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Comprehensive Clinical Nephrology

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SIXTH EDITION

John Feehally, DM, FRCP
Professor of Renal Medicine
The John Walls Renal Unit
Leicester General Hospital
Leicester, United Kingdom

Jürgen Floege, MD, FERA
Professor of Medicine
Director
Division of Nephrology and Clinical Immunology
RWTH University of Aachen
Aachen, Germany

Marcello Tonelli, MD, SM, MSc, FRCPC
Associate Vice President (Research)
Department of Medicine
University of Calgary
Calgary, Alberta, Canada

Richard J. Johnson, MD
Professor of Medicine
Division Chief
Tomas Berl Professor of Nephrology
University of Colorado–Denver
Denver, Colorado, USA

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Three dimensional reconstruction of mouse glomeruli in which podocyte nuclei are labelled in green. The vasculature was labelled in red using CD31 antibody. Image was provided by Dr. Victor Puelles and Prof. Marcus Moeller from RWTH Aachen University Clinic, Dep. of Nephrology and Clinical Immunology, Aachen, Germany.

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PREFACE

In the sixth edition of *Comprehensive Clinical Nephrology,* we continue to offer a text for fellows, practicing nephrologists, and internists that covers all aspects of the clinical work of the nephrologist, including fluids and electrolytes, hypertension, diabetes, dialysis, and transplantation. We recognize that this single volume does not compete with multivolume or highly referenced online texts, and it remains our goal to provide "comprehensive" coverage of clinical nephrology yet also ensure that inquiring nephrologists can find the key scientific issues and pathophysiology that underlie their clinical work.

All chapters have been extensively revised and updated in response to the advice and comments that we have received from many readers and colleagues. These revisions include latest developments, such as new insights into complement mediated glomerular diseases, and the latest data on epidemiology and consequences of acute kidney injury and renal replacement therapy. Also included is a chapter on the emerging problem of endemic nephropathies in low and middle income countries. This edition retains the consistent design of the algorithms, which are a popular feature of the book, to emphasize different aspects of the information provided: yellow boxes for general information, blue boxes for necessary investigations, and green boxes for therapeutic interventions. By popular demand we continue to offer readers access to the images from the book. We are pleased to see them used in lectures and seminars in many parts of the world.

This is the third edition that features access to a companion Expert Consult website, with fully searchable text, a downloadable image library, and links to PubMed. New to this edition is an online question bank with more than 400 multiple-choice questions.

And finally, we welcome a new co-editor, Marcello Tonelli, who will bring great epidemiological expertise (and significantly lower the average age of the editors).

John Feehally
Jürgen Floege
Marcello Tonelli
Richard J. Johnson

LIST OF CONTRIBUTORS

The editor(s) would like to acknowledge and offer grateful thanks for the input of all previous editions' contributors, without whom this new edition would not have been possible.

Emaad Abdel-Rahman, MBBS
Professor of Clinical Internal Medicine
Division of Nephrology
University of Virginia Health System
Charlottesville, VA, USA

Horacio J. Adrogué, MD
Professor of Medicine
Baylor College of Medicine
Chief, Clinical Nephrology and Hypertension
Houston Methodist Hospital
Houston, TX, USA

Ala Abudayyeh, MD
University of Texas MD Anderson Cancer Center
Houston, TX;
Section of Nephrology
Department of Medicine
Yale University School of Medicine
New Haven, CT, USA

Sharon Adler, MD
Professor of Medicine
Chief and Program Director
Division of Nephrology and Hypertension
Los Angeles Biomedical Research Institute at Harbor University of California–Los Angeles
David Geffen School of Medicine
Torrance, CA, USA

Anupam Agarwal, MD
Professor and Director
Division of Nephrology
Marie S. Ingalls Endowed Chair in Nephrology
University of Alabama at Birmingham
Birmingham, AL, USA

Shikha Aggarwal, MBBS (HONS) FRACP
Consultant Nephrologist
Department of Nephrology Mater Hospital
Sydney, Australia

Venkatesh Aiyagari, MBBS, DM, FAHA
Professor
Department of Neurological Surgery and Neurology and Neurotherapeutics
University of Texas Southwestern Medical Center
Dallas, TX, USA

Kawther F. Alquadan, MD
Assistant Professor of Medicine
University of Florida
Gainesville, FL, USA

Gerald B. Appel, MD
Director
The Glomerular Kidney Center at Columbia University Medical Center;
Professor of Medicine at Columbia University
College of Physicians and Surgeons
New York, NY, USA

Fatiu A. Arogundade, MBBS, FMCP, FWACP
Associate Professor and Consultant Nephrologist
Department of Medicine
Obafemi Awolowo University and Teaching Hospitals Complex
Ile-Ife, Osun State, Nigeria

Vicente Arroyo, MD, PhD
Director of the EASL-CLIF Consortium-Efclif.
Barcelona, Spain

Stephen R. Ash, MD, FACP
Director of Dialysis, Department of Nephrology
Indiana University Health Arnett;
Chairman and Director
Research and Development
HemoCleanse, Inc. and Ash Access Technology, Inc.
Lafayette, IN, USA

Shazia Ashraf, MS
Division of Nephrology
Boston Children's Hospital
Harvard Medical School
Boston, MA, USA

Pierre Aucouturier, PhD
Professor of Immunology at Pierre et Marie Curie University
Department of Biologic Immunology
Pôle de Biologie Médicale et Pathologie Hôpitaux Universitaires de l'Est Parisien
Paris, France

Matthew A. Bailey, PhD
Reader in Renal Physiology
The Centre for Cardiovascular Science
The University of Edinburgh
Edinburgh, UK

George L. Bakris, MD
Professor of Medicine, Director
American Society of Hypertension Comprehensive Hypertension Center
Department of Medicine
University of Chicago
Chicago, IL, USA

Adam D. Barlow, MD, FRCS
Consultant Transplant Surgeon
Leeds Teaching Hospitals NHS Trust
Leeds, UK

Rashad S. Barsoum, MD, FRCP, FRCPE
Emeritus Professor of Medicine
Kasr-El-Aini Medical School
Cairo University
Cairo, Egypt

Ariela Benigni, PhD
IRCCS - Istituto di Ricerche Farmacologiche Mario Negri
Bergamo, Italy

Tomas Berl, MD
Professor of Medicine
Division of Renal Diseases and Hypertension, Department of Medicine
University of Colorado Denver
Denver, CO, USA

Gemma Bircher, MSc, BSc (hons), RD
Dietetic Manager
Renal Dietitians
Leicester General Hospital
Leicester, England

Detlef Bockenhauer, PhD
Professor of Paediatric Nephrology
UCL Centre for Nephrology;
Honorary Consultant
Great Ormond Street Hospital for Children NHS Foundation Trust
London, UK

Peter Boor, MD, PhD
Pathologist
Institute of Pathology
Uniklinik RWTH Aachen
Aachen, Germany

Josée Bouchard, MD
Associate Professor of Medicine
Hôpital du Sacré-Coeur de Montréal, Université de Montréal
Montréal, Canada

Kate Bramham
Clinical Lecturer in Renal Sciences
Department of Renal Medicine
Division of Transplantation and Mucosal Biology
King's College London
London, UK

Edwina A. Brown, DM, FRCP
Professor of Renal Medicine, Imperial College London;
Consultant Nephrologist
Imperial College Renal and Transplant Centre
Hammersmith Hospital
London, UK

Mark A. Brown, MD, MB, BS
Professor of Renal Medicine
St. George Hospital and University of New South Wales
Sydney, Australia

Emmanuel A. Burdmann, MD, PhD
Associate Professor, Division of Nephrology
University of São Paulo Medical School
São Paulo, Brazil

David A. Bushinsky, MD
John J. Kuiper Distinguished Professor of Medicine and of Pharmacology and Physiology
Department of Medicine
University of Rochester School of Medicine and Dentistry
Rochester, NY, USA

Gabriel Cara-Fuentes, MD
Clinical Lecturer
Pediatrics Nephrology
University of Michigan
Ann Arbor, MI, USA

Michael J. Casey, MD, MS
Associate Professor of Medicine
University of Florida
Gainesville, Florida, USA

Daniel C. Cattran, MD, FRCPC
Professor of Medicine
University of Toronto;
Senior Scientist
Toronto General Research Institute
Toronto, ON, Canada

Matthew J. Cervelli, BPharm
Clinical Pharmacist Specialist
Royal Adelaide Hospital
Adelaide, Australia

Steven J. Chadban, PhD, Bmed(Hons), FRACP
Clinical Professor
Nephrologist, and Transplant Physician
Royal Prince Alfred Hospital and University of Sydney
Sydney, Australia

Christopher Chan, MD
Director of Nephrology – UHN
R Fraser Elliott Chair in Home Dialysis
Professor of Medicine
Deputy Physician in Chief of Economics
Toronto, ON, Canada

Melanie M. Y. Chan, MA, MRCP
Clinical Lecturer in Renal Medicine and Transplantation
University College London Centre for Nephrology
Royal Free London National Health Service Foundation Trust
London, UK

Jeremy R. Chapman, MD, FRACP, FRCP
Director of Renal Medicine
Centre for Transplant and Renal Research
Sydney University, Westmead Hospital
Westmead, Australia

Karen E. Charlton, PhD, Adv APD, RPHNutr
Associate Professor
School of Medicine, Faculty of Science, Medicine and Health
University of Wollongong
New South Wales, Australia

Wei Chen, MD
Assistant Professor
Department of Medicine
University of Rochester School of Medicine and Dentistry
Rochester, NY, USA

Yipu Chen, MD
Professor of Medicine
Division of Nephrology
Beijing Anzhen Hospital
Capital Medical University
Beijing, People's Republic of China

John O. Connolly, PhD, FRCP
Consultant Nephrologist
University College London Centre for Nephrology
Royal Free London National Health Service Foundation Trust
London, UK

H. Terence Cook, MB, BS, FRCPath
Professor of Renal Pathology
Centre for Complement and Inflammation Research
Department of Medicine
Imperial College
London, UK

James E. Cooper, MD
Associate Professor
Department of Medicine
Renal Division
University of Colorado,
Aurora, CO, USA

Vivette D. D'Agati, MD
Director of Renal Pathology at Columbia University Medical Center and Professor of Pathology at Columbia University
College of Physicians and Surgeons
New York, NY, USA

Kevin Damman, MD, PhD
Cardiologist
Department of Cardiology
University Medical Center Groningen
Groningen, The Netherlands

Gabriel M. Danovitch, MD
Distinguished Professor of Medicine
David Geffen School of Medicine at University of California-Los Angeles;
Medical Director, Kidney Transplant Program
Ronald Reagan Medical Center at University of California-Los Angeles
Los Angeles, CA, USA

Simon J. Davies, MD, BSc, FRCP
Professor of Nephrology and Dialysis Medicine
Institute for Science and Technology in Medicine
Keele University;
Consultant Nephrologist
Department of Nephrology
University Hospital of North Staffordshire
Staffordshire, UK

Wayne Derman, MBChB, PhD, FFIMS
Professor
Institute of Sport and Exercise Medicine
Division of Orthopaedic Surgery
Stellenbosch University
IOC Research Centre
Matieland, South Africa

An S. De Vriese, MD, PhD
Division of Nephrology
AZ Sint-Jan Brugge
Brugge, Belgium

James E. Dyer, MBChB, BSc Hons
Clinical Research Fellow
Department of Urology
Leicester General Hospital
Leicester, UK

Kai-Uwe Eckardt, MD
Professor of Medicine
Department of Nephrology and Medical Intensive Care
Charité-Universitätsmedizin Berlin
Berlin, Germany

David H. Ellison, MD
Professor of Medicine and Physiology and Pharmacology
Department of Medicine
Oregon Health and Science University and VA Portland Health Care System
Portland, OR, USA

Marlies Elger, PhD
Department of Neuroanatomy
Medical Faculty Mannheim
University of Heidelberg
Mannheim, Germany

William J. Elliott, MD, PhD
Professor of Preventive Medicine
Internal Medicine and Pharmacology;
Chief, Division of Pharmacology;
Chair, Department of Biomedical Sciences
Pacific Northwest University of Health Sciences
Yakima, WA, USA

Pieter Evenepoel, MD, PhD
Professor, Nephrology and Renal Transplantation
University Hospital Leuven
Leuven, Belgium

Ronald J. Falk, MD
Nan and Hugh Cullman Eminent Professor and Chair of Medicine
Department of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Tarek S. Fayad, MD
Professor of Medicine
Kasr El-Aini Medical School
Cairo University
Cairo, Egypt

John Feehally, DM, FRCP
Professor of Renal Medicine
The John Walls Renal Unit
Leicester General Hospital
Leicester, UK

Javier Fernández, MD, PhD
Head of the Liver ICU
Hospital Clinic Barcelona
University of Barcelona
Barcelona, Spain

Fernando C. Fervenza, MD, PhD
Division of Nephrology and Hypertension
Mayo Clinic
Rochester, MN, USA

Evelyne A. Fischer, MD
Institut de Biologie de l'Ecole Normale Superieure
Cell Division and Neurogenesis
INSERM
Paris, France

Jonathan S. Fisher, MD, FACS
Surgical Director of Pancreas Transplantation
Scripps Center for Organ Transplantation
Scripps Clinic and Green Hospital
La Jolla, CA, USA

Jürgen Floege, MD, FERA
Professor of Medicine;
Director, Division of Nephrology and Clinical Immunology
RWTH University of Aachen
Aachen, Germany

Giovanni B. Fogazzi, MD
Honorary Director
Clinical and Research Laboratory on Urinary Sediment
U.O. di Nefrologia, Dialisi e Trapianto di rene
Fondazione
IRCCS, Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy

John W. Foreman, MD
Professor and Chief, Division of Pediatric Nephrology
Department of Pediatrics
Duke University Medical Center
Durham, NC, USA

Kevin M. Gallagher, MBChB BMedSci MSc MRCSed
MRC/Kidney Research UK/GSK Clinical Research Fellow
Tissue Injury and Repair Group
University of Edinburgh
Edinburgh, UK

Ramón García-Trabanino, MD, MSc, FASN
Centro de Hemodiálisis
San Salvador, El Salvador
Fondo Social de Emergencia para la Salud de Tierra Blanca
Usulután, El Salvador

Giuseppe Garigali, ScD
Clinical and Research Laboratory on Urinary Sediment
Unità Operativa di Nefrologia
Dialisi e Trapianto di rene Fondazione
IRCCS, Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy

Eduardo H. Garin, MD
Professor, Paediatrics
University of Florida
Gainesville, FL, USA

F. John Gennari, MD
Professor Emeritus
Department of Medicine
University of Vermont College of Medicine
Burlington, VT, USA

Matthias Girndt, MD
Department of Internal Medicine II
Martin-Luther-University Halle-Wittenberg
Halle/Saale, Germany

Richard J. Glassock, MD
Emeritus Professor of Medicine
Department of Medicine
David Geffen School of Medicine at University of California–Los Angeles
Los Angeles, CA, USA

David J. A. Goldsmith, MA FRCP FASN FERN
Nephrologist, Guy's and St Thomas' NHS Foundation Trust
London, UK

Philip B. Gorelick, MD, MPH, FACP
Professor
Department of Translational Science and Molecular Medicine
College of Human Medicine
Michigan State University
Grand Rapids, MI;
Medical Director
Mercy Health Hauenstein Neurosciences
Grand Rapids, MI, USA

Morgan E. Grams, MD
Associate Professor
School of Medicine, Division of Cardiovascular and Clinical Epidemiology
Welch Center for Prevention, Epidemiology and Clinical Research
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD, USA

Barbara A. Greco, MD
Associate Clinical Professor of Medicine
Department of Nephrology
Baystate Medical Center, Tufts;
Western New England Renal and Transplant Associates
Springfield, MA, USA

Lisa M. Guay-Woodford, MD
Professor and Director
Center for Translational Science
Children's National Health System and The George Washington University
Washington, DC, USA

Nabil J. Haddad, MD
Associate Professor of Clinical Medicine
Division of Nephrology
Department of Internal Medicine
The Ohio State University Medical Center
Columbus, OH, USA

Peter C. Harris, PhD
Professor of Biochemistry/Molecular Biology and Medicine
Division of Nephrology and Hypertension
Mayo Clinic
Rochester, MN, USA

Leah Haseley, MD
Clinical Professor of Medicine
Division of Nephrology
University of Washington
Seattle, WA, USA

Lee A. Hebert, MD
Professor of Medicine
Department of Internal Medicine
Division of Nephrology
The Ohio State University Medical Center
Columbus, OH, USA

Gunnar H. Heine, MD
Department of Internal Medicine IV
University of the Saarland
Homburg/Saar, Germany

Charles A. Herzog, MD
Professor of Medicine
University of Minnesota;
Division of Cardiology
Department of Medicine
Hennepin County Medical Center and University of Minnesota
Minneapolis, MN, USA

Friedhelm Hildebrandt, MD
Division of Nephrology
Boston Children's Hospital,
Harvard Medical School
Boston, MA, USA

Thomas Hooton, MD
Professor of Clinical Medicine
Division of Infectious Diseases
Department of Medicine
University of Miami Miller School of Medicine;
Chief of Medicine
Miami Veterans Administration Healthcare System
Miami, FL, USA

Pascal Houillier, MD, PhD
Professor of Physiology
Department of Physiology
Paris Descartes University
Georges Pompidou Hospital
Paris, France

Jeremy Hughes, MA, MB, BS, PhD, FRCPE
Professor of Experimental Nephrology
Medical Research Council Centre for Inflammation Research
University of Edinburgh;
Honorary Consultant Physician
Edinburgh Royal Infirmary
Edinburgh, UK

Enyu Imai, MD, PhD
Nakayamadera Imai Clinic
Takarazuka, Hyogo, Japan

Lesley A. Inker, MD, MS
William B. Schwartz Division of Nephrology
Tufts Medical Center;
Associate Professor Medicine
Tufts University School of Medicine
Boston, MA, USA

Ashley B. Irish, MBBS, FRACP
Consultant Nephrologist
Department of Nephrology and Renal Transplantation
Fiona Stanley Hospital
Murdoch, Western Australia, Australia

David Jayne, MD
Reader in Vasculitis
Department of Medicine
University of Cambridge
Cambridge, UK

J. Ashley Jefferson, MD, FRCP
Associate Professor of Medicine
Division of Nephrology
University of Washington
Seattle, WA, USA

J. Charles Jennette, MD
Kennith M. Brinkhous Distinguished Professor and Chair of Pathology and Laboratory Medicine
Department of Pathology and Laboratory Medicine
University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Vivekanand Jha, MD, DM, FRCP
Professor
Department of Nephrology
Postgraduate Institute of Medical Education and Research
Chandigarh, India;
Executive Director
George Institute for Global Health
New Delhi, India

Richard J. Johnson, MD
Professor of Medicine
Tomas Berl Professor of Nephrology
University of Colorado–Denver
Denver, CO, USA

Eric Judd, MD, MS
Assistant Professor
Division of Nephrology
University of Alabama at Birmingham
Birmingham, AL, USA

Luis A. Juncos, MD
Chief of Nephrology
Central Arkansas
Veterans Healthcare Systems;
Professor of Medicine
University of Arkansas for Medical Sciences
Little Rock, AR, USA

Nigel Suren Kanagasundaram, MD, MB ChB, FRCP
Honorary Clinical Senior Lecturer
Institute of Cellular Medicine
Newcastle University;
Consultant Nephrologist
Renal Services
Newcastle upon Tyne Hospitals National Health Service Foundation Trust
Newcastle upon Tyne, UK

John Kanellis, PhD, MBBS(Hons), FRACP
Nephrologist
Department of Nephrology
Monash Medical Centre;
Department of Medicine
Monash University
Clayton, Australia

Clifford E. Kashtan, MD
Professor of Pediatrics
Department of Pediatrics
Division of Pediatric Nephrology
University of Minnesota Medical School
Minneapolis, MN, USA

Bryan Kestenbaum, MD, MS
Professor
University of Washington
Kidney Research Institute
Seattle, WA, USA

Carol A. Kauffman, MD
Professor of Internal Medicine
University of Michigan Medical School;
Chief, Infectious Diseases
Veteran Affairs Ann Arbor Healthcare System
Ann Arbor, MI, USA

Amir Kazory, MD
Associate Professor of Medicine
Division of Nephrology, Hypertension, and Renal Transplantation
University of Florida
College of Medicine
Gainesville, FL, USA

Claire Kennedy, MB BCh BAO, BMed Sci
Clinical Research Fellow
Beaumont Hospital and Royal College of Surgeons in Ireland
Dublin, Ireland

Peter G. Kerr, PhD, MB, BS, FRACP
Professor and Director
Department of Nephrology
Monash Medical Centre;
Professor
Department of Medicine
Monash University
Clayton, Australia

Markus Ketteler, MD, FERA
Division of Nephrology
Klinikum Coburg GmbH
Coburg, Germany

Dr. Vijay Kher, MD, DM, FAMS, FRCPE
Chairman
Division of Nephrology & Renal Transplant Medicine
Fortis Escorts Kidney and Urology Institute
Fortis Escorts Hospital
India

Jeffrey B. Kopp, MD
Branch Chief
Kidney Disease Branch
NIDDK, NIH
Bethesda, MD, USA

Peter Kotanko, MD
Research Director
Renal Research Institute
New York, NY, USA

Wilhelm Kriz, MD
Department of Neuroanatomy, Medical Faculty Mannheim
University of Heidelberg
Mannheim, Germany

Jayakumar K. P., MD DNB (Med) DM DNB(Nephro) FISN
Professor
Department of Nephrology
Govt Medical College
Kottayam Kerala India

Martin K. Kuhlmann, MD
Director
Department of Internal Medicine
Nephrology
Vivantes Klinikum im Friedrichshain
Berlin, Germany

Dirk R. Kuypers, MD, PhD
Professor
Department of Nephrology and Renal Transplantation
University Hospitals Leuven
Leuven, Belgium

William J. Lawton, MD, FACP
Associate Professor Emeritus
Department of Internal Medicine
Nephrology-Hypertension Division
University of Iowa Carver College of Medicine
Iowa City, IA, USA

Andrew S. Levey, MD
Chief, Division of Nephrology
William B. Schwartz Division of Nephrology
Tufts Medical Center;
Dr. Gerald J. and Dorothy R. Friedman Professor of Medicine
Tufts University School of Medicine
Boston, MA, USA

Nathan W. Levin, MD
Visiting Professor
Mount Sinai Icahn school of Medicine
New York, NY

Jeremy Levy, MD, PhD, FRCP
Consultant Nephrologist
Renal and Transplant Centre
Imperial College Healthcare National Health Service Trust
London, UK

Andrew Lewington, MD, BSc Med, FRCP, FRCPE
Honorary Clinical Associate Professor
Department of Medicine
University of Leeds;
Consultant
Renal Physician
Department of Renal Medicine
St. James's University Hospital
Leeds, UK

Stuart L. Linas, MD
Professor of Medicine
Division of Renal Diseases and Hypertension
University of Colorado School of Medicine and Chief of Nephrology
Denver Health Medical Center
Denver, CO, USA

Iain C. Macdougall, BSc, MD, FRCP
Consultant Nephrologist and Professor of Clinical Nephrology
Department of Renal Medicine
King's College Hospital
London, UK

Etienne Macedo, MD
Assistant Adjunct Professor
University of California San Diego
San Diego, CA, USA

Nicolaos E. Madias, MD, FASN
Maurice S. Segal, MD, Professor of Medicine
Tufts University School of Medicine
Physician, Division of Nephrology
St. Elizabeth's Medical Center
Boston, MA, USA

Colm C. Magee, MD, MPH
Consultant Nephrologist
Beaumont Hospital;
Lecturer in Medicine
Royal College of Surgeons in Ireland
Dublin, Ireland

Christopher L. Marsh, MD, FACS
Division Chief
Scripps Center for Organ Transplantation
Scripps Clinic and Green Hospital
La Jolla, CA, USA

Mark R. Marshall, MBChB, MPH(Hons), FRACP
Honorary Associate Professor
Faculty of Medical and Health Sciences
South Auckland Clinical School;
Clinical Director
Department of Renal Medicine
Counties Manukau District Health Board
Auckland, New Zealand

Kevin J. Martin, MB, BCH, FASN
Professor of Internal Medicine
Director
Division of Nephrology
St Louis University
St Louis, MO, USA

Ranjiv Mathews, MD
Professor of Urology and Pediatrics;
Director of Pediatric Urology
Division of Urology
Department of Surgery
Southern Illinois University
School of Medicine
Springfield, IL, USA

Tej K. Mattoo, MD, DCH, FRCP (UK), FAAP
Professor and Acting Chair of Pediatrics
Wayne State University School of Medicine;
Chief, Pediatric Nephrology and Hypertension
Children's Hospital of Michigan
Detroit, MI, USA

Stephen P. McDonald, PhD FRACP
Director of Dialysis and Senior Staff Specialist
Central Adelaide Local Health Network
Royal Adelaide Hospital (RAH);
Executive Officer
Australia and New Zealand Dialysis & Transplant Registry
SA Health and Medical Research Institute;
Clinical Professor
Adelaide Medical School
University of Adelaide
Adelaide, Australia

Ravindra L. Mehta, MD
Professor of Medicine
University of California San Diego
San Diego, CA, USA

J. Kilian Mellon, MD, FRCS (Urol)
Professor of Urology
Department of Urology
Leicester General Hospital
Leicester, UK

Rebeca D. Monk, MD
Professor
Department of Medicine
University of Rochester School of Medicine and Dentistry
Rochester, NY, USA

Rosa M. Montero, MRCP MD AFHEA
Honorary Clinical Senior Lecturer
King's College
London, UK

Christian Morath, MD
Division of Nephrology
Heidelberg University Hospital
Heidelberg, Germany

Bruno Moulin, MD, PhD
Professor of Nephrology and Transplantation
Hôpitaux Universitaires de Strasbourg
Strasbourg, France

Anja S. Mühlfeld, MD
Consultant, Division of Nephrology and Immunology
Uniklinikum RWTH Aachen University
Aachen, Germany

William R. Mulley, PhD, B.Med(Hons), FRACP
Nephrologist, Department of Nephrology
Monash Medical Centre;
Senior Lecturer
Department of Medicine
Monash University
Clayton, Australia

Fliss E. Murtagh
Professor of Palliative Care
Wolfson Palliative Care Research Centre,
Hull York Medical School,
University of Hull,
Hull, UK

Saraladevi Naicker, MD, PhD
Professor of Nephrology
Division of Nephrology
Department of Internal Medicine
University of the Witwatersrand
Faculty of Health Sciences
Johannesburg, South Africa

Masaomi Nangaku, MD, PhD
Professor and Head
Division of Nephrology and Endocrinology
The University of Tokyo School of Medicine
Tokyo, Japan

Cynthia C. Nast, MD
Professor of Pathology
Department of Pathology
Cedars-Sinai Medical Center
Los Angeles, CA, USA

A. Neil Turner, PhD, FRCP
Professor of Nephrology
Department of Renal Medicine
Royal Infirmary;
Centre for Inflammation
University of Edinburgh
Edinburgh, Scotland

Guy H. Neild, MD, FRCP, FRCPath
Professor of Nephrology (Emeritus)
University College London Centre for Nephrology
London, UK

Michael L. Nicholson, DSc, MD, FRCS
Professor of Transplant Surgery
Department of Surgery
University of Cambridge, Cambridge, UK

Marina Noris, PhD
Head
Laboratory of Immunology and Genetics of Transplantation and Rare Diseases
Department of Molecular Medicine
IRCSS–Istituto di Ricerche Farmacologiche "Mario Negri,"
Bergamo, Italy

W. Charles O'Neill, MD
Professor of Medicine
Director of Ultrasonography
Renal Division, Department of Medicine
Emory University
Atlanta, GA, USA

Mohamed Osman, MD
Fellow, Neurocritical Care
Department of Neurological Surgery and Neurology and Neurotherapeutics
University of Texas Southwestern Medical Center
Dallas, TX, USA

Raj P. Pal, BSc(Hons), MB ChB, MD, FRCS
Department of Urology
Leicester General Hospital
Leicester, UK

Biff F. Palmer, MD
Professor of Internal Medicine
Distinguished Teaching Professor
Department of Medicine
University of Texas Southwestern Medical Center
Dallas, Texas, USA

Antonelli Pani
Section of Nephrology and Dialysis
AO Brotzu Hospital
Sardinia, Italy

Neesh Pannu, MD, SM
Associate Professor
Department of Medicine
University of Alberta
Edmonton, Alberta, Canada

Samir V. Parikh, MD
Assistant Professor of Medicine
Department of Internal Medicine
Division of Nephrology
The Ohio State University Wexner Medical Center
Columbus, OH, USA

Alice K. Pau, Pharm D
Division of Clinical Research
NIH-NIAID
Bethesda, MD, USA

Norberto Perico, MD
IRCCS - Istituto di Ricerche Farmacologiche Mario Negri
Bergamo, Italy

Phuong-Chi T. Pham, MD, FASN
Chief
Division of Nephrology and Hypertension
Olive View–University of California Los Angeles (UCLA) Medical Center;
Program Director
Olive View–UCLA Nephrology Fellowship Program
Los Angeles, CA, USA

Phuong-Anh T. Pham, MD, FACC
Division of Cardiology
Interventional Cardiology
VA Nebraska-Western Iowa Health Care System
Omaha, NE, USA

Phuong-Thu T. Pham, MD, FASN
Clinical Professor of Medicine
David Geffen School of Medicine at University of California-Los Angeles
Division of Nephrology;
Director
Outpatient Services
Kidney Transplant Program
Ronald Reagan Medical Center at University of California-Los Angeles
Los Angeles, CA, USA

Son V. Pham, MD, FACC
Chief of Cardiology
South Texas Veterans Health Care System
Assistant Clinical Professor of Medicine
University of Texas Health Science Center, San Antonio
San Antonio, TX, USA

Richard G. Phelps, PhD, FRCP
Senior Lecturer in Nephrology
MRC Centre for Inflammation Research
University of Edinburgh;
Honorary Consultant
Renal Medicine
Royal Infirmary of Edinburgh
Edinburgh, UK

Mark A. Perazella, MD
University of Texas MD Anderson Cancer Center
Houston, TX;
Section of Nephrology
Department of Medicine
Yale University School of Medicine
New Haven, CN, USA

Matthew C. Pickering, PhD, MB, BS
Professor of Rheumatology
Centre for Complement and Inflammation Research
Department of Medicine
Imperial College
London, UK

Kevan R. Polkinghorne, PhD, MBChB, M Clin Epi, BHB, FRACP
Associate Professor
Department of Nephrology
Monash Medical Centre;
Associate Professor
Department of Medicine
Epidemiology and Preventative Medicine
Monash University
Melbourne, Australia

Brian Rayner, MBChB, FCP, MMed, PhD
Professor
Division of Nephrology and Hypertension
University of Cape Town
Cape Town, South Africa

Hugh C. Rayner, MD, MA, DipMedEd, FRCP
Consultant Nephrologist
Department of Renal Medicine
Heart of England National Health Service Foundation Trust
Birmingham, UK

Giuseppe Remuzzi, MD, FRCP
Director, Unit of Nephrology and Dialysis, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII;
Director, IRCCS -Istituto di Ricerche Farmacologiche "Mario Negri," Bergamo, Italy;
Chiara Fama Professor of Nephrology, Department of Biomedical and Clinical Sciences, University of Milan, Italy

Michelle N. Rheault, MD
Associate Professor
Division of Paediatric Nephrology
University of Minnesota
Minneapolis, MN, USA

A. Mark Richards, MD, PhD, DSc, MB, ChB
Professor
Department of Medicine
University of Otago Christchurch
Christchurch, New Zealand;
Director
Cardiovascular Research Institute
National University of Singapore
Singapore

[†]Bengt Rippe, MD, PhD
Formerly Professor
Department of Nephrology
University Hospital of Lund
Lund, Sweden

Bernardo Rodriguez-Iturbe, MD
Professor of Medicine
Department of Nephrology
Hospital Universitario and Universidad del Zulia,
Maracaibo, Zulia, Venezuela

Pierre Ronco, MD, PhD
Professor of Nephrology
Pierre et Marie Curie University;
Department of Nephrology and Dialysis
Hôpital Tenon
Paris, France

Mitchell H. Rosner, MD
Professor of Medicine
Division of Nephrology
University of Virginia Health System
Charlottesville, VA, USA

Edward A. Ross, MD
Chair and Professor, Department of Internal Medicine
University of Central Florida
College of Medicine
Orlando, FL, USA

[†]Deceased.

Jérôme A. Rossert, MD, PhD
Global Clinical Development
Vertex Pharmaceuticals
Boston, MA, USA

Brad H. Rovin, MD
The Lee A. Hebert Distinguished Professor of Nephrology
Director
Division of Nephrology
The Ohio State University Wexner Medical Center
Columbus, OH, USA

Piero L. Ruggenenti, MD
Assistant Professor
Unit of Nephrology
Azienda Ospedaliera Papa Giovanni;
Head
Department of Renal Medicine
IRCSS–Instituto di Ricerche Farmacologiche "Mario Negri,"
Bergamo, Italy

Graeme R. Russ, PhD, MBBS, FRACP
Royal Adelaide Hospital
Adelaide, Australia

David J. Salant, MD, BCh
Norman G. Levinsky Professor
Renal Section
Department of Medicine
Boston University School of Medicine
Boston, MA, USA

Martin A. Samuels, MD, DSc(hon), FAAN, MACP, FRCP
Miriam Sydney Joseph Professor of Neurology
Harvard Medical School;
Chair
Department of Neurology
Brigham and Women's Hospital;
Senior Consultant, Neurology
Massachusetts General Hospital
Boston, MA, USA

Paul W. Sanders, MD
Thomas E. Andreoli, M.D., Endowed Chair in Nephrology
University of Alabama at Birmingham;
Chief, Renal Section
Veterans Affairs Medical Center
Birmingham, AL, USA

Jeff M. Sands, MD
Juha P. Kokko Professor of Medicine and Physiology
Renal Division
Department of Medicine
Emory University
Atlanta, GA, USA

Pantelis A. Sarafidis, MD, MSc, PhD
Assistant Professor and Honorary Consultant in Nephrology
Department of Nephrology
Hippokration Hospital
Aristotle University of Thessaloniki
Thessaloniki, Greece

Joanna M. Schaenman, MD, PhD
Department of Medicine
Ronald Reagan UCLA Medical Center
Los Angeles, CA, USA

Robert W. Schrier, MD
Professor Emeritus
Department of Medicine
University of Colorado School of Medicine
Aurora, CO, USA

Alan Segal, MD
Associate Professor
Division of Nephrology
Department of Medicine, University of Vermont College of Medicine
Burlington, VT, USA

Mark S. Segal, MD, PhD
Professor and Chief
J. Robert Cade Professor of Medicine
Division of Nephrology
Hypertension & Renal Transplantation
University of Florida College of Medicine
Gainesville, FL USA

Julian L. Seifter, MD
Brigham and Women's Hospital
Boston, MA, USA

Sanjeev Sethi, MD, PhD
Division of Anatomic Pathology
Mayo Clinic
Rochester, MN, USA

Kumar Sharma, MD, FAHA
Hillis Endowed Chair and Professor of Medicine
Chief
Division of Nephrology
Vice Chair of Research, Department of Medicine
University of Texas Health San Antonio
San Antonio, Texas, USA

Claire C. Sharpe, MBBS PhD FRCP
Reader in Renal Sciences
King's College Hospital;
Consultant Nephrologist
King's College Hospital
London, UK

Visith Sitprija, MD, PhD, FACP, FRCP, FRACP, FRCPE
Director
Queen Saovabha Memorial Institute
Bangkok, Thailand

Peter Stenvinkel, MD, PhD
Professor
Senior Lecturer, Department of Nephrology
Karolinska Institute
Karolinska University Hospital at Huddinge
Stockholm, Sweden

Eric Stites, MD
Assistant Professor
Division of Nephrology and Hypertension
University of Colorado-Denver
Aurora, Colorado, USA

Tetsuhiro Tanaka
Division of Nephrology and Endocrinology
The University of Tokyo School of Medicine
Tokyo, Japan

Sydney Tang
Chair of Renal Medicine and Yu Endowed Professor in Nephrology
Division of Nephrology
Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Hong Kong, China

Laurie A. Tomlinson, MBBS, PhD
Associate Professor
Faculty of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
London, UK

Marcello Tonelli, MD, SM, MSc, FRCPC
Associate Vice President (Research)
Department of Medicine
University of Calgary
Calgary, Alberta, Canada

Li-Li Tong, MD
Associate Professor of Medicine
Division of Nephrology and Hypertension
Los Angeles Biomedical Research Institute at Harbor University of California–Los Angeles
David Geffen School of Medicine
Torrance, CA, USA

Peter S. Topham, MD, MB, ChB
Consultant Nephrologist
John Walls Renal Unit
University Hospitals of Leicester NHS Trust
Leicester, UK

Jan H. M. Tordoir, PhD
Vascular Surgeon
Director of the Vascular Laboratory
Department of Surgery
Maastricht University Medical Center
Maastricht, The Netherlands

Vicente E. Torres, MD, PhD
Professor of Medicine
Division of Nephroogy and Hypertension
Mayo Clinic
Rochester, MN, USA

A. Neil Turner, PhD, FRCP
Professor of Nephrology
MRC Centre for Inflammation Research
University of Edinburgh;
Honorary Consultant
Renal Medicine
Royal Infirmary of Edinburgh
Edinburgh, UK

Kausik Umanath, MD MS
Section Head
Clinical Trials Research
Division of Nephrology and Hypertension
Henry Ford Hospital
Detroit, MN, USA

Robert J. Unwin, PhD, BM, FRCP, FSB CBiol
Professor of Nephrology and Physiology
UCL Centre for Nephrology
University College London
London, UK

Christoph Wanner, MD
Professor of Medicine
Chief
Division of Nephrology
University Hospital Würzburg
Würzburg, Germany

R. Kasi Visweswaran, MD, DM, FRCP (Edin)
Professor
Ananthapuri Hospitals and Research Center
Thiruvananthapuram
Kerala, India

Shikha Wadhwani, MD
Fellow in Glomerular Diseases
Division of Nephrology
The Ohio State University Wexner Medical Center
Columbus, OH, USA

Haimanot Wasse, MD, MPH
Professor and Vice Chair; Director of Interventional Nephrology
Rush University Medical Center
Chicago, IN, USA

I. David Weiner, MD
Professor of Medicine and Physiology and Functional Genomics
Division of Nephrology
Hypertension and Renal Transplantation
University of Florida College of Medicine
Nephrology and Hypertension Section
North Florida/South Georgia Veterans Health System
Gainesville, FL, USA

David C. Wheeler, MBChB, MD
Professor of Kidney Medicine
Centre for Nephrology
University College London Medical School
London, UK

Martin E. Wilkie, MD, FRCP
Consultant Renal Physician and Honorary Reader
Editor in Chief
Peritoneal Dialysis International
Sheffield Kidney Institute
Northern General Hospital
Sheffield, UK

Bryan Williams, MD
Professor of Medicine
Institute of Cardiovascular Science
University College London
London, UK

Charles S. Wingo, MD
Professor of Medicine and Physiology and Functional Genomics
Division of Nephrology, Hypertension and Renal Transplantation
University of Florida College of Medicine
Nephrology and Hypertension Section, North Florida/South Georgia Veterans Health System
Gainesville, FL, USA

Alexander C. Wiseman, MD
Associate Professor
Division of Renal Diseases and Hypertension
University of Colorado;
Medical Director
Kidney and Pancreas Transplant Programs
University of Colorado Hospital
Aurora, CO, USA

Karl L. Womer, MD
Professor of Medicine
University of Florida
Gainesville, FL, USA

Graham Woodrow, MBChB, MD, FRCP
Consultant Nephrologist
Renal Unit
St. James's University Hospital
Leeds, UK

Melanie Wyld, MBBS, MPH
Renal Department
Royal Prince Alfred Hospital Sydney Australia
University of Sydney
Australia

David C. Wymer, MD
Associate Professor Medicine and Radiology
Associate Chair Radiology
Department of Radiology
University of Florida
Gainesville, FL, USA

David T.G. Wymer, MD
Assistant Professor
Department of Radiology
Mount Sinai Medical Center
Miami, FL, USA

Xueqing Yu, MD, PhD
Professor of Medicine;
Director
Institute of Nephrology
The First Affiliated Hospital
Sun Yat-Sen University
Guangzhou, China

Martin Zeier, MD
Division of Nephrology
Heidelberg University Hospital
Heidelberg, Germany

To our mentors in nephrology—especially Bill Couser, Stewart Cameron, Karl M. Koch, and Kailash Jindal.

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John Feehally

Jürgen Floege

Marcello Tonelli

Richard J. Johnson

1

Renal Anatomy

Wilhelm Kriz, Marlies Elger

The complex structure of the mammalian kidney is best understood in the unipapillary form that is common to all small species. Fig. 1.1 is a schematic coronal section through a unipapillary kidney, with a cortex enclosing a pyramid-shaped medulla, the tip (papilla) of which protrudes into the renal pelvis. The medulla is divided into an outer and an inner medulla; the outer medulla is further subdivided into an outer and an inner stripe.

STRUCTURE OF THE KIDNEY

The specific components of the kidney are the nephrons, the collecting ducts (CDs), and a unique microvasculature.[1] The multipapillary kidney of humans contains approximately 1 million nephrons, although this number varies considerably. The number of nephrons is already established during prenatal development; after birth, new nephrons cannot be developed and a lost nephron cannot be replaced.

Nephrons

A nephron consists of a renal corpuscle *(glomerulus)* connected to a complicated and twisted tubule that finally drains into a CD (Fig. 1.2 and Table 1.1). Three types of nephron can be distinguished by the location of renal corpuscles within the cortex: superficial, midcortical, and juxtamedullary nephrons. The tubular part of the nephron consists of a proximal tubule and a distal tubule connected by a loop of Henle[2] (see later discussion). There are two types of nephrons: those with long loops of Henle and those with short loops. Short loops turn back in the outer medulla or even in the cortex (cortical loops). Long loops turn back at successive levels of the inner medulla.

Collecting Ducts

A CD is formed in the renal cortex when several nephrons join. A connecting tubule (CNT) is interposed between a nephron and a cortical CD. Cortical CDs descend within the medullary rays of the cortex. Then they traverse the outer medulla as unbranched tubes. On entering the inner medulla, they fuse successively and open finally as papillary ducts into the renal pelvis (see Fig. 1.2 and Table 1.1).

Microvasculature

The microvascular pattern of the kidney is similarly organized in mammalian species[1,3] (Fig. 1.3; see also Fig. 1.1). The renal artery, after entering the renal sinus, finally divides into the interlobar arteries, which extend toward the cortex in the space between the wall of the pelvis (or calyx) and the adjacent cortical tissue. At the junction between cortex and medulla, the interlobar arteries divide and pass over into the arcuate arteries, which also branch. The arcuate arteries give rise to the cortical radial arteries (interlobular arteries), which ascend radially through the cortex. No arteries penetrate the medulla.

Afferent arterioles supply the glomerular tufts and generally arise from cortical radial arteries. As a result, the blood supply of the peritubular capillaries of the cortex and the medulla is exclusively *postglomerular.*

Glomeruli are drained by efferent arterioles. Two basic types of efferent arterioles can be distinguished: cortical and juxtamedullary. *Cortical* efferent arterioles, which derive from superficial and midcortical glomeruli, supply the capillary plexus of the cortex. The efferent arterioles of *juxtamedullary* glomeruli represent the supplying vessels of the renal medulla. Within the outer stripe of the medulla, these vessels divide into the *descending* vasa recta and then penetrate the inner stripe in cone-shaped vascular bundles. At intervals, individual vessels leave the bundles to supply the capillary plexus at the adjacent medullary level.

Ascending vasa recta drain the renal medulla. In the inner medulla, the vasa recta arise at every level, ascending as unbranched vessels, and traverse the inner stripe within the vascular bundles. The ascending vasa recta that drain the inner stripe may join the vascular bundles or may ascend directly to the outer stripe between the bundles. All the ascending vasa recta traverse the outer stripe as individual wavy vessels with wide lumina interspersed among the tubules. Because true capillaries derived from direct branches of efferent arterioles are relatively scarce, the ascending vasa recta form the capillary plexus of the outer stripe. The ascending vasa recta empty into arcuate veins.

The vascular bundles represent a countercurrent exchanger between the blood entering and that leaving the medulla. In addition, the organization of the vascular bundles results in a separation of the blood flow to the inner stripe from that to the inner medulla. Descending vasa recta supplying the inner medulla traverse the inner stripe within the vascular bundles. Therefore blood flowing to the inner medulla has not been exposed previously to tubules of the inner or outer stripe. All ascending vasa recta originating from the inner medulla traverse the inner stripe within the vascular bundles. Thus blood that has perfused tubules of the inner medulla does not subsequently perfuse tubules of

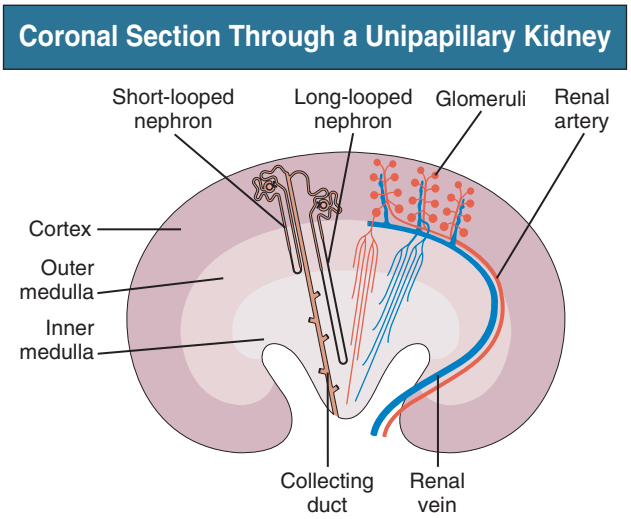

Fig. 1.1 Coronal section through a unipapillary kidney.

TABLE 1.1 Subdivisions of the Nephron and Collecting Duct System

Section	Subsections
Nephron	
Renal corpuscle	*Glomerulus:* term used most frequently to refer to entire renal corpuscle
	Bowman capsule
Proximal tubule	Convoluted part
	Straight part (pars recta), or thick descending limb of Henle loop
Intermediate tubule	Descending part, or thin descending limb of Henle loop
	Ascending part, or thin ascending limb of Henle loop
Distal tubule	Straight part, or thick ascending limb of Henle loop: subdivided into medullary and cortical parts; the cortical part contains the macula densa in its terminal portion
	Convoluted part
Collecting Duct System	
Connecting tubule	Includes the arcades in most species
Collecting duct	Cortical collecting duct
	Outer medullary collecting duct: subdivided into an outer stripe and an inner stripe portion
	Inner medullary collecting duct: subdivided into basal, middle, and papillary portions

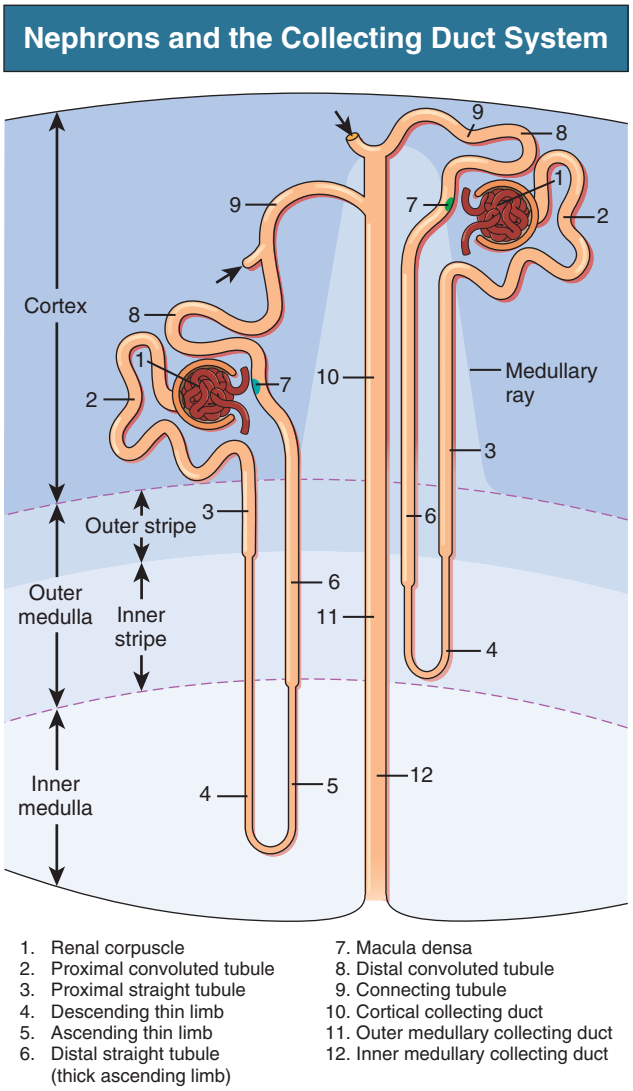

Fig. 1.2 Nephrons and the collecting duct system. Shown are short-looped and long-looped nephrons, together with a collecting duct (not drawn to scale). *Arrows* denote confluence of further nephrons.

the inner stripe. However, the blood returning from either the inner medulla or the inner stripe afterward does perfuse the tubules of the outer stripe.

The intrarenal veins accompany the arteries. Central to the renal drainage of the kidney are the arcuate veins, which, in contrast to arcuate arteries, do form real anastomosing arches at the corticomedullary border.

The intrarenal arteries and the afferent and efferent glomerular arterioles are accompanied by sympathetic nerve fibers and terminal axons representing the efferent nerves of the kidney.[1] Tubules have direct contact to terminal axons only when the tubules are located around the arteries or the arterioles. Tubular innervation consists of "occasional fibers adjacent to perivascular tubules."[4] The density of nerve contacts to convoluted proximal tubules is low; contacts to straight proximal tubules, thick ascending limbs of Henle loops, and CDs have never been encountered. Afferent nerves of the kidney are believed to be sparse.[5]

Glomerulus (Renal Corpuscle)

The glomerulus comprises a tuft of specialized capillaries attached to the mesangium, both of which are enclosed in a pouch-like extension of the tubule that represents the Bowman capsule (Figs. 1.4 and 1.5). The capillaries together with the mesangium are covered by epithelial cells (podocytes) forming the visceral epithelium of the Bowman capsule. At the vascular pole, this is reflected to become the parietal epithelium of the Bowman capsule. At the interface between the glomerular capillaries and the mesangium on one side and the podocyte layer on the

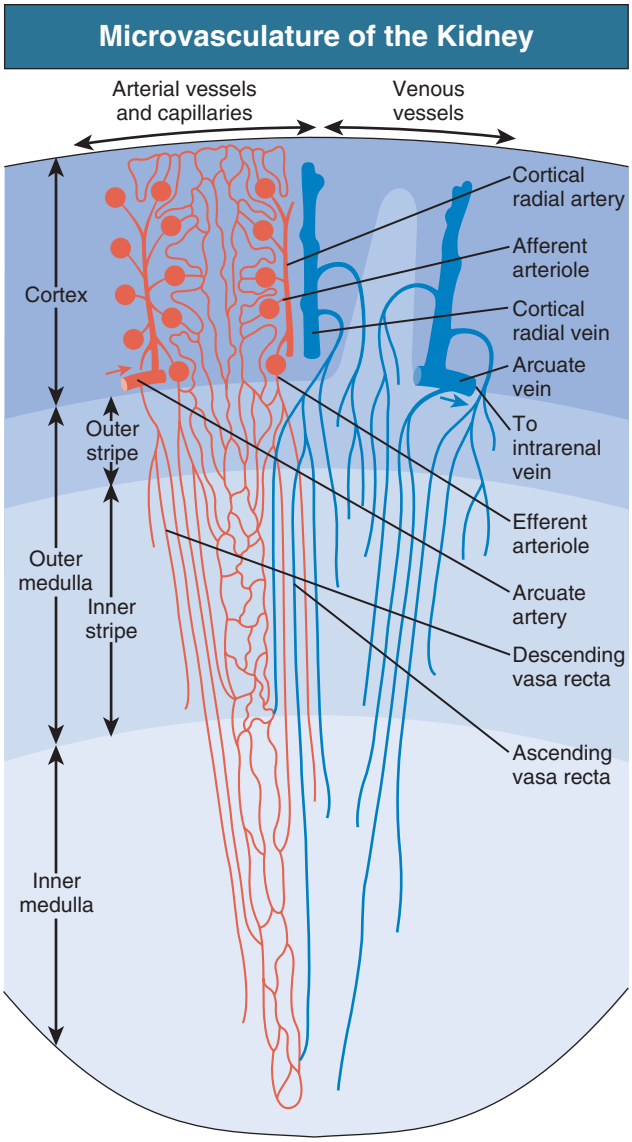

Fig. 1.3 Microvasculature of the Kidney. Afferent arterioles supply the glomeruli, and efferent arterioles leave the glomeruli and divide into the descending vasa recta, which together with the ascending vasa recta form the vascular bundles of the renal medulla. The vasa recta ascending from the inner medulla all traverse the inner stripe within the vascular bundles, whereas most of the vasa recta from the inner stripe of the outer medulla ascend outside the bundles. Both types traverse the outer stripe as wide, tortuous channels.

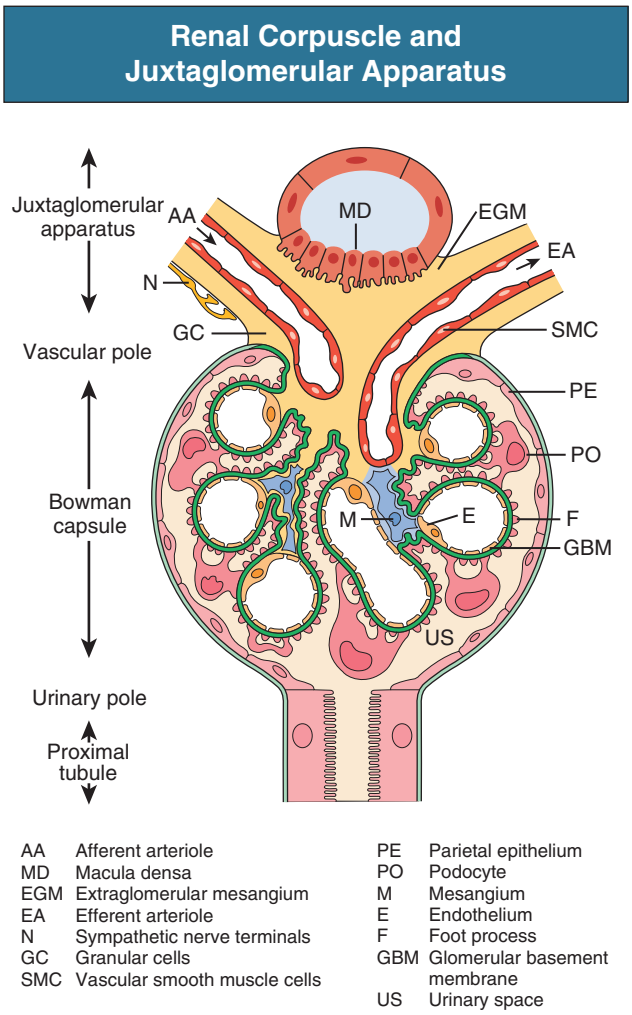

Fig. 1.4 Glomerulus and juxtaglomerular apparatus. (Modified with permission from reference 1.)

other side, the glomerular basement membrane (GBM) is developed. The space between both layers of the Bowman capsule represents the urinary space, which at the urinary pole continues as the tubule lumen.

On entering the tuft, the afferent arteriole immediately divides into several primary capillary branches, each of which gives rise to an anastomosing capillary network representing a glomerular lobule. In contrast, the efferent arteriole is already established inside the tuft by confluence of capillaries from each lobule.[6] Thus the efferent arteriole has a significant intraglomerular segment located within the glomerular stalk.

Glomerular capillaries are a unique type of blood vessel composed of nothing but an endothelial tube (Figs. 1.6 and 1.7). A small stripe of the outer aspect of this tube directly abuts the mesangium; the major part bulges toward the urinary space and is covered by the GBM and the podocyte layer. This peripheral portion of the capillary wall represents the filtration area.

Glomerular Basement Membrane

The GBM serves as the skeleton of the glomerular tuft. This membrane is a complexly folded sack with an opening at the glomerular hilum (see Fig. 1.4). The outer aspect of this GBM sack is completely covered with podocytes. The interior of the sack is filled with the capillaries and the mesangium. As a result, on its inner aspect, the GBM is in contact with either capillaries or the mesangium. At any transition between these two locations, the GBM changes from a convex pericapillary to a concave perimesangial course; the turning points are called *mesangial angles*. In electron micrographs of traditionally fixed tissue, the GBM appears as a trilaminar structure, with a lamina densa bounded by two less dense layers, the lamina rara interna and lamina rara externa (see Fig. 1.7). Studies with freeze techniques reveal only one thick, dense layer directly attached to the bases of the epithelium and endothelium.[7]

The major components of the GBM include type IV collagen, laminin, and heparan sulfate proteoglycans, as in basement membranes at other sites. However, the GBM has several unique properties, notably a distinct spectrum of type IV collagen and laminin isoforms. The mature GBM consists of type IV collagen made of α3, α4, and α5 chains and laminin 11, made of α5, β2, and γ1 chains.[8] Type IV collagen is the antigenic target in Goodpasture disease (see Chapter 16), and mutations in the

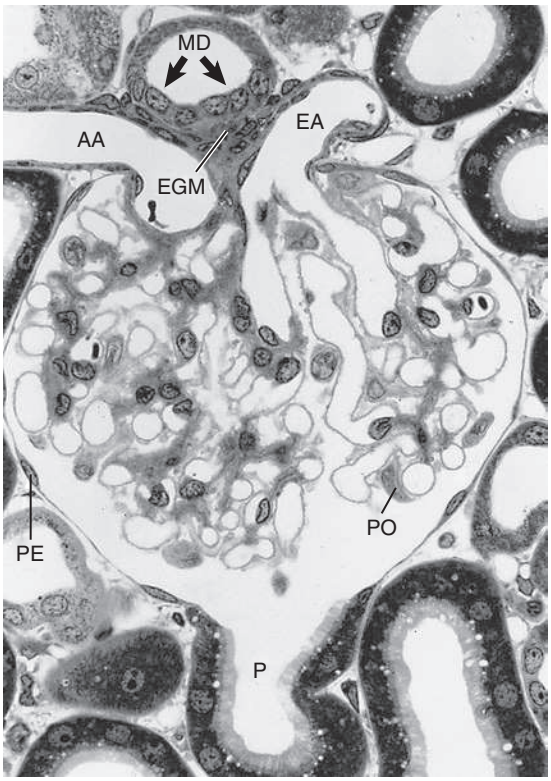

Fig. 1.5 Longitudinal section through a glomerulus (rat). At the vascular pole, the afferent arteriole *(AA),* the efferent arteriole *(EA),* the extraglomerular mesangium *(EGM),* and the macula densa *(MD)* are seen; *PO,* podocyte. At the urinary pole, the parietal epithelium *(PE)* transforms into the proximal tubule *(P).* (Light microscopy; magnification ×390.)

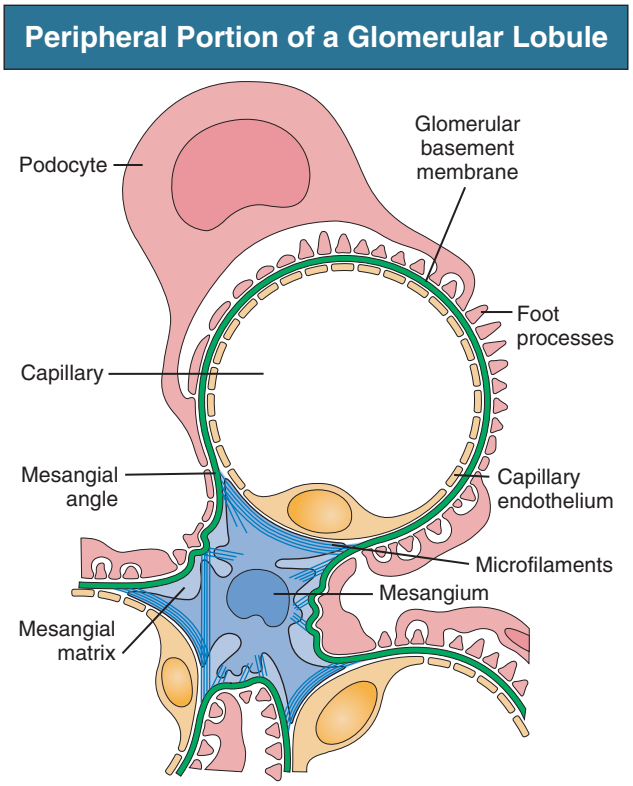

Fig. 1.6 Peripheral portion of a glomerular lobule. This part shows a capillary, the axial position of the mesangium, and the visceral epithelium (podocytes). At the capillary-mesangial interface, the capillary endothelium directly abuts the mesangium.

genes of the α3, α4, and α5 chains are responsible for Alport syndrome (see Chapter 46).

Current models depict the basic structure of the GBM as a three-dimensional network of type IV collagen.[7] The type IV collagen monomer consists of a triple helix that is 400 nm in length, with a large, noncollagenous globular domain at its C-terminal end called NC1. At the N terminus, the helix possesses a triple helical rod 60 nm long: the 7S domain. Interactions between the 7S domains of two triple helices or the NC1 domains of four triple helices allow type IV collagen monomers to form dimers and tetramers. In addition, triple helical strands interconnect by lateral associations through binding of NC1 domains to sites along the collagenous region. This network is complemented by an interconnected network of laminin 11, resulting in a flexible, nonfibrillar polygonal assembly that provides mechanical strength and elasticity to the basement membrane and serves as a scaffold for alignment of other matrix components.[9,10]

The electronegative charge of the GBM mainly results from the presence of polyanionic proteoglycans. The major proteoglycans of the GBM are heparan sulfate proteoglycans, including perlecan and agrin. Proteoglycan molecules aggregate to form a meshwork that is kept well hydrated by water molecules trapped in the interstices of the matrix.

Mesangium

Three major cell types occur within the glomerular tuft, all of which are in close contact with the GBM: mesangial cells, endothelial cells, and podocytes. The mesangial/endothelial/podocyte cell ratio is 2:3:1 in the rat. The mesangial cells and mesangial matrix establish the glomerular mesangium.

Mesangial cells. Mesangial cells are irregular in shape, with many processes extending from the cell body toward the GBM (see Figs. 1.6 and 1.7). In these processes, dense assemblies of microfilaments are found, containing α-smooth muscle actin, myosin, and α-actinin.[11]

The processes are attached to the GBM directly or through the interposition of microfibrils The GBM represents the effector structure of mesangial contractility. Mesangial cell–GBM connections are found throughout the mesangium-GBM interface but are especially prominent at the turning points of the GBM infoldings (mesangial angles). The folding pattern of the GBM is permanently challenged by the expansile forces of the high intraglomerular perfusion pressure. Centripetal mesangial cell contraction balances the expansile forces. Thus the folding pattern of the GBM, including the complex convolutions of glomerular capillaries, are maintained by mesangial cells.

Mesangial cells possess a great variety of receptors, including those for angiotensin II (Ang II), vasopressin, atrial natriuretic factor, prostaglandins, transforming growth factor β (TGF-β), and other growth factors (platelet-derived growth factor [PDGF], epidermal growth factor [EGF], connective tissue growth factor [CTGF]).[12]

Mesangial matrix. The mesangial matrix fills the highly irregular spaces between the mesangial cells and the perimesangial GBM, anchoring the mesangial cells to the GBM.[6] Many common extracellular matrix proteins have been demonstrated within the mesangial matrix, including collagen types IV, V, and VI and microfibrillar protein components such as fibrillin and the 31-kilodalton microfibril-associated glycoprotein. The matrix also contains several glycoproteins, most abundantly fibronectin.

Endothelium

Glomerular endothelial cells consist of cell bodies and peripherally located, attenuated, and highly fenestrated cytoplasmic sheets (see Figs.

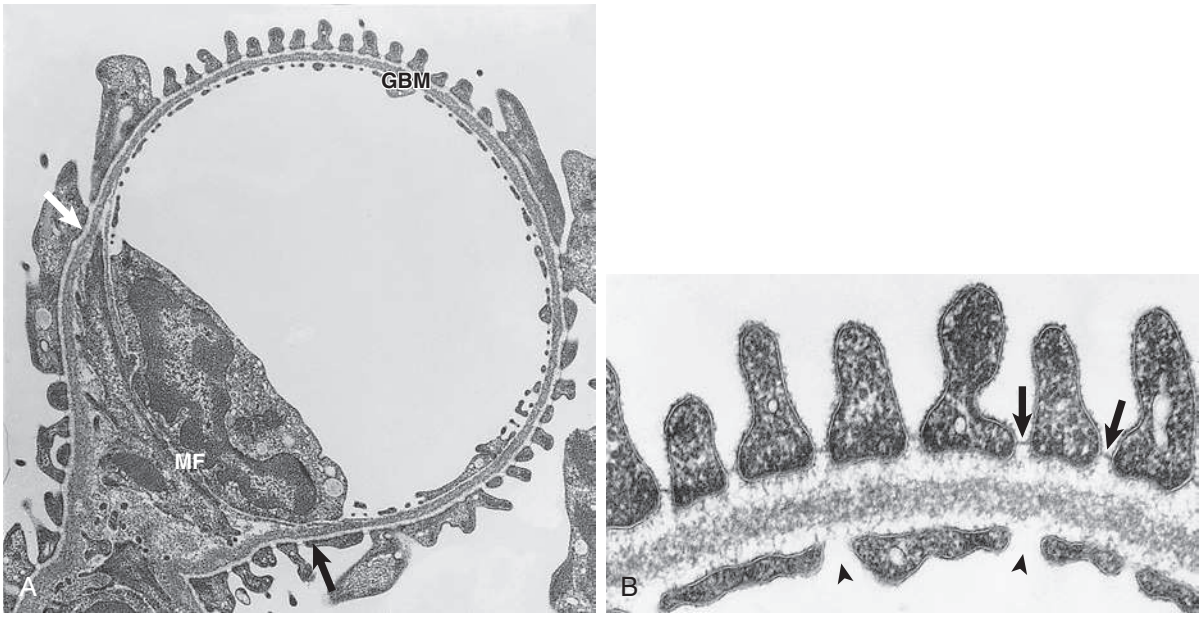

Fig. 1.7 Glomerular capillary. (A)The layer of interdigitating podocyte processes and the glomerular basement membrane *(GBM)* do not completely encircle the capillary. At the mesangial angles *(arrows),* both deviate from a pericapillary course and cover the mesangium. Mesangial cell processes containing dense bundles of microfilaments *(MF),* interconnect the GBM, and bridge the distance between the two mesangial angles. (B) Filtration barrier. The peripheral part of the glomerular capillary wall comprises the endothelium with open pores *(arrowheads),* the GBM, and the interdigitating foot processes (FPs). The GBM shows a lamina densa bounded by the lamina rara interna and externa. The FPs are separated by filtration slits bridged by thin diaphragms *(arrows).* (Transmission electron microscopy [TEM]; magnification: **A,** [×8770]; **B,** [×50,440].)

1.6 and 1.7). Glomerular endothelial pores lack diaphragms, which are encountered only in the endothelium of the final tributaries to the efferent arteriole.[6] The round to oval pores have a diameter of 50 to 100 nm. A negatively charged layer of membrane-bound and loosely attached molecules (glycocalyx) covers the entire luminal surface, including, as sieve plugs, the endothelial pores.[13] Endothelial cells are active participants in processes controlling coagulation and inflammation. Endothelial cells have receptors for vascular endothelial growth factor (VEGF), angiopoietins, and TGFβ-1, among others. They synthesize and release PDGF-B, endothelin-1, and endothelium-derived relaxing factor (EDRF), among others.[14]

Visceral Epithelium (Podocytes)

The visceral epithelium of the Bowman capsule comprises highly differentiated cells, the podocytes (Fig. 1.8; see also Fig. 1.6). Differentiated podocytes are unable to replicate; therefore lost podocytes cannot be replaced in the adult. All efforts of the last decade to find progenitor cells that might migrate into the tuft and replace lost podocytes have failed.

Podocytes have a voluminous cell body that floats within the urinary space, separated from the GBM by a subpodocyte space.[15] The cell bodies give rise to primary processes that fall apart into foot processes (FPs) that fix the cells to the capillaries, i.e. to the GBM. Sporadic FPs also may arise directly from the cell body. The FPs of neighboring podocytes regularly interdigitate with each other, leaving meandering slits (filtration slits) between them that are bridged by a complex extracellular structure, the *slit diaphragm* (SD) that may be seen as a modified adherens junction (Fig. 1.9; see also Figs. 1.6 to 1.8). Traditional scanning electron micrograph (SEM) pictures (see Fig.1.8A) do not convey the correct pattern of how FPs interdigitate and adhere to the GBM. As seen by block-face SEM (see Fig. 1.8B), individual FPs may terminate with a final branching and primary processes fall off into basal ridges that actually are also FPs.[16] Thus the interdigitating FP pattern as it adheres to the GBM is completely homogeneous, forming a uniform cover of interdigitating filopodia.

In contrast to the cell body, which harbors a prominent endoplasmic reticulum and Golgi system and has well-developed endocytotic and autophagic machinery, the cell processes apart from endocytotic elements contain only a few organelles. A sophisticated cytoskeleton accounts for the complex shape of the cells. In the cell body and the primary processes, microtubules and intermediate filaments (vimentin, desmin) dominate. Within the FPs, microfilaments (β-actin) form prominent U-shaped bundles arranged in the longitudinal axis of two successive FPs in an overlapping pattern. Above, the bends of these bundles are linked to the microtubules of the primary processes; peripherally, these bundles terminate in the dense cytoplasm associated with the sole plates, being part of the anchoring system of the FPs to the GBM (see later discussion). In addition, FPs have well developed sub-plasmalemmal actin network that has intimate contact to the anchor line of the SD and diffusely to the actin bundles. Multiple actin-associated proteins, including α-actinin-4 and synaptopodin myosin (myo-1e), among many others, establish the specific cytoskeleton in podocytes.[19]

The luminal membrane contains a great variety of receptors (see later discussion), and together with the luminal surface of the SD it is covered by a thick surface coat that is rich in sialoglycoproteins, including podocalyxin and podoendin, accounting for the high negative surface charge of the podocytes.

The abluminal cell membrane comprises a narrow band of lateral cell membrane extending from the SD to the GBM and, most important, the soles of the FPs abutting to the GBM. A complex anchoring system connects the cytoskeleton of the FPs to the GBM. Two systems are known: (1) α3β1 integrin dimers interconnect the cytoplasmic focal adhesion proteins vinculin, paxillin, and talin with the α3, α4, and α5

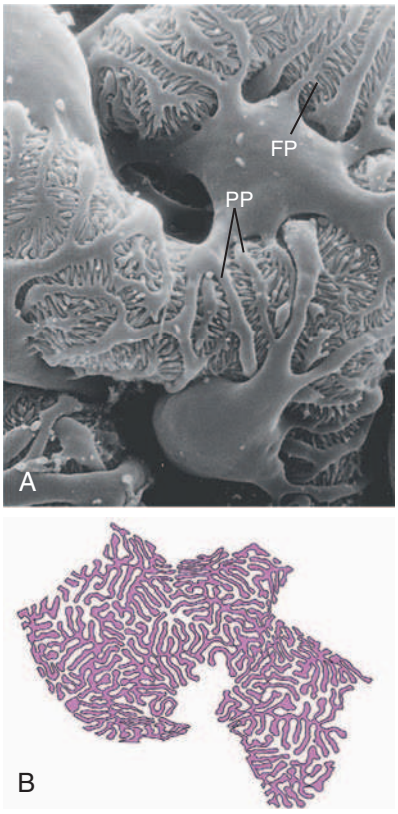

Fig. 1.8 Branching pattern of podocyte foot processes (rat). (A) Scanning electron micrograph (SEM) showing the urinary side of the podocyte cover of a glomerular capillary consisting of cell bodies, large primary processes *(PP)* and interdigitating foot processes *(FP)* separated by the filtration slits. (B) Drawing of the basal aspect of the FP-branching pattern as seen by block-face SEM. A fully homogeneous branching pattern of FPs attaches to the glomerular basement membrane (GBM) that may be compared with a pattern of interdigitating filopodia connected by adherens junctions. The high degree of branching (not seen from the luminal aspect) provides a high degree of adaptability to area changes of the underlying GBM. (**B,** From reference 45, with permission.)

chains of type IV collagen and laminin 521; and (2) β-α-dystroglycans interconnect the cytoplasmic adapter protein utrophin with agrin and laminin α5 chains in the GBM.[9]

The junctional connection of podocyte FPs by the SD bridging the filtration slits is complex and unique. The filtration slits have a constant width of approximately 30 to 40 nm: thus the SD has to connect the FPs over a considerable distance. By transmission electron microscopy (TEM), in routinely glutaraldehyde-fixed material, the SD shows up as a single dark line in cross sections and in an en-face view as a homogenous network of fibrillar structures interconnecting both membranes. Combined tannic acid and glutaraldehyde–fixed tissue reveals, in en-face view, a zipper-like structure with a row of pores approximately 14 × 2 nm on either side of a central bar. The transmembrane proteins that establish the slit diaphragm (SD) and its connection to the actin cytoskeleton of the FPs include nephrin, P-cadherin, FAT1, NEPH 1-3, podocin, and CD2AP, among others[20] (see Fig. 1.9).

Podocytes contain a great variety of surface receptors and ion channels, many of which accumulate close to the SD; the schematic in Fig. 1.9 shows some of them. They include receptors for cyclic guanosine monophosphate (cGMP) signaling, stimulated by natriuretic peptides (atrial natriuretic peptide [ANP], brain natriuretic peptide [BNP], and C-type natriuretic peptide [CNP]) and nitric oxide; receptors for cyclic adenosine monophosphate (cAMP) signaling stimulated by prostaglandin E_2 (PGE_2), dopamine, VEGF, isoproterenol, parathyroid hormone (PTH), PTH-related peptide; and receptors for Ca^{2+} signaling stimulated by numerous ligands, including angiotensin II, acetylcholine, PGF2, arginine vasopressin (AVP), adenosine triphosphate (ATP), endothelin, and histamine.[20] Among the transient receptor potential (TRP) cation channels, TRPC5 and TRPC6 have received much attention.[21-23] The major target of this signaling orchestra is the cytoskeleton (see later discussion). Other receptors, such as for TGF-β, fibroblast growth factor (FGF-2), and other cytokines/chemokines, have been shown to be involved in synthesis functions (GBM components) or in development of podocyte diseases.[20] Megalin is a multiligand endocytotic receptor and the major antigen of Heymann nephritis in the rat,[24] but is not present in humans.[12] On the other hand, podocytes, by paracrine and autocrine signaling, regulate the interplay with endothelial and mesangial cells; during development they are responsible for building a glomerulus. VEGF, angiopoietins, and PDGF, among others, are of crucial importance for the homeostatic maintenance of the tuft.[25]

Function and Maintenance of the Filtration Barrier

Most glomerular diseases start in the glomerulus, beginning with the breakdown of the filtration barrier. It is commonly accepted that the physical forces associated with filtration represent crucial challenges that account for the break down; they comprise filtration pressure and filtrate flow.

Filtration pressure and expansion. Traditionally, the high transmural hydrostatic pressure gradients necessary for filtration have been considered the main challenge to the filtration barrier. Podocyte FPs were considered a kind of pericyte process counteracting variations and derailments in perfusion pressures. This view has been challenged since we learned that the major way podocytes are lost (under any circumstances) is by detachment from the GBM as viable cells. It seems self-contradictory that FPs, which need their cytoskeleton to continually adapt their pattern of attachment to the GBM (see later discussion), would simultaneously function as contractile pericyte-like processes, counteracting the expansion of the GBM by increasing their tone. Consequently, it may be concluded that the principal burden for counteracting transmural pressure gradients (i.e., for developing wall tension) falls instead on the GBM.[26]

As described earlier, the GBM is an elastic membrane that expands or shrinks in surface area with increasing or decreasing transmural hydrostatic pressure, respectively. Its expansion decreases with increasing pressure and is limited.

Expansion of the GBM affords the immediate coordinated increase in the cover by interdigitated FPs; thus the FPs and the SD have to increase correspondingly (and vice versa when pressure decreases). The ability for such acute adaptions has been previously shown in the isolated perfused kidney. It is suggested that the changes in FP length occur by actin polymerization/depolymerization and the changes in SD length by coordinated exocytotic and endocytotic processes of SD components.[26,27]

An orchestrated connection between the mobility of the actin cytoskeleton and the dynamics of the SD has been uncovered in great depth by innumerable studies during the past two decades.[28,29]

Filtrate flow and shear stress. The flow of the filtrate through the filtration barrier represents by far the highest extravascular fluid flow in the body. It consists of the outflow from glomerular capillaries, through the GBM, and into the Bowman space. This latter step creates a problem: in contrast to the exit of filtrate from capillaries, where flow presses the endothelium against the basement membrane, its entry into the Bowman space tends to separate the podocytes from

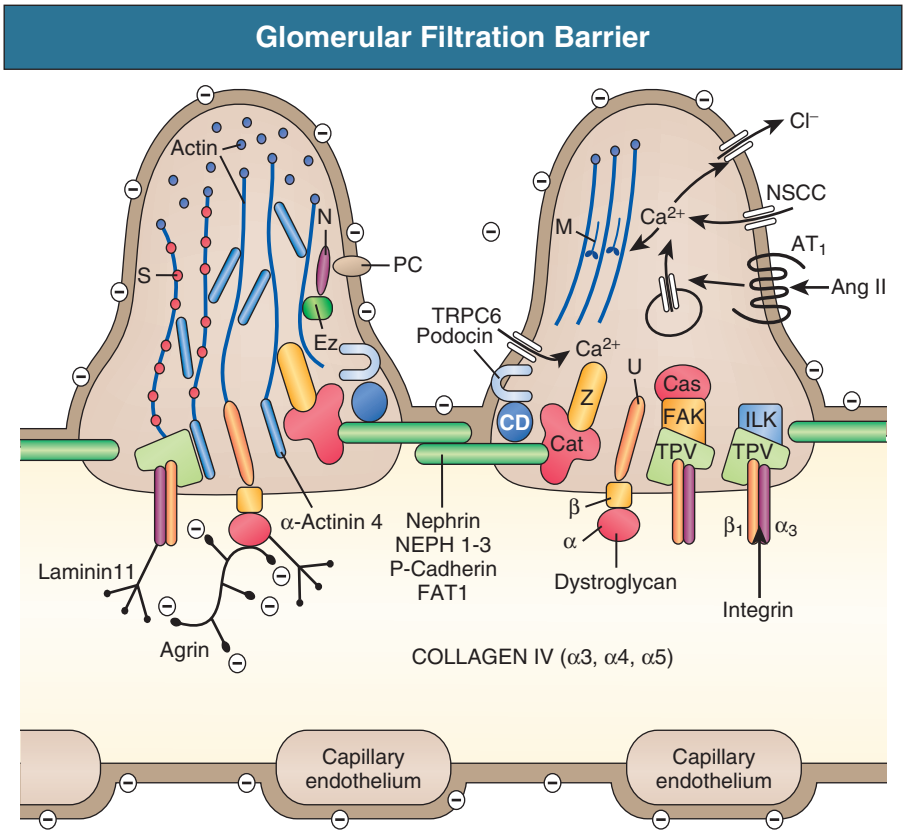

Fig. 1.9 Glomerular filtration barrier. Two podocyte foot processes (FPs) bridged by the slit membrane (SM), the glomerular basement membrane (GBM) and the porous capillary endothelium, are shown. The surfaces of podocytes and of the endothelium are covered by a negatively charged glycocalyx containing the sialoprotein podocalyxin *(PC)*. The GBM is mainly composed of type IV collagen (α3, α4, and α5), laminin 11 (α5, β2, and γ1 chains), and the heparan sulfate proteoglycan agrin. The SM represents a porous proteinaceous membrane composed of (as far as is known) nephrin, NEPH 1-3, P-cadherin, and FAT1. The actin-based cytoskeleton of the FPs connects to both the GBM and the SM. Regarding the connections to the GBM, β1α3 integrin dimers specifically interconnect the talin, paxillin, vinculin *(TPV)* complex to laminin 11; the β- and α-dystroglycans interconnect utrophin to agrin. The SM proteins are joined to the cytoskeleton by various adapter proteins, including podocin, Zonula Occludens protein 1 (ZO-1; Z), CD2-associated protein *(CD)*, and catenins *(Cat)*. Among the nonselective cation channels *(NSCC)*, TRPC6 associates with podocin (and nephrin, not shown) at the SM. Only the angiotensin II *(Ang II)* type 1 receptor *(AT_1)* is shown as an example of the many surface receptors. *Cas*, p130Cas; *Ez*, ezrin; *FAK*, focal adhesion kinase; *ILK*, integrin-linked kinase; *M*, myosin; *N*, Na^+-H^+ exchanger regulatory factor (NHERF2); *S*, synaptopodin. (Modified from reference 17.)

the GBM. The insight that the major way of losing podocytes in disease is by detachment has brought the shear stress created by the filtrate flow into discussion.

The strength of the shear stress depends on the flow rate and the geometry of the channel; the narrower the channel or the higher the flow velocity, the higher is the shear stress. In rats the filtrate flow amounts to 30 nl/min, creating a shear stress to the FPs within the filtration slit as high as 8 Pa.[30] Much lower values of shear stress to the podocyte cell bodies may lead to detachment when podocytes come to lie within the urinary orifice.[27] Moreover, a high sensitivity of podocytes to shear stress has been shown in cell culture studies.

This led to a new view of the relevance of the SM (in addition to its barrier function; see later discussion). Shear stress tends to lead to deformations of the lateral walls of FPs, and thus widens the slit. The interconnection of both opposite FPs by the SD at the narrowest site of the slit is ideally positioned to counteract these destabilizing forces. The SD uses the shear stress against one side of the slit to balance the shear stress against the opposite side. This means that during filtrate flow the SD is permanently under tension that counteracts the shear stress to both sides of the slit.[27]

Barrier function. Filtrate flow through the barrier occurs along an extracellular route, including the endothelial pores, GBM, and SD (see Figs. 1.7 and 1.9). The barrier shows a high permeability for water, small solutes, and ions, whereas the barrier is fairly tight for macromolecules, selective for size, shape, and charge.[20] The charge selectivity of the barrier results from the dense accumulation of negatively charged molecules throughout the entire depth of the filtration barrier, most importantly the surface coat of endothelial cells, and from the high content of negatively charged heparan sulfate proteoglycans in the GBM. Most plasma proteins, including albumin, are negatively charged, and thus their repulsion is dominantly charge dependent.

The size/shape selectivity seems to be established by the SD.[13] Uncharged macromolecules up to an effective radius of 1.8 nm pass freely through the filter. Larger components are increasingly restricted (indicated by their fractional clearances, which progressively decrease) and are totally restricted at effective radii of more than 4 nm. Plasma

albumin has an effective radius of 3.6 nm; without the repulsion from the negative charge, plasma albumin would pass through the filter in considerable amounts.

Studies by the group of Marcus Moeller proposed an electrophoretic mechanism for the repulsion and exclusion of plasma proteins from the glomerular filter.[31,32] According to their hypothesis, the flow of the filtrate through the charged filter creates a streaming potential. This electrical field is negatively charged on the urinary side of the glomerular filter compared with the capillary side by approximately –0.05 mV/10 mm Hg filtration pressure. Thus the negatively charged molecules (albumin) that approach the filter will be exposed to an electrophoretic force that drives them back toward the capillary lumen. The charm of this hypothesis consists of being independent of any structural pore preventing their passage. The barrier actually consists of a strictly filtration-dependent potential difference; without sufficient convective flow of filtrate, the barrier will become permeable.[31,32]

Pathology. The hypothesis that the mechanical interconnection of the FPs by the SD is the most vulnerable structure to the physical challenges of filtration is supported by the pathologic changes. The loss of the SD connection between adjacent FPs represents the earliest failure that starts the detachment of podocytes.[27]

This can be interpreted as the loss of local control of filtrate flow. Unchanneled filtrate flow through such leaks will exert unbalanced shear stress to the FPs, initiating locally the detachment of FPs. Repair of such leaks seems impossible in the face of ongoing filtrate flow, accounting for the observation that the damage will proceed.

Taken together, the layer of interdigitating FPs interconnected by the SD regulates the entry of the filtrate flow into the Bowman space by channeling the flow through the filtration slits. The geometry of the slits is maintained against the shear forces to both opposite FPs through the interconnection of opposing FPs by the SD. Loss of the junctional connection is detrimental because it opens leaks for uncontrolled filtrate flow with the tendency to increase the leaks.[33]

Parietal Epithelium

The parietal epithelium of the Bowman capsule consists of squamous epithelial cells resting on a basement membrane (see Figs. 1.4 and 1.5). The flat cells are filled with bundles of actin filaments running in all directions. In contrast to the GBM, the parietal basement membrane comprises several proteoglycan-dense layers that, in addition to type IV, contain type XIV collagen. The predominant proteoglycan of the parietal basement membrane is a chondroitin sulfate proteoglycan.[34]

Renal Tubule

The renal tubule is subdivided into several distinct segments: a proximal tubule (convoluted and straight portions), an intermediate tubule, a distal tubule (straight and convoluted portion), a CNT, and the CD (see Figs. 1.1 and 1.3).[1,2,34] The loop of Henle comprises the straight part of the proximal tubule (representing the thick descending limb), the thin descending and the thin ascending limbs (both thin limbs together represent the intermediate tubule), and the thick ascending limb (representing the straight portion of the distal tubule), which includes the macula densa. The CNT connects the nephron to the CD system.

The renal tubules are outlined by an epithelium that comprises a single layer of cells anchored to a basement membrane. The epithelial cells have multiple transport functions and show numerous structural adaptations to their special roles. They are connected apically by a junctional complex consisting of a tight junction (zonula occludens), an adherens junction, and, at some sites, a desmosome. As a result of this organization, two different pathways through the epithelium exist (Fig. 1.10): a transcellular pathway, including the transport across the luminal and basolateral cell membrane and through the cytoplasm and a paracellular pathway through the junctional complex and the lateral intercellular spaces. The functional characteristics of paracellular transport are determined by the tight junction, which differs markedly in its elaboration in the various tubular segments. The transcellular transport is determined by the specific channels, carriers, and transporters included in the apical and basolateral cell membranes. The various nephron segments differ markedly in function, distribution of transport proteins, and responsiveness to hormones and drugs such as diuretics. The cell surface area of the plasmalemmal compartments carrying the transport systems is extensively enlarged in many tubule cells, that is, by microvilli at the luminal membrane domain, by lamellar folds of the basolateral membrane interdigitating with those of the neighboring cells (interdigitations), or by lamellar folds of the basal cell membrane invaginating into its own cells (invaginations).

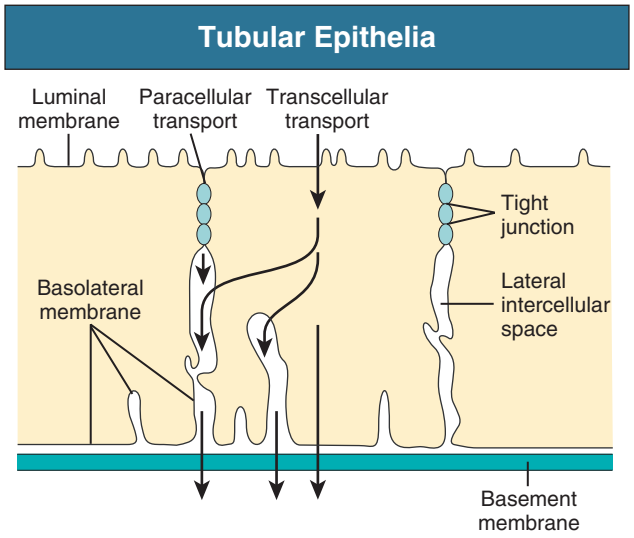

Fig. 1.10 Tubular epithelia. Transport across the epithelium may follow two routes: transcellular, across luminal and basolateral membranes, and paracellular, through the tight junction and intercellular spaces.

Proximal Tubule

The proximal tubule reabsorbs the bulk of filtered water and solutes (Fig. 1.11). The proximal tubule is generally subdivided into three segments (known as S_1, S_2, and S_3) that differ considerably in cellular organization and, consequently, also in function.[35] Generally, the proximal tubule has a prominent brush border and e xtensive interdigitation by basolateral cell processes. This lateral cell interdigitation extends up to the leaky tight junction, thus increasing the tight junctional belt in length and providing a greatly increased passage for the passive transport of ions. Proximal tubule cells have large prominent mitochondria intimately associated with the basolateral cell membrane where the Na^+,K^+–adenosine triphosphatase (Na^+,K^+-ATPase) is located; this machinery is the molecular mechanism initiating numerous secondary transcellular transport processes. The luminal transporter for Na^+ reabsorption specific for the proximal tubule is the Na^+-H^+ exchanger (NHE3) located in the plasma membrane of the apical microvilli and accounts for reabsorption of most of the filtered sodium. Further, sodium-coupled transporters in the microvillous membrane are the sodium-glucose cotransporters SGLT2 and SGLT1 and several sodium-phosphate cotransporters. The abundance of channel protein aquaporin 1 in the apical microvillous membrane and the basolateral cell membrane accounts for the high hydraulic permeability for water of this epithelium. An apical tubulovesicular compartment is part of the prominent

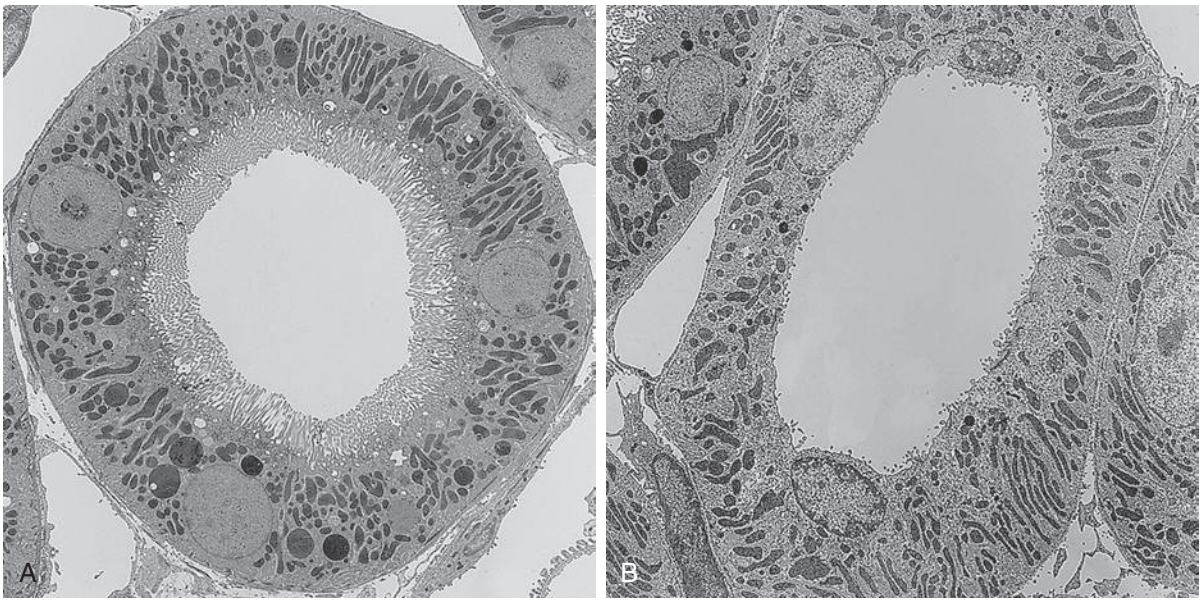

Fig. 1.11 Tubules of the renal cortex. (A) Proximal convoluted tubule is equipped with a brush border and a prominent vacuolar apparatus in the apical cytoplasm. The rest of the cytoplasm is occupied by a basal labyrinth consisting of large mitochondria associated with basolateral cell membranes. (B) Distal convoluted tubule also has interdigitated basolateral cell membranes intimately associated with large mitochondria. In contrast to the proximal tubule, however, the apical surface is amplified only by some stubby microvilli. (TEM; **A,** ×1530; **B,** ×1830.)

endosomal-lysosomal system and is responsible for the reabsorption of macromolecules (polypeptides and proteins such as albumin) that have passed the glomerular filter. The proximal tubule segment S_3, including portions of S_2, in addition, are engaged in many secretory processes of toxic substances and drugs via organic anion transporters and anorganic cation transporters. Proximal tubule cells are electrically coupled by gap junctions.

Intermediate Tubule

The intermediate tubule comprises the thin portion of the loop of Henle displaying a flat epithelium and consists of a thin descending and (only in long loops) a thin ascending limb (Fig. 1.12; see also Fig. 1.2). The thin descending limb, like the proximal tubule, is highly permeable for water (the channels are of aquaporin 1), whereas, beginning at the turning point, the thin ascending limb is impermeable to water. The latter has a highly interdigitated epithelium also along the tight junction, which is highly permeable to ions.

Distal Straight Tubule (Thick Ascending Limb of the Loop of Henle)

The thick ascending limb of the loop of Henle is often called the diluting segment. It is water impermeable but reabsorbs considerable amounts of sodium and chloride, resulting in the separation of salt from water. The salt is trapped in the medulla (see Fig. 1.12), whereas the water is carried away into the cortex, where it may return into the systemic circulation. The specific transporter for Na^+ reabsorption in this segment is the $Na^{2+}K^{2+}2Cl^-$ symporter (NKCC2), which is specifically inhibited by loop diuretics such as furosemide. This transporter is inserted in the luminal membrane, which is amplified by only solitary microvilli. The tight junctions of the thick ascending limb are elongated by lateral interdigitation of the cells. They have a comparatively low overall permeability; however, they contain the protein Claudin 16 for paracellular reabsorption of divalent ions, notably of magnesium. The cells are heavily interdigitated by basolateral cell processes, associated with large mitochondria supplying the energy for the transepithelial transport. The cells synthesize a specific protein, the Tamm-Horsfall protein, and release it into the tubular lumen. This protein is thought to be important for preventing the formation of kidney stones. A short distance before the transition to the distal convoluted tubule, the thick ascending limb contains the macula densa, which adheres to the glomerulus of the same nephron (see Juxtaglomerular Apparatus).

Distal Convoluted Tubule

The epithelium exhibits the most extensive basolateral interdigitation of the cells and the greatest numerical density of mitochondria compared with all other nephron portions (see Fig. 1.11). Apically, the cells are equipped with numerous solitary microvilli. The specific Na^+ transporter of the distal convoluted tubule is the luminal $Na^{2+}Cl^-$ cotransport system (NCC), which can be inhibited by the thiazide diuretics. Magnesium is reabsorbed via the transient receptor potential channel melastatin subtype 6 (TRPM6) in the luminal membrane and, along the paracellular route, through the tight junctional proteins Claudin 16 and 19.

COLLECTING DUCT SYSTEM

The CD system (see Fig. 1.2) includes the CNT and the cortical and medullary CDs. The embryologic origin of the CNT, which is interposed between the distal convoluted tubule and the CD, is unclear in whether it derives from the nephron anlage or the ureteral bud. Two nephrons may join at the level of the CNT, forming an arcade. Two types of cell establish the CNT: the CNT cell, which is specific to the CNT, and the intercalated (IC) cell, which is also present in varying amounts in the distal convoluted tubule and in the CD. The CNT cells are similar to the CD cells in cellular organization. Both cell types share sensitivity