# Understanding Kidney Diseases

Hugh C. Rayner
Mark E. Thomas
David V. Milford

*Second Edition*

Springer

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# Foreword to the First Edition

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 moulded 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.

## Reviews of the First Edition

### An Excellent Nephrology Textbook for Medical Students and Junior Doctors

Renal medicine is often deemed to be a complex subject for many medical students and junior doctors. There is currently a paucity of resources which helps them understand and appreciate this fascinating speciality. This book is thus a valuable tool for both students and doctors in training as the book teaches the subject of renal medicine in a very practical and enjoyable manner.

I really like the format of each chapter in this book. Each chapter begins with an outline of the key points to help focus the reader's mind. In addition, there are also several case studies and beautiful illustrations which help to explain the fundamental aspects of each chapter.

The authors have successfully covered a wide breadth of topics within the speciality without overwhelming the reader with too much factual knowledge. This concise and well-written book will not only enhance the reader's understanding of renal medicine but also increase the confidence of both students and junior doctors when they assess a patient with kidney disease.

I thoroughly recommend this book to all medical students and junior doctors.

Weng Chin Oh
UK and Ireland Renal SpR Club

This book goes a long way to remediating the deficiencies [of other books] and is a must-have for any medical student or junior doctor struggling with the subject, as well as for doctors in training considering a career in renal medicine.

In this book the authors do not just manage to impart knowledge and information, but a career's worth of experience. This book can be used well as a reference tool.

Matthew Graham-Brown
Renalmed.co.uk

## Customer Reviews

### A Brilliant Guide for Medical Students, and Beyond!

Having just started specialty medical rotations as part of my fourth year clinical studies, this book has proved invaluable for my learning and understanding of kidney disease and renal medicine. I really like the structure of the book and the contextualised case examples per chapter. A definite must-have book for students and doctors alike!

### Great for Students

I have just started the clinical part of medical school and this textbook has been great—it has pretty much everything you need to know about the kidneys in it, set out clearly and well explained.

### Book Well Worth Reading

Beautifully written, clear and to the point. Reads like a storybook. I would highly recommend to anyone who feels nephrology is too complex and complicated to understand.

### Great Book!

Easily laid out, great for quickly brushing up nephrology skills.

Donal O'Donoghue OBE
First NHS National Clinical Director for Kidney Care
London, UK

# Foreword to the Second Edition

*Understanding Kidney Diseases* is already in its second edition after only 4 years. This is a remarkable achievement for any new clinical textbook. What makes this book so special and so successful?

Reading the various chapters makes it obvious that it is written by experienced clinicians for clinicians, as well as for others dealing with kidney disease. Each chapter provides descriptions with detailed data on actual patients. You feel like you are attending teaching rounds, where full histories, physical findings and laboratory data are presented and then discussed. The authors actually invoke Dr. Osler, the father of clinical medicine. They succeed in following his style of clinical case discussions that include pathophysiology and treatment options.

As the title of this book says, its goal is to teach "understanding". In clinical medicine it is the understanding of interrelated pathophysiology that allows clinicians to keep the wealth of individual facts together in their minds. There is a huge amount of factual knowledge transmitted in this book even though it is remarkably easy reading. This combination is a rare and amazing achievement of Dr. Hugh Rayner and his two co-authors.

The headings of chapters are refreshingly original; they entice you to continue by suggesting that the text will be fun to read. This second edition has an expanded section on Acid-Base and a new chapter on Stone Disease. The new Frequently Asked Questions chapter gives answers uniquely in plain English, thus teaching understandable communication with kidney patients. The focus on quality-of-life and end-of-life issues is welcome for dealing with advanced kidney disease. It is great that these topics were integrated with straight science, a rarity in textbooks. A large appendix of multiple-choice questions gives readers the opportunity to help their retention of factual knowledge. Furthermore, each chapter provides highly relevant and recently updated references to allow readers the opportunity for more in-depth reading on particular issues and gain further understanding of the factual statements in the text.

This book on the understanding of the many complex topics and pathophysiologies in kidney disease will be invaluable for practicing clinicians in general

medicine and in nephrology. I congratulate Drs. Rayner, Thomas and Milford for making teaching so exemplary, learning so enjoyable and the clinical facts so easy to understand and remember.

Vivant sequentes

Prof Friedrich K. Port MD, MS, FACP
University of Michigan
Ann Arbor, MI, USA

# Words with Pictures: The Gift of Graphical Data Presentation

This book can be seen as a successful product of the experience of information technology in renal clinical practice over four decades. It builds on the 1980s exploration of renal clinical IT, skilfully distilled using clinical and educational principles. It presents a general incorporation of those piecemeal insights, especially the gift of graphical data presentation. This was one of the earliest applications of computers in the clinic, and it turbo-charged the early enthusiasts in their unconstrained delving into the possibilities of digital renal clinical support (https://renal.org/history/history-of-renal-it/).

We are addressing fundamentals here. Clinical events in renal disease, and the laboratory data that calibrate them, come from an antecedent past and are destined to resolve in a conceivable future. These trajectories offer time-series that can be better understood through some form of notation. Our most familiar time-series is a written musical score—a completed trajectory, the repeated patterns of which bring deep satisfaction.

Before digitisation, published diagrams of illness trajectories were likewise drawings of completed clinical features and measurements. In real time, an incomplete, unfolding picture of a disorder is the inestimable value of graphical data presentation. Such pictorial integration of events and findings is a core guide to effective clinical practice for all but the "graphically tone-deaf". This second edition exposes and transfers clinical experience by emphasising and rehearsing those pictures.

The discrimination of a diagnostic signal from noise is a quintessential skill of the clinician. The camouflage of appearances must be penetrated to reveal the patterns of disease. An unstructured clinical situation appears chaotic (a cacophony) until some virtual order is introduced, either by the evolution of serial evidence or by revelation, in the recognition of a pattern in events. Such patterns come in various forms but a graphical message is the easiest to read and troubleshoot.

A verified pattern of disorder allows the relaxation of anxious diagnostic effort, a considered prediction of outcome and balanced treatment decisions. These are the basis of convincing reassurance of the patient and the best-founded route to their taking back some control of their well-being.

Renal Medicine was an ideal specialty in which to develop clinical IT and continues to supply model scenarios for exploring new digital techniques. This volume

from experienced polymaths is a secure guide as the digital revolution rages on. The graphical portraits of renal disorders bring them comprehensively within the grasp of aspiring clinicians and serve to promote career-long habits of clinical engagement.

Es Will FRCP, FBRS
Chairman of the British Renal Computing Group 1982-8,
Secretary of the UK Renal Registry 1997-2007

# Preface

Kidney diseases are common: in 2017 an estimated 850 million adults had kidney disease worldwide [1]. In 2013, reduced GFR was associated with 4% of deaths [2]. So, being proficient in assessing and managing someone with a kidney disease is an essential skill for all doctors.

This book provides you with the information and explanations you need to understand kidney diseases. The chapters follow the sequence taken during a consultation in a clinic or when clerking a patient on the ward. At each stage we explain the principles and concepts underlying the things that may make kidney medicine seem difficult.

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 presents 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. Crucially, it also shows patients how they are getting on.

We have illustrated the book with case examples 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. Throughout the book, we have included references to detailed reviews and original research studies if you wish to explore items in greater depth.

The first edition of this book discussed the value of writing outpatient letters directly to patients. The Academy of Medical Royal Colleges in the UK has since endorsed this as best practice and published guidance about how to do it [3]. An educational article in the *British Medical Journal* builds upon that guidance [4]. Clinic letters written to patients help them understand their condition and its treatment. In this edition we have included some frequently asked questions. We suggest you use these as an exercise in communicating effectively with patients. We have provided answers written in plain English for you to compare.

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

Birmingham, UK Hugh C. Rayner
Birmingham, UK Mark E. Thomas
Birmingham, UK David V. Milford

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# 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.

# Contents

# About the Authors

**Hugh C. 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, teaching renal medicine to undergraduates and trainee doctors.

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 retired from clinical nephrology practice in December 2019.

**Mark E. Thomas** studied Biological Sciences and Medicine as an undergraduate at King's College London and Westminster Medical School. After postgraduate training, he was a Research Fellow at Washington University Medical School in St Louis, USA, for three years, studying models of proteinuric renal disease. This interest continued during Senior Registrar training in Leicester. He has been a Consultant Nephrologist and Physician 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, anaemia management in CKD and end of life care for the UK National Institute for Health and Care Excellence (NICE).

**David V. 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.

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# Kidney Anatomy and Physiology: The Basis of Clinical Nephrology

1

## The Anatomy of the Kidney

The kidneys are complex and beautiful organs. Anatomical studies using light and electron microscopy reveal their complex internal structure (Figs. 1.1, 1.2, 1.3, 1.4 and 1.5).

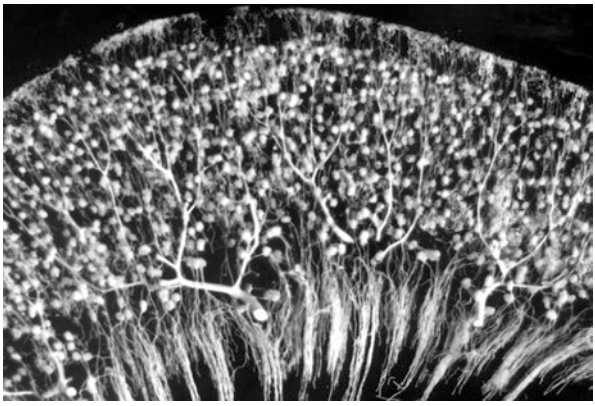

**Fig. 1.1** Longitudinal section through the cortex and outer medulla of a rabbit kidney in which the artery has been injected with white Microfil. Microfil has filled the arteries, arterioles, glomerular tufts and the early part of the post-glomerular capillaries in the cortex and outer medulla. (Courtesy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


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**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)

## Turning Blood into Urine

The kidneys play a central role in homeostasis [2]. They use exquisite sensory mechanisms [3] to 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 the cardiac output of blood goes to the kidneys and about 20% of the plasma passing through the kidneys is filtered. Of the 170 L of glomerular filtrate produced per day, 99% is reabsorbed as it flows along the nephrons, leaving only about 1.5 L to emerge as urine.

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 bodies

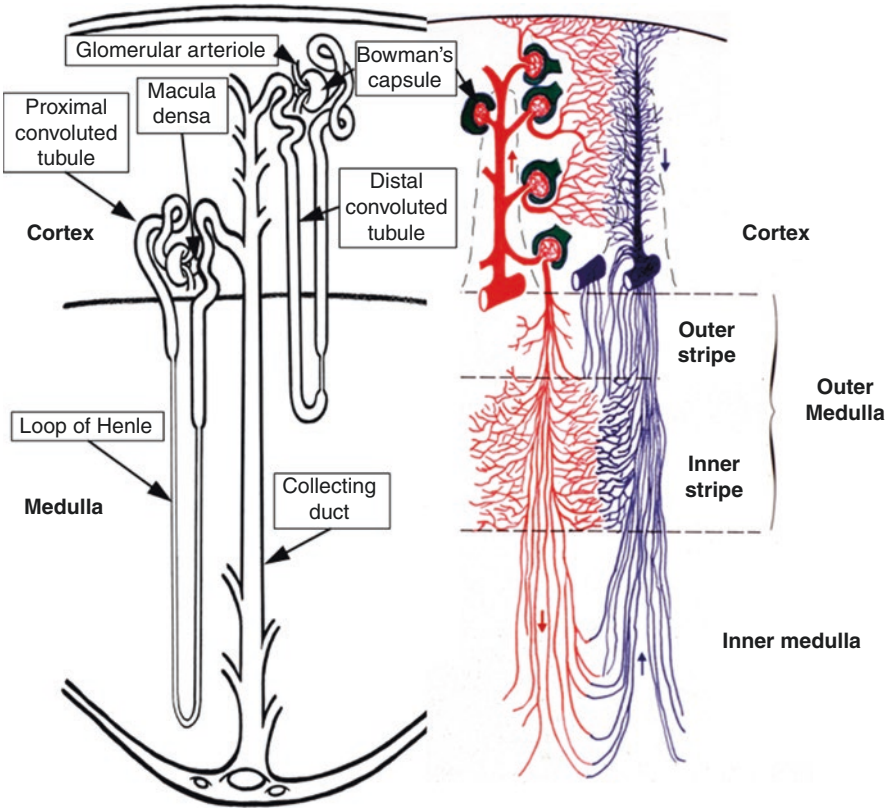


**Fig. 1.3** Nephrons and their blood supply. **Left**: a short looped- and a long looped-nephron. **Right**: the different vascular territories and their location in the four renal zones. For clarity, the cortex has been widened and the inner medulla compressed

The structure, arrangement and electrical charge of the collagen protein molecules that form the filtration barrier determine the composition of glomerular filtrate. 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. Some of this passes through the podocytes by transcytosis [11]. Angiotensin II increases the amount of albumin passing through the barrier. Almost all the filtered albumin is reabsorbed into the proximal tubular cells [12].

The 80% of plasma that is not filtered flows through the peritubular capillaries. Here, active transporters on the surface of the proximal tubules next to the capillaries pump large and protein-bound molecules into the tubular cell and then out into the lumen. This is important for the excretion of many endogenous toxins and drugs [13].

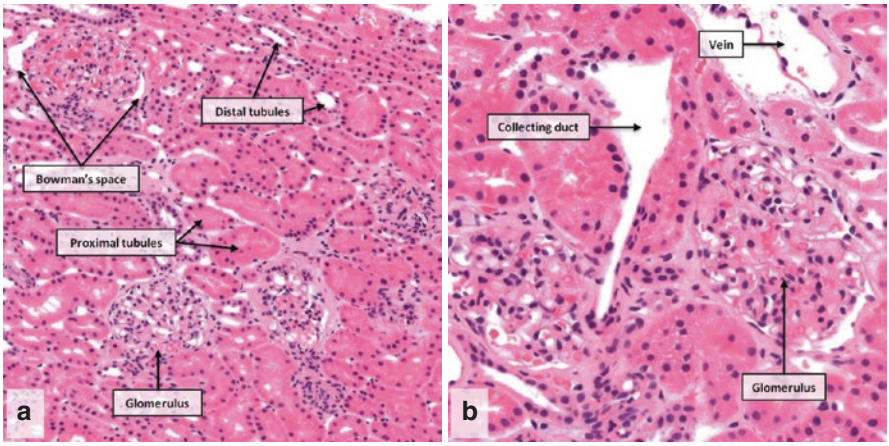


**Fig. 1.4** (**a**, **b**) Light micrographs of normal renal cortex with the main structures indicated. Haematoxylin and eosin; (**a**) ×100, (**b**) ×200

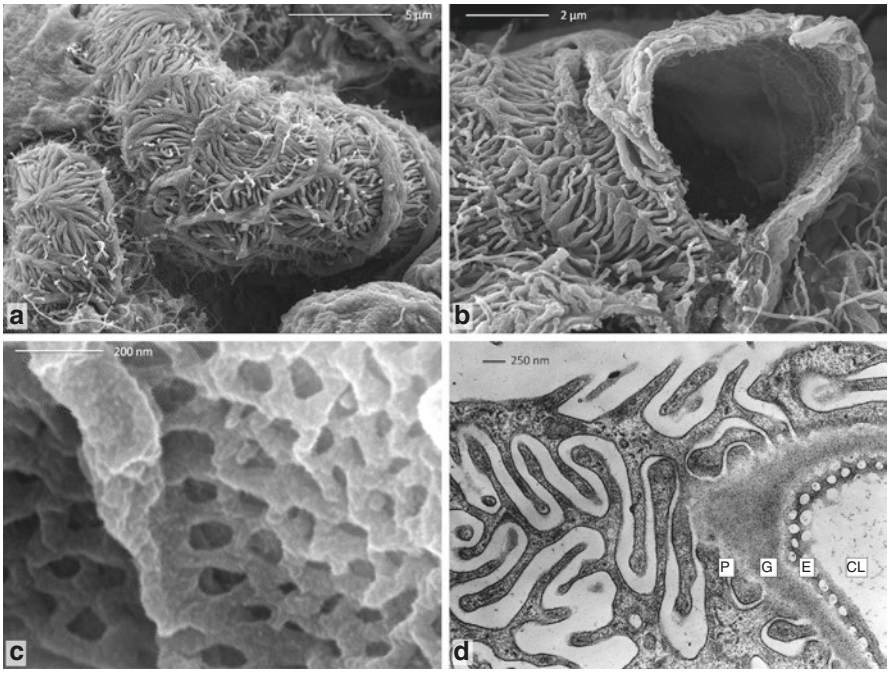


**Fig. 1.5** Scanning electron micrographs of a mouse glomerular capillary. (**a**) The surface of a capillary showing podocyte (5000× by SecretDisc). (**b**) A cut open capillary revealing the endothelial lining (10,000× by SecretDisc). (**c**) The inner surface showing fenestrations in the endothelial 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]

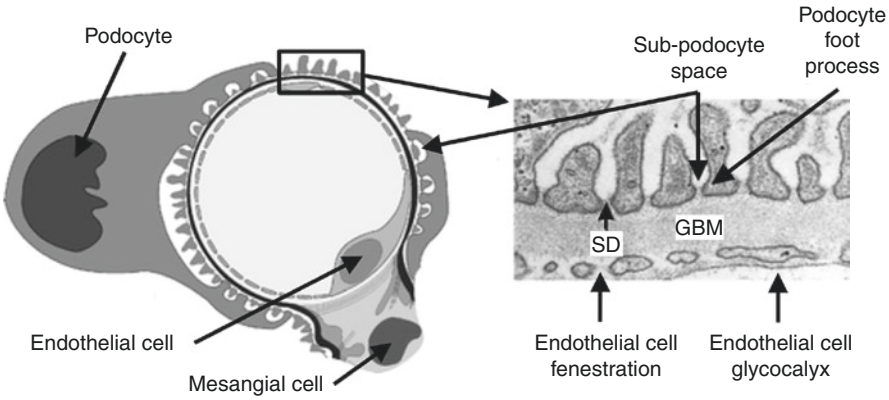


**Fig. 1.6** The cells and five structural components that form the glomerular filtration barrier. *SD* slit diaphragm, *GBM* glomerular basement membrane

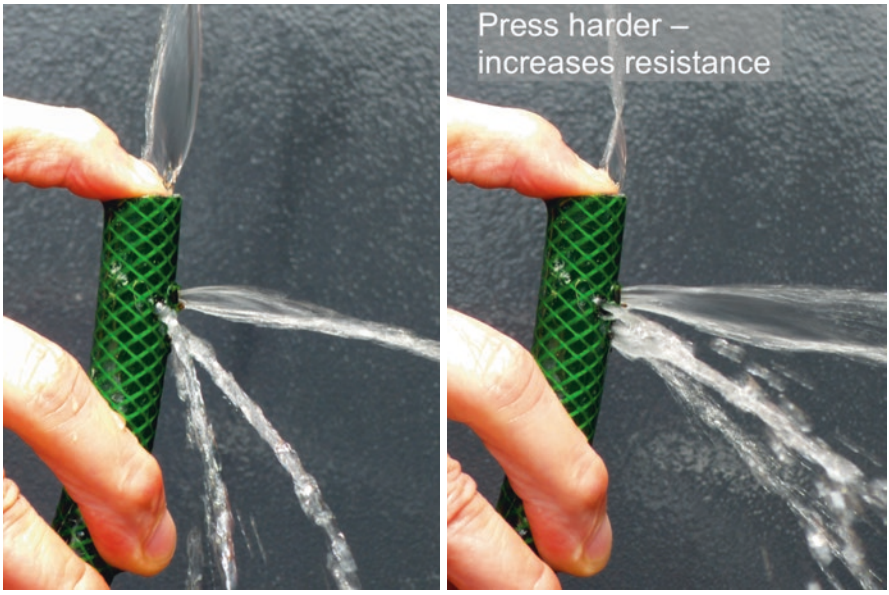


**Fig. 1.7** The hose from the tap represents the afferent arteriole. Holes have been made near the end of the hose to represent fenestrations in the glomerular capillary wall. Pressing the finger on the end of the hose simulates increased resistance in the efferent arteriole. This increases glomerular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

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, angiotensin II causes constriction of the efferent arteriole. 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.

## 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. In the first week after birth, kidney blood flow increases rapidly 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 (Fig. 1.8).

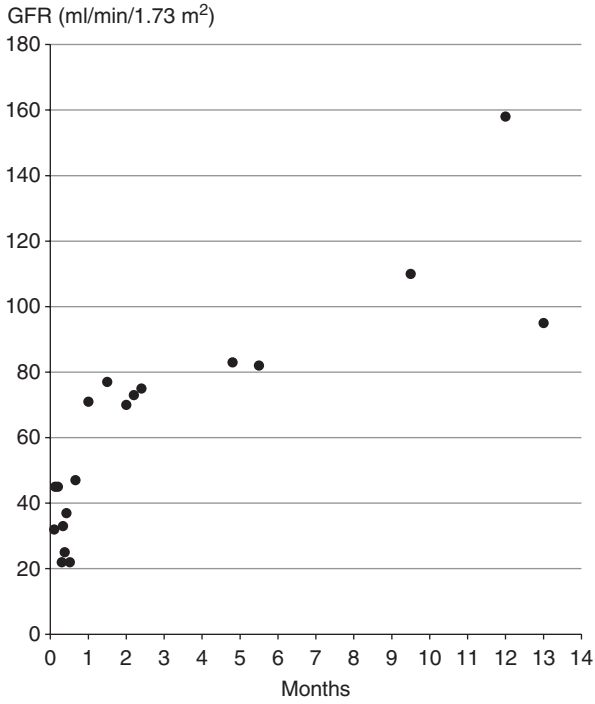


**Fig. 1.8** Glomerular filtration rate (GFR) measured by a single injection technique in infants aged up to 13 months. (Redrawn using data from [14])

There is huge variation between people in the number of glomeruli per kidney. The average is approximately 800,000 but numbers can vary ninefold from approximately 200,000 to 1,800,000 [15].

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 glomeruli compared to those with the most. Enlarged glomeruli are found in people who are born prematurely, have a low birth weight, massive obesity, hypertension and cardiovascular disease, and are associated with an increased risk of chronic kidney disease [16, 17].

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 (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 [18]. Values for females are similar. Urine albumin excretion does not change with age [19].

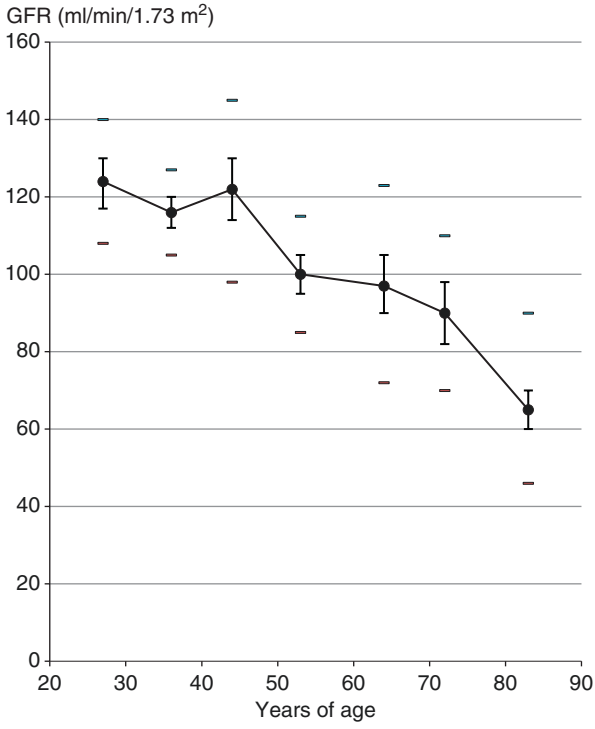


**Fig. 1.9** Changes in glomerular filtration rate (GFR) with age. GFR was measured using the 'gold standard' inulin clearance method in 75 healthy males. Error bars indicate standard deviation of the mean. Outer lines indicate standard deviation of the distribution. (Redrawn from [17])

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# Measuring Kidney Function: How to Use Laboratory Tests to Measure Glomerular Filtration Rate

2

## How Can Kidney Function Be Measured?

To assess someone's kidney function, we would ideally measure their glomerular filtration rate (GFR). This can be done using a radioisotope tracer that is cleared from the blood solely by glomerular filtration, such as Cr-51 EDTA or Tc-99m DTPA. This technique is useful for research and when precise measurements of GFR are required but it is impractical for routine repeated measurements.

Routine assessment of kidney function uses the concentration of a substance produced by the body: creatinine, urea or cystatin C. The concentration of these substances is determined by the balance between the rates of their production and excretion. When the rates of production and excretion remain stable, equilibrium is reached.

The rate of excretion of a substance by filtration depends upon the volume filtered per unit of time and the concentration of the substance in the filtrate. If the volume filtered per unit of time—the glomerular filtration rate—is kept constant, the concentration in the blood depends upon the production rate. If the production rate is kept constant, the concentration in the blood depends upon the excretion rate.

When production and excretion are stable and in equilibrium, the volume of water in which a substance is dissolved does not affect its concentration. For example, patients who are chronically fluid overloaded do not have a lower concentration of urea due to dilution. Conversely, the higher concentration of urea found in patients who are dehydrated is due to the reduced excretion of urea, not haemoconcentration.

The ideal substance to be used to measure glomerular filtration would be produced at a constant rate, freely filtered by glomeruli, and neither reabsorbed nor secreted by the tubules. Creatinine fulfils some but not all of these criteria. It is released into the bloodstream at a fairly constant rate from the breakdown of creatine in healthy skeletal muscles and is freely filtered by the glomeruli. However, 10 to 20% of total creatinine excretion is by secretion into the tubules. As GFR declines,



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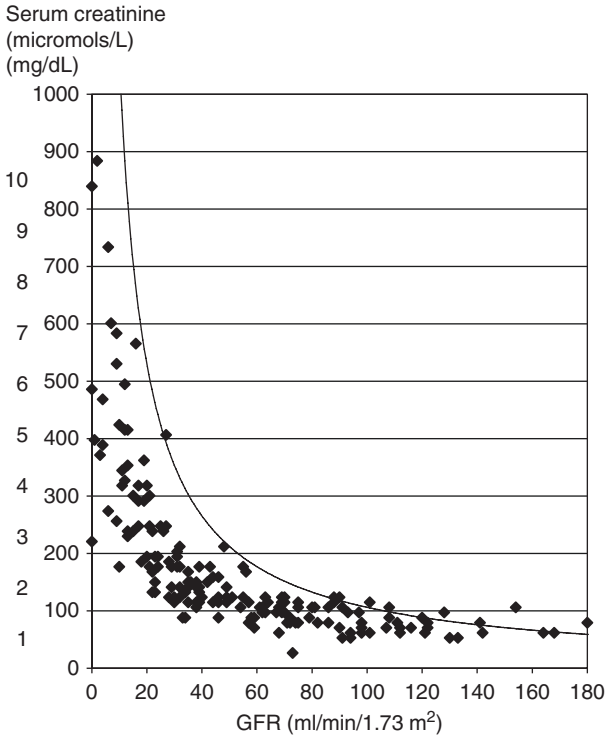


**Fig. 2.1** Simultaneous measurements of serum creatinine and GFR (by inulin clearance) in over 100 individuals. The continuous line represents the relationship between serum creatinine and GFR that would be found if creatinine was only filtered by glomeruli and not secreted by the tubules. (Redrawn from [1])

tubular secretion keeps the creatinine concentration lower than would otherwise be the case. This is shown by comparing measurements of serum creatinine and GFR (Fig. 2.1).

The curved relationship between creatinine and GFR makes changes in serum creatinine hard to interpret. Figure 2.2 shows a graph of serum creatinine against time in a man with declining kidney function. The shape of the line suggests that the rate of loss of kidney function accelerates over the years.

If we now add in GFR values, it is clear that kidney function has actually declined at a constant rate over the whole period (Fig. 2.3).

Because of the inverse curved relationship between GFR and creatinine, the drop in eGFR from 116 to 60 during the first 5 years causes a smaller increase in serum creatinine than the decline from 60 to 30 over the next 3 years.

## How Can GFR Be Estimated from Serum Creatinine?

To make serum creatinine results easy to interpret we need to convert them into estimates of the GFR (eGFR). Equations to do the conversion have been derived from databases containing simultaneous measurements of GFR, by a radioisotope clearance technique, and serum creatinine concentration. The four-variable