Seldin and Giebisch

THE KIDNEY
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Editors

Donald W. Seldin, M.D.

Chairman
Department of Internal Medicine
The University of Texas Health Science Center at Dallas
Southwestern Medical School
Dallas, Texas

Gerhard Giebisch, M.D.

Department of Physiology
Yale University School of Medicine
New Haven, Connecticut

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THE KIDNEY

Physiology and Pathophysiology

The editors dedicate this book
to the memory of
John P. Peters and Robert F. Pitts
for their distinguished roles as
educators and investigators

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The editors are especially proud to have been able to enlist the participation of distinguished experts from all over the world and wish to thank them for the high quality of their contributions as well as their forebearance in responding to suggestions.

Preface

Before the Second World War, an understanding of kidney function in broad outline had gradually emerged. The filtration-reabsorption theory formulated by Cushny and based on earlier proposals by Ludwig was placed on firm footing by the pioneering micropuncture studies of Richards, Wearn, Walker, and their associates. Marshall and his school, resurrecting the earlier views of Heidenhain, demonstrated the participation of tubular secretion in urine formation. It became clear that three processes, glomerular filtration, tubular reabsorption, and tubular secretion mediated the urinary excretion of water and electrolytes.

Two great methodologic advances facilitated the translation of this conceptual framework into quantitative terms. Smith, Rehberg, and their associates successfully elaborated and then applied noninvasive techniques to the measurement of renal hemodynamics in both animals and human subjects. As a consequence, it became possible to assess quantitatively glomerular filtration rate, renal blood flow, and tubular secretion under normal and abnormal circumstances. At the same time, Peters and Van Slyke developed and consolidated a precise methodology for measurement of the composition of body fluids and urine.

The initial studies emanating from these conceptual and methodologic developments were utilized principally for a static portrayal of the chemical composition of body fluids and urine. The function of the kidney as a regulatory organ governing the maintenance of the volume and composition of body fluids was only dimly perceived. The mechanisms responsible for the adjustments of renal function under the impact of physiologic disturbances or frank disease states were almost wholly unknown. In part, this focus on chemical anatomy was the inevitable expression of technical limitations: Analytic methods were painfully cumbersome and time-consuming, and usually required substantial amounts of material; furthermore, many critical constituents simply could not be measured. In part, this narrow preoccupation with static steady state measurements reflected the relatively primitive conceptual system: The kidney was conceived in the main as a black box, so that input in the form of glomerular filtration and output as urine flow constituted the principal analytic framework.

It was the application to biologic systems of the methods and principles of the generalizing sciences, physics and chemistry, after World War II, that transformed renal physiology from a crude empirical enterprise into a formidable discipline of explanatory power and technical sophistication. Powerful analytic methods—typified early by the flame photometer and later by sensitive micromethods involving isotopes, microchemistry, immunoassay, microelectrodes, electron microscopy, optics, nuclear magnetic resonance, and the like—paved the way for truly novel advances. At first, the newer analytic armamentarium was utilized by Albright, Peters, Pitts, and many others in balance and clearance studies to investigate the adaptations in renal function under the impact of physiologic and pathologic derangements. Then, the reintroduction of micropuncture and the development of microperfusion of isolated tubules permitted an assessment of segmental function which Richards and his associates, a decade earlier, had just begun. At the same time, the introduction by Ussing and his associates of an isolated two-membrane epithelial system, the frog skin, provided an enormously fruitful model for the exploration of the transport properties of the renal tubule. Later still, the study of membrane vesicles *in vitro*, coupled with micromethods of exquisite sensitivity, permitted the formulation of principles of cellular and epithelial function. As a result, the investigation of renal physiology could progress from the analysis of the whole organ to the level of the nephron and finally to the basic domains of epithelial and cellular function. The fundamental mechanisms underlying changes in overall renal function were now available for study and began to provide a conceptual framework for powerful theories of renal regulation.

These advances in renal physiology were paralleled by a similar transformation in the understanding of renal disease. The development of electron microscopy and immunofluorescent techniques, together with the explosive progress in immunologic theory, resulted in the new discipline of immunonephrology. An understanding of the pathogenesis of the major renal diseases began to emerge. It was now possible to design rational therapy to interrupt injurious processes originating in immunologic disturbances, coagulation, and inflammation.

The recognition of the kidney as an endocrine organ served to expand the study of the kidney outside its traditional arena of renal physiology and renal disease. It was first appreciated that the kidney was the target of circulating hormones, such as antidiuretic hormone, parathyroid hormone, aldosterone, glucocorticoids, growth hormone, and the like. Then the kidney was found to secrete hormones acting on such distant sites as blood vessels, bone marrow, and bone. Finally, various humoral agents, produced by the kidney, were shown to act within intrarenal loci. The integration of the rapidly advancing disciplines of renal physiology, immunonephrology, and renal endocrinology transmuted the study of kidney function into the new specialty of nephrology.

The focus of these volumes has been principally on renal physiology, conceived broadly as the study of those processes by which the kidney maintains the volume and composition of the body in the face of physiologic demands and pathologic disturbances. Rather than presenting superficial coverage on the many aspects of nephrology, the editors decided to omit an analysis of specific renal diseases, immunonephrology, and such modalities of therapy as transplantation and dialysis. These are complex areas that clearly deserve separate treatment in depth.

Section I analyzes the principles governing the exchange of water and solutes within the body fluid compartments. Consideration is first given to the factors involved in external balance. Thereafter, exchanges within the body compartments are explored. This compartmental analysis is followed by a treatment of the basic principles underlying solute and solvent transport. Section II explores the organization of the kidney from the standpoint of structure and development; then functional organization, examined in terms of the categories of renal hemodynamics, tubular function, and hormonal regulation, is considered in depth.

Section III deals in depth with the regulation of water and electrolyte balance. Ideally, such a treatment would involve a reduction of normal and deranged overall renal function to a segmental level, then to a cellular and membrane level, and finally to a molecular level where the properties of pumps and membranes would provide the explanatory framework for macroscopic phenomena. Such a thoroughgoing reduction is not yet possible. However, in the case of each constituent the basic mechanisms of transport are first considered, the regulatory influences are explored, and the derangements are analyzed, so far as possible, in terms of physiologic principles developed.

Section IV is devoted to a consideration of the failure of the kidney and the action of various pharmacologic agents, both in a setting of impaired renal function and as the cause of other derangements.

It is our hope that the basic principles presented here will furnish an explanatory framework for the understanding of the principles underlying internal exchanges of water and electrolytes and of the key regulatory role of the kidney in responding to normal as well as abnormal disturbances.

DONALD W. SELDIN
GERHARD GIEBISCH

Contributors

John W. Adamson *Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington 98195*

Zalman S. Agus *Renal Electrolyte Section, Department of Medicine, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, Pennsylvania 19104*

Allen C. Alfrey *Department of Renal Medicine, Denver Veterans Administration Medical Center, and Department of Medicine, University of Colorado Medical School, Denver, Colorado 80220*

Robert J. Anderson *Division of Renal Diseases, Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262*

Thomas E. Andreoli *Department of Internal Medicine, University of Texas Medical School at Houston, Houston, Texas 77025*

Jeffrey Atkinson *Institute of Pharmacology, University of Lausanne, Bugnon 21, CH-1011 Lausanne, Switzerland*

Knut Aukland *Department of Physiology, University of Bergen, N-5000 Bergen, Norway*

Christine P. Bastl *Department of Medicine, Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140*

Daniel C. Batlle *Section of Nephrology, Department of Medicine, University of Illinois College of Medicine, 840 South Wood Street, Chicago, Illinois 60612*

Christine Baylis *Department of Medicine, University of California, San Diego, California 92093*

Michel Bergeron *Department of Physiology, University of Montreal, McGill University, Montreal, Quebec, H3G 1Y6 Canada*

Robert W. Berliner *Departments of Physiology and Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510*

Margaret Bia *Department of Medicine, Yale University School of Medicine, New Haven, Connecticut 06510*

Daniel G. Bichet *Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262; Present address: Department of Nephrology, Hôpital du Sacré-Coeur, University of Montreal, 5400 ouest, Boul. Gouin, Montréal, Québec, H4J 1C5 Canada*

Roland C. Blantz *Department of Medicine, University of California, San Diego, School of Medicine, La Jolla, California 92093; and Veterans Administration Medical Center, San Diego, California 92161*

Walter F. Boron *Department of Physiology, Yale University School of Medicine, New Haven, Connecticut 06510*

Jesper Brahm *Department of Biophysics, The Panum Institute, University of Copenhagen, Blegdamsvej 3c, DK-2200, Copenhagen N, Denmark*

Robert A. Branch *Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232*

Barry M. Brenner *Laboratory of Kidney and Electrolyte Physiology, Departments of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts 02115*

Neal S. Bricker *Program in Kidney Diseases, Department of Medicine, University of California School of Medicine, Los Angeles, California 90024*

Josephine Briggs *Department of Physiology, University of Munich, Pettenkoferstrasse 12, D-8000 Munich 2, Federal Republic of Germany*

Maria José F. Camargo *Department of Physiology, Cornell University Medical College, 1300 York Avenue, New York, New York 10021*

Danielle Chabardes *Laboratory of Cellular Physiology, College of France, 75231 Paris Cedex 05, France*

Evelyn M. Clarkson *Charing Cross Hospital Medical School, London, W6 8RF, United Kingdom*

Jordan J. Cohen *University of Chicago Pritzker School of Medicine, Department of Medicine, and Michael Reese Hospital and Medical Center, Chicago, Illinois 60616*

Romulo E. Colindres *Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514*

Alan W. Cuthbert *Department of Pharmacology, University of Cambridge, Hills Road, Cambridge, CB2 2QD, United Kingdom*

William H. Dantzler *Department of Physiology, College of Medicine, University of Arizona, Tucson, Arizona 85724*

Peter Deetjen *Institute of Physiology, University of Innsbruck, A-6010, Innsbruck, Austria*

Ralph A. DeFronzo *Department of Medicine, Yale University School of Medicine, New Haven, Connecticut 06510*

Vincent W. Dennis *Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710*

Hugh E. de Wardener *Charing Cross Hospital Medical School, London, W6 8RF, United Kingdom*

Paul De Weer *Department of Physiology and Biophysics, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110*

John H. Dirks *Department of Medicine, Acute Care Unit, Health Sciences Center, University of British Columbia, Vancouver, V6T 1W5 British Columbia*

Thomas P. Dousa *Nephrology Research Unit, Division of Nephrology, Departments of Medicine and Physiology, Mayo Clinic and Foundation, Mayo Medical School, Rochester, Minnesota 55905*

Lance D. Dworkin *Laboratory of Kidney and Electrolyte Physiology, and Departments of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts 02115*

Laurence E. Earley *Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104*

J. Michael Edwardson *Department of Pharmacology, University of Cambridge, Hills Road, Cambridge, CB2 2QD, United Kingdom*

Garabed Eknoyan *Department of Medicine, Baylor College of Medicine, 1200 Moursund, Houston, Texas 77030*

Michael Emmett *Department of Internal Medicine, University of Texas Health Science Center at Dallas, Southwestern Medical School, and Baylor University Medical School, Dallas, Texas 75235*

James T. Fitzsimons *Physiological Laboratory, University of Cambridge, Downing Street, Cambridge, CB2 3EG, United Kingdom*

Robert E. Forster *Department of Physiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104*

Irving H. Fox *Departments of Internal Medicine and Biological Chemistry, Human Purine Research Center, University of Michigan, Ann Arbor, Michigan 48109*

Harry A. Fozzard *Department of Medicine, and Department of Pharmacological and Physiological Sciences, The University of Chicago, Chicago, Illinois 60637*

J. Pedro Frommer *Department of Medicine, Veterans Administration Hospital, 2002 Holcombe, Houston, Texas 77211*

Eberhard Frömter *Center for Physiology, Clinical Center, J.W. Goethe University, 6000 Frankfurt am Main 70, Federal Republic of Germany*

Kathi Geering *Institute of Pharmacology, University of Lausanne, Bugnon 21, CH-1011 Lausanne, Switzerland*

Michael A. Geheb *Department of Medicine, Wayne State University, Detroit, Michigan 48201*

Gerhard Giebisch *Department of Physiology, Yale University School of Medicine, New Haven, Connecticut 06510*

Jan P. Goldberg *Division of Renal Diseases, Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262*

Stanley Goldfarb *Department of Medicine, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, Pennsylvania 19104*

Marc B. Goldstein *Department of Medicine, Renal Division, University of Toronto School of Medicine, and St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8 Canada*

Carl W. Gottschalk *Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514*

Rainer Greger *Max Planck Institute for Biophysics, D-6000 Frankfurt/Main, Federal Republic of Germany*

Gerhard Gstraunthaler *Department of Physiology, University of Munich, Pettenkoferstrasse 12, D-8000 Munich 2, Federal Republic of Germany*

Mitchell L. Halperin *Renal Division, University of Toronto School of Medicine, and St. Michael's Hospital, 38 Shuter Street, Toronto, Ontario, M5B 1A6 Canada*

Marc Hammerman *Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110*

Aviad Haramati *Nephrology Research Laboratories, Department of Physiology and Biophysics, Mayo Clinic and Foundation, Rochester, Minnesota 55905*

Robert H. Harris *Department of Medicine, Duke University School of Medicine, and Veterans Administration Medical Centers, Durham, North Carolina 27705*

Steven C. Hebert *Brigham and Women's Hospital, Department of Medicine, Renal Division, 75 Francis Street, Boston, Massachusetts 02115*

William L. Henrich *Department of Internal Medicine, University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, and Dallas Veterans Administration Medical Center, Dallas, Texas 75235*

Klaus Hierholzer *Department of Clinical Physiology, Steglitz Clinic, Free University of Berlin, D-1000 Berlin 45, Federal Republic of Germany*

Norman K. Hollenberg *Department of Radiology, Harvard Medical School, and Brigham and Women's Hospital, 50 Binney Street, Boston, Massachusetts 02115*

Michael Horster *Institute of Physiology, University of Munich, D-8000 Munich 2, Federal Republic of Germany*

Michael H. Humphreys *Division of Nephrology, San Francisco General Hospital, San Francisco, California 94110*

Gernot B. Irsigler *Department of Medicine, Pulmonary Unit, H.F. Verwoerd Hospital, and University of Pretoria, Pretoria 0181, Republic of South Africa*

Edwin K. Jackson *Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232*

Harry R. Jacobson *Department of Internal Medicine, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas, 75235*

Rex. L. Jamison *Division of Nephrology, Stanford University School of Medicine, Stanford, California 94305*

Paul C. Johnson *Department of Physiology, University of Arizona Health Sciences Center, Tucson, Arizona 85724*

Robert L. Johnson, Jr. *Division of Pulmonary Research, Department of Medicine, University of Texas Health Science Center, Southwestern Medical Center, Dallas, Texas, 75235*

Robert L. Jungas *Department of Physiology, School of Medicine, University of Connecticut Health Center, Farmington, Connecticut 06032*

Brigitte Kaissling *Anatomical Institute, University of Basel, CH-4056 Basel, Switzerland*

Norman M. Kaplan *Department of Internal Medicine, University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235*

Elaine M. Kaptein *Division of Nephrology, School of Medicine, University of Southern California, Los Angeles, California 90033*

Adrian I. Katz *Department of Obstetrics and Gynecology, Department of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637*

Murray A. Katz *Renal Section, Department of Internal Medicine, Tucson Veterans Administration Medical Center, and Department of Physiology, University of Arizona Health Science Center, Tucson, Arizona 85724*

William N. Kelley *Departments of Internal Medicine and Biological Chemistry, Human Purine Research Center, University of Michigan, Ann Arbor, Michigan 48109*

Priscilla Kincaid-Smith *University of Melbourne, Department of Medicine, Royal Melbourne Hospital, Grattan Street, Parkville Victoria 3052 Australia*

Rolfe Kinne *Max-Planck-Institut für Systemphysiologie, Rheinlanddam 210, 4600 Dortmund 1, Federal Republic of Germany*

Evamaria Kinne-Saffran *Max-Planck-Institut für Systemphysiologie, Rheinlanddam 201, D-4600 Dortmund 1, Federal Republic of Germany*

Saulo Klahr *Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110*

James P. Knochel *Department of Internal Medicine, University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235*

Franklyn G. Knox *Nephrology Research Laboratories, Department of Physiology and Biophysics, Mayo Clinic and Foundation, Rochester, Minnesota 55905*

Bruce Koeppen *Department of Medicine and Physiology, University of Connecticut, Farmington, Connecticut 06032*

Juha P. Kokko *Department of Internal Medicine, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235*

Poul Kristensen *Institute of Biological Chemistry A, August Krogh Institute, 13 Universitetsparken, DK-2100 Copenhagen Ø, Denmark*

Wilhelm Kriz *Anatomical Institute, University of Heidelberg, D-6900 Heidelberg 1, Federal Republic of Germany*

Robert T. Kunau, Jr. *Department of Medicine, University of Texas Health Science Center, San Antonio, Texas 78285*

Kiyoshi Kurokawa *Nephrology Section, Medical and Research Services, Veterans Administration Wadsworth Medical Center, Los Angeles, California 90073; and Department of Medicine, University of California at Los Angeles, Los Angeles, California 90024*

Neil A. Kurtzman *Section of Nephrology, Department of Medicine, University of Illinois College of Medicine, 840 South Wood Street, Chicago, Illinois 60612*

Alexander Leaf *Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02114*

Moshe Levi *Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262*

Michael M. Levine *Program in Kidney Diseases, Department of Medicine, University of California School of Medicine, Los Angeles, California 90024*

Mortimer Levy *Nephrology Division, Royal Victoria Hospital, McGill University, Montreal, Quebec, H3G 1Y6 Canada*

Marshall D. Lindheimer *Department of Obstetrics and Gynecology, Department of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637*

Thomas Maack *Department of Physiology, Cornell University Medical College, 1300 York Avenue, New York, New York 10021*

Anthony D. C. Macknight *Department of Physiology, University of Otago Medical School, P.O. Box 913, Dunedin, New Zealand*

Nicolaos E. Madias *Division of Nephrology, Tufts University School of Medicine, and Tufts–New England Medical Center, Boston, Massachusetts 02111*

Rhoda K. Makoff *Program in Kidney Diseases, Department of Medicine, University of California School of Medicine, Los Angeles, California 90024*

Gerhard Malnic *Department of Physiology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil*

Harry S. Margolius *Departments of Medicine and Pharmacology, Medical University of South Carolina, Charleston, South Carolina 29425*

June Mason *Department of Physiology, University of Munich, Pettenkoferstrasse 12, D-8000 Munich 2, Federal Republic of Germany*

Shaul G. Massry *Division of Nephrology, School of Medicine, University of Southern California, Los Angeles, California 90033*

William E. Mitch *Department of Medicine, Harvard Medical School, and Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115*

François Morel *Laboratory of Cellular Physiology, College of France, 75231 Paris Cedex 05, France*

Gail Morrison *Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104*

N. G. Moss *Department of Physiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514*

Robert G. Narins *Department of Medicine, Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140*

John A. Oates *Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232*

Jarle Ofstad *Department of Medicine, University of Bergen, N-5000 Bergen, Norway*

Charles Y. C. Pak *Section of Mineral Metabolism, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235*

C. Hyung Park *Department of Physiology, Cornell University Medical College, 1300 York Avenue, New York, New York 10021*

Jerry S. Powell *Division of Hematology, Department of Medicine, University of Washington, Seattle, Washington 98195*

Gary A. Quamme *Department of Medicine, Acute Care Unit, Health Sciences Center, University of British Columbia, Vancouver, V6T 1W5 British Columbia*

Murugappan Ramanathan *Division of Pulmonary Research, Department of Medicine, University of Texas Health Science Center, Dallas, Texas 75235*

Floyd C. Rector, Jr. *Division of Nephrology and Cardiovascular Institute, Department of Medicine, University of California at San Francisco, San Francisco, California 94143*

H. John Reineck *Department of Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284*

Robert M. A. Richardson *University of Toronto, Toronto General Hospital, 101 College Street, Toronto, Ontario M5G 1L7 Canada*

Gary L. Robertson *University of Chicago Pritzker School of Medicine, Department of Medicine, and Michael Reese Hospital and Medical Center, Chicago, Illinois 60616*

Roscoe R. Robinson *Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee 37203*

Françoise Roch-Ramel *Institute of Pharmacology, University of Lausanne, Bugnon 21, CH-1011 Lausanne, Switzerland*

Bernard C. Rossier *Institute of Pharmacology, University of Lausanne, Bugnon 21, CH-1011 Lausanne, Switzerland*

Denis R. Roy *Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, California 94305*

Michael R. Rudnick *Department of Medicine, Temple University Health Sciences Center, Philadelphia, Pennsylvania 19140*

F. Sauer *Max-Planck Institute for Biophysics, Kennedyallee 70, 6000 Frankfurt am Main 70, Federal Republic of Germany*

Jürgen Schnermann *Department of Physiology, University of Munich, Pettenkoferstrasse 12, D-8000 Munich 2, Federal Republic of Germany*

Robert W. Schrier *Department of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262*

Gerald Schulman *Department of Medicine, Harvard Medical School, and Brigham and Women's Hospital, 50 Binney Street, Boston, Massachusetts 02115*

Stanley G. Schultz *Department of Physiology and Cell Biology, University of Texas Medical School at Houston, Houston, Texas, 77025*

Victor L. Schuster *Department of Internal Medicine, The University of Iowa Hospitals and Clinics, University of Iowa, Iowa City, Iowa 52242*

Charles R. Scriver *Departments of Biology and Pediatrics, and Center for Human Genetics, McGill University, Montreal, Quebec, H3G 1Y6 Canada*

Donald W. Seldin *Department of Internal Medicine, University of Texas Health Science Center, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235*

John W. Severinghaus *Department of Anesthesia and Cardiovascular Research Institute, University of California Medical Center, San Francisco, California 94143*

Michael S. Shapiro *Program in Kidney Diseases, Department of Medicine, University of California School of Medicine, Los Angeles, California 90024*

Arthur W. Siebens *Department of Physiology, Yale University School of Medicine, New Haven, Connecticut 06510*

Stefan Silbernagl *Department of Physiology, University of Würzburg, Röntgenring 9, D-8700 Würzburg, Federal Republic of Germany*

Eduardo Slatopolsky *Renal Division, and Division of Bone and Mineral Metabolism, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110*

Adrian Spitzer *Division of Nephrology, Department of Pediatrics, Albert Einstein College of Medicine, Rose F. Kennedy Center, 1410 Pelham Parkway South, Bronx, New York 10461*

Jay H. Stein *Department of Internal Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284*

Philip R. Steinmetz *Department of Medicine, University of Connecticut School of Medicine, Farmington, Connecticut 06032*

Bobby J. Stinebaugh *Department of Medicine, Baylor College of Medicine, and The Methodist Hospital, 6565 Fanin Boulevard, Houston, Texas 77030*

Wadi N. Suki *Department of Medicine, Baylor College of Medicine, and The Methodist Hospital, 6565 Fanin, Houston, Texas 77030*

Ann Taylor *University Laboratory of Physiology, Parks Road, Oxford, OX1 3PT, United Kingdom*

Klaus Thurau *Department of Physiology, University of Munich, D-8000 Munich 2, Pettenkoferstrasse 12, Federal Republic of Germany*

Karl J. Ullrich *Max Planck Institute for Biophysics, D-6000 Frankfurt/Main, Federal Republic of Germany*

Hans H. Ussing *Institute of Biological Chemistry A, August Krogh Institute, 13 Universitetsparken, DK-2100 Copenhagen Ø, Denmark*

Hans von Baeyer *Department of Nephrology, Klinikum Westend, Free University of Berlin, Berlin, Federal Republic of Germany*

Mackenzie Walser *The Johns Hopkins School of Medicine, Department of Pharmacology and Experimental Therapeutics, 725 North Wolfe Street, Baltimore, Maryland 21205*

Irwin M. Weiner *Department of Pharmacology, State University of New York, Upstate Medical Center, Syracuse, New York 13210*

Alan M. Weinstein *Department of Physiology, Cornell University Medical College and Rogosin Kidney Center, The New York Hospital, New York, New York 10021*

Guillermo Whittembury *Venezuelan Institute of Scientific Investigations, and International Institute of Advanced Studies, Apartado 1827, Caracas 1010-A, Venezuela*

Michael P. Whyte *Renal Division, and Division of Bone and Mineral Metabolism, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110*

Jens Otto Wieth* *Department of Biophysics, The Panum Institute, University of Copenhagen, Blegdamsvej 3c, DK-2200 Copenhagen N, Denmark*

Christopher S. Wilcox *Veterans Administration Medical Center, Renal Medicine and Hypertension, Archer Road, Gainesville, Florida 32602*

Erich E. Windhager *Department of Physiology, Cornell University Medical College, The New York Hospital, 1300 York Avenue, New York, New York 10021*

Mats Wolgast *Uppsala University, Biomedical Center, Institute for Physiology, Box 572, S-751 23 Uppsala Sweden*

Fred. S. Wright *Departments of Medicine and Physiology, Yale University School of Medicine, New Haven, Connecticut 06510; and Veterans Administration Medical Center, West Spring Street, West Haven, Connecticut 06516*

William E. Yarger *Department of Medicine, Duke University School of Medicine, and Veterans Administration Medical Centers, Durham, North Carolina 27705*

*Deceased