Postgraduate Nephrology

Third Edition

Roger Gabriel, BA. MB. MSc. FRCP. DCH

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Roger Gabriel, BA, MB, MSc, FRCP, DCH
Renal Physician, St Mary's Hospital, London

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Preface to the third edition

This third edition of *Postgraduate Nephrology* differs from its predecessors because renal medicine has changed substantially in terms of what is known and of available treatments. In addition, higher examinations in medicine now demand more basic scientific information.

Two chapters have been discarded, three chapters have been rewritten entirely and two new chapters added. There are now 52 Figures and 53 Tables. The index has been strengthened. At the end of most chapters I have included a section of 'Further reading' which will direct the reader toward review studies and original articles. Major reference books are cited at the end of the first chapter.

Three people deserve recognition for their help. First, I thank my wife for reading and correcting the manuscript. Secondly, the majority of the new diagrams reflect the skill of Mrs Louise Perks. Thirdly, the subeditor Gillian Clarke has ensured a readable text. In addition, I acknowledge stimulation and ideas generated by colleagues, medical, nursing and surgical, at St Mary's Hospital.

Postgraduate Nephrology now reflects renal medicine in the mid 1980s and will, I hope, serve candidates for higher medical examinations, doctors with renal patients, renal unit staff and the patients themselves.

R. G.

Preface to the first edition

Possession of the MRCP diploma has become the entrance to serious postgraduate training. The sooner a doctor can obtain the qualification the more quickly he can continue with his career. This monograph has been written primarily for the Membership candidate to cover the necessary facts as succinctly as possible. Some parts of the text will also be of use to final year medical students and, I hope, for the nursing staff of nephrology wards and renal units. There is no bibliography – preparation for the Membership does not allow time to consult original works.

Throughout the writing of the book I have received a great deal of help from my wife who has read the manuscript twice, corrected the spelling and grammatical errors and added paediatric information. I am also happy to acknowledge the help given me by colleagues in the Medical Unit, and the house physicians of Westminster Hospital, together with medical students of Westminster Medical School in reading the text and giving useful advice. It is a pleasure to thank Professor M. D. Milne for his kind Foreword. The editorial Staff of Butterworths have been very helpful during the writing of this book.

Any errors which are found in this book are my responsibility and if anyone has the energy to point them out to me I will try to correct them in any subsequent edition.

R. G.

Contents

Chapter 1

Aspects of structure and function

It is impossible to gain an adequate understanding of renal disease and its investigations without first appreciating something of the structure and functions of the kidney. This chapter is synoptic: details are available in textbooks of anatomy and physiology.

Aspects of structure

Figure 1.1 emphasizes the complexity of the vascular supply of the kidney in the cortex and medulla, the length of the loops of Henle and the termination of the collecting ducts in the papillae.

In the adult the bipolar length of each kidney is about 13 cm, which is approximately the length of three lumbar vertebral bodies. A kidney weighs about 150 g. The hilum lies opposite L1.

Sympathetic nerves from T11–L1 and parasympathetic fibres from the splanchnic nerves reach the kidney via the vascular pole and hilum. Arteries and arterioles are innervated. Lymphatic channels pass to abdominal nodes.

Abdominal renal structure and position

The main abnormalities recognized are:

1 Bifid kidneys of various degrees – duplex, partial duplex, duplex ureters, some joining as they run towards the pelvis and in some the ureter from the lower renal moiety entering the bladder abnormally, allowing reflux of urine (p. 75).
2 Solitary kidneys – occurring in about 1 in 1000 people.
3 Pelvic kidney – where the organ lies over the iliac bone and sacroiliac joint.
4 Horseshoe kidney – this is often supplied by a leash of renal arteries.

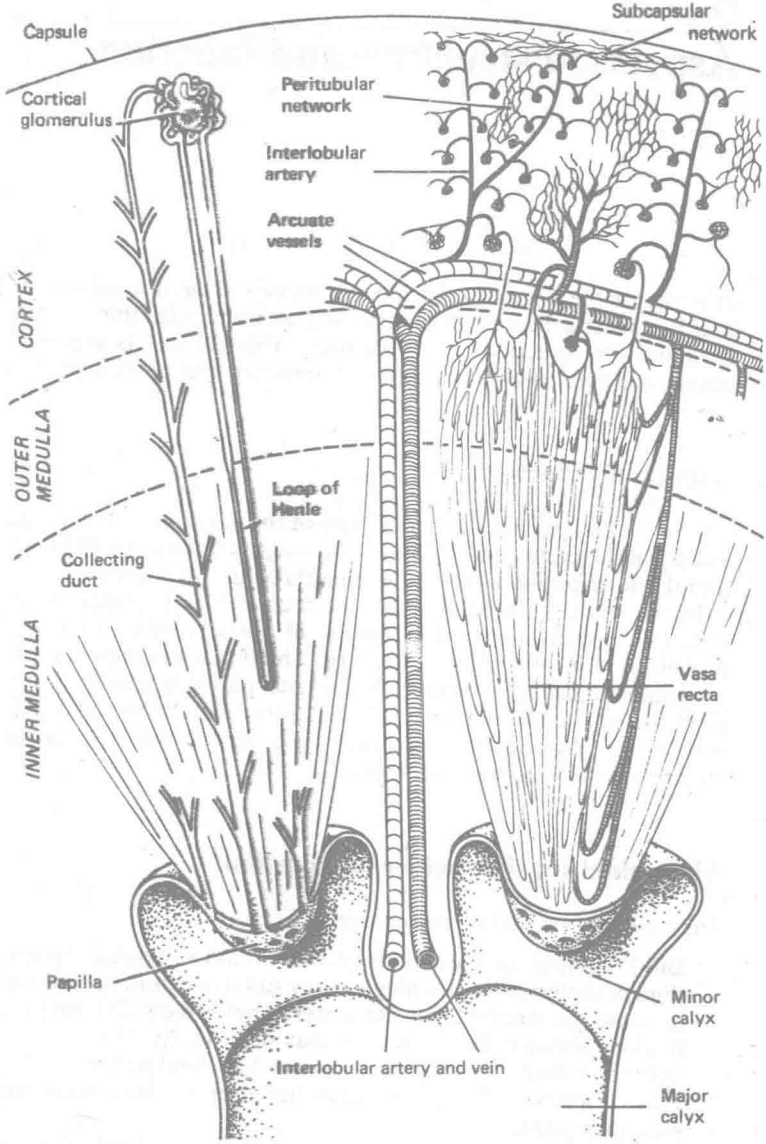

Figure 1.1 A diagram of the vascular supply and distribution of tubules in the kidney

5 Crossed ectopia when both kidneys lie on one side and are partially fused but the ureters enter the bladder in the normal manner.
6 Supernumerary kidneys.
7 Hypoplastic and dysplastic kidneys.

It is not uncommon for a kidney to have more than one artery or vein. This is only of consequence at transplantation, when multiple vessels may preclude adequate vascular anastomoses.

Aspects of function

The microvasculature of the kidney is not a rigid anatomical structure but is a capillary bed constantly altering in tone in response to changes in arterial pressure, the concentrations of local and distantly produced hormones, together with the varying needs of solute, hydrogen ion and water excretion. Glomerular filtration rate (GFR) and renal plasma flow (RPF) change little despite wide variations of perfusion pressure (*Figure 1.2*). Stability

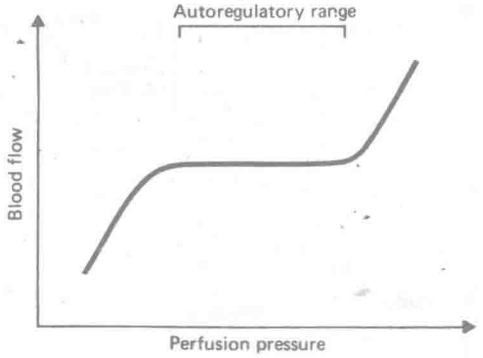

Figure 1.2 The effects of changes in perfusion pressure upon renal blood flow

of GFR and RPF is achieved by alterations in resistance in afferent and efferent glomerular arterioles and is maintained in denervated kidneys. This constancy of GFR is termed autoregulation. All organs possess similar features but autoregulation is best developed in kidney and brain. Control of renal blood flow (RBF) is central to renal function. Many of the factors which influence renal vascular tone are shown in *Figure 1.3*. It is not suggested that the various stimulatory or inhibitory factors produce effects of a

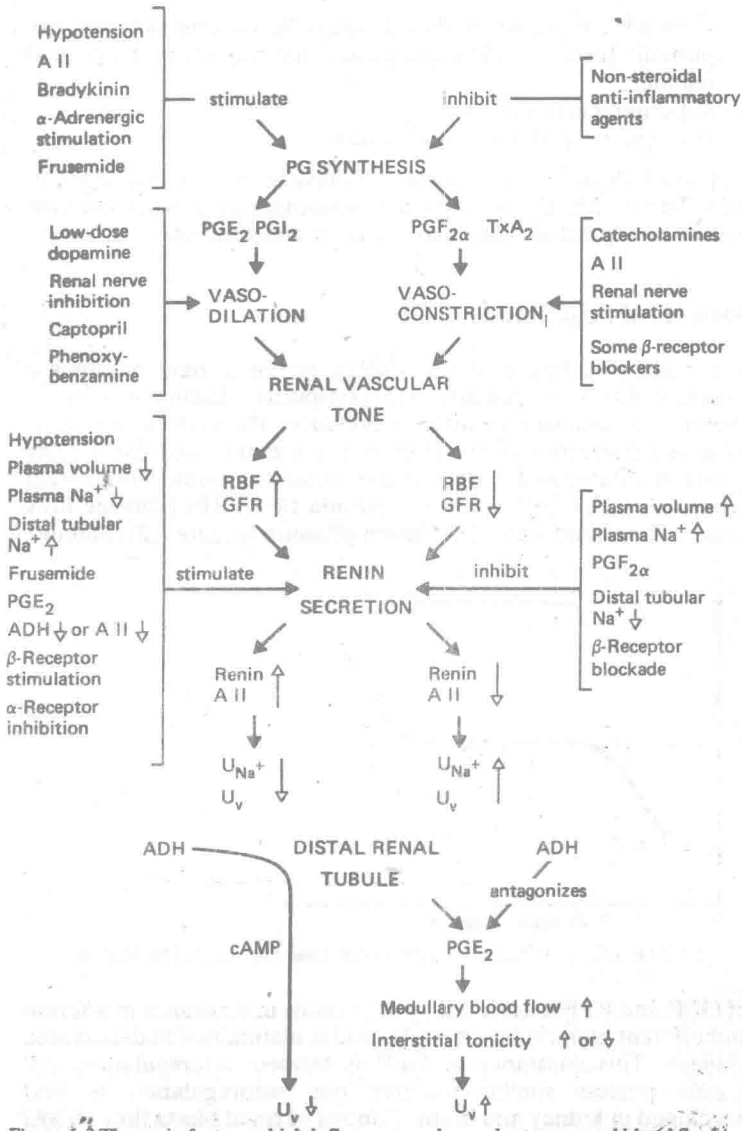

Figure 1.3 The main factors which influence renal vascular tone, renal blood flow, glomerular filtration rate and urine volume. A II = angiotensin II; ADH = antidiuretic hormone; PG = prostaglandin; PGI_2 = epoprostenol (prostacycline); TxA_2 = thromboxane; U_{Na} = urine sodium; U_v = urine volume

similar magnitude, nor are all the factors necessarily operative at any one time, but their interactions lead to continuous fine control of RBF and GFR.

Hormonal control of renal vascular tone

There are three main systems involved in the regulation of RBF:

1 Renal prostaglandin system.
2 Renin–angiotensin system.
3 Kallikrein–kinin system.

The renal medulla is very rich in prostaglandins (PGs). They act locally close to their site of synthesis. PGs are protective when vasoconstriction or ischaemia occur. Either event causes synthesis

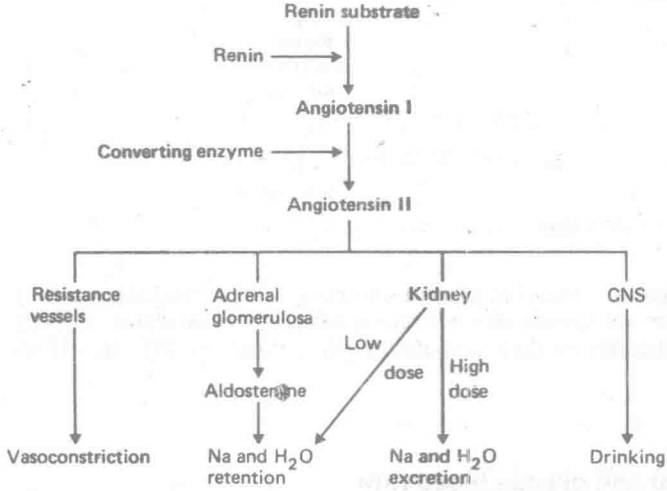

Figure 1.4 Generation and actions of angiotensin II

of vasodilatory PGE_2 and PGI_2. Whether PGs aid in modulation of renal vascular tone minute by minute is not yet known.

Renin is synthesized and stored in the granules of the juxtaglomerular apparatus. Most of the renin-containing cells abut glomerular afferent arterioles. Secretion of renin leads to the generation of angiotensin II (A II) which is a potent vasoconstrictor. It leads to the generation of aldosterone and hence to changes

in sodium and water excretion. A II may also stimulate drinking. These events are shown in *Figure 1.4*. Whether the renin–angiotensin system is a direct factor in the control of RBF is not clear but A II may function within the kidney by modulation of vasodilatory PGs.

The kinins are a series of vasodilatory polypeptide hormones: the most important are bradykinin and kallidin. Kinins are released from kinogen by the peptidase kallikrein (*Figure 1.5*).

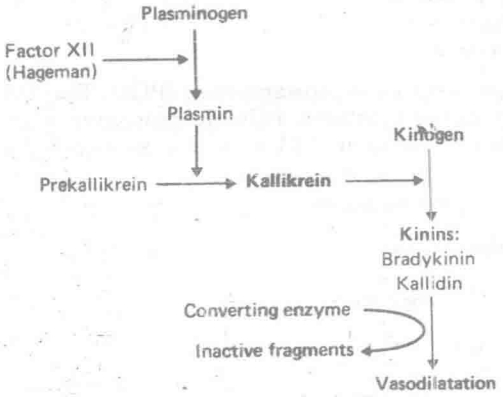

Figure 1.5 The kallikrein–kinin system

Kallikrein is found in plasma and many tissues, including kidney. It is not yet known whether kinins dilate renal vasculature directly, or indirectly by their stimulation of vasodilatory PGs (*see Figure 1.3*).

Renal and plasma blood flow

Renal blood flow is of the order of $1.2\ l \cdot min^{-1} \cdot 1.73^{-2}$ body surface area – about one-quarter of the cardiac output. RBF reaches adult proportions by the age of 3 years. After the age of 30, RBF declines such that by the age of 90 it is about one-half that of young adults. The cortex receives about 85 per cent of RBF but, because the overall flow is so high, medullary circulation is not sluggish.

In clinical practice RPF is rarely measured. The classic technique is by application of the Fick principle to the

disappearance of an indicator substance passing through the kidney and its appearance in the urine. Thus:

$$\text{RPF} = \frac{\text{urine concentration of substance} \times U_v}{\text{renal A} - \text{V difference of substance}}$$

where U_v is urine volume. The indicator used is *p*-aminohippurate (PAH). PAH clearance is about 90 per cent in one passage through the kidney and it is not extracted by other organs. Thus the formula for RPF can be simplified to:

$$\text{RPF} = \frac{\text{urine concentration of substance} \times U_v}{\text{peripheral venous concentration of PAH}}$$

For simplicity and accuracy PAH is labelled with ^{123}I. In the adult, RPF is about $650\,ml \cdot min^{-1}$. RPF and RBF are related by the formula:

$$\text{RBF} = \text{RPF} \times \left(\frac{1}{1 - \text{haematocrit}}\right)$$

Factors influencing RPF are shown in *Table 1.1.*

TABLE 1.1. Factors affecting renal plasma flow

Increase	*Decrease*
1 Supine posture	1 Upright stance
2 Pregnancy (p. 248)	2 Vigorous exercise or extreme emotion
3 Fever	3 Hypoxia
	4 Hypotension
	5 Salt and water depletion
	6 Pain

Note that factors 3–6 are pathological.

Summary of renal function

The major functions of the kidney are:

1 Regulation of volume of body fluids.
2 Regulation of solutes.
3 Regulation of pH.
4 Concentration of urine above plasma.
5 Renin secretion (p. 217).
6 1α-Hydroxylase activity (p. 183).

7 Erythropoietin production (p. 158).
8 Aid in control of systemic blood pressure via 1, 2 and 5 above.
9 Excretion of water-soluble drugs and their metabolites (p. 277).

Reference to many of the above features will be made in appropriate sections of the book. Whilst excretion of drugs is not a normal renal function, this feature is of sufficient importance to emphasize here.

Routes of water loss

A knowledge of the routes from which water is lost is essential for clinical practice. Routes and volumes are shown in *Table 1.2*.

TABLE 1.2. Approximate volumes ($ml \cdot day^{-1}$) of water loss in a healthy 70 kg male in a temperate climate

Skin	300–500	insensible
Lungs	500–700	
Gut	50–200	
Kidney	1000+	

In the presence of fever or tachypnoea, insensible losses are increased and such individuals may be too ill to drink adequately. In temperate climates loss of fluid from the gut is of clinical importance primarily in infants and patients with chronic renal failure. In the healthy adult, urine volume (U_v) can be as little as $500\,ml \cdot day^{-1}$ but frequently exceeds this, reflecting the fluid intake preference of the individual. Much of the free water clearance in normal people is positive; that is, most urine is dilute. Above 8 years of age U_v is of adult proportions.

Body fluid compartments

Sixty per cent of body weight of healthy men and 50 per cent in women is water. Women have more adipose tissue than men. One g of fat is associated with 0.1 g water; 1 g protein or glycogen is associated with 3 g water.

Total body water is divided into intracellular and extracellular fluid, the latter being interstitial and intravascular. In a 70 kg male total body water is 42 litres, 28 litres being intracellular and 14 litres extravascular. The intravascular (plasma) volume is 4 litres and interstitial volume 10 litres. Appreciation of these volumes aids logical clinical fluid balance manipulations.

Body water

Serum is about 94 per cent water by volume. The 6 per cent of solids are chiefly proteins. Serum solids can be measured by weighing a beaker containing serum, evaporating to dryness and then reweighing the beaker. Serum solids are raised in:

1 Myeloma.
2 Hyperlipidaemias.
3 Postmannitol.

Cells are about 75 per cent water by volume.

Water clearance

Free water clearance (C_W) is that volume of water which has to be added to, or removed from, urine to make it isosmotic with plasma. Thus C_W is negative in concentrated urine and positive in dilute urine.

Water excretion

The complexity of water handling by the kidney and flexibility in urine flow rate is shown in *Table 1.3*.

TABLE 1.3. Renal water excretion

Site	*Mechanism*	*Volume* ($ml \cdot min^{-1}$)
Proximal tubules	Obligatory reabsorption	120
Distal tubules	Facultative reabsorption	20
Bladder	Passive	0.5–20

Factors affecting urine flow and concentration

The major determinants of these variables are:

1 GFR and plasma composition.
2 Proximal tubular reabsorption.
3 Distal tubule and Henle loop sodium reabsorption.
4 Distal tubule and collecting duct permeability to water (ADH controlled).
5 Medullary solute concentration.

Multiple variables are involved which include disease processes, ageing and varying solute and solvent ingestion (*see also* pp. 167 and 284).

Ion excretion

The kidney has a similar complexity and flexibility in ion excretion as it has for water. The mechanisms allow maintenance of water and electrolyte balance under dietary or environmental extremes.

TABLE 1.4. Some filtered and excreted urinary ions

Ion	*Filtered* (mmol·24 h^{-1})	*Percentage absorbed*	*Urine concentration* (mmol·24 h^{-1})
Na^+	24 000	99.6	80–200
Cl^-	20 000	99.5	80–200
HCO_3^-	5 000	>99.9	2
K^+	700	93	30–150

Table 1.4 gives approximate concentration of ions filtered by glomeruli, the percentage absorbed and the amounts reaching the bladder.

Clearance

The clearance of a substance is the volume of plasma completely cleared of that substance in unit time. Clearance is calculated from the formula:

$$\frac{UV}{P} \times 100$$

where U = urine concentration of clearance substance, V = volume of urine in $ml \cdot min^{-1}$ and P = plasma concentration of clearance substance. The calculation assumes that the concentration of P is constant for the duration of the collection. Traditionally a clinical clearance study is performed over a 24-hour period but shorter intervals are adequate.

If a substance is freely filtered across glomerular capillaries – that is, is neither bound to serum protein nor sieved during filtration, is uncharged, is biologically inert and is neither secreted nor reabsorbed by tubules – then its rate of excretion is equal to its rate of filtration:

$$UV = GFR \times P$$

For substances possessing the above properties:

$$\text{Clearance} = GFR$$

Substances used to measure GFR

The following are used to derive GFR:

1 Creatinine.
2 ^{51}Cr-EDTA.
3 Inulin.

Creatinine is the most widely used; its limitations are discussed on p. 24. ^{51}Cr-EDTA (ethylenediamine tetra-acetic acid) clearance has the major advantages of accuracy and not requiring urine collection. The dose is only 3.7 megabecquerels (MBq, 100 μCi). Inulin, a polymer of fructose derived from dahlia plants or Jerusalem artichokes, is the ideal substance for determining GFR. Because the measurement of inulin is difficult, inulin GFR (C_{in}) is used only in research studies.

$$C_{in} = \frac{U_{in}V}{P_{in}} = 120 \pm 15\ ml \cdot min^{-1} \cdot 1.73\ m^{-2} \text{ body surface area}$$

Body surface area is obtained from height and weight tables. GFR rises during the first 2 years of life, remains constant to middle age and then, like RBF, declines to 50–60 $ml \cdot min^{-1} \cdot 1.73^{-2}$ surface area in old age. GFR increases by 10–20 per cent premenstrually in normal women. GFR is sometimes expressed in $l \cdot h^{-1}$ or $l \cdot day^{-1}$ and is about 7.2 and 180 respectively.