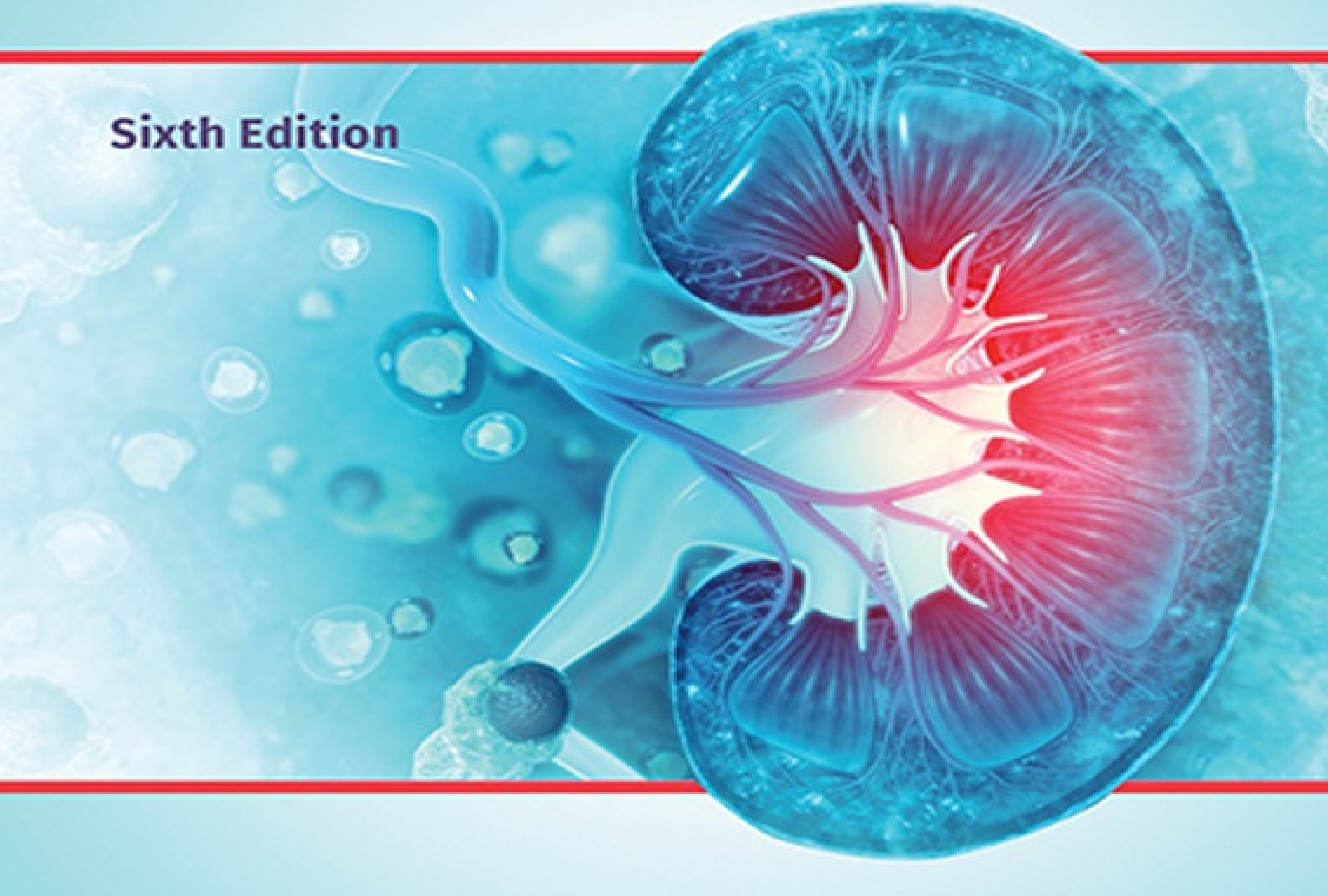
Renal Pathophysiology

THE ESSENTIALS

Sixth Edition



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Wolters Kluwer

RENAL PATHOPHYSIOLOGY
The Essentials

SIXTH EDITION

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Overview of Renal Physiology

OBJECTIVES

By the end of this chapter, you should have an understanding of each of the following issues:

- The concept of steady state or balance; the time point where there are no net changes in a measured value
- The general mechanisms by which solute reabsorption and secretion occur in the different nephron segments
- The factors regulating the glomerular filtration rate
- The mechanisms by which the glomerular filtration rate is measured in patients

Introduction

A brief review of the basic principles involved in renal physiology is helpful in understanding the mechanisms by which disease might occur. Tubular functions will be discussed, with a major emphasis on sodium and water reabsorption. The glomerular filtration rate (GFR) including its regulation and how it is estimated in the clinical setting will also be reviewed.

The kidney performs two major functions:

- It participates in the maintenance of a relatively constant extracellular environment that is necessary for the cells (and organism) to function normally. This is achieved by excretion of some waste products of metabolism (such as urea, creatinine, and uric acid) and of water and electrolytes that are derived primarily from dietary intake. **Balance** or **steady state** is a key principle in understanding renal functions. Balance is maintained by keeping the rate of excretion equal to the sum of **net intake** plus endogenous production:

$$\text{Excretion} = \text{Net intake} + \text{Endogenous production}$$

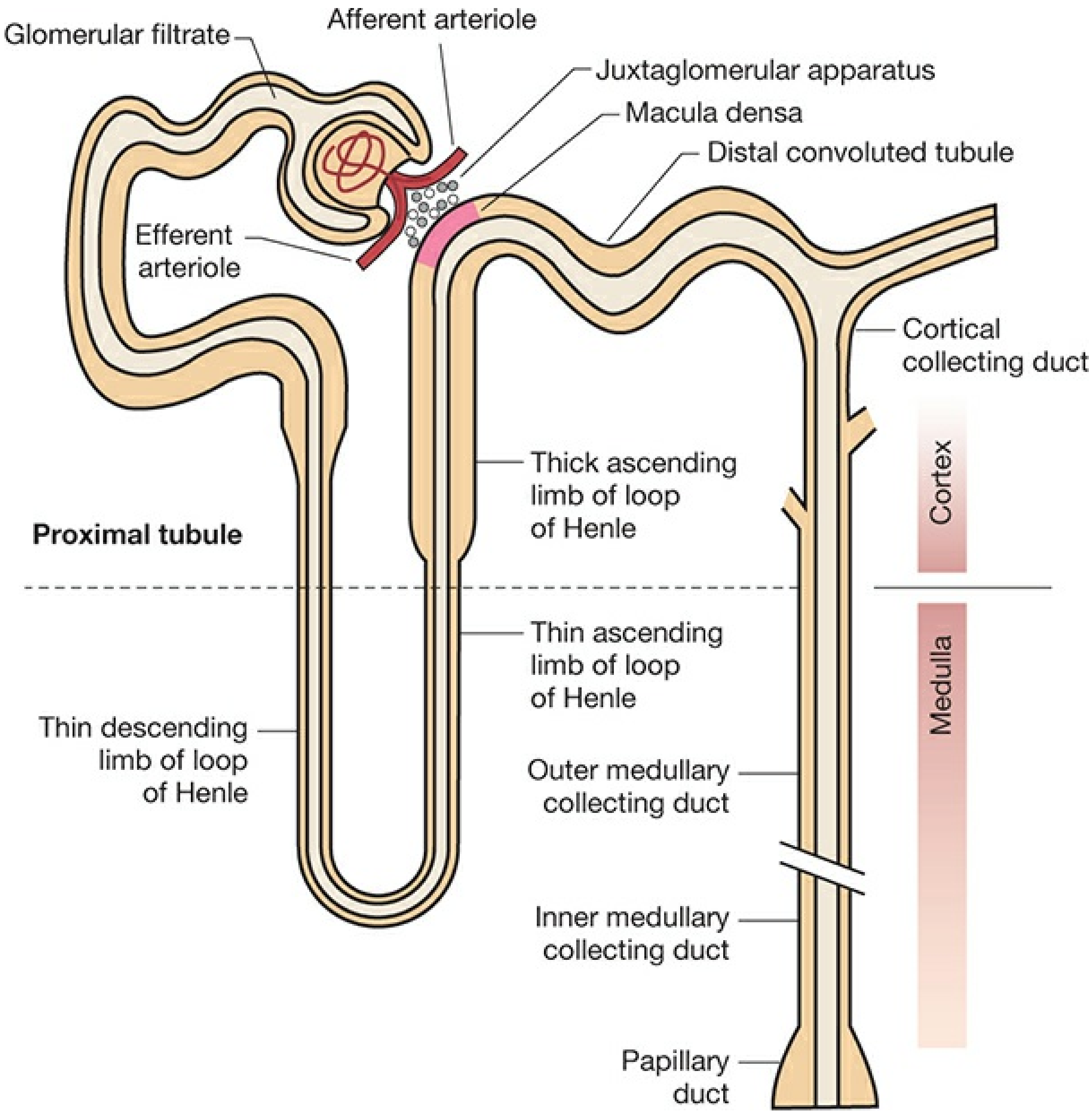
  Net intake is the excess substance remaining in the body after meeting metabolic needs. As will be seen, the kidney is able to individually regulate the excretion of water and solutes (such as sodium, potassium, and hydrogen) largely by changes in tubular reabsorption or secretion. If, for example, sodium intake is increased, the excess sodium can be excreted without requiring alterations in the excretion of water or other electrolytes.
- It secretes hormones that participate in the regulation of systemic and renal hemodynamics (renin, angiotensin II, and prostaglandins), red cell production (erythropoietin), and mineral metabolism (calcitriol [1,25-OH dihydroxy vitamin D], the major active metabolite of vitamin D).

  The kidney also performs a number of miscellaneous functions such as the catabolism of peptide hormones and the synthesis of glucose (gluconeogenesis) under fasting conditions.

Relationship Between Filtration and Excretion

The normal GFR ranges from 130 to 145 L/day (90 to 100 mL/min) in women and from 165 to 180 L/day (115 to 125 mL/min) in men. This represents a volume that is more than 10 times that of extracellular fluid and ~60 times that of plasma (see Fig. 2.5 for estimation of these volumes); as a result, survival requires that virtually all of the filtered solutes and water be returned to the systemic circulation by tubular reabsorption.

Preventing excessive urinary sodium loss is essential to the maintenance of the extracellular and plasma volumes (see Chapter 2). Figure 1.1 shows the organization of the nephron, and Table 1.1 lists the relative contribution of the different nephron segments to the reabsorption of filtered sodium and the neurohumoral factors involved in regulating transport at that site. The bulk of the filtered sodium is reabsorbed in the proximal tubule and loop of Henle; however, day-to-day regulation primarily occurs in the collecting ducts, where the final composition of the urine is determined.



■ **FIGURE 1.1. Anatomy of the nephron.** Filtrate forms at the glomerulus and enters the proximal tubule. It then flows down the descending limb of the loop of Henle into the medulla, makes a hairpin turn, and then ascends back into the cortex. The next segment of the tubule is the distal convoluted tubule that becomes the cortical collecting duct and then the outer and inner medullary collecting duct before entering the papilla through the papillary duct. The sites and mechanisms of sodium reabsorption are summarized in Table 1.1. (Modified with permission of John Wiley & Sons – Books from O'Callaghan CA, Brenner BM. *The Kidney at a Glance*. Blackwell Publishers; 2000, permission conveyed through Copyright Clearance Center, Inc.)

TABLE 1.1. Sites and Mechanisms of Renal Sodium Reabsorption

Tubule Segment	Percent Filtered Na Reabsorbed	Mechanisms of Na Entry	Regulatory Factors (Major)
Proximal tubule	50%-55%	Na^+-H^+ exchange; cotransport with glucose, amino acids, phosphate, and other organic solutes	Angiotensin II; norepinephrine; glomerular filtration rate
Loop of Henle	35%-40%	Na^+-K^+-$2Cl^-$ cotransport	Flow dependent
Distal tubule	5%-8%	Na^+-Cl^- cotransport	Flow dependent
Collecting tubules	2%-3%	Na^+ channels	Aldosterone; atrial natriuretic peptide

This regulatory system for solute excretion is highly efficient. For example, the filtered sodium load in a patient with a GFR of 180 L/day and a plasma water sodium concentration of 140 mEq/L is 25,200 mEq. Normal dietary sodium intake ranges from 80 to 250 mEq/day. Thus, more than 99% of the filtered sodium must be reabsorbed to remain in balance. Furthermore, increasing sodium intake by 25 mEq/day requires a trivial increase in the rate of sodium reabsorption of <0.1% (25 ÷ 25,200 = 0.1%).

The following discussion emphasizes the mechanisms by which sodium is reabsorbed in different nephron segments. The regulation of water, hydrogen, potassium, calcium, magnesium, and phosphate handling in the kidney is reviewed in the following chapters.

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Pathogenesis of Major Glomerular and Vascular Diseases

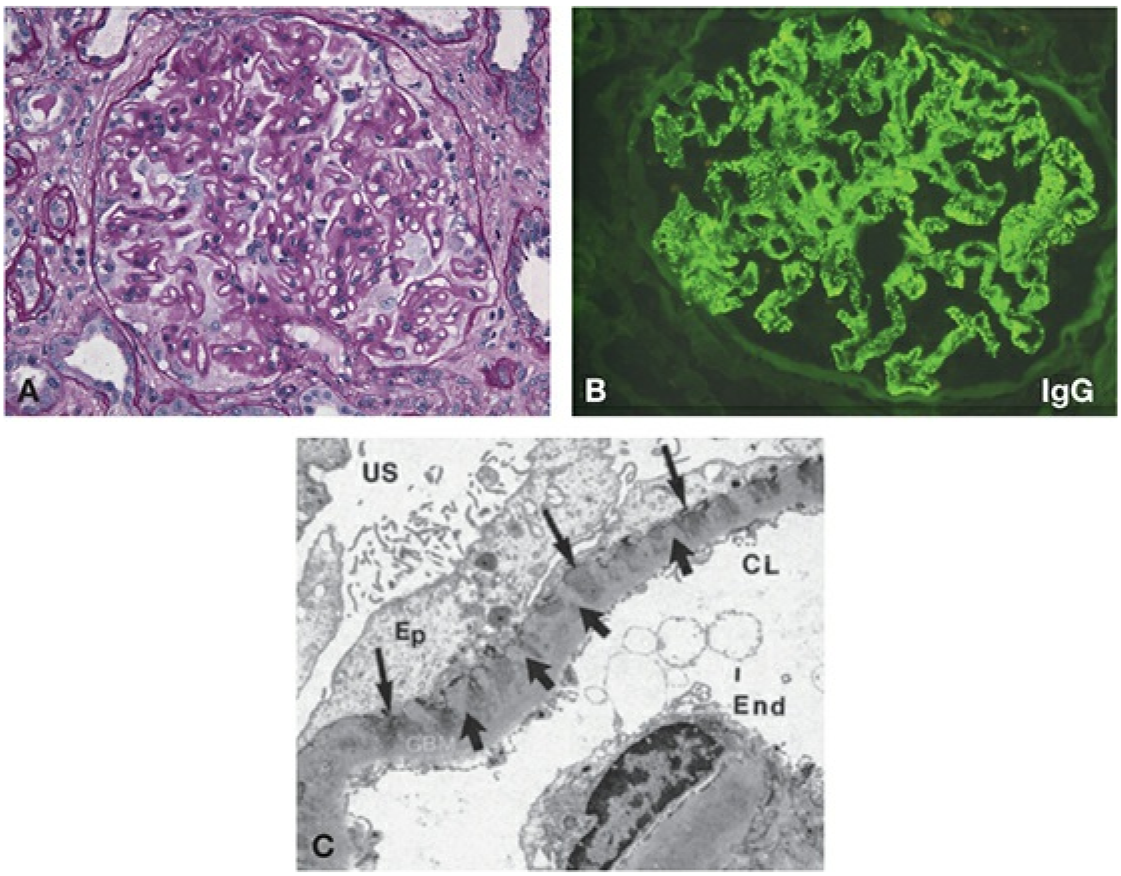
CASE PRESENTATION-1

A 27-year-old man consults his family physician because of the recent onset of edema. He has no other relevant history, and the physical examination is remarkable only for significant pitting edema in the lower extremities. His blood pressure is 135/80 mm Hg.

The blood and urine tests reveal the following:

Blood urea nitrogen	= 15 mg/dL
Creatinine	= 0.9 mg/dL
Albumin	= 1.7 g/dL (normal = 3.5-5 g/dL)
Urinalysis	= 4+ protein (by dipstick)
Sediment	= oval fat bodies, occasional hyaline casts, rare red cells

The total protein-to-creatinine ratio is 10.8, suggesting that daily protein excretion is approximately 10.8 g/day/1.73 m^2 body surface area (normal <150 mg/day; see Chapter 8). The kidney biopsy findings are illustrated in Figure 9.1.



■ **FIGURE 9.1. Membranous glomerulopathy, a noninflammatory immune complex–mediated disease. A.** Light microscopic examination of the periodic acid–Schiff (PAS)-stained section shows open capillaries without inflammation. The glomerular basement membranes (GBMs) appear distinctly thickened, especially when compared with the tubular basement membranes (PAS). **B.** The presence of immunoglobulins within the thickened capillary wall is demonstrated in this immunofluorescence micrograph; a frozen section of the kidney cortex was incubated with fluorescein-tagged rabbit antibody to human gamma heavy chains (fluorescein isothiocyanate [FITC]-labeled anti-immunoglobulin G [IgG]). The distribution of the IgG-containing immune complexes is diffuse and granular and follows the GBM. Small amounts of complement are also detected in a similar distribution (not illustrated). **C.** This electron micrograph shows the characteristic subepithelial electron-dense deposits (*long arrows*), which appear on the outer aspect of the GBM. Adjacent immune deposits are separated by extensions of the basement membrane, or "spikes"; this additional basement membrane material surrounds the deposits like a calyx and imparts to the GBM the thickened appearance. Notice an intact delicate fenestrated endothelial layer (End) separating the basement membrane from the capillary lumen (CL) and complete absence of inflammation. The visceral epithelial cell (Ep) has lost its interdigitating foot processes, which are now replaced by a continuous epithelium. Numerous microvillous cell surface extensions reach into the urinary space (US). This pattern of injury is characteristic for membranous nephropathy, one of the conditions in humans associated with nephrotic syndrome.

CASE PRESENTATION-2

A 16-year-old girl notes the sudden onset of periorbital edema and dark maroon urine. This is a rather frightening experience for the patient and her parents, and it prompts an immediate visit to the emergency ward.

The patient had been in good health until 2 weeks prior to consultation, when she developed a sore throat in connection with an upper respiratory tract infection. This was accompanied by persistent fever, forcing her to miss school for 3 days. The fever and the respiratory symptoms resolved spontaneously.

Physical examination revealed an elevated blood pressure of 150/105 mm Hg, edema of the face, and only minimal inflammation of the pharynx. The blood and urine tests reveal the following:

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