

# Understanding Kidney Diseases

Hugh Rayner  
Mark Thomas  
David Milford

 Springer

# Understanding Kidney Diseases



Hugh Rayner • Mark Thomas • David Milford

# Understanding Kidney Diseases

 Springer

Hugh Rayner  
Department of Renal Medicine  
Birmingham Heartlands Hospital  
Birmingham  
UK

David Milford  
Birmingham Children's Hospital  
Birmingham  
UK

Mark Thomas  
Department of Renal Medicine  
Birmingham Heartlands Hospital  
Birmingham  
UK

ISBN 978-3-319-23457-1      ISBN 978-3-319-23458-8 (eBook)  
DOI 10.1007/978-3-319-23458-8

Library of Congress Control Number: 2015956618

Springer Cham Heidelberg New York Dordrecht London  
© Springer International Publishing Switzerland 2016

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media  
([www.springer.com](http://www.springer.com))

*We dedicate this book to people who live  
with kidney disease and the clinicians who  
care for them.*



# Foreword

Great teachers make their subjects appealing. Doctors Rayner, Thomas and Milford have certainly done that for renal science and kidney medicine. They have taken up-to-date molecular biology, physiology made complicated at medical school, innovative therapeutics and an intimate understanding of twenty-first century holistic healthcare, and molded a superb monograph accessible to students, vital for doctors in training and definitely of value for all practitioners of kidney care.

Kidney disease is common, harmful and treatable. Early detection, accurate diagnosis, systematic monitoring and evidence-based interventions are the key to improving outcomes. Doctor Rayner and colleagues bring their experience as front-line clinicians, researchers and educators to explain kidney problems clearly and concisely, simplifying where possible and highlighting areas of controversy or ambiguity where necessary.

Given the central role of the kidneys in maintaining the *milieu intérieur*, it is not surprising that kidney diseases provide a route to understanding a range of other metabolic, immunological and genetic conditions. This book balances clarity in describing these classic disorders with insights into the interaction between diseases in multimorbid patients. The compassion of the authors as practicing physicians is revealed in the excellent chapter on planning for transplantation or dialysis.

Those who have the pleasure of reading this book will gain a deep understanding of kidney diseases, knowledge of contemporary treatments and familiarity with systems to manage populations and personalise care. They will be better doctors and able to apply the lessons learned in whichever branch of medicine they practice.

Professor Donal O'Donoghue  
President of the Renal Association  
First NHS National Clinical Director for Kidney Care  
Salford, UK



# About the Authors

**Dr. Hugh Rayner** gained a first class degree in physiology at Cambridge University before qualifying with honours at the London Hospital Medical College in 1981. He was awarded an MD from the University of Leicester for studies on experimental models of kidney disease. After a number of training posts, including a year as clinical fellow in Melbourne, Australia, he was appointed as a consultant in renal and general medicine in Birmingham in 1993.

As part of his studies for the Diploma in Medical Education from Dundee University in 1996, he presented a dissertation on the interpretation of serum creatinine and published a consensus curriculum for undergraduate renal medicine [1]. He is a full-time nephrologist, clinical lead for the West Midlands Renal Network, and continues to teach renal medicine to undergraduates and trainee doctors.

**Dr. Mark Thomas** studied Biological Sciences and Medicine as an undergraduate at Kings College London and Westminster Medical School. After postgraduate training, he was a Research Fellow at Washington University Medical School in St Louis, USA, for 3 years, studying models of proteinuric renal disease. This interest continued during Senior Registrar training in Leicester. He has been a Consultant Nephrologist and Physician at the Heart of England Foundation Trust in Birmingham since 1998.

He has had a clinical research interest in acute kidney injury (AKI) for some years, including earlier detection and intervention in AKI. He is chief investigator for the Acute Kidney Outreach to Reduce Deterioration and Death (AKORDD) study, a large pilot study of AKI outreach. He has chaired clinical guideline development groups for AKI and anaemia management in CKD for the UK National Institute for Health and Care Excellence (NICE).

**Dr. David Milford** commenced basic paediatric training in 1983 and higher paediatric training at Sheffield Children's Hospital in 1986. He undertook research in the Department of Nephrology, Birmingham Children's Hospital, into the epidemiology of diarrhoea-associated haemolytic uraemic syndrome, resulting in several

major publications and a thesis for Doctor of Medicine. He was appointed consultant nephrologist at Birmingham Children's Hospital in 1992. His interests include hypertension, acute kidney injury and renal transplantation.

## **Reference**

1. Rayner HC. A model undergraduate core curriculum in adult renal medicine. *Med Teacher*. 1995;17:409–12.

# Preface

This book provides you with the essential understanding you need to assess someone with kidney disease. The chapters follow the sequence taken during a consultation in a clinic or when clerking a patient. At each stage, we explain the principles and concepts underlying the things that make renal medicine seem difficult. We aim to answer those questions you may have been afraid to ask:

- What should I ask about and what tests should I order?
- How do I tell if kidney failure is acute or chronic?
- Are ACE inhibitors good or bad?

and many more.

Time is an important factor in kidney diseases. The same diagnosis can cause different symptoms and signs as the disease progresses over days, months, years and decades. It can be hard to make sense of one disease that can present in many different ways. To overcome this problem, we have included over 200 figures, including lots of graphs and charts. As Arthur Brisbane, the American newspaper editor said: “Use a picture. It’s worth a thousand words”.

The commonest chart is the graph of the eGFR (estimated glomerular filtration rate). This shows you how kidney function changes over time and helps you to make a diagnosis, decide when to do tests, monitor response to treatment, and plan dialysis and transplantation. And crucially, it shows the patient how they are getting on.

We have illustrated the book with case examples that are based upon patients we have cared for. Details have been altered to protect confidentiality and the patients have given written consent for information about them to be used. We hope their stories make the diseases more understandable and memorable, and that you will be stimulated to learn more about this fascinating subject.

We have included references to detailed reviews and original research studies if you wish to explore items in greater depth.

Birmingham, UK  
Birmingham, UK  
Birmingham, UK

Hugh Rayner  
Mark Thomas  
David Milford



# Disclaimer

Although every effort is made to ensure that the information in this book is accurate, the ultimate responsibility for assessment and treatment of a patient rests with the practicing physician. Neither the publishers nor the authors can be held responsible for errors or for any consequences arising from the use of information contained herein.



# Acknowledgements

We are indebted to the following for their contributions:

Roger Adkins, Colin Aldridge, Lise Bankir, Indy Dasgupta, Simon Dodds, Jo Ewing, John Evans, Agnes Fogo, Jonathan Freedman, Matthew Graham-Brown, Aarn Huissoon, Thirumala Krishna, Chris Lote, Thomas Mettang, Donal O'Donoghue, Michael Riste, Steve Smith, David Tudway, Es Will, Teun Wilmink, Chris Winearls.

Pathology images by Gerald Langman.

Clinical images by *mediahub agency*.

Additional artwork by Anthony Williams and Andrea Tibbitts.



# Contents

<b>1 Kidney Anatomy and Physiology</b> . . . . .	1
The Basis of Clinical Nephrology	
The Anatomy of the Kidney . . . . .	1
Turning Blood into Urine . . . . .	1
Changes in Kidney Function over a Lifetime . . . . .	5
References . . . . .	10
<b>2 Measuring Kidney Function</b> . . . . .	11
Quantifying Glomerular Filtration from Laboratory Tests	
How Can Kidney Function Be Measured? . . . . .	11
How Can GFR Be Estimated from Serum Creatinine? . . . . .	13
Are These Estimates Accurate and Reliable? . . . . .	15
Interpreting eGFR Values. . . . .	17
Not All Changes in Serum Creatinine Are Caused by Changes in GFR . . . . .	23
Dietary Creatinine . . . . .	24
Changes in Muscle Mass . . . . .	25
Tubular Secretion of Creatinine. . . . .	25
Serum Urea and Creatinine – Different Measures of Kidney Function . . . . .	26
References . . . . .	28
<b>3 Plot All the Dots</b> . . . . .	31
Graphs Reveal the Progression of Kidney Disease	
Analysing Variation in eGFR . . . . .	34
Interpreting Variation in an eGFR Graph. . . . .	38
Acute Kidney Injury – Equilibrating Creatinine . . . . .	42
Dealing with Missing Data . . . . .	44
Acute-On-Chronic Kidney Disease – Time in Two Dimensions. . . . .	45
References . . . . .	48

**4 How Are You Feeling?** . . . . . 51  
 The Symptoms of Uraemia

Stages of CKD . . . . . 51  
 Uraemia and the Nervous System . . . . . 52  
 References . . . . . 57

**5 Do You Have Any Long-Term Health Conditions?** . . . . . 59  
 Kidney Involvement in Multisystem Diseases

Diabetes Mellitus . . . . . 59  
 Atherosclerosis . . . . . 67  
 Renal Artery Stenosis . . . . . 67  
 Cholesterol Crystal Embolisation (Atheroembolic Disease) . . . . . 71  
 Chronic Infection and Inflammation . . . . . 73  
 References . . . . . 74

**6 Are You Pregnant or Planning a Pregnancy?** . . . . . 77  
 How Pregnancy Affects the Kidneys and Vice Versa

Risks to the Baby . . . . . 77  
 Risks to the Mother . . . . . 77  
 Pre-Eclampsia . . . . . 79  
 References . . . . . 81

**7 What Is Your Family History?** . . . . . 83  
 The Molecular Genetics of Inherited Kidney Diseases

The Glomerular Filtration Barrier . . . . . 84  
 Alport Syndrome . . . . . 84  
 Congenital Nephrotic Syndrome . . . . . 84  
 The Tubules . . . . . 86  
 The Proximal Tubule . . . . . 86  
 The Loop of Henle . . . . . 86  
 The Distal Tubule . . . . . 87  
 The Collecting Duct . . . . . 89  
 Uromodulin . . . . . 90  
 Cystic Kidney Diseases . . . . . 91  
 Kidney Tumours . . . . . 94  
 The Lower Urinary Tract . . . . . 95  
 References . . . . . 99

**8 What Have You Been Taking?** . . . . . 103  
 Nephrotoxicity from Medications and Other Chemicals

Vasoactive Drugs . . . . . 103  
 ACE inhibitors and Angiotensin Receptor Blockers . . . . . 104  
 Non-steroidal Anti-inflammatory Drugs . . . . . 107  
 Calcineurin Inhibitors – Two Sides of a Coin . . . . . 108  
 Mixing Vasoactive Drugs to Make MINT Cocktails . . . . . 108

Tubulotoxic Drugs . . . . .	110
Lithium . . . . .	110
Aminoglycoside Antibiotics – Gentamicin . . . . .	112
Interstitial Nephritis . . . . .	112
Metformin – Villain or Victim? . . . . .	112
Kidney Diseases Due to Toxins . . . . .	113
Cocaine and Heroin . . . . .	113
Mushroom Poisoning . . . . .	114
Chemical Poisoning . . . . .	114
References . . . . .	114
<b>9 Height and Weight . . . . .</b>	<b>117</b>
The Effects of Kidney Disease on Body Size and Composition	
Growing Up with Kidney Disease . . . . .	117
Transitional Care . . . . .	123
Obesity and Risk . . . . .	123
References . . . . .	123
<b>10 Blood Pressure . . . . .</b>	<b>125</b>
A Common Theme in Kidney Disease	
Diurnal Variation in Blood Pressure . . . . .	126
Controlling Blood Pressure – Key to Preserving Kidney Function . . . . .	129
References . . . . .	131
<b>11 Test the Urine . . . . .</b>	<b>133</b>
Understanding Haematuria, Proteinuria and Urinary Infection	
Haematuria . . . . .	134
How Red Cells Cross the Glomerular Filtration Barrier . . . . .	135
The Clinical Significance of Haematuria . . . . .	136
Myoglobinuria . . . . .	142
Proteinuria . . . . .	143
Nephrotic Syndrome . . . . .	149
Urine Infection . . . . .	152
References . . . . .	158
<b>12 Examine the Patient . . . . .</b>	<b>161</b>
Physical Signs Related to Kidney Diseases	
Fluid Balance . . . . .	161
How Salt and Water Is Distributed in the Body . . . . .	161
How Excess Salt and Water Can Be Removed . . . . .	163
Assessing Fluid Balance in Acutely Ill Patients . . . . .	164
Physical Signs of Kidney Disease . . . . .	167
Examine the Abdomen . . . . .	170
References . . . . .	171

<b>13 Full Blood Count, Urea and Electrolytes, Bicarbonate, Bone Profile</b> . . . . .	173
Laboratory Results and Kidney Diseases	
Anaemia . . . . .	173
Erythropoietin and the Regulation of Haemoglobin . . . . .	173
Why in the Kidneys? . . . . .	175
Kidney Disease Linked to Causes of Anaemia . . . . .	176
Acid, Base, Bicarbonate and Total CO <sub>2</sub> . . . . .	180
Vitamin D, Minerals, Bones and Blood Vessels . . . . .	181
Why is Vitamin D Activated in the Kidneys? . . . . .	184
Hyperparathyroidism . . . . .	184
Parathyroidectomy . . . . .	186
Hypercalcaemia . . . . .	189
References . . . . .	194
<b>14 Immunology</b> . . . . .	197
Serological Tests That Help Diagnose Kidney Diseases	
Do the Right Test on the Right Patient . . . . .	197
Immunoglobulins, Protein Electrophoresis, Free Light Chains in Serum and Urine . . . . .	198
Multiple Myeloma . . . . .	199
Amyloidosis . . . . .	200
Anti-nuclear Antibody, Anti-dsDNA Antibody . . . . .	202
Complement C3 and C4 . . . . .	202
Anti-streptolysin O (ASO) and Anti-DNAse B Antibodies . . . . .	204
Anti-neutrophil Cytoplasmic Antibody (ANCA) . . . . .	204
Anti-glomerular Basement Membrane Antibody (Anti-GBM ab) . . . . .	210
Anti-phospholipase A <sub>2</sub> Receptor Antibody (Anti-PLA <sub>2</sub> R ab) . . . . .	211
References . . . . .	213
<b>15 Image the Urinary Tract</b> . . . . .	215
Strengths and Weaknesses of Different Radiology Modalities	
Ultrasound . . . . .	215
Appearances in Kidney Disease . . . . .	215
Urinary Tract Obstruction . . . . .	220
Isotope Renography . . . . .	223
Computed Tomography . . . . .	226
The Risks and Benefits of Using Contrast Media . . . . .	227
References . . . . .	229
<b>16 Should We Do a Kidney Biopsy?</b> . . . . .	231
Balancing the Diagnostic Benefits Against the Clinical Risks	
‘Primum Non Nocere’ – First, Do No Harm . . . . .	231
Is It Diabetic Nephropathy? . . . . .	232
References . . . . .	236

<b>17 Make a Plan</b> .....	237
When and How to Prepare for End-Stage Kidney Disease	
Understanding Risk and Predicting the Future .....	237
Competing Risks: Dialysis or Death? .....	240
Prognostication: “Be Prepared” .....	241
Writing Letters to Patients .....	248
Choosing Treatment: Transplant, Haemodialysis, Peritoneal Dialysis or No Dialysis? .....	249
When Should Dialysis Be Started? .....	249
Care of the Whole Person .....	250
References .....	251
<b>18 Renal Replacement Therapy</b> .....	255
Common Problems in Dialysis and Transplant Patients	
Haemodialysis .....	255
Vascular Access .....	255
Complications of a Haemodialysis Catheter .....	262
Peritoneal Dialysis .....	262
Fluid Balance in a Dialysis Patient .....	263
Kidney Transplant .....	265
Causes of a Decline in Transplant Function .....	266
Infection .....	267
Malignancy .....	269
References .....	273
<b>19 Epilogue</b> .....	275
Scaling-Up Kidney Care from One Individual to a Whole Population	
References .....	277
<b>Multiple Choice Questions</b> .....	279
<b>Multiple Choice Question Answers</b> .....	289
<b>Index of Case Reports</b> .....	291
<b>Index of Histopathology, Radiology and Clinical Images</b> .....	293
<b>Index</b> .....	295

# Chapter 1

## Kidney Anatomy and Physiology

### The Basis of Clinical Nephrology

**Abstract** In this chapter we explain:

- The basic anatomy and physiology of the kidney
- How kidney function changes through life

### The Anatomy of the Kidney

The kidneys are complex and beautiful organs. Their internal structure is revealed by anatomical studies using light and electron microscopy (Figs. 1.1, 1.2, 1.3, 1.4 and 1.5).

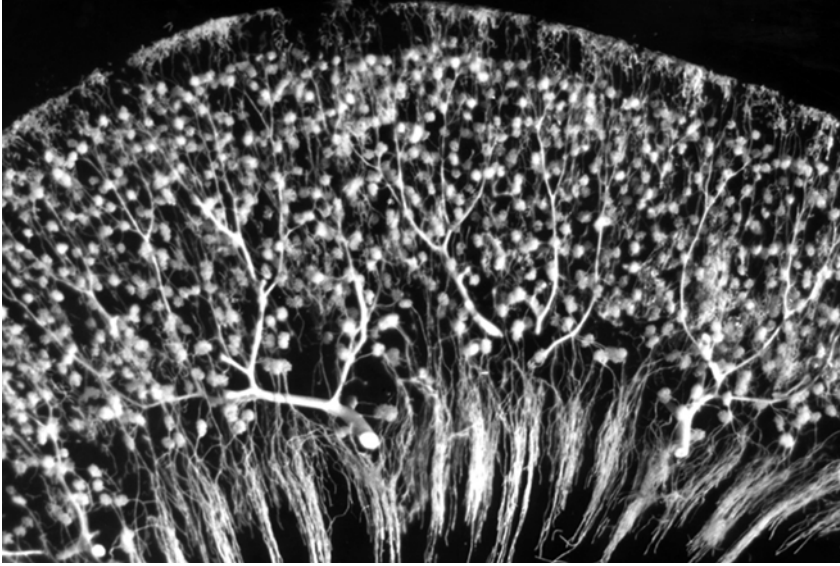
### Turning Blood into Urine

The kidneys are central to homeostasis [2]. Through exquisite sensory mechanisms [3] they regulate blood pressure, water [4], sodium [5], potassium [6], acidity [7], bone minerals [8], and haemoglobin. But their core function is the excretion of the waste products of metabolism in urine.

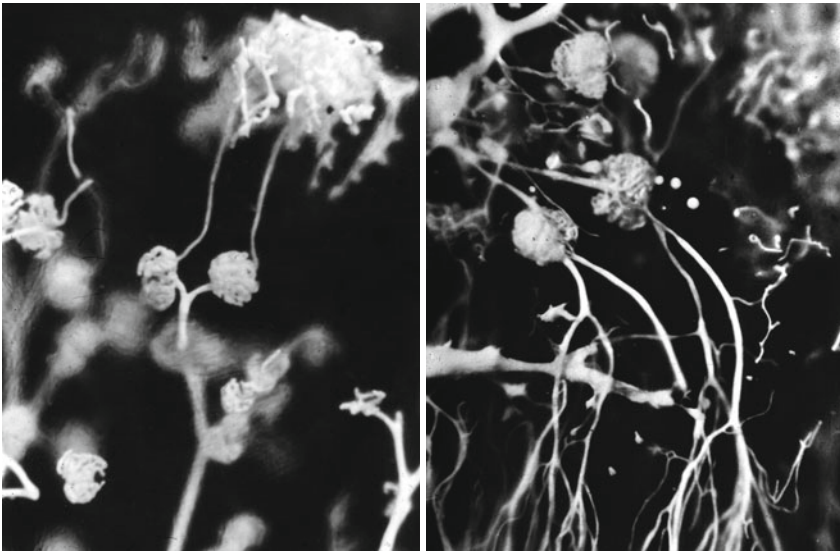
About 22 % of cardiac output goes to the kidneys and about 20 % of the plasma is filtered, producing about 170 L of glomerular filtrate per day. Ninety-nine percent of this is reabsorbed as it flows along the nephrons so only about 1.5 L of urine is produced per day.

Filtration occurs through the glomerular filtration barrier [9]. This is made up of five layers [10] (Fig. 1.6):

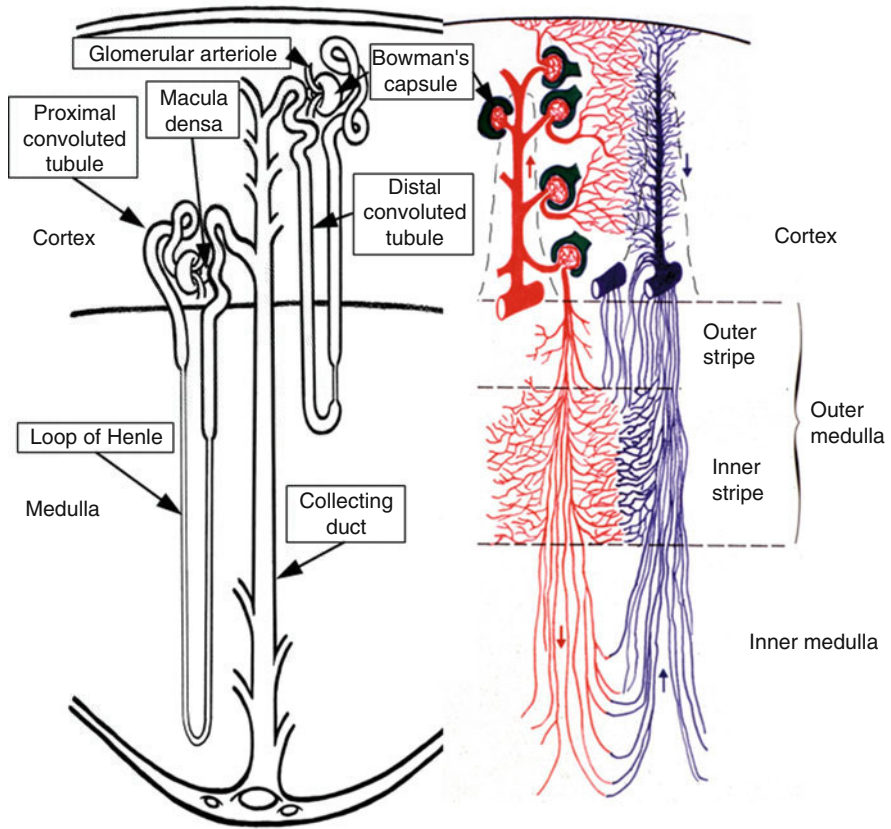
- the glycocalyx covering the surface of the endothelial cells
- holes (fenestrations) in the glomerular endothelial cells
- the glomerular basement membrane
- the slit diaphragm between the foot-processes of the podocytes
- the sub-podocyte space between the slit diaphragm and the podocyte cell body



**Fig. 1.1** Longitudinal section through the cortex and outer medulla of a rabbit kidney in which the artery has been injected with white Microfil. Microfil has filled the arteries, arterioles, glomerular tufts and the early part of the post-glomerular capillaries in the cortex and outer medulla (Courtesy of Dr Lise Bankir, Centre de Recherche des Cordeliers, Paris, France)



**Fig. 1.2** Rabbit kidney injected with white Microfil through the renal artery. *Left:* detail of a longitudinal section showing a small part of the superficial cortex. The glomerular tufts of two superficial glomeruli are visible with their post-glomerular capillaries located in the very superficial cortex. *Right:* detail of a longitudinal section showing part of the deep cortex and the outer stripe of the outer medulla. The glomerular tufts of two juxtamedullary glomeruli are visible with their efferent arterioles that run towards the outer medulla where they give rise to vascular bundles (Courtesy of Dr Lise Bankir, Centre de Recherche des Cordeliers, Paris, France)



**Fig. 1.3** Nephrons and their blood supply. *Left:* a short looped- and a long looped-nephron. *Right:* the different vascular territories and their location in the four renal zones. For clarity, the cortex has been widened and the inner medulla compressed

The composition of glomerular filtrate is determined by the structure, arrangement and electrical charge of the collagen protein molecules that form the filtration barrier. So glomerular filtration is both size-selective and charge-selective; molecules that are too large or too highly charged cannot get through.

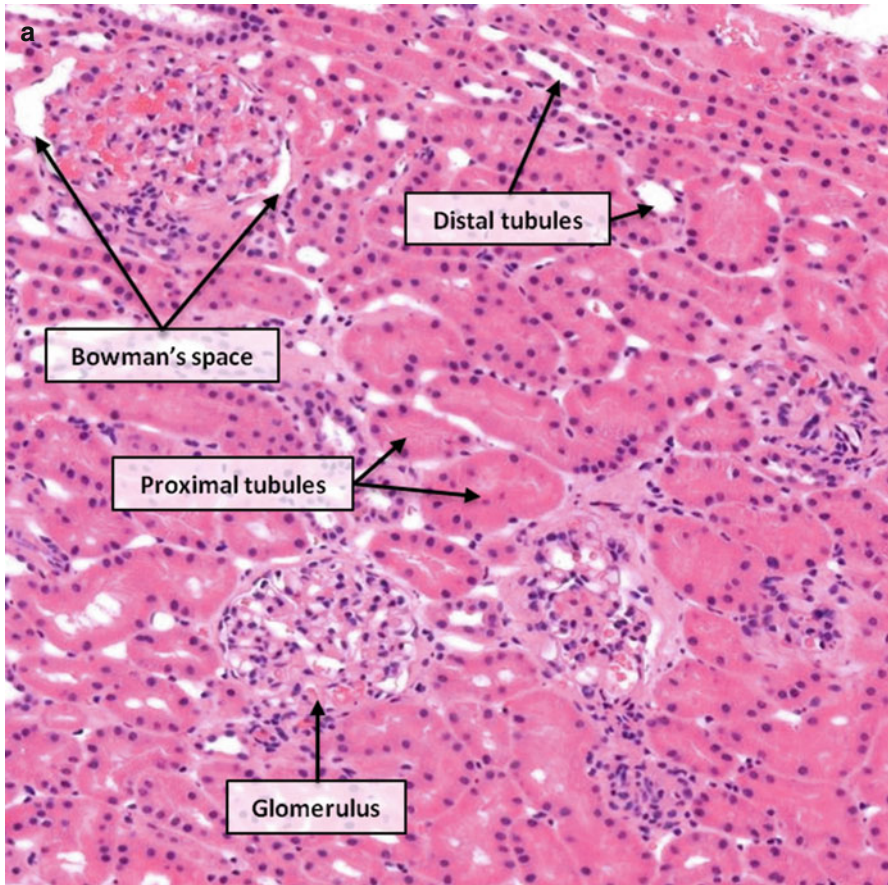
A substantial amount of albumin does get through the barrier, between 3.3 and 5.7 g per day. A proportion passes from the sub-podocyte space through the podocytes by transcytosis [11]. Passage of albumin through the barrier is increased by angiotensin II. Almost all the filtered albumin is reabsorbed by active uptake into the proximal tubular cells [12].

A simple model of the haemodynamics of glomerular filtration can be made from a garden hose (Fig. 1.7).

Glomerular filtration is held constant over a wide range of systemic and renal artery pressures by a process called autoregulation. Constriction and dilatation of the afferent arteriole is controlled by the macula densa, which is adjacent to the glomerulus. The macula densa senses the flow of sodium chloride through the

tubule next to it. When this flow is increased, the macula densa causes constriction of the afferent arteriole to reduce the glomerular filtration rate.

Conversely, if the pressure of blood flowing into the kidney falls, the resistance in the afferent arteriole is reduced to maintain the pressure within the glomerulus. If the inflow pressure continues to drop, the efferent arteriole constricts under the influence of angiotensin II. This maintains the filtration pressure within the glomerulus. In our simple model (Fig. 1.7) pressing on the end of the hose represents the effect of angiotensin II, increasing the resistance to flow of blood out of the glomerulus via the efferent arteriole.



**Figs. 1.4 (a, b)** Light micrographs of normal renal cortex with the main structures indicated. Haematoxylin and eosin; **a**  $\times 100$ , **b**  $\times 200$

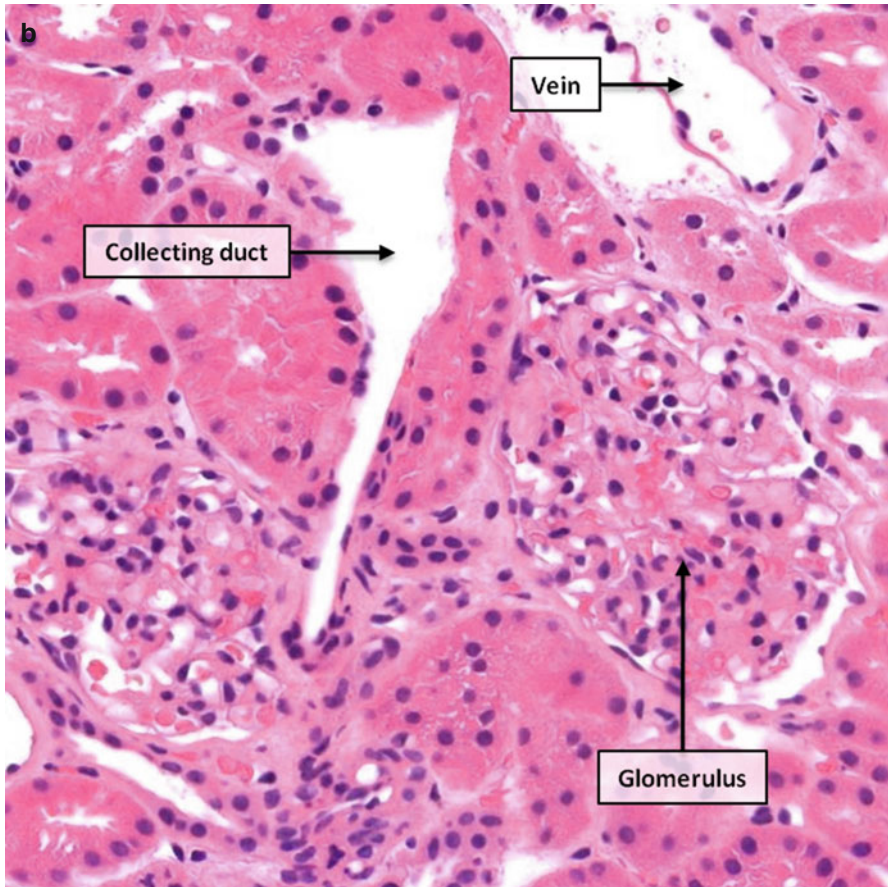
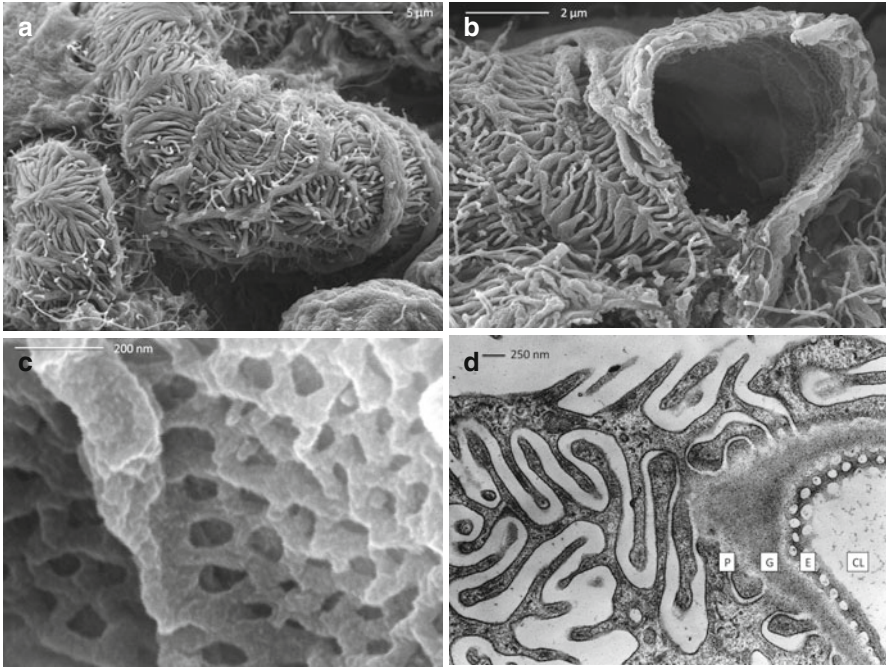


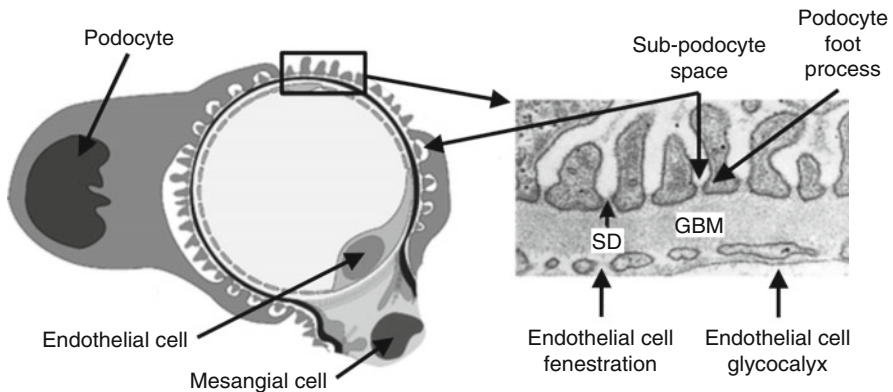
Fig. 1.4 (continued)

## Changes in Kidney Function over a Lifetime

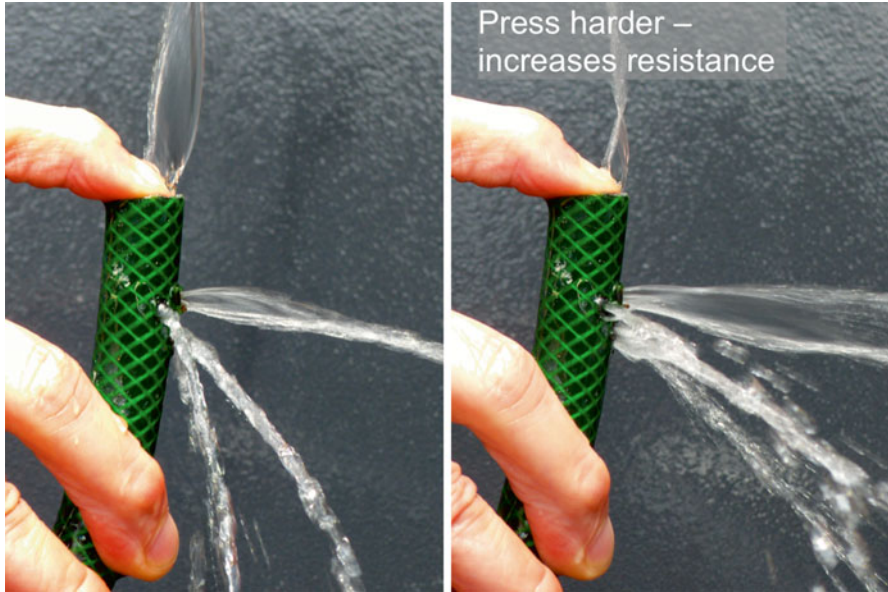
In the uterus, only about 2 % of cardiac output goes to the kidneys. Excretion of waste products produced by the foetus is via the placenta. Renal blood flow increases rapidly in the first week after birth as flow in the aorta increases and renal vascular resistance falls. By 1 month of age it has doubled and by 1 year it has reached adult levels in proportion to body size. Similarly, glomerular filtration rate (GFR) is about 10 % of the adult value at birth, rises rapidly in the first month and reaches adult levels by 1 year of age (see Fig. 1.8).



**Fig. 1.5** Scanning electron micrographs of a mouse glomerular capillary. (a) The surface of a capillary showing podocyte (5000 $\times$  by SecretDisc). (b) A cut open capillary revealing the endothelial lining (10,000 $\times$  by SecretDisc). (c) The inner surface showing fenestrations in the endothelial cells (100,000 $\times$  by SecretDisc). (d) Transmission electron micrograph of a section of glomerular capillary wall showing the layers that form the glomerular filtration barrier. *CL* capillary lumen, *E* endothelial cell fenestrations, *G* glomerular basement membrane, *P* podocyte slit diaphragm (Image **d** made available by James D. Jamieson and the Department of Cell Biology, Yale University School of Medicine. Original 3.25 in.  $\times$  4 in. lantern slides were scanned at 600 dpi. Original magnification  $\times$ 16,000. The original work has been cropped and modified with labels) [1]



**Fig. 1.6** The cells and five structural components that form the glomerular filtration barrier. *SD* slit diaphragm, *GBM* glomerular basement membrane

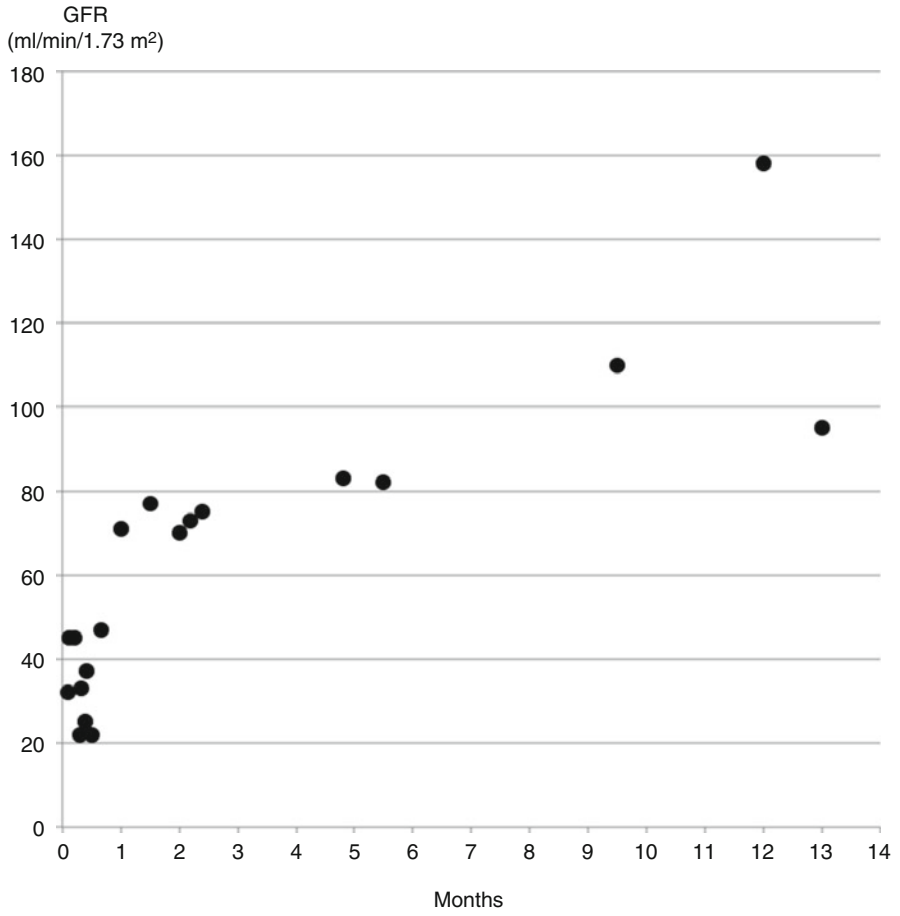


**Fig. 1.7** The hose from the tap represents the afferent arteriole. Holes have been made near the end of the hose to represent fenestrations in the glomerular capillary wall. Pressing the finger on the end of the hose increases resistance in the efferent arteriole. This increases glomerular filtration pressure and flow rate

There is huge variation between people in the number of glomeruli per kidney. The average is approximately 800,000 but numbers can vary nine fold from approximately 200,000 to 1,800,000 [14].

There is less variation between people in GFR because the size and filtration rate per glomerulus increases as the number of glomeruli decreases. On average glomeruli are twice as big in people with the fewest compared to those with the most. Enlarged glomeruli are a feature of low birth weight, massive obesity, hypertension and cardiovascular disease, and are a sign of an increased risk of chronic kidney disease [15].

After the age of about 45 years there is a steady decline in the number of functioning nephrons as glomeruli undergo sclerosis. This is reflected in a decline in kidney blood flow and GFR (see Fig. 1.9). In males at age 40 years the mean kidney blood flow is 600 mL/min/1.73 m<sup>2</sup> and GFR is 120 mL/min/1.73 m<sup>2</sup>. By age 80 years these have reduced to 300 and 70 mL/min/1.73 m<sup>2</sup> respectively [16]. Values for females are similar.



**Fig. 1.8** Glomerular filtration rate (GFR) measured by a single injection technique in infants aged up to 13 months (Redrawn using data from Aperia et al. [13])