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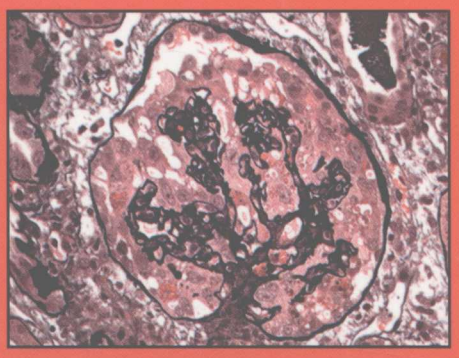

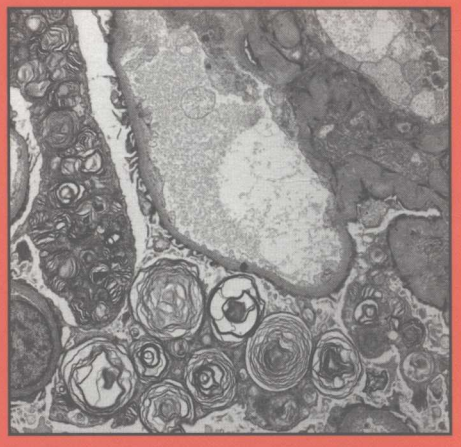

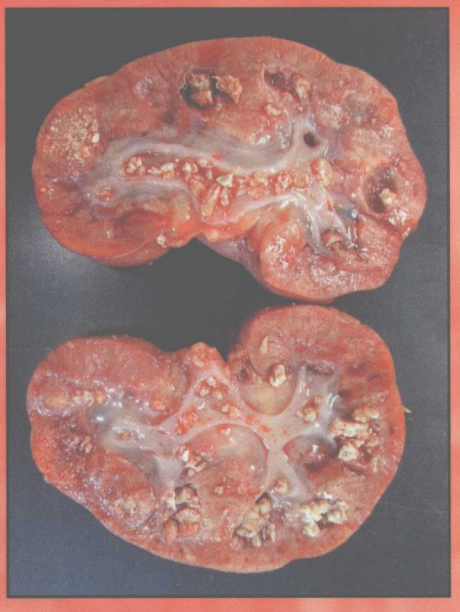

SILVA'S Diagnostic Renal Pathology

EDITED BY Xin Jin (Joseph) Zhou, Zoltan G. Laszik, Tibor Nadasdy, and Vivette D. D'Agati

CAMBRIDGE Medicine

Silva's Diagnostic Renal Pathology

Second Edition

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University Printing House, Cambridge CB2 8BS, United Kingdom

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning and research at the highest international levels of excellence.

www.cambridge.org
Information on this title: www.cambridge.org/9781316613986

First published 2009
Second edition 2017

Printed in the United Kingdom by Clays, St Ives plc

A catalogue record for this publication is available from the British Library

9781316613986 (Mixed Media)
9781107053137 (Hardback)
9781107281981 (Cambridge Core)

Silva's Diagnostic Renal Pathology

Second Edition

ZHOU

To my loving wife, Jian Wang, and our wonderful children, Jason and Jaclyn

LASZIK

To my beautiful wife, Erika, and our wonderful children, Nandi, Laura, and Aron

NADASDY

To my wife, Gyongyi, and my daughters, Krisztina and Orsolya

D'AGATI

To my devoted husband, Edward Imperatore, and my loving children, Edward and Paul, without whose constant support and encouragement my academic career would not be possible

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Foreword

This is written to acknowledge all those who make our subspecialty wonderful and fun. Indeed, all of what we know in renal pathology is because of the efforts of an extraordinary number of investigators both clinical and experimental throughout the world. We know them and the essential work they produce through the medical literature, courses, lectures, and "hall-way discussions." This book is a compilation of so much work, effort, talent, knowledge, and creativity by so many.

The Renal Pathology Club (now known as the Renal Pathology Society) started with a dozen or two pathologists, but has grown considerably to encompass 500 renal pathologists from over 35 countries. We meet regularly to learn from each other and to consider what is known and what is unknown (and what needs to be studied). In fact, not only do all the members of the Renal Pathology Society contribute to all our knowledge, but help "raise the bar" for all of us through presentations at the various Congresses, courses like the Columbia P&S Renal Biopsy course (under the able direction of Dr. Vivette D'Agati), and much less visiting professorships at many university medical schools. I am proud to be a part of the collegium of renal pathologists throughout the world. My own best times are with my colleagues in nephrology and I thank you for that. Indeed, it was not unusual to sit at a dinner table (e.g., Renal Pathology Society, etc.) with renal pathologists I knew so many years from the literature but not yet met in person. Recalling their papers led to the beginning of a personal friendship. We are colleagues, collaborators, confidants, competitors (collegial competition serves to make us all better) and (sometimes) characters whose legends will continue for quite some time (no names here). The peer-review process continues to improve our papers; we all have reviewed and been reviewed. I have yet to receive the old saw that says: "Your paper is both original and interesting. Unfortunately what is interesting is already known, and what is original is wrong" (or close to that)! We also owe a great acknowledgment to our stimulating fellows in nephropathology. I have been fortunate enough to have a number of great ones, several of whom are co-authors and co-editors of this book.

We pathologists serve as physician's physicians, better known as consultants. It is my experience that the most important (and fun) part of our profession is the interaction with the nephrologists. Our nephrology colleagues (in my case Drs. G. Appel, R. Toto, K. Kaufman, and a large number of others) continue to teach us as much as we teach them, for the benefit of all. We renal pathologists can still provide the best indicators of diagnosis, prognosis, guide the therapy, heurism – what to do next for the patient – and method(s) of proper follow-up for the patient's renal disease. As Dr. Pirani (one of my many mentors) once wrote: "Pathology and the microscope are where function meets morphology".

A few years ago, I did a small survey of approximately three dozen renowned pathologists with great consultation services (covering most of the organ systems). I learned a lot in this survey about the major traits of great consultants, including: (a) knowing what the clinician needed to know and being an indispensable part of the health care delivery team for the patient; (b) open and clear communication – knowing what you know and what you don't know, and not being afraid of asking others for their judgment on difficult cases; (c) obtaining the entire relevant clinical and laboratory data and integrating all sources of information; (d) remaining up-to-date on the literature; (e) incorporating new advances and appropriately validated technology; (f) knowing the outcome of your diagnosis; and (g) as the old saying goes – availability, affability, accountability, and ability. There are many more aspects of being and becoming the best consultant possible, and it is probably the most pleasurable and important endeavor we perform.

However, our work is not done. The renal biopsy continues to be the "gold standard" clinical studies in the foreseeable future. If one looks at the great Nephrology texts, one will see that many (usually a majority) of the chapters are divided by diseases only the renal pathologist can diagnose with certainty in the individual patient. However, as Dr. Pirani has stated, "the renal biopsy will hopefully lead to studies and techniques, that will replace the renal biopsy." Advances in immunology, molecular biology, and the "-omics" will make the future a very exciting place to be. In part, the future is already here, and we are seeing creative renal investigators introducing new techniques for more exact diagnosis, prognosis, therapeutic regimens, and methods of follow-up, much less the essential understanding of the basic mechanisms. There are lots of things that still need to be done (even more than before, now that we are learning what we didn't know).

Finally, as Dr. Pirani once said: "we owe to the patients a gratitude and responsibility." If not for these patients and

a huge effort by so many, we would not have advanced as far as we have. On behalf of all those we serve – our patients, physicians, students, and those to come – I/we thank you for all you have done, are doing, and will do in the future. Progress will continue. As Enrico Fermi once said at the end of a speech: "Now, let's get to work."

Fred Silva, MD

Preface to the First Edition

If you do not know the names of things, the knowledge of them is lost, too.

– *Carl Linnaeus*

Throughout our many combined years of teaching renal pathology, we have been impressed by the challenges to students learning the subject for the first time. There are many reasons why the study of renal pathology is considered difficult. First, there is insufficient knowledge of the normal histology/structure of the kidney. Second, one disease can manifest many different morphologic patterns, while a particular morphologic pattern can be produced by different diseases or etiologic factors. And finally, several different names (synonyms) have been applied to particular patterns or diseases. Yet, the many years of teaching have convinced us that there can be a systematic and orderly approach to the study of renal pathology. Therefore, a new book emphasizing an algorithmic, deductive approach to the interpretation of renal pathology seemed timely. This book organizes the various renal patterns and diseases in a standardized fashion, with emphasis on clinical–pathologic correlations. We have limited our inclusion of renal morphologic patterns to comparatively stable taxonomic groups covering the major diagnostic entities accepted by the published literature.

Standardized names and terminology are essential for communication among renal experts, whether they are clinicians or pathologists. The terminology used in this book is generally consistent with that used by most North American renal pathologists. Wherever possible, we have applied the widely recognized International Nomenclature of Disease (IND), a joint project of the Council for International Organization of Medical Sciences and the World Health Organization. The purpose is to ease communications and facilitate the storage and retrieval of medical information. As noted by the IND, a "few diseases have a single recognized name; most have several different . . . names. The principle objective of the IND is to provide . . . a single recommended name" (specific, unambiguous, self-descriptive, simple, and based on cause whenever feasible). It is meant to be a truly international language of disease. The importance of precise terminology and diagnostic criteria cannot be overstated.

The approach and classification used in this book are neither unique nor original. They are based on the "capture" of ideas from the many members of the Renal Pathology Society, Inc., and from major courses in the field, such as Medical Diseases of the Kidney, a postgraduate course held annually for more than 30 years by the Columbia University College of Physicians and Surgeons in New York City, under the direction of Dr. Vivette D'Agati. The approach to renal biopsy has been influenced enormously by Dr. Conrad L. Pirani, and it should come as no surprise that the editors of this book have either studied directly under him (V.D., F.G.S.) or been mentored directly by Dr. Pirani's student, Dr. Silva (X.J.Z., Z.L., and T.N.).

A useful classification (and the subsequent approach to diagnosis) should be based on the following requirements.

1. The classification should be clinically relevant and provide useful information to the clinician (about diagnosis, prognosis, identification of clinical subsets, optimal choice of therapy, evaluation of response to therapy, and future management).
2. It should be based on facts (reflecting the ideals of evidence-based medicine), be scientifically correct, and incorporate our current level of biologic understanding.
3. It should be relatively easy to use by pathologists throughout the world and be reproducible between observers.

The approach of *Silva's Diagnostic Renal Pathology*, which incorporates these principles, is morphologically based and designed for practicing anatomic (and renal) pathologists. By maintaining a high level of expertise in renal pathology, pathologists can ensure that the current trend of increasing use of renal biopsy for diagnosis and patient management will continue.

Many algorithms that collectively detail the clinical, laboratory, and pathologic patterns of renal disease have been included. These algorithms, based upon clinical and morphologic findings, will allow one to find the correct diagnosis. The algorithms provide a simplified road map that directs the reader to the major patterns of interest. To this end, we have adopted a combined "clinical and pathologic" classification scheme in this book. We have always found it ironic that most dictionaries, atlases, and textbooks require a priori that one knows what something is (e.g., what the diagnosis is and how to spell a particular word) in order to look it up and find the relevant entry. We hope that this book will eliminate that problem.

We believe that the approach in this book, neither final nor perfect, will allow the student to discover and categorize the

type of renal involvement, correlate it with the clinical and laboratory findings, and determine the renal prognosis and optimal therapy. Of course, there are always "varieties" or "cross-overs" or "dual diseases," which render exact classification difficult. Nonetheless, a good description is always reliable. More atypical or unusual cases are likely to be referred for renal biopsy, because the clinically obvious cases (e.g., minimal change nephrotic syndrome in children, acute postinfectious glomerulonephritis, diabetic nephropathy with retinopathy) often are not biopsied unless they exhibit atypical features. In the end, it is the renal morphology interpreted in an informed clinical context that leads pathologists to an accurate diagnosis. Although this book is intended as a practical guide for the diagnostic pathologist with primary responsibility for renal biopsy interpretation, as "clinical biologists" we should not lose sight of the pathogenetic factors behind the morphology. Thus, we have included a short section on "Pathogenesis" in each of the chapters.

The authors each bring their own unique personal insights to their individual chapters. However, we have attempted to bind them together through a unanimity of purpose, as reflected in their similar styles and analytic approaches.

At each step, the renal pathologist is integrating knowledge about the light microscopy, fluorescence microscopy, electron microscopy, renal functional studies, urinalysis, systemic findings, medication history, serologies, and radiologic studies. It is this multidisciplinary approach that constitutes the most rewarding aspect of renal pathology. Despite the complexity of the subject material, we hope that the approach outlined in this book will provide a user-friendly guide into this fascinating field.

As our mentor, Dr. Conrad Pirani, often said, it is important that clinical nephrologists and pathologists work closely together for the good of the patient. The pathologist cannot function in isolation. The most difficult diagnostic dilemmas can usually be solved by combining the knowledge of clinician and pathologist on an individual case. As Dr. Pirani has stated in a renal biopsy textbook, "[s]tructure and function have finally met at the microscope." The pathologist and nephrologist can learn a great deal from each other by reviewing cases together over the multiheaded microscope.

Lastly, we would like to thank the renal patients, physicians, and pathologists without whom we would not have had the opportunity to collect these biopsy materials for teaching purposes. We thank them for providing us with such valuable illustrative cases. We, pathologists, strive to understand what we see and place it in a diagnostic context that guides the nephrologist toward more specific therapies. As better and more targeted therapies are developed, an accurate biopsy interpretation will become even more important. It is highly likely that the renal biopsy will continue to be cost-effective for all those we serve – our patients and our clinicians.

Preface to the Second Edition

When we launched the first edition of the *Silva's Diagnostic Renal Pathology*, we envisioned to fill a niche somewhere between the existing encyclopedic texts and the various atlases. The format of this new book should emphasize on "how to approach the diagnosis of renal diseases" using an algorithmic and deductive method. We have adopted a combined "clinical and pathologic" classification scheme in this book so that the readers can quickly focus on the aspect of the condition of interest. Since the publication of this book seven years ago, several quite positive book reviews were published in prestigious nephrology and pathology journals. The responses from pathologists, nephrologists, and trainees both in pathology and nephrology are overwhelmingly laudatory. The requests from readers and the advances in all aspects of kidney diseases mandate a new edition.

Although with considerable excitement, we started the second edition with great humility and trepidation. Dr. Fred Silva, a remarkable medical scholar and nephropathologist, has decided to hand over the baton to us. All editors have been mentored by him at certain stages of our careers, and we shall always be in his debt for his mentoring, friendship, and support. Even though Dr. Silva was not directly involved in editing this edition, his guidance and wisdom is invaluable to the success of the second edition.

Major advances have occurred in renal pathology in recent years requiring significant changes in the content of this book. All chapters have been extensively revised and updated. Content on renal development has been added in Chapter 1. Rapidly progressive glomerulonephritis has become a separate chapter owing to the clinical importance of and enormous new advances in crescentic glomerulonephritis. Given the interesting parallels between aging and end-stage renal disease, these two chapters are combined. Since the focus of this book is medical diseases of the kidney, the chapter on renal tumor has been deleted. Instead, an outstanding and most authoritative chapter on digital renal pathology is included.

We are deeply honored and grateful that a group of internationally acclaimed renal experts have joined us to present this information in an algorithmic, authoritative, concise, and yet comprehensive fashion. We thank them for their unrivaled scholarship and unmatched cooperation.

Abbreviations

ACA	Affordable Care Act
ACD	acquired cystic disease
ACE	angiotensin-converting enzyme
ACL	anticardiolipin
ACR	American College of Rheumatology
ADAS	autosomal dominant Alport syndrome
ADPKD	autosomal dominant polycystic kidney disease
ADTKD	autosomal dominant tubulointerstitial kidney disease
AKI	acute kidney injury
AMPK	AMP-activated kinase
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
APCA	anticitrullinated peptide antibodies
APIGN	acute postinfectious glomerulonephritis
APL	antiphospholipid antibody
APOL-1	apolipoprotein L-1
APRT	adenine phosphoribosyltransferase
APS	antiphospholipid antibody syndrome
APSGN	acute poststreptococcal glomerulonephritis
APSN	antiphospholipid syndrome nephropathy
aPTT	activated partial thromboplastin time
ARA	American Rheumatism Association
ARAS	autosomal recessive Alport syndrome
ARB	angiotensin receptor blocker
ARCD	acquired renal cystic disease
ARPKD	autosomal recessive polycystic kidney disease
ART	anti-retroviral therapy
AS	Alport syndrome
ASO	antistreptolysin O
ATA	American Telemedicine Association
ATIN	acute tubulointerstitial nephritis
ATL	ascending thin limb
ATN	acute tubular necrosis
ATTR	transthyretin-associated
AVR	ascending vasa recta
AZA	azathioprine
Bmp	bone morphogenetic protein
BMT	bone marrow transplantation
Bp	blood pressure
BSA	bovine serum albumin
C1qN	C1q nephropathy
C3GN	C3 glomerulonephritis
CAD	computer-aided diagnostics
CADI	chronic allograft damage index
CAKUT	congenital anomalies of the kidney and urinary tract
CAN	chronic allograft nephropathy
CAP	College of American Pathologists
cAMP	cyclic adenosine monophosphate
CBIR	Content Based Image Retrieval
CCD	charged coupled device; cortical collecting duct
CD	collecting duct
CD2AP	CD2-associated protein
CDK	cyclin-dependent kinase
CFH	complement factor H
CFTR	cystic fibrosis transmembrane conductance regulator
CIC	circulating immune complex
CKD	chronic kidney disease
CMOS	complementary metal oxide semiconductor
CMV	cytomegalovirus
CNF	congenital nephrotic syndrome of the Finnish type
CNI	calcineurin inhibitors
CNS	congenital nephrotic syndrome
CNT	connecting tubule
CNV	copy number variant
CBC	complete blood count
COX-2	cyclooxygenase-2
CRAB	hypercalcemia, renal failure, anemia, and bone lesions
CRP	complement regulatory proteins
CT	computed tomography
CTGF	connecting tubule glomerular feedback; connective tissue growth factor
DAA	direct-acting antiviral
DAF	decay-accelerating factor
DC	dendritic cell
DCT	distal convoluted tubule
DDD	dense deposit disease
DGS	diabetic glomerulosclerosis
DHA	dihydroxyadenine
DIC	disseminated intravascular coagulation
DILS	diffuse infiltrative lymphocytosis syndrome
DM	diabetes mellitus

DMH	diffuse mesangial hypercellularity
DMS	diffuse mesangial sclerosis
DNP	diabetic nephropathy
DSA	donor-specific antibody
DTL	descending thin limb
DVR	descending vasa recta
EBM	epidermal basement membrane
EBV	Epstein–Barr virus
ECHO	Enteric Cytopathic Human Orphan
EDTA	ethylene diamine tetraacetic acid
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
eGFR	estimated glomerular filtration rate
EM	electron microscopy
EMP	endothelial microparticle
ENA	extractable nuclear antigens
ER	endoplasmic reticulum
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FDP	fibrin degradation products
FGF23	fibroblastic growth factor 23
FMF	Familial Mediterranean fever
FSGS	focal segmental glomerulosclerosis
GAG	glycosaminoglycan
GBM	glomerular basement membrane
GCK	glomerulocystic kidney
GCKD	glomerulocystic kidney disease
GDNF	glial-derived neurotrophic factor
GFR	glomerular filtration rate
GI	gastrointestinal
GINA	Genetic Information Nondiscrimination Act
GN	glomerulonephritis
GPA	granulomatosis with polyangiitis
GSD	glycogen storage disease
GUDMAP	Genitourinary Developmental Molecular Anatomy Project
GVHD	graft versus host disease
GWAS	genome-wide association study
H&E	hematoxylin and eosin
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCDD	heavy chain deposition disease
HCV	hepatitis C virus
HDL	high-density lipoprotein
HELLP	hemolysis, elevated liver enzymes, and low platelets
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HIVAN	human immunodeficiency virus-associated nephropathy
HSCT	hematopoietic stem cell transplant
HSP	Henoch–Schönlein purpura
HSPG	heparan sulfate proteoglycans
HTA	host targeting agent
HUS	hemolytic uremic syndrome
IBD	inflammatory bowel disease
IC	immune complex; intercalated cell
IE	infective endocarditis
IF	immunofluorescence
IgA	immunoglobulin A
IgAN	immunoglobulin A nephropathy
IgAV	IgA vasculitis
IHC	immunohistochemistry
ILK	integrin-linked kinase
IMCD	inner medullary collecting duct
IND	International Nomenclature of Disease
INR	international normalized ratio
IP	immunoperoxidase
IPS	interpodocyte space; in-plane switching
iPSC	induced pluripotent stem cell
IRGN	infection-related GN
IRIS	immune reconstitution inflammatory syndrome
ISKDC	International Study of Kidney Diseases in Children
ISN	International Society of Nephrology
ITG	immunotactoid glomerulopathy
IUGR	intrauterine growth restriction
IVIG	intravenous immunoglobulin
JG	juxtaglomerular
JGA	juxtaglomerular apparatus
JMS	Jones' methenamine silver
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LA	lupus anticoagulant
LAMP-2	lysosome-associated membrane protein 2
LCAT	lecithin cholesterol acyltransferase
LCDD	light chain deposition disease
LCKD	localized (or segmental) cystic kidney disease
LDL	low-density lipoprotein
LHCDD	light and heavy chain deposition disease
LIS	laboratory information system
LM	light microscopy
LMWH	low molecular weight heparin
LN	lupus nephritis
LPHS	loin pain hematuria syndrome
LPS	lipopolysaccharide
LVH	left ventricular hypertrophy
LYVE-1	lymphatic endothelial hyaluronan receptor-1
MAC	membrane attack complex
MAGUK	membrane-associated guanylate kinase
MAP	mean arterial pressure
MAPS	microangiopathic antiphospholipid-associated syndrome
MARP	million age-related population
MBL	mannose-binding lectin
MCD	minimal change disease
MCTD	mixed connective tissue disease
MCP	membrane cofactor protein
MD	macula densa
MDRD	Modification of Diet in Renal Disease
MEFV	Mediterranean fever (gene)
MET	mesenchymal-to-epithelial transition

MGRS	monoclonal gammopathy of renal significance
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MIDD	monoclonal immunoglobulin deposition disease
MMF	mycophenolate mofetil
MMP	metalloproteinase
MN	membranous nephropathy
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MRI	magnetic resonance imaging
MSK	medullary sponge kidney
mTOR	mammalian target of rapamycin
NA	Numerical Aperture
NAPlr	nephritis-associated plasmin receptor
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NCAM1	neural cell adhesion molecule
NCC	Na^+Cl^- cotransporter
NEP	neutral endopeptidase
NET	neutrophilic extracellular trap
NPSS	NEPTUNE pathology scoring system
nNOS	neuronal nitric oxide synthase
NOS	not otherwise specified
NPHP	nephronophthisis
NS	nephrotic syndrome; non-structural
NSAID	non-steroidal anti-inflammatory drug
OMCD	outer medullary collecting duct
ORG	obesity-related glomerulopathy
PAN	polyarteritis nodosa
PAS	periodic acid–Schiff
PCNA	proliferating cell nuclear antigen
PDGF	platelet-derived growth factor
PDGF-B	platelet-derived growth factor-B
PDGF-RB	platelet-derived growth factor-B receptor
PEC	parietal epithelial cell
PHN	passive Heymann nephritis
PKD	polycystic kidney disease
PMN	polymorphonuclear leukocyte
PR	Peg-interferon and ribavirin
PRA	panel-reactive antibodies
PT	prothrombin time
PTC	peritubular capillaries
PT-BB	proximal tubular brush border
PTH	parathyroid hormone
PTLD	posttransplant lymphoproliferative disorders
PTMA	post-transplantation thrombotic microangiopathy
pVHL	von Hippel–Lindau protein
RA	rheumatoid arthritis
RAAS	renin–angiotensin–aldosterone system
RAS	renin–angiotensin system
RBC	red blood cell
RCAD	renal cysts and diabetes
RCC	renal cell carcinoma
RF	rheumatoid factor
RMIC	renomedullary interstitial cell
ROS	reactive oxygen species
RPGN	rapidly progressive glomerulonephritis
RPS	Renal Pathology Society
RRT	renal replacement therapy
RVT	renal vein thrombosis
SAA	serum amyloid A
SD	slit diaphragm
SEM	scanning electron microscopy
SEP	subpodocyte exit pore
SLE	systemic lupus erythematosus
SMA	smooth muscle actin
SNP	single nucleotide polymorphism
SPEB	streptococcal pyrogenic exotoxin B
SPNSG	Southwest Pediatric Nephrology Study Group
SPS	subpodocyte space
SS	Sjogren's syndrome
STC	scattered tubular cell
STEC	Shiga toxin-producing *Escherichia coli*
STORM	stochastic optical reconstruction microscopy
suPAR	soluble urokinase plasminogen activator receptor
SVR	sustained virologic remission
SVV	small vessel vasculitis
TAL	thick ascending limb
TALH	thick ascending limbs of Henle
TA-P	time-average proteinuria
TMA	thrombotic microangiopathy
TBM	tubular basement membrane
TBMN	thin basement membrane nephropathy
TCC	terminal complement complex
TCR	T-cell receptor
TENS	transcutaneous electrical nerve stimulation
TG	transplant glomerulopathy
TGF	transforming growth factor
TLR	Toll-like receptor
TM	thrombomodulin
TMA	thrombotic microangiopathy
TNF	tumor necrosis factor
TRI	tubuloreticular inclusion
TRU	tubuloreticular inclusion
TSC	tuberous sclerosis complex
TTP	thrombotic thrombocytopenic purpura
TTR	transthyretin
TWEAK	TNF-like weak inducer of apoptosis
UB	ureteric bud
UPJ	ureteropelvic junction
USRDS	United States Renal Data System
VDRL	Venereal Disease Research Laboratories
VEGF	vascular endothelial growth factor
VEGFA	vascular endothelial growth factor A
VHLD	von Hippel–Lindau disease
VLDL	very low-density lipoprotein
vWF	von Willebrand factor
WM	Waldenstrom macroglobulinemia
WRN	warfarin-related nephropathy
WSI	whole-slide image
XLAS	X-linked Alport syndrome

Contents

Chapter 1

Renal Development and Anatomy

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Knowledge of the intricate structures of the developing kidney and the adult kidney provides insight into their functions and facilitates an understanding of renal diseases. One cannot recognize what is abnormal in the kidney if one does not know what is normal. This chapter considers kidney development, both its morphogenesis and regulatory mechanisms, followed by the anatomy and function of the adult kidney. The focus is on the human kidney, but some insights largely derived from other mammals will be discussed.

Renal Development

How can a kidney of elaborate nephrons with multiple cell types develop from aggregates of primitive mesenchymal cells? It is one of science's most profound questions. Renal development is dynamic and represents a classic model for studying organogenesis. The kidney builds itself from the "adaptive self-organization" of DNA, RNA and proteins which leads to cell differentiation, intercellular interactions and construction of complex tissue compartments (1). A basic understanding of kidney development provides a framework to enhance our knowledge of congenital anomalies of the kidney and urinary tract (CAKUT), the most common cause of pediatric chronic kidney disease (2). Studies of the developing kidney will also likely yield insights into adult kidney disorders, including renal repair after injury and renal cancer. Finally, a detailed comprehension will be necessary for renal regenerative biologic studies using stem/progenitor cells, chemical compounds and decellularized matrices (scaffolds).

Embryonic Kidneys

The urogenital system is the last organ system to form and the metanephric (permanent) kidney is the last of three excretory organs to develop. The pronephros, mesonephros and metanephros form in a cranial to caudal sequence from the intermediate mesoderm, which is situated between the dorsal somites and the lateral plate mesoderm. The pronephros and mesonephros are transient embryonic structures in mammals, although their sequential development is essential for formation of the metanephros.

Silva's Diagnostic Renal Pathology 2nd edn. ed. Zhou *et al.* Published by Cambridge University Press.