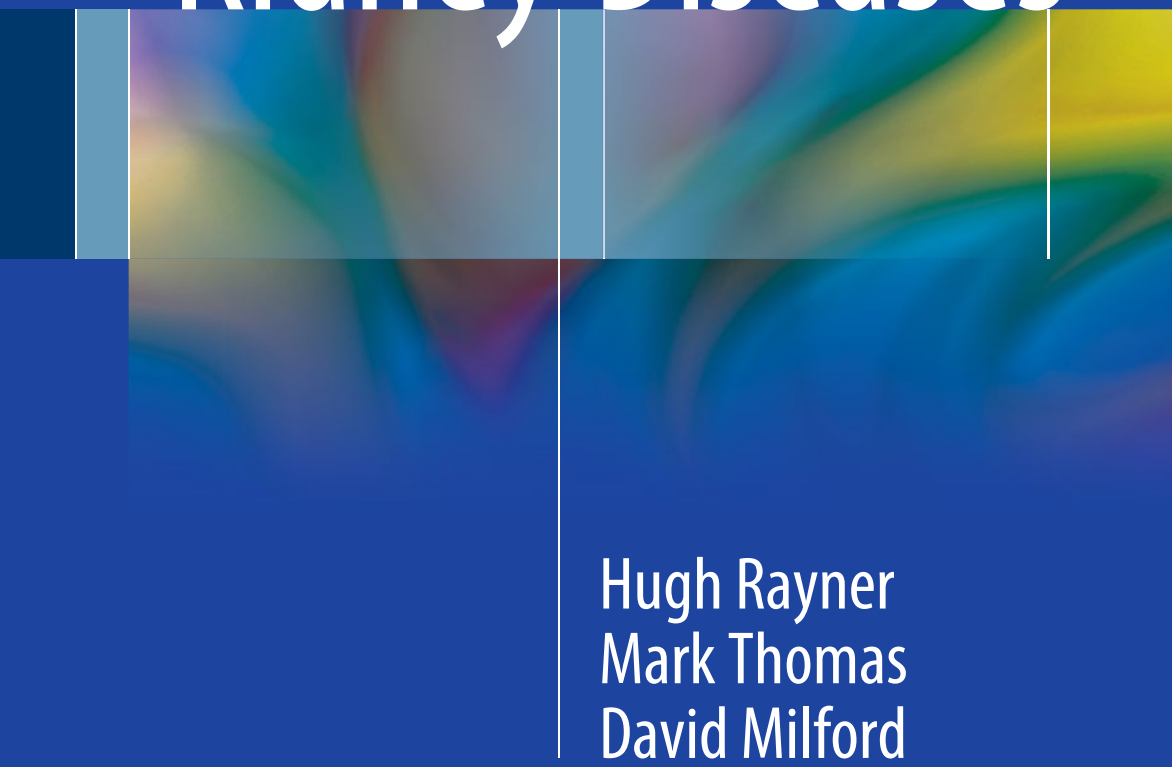
Understanding Kidney Diseases



Hugh Rayner
Mark Thomas
David Milford

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Hugh Rayner
Department of Renal Medicine
Birmingham Heartlands Hospital
Birmingham
UK

Mark Thomas
Department of Renal Medicine
Birmingham Heartlands Hospital
Birmingham
UK

David Milford
Birmingham Children's Hospital
Birmingham
UK

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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 — Hugh Rayner
Birmingham, UK — Mark Thomas
Birmingham, UK — 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.

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Contents

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

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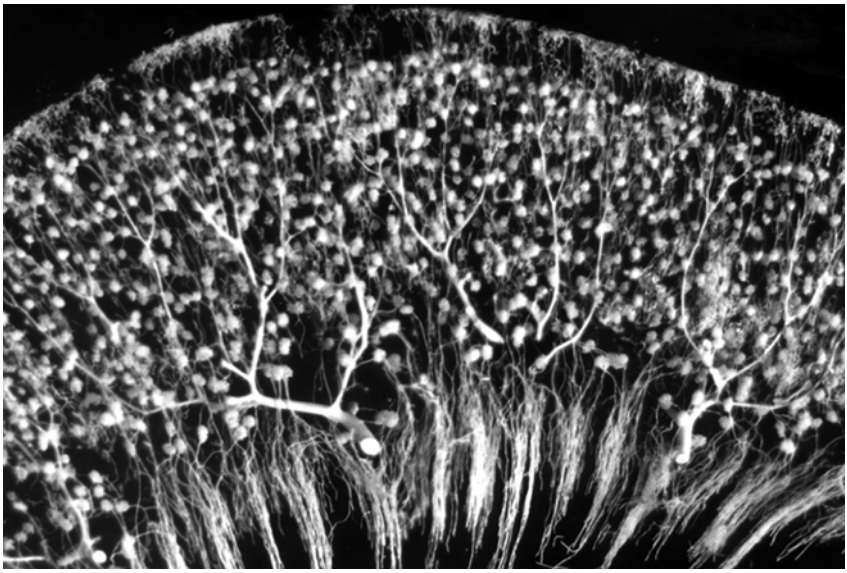


Fig. 1.1 Longitudinal section through the cortex and outer medulla of a rabbit kidney in which the artery has been injected with white Microfil. Microfil has filled the arteries, arterioles, glomerular tufts and the early part of the post-glomerular capillaries in the cortex and outer medulla (Courtesy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

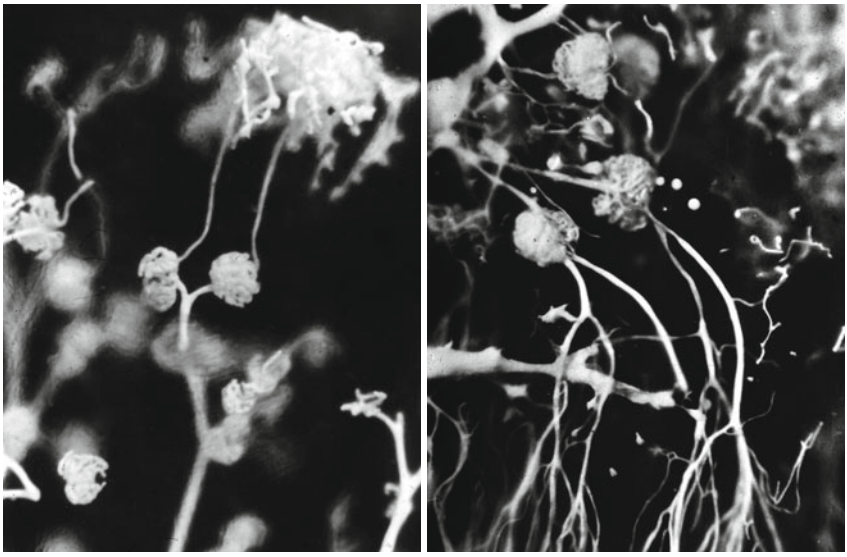


Fig. 1.2 Rabbit kidney injected with white Microfil through the renal artery. *Left*: detail of a longitudinal section showing a small part of the superficial cortex. The glomerular tufts of two superficial glomeruli are visible with their post-glomerular capillaries located in the very superficial cortex. *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)

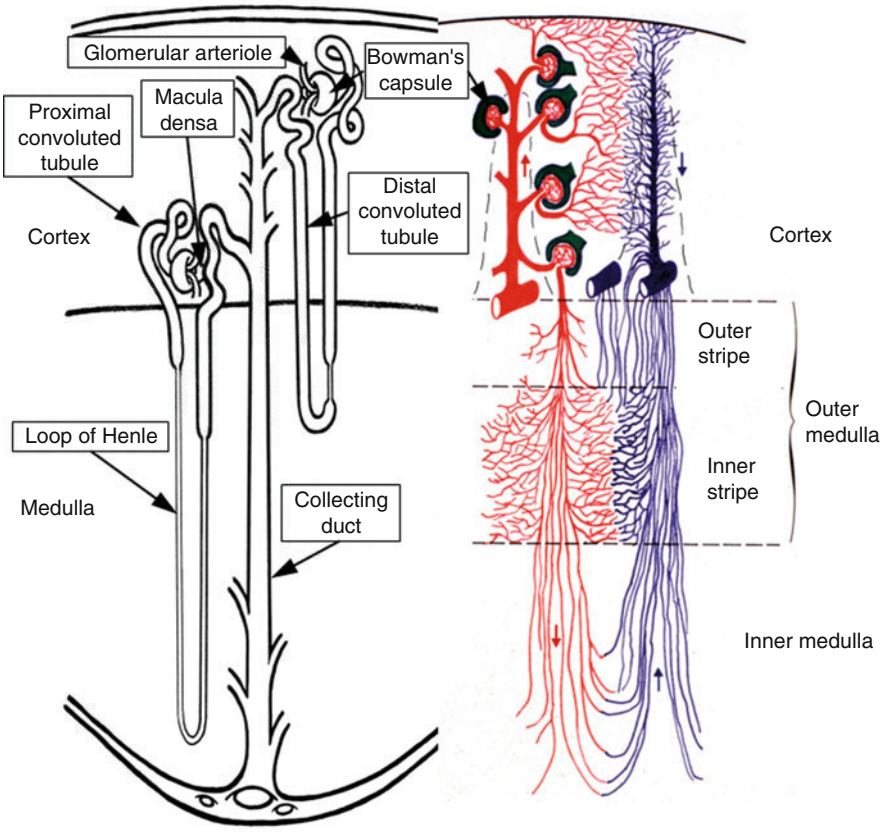


Fig. 1.3 Nephons and their blood supply. *Left*: a short looped- and a long looped-nephron. *Right*: the different vascular territories and their location in the four renal zones. For clarity, the cortex has been widened and the inner medulla compressed

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.

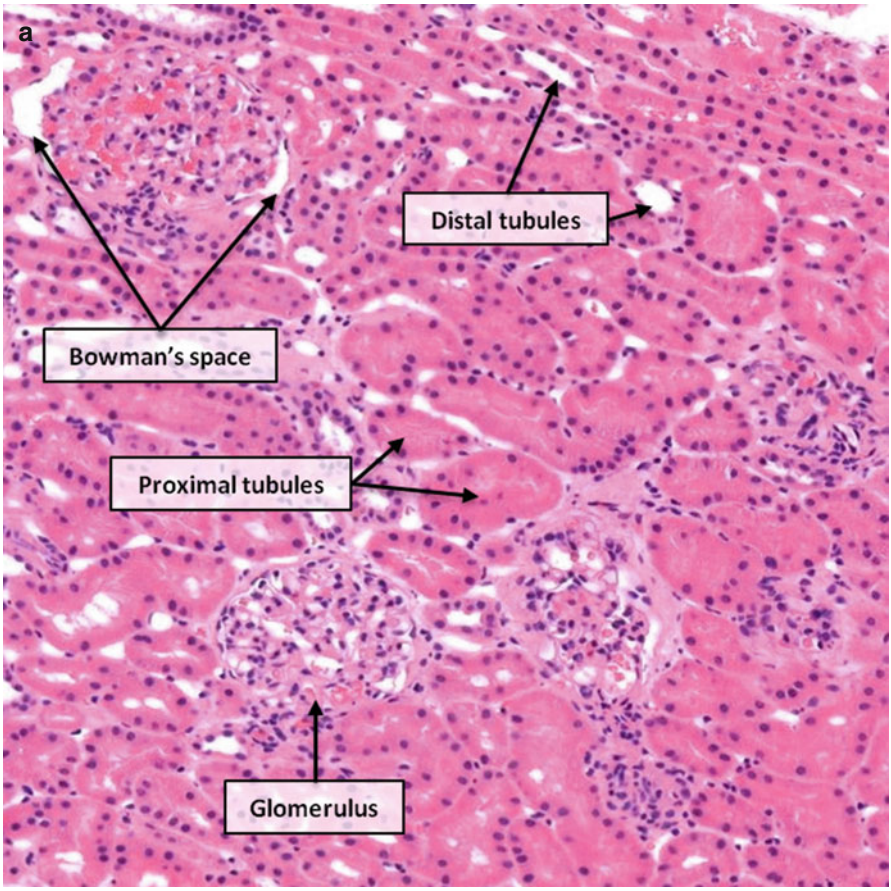
A substantial amount of albumin does get through the barrier, between 3.3 and 5.7 g per day. A proportion passes from the sub-podocyte space through the podocytes by transcytosis [11]. Passage of albumin through the barrier is increased by angiotensin II. Almost all the filtered albumin is reabsorbed 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** ×100, **b** ×200

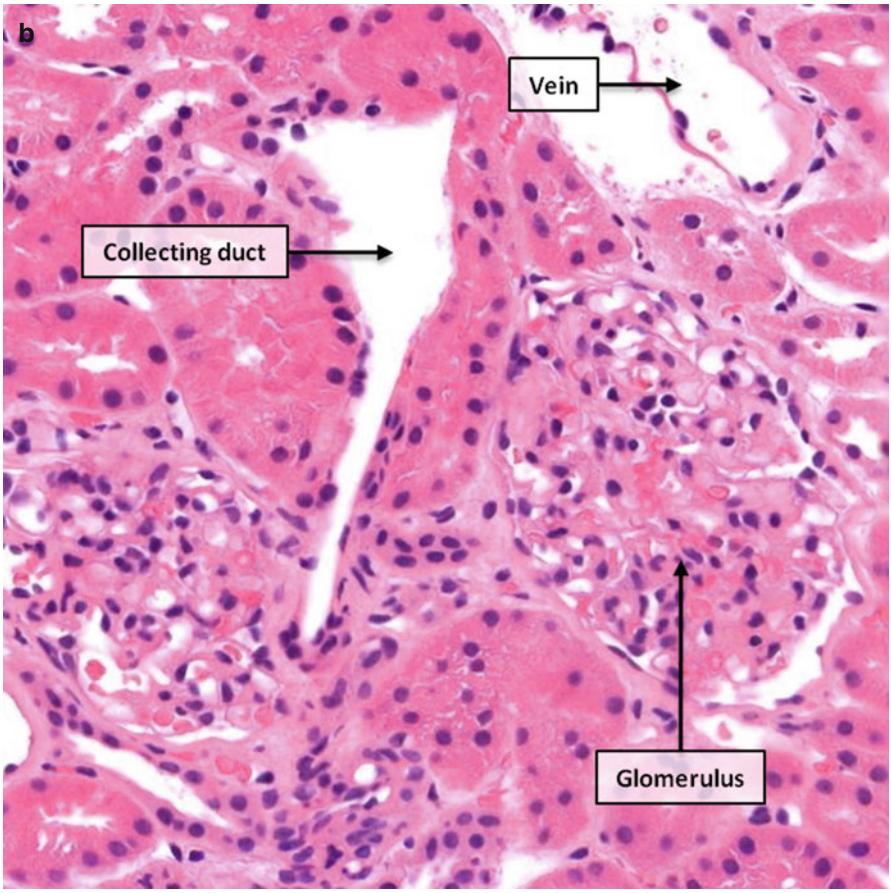


Fig. 1.4 (continued)

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).

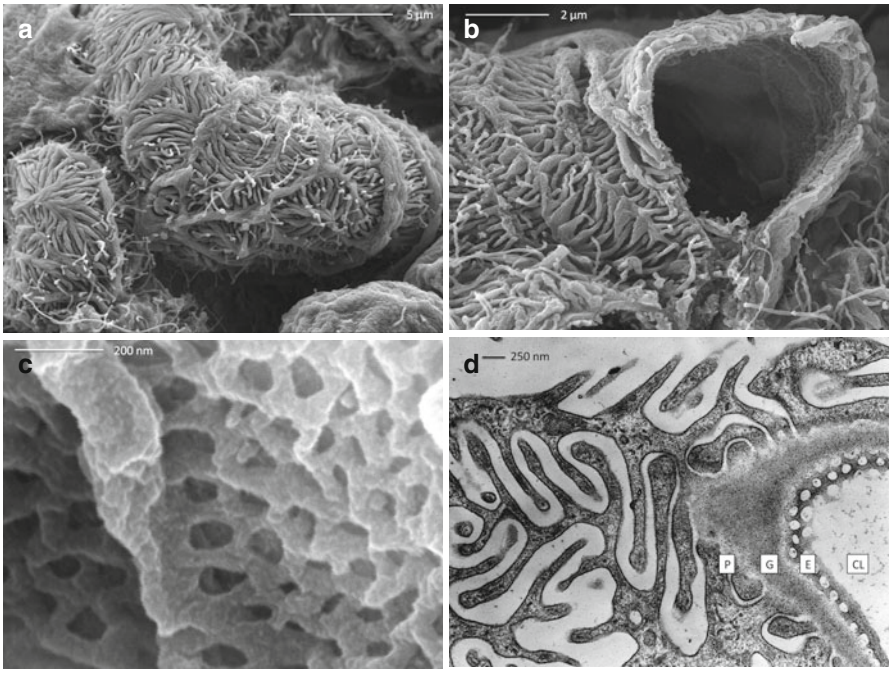


Fig. 1.5 Scanning electron micrographs of a mouse glomerular capillary. (**a**) The surface of a capillary showing podocyte (5000× by SecretDisc). (**b**) A cut open capillary revealing the endothelial lining (10,000× by SecretDisc). (**c**) The inner surface showing fenestrations in the endothelial cells (100,000× 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.×4 in. lantern slides were scanned at 600 dpi. Original magnification ×16,000. The original work has been cropped and modified with labels) [1]

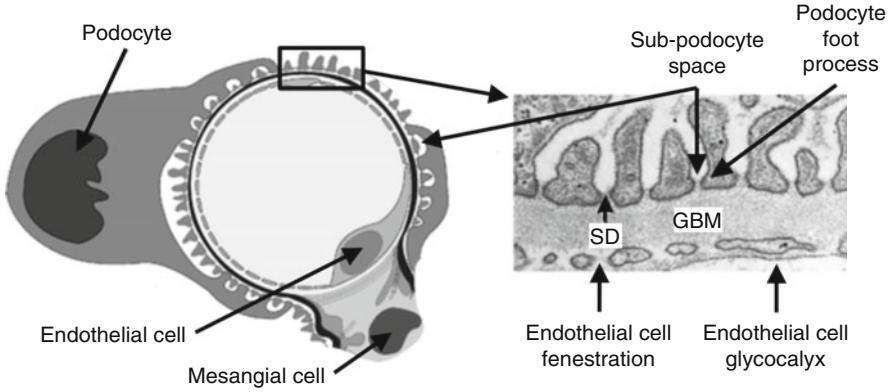


Fig. 1.6 The cells and five structural components that form the glomerular filtration barrier. *SD* slit diaphragm, *GBM* glomerular basement membrane

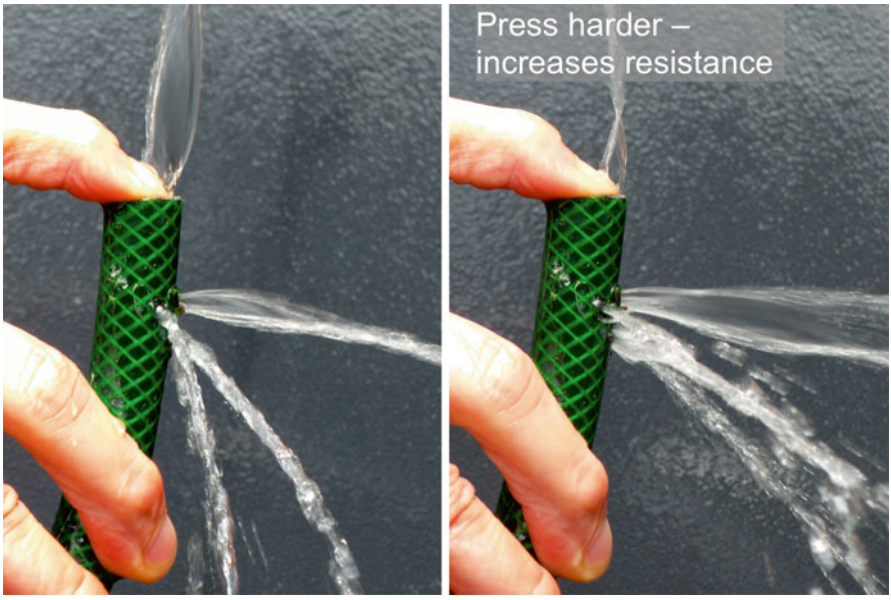


Fig. 1.7 The hose from the tap represents the afferent arteriole. Holes have been made near the end of the hose to represent fenestrations in the glomerular capillary wall. Pressing the finger on the end of the hose increases resistance in the efferent arteriole. This increases glomerular filtration 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^2 and GFR is 120 mL/min/1.73 m^2. By age 80 years these have reduced to 300 and 70 mL/min/1.73 m^2 respectively [16]. Values for females are similar.

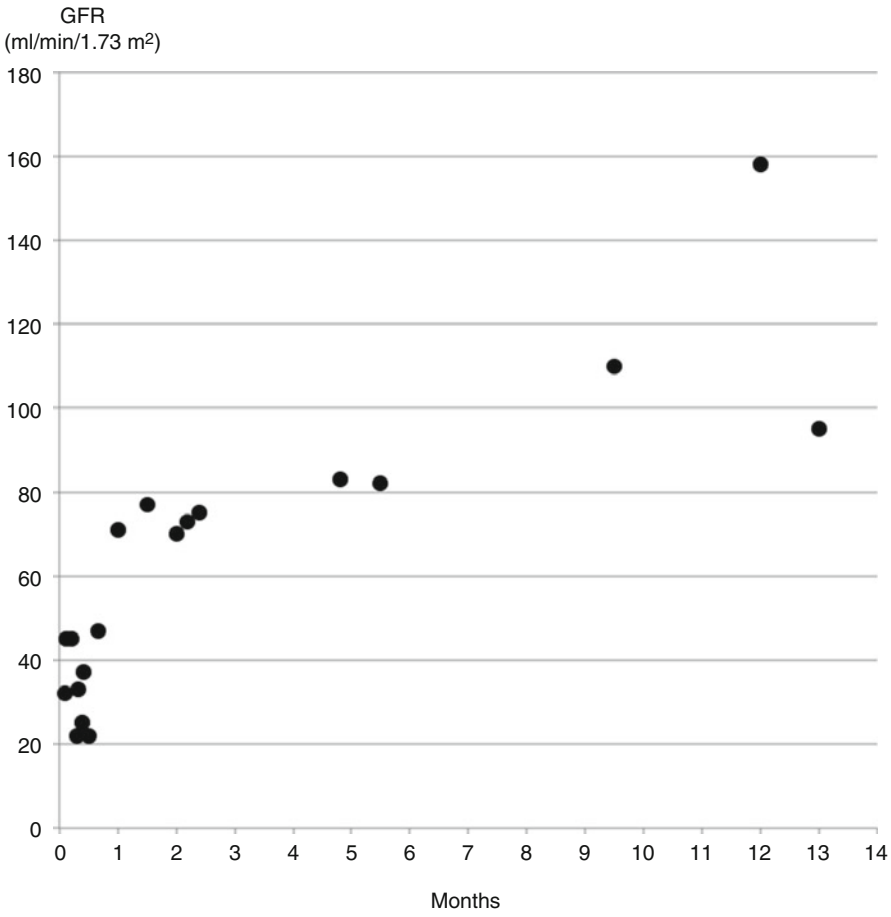


Fig. 1.8 Glomerular filtration rate (GFR) measured by a single injection technique in infants aged up to 13 months (Redrawn using data from Aperia et al. [13])