualified authors to contribute critical articles reviewing significant developments within each major discipline. The Editor-in-Chief invites those interested in serving as future Editorial Committee members to communicate directly with him. Annual Reviews is administered by a Board of Directors, whose members serve without compensation.

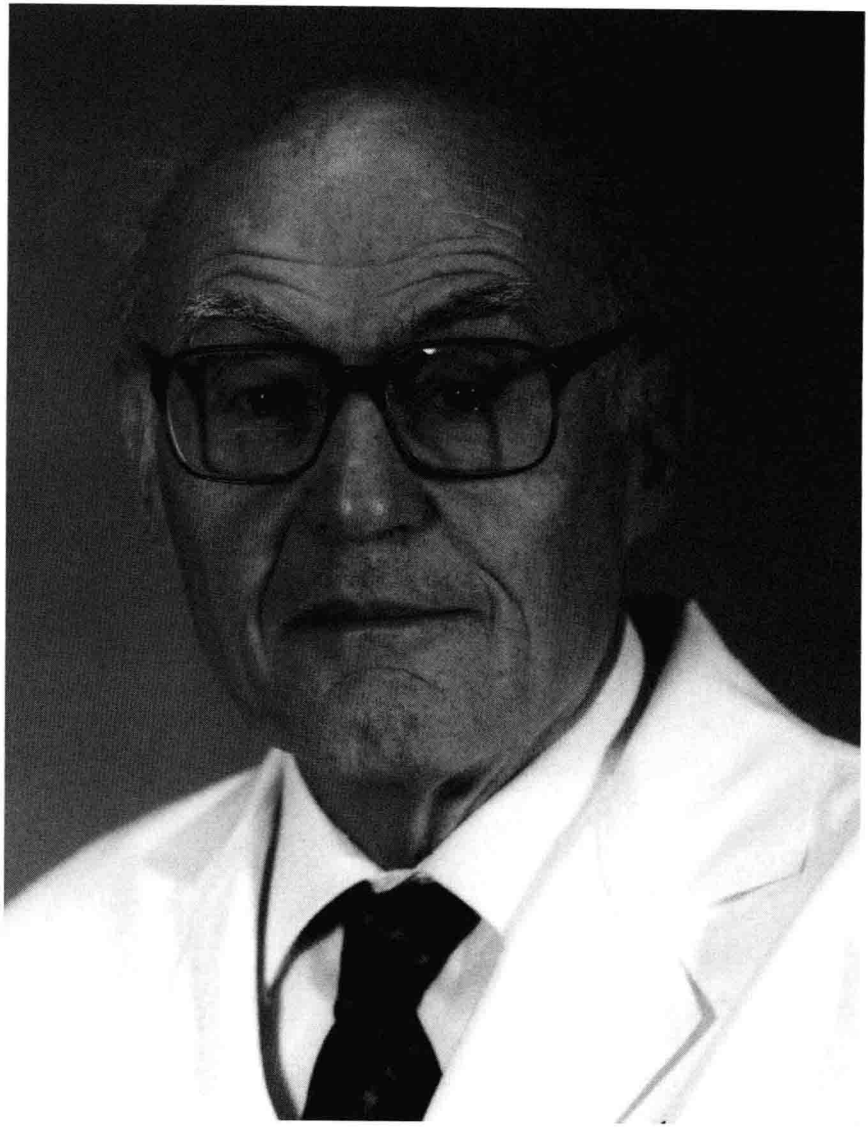


**Annual Reviews of**

Anthropology
Astronomy and Astrophysics
Biochemistry
Biomedical Engineering
Biophysics and Biomolecular Structure
Cell and Developmental Biology
Earth and Planetary Sciences
Ecology and Systematics
Energy and the Environment
Entomology
Fluid Mechanics
Genetics
Genomics and Human Genetics
Immunology
Materials Science
Medicine
Microbiology
Neuroscience
Nuclear and Particle Science
Nutrition
Pharmacology and Toxicology
Physical Chemistry
Physiology
Phytopathology
Plant Physiology and Plant Molecular Biology
Political Science
Psychology
Public Health
Sociology

SPECIAL PUBLICATIONS

Excitement and Fascination of Science, Vols. 1, 2, 3, and 4



Alexander Leaf

*Annual Review of Physiology,*
*Volume 63, 2001*

# CONTENTS

Annu. Rev. Physiol. 2001. 63:1–14


# MEDICINE OR PHYSIOLOGY: My Personal Mix

Alexander Leaf, M.D.
*Departments of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02129; e-mail: aleaf@partners.org*

**Key Words** autobiography, polyunsaturated fatty acids, cell volume regulation, sodium transport, preventive medicine

## INTRODUCTION

As a physician and a clinician, I feel especially honored to be invited to prepare this prefatory chapter but more than a little intimidated in accepting to do so. In fact, when first invited by the Editor to do this, I looked up the prefatory chapters for the past decade. I responded that my small incursions into physiology did not qualify me to join the ranks of the eminent physiologists who have graced these Annual Reviews with their comments in the past. So why am I now interrupting that distinguished succession? Later in a moment of moderate euphoria, engendered by having just been awarded two separate National Institutes of Health grants, I have forsaken my better judgement and succumbed to temptation.

### Early Life and Education

I was born in 1920 in Yokohama, Japan. My parents had escaped from Russia via the Trans Siberian railway one year before the Bolshevik revolution, just as von Hindenburg was beginning his rout of the Czarist's troops, which had been advancing into Prussia on the German eastern front. We left Japan for the United States, when I was two-years old, and settled in Seattle. I had an idyllic boyhood there fully enjoying my playmates; the woods and lake near our house; the mild but wet winters; swimming and sailing on Lake Washington and Puget Sound; Mount Rainer, spectacular across the lake; and all the beauties then of the Pacific Northwest. School was boring with its repetitiveness so I enjoyed the sociability that it afforded but did poorly scholastically. In high school things changed. There were several interesting courses. Especially the chemistry and physics courses were excellent and superbly taught. Unfortunately, the mathematics classes to which I was assigned were poorly taught so I learned little of that; my other major deficiency was in reading, which was very slow. Later, I took a speed reading course at Harvard. I succeeded in doubling my reading speed and exactly halved my comprehension. I was only little more successful with math. When I was inducted

0066-4278/01/0315-0001$14.00 

into the Army Medical Corps, I took a text of integral and differential calculus with me and waded through that in boot camp, during a steaming summer in San Antonio. But both the slow reading and the inability to formulate or summarize concepts in mathematical expression have remained real professional handicaps.

Attending the University of Washington was also enjoyable. I decided to major in chemistry and found the instruction to be stimulating and my classmates good but competitive company. I lived at home. I had been awarded a partial scholarship to Harvard, but my father thought I should remain at home. It was still the Depression years, and the $30 quarterly tuition at the University of Washington did help. My older brother, one year my senior but two years ahead of me scholastically, was soon to go East to pursue his doctoral studies in chemistry.

During my final two years in high school and increasingly during the university time, my father unobtrusively became a pivotal figure in my education. He proved a gold mine of erudition, and I consulted him on many topics. He counseled my brother and me to take as many science courses at school as we could, saying that learning science required demonstrations and laboratory exercises, which were only readily available in schools, whereas cultural subjects we could learn on our own to the extent that we were so motivated. Our home was filled with classical culture from the music and literature, which both my parents loved and encouraged us to hear and read, to lengthy discussions on politics, society, science, religion, philosophy, and literature, at home and with classmates. Both my parents were raised in strict, orthodox Jewish families, and they resolved that their children would not receive any religious indoctrination but be free to make their own choices. My own agnosticism has been strongly bolstered by Karl Popper's analysis of the distinction that science seeks to increase our understanding of our physical and biologic world through careful observation and experimentation, which test negatable hypotheses, whereas the beliefs of religion are not testable but must be accepted on faith.

This lack of a religious identity set me aside from most of my classmates and friends, but even more so did my family's attitude toward how our free time should be spent. With summer school vacations, all of my friends, encouraged by their parents, rushed to get jobs and make money. My father, on the contrary, advised that this was my age of rapid learning and encouraged me to read, take up hobbies, enjoy the outdoors, and practice my flute playing, which with the compositions of Bach, has provided me much pleasure but little expertise. Later, he said, my time would be occupied with supporting a family and there would be little time for scholarship. My father was a dentist, and we were a middle-class family. His own formal education had been very limited in Czarist Russia but that had not diminished his personal, informal scholarly interests.

The summer of my final year in high school I did follow the custom of my neighborhood peers and got a job, working on the construction of the Grand Coulee Dam as a common laborer. My assignment was to brush and sweep clean the tops of the 100-foot square concrete blocks, preparing the surface for the next layer of concrete to be poured. I worked the graveyard shift, from midnight to

8:00 A.M. It seemed grueling, back-breaking work, but it had one salutatory effect; it got me through medical school. I figured there had to be some easier way to make a living!

During my attendance at the university, war clouds were gathering ominously over Europe, creating uncertainty and unrest on our campuses. I made a hasty decision at the beginning of my third year to change my study major from chemistry to premed, feeling that whatever the future might bring, as a physician I would always be helping people. More recent observations and experiences have given me pause to revise that comfortable assumption regarding the role of my profession in society. The courses I had taken during my first two years fulfilled most of the academic requirements of my new major, so I needed to take only a few additional biology classes. This I did by adding them hastily to my chemistry classes, but the class in structural biology, which required dissection of brine-pickled cat cadavers during a warm Seattle summer in the small, unventilated Anatomy Shed almost dissuaded me from pursuing a career in medicine. I even squeezed in my first taste of research during my last two summers in an elective offering in chemical oceanography at the University of Washington's Marine Biology Laboratories in Friday Harbor on San Juan Island in in the Straits of Juan de Fucca. My problem was most mundane–to measure gravimetrically the calcium concentration in sea water sampled from varying depths at specific sites as a means of determining the currents in the Pacific by application of the Bjerknes atmospheric equations—but the setting of the Laboratories was unbelievably beautiful.

By halfway through the third academic year, it seemed likely that I would complete my required courses of study, so I started writing applications for acceptance to medical schools. The University of Washington allowed me to finish my studies in three years, and with satisfactory completion of the first year of medical school, I would be awarded a University of Washington baccalaureate degree in science. It was still possible to enter medical schools with only three years of college and with my high scholastic record, I felt the probability of acceptance was fairly likely. But there was no medical school in Washington in those days so I applied to many schools in the East. There followed a period of increasing anxiety as one after the other of the prestigious schools to which I had applied returned rejection notices to me. This was further heightened when family friends and even my revered atomic energy physics professor advised that it was unlikely that medical schools would accept a Jewish applicant. At last I received an acceptance notice from the University of Michigan and could start to make plans for new experiences in Ann Arbor, where I matriculated in the Fall of 1940.

## Medical School

Medical School turned out to be a surprising experience. My previous classmates in chemistry were to be future scientists and engineers, and all seemed motivated to learn as much science as possible. My medical school classmates were a very heterogeneous group. They came from a variety of educational backgrounds, many