CHAPTER
ONE

INTRODUCTION TO RENAL FUNCTION

The kidney normally performs a number of essential functions:

- It participates in the maintenance of the constant extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of some of the waste products of metabolism (such as urea, creatinine, and uric acid) and by specifically adjusting the urinary excretion of water and electrolytes to match net intake and endogenous production. As will be seen, the kidney is able to *regulate individually* the excretion of water and solutes such as sodium, potassium, and hydrogen largely by changes in tubular reabsorption or secretion.
- It secretes hormones that participate in the regulation of systemic and renal hemodynamics (renin, angiotensin II, prostaglandins, nitric oxide, endothelin, and bradykinin), red blood cell production (erythropoietin), and calcium, phosphorus, and bone metabolism (1,25-dihydroxyvitamin D_3 or calcitriol).
- It performs such miscellaneous functions as catabolism of peptide hormones[1,2] and synthesis of glucose (gluconeogenesis) in fasting condition.[3,4]

This chapter will review briefly the morphology of the kidney and the basic processes of reabsorption and secretion. The regulation of renal hemodynamics,

the specific functions of the different nephron segments, and the relationships between hormones and the kidney will then be discussed in the ensuing chapters.

RENAL MORPHOLOGY

The basic unit of the kidney is the *nephron*, with each kidney in humans containing approximately 1.0 to 1.3 million nephrons.

Each nephron consists of a glomerulus, which is a tuft of capillaries interposed between two arterioles (the afferent and efferent arterioles), and a series of tubules lined by a continuous layer of epithelial cells (Fig. 1-1). The glomeruli are located in the outer part of the kidney, called the *cortex*, whereas the tubules are presented in both the cortex and the inner part of the kidney, the *medulla* (Figs. 1-1 and 1-2).

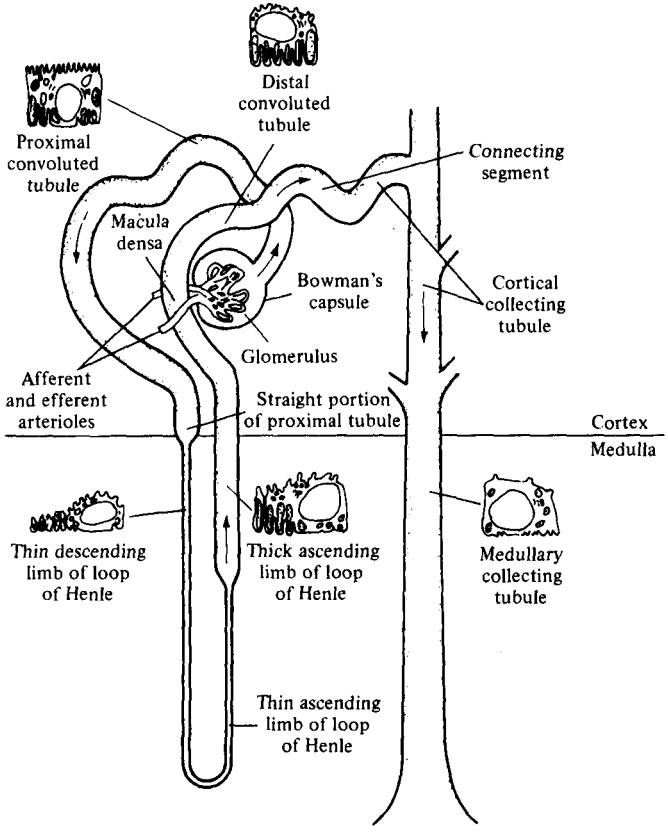

Figure 1-1 Anatomic relationships of the component parts of the nephron. (*Adapted from Vander R,* Renal Physiology, *2d ed, McGraw-Hill, New York, 1980.*)

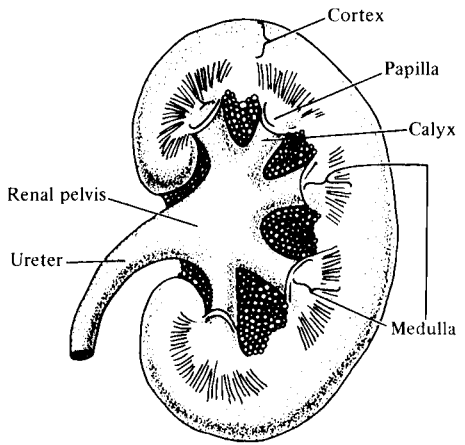

Figure 1-2 Section of a human kidney. The outer portion (the cortex) contains all the glomeruli. The tubules are located in both the cortex and the medulla, with the collecting tubules forming a large portion of the inner medulla (the papilla). Urine leaving the collecting tubules drains sequentially into the calyces, renal pelvis, ureter, and then the bladder. (*Adapted from Vander R,* Renal Physiology, *2d ed, McGraw-Hill, New York, 1980.*)

The initial step in the excretory function of the nephron is the formation of an ultrafiltrate of plasma across the glomerulus. This fluid then passes through the tubules and is modified in *two ways*: by reabsorption and by secretion. *Reabsorption* refers to the removal of a substance from the filtrate, whereas *secretion* refers to the addition of a substance to the filtrate. As will be seen, the different tubular segments make varying contributions to these processes.

Fluid filtered across the glomerulus enters Bowman's space and then the proximal tubule (Fig. 1-1). The *proximal tubule* is composed anatomically of an initial convoluted segment and a later straight segment, the pars recta, which enters the outer medulla. The *loop of Henle* begins abruptly at the end of the pars recta. It generally includes a thin descending limb and thin and thick segments of the ascending limb. The hairpin configuration of the loop of Henle plays a major role in the excretion of a hyperosmotic urine.

It is important to note that the length of the loops of Henle is not uniform (Fig. 1-3). Approximately 40 percent of nephrons have short loops that penetrate only the outer medulla or may even turn around in the cortex; these short loops lack a thin ascending limb.[5] The remaining 60 percent have long loops that course through the medulla and may extend down to the papilla (the innermost portion of the medulla). The length of the loops is largely determined by the cortical location of the glomerulus: Glomeruli in the outer cortex (about 30 percent) have only short loops; those in the juxtamedullary region (about 10 percent) have only long loops; and those in the midcortex may have either short or long loops (Fig. 1-3).

The thick ascending limb also has a cortical segment that returns to the region of the parent glomerulus. It is in this area, where the tubule approaches the afferent glomerular arteriole, that the specialized tubular cells of the *macula densa* are located (Fig. 1-4). The juxtaglomerular cells of the afferent arteriole and the macula densa compose the juxtaglomerular apparatus, which plays a central role in renin secretion (see Chap. 2).

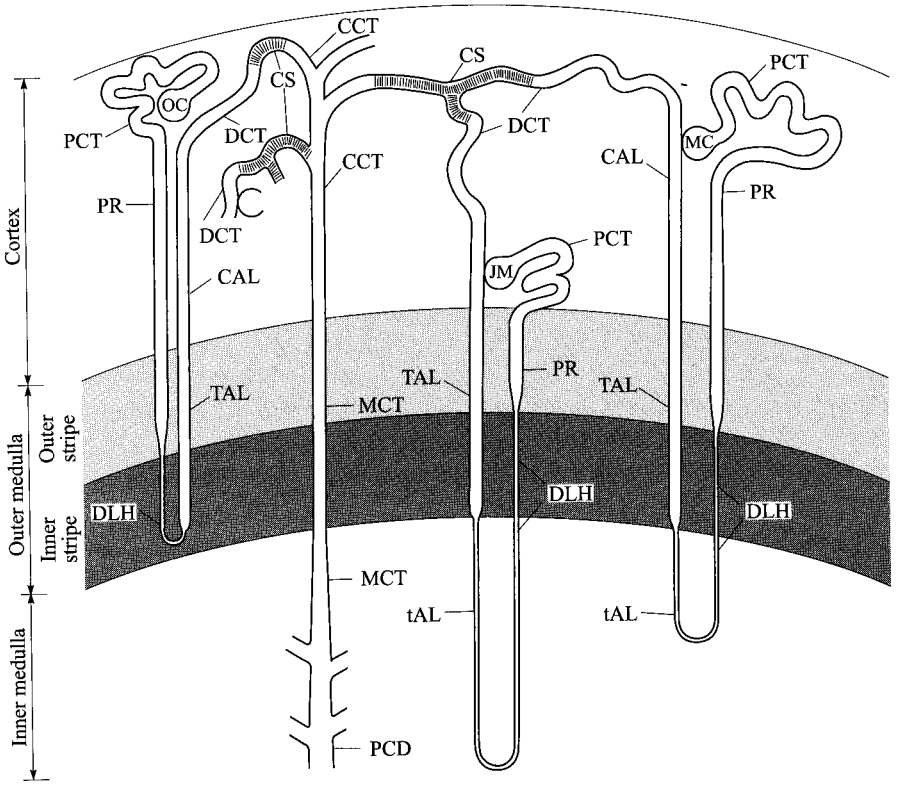

Figure 1-3 Anatomic relationships of the different nephron segments according to location of the glomeruli in the outer cortex (OC), midcortex (MC), or juxtamedullary area (JM). The major nephron segments are labeled as follows: PCT = proximal convoluted tubule; PR = pars recta, which ends in the S_3 segment at the junction of the outer and inner stripes in the outer medulla; DLH = descending limb of the loop of Henle; tAL = thin ascending limb, which is not present in outer cortical nephrons that have short loops of Henle; TAL = medullary thick ascending limb; CAL = cortical thick ascending limb, which ends in the macula densa adjacent to the parent glomerulus (see Fig. 1-4); DCT = distal convoluted tubule; CS = connecting segment; CCT = cortical collecting tubule; MCT = medullary collecting tubule; and PCD = papillary collecting duct, at the end of the medullary collecting tubule. (*Adapted from Jacobson HR*, Am J Physiol *241:F203, 1981. Used with permission.*)

After the macula densa, there are three cortical segments (Fig. 1-3): The *distal convoluted tubule*, the *connecting segment* (previously considered part of the late distal tubule), and the *cortical collecting tubule*.[6,7] The connecting segments of many nephrons drain into a single collecting tubule. Fluid leaving the cortical collecting tubule flows into the *medullary collecting tubule* and then drains sequentially into the calyces, the renal pelvis, the ureters, and the bladder (Fig. 1-2).

The segmental subdivision of the nephron is based upon different permeability and transport characteristics that translate into important differences in function.[5] In general, the proximal tubule and loop of Henle reabsorb the bulk of the filtered solutes and water, while the collecting tubules make the final small changes in

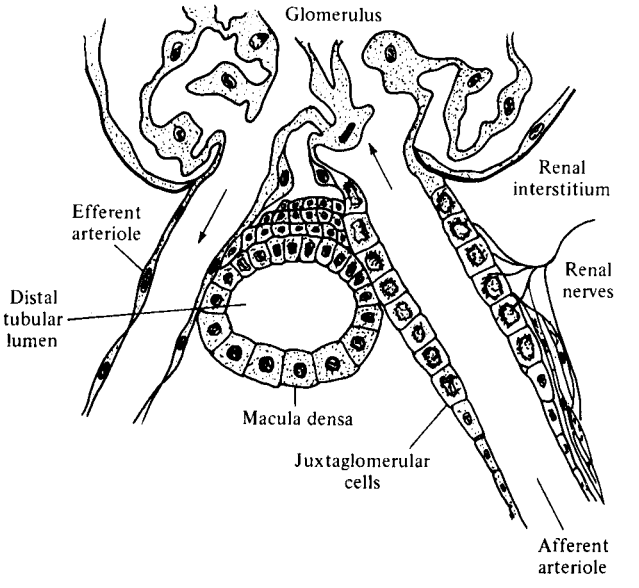

Figure 1-4 Diagram of the juxtaglomerular apparatus. The juxtaglomerular cells in the wall of the afferent arteriole secrete renin into the lumen of the afferent arteriole and the renal lymph. Stretch receptors in the afferent arteriole, the sympathetic nerves ending in the juxtaglomerular cells, and the composition of the tubular fluid reaching the macula densa all contribute to the regulation of renin secretion. (*Adapted from Davis JO*, Am J Med *55:333, 1973. Used with permission.*)

urinary composition that permit solute and water excretion to vary appropriately with alterations in dietary intake.

There may also be significant heterogeneity within a given tubular segment, particularly in the proximal tubule and cortical collecting tubule. In the latter segment, for example, there are two cell types with very different functions: The *principal cells* reabsorb sodium and chloride and secrete potassium, in part under the influence of aldosterone; and the *intercalated cells* secrete hydrogen or bicarbonate and reabsorb potassium, but play no role in sodium balance.[6]

REABSORPTION AND SECRETION

The rate of glomerular filtration averages 135 to 180 L/day in a normal adult. Since this represents a volume that is more than 10 times that of the extracellular fluid and approximately 60 times that of the plasma, it is evident that almost all of this fluid must be returned to the systemic circulation. This process is called *tubular reabsorption* and can occur either across the cell or via the paracellular route between the cells. With transcellular reabsorption, the substance to be reabsorbed is first transported from the tubular lumen into the cell, usually across the luminal aspect of the cell membrane; next, it moves across the basolateral (or peritubular)

aspect of the cell membrane into the interstitium and then the capillaries that surround the tubules (Fig. 1-5). With paracellular reabsorption, the substance to be reabsorbed moves from the tubular lumen across the tight junction at the luminal surface of adjacent cells (see below) into the interstitium and then into the peritubular capillaries.

Most reabsorbed solutes are returned to the systemic circulation intact. However, some are metabolized within the cell, particularly low-molecular-weight proteins in the proximal tubule.

Solutes can also move in the opposite direction, from the peritubular capillary through the cell and into the urine. This process is called *tubular secretion* (Fig. 1-5).

Filtered solutes and water may be transported by one or both of these mechanisms. For example, Na^+, Cl^-, and H_2O are reabsorbed; hydrogen ions are secreted; K^+ and uric acid are both reabsorbed and secreted; and filtered creatinine is excreted virtually unchanged, since it is not reabsorbed and only a small amount is normally added to the urine by secretion.

The transcellular reabsorption or secretion of almost all solutes is facilitated by *protein carriers* or *ion-specific channels*; these transport processes are essential, since free diffusion of ions is limited by the lipid bilayer of the cell membrane. The spatial orientation of the cells is also important, because the luminal and basolateral aspects of the cell membrane, which are separated by the *tight junction*, have different functional characteristics.

As an example, filtered sodium enters the cell passively down a favorable electrochemical gradient, since the active Na^+-K^+-ATPase pump in the basolateral membrane maintains the cell Na^+ concentration at a low level and makes the cell interior electronegative. Sodium entry occurs by a variety of mechanisms at different nephron sites, such as Na^+-H^+ exchange and Na^+-glucose cotransport in the proximal tubule, a Na^+-K^+-$2Cl^-$ carrier protein in the cortical collecting tubule and papillary collecting duct (Fig. 1-6). The sodium that enters the cells is then returned to the systemic circulation by the Na^+-K^+-ATPase pump in the basolateral membrane.[8] Removal of this Na^+ from the cell maintains the cell Na^+

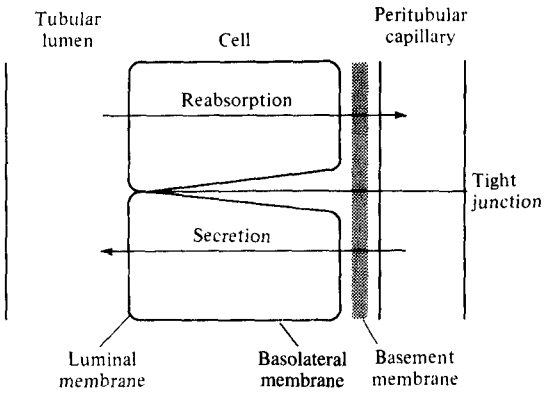

Figure 1-5 Schematic representation of reabsorption and secretion in the nephron.

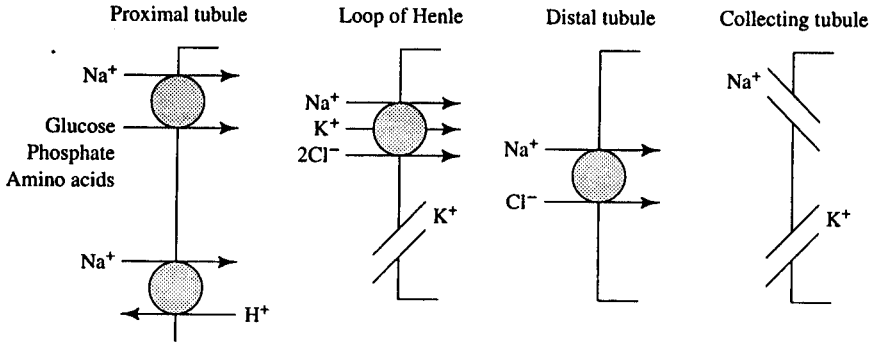

Figure 1-6 Major mechanisms of passive Na^+ entry into the cells across the luminal (apical) membrane in the different nephron segments. With the exception of the selective Na^+ channels in the collecting tubules, Na^+ reabsorption in the more proximal segments is linked to the reabsorption or secretion of other solutes. (*Adapted from Rose BD*, Kidney Int *39:336, 1991. Used with permission from* Kidney International.)

concentration at a low level, thereby promoting further diffusion of luminal Na^+ into the cell and continued Na^+ reabsorption.

This simple summary of the mechanism of Na^+ transport illustrates that reabsorption can involve both active and passive mechanisms. This is also true for tubular secretion. Potassium, for example, is secreted from the cortical collecting tubule cell into the lumen. The Na^+-K^+-ATPase pump in the basolateral membrane actively transports K^+ from the peritubular capillary into the cell; the ensuing rise in the cell K^+ concentration then promotes secretion into the lumen via K^+ channels in the luminal membrane.

The tubular cells perform these functions in an extremely efficient manner, reabsorbing almost all the filtrate to maintain the balance between intake and excretion. In an individual on a normal diet, more than 98 to 99 percent of the filtered H_2O, Na^+, Cl^-, and HCO_3^- is reabsorbed (Table 1-1). Although this process of filtration and almost complete reabsorption may seem inefficient, a high rate of filtration is required for the excretion of those waste products of metabolism (such as urea and creatinine) that enter the urine primarily by glomerular filtration.

Role of the Tight Junction

The tight junction is composed primarily of the zona occludens, which is a strand-like structure on the luminal membrane that brings adjacent cells into apposition at their luminal surface.[9,10] Within the kidney, the tight junction has two important effects on segmental function.[9,11,12]

- It serves as a relative barrier or gate to the passive diffusion of solutes and water between the cells.

Table 1-1 Summary of the net daily reabsorptive work performed by the kidney[a]

Substance	Filtered	Excreted	Percent net reabsorption
Water	180 liters	0.5–3 liters	98–99
Na^+	26,000 meq	100–250 meq	> 99
Cl^-	21,000 meq	100–250 meq	> 99
HCO_3^-	4800 meq	0	~ 100
K^+	800 meq	40–120 meq	85–95[b]
Urea	54 g	27–32 g	40–50

[a] These values are for a normal adult man on a typical Western diet. The glomerular filtration rate and therefore the filtered load of solutes and water is approximately 25 percent lower in women.

[b] The net reabsorption of K^+ reflects the interplay of two processes: the reabsorption of almost all of the filtered K^+ in the proximal tubule and loop of Henle and the secretion of K^+ into the lumen, primarily in the cortical collecting tubule under the influence of aldosterone. This latter process is the primary determinant of urinary K^+ excretion (see Chap. 12).

- It serves as a boundary or fence between the luminal (or apical) and basolateral membranes.

It has been proposed that these two functions—paracellular gate and fence for polarity—are mediated by different kinds of molecular contacts between the tight junction strands: The gate function may be due to contact between strands on apposing cells, while the fence function may be due to contact between the particles forming the strands within a single cell.[12]

The "leakiness" of the tight junction barrier to passive diffusion varies with the nephron segment. The barrier is relatively leaky in the proximal tubule, with as much as one-third of proximal Na^+ reabsorption occurring via this paracellular route. This leakiness is important, because it allows the proximal tubule to efficiently reabsorb 55 to 60 percent of the filtrate (or over 90 L/day).

In comparison, the collecting tubule is a relatively "tight" epithelium with a thicker tight junction than the proximal tubule.[9] As a result, diffusion across the tight junction is limited. This relative impermeability to passive paracellular transport allows this segment to *create and sustain* very large transepithelial concentration gradients. As an example, the medullary collecting tubule is able to lower the urine pH to 4.5, which represents a H^+ concentration that is almost 1000 times greater than that in the plasma (where the pH is about 7.40). The proximal tubule, on the other hand, can only reduce the tubular fluid pH to about 6.8, which represents a H^+ concentration only four times higher than that in the plasma.

The boundary function of the tight junction is thought to play an important role in the maintenance of the polarity of the two membranes, preventing lateral movement of transporters or channels from one membrane to the other.[9,11,12] Membrane polarity is an essential component of reabsorption or secretion in the renal tubular cells, as each component of the cell membrane plays an important role:[13]

- *Luminal membrane*: The luminal (or apical) membrane contains the channels or carriers that allow filtered solutes to enter the cells or some cellular solutes to be secreted into the lumen (Fig. 1-6).
- *Basolateral membrane*: The basolateral membrane performs two major functions. That part of the membrane adjacent to the luminal membrane (also called the lateral membrane) contains the components of the tight junction and the cell adhesion molecules that participate in cell-cell contact and communication. The more distal part of this membrane (also called the basolateral or basal-lateral membrane) plays an essential role in ion transport and hormone responsiveness, as it contains the Na^+-K^+-ATPase pumps, hormone receptors, and solute carriers and channels.
- *Basal membrane*: The basal membrane contains the basement membrane receptors that allow the cell to be anchored to the basement membrane.

As an example of transcellular transport, filtered Na^+ enters the cells across the luminal membrane via specific transporters or channels; it is then returned to the systemic circulation by the Na^+-K^+-ATPase pump to the basolateral membrane. Disruption of this normal polarity, as with opening of the tight junctions due to ischemia, is associated with an impairment in Na^+ reabsorption.[11] This may be mediated in part by the translocation of functioning Na^+-K^+-ATPase pumps onto the luminal membrane.[14]

The signals that govern the initial insertion of a protein into the luminal or basolateral membrane are incompletely understood. One signal appears to be the presence of cassettes of unique amino acids (located within the sequences of the proteins themselves) that relay localization information to cellular sorting machinery. One such amino acid motif, contiguous leucines located in the cytoplasmic tail, helps direct the vasopressin V_2 receptor to the basolateral membrane.[15]

Another mechanism may involve the type of membrane anchor: Studies in kidney cells suggest that the presence of glycosyl-phosphatidylinositol (GPI) at the C-terminal end of the protein leads to specific insertion on the luminal membrane, perhaps because this membrane is rich in glycosphingolipids.[16,17] On the other hand, the localization of the Na^+-K^+-ATPase pump to the basolateral membrane may be mediated by specific attachment to basolateral cytoskeletal proteins, such as actin microfilaments and ankyrin.[11,18] Disruption of the actin microfilaments following ischemia impairs this tethering function, allowing Na^+-K^+-ATPase pumps to diffuse onto the luminal membrane through the now open tight junctions, thereby impairing net Na^+ reabsorption.[11]

The attachment to actin and fodrin also may promote the basolateral localization of Na^+-K^+-ATPase pumps by preventing their endocytic removal. Pumps that do get inserted into the luminal membrane are removed at a rate 40 times faster than those inserted into the basolateral membrane.[19]

Aberrant localization of membrane proteins may contribute to the development of multiple disorders, such as autosomal dominant polycystic kidney disease (ADPKD). ADPKD is in most cases caused by mutations in a membrane protein termed polycystin,[20] which appears to be involved in cell adhesion.[21] Abnormal

apical polarity of the Na^+-K^+-ATPase pumps in these patients may cause sodium secretion into and fluid accumulation in epithelial cysts.[22] In addition, abnormal epithelial proliferation within the cysts may be due to apical mislocation of epidermal growth factor receptors. The correlation between polycystin mutations and abnormal polarity is unclear, but may result from the dampened expression of fetal genes.

Membrane Recycling

In addition to proper polarity, normal functioning of transporting epithelia requires the delivery of newly synthesized and recycled membrane components to precise locations in the cell membrane.[23] For example, antidiuretic hormone combines with its receptor on the *basolateral membrane* of collecting tubular cells. This initiates a sequence of events in which preformed water channels (called aquaporin-2) in cytoplasmic vesicles are specifically inserted into the luminal membrane, thereby allowing the reabsorption of luminal water. The hormone-receptor complex is internalized by endocytosis in clathrin-coated pits and then enters acidic endosomes, where the hormone and receptor are split (Fig. 1-7).[23] The former is metabolized within the cell, while the receptor is returned to the basolateral membrane. Attenuation of the ADH effect is associated with endocytosis of only those areas of the luminal membrane that contain water channels, thereby restoring the relative water impermeability of the luminal membrane.

The signaling events that control membrane recycling are incompletely understood, but activation of adenylyl cyclase appears to be involved.[24] In addition, the structure of aquaporin-2 helps dictate cellular distribution and recycling. Mutations of the aquaporin-2 gene can cause resistance to antidiuretic hormone

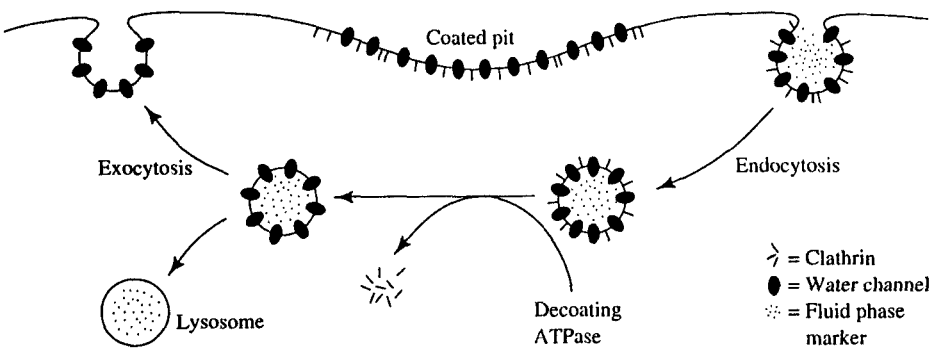

Figure 1-7 Proposed pathways of recycling of luminal membrane water channels in principal cells in the collecting tubule. Water channels are concentrated in clathrin-coated pits at the cell surface and are endocytosed in coated vesicles. These vesicles are rapidly decoated; the water channels may escape degradation and be recycled to the luminal membrane in the presence of ADH. (*From Brown D*, Kidney Int *256:F1, 1989. Used by permission from* Kidney International.)

(called nephrogenic diabetes insipidus). In the families reported thus far, the defect appears to involve misrouting and/or loss of function.[25,26]

Composition of Urine

The composition of the urine differs from that of the relatively constant extracellular fluid in two important ways. First, the quantity of solutes and water in the urine is highly variable, being dependent upon the intake of these substances. A normal subject, for example, appropriately excretes more Na^+ on a high-salt diet than on a low-salt diet. In both instances, the steady-state and therefore the extracellular volume is maintained, as output equals intake. Similarly, the urine volume is greater after a water load than after water restriction, resulting in a stable plasma Na^+ concentration.* This relation to intake means that there are *no absolute "normal" values for urinary solute or water excretion.* We can only describe a normal range which merely reflects the range of dietary intake, e.g., 100 to 250 meq/day for Na^+.

Second, ions compose 95 percent of the extracellular fluid solutes; in comparison, the urine has high concentrations of uncharged molecules, particularly urea. This allows urea and other metabolic end products to be excreted, rather than accumulating in the body.

Summary of Nephron Function

The following chapters in Part One will describe the roles of the different nephron segments in the regulation of solute and water homeostasis. These functions are summarized in Table 1-2.

As can be seen, there are marked differences in segmental function, a finding consistent with the differences in segmental histology (Fig. 1-1) and permeability and transport characteristics.[5] In addition, multiple sites participate in the regulation of the rates of excretion of the different substances in the filtrate. This diversity provides the flexibility that allows the kidney to maintain solute and water balance, even in the presence of major changes in dietary intake.

ATOMIC WEIGHT AND MOLARITY

The efficacy of regulation of solute and water balance is estimated clinically by measurement of the plasma concentrations of the appropriate substances. It is therefore important to be aware of the different ways in which solute concen-

* These changes in Na^+ and water excretion are relatively precise, so that increasing Na^+ intake from 100 to 200 meq/day, for example, results in a parallel rise in Na^+ excretion. If, as depicted in Table 1-1, 26,000 meq of Na^+ is filtered per day, then a 100-meq increase in excretion represents a change involving less than 0.5 percent of the filtered load. This illustrates the high degree of efficiency required to maintain salt and water balance.

Table 1-2 Contribution of the different nephron segments to solute and water homeostasis

Nephron segment	Major functions
Glomerulus	Forms an ultrafiltrate of plasma
Proximal tubule	Reabsorbs isosmotically 65 to 70 percent of the filtered NaCl and water
	Reabsorbs 90 percent of the filtered HCO_3^- (by H^+ secretion), mostly in early proximal tubule
	Major site of ammonia production in nephron
	Reabsorbs almost all of filtered glucose and amino acids
	Reabsorbs K^+, phosphate, calcium, magnesium, urea, and uric acid
	Secretes organic anions (such as urate) and cations, including many protein-bound drugs
Loop of Henle	Reabsorbs 15 to 25 percent of filtered NaCl
	Countercurrent multiplier, as NaCl reabsorbed in excess of water
	Major site of active regulation of magnesium excretion
Distal tubule	Reabsorbs a small fraction of filtered NaCl
	Major site, with connecting segment, of active regulation of calcium excretion
Connecting segment and cortical collecting tubule	Principal cells reabsorb Na^+ and Cl^- and secret K^+, in part under influence of aldosterone
	Intercalated cells secrete H^+, reabsorb K^+, and, in metabolic alkalosis, secrete HCO_3^-
	Reabsorb water in presence of antidiuretic hormone
Medullary collecting tubule	Site of final modification of the urine
	Reabsorb NaCl; urine NaCl concentration can be reduced to less than 1 meq/L
	Reabsorb water and urea relative to amount of antidiuretic hormone present, allowing a dilute or concentrated urine to be excreted
	Secrete H^+ and NH_3; urine pH can be reduced to as low as 4.5 to 5.0
	Can contribute to potassium balance by reabsorption or secretion of K^+

tration can be measured—in milligrams per deciliter (mg/dL), millimoles per liter (mmol/L), milliequivalents per liter (meq/L), or milliosmoles per liter or per kg (mosmol/L or mosmol/kg). For sodium ion (Na^+), 2.3 mg/dL (or 23 mg/L), 1 mmol/L, 1 meq/L, and 1 mosmol/kg all refer to the same concentration of Na^+.

Table 1-3 lists the atomic weights of the most important elements in the body. The atomic weight is an assigned number that allows comparison of the relative weights of the different elements. By definition, one atom of oxygen is assigned a weight of 16, and the atomic weights of the other elements are determined in relation to that of oxygen. In a molecule, i.e., a substance containing two or more atoms, the molecular weight is equal to the sum of the atomic weights of the individual atoms. As an example, the molecular weight of water (H_2O) is 18, since $[(2 \times 1) + 16] = 18$.

Table 1-3 Atomic and molecular weights of physiologically important substances

Substance	Symbol or formula	Atomic or molecular weight
Calcium ion	Ca^{2+}	40.1
Carbon	C	12.0
Chloride ion	Cl^-	35.5
Hydrogen ion	H^+	1.0
Magnesium ion	Mg^{2+}	24.3
Nitrogen	N	14.0
Oxygen	O	16.0
Phosphorus	P	31.0
Potassium ion	K^+	39.1
Sodium ion	Na^+	23.0
Sulfur	S	32.1
Ammonia	NH_3	17.0
Ammonium	NH_4^+	18.0
Bicarbonate ion	HCO_3^-	61.0
Carbon dioxide	CO_2	44.0
Glucose	$C_6H_{12}O_6$	180.0
Phosphate ion	PO_4^{3-}	95.0
Sulfate ion	SO_4^{2-}	96.1
Urea	NH_2CONH_2	60.0
Water	H_2O	18.0

One mole (mol) of any substance is defined as the molecular (or atomic) weight of that substance in grams. Similarly, one millimole (mmol) is equal to one-thousandth of a mole or the molecular (or atomic) weight in milligrams. Since the atomic weight of Na^+ is 23, 23 mg is 1 mmol and 23 mg of Na^+ in 1 liter of water represents a Na^+ concentration (written as $[Na^+]$ or 1 mmol/L. The concept of molarity is important because, from Avogadro's law, 1 mol of any nondissociable substance contains the same number of particles (approximately 6.02×10^{23}). Thus, 1 mmol of Na^+ contains the same number of atoms as 1 mmol of Cl^- even though the former weighs 23 mg and the latter weights 35.5 mg. However, 1 mmol of NaCl (58.5 mg) largely dissociates into Na^+ and Cl^- ions and therefore contains *almost twice as many particles*. As will be seen, these relationships are important in understanding electrochemical equivalence and in the measurement of osmotic pressure.

Although the concentrations of uncharged molecules, e.g., glucose and urea, also can be measured in millimoles per liter, they are more commonly measured in the clinical laboratory as milligrams per deciliter. For example, the molecular weight (mol wt) of glucose is 180. Consequently, a glucose concentration of 180 mg/L (or 18 mg/dL) is equal to 1 mmol/L. To convert from milligrams per deciliter to millimoles per liter, the following formula can be used:

$$\text{mmol/L} = \frac{\text{mg/dL} \times 10}{\text{mol wt}} \tag{1-1}$$

(The multiple of 10 is used to convert milligrams per deciliter into milligrams per liter.)

Electrochemical Equivalence

Positively charged particles are called *cations*, and negatively charged particles are called *anions*. When cations and anions combine, they do so according to their ionic charge (or valance), not according to their weight. Electrochemical equivalence refers to the combining power of an ion. One equivalent is defined as the weight in grams of an element that combines with or replaces 1 g of hydrogen ion (H^+). Since 1 g of H^+ is equal to 1 mol of H^+ (containing approximately 6.02×10^{23} particles), 1 mol of any univalent anion (charge equals 1^-) will combine with this H^+ and is equal to one equivalent (eq). Thus:

$$\underset{(1\,g)}{1\,mol\,H^+} + \underset{(35.5\,g)}{1\,mol\,Cl^-} \rightarrow \underset{(36.5\,g)}{1\,mol\,HCl}$$

By similar reasoning, 1 mol of a univalent cation (charge equals 1^+) also is equal to 1 eq, since it can replace H^+ and combine with 1 eq of Cl^-. For example,

$$\underset{(23\,g)}{1\,mol\,Na^+} + \underset{(35.5\,g)}{1\,mol\,Cl^-} \rightarrow \underset{(58.5\,g)}{1\,mol\,NaCl}$$

In contrast, ionized calcium (Ca^{2+}) is a divalent cation (charge equals 2^+). Consequently, 1 mol of Ca^{2+} will combine with 2 mol of Cl^- and is equal to 2 eq:

$$\underset{(40\,g)}{1\,mol\,Ca^{2+}} + \underset{(71\,g)}{2\,mol\,Cl^-} \rightarrow \underset{(111\,g)}{1\,mol\,CaCl_2}$$

The body fluids are relatively dilute, and most ions are present in milliequivalent quantities (one-thousandth of 1 eq equals 1 meq). To convert from units of millimoles per liter to milliequivalents per liter, the following formulas can be used:

$$meq/L = mmol/L \times valence \tag{1-2}$$

or from Eq. (1-1),

$$meq/L = \frac{mg/dL \times 10}{mol\,wt} \times valence \tag{1-3}$$

There are two advantages to measuring ionic concentrations in milliequivalents per liter. First, it emphasizes the principle that *ions combine milliequivalent for milliequivalent*, not millimole for millimole or milligram for milligram. Second, to maintain *electroneutrality*, there is an equal number of milliequivalents of cations and anions in the body fluids. As will be described in later chapters, the need to preserve electroneutrality is an important determinant of ion transport in the kidney and ion movement between the cells and the extracellular fluid. This obligatory relationship cannot be appreciated if the ionic concentrations are measured in millimoles per liter or in milligrams per deciliter (Table 1-4).

Table 1-4 Normal plasma electrolyte concentrations

Electrolyte	meq/L	mmol/L
Cations		
Na^+	142.0	142.0
K^+	4.3	4.3
Ca^{2+}[a]	2.5	1.25
Mg^{2+}[a]	1.1	0.55
Total	149.9	148.1
Anions		
Cl^-	104.0	104.0
HCO_3^-	24.0	24.0
$H_2PO_4^-$, HPO_4^{2-}	2.0	1.1
Proteins	14.0	0.9
Other[b]	5.9	5.5
Total	149.9	135.5

[a] The values of Ca^{2+} and Mg^{2+} include only the ionized (unbound) form of these ions.

[b] This includes SO_4^{2-} and organic anions such as lactate.

Despite these advantages, not all ions can be easily measured in milliequivalents per liter. The total calcium (Ca^{2+}) concentration in the blood is approximately 10 mg/dL. From Eq. (3),

$$\text{meq/L of } Ca^{2+} = \frac{10 \times 10}{40} \times 2 = 5 \text{ meq/L}$$

However, roughly 50 to 55 percent of plasma Ca^{2+} is bound by albumin and, to a much lesser degree, citrate, so that the physiologically important *ionized* (or unbound) Ca^{2+} concentration is only 2.0 to 2.5 meq/L.

There is a different problem with phosphate, since it can exist in different ionic forms—as $H_2PO_4^-$, HPO_4^{2-}, or PO_4^{3-}—and an exact valence cannot be given. We can estimate an approximate valence of minus 1.8 because roughly 80 percent of extracellular phosphate exists as HPO_4^{2-} and 20 percent as $H_2PO_4^-$. If the normal serum phosphorus concentration is 3.5 mg/dL (phosphate in the blood is measured as inorganic phosphorus), then

$$\text{meq/L of phosphate} = \frac{3.5 \times 10}{31} \times 1.8 = 2 \text{ meq/L}$$

Similarly, only an average valence can be given for the polyvalent protein anions. If the plasma protein concentration is 0.9 mmol/L and the average valance is minus 15, then from Eq. (1-2),

$$\text{meq/L of protein} = 0.9 \times 15 = 14 \text{ meq/L}$$

Osmotic Pressure and Osmolality

Another unit of measurement is osmotic pressure, which determines the distribution of water among the different fluid compartments, particularly between the extracellular and intracellular fluids (see Chap. 7). The osmotic pressure generated by a solution is proportional to the *number of particles* per unit volume of solvent, not to the type, valence, or weight of the particles.

The unit of measurement of osmotic pressure is the osmole. One osmole (osmol) is defined as 1 g molecular weight (1 mol) of any nondissociable substance (such as glucose) and contains 6.02×10^{23} particles. In the relatively dilute fluids in the body, the osmotic pressure is measured in milliosmoles (one-thousandth of an osmole) per kilogram of water (mosmol/kg). Since most solutes are measured in the laboratory in units of millimoles per liter, milligrams per deciliter, or milliequivalents per liter, the following formulas must be used to convert into mosmol/kg:

$$\text{mosmol/kg} = n \times \text{mmol/L}$$

or, from Eqs. (1-1) and (1-2),

$$\text{mosmol/kg} = n \times \frac{\text{mg/dL} \times 10}{\text{mol wt}} \tag{1-4}$$

$$\text{mosmol/kg} = n \times \frac{\text{meq/L}}{\text{valence}} \tag{1-5}$$

where n is the number of dissociable particles per molecule. When $n = 1$, as for Na^+, Cl^-, Ca^{2+}, urea, and glucose, 1 mmol/L will generate a potential osmotic pressure of 1 mosmol/kg. If, however, a compound dissociates into two or more particles, 1 mmol/L will generate an osmotic pressure greater than 1 mosmol/kg. At the concentrations present in the body, for example, ionic interactions reduce the random movement of NaCl so that it acts as if it were only 75 percent, rather than 100 percent, dissociated. Thus, for each 1 mmol/L of NaCl, there will be 0.75 mmol/L each of Na^+ and Cl^- and 0.25 mmol/L of NaCl, or 1.75 mosmol/kg (Table 1-5).[27]

Table 1-5 Relationship between various units of measurement

Substance	Atomic or molecular weight	mmol	meq	mosmol
Na^+	23	1	1	1
Cl^-	35.5	1	1	1
NaCl	58.5	1	2 (Na^+, Cl^-)	1.75[a]
$CaCl_2$	111	1	4 (Ca^{2+}, $2Cl^-$)	~ 3[a]
Glucose	180	1	...	1

[a] Both NaCl and $CaCl_2$ behave as if they are incompletely dissociated because ionic interactions limit the random movement or activity of the ions; see text for details.

In the laboratory, the osmotic concentration of a solution is measured not as an osmotic pressure but according to other properties of solutes, such as their ability to depress the freezing point or the vapor pressure of water. Solute-free water freezes at 0°C. If 1 osmol of any solute (or combination of solutes) is added to 1 kg of water, the freezing point of this water will be depressed by 1.86°C. This observation can be used to calculate the osmotic concentration of a solution. As an example, the freezing point of the plasma water is normally about −0.521°C. This represents an osmolality of 0.280 osmol/kg (0.521/1.86) or 280 mosmol/kg.

Only solutes that *cannot cross the membrane separating two compartments* generate an effective osmotic pressure. Thus, a lipid-soluble solute such as urea, which can cross the lipid bilayer of cell membranes, does not contribute to osmotic pressure but will be measured as part of the plasma osmolality by freezing point or vapor pressure depression. There is therefore a difference between the total osmolality and the effective osmolality of a solution, with the latter being determined only by osmotically active solutes (such as Na^+ and K^+ across the cell membrane) (see Chap. 7).

REFERENCES

1. Carone FA, Peterson DR. Hydrolysis and transport of small peptides by the proximal tubule. *Am J Physiol* 283:F151, 1980.
2. Madsen KM, Park CH. Lysosome distribution and cathepsin B and L activity along the rabbit proximal tubule. *Am J Physiol* 253:F1290, 1987.
3. Owen OE, Felig P, Morgan AP, et al. Liver and kidney metabolism during prolonged starvation. *J Clin Invest* 48:574, 1969.
4. Burch HB, Narins RG, Chu C, et al. Distribution along the rat nephron of three enzymes of gluconeogenesis in acidosis and starvation. *Am J Physiol* 235:F246, 1978.
5. Jacobson HR. Functional segmentation of the mammalian nephron. *Am J Physiol* 241:F203, 1981.
6. Madsen KM, Tisher CC. Structural-functional relationships along the distal nephron. *Am J Physiol* 250:F1, 1986.
7. Imai M. The connecting tubule: A functional subdivision of the rabbit distal nephron segments. *Kidney Int* 15:346, 1979.
8. Doucet A. Function and control of Na-K-ATPase in single nephron segments of the mammalian kidney. *Kidney Int* 34:749, 1988.
9. Gumbiner B. Structure, biochemistry, and assembly of tight junctions. *Am J Physiol* 253:C749, 1987.
10. Madara JL. Loosening tight junctions: Lessons from the intestine. *J Clin Invest* 83:1089, 1989.
11. Molitoris BA. Ischemia-induced loss of epithelial polarity: Potential role of the actin cytoskeleton. *Am J Physiol* 260:F769, 1991.
12. Mandel LJ, Bacallao R, Zampighi G. Uncoupling of the molecular "fence" and paracellular "gate" functions in epithelial tight junctions. *Nature* 361:552, 1993.
13. Rodriguez-Boulan E, Nelson WJ. Morphogenesis of the polarized epithelial cell phenotype. *Science* 245:718, 1989.
14. Molitoris BA. Na^+-K^+-ATPase that redistributes to apical membrane during ATP depletion remains functional. *Am J Physiol* 265:F693, 1993.
15. Brown D, Breton S. Sorting proteins to their target membranes. *Kidney Int* 57:816, 2000.
16. Brown DA, Crise B, Rose JK. Mechanism of membrane anchoring affects polarized expression of two proteins in MDCK cells. *Science* 245:1499, 1989.

17. Brown D, Waneck GL. Glycosyl-phosphatidylinositol-anchored membrane proteins. *J Am Soc Nephrol* 3:895, 1992.
18. Nelson WJ, Hammerton RW. A membrane-cytoskeletal complex containing Na^+-K^+-ATPase, ankyrin, and fodrin in Madin-Darby canine kidney (MDCK) cells: Implications for the biogenesis of epithelial cell polarity. *J Cell Biol* 108:893, 1989.
19. Hammerton RW, Krzeminski KA, Mays RW, et al. Mechanism for regulating cell surface distribution of Na^+-K^+-ATPase in polarized epithelial cells. *Science* 254:847, 1991.
20. Geng L, Segal Y, Peissel B, et al. Identification and localization of polycystin, the PKD1 gene product. *J Clin Invest* 98:2674, 1996.
21. Huan Y, van Adelsberg J. Polycystin-1, the PKD1 gene product, is in a complex containing E-cadherin and the catenins. *J Clin Invest* 104:1459, 1999.
22. Wilson PD. Epithelial cell polarity and disease. *Am J Physiol* 272:F434, 1997.
23. Brown D. Membrane recycling and epithelial cell function. *Am J Physiol* 256:F1, 1989.
24. Bichet DG, Oksche A, Rosenthal W. Congenital nephrogenic diabetes insipidus. *J Am Soc Nephrol* 8:1951, 1997.
25. Mulder SM, Knoers NV, Van Lieburg AF, et al. New mutations in the AQP2 gene in nephrogenic diabetes insipidus resulting in functional but misrouted water channels. *J Am Soc Nephrol* 8:242, 1997.
26. Hochberg Z, van Lieburg A, Even L, et al. Autosomal recessive nephrogenic diabetes insipidus caused by an aquaporin-2 mutation. *J Clin Endocrinol Metab* 82:686, 1997.
27. Edelman IS, Leibman J, O'Meara MP, Birkenfeld L. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest* 37:1236, 1958.

CHAPTER
TWO

RENAL CIRCULATION AND GLOMERULAR FILTRATION RATE

The blood flow to the kidneys averages 20 percent of the cardiac output. In terms of flow per 100 g weight, the renal blood flow (RBF) is four times greater than the blood flow to the liver or exercising muscle and eight times coronary blood flow.

Blood enters the kidney through the renal arteries and passes through serial branches (interlobar, arcuate, interlobular) before entering the glomeruli via the capillary wall then leaves the glomeruli via the efferent arterioles and enters the postglomerular capillaries. In the cortex, these capillaries run in apposition to the adjacent tubules, although not necessarily to the tubule segments from the same glomerulus.[1] In addition, branches from the efferent arterioles of the juxtamedullary glomeruli enter the medulla and form the vasa recta capillaries (Fig. 2-1). Blood returns to the systemic circulation through veins similar to the arteries in name and location.

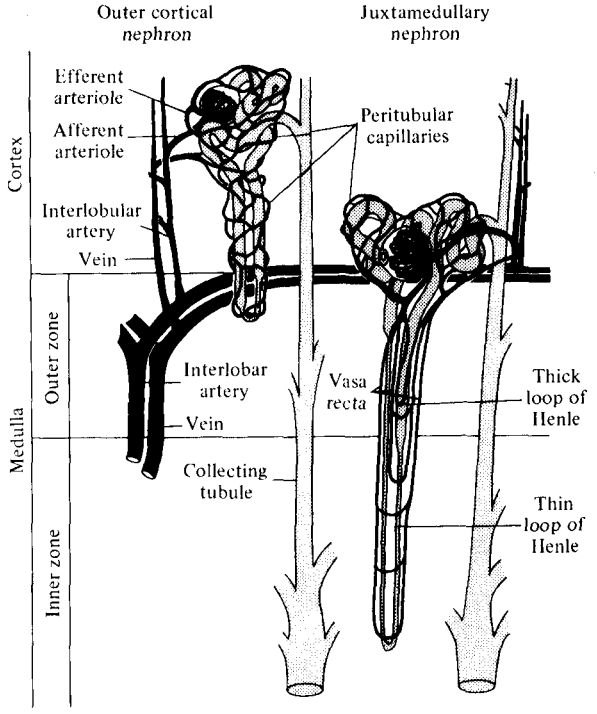

Figure 2-1 Comparison of the anatomy and blood supplies of outer cortical and juxtamedullary nephrons. Note that the efferent arterioles from the juxtamedullary nephrons not only form peritubular capillaries around the convoluted tubules but enter the medulla and form the vasa recta capillaries. (*Adapted from Pitts RF,* Physiology of the Kidney and Body Fluids, *3d ed. Copyright, 1974 by Year Book Medical Publishers, Inc, Chicago. Used by permission.*)

The renal circulation affects urine formation in the following ways:

1. The rate of glomerular filtration is an important determinant of solute and water excretion.
2. The peritubular capillaries in the cortex return reabsorbed solutes and water to the systemic circulation and can modulate the degree of proximal tubular reabsorption and secretion (see Chap. 3).
3. The vasa recta capillaries in the medulla return reabsorbed salt and water to the systemic circulation and participate in the countercurrent mechanism, permitting the conservation of water by the excretion of a hyperosmotic urine (see Chap. 4).

The remainder of this chapter will review glomerular function, the factors responsible for the regulation of the glomerular filtration rate (GFR) and renal plasma flow, and the clinical methods used to measure these parameters.

GLOMERULAR ANATOMY AND FUNCTION

The glomerulus consists of a tuft of capillaries that is interposed between the afferent and efferent arterioles. Each glomerulus is enclosed within an epithelial cell capsule (Bowman's capsule) that is continuous both with the epithelial cells that surround the glomerular capillaries and with the cells of the proximal convoluted tubule (Fig. 2-2).[2] Thus, the glomerular capillary wall, through which the filtrate must pass, consists of three layers: the fenestrated endothelial cell, the *glomerular basement membrane* (GBM), and the epithelial cell. The epithelial cells are attached to the GBM by discrete foot processes. The pores between the

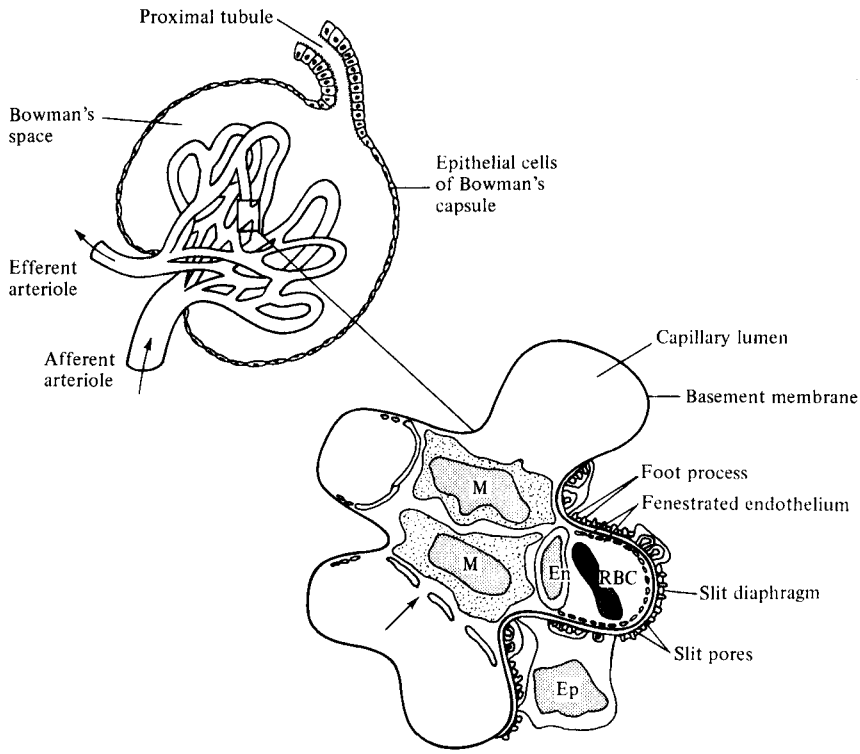

Figure 2-2 Anatomy of the glomerulus. The bottom drawing is a diagram of part of a capillary tuft with the mesangial cells (M) in the middle surrounded by capillaries. The capillary wall has three layers composed of the fenestrated endothelial cells (En), the basement membrane, and the epithelial cells (Ep), which attach to the basement membrane by discrete foot processes. Between the foot processes are slit pores which are closed by a thin membrane, the slit diaphragm. The glomerular basement surrounds the capillary loops, but most of the mesangium is separated from the capillary lumen only by the relatively permeable fenestrated endothelium (arrow). (*Adapted from Vander R,* Renal Physiology, *2d ed, McGraw-Hill, New York, 1980, and Latta H, in* Handbook of Physiology, *sec 8, Renal Physiology, vol I, Orloff J, Berliner RW, Geiger R, eds, American Physiological Society, Washington, DC, 1973. Used with permission.*)

foot processes (slit pores) are closed by a thin membrane called the *slit diaphragm*, which functions as a modified adherent junction (Fig. 2-2).[3]

The GBM is a fusion product of basement membrane material produced by the glomerular epithelial and endothelial cells.[4,5] It performs a variety of functions, including maintenance of normal glomerular architecture, anchoring of adjacent cells, and acting as a barrier to the filtration of macromolecules. It consists of the following major constituents:[4]

- Type IV collagen, which forms cords that provide the basic superstructure of the GBM.
- A variety of substances that fill the spaces between the cords, including laminin, nidogen, and heparan sulfate proteoglycans.[6] Laminin and nidogen form a tight complex, one of the major functions of which is cell adhesion to the GBM. In comparison, anionic heparan sulfate proteoglycans are largely responsible for the charge barrier to the filtration of anionic macromolecules (see below).

An abnormality in type IV collagen is responsible for the disorder hereditary nephritis (Alport's syndrome), which is a progressive form of glomerular disease (at least in males) that is often associated with hearing loss and lenticular abnormalities. The primary defect in almost all patients appears to reside in the noncollagenous domain of type IV collagen, involving the gene coding for the α_5 chain which is located on the X chromosome, the COL4A5 gene.[7,8] Abnormalities in the α_3 and α_4 chains of type IV collagen may also cause hereditary nephritis, which is not surprising, since the α_3, α_4, and α_5 chains combine to form a novel collagen that is expressed in the glomerulus and a few other tissues.[9]

Filtration Barrier and Protein Excretion

One of the major functions of the glomerulus is to allow the filtration of small solutes (such as sodium and urea) and water, while restricting the passage of larger molecules (Fig. 2-3). Solutes up to the size of inulin (mol wt 5200) are freely filtered. On the other hand, myoglobin (mol wt 17,000) is filtered less completely than inulin, while albumin (mol wt 69,000) is filtered only to a minor degree. Filtration is also limited for ions or drugs that are bound to albumin, such as roughly 40 percent of the circulating calcium.

This difference in filtration of solutes is important physiologically. The free filtration of sodium, potassium, and urea, for example, allows the kidney to maintain the steady state by excreting the load derived from dietary intake and endogenous metabolism. On the other hand, the restricted filtration of larger proteins prevents such potential problems as negative nitrogen balance, the development of hypoalbuminemia, and infection due to the loss of immunoglobulin gamma (IgG).

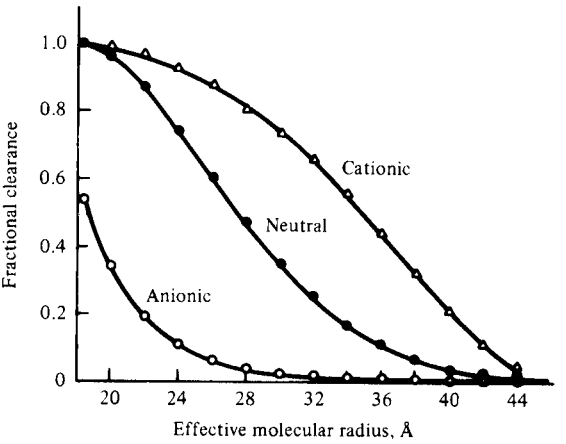

Figure 2-3 Fractional clearances (the ratio of the filtration of a substance to that of inulin, which is freely filtered) of anionic, neutral, and cationic dextrans as a function of effective molecular radius. Both molecular size and charge are important determinants of filtration, as smaller or cationic dextrans are more easily filtered. As a reference, the effective molecular radius of albumin (which is anionic in the physiologic pH range) is 36 Å. (*From Bohrer MP, Baylis C, Humes HD, et al,* J Clin Invest *1978; 61:72, by copyright permission of the American Society for Clinical Investigation.*)

Size selectivity

As illustrated in Fig. 2-3, the GBM is both *size-* and *charge*-selective, as smaller and cationic molecules are more likely to be filtered. Both the GBM and the slit diaphragms between the foot processes of the epithelial cell contribute to size selectivity.[10,11]

The size limitation in the GBM represents functional pores in the spaces between the tightly packed cords of type IV collagen.[12] In addition, the cellular components of the glomerular capillary wall are also important determinants of glomerular permeability.[13] This is illustrated by the following observations:

- Macromolecules that pass through the GBM often accumulate below the slit diaphragms rather than passing into the urinary space.
- In vitro studies of isolated GBM indicate that the GBM is much more permeable to macromolecules than the intact glomerulus; the net effect is that the glomerular cells may be responsible for as much as 90 percent of the barrier to filtration.[14]
- Increased protein filtration in glomerular diseases may primarily occur in areas of focal foot process detachment.[15]
- A mutation in the gene for nephrin, the first protein to be specifically located at the slit diaphragm, results in congenital nephrotic syndrome.[16]

Most of the pores in the glomerular capillary wall are relatively small (mean radius about 42 Å).[17]* They partially restrict the filtration of albumin (mean radius 36 Å) but allow the passage of smaller solutes and water.[18] The endothelial

* The data in Fig. 2-3 used dextrans of different sizes. However, dextrans are long and pliable and may underestimate the impermeability to round macromolecules such as albumin. Studies using ficoll, which behaves as an ideal solid sphere, have estimated the pore radius to be 42 Å.[17]

cells, in comparison, do not contribute to size selectivity, since the endothelial fenestrae are relatively wide open and do not begin to restrict the passage of neutral macromolecules until their radius is larger than 375 Å.[19] These cells do, however, contribute to charge selectivity.

There is also a much less numerous second population (less than 0.5 percent) of larger pores that permit the passage of macromolecules (including IgG) as large as 70 Å.[18] In normal subjects, however, only a very small amount of filtrate passes through these pores.

Charge selectivity Molecular charge is a second major determinant of filtration across the GBM.[10,11,20] As illustrated in Fig. 2-3, cationic and neutral dextrans are filtered to a greater degree than anionic dextran sulfates of similar molecular sizes. This inhibitory effect of charge is due in part to *electrostatic repulsion* by anionic sites both in the endothelial fenestrae and in the GBM. The negative charge is primarily composed of heparan sulfate proteoglycans* (which are produced by the glomerular epithelial and endothelial cells).[2,21]

Albumin is a polyanion in the physiologic pH range. As with dextran sulfate, albumin filtration is only about 5 percent that of neutral dextran of the same molecular radius. Thus, charge as well as size limits the filtration of albumin. However, the importance of charge selectivity may not be as great as previously thought.[23,24]

Dextran infusions have also been used in humans both to assess normal function and to determine the mechanism of the increase in protein excretion that typically occurs in glomerular diseases.[20,25] As illustrated in Fig. 2-4, for example, there is an increased number of larger pores, as evidenced by a selective elevation in the clearance of neutral dextrans that are larger than 52 Å in diameter. Tunnels and cavities in the glomerular basement membrane appear to be the pathways for protein leakage.[26]

The net effect of loss of size selectivity is enhanced excretion of IgG (radius about 55 Å) as well as albumin.[27] This pattern has been demonstrated in most glomerular diseases, including membranous nephropathy, minimal change disease, focal glomerulosclerosis, and diabetic nephropathy.[20,28,29] In these conditions, however, the size defect can account for all of the increase in albumin excretion in only about one-half of cases, suggesting a concurrent defect in charge selectivity which may be most prominent in minimal change disease.[25]

Figure 2-4 also illustrates an important clinical difference between the filtration of larger proteins and that of smaller solutes and water. The reduced clearance of smaller molecules in most proteinuric states reflects a decrease in surface area (due to fewer functioning pores) induced by the glomerular disease. At the same time, there is increased clearance of large proteins due to an enhanced number of larger pores (which still represent a very small fraction of the total

* A different anionic compound, podocalyxin, lines the sides of the epithelial cell foot processes and is probably responsible, again by electrostatic repulsion, for maintaining the separation of adjacent foot processes.[22]

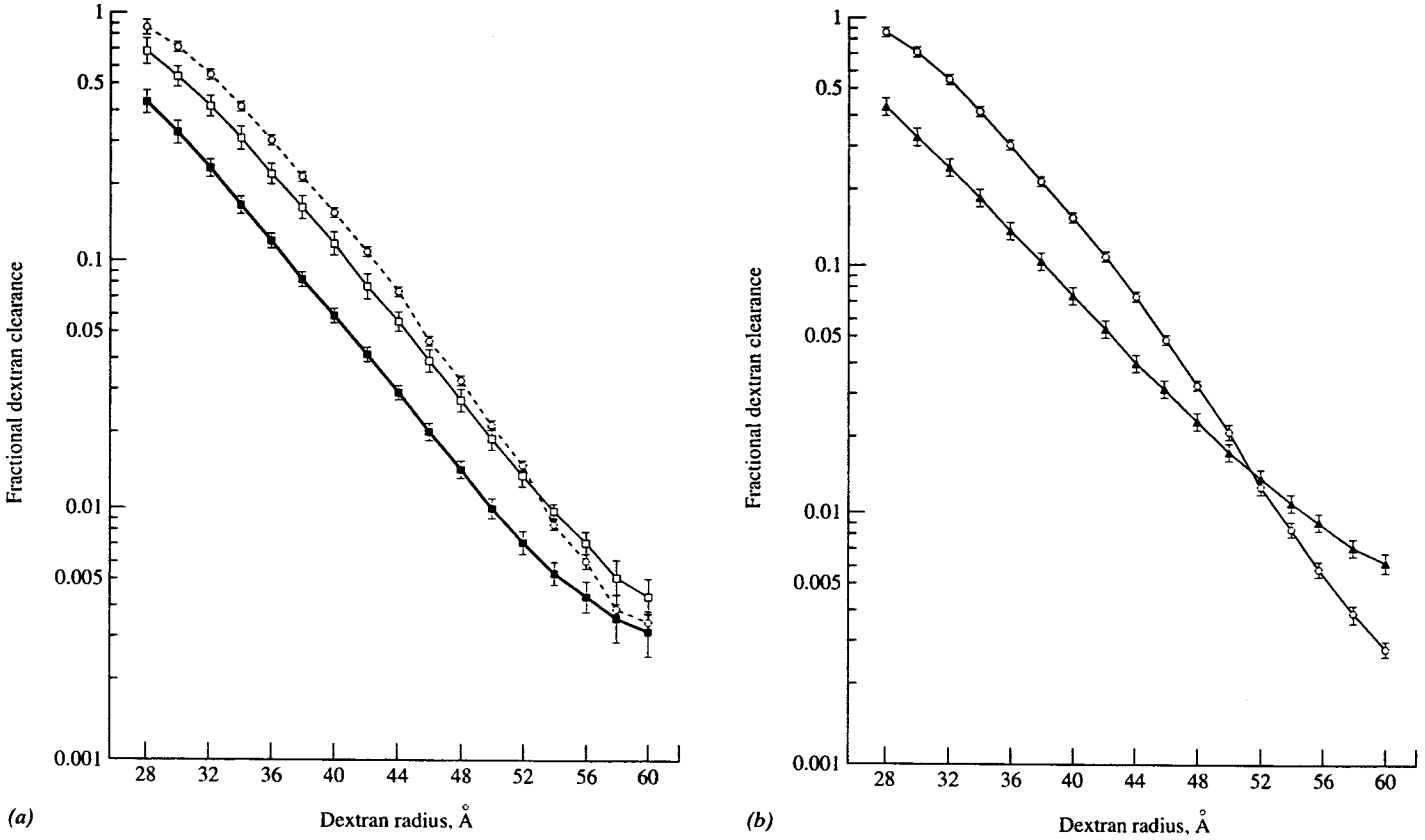

Figure 2-4 Dextran sieving profiles in patients with heavy proteinuria and the nephrotic syndrome. A fractional dextran clearance of 1 represents complete filtration. (*a*) Profiles in patients with minimal change disease when nephrotic (solid squares) and when in remission (open squares) compared to normal controls (open circles). Patients in remission are similar to controls, but during the active phase they have reduced clearance of dextrans of all sizes. Thus, the proteinuria cannot be due primarily to defective size selectivity, suggesting a primary role for loss of charge selectivity. (*b*) Profiles in patients with focal glomerulosclerosis (triangles) compared to normal controls (circles). The patients have decreased clearance of smaller dextrans but increased clearance of dextrans with a radius above 52 Å, suggesting an increased number of larger pores. (*From Guasch A, Hashimoto H, Sibley RK, et al,* Am J Physiol *260:F728, 1991. Used with permission.*)

number of pores) and perhaps partial loss of the charge barrier (which does not affect the filtration of smaller molecules).

Other Functions

The glomerular cells also have synthetic, phagocytic, and endocrine functions. The epithelial cells, for example, are thought to be responsible for the synthesis of the GBM and for the removal of circulating macromolecules that are able to pass through the GBM and enter the subepithelial space.[2,30] The endothelial cells, on the other hand, regulate vasomotor tone, in part via the release of prostacyclin, endothelin, and nitric oxide. They may also play an important role in inflammatory disorders involving the glomerulus by expressing adhesion molecules that promote the accumulation of inflammatory cells.[31]

The mesangium, in comparison, is composed of two different types of cells. One is the mesangial cell, which has microfilaments similar to those of smooth muscle cells.[32,33] After glomerular injury or depopulation of resident mesangial cells, new mesangial cells may originate from cells that normally reside in the juxtaglomerular apparatus.[34] These cells do not appear to be macrophages or smooth muscle or endothelial cells, or to excrete renin.

The intrinsic mesangial cells can respond to angiotensin II (which is locally produced by the endothelial cells in the afferent arteriole) and can synthesize prostaglandins, both of which play an important role in the regulation of glomerular hemodynamics (see below and Chap. 6).[35] These cells also may be involved in immune-mediated glomerular diseases. They can both release a number of cytokines (including interleukin-1, interleukin-6, chemokines, and epidermal growth factor) and proliferate in response to cytokines (such as platelet-derived growth factor and epidermal growth factor).[33,36,37] These actions can contribute to the hypercellularity, mesangial matrix expansion, and glomerular injury that are often seen in these disorders.

The second cell type in the mesangium consists of circulating macrophages and monocytes that move into and out of the mesangium. These cells may have a primary phagocytic function, removing those macromolecules that enter the capillary wall but are unable to cross the basement membrane and move into the urinary space; they may also contribute to local inflammation in immune-mediated glomerular diseases.[38] Macromolecule entry into and subsequent removal from the mesangium can occur because most of the mesangium is separated from the capillary lumen only by the relatively permeable fenestrated endothelium, not by basement membrane (see Fig. 2-2).

RENIN-ANGIOTENSIN SYSTEM

Although the physiology of those hormones that importantly affect renal function is discussed in Chap. 6, antiotensin II plays such a central role in the regulation of

the glomerular filtration rate that it is useful to review the renin-angiotensin system at this time.

The *afferent arteriole* of each glomerulus contains specialized cells, called the juxtaglomerular cells (see Fig. 1-4). These cells synthesize the precursor prorenin, which is cleaved into the active proteolytic enzyme renin. Active renin is then stored in and released from secretory granules.[39,40]* More proximal cells in the interlobular artery can also be recruited for renin release when the stimulus is prolonged.[41]

Renal hypoperfusion, produced by hypotension or volume depletion, and increased sympathetic activity are the major physiologic stimuli to renin secretion (Fig. 2-5). There is a gradient of response according to the location of the glomeruli: Renin release is most prominent in the outer cortical (or superficial) glomeruli, with a lesser response being seen in the midcortex and very little renin being secreted in the juxtamedullary glomeruli.[44] This pattern may reflect changes in

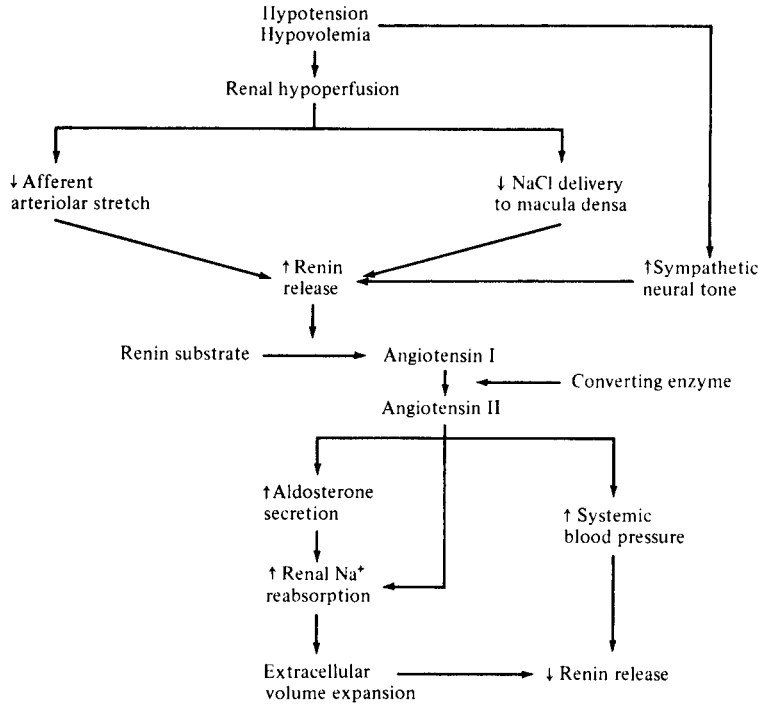

Figure 2-5 Renin-angiotensin-aldosterone system.

*Prorenin is also secreted into the systemic circulation, accounting for 50 to 90 percent of circulating renin.[40] The physiological role of prorenin is unclear, since it has no direct effect on systemic hemodynamics and does not appear to be converted into active renin in the systemic circulation.[42] There is evidence, however, that the uterus also secretes renin and prorenin, and that the latter may play a local role in the regulation of uterine function, particularly during pregnancy.[43]

glomerular perfusion pressure: The juxtamedullary glomeruli are closest to the interlobular artery (Fig. 2-1), whereas the outer cortical glomeruli are furthest away and perfused at a lower pressure. The physiologic significance of these observations is unclear.

Renin initiates a sequence of steps that begins with cleavage of a decapeptide angiotensin I from renin substrate (angiotensinogen), an α_2-globulin produced in the liver (and other organs including the kidney).[45,46] Angiotensin I is then converted into the octapeptide angiotensin II. This reaction is catalyzed by an enzyme called angiotensin converting enzyme (ACE), which is located in the lung, the luminal membrane of vascular endothelial cells, the glomerulus itself, and other organs.

Local Renin-Angiotensin Systems

The concentration of ACE is highest in the lung, and it had been thought that most angiotensin II formation occurred in the pulmonary circulation. It is now clear, however, that there are *extrarenal* renin-angiotensin systems and that angiotensin II can be synthesized at a variety of sites, including the kidney, vascular endothelium, adrenal gland, and brain.[45,47-49] These extrarenal systems may account for the persistent, although low, plasma levels of angiotensin II in anephric subjects.[50]

It is presumed that local angiotensin II production is important for the regulation of local processes. Volume depletion, for example, leads to an increase in renal messenger ribonucleic acid (RNA) expression for both renin (in the glomerulus) and angiotensinogen (in the proximal tubule).[51] Activation of the local renin system may be mediated by local factors such as prostaglandins, nitric oxide, and endothelin.[49]

The proximal tubule also contains ACE and angiotensin II receptors, suggesting that local angiotensin II formation can occur and stimulate Na^+ reabsorption.[52] The observation that the concentration of angiotensin II in the peritubular capillary and proximal tubule is approximately *1000 times* higher than that in the systemic circulation is consistent with the possibility of a local effect.[53] This can be achieved without releasing enough renin into the circulation to induce systemic vasoconstriction.

One clinical consequence of these observations is that measurement of the plasma renin activity or angiotensin II concentration may be a misleading estimate of the tissue activity of this system. In some patients with essential hypertension, for example, angiotensin II appears to be responsible for persistent renal vasoconstriction and sodium retention, even though the plasma levels of renin and angiotensin II are similar to those in hypertensives with normal renal perfusion.[54] These findings suggest a selective increase in the activity of the *intrarenal* renin-angiotensin system; the mechanism by which this occurs is not known. A similar selective activation of the intrarenal renin-angiotensin system may occur in stable congestive heart failure.[46]

Local generation of angiotensin II also can occur in vascular endothelium, where it may play an important role in the regulation of vascular tone and possibly in the development of hypertension.[45,55] Volume depletion increases angiotensinogen messenger (mRNA) levels in aortic smooth muscle. If this results in enhanced release of angiotensinogen, then either locally produced or systemic renin could initiate the sequential formation of angiotensin I and, via endothelial converting enzyme, angiotensin II.

These local effects could explain why ACE inhibitors are very useful antihypertensive agents, even in patients with low plasma renin activity and low circulating levels of angiotensin II.[47,56] Although the findings in humans are only indirect, the potential importance of local renin-angiotensin systems in the genesis of hypertension has been more convincingly demonstrated in experiments in which a mouse renin gene was inserted into rats. The presence of this extra gene for renin led to severe hypertension that was largely corrected by an ACE inhibitor or an angiotensin II receptor antagonist.[57] Despite this evidence for angiotensin-mediated hypertension, the plasma renin activity, plasma angiotensin II level, and renal renin content were all below normal, while adrenal renin content and vascular angiotensin generation were markedly elevated.[57,58] Thus, the elevation in blood pressure in this low (plasma) renin form of hypertension was mediated by local renin release in the adrenal gland and perhaps vascular endothelium.

Actions of Angiotensin II

Angiotensin II has two major systemic effects: systemic vasoconstriction and sodium and water retention. Both of these actions will tend to reverse the hypovolemia or hypotension that is usually responsible for the stimulation of renin secretion (Fig. 2-5).[59,60]

The effects of angiotensin II are mediated by binding to specific angiotensin II receptors: AT_1 and AT_2.[61] The vascular and renal tubular actions are primarily mediated by the AT_1 receptors.[61,62] The effects of the AT_2 receptors are less well understood; they may contribute to the tubular actions of angiotensin II and to the regulation of cell proliferation in the arterial wall.[61,63,64]

Renal sodium and water retention Angiotensin II promotes renal NaCl and H_2O retention and therefore expansion of the plasma volume. This occurs by at least two mechanisms: by direct stimulation of Na^+ reabsorption in the early proximal tubule[60,65,66] and by increased secretion of aldosterone from the adrenal cortex, which enhances Na^+ transport in the cortical collecting tubule. Both systemic angiotensin II and angiotensin II generated within the adrenal gland contribute to the stimulation of aldosterone release (see Chap. 6).[51]

The proximal effect of angiotensin II appears to result at least in part from activation of the Na^+-H^+ antiporter in the luminal membrane (see page 000).[67,68,69] This enhancement of Na^+-H^+ exchange appears to be mediated by two angiotension II–dependent pathways (see Figs. 6-1 and 6-2): stimulation of an inhibitory G protein that decreases cyclic AMP generation, thereby minimizing the

normally suppressive effect of cyclic AMP on Na^+-H^+ exchange,[67] and, to a lesser degree, stimulation of phosphatidylinositol turnover, resulting in the generation of protein kinase C.[68]

Studies using a highly specific AT_1 receptor antagonist suggest that angiotensin II may be responsible for as much as 40 to 50 percent of Na^+ and H_2O reabsorption in the initial S_1 segment of the proximal tubule.[64,70] The AT_2 receptors also appear to contribute to this response.[64] There is a much lesser effect in the more distal part of the proximal tubule, where there are fewer angiotensin II receptors.

Systemic vasoconstriction Angiotensin II produces arteriolar vasoconstriction, which, by elevating systemic vascular resistance, increases the systemic blood pressure. In addition to a direct action of angiotensin II on vascular smooth muscle (which appears to be mediated primarily by protein kinase C generation[71]), experimental observations suggest that enhanced sensitivity to and facilitated release of norepinephrine may also play a contributory role.[72,73] However, the applicability of the angiotensin II–norepinephrine relationship to humans is uncertain; it may be that only high angiotensin II levels, such as those seen with advanced congestive heart failure, are sufficient to stimulate norepinephrine release.[74]

The net effect is that angiotensin II plays an *important role in the maintenance of blood pressure* in all circumstances in which renin secretion is enhanced and circulating angiotensin II levels are high. This is true in the hypertension associated with renal artery stenosis (in which renal ischemia stimulates renin release) as well as in normotensive states associated with effective circulating volume depletion,* such as true volume depletion, heart failure, and hepatic cirrhosis.[75-77] As an example, the administration of an angiotensin II inhibitor to a normotensive patient with hepatic cirrhosis can lower the blood pressure by as much as 25 mmHg, possibly leading to symptomatic hypotension.[77]

The vascular action of angiotensin II involves enhanced phosphatidylinositol turnover (see Fig. 6-2), rather than the generation of cyclic AMP, as in the proximal tubule.[78] The ensuing formation of diacylglycerol leads to the release of arachidonic acid, which can then be converted into prostaglandins or, via the lipoxygenase pathway, into metabolites of hydroxyeicosatetraenoic acid.[79] The latter compounds partially mediate angiotensin II–induced vasoconstriction (as well as aldosterone release),[79] whereas vasodilator prostaglandins tend to minimize the increase in vascular resistance.

Regulation of GFR In addition to influencing systemic hemodynamics, angiotensin II plays an important role in the regulation of GFR and renal blood flow.[60] Although the clinical implications of these effects will be discussed below, it is helpful to review them briefly at this time. Angiotensin II can affect renal blood

* The concept of effective circulating volume depletion is defined in Chap. 8.

flow and the GFR by constricting the efferent and afferent glomerular arterioles and the interlobular artery.[80-82] These responses may be mediated at least in part by the local generation of the vasoconstrictor thromboxane A_2.[83]

Although both afferent and efferent arterioles are constricted, the efferent arteriole has a smaller basal diameter; as a result, the increase in efferent resistance may be as much as three times greater than that at the afferent arteriole.[84]* The net effect is a reduction in renal blood flow (due to the increase in renal vascular resistance) and an elevation in the hydraulic pressure in the glomerular capillary (P_{gc}), which tends to *maintain the GFR* when the renin-angiotensin system is activated by a fall in systemic pressure.

The likelihood of excessive renal vasoconstriction is minimized because angiotensin II also stimulates the release of vasodilator prostaglandins from the glomeruli.[86] The importance of this response can be illustrated by blocking the increase in prostaglandin synthesis with a nonsteroidal anti-inflammatory drug. In this setting, a low-sodium diet leads to more marked renal ischemia and, due to the decline in perfusion, a substantial reduction in GFR (see Fig. 2-10, below).[87] Similarly, the degree of *systemic* vasoconstriction may also be minimized by the local angiotensin II–induced release of prostacyclin.[88]

Angiotensin II has two other effects that can influence the GFR. First, it constricts the glomerular mesangium at higher concentrations, thereby lowering the surface area available for filtration. Second, angiotensin II sensitizes the afferent arteriole to the constricting signal of tubuloglomerular feedback (see "Tubuloglomerular Feedback," below).[60]

The net result is that angiotensin II has counteracting effects on the regulation of GFR: The increase in P_{gc} will tend to increase filtration, while the reduction in renal blood flow and mesangial contraction will tend to reduce filtration. The result is variable in different conditions, although how this occurs is incompletely understood. When renal perfusion pressure is reduced, as in renal artery stenosis, angiotensin II acts to maintain the GFR, and the administration of an ACE inhibitor can cause acute renal failure. In comparison, the GFR may be reduced by angiotensin II in hypertension and congestive heart failure.[60,89]

Control of Renin Secretion

In normal subjects, the major determinant of renin secretion is Na^+ intake: A high intake expands the extracellular volume and decreases renin release, whereas a low intake (or fluid loss from any site) leads to a reduction in extracellular volume and stimulation of renin secretion. Acute increases in renin secretion, as with volume depletion, primarily reflect the release of preformed renin from secretory granules.[40] More chronic stimuli lead to increased synthesis of new prorenin and renin.[40]

* The disparate afferent and efferent effects of angiotensin II may also be in part related to different mechanisms of constriction. Calcium channel blockers abolish the afferent response while having little or no effect on the increase in efferent tone.[85]

The associated changes in angiotensin II and aldosterone production induced by renin then allow Na^+ to be excreted with volume expansion or retained with volume depletion. Intrarenally formed angiotensin II probably plays at least a contributory role in this response, as illustrated by the rise in mRNA for both renin and angiotensin substrate in the renal cortex following a low-sodium diet.[90]

These changes in volume are primarily sensed at one or more of three sites, leading to the activation of effectors that govern the release of renin (Fig. 2-5):[39] (1) baroreceptors (or stretch receptors) in the wall of the afferent arteriole;[91] (2) the cardiac and arterial baroreceptors, which regulate sympathetic neural activity and the level of circulating catecholamines, both of which enhance renin secretion via the β_1-adrenergic receptors;[92,93] and (3) the cells of the macula densa in the early distal tubule (see Fig. 1-4), which appear to be stimulated by a reduction in chloride delivery, particularly in the Cl^- concentration in the fluid delivered to this site.[94,95]

Baroreceptors The baroreceptors respond to changes in stretch in the afferent arteriolar wall. The ensuing alterations in renin release appear to be mediated by enhanced calcium entry into the cells when renal perfusion pressure is increased[96] and by the local release of prostanoids, particularly prostacyclin, when renal perfusion pressure is reduced.[92,97,98]

Macula densa The macula densa dependence upon Cl^- is related to the characteristics of the Na^+-K^+-$2Cl^-$ cotransporter in the luminal membrane of the thick ascending limb and macula densa that promotes the entry of these ions into the cell (see Fig. 4-2).[94,99,100] The activity of this transporter is maximally stimulated at low concentrations of Na^+ and K^+, but is regulated within the physiologic range by alterations in the concentration of Cl^- (see Fig. 4-3).[94] As an example, the decrease in proximal NaCl reabsorption that is seen with volume expansion will enhance the Cl^- concentration at the macula densa, thereby reducing renin secretion. In comparison, the administration of Na^+ with other anions (bicarbonate, acetate) has little effect, since the tubular fluid Cl^- concentration will not rise.[94,95]

The importance of Na^+-K^+-$2Cl^-$ cotransport in the macula densa may explain the ability of loop diuretics to specifically enhance renin release. Although any diuretic can increase renin release by inducing volume depletion, the loop diuretics directly inhibit the Na^+-K^+-$2Cl^-$ transporter (see Chap. 15); as a result, less Cl^- is reabsorbed, thereby stimulating renin secretion.[94,101] The thiazide-type diuretics, on the other hand, inhibit Na^+-Cl^- cotransport primarily in the distal tubule and connecting segment; they do not directly affect the macula densa or renin release.[101]

Two factors may contribute to the mechanism by which the macula densa affects renin secretion: adenosine and PGE_2.[92,96,102,103] As an example, adenosine may mediate at least part of the suppression of renin secretion with NaCl delivery to the macula densa is increased.[102,103] The adenosine required to mediate this response may be derived from the breakdown of adenosine triphosphate (ATP) that occurs as the increase in delivery leads to enhanced local NaCl reabsorption.

On the other hand, the rise in renin release seen when NaCl delivery is reduced (as in hypovolemic states) may be mediated by increased production of PGE_2.[97,104] This effect may be related to enhanced activity of COX-2 (an isoform of cyclooxygenase) in epithelial cells located near the macula densa.[105]

The interaction between the renin-angiotensin system and prostaglandins may seem confusing, since each stimulates the secretion of the other[86,87,92,98] and they induce opposing vascular actions—vasoconstriction with angiotensin II and vasodilation with most prostaglandins. However, angiotensin II is a systemic vasoconstrictor, whereas the prostaglandins act locally, because they are rapidly metabolized when they enter the systemic circulation. Thus, the net effect of simultaneous renal secretion of angiotensin II and prostaglandins is that angiotensin II can cause systemic vasoconstriction and raise the blood pressure, while the prostaglandins minimize the degree of renal vasoconstriction, thereby maintaining renal blood flow and GFR.[87]

The contributions of the three major factors governing renin release can be appreciated from the response to hypovolemia (see Chap. 8). The decrease in volume initially lowers the blood pressure, which diminishes the stretch in the afferent arteriole, increases sympathetic activity, and reduces NaCl delivery to the macula densa (in part by enhancing proximal reabsorption).[94] Each of these changes then promotes renin secretion. This response can be largely abolished by inhibiting its mediators with a combination of indomethacin (which inhibits prostaglandin synthesis) and propranolol (a β-adrenergic blocker).[106]

On the other hand, renin release is diminished by volume expansion (as with a high Na^+ intake). In addition to reversal of the above sequence, atrial natriuretic peptide also may contribute by directly impairing the secretion of both renin and aldosterone.[107]

DETERMINANTS OF GLOMERULAR FILTRATION RATE

The initial step in urine formation is the separation of an ultrafiltrate of plasma across the wall of the glomerular capillary. As with other capillaries, fluid movement across the glomerulus is governed by Starling's forces, being proportional to the permeability of the membrane and to the balance between the hydraulic and oncotic pressure gradients (see Chap. 7):

$$\begin{aligned} GFR &= LpS\ (\Delta \text{ hydraulic pressure} - \Delta \text{ oncotic pressure}) \\ &= LpS\ [(P_{gc} - P_{bs}) - s(\pi_p - \pi_{bs})] \end{aligned} \tag{2-1}$$

where Lp is the unit permeability (or porosity) of the capillary wall, S is the surface area available for filtration, P_{gc} and P_{bs} are the hydraulic pressures in the glomerular capillary and Bowman's space, π_p and π_{bs} are the oncotic pressures in the plasma entering the glomerulus and in Bowman's space, and s represents the reflection coefficient of proteins across the capillary wall (with values ranging from 0 if completely permeable to 1 if completely impermeable). Since the filtrate is essentially protein free, π_{bs} is 0 and s is 1. Thus,

$$GFR = LpS\ (P_{gc} - P_{bs} - \pi_p) \tag{2-2}$$

The GFR in normal adults is approximately 95 ± 20 mL/min in women and 120 ± 25 mL/min in men.[108] This degree of filtration is, per weight, more than 1000 times that in muscle capillaries. Two factors account for this difference: (1) The LpS of the glomerulus is 50 to 100 times that of a muscle capillary, and (2) the capillary hydraulic pressure and therefore the mean gradient favoring filtration ($P_{gc} - P_{bs} - \pi_p$) is much greater in the glomerulus than in a muscle capillary (Table 2-1).[109-111] Although almost all of the filtered electrolytes and water are reabsorbed, the higher GFR is required to allow the filtration and subsequent excretion of a variety of metabolic waste products such as urea and creatinine (see below).

Filtration Equilibrium

Changes in the GFR can be produced by alterations in any of the factors in Eq. (2-2) or in the rate of renal plasma flow (RPF). Before discussing the mechanisms by which these hemodynamic forces are regulated, it is important to first review how they change as fluid moves through the glomeruli. Experimental studies in rats and primates have demonstrated that the hydraulic pressures in the glomerulus and Bowman's space remain relatively constant; the capillary oncotic pressure, however, *progressively rises* due to the filtration of protein-free fluid.

Table 2-1 Approximate values for Starling's forces in muscle and glomerulus[a]

		Glomerulus (primate)	
	Skeletal muscle (human)	Afferent arteriole	Efferent arteriole
Hydraulic pressure			
Capillary	17.3	46	45
Interstitium	−3.0	10	10
Mean gradient	20.3	36	35
Oncotic pressure			
Capillary	28	23	35[b]
Interstitium	8	0	0
Mean gradient	20	23	35
Net gradient favoring filtration ($\Delta P - \Delta\pi$)	+0.3	+13	0
+ = filtration			
− = absorption		(Mean = +6 mmHg)	

[a] Units are mmHg. Values are from Refs. 109 and 110.

[b] The capillary oncotic pressure rises in the glomerulus because of the filtration of relatively protein-free fluid.

The net result of these changes is depicted in Fig. 2-6.[110-112] The gradient favoring filtration normally averages about 13 mmHg at the afferent arteriole but *falls to zero* before the efferent arteriole because of the elevation in plasma oncotic pressure (from 23 to 35 mmHg).

This phenomenon is called *filtration equilibrium* and, in the primate, occurs after the filtration of 20 percent of the RPF, a filtration fraction similar to that seen in humans* (where approximate normal values for the GFR and RPF are 125 and 625 mL/min, respectively). Further filtration *at the same RPF* cannot occur, i.e., the GFR cannot exceed 20 percent of the RPF, without an increase in P_{gc} or a reduction in π_p.

The presence of filtration equilibrium also means that the RPF becomes an important determinant of the GFR.[111,114] If, for example, the RPF is diminished with no alteration in P_{gc}, then filtration equilibrium will still be reached after the filtration of 20 percent of the RPF. Thus, the *GFR will fall in proportion to the decrement in RPF*, so that a 15 percent reduction in RPF will induce a 15 percent decline in GFR. Conversely, a 15 percent elevation in RPF will lead to a 15 percent rise in GFR.

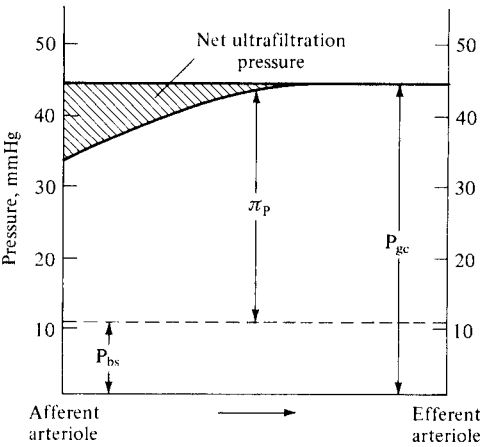

Figure 2-6 Depiction of the hemodynamic forces along the length of the primate glomerular capillary. The dotted line represents the hydraulic pressure in Bowman's space, P_{bs}. The plasma oncotic pressure is added to this so that the middle solid line represents the sum of the forces retarding filtration: $P_{bs}+\pi_p$. The upper solid line represents the glomerular hydrostatic pressure (P_{gc}), and the shaded area depicts the net gradient favoring filtration, $P_{gc} - P_{bs} - \pi_p$, which is +13 mmHg at the afferent arteriole. As a result of ultrafiltration of protein-free fluid, π_p increases until the filtration gradient is abolished and filtration ceases. This is in contrast to muscle capillaries, where filtration is limited by a decline in capillary hydraulic pressure. (*Adapted from Maddox DA, Deen WM, Brenner BM*, Kidney Int *5:271, 1974, and Deen WM, Robertson CR, Brenner BM*, Am J Physiol *223:1178, 1972. Used with permission from* Kidney International.)

*The applicability of this model of glomerular filtration to humans is speculative, since only limited information is available.[112] Studies with glomeruli obtained from cadavers have revealed that the net permeability of the human glomerulus is higher than that in most other animals.[113] As a result, the net gradient favoring filtration has to be only about 4 mmHg, versus 6 mmHg in the primate, as in Table 2-1.

Note that the oncotic pressure of the fluid leaving the efferent arteriole and entering the peritubular capillary is determined both by the protein concentration in the plasma entering the glomerulus and by the degree to which the plasma proteins are concentrated due to the removal of the protein-free filtrate, i.e., by the filtration fraction GFR/RPF. As will be seen, the filtration fraction and the peritubular capillary oncotic pressure are important determinants of proximal tubular sodium and water reabsorption (see page 84).

Capillary Hydraulic Pressure and Arteriolar Resistance

The glomerular capillaries are uniquely interposed between two arterioles. As a result, the P_{gc} is determined by three factors: the aortic pressure, the resistance at the afferent arteriole, and the resistance at the efferent arteriole. The ability to regulate arteriolar resistances permits *rapid regulation of the GFR through changes in the* P_{gc}. Constriction of the *afferent* arteriole, for example, reduces both P_{gc} and GFR, since less of the systemic pressure is transmitted to the glomerulus; dilation of the afferent arteriole, on the other hand, enhances both of these parameters (Fig. 2-7). In comparison, constriction of the *efferent* arteriole retards fluid movement from the glomerulus into the efferent arteriole, increasing P_{gc} and GFR; dilation of the efferent arteriole facilitates fluid entry into the efferent arteriole, diminishing both of these parameters (Fig. 2-7).

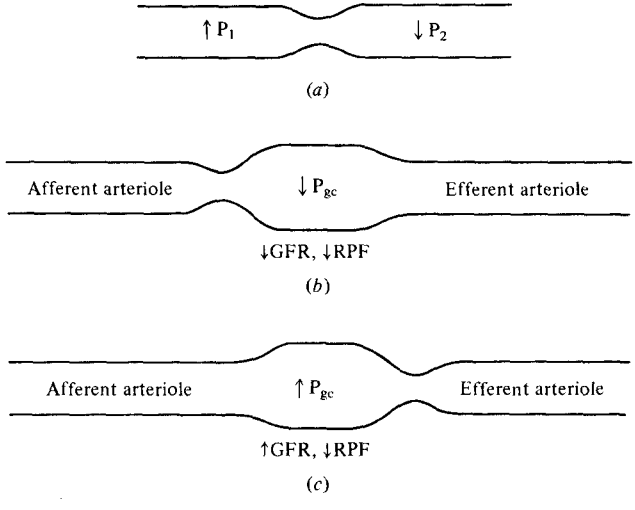

Figure 2-7 Relationship between arteriolar resistance, GFR, and RPF. (*a*) If flow is constant, constriction of a vessel results in a rise in pressure proximally (P_1) and a fall distally (P_2). (*b*) Constriction of the afferent arteriole reduces P_{gc} and GFR. (*c*) Constriction of the efferent arteriole, on the other hand, tends to increase P_{gc} and GFR. Since constriction of either arteriole also increases renal vascular resistance, RPF will fall in both (*b*) and (*c*). Arteriolar vasodilation has the opposite effects. For example, decreasing efferent arteriolar tone (as with an ACE inhibitor, which reduces the formation of angiotensin II) will lower the P_{gc}.

Arteriolar tone also affects the RPF. In the kidney, the resistance to flow across the arterioles constitutes 85 percent of renal vascular resistance, the remaining 15 percent coming from the peritubular capillaries and renal veins.[115] The relationship between RPF, the ΔP across the renal circulation, and renal vascular resistance can be expressed by the following equation:

$$\text{RPF} = \frac{\text{aortic pressure} - \text{renal venous pressure}}{\text{renal vascular resistance}} \tag{2-3}$$

This relation shows that an increase in tone at either end of the glomerulus will elevate total renal resistance and reduce RPF. Thus, GFR and RPF are regulated *in parallel* at the afferent arteriole, e.g., constriction decreases both, and *inversely* at the efferent arteriole, e.g., constriction reduces RPF but may augment P_{gc} and GFR. As a result, alterations in efferent (but not afferent) arteriolar tone affect the ratio of the GFR to the RPF (i.e., the filtration fraction), since these parameters will tend to change in opposite directions.

The opposing effects of efferent arteriolar tone on P_{gc} and RPF also mean that the direct relationship between this resistance and the GFR (Fig. 2-7) must be modified, since the RPF is an independent determinant of GFR. As an example, although efferent arteriolar constriction increases P_{gc}, the concomitant elevation in renal vascular resistance will reduce RPF, which will tend to lower the GFR. Depending upon the magnitude of efferent constriction, the net effect may be an increase, no change, or, if RPF is sufficiently reduced, even a fall in GFR.

Arteriolar resistance is partially under intrinsic myogenic control, but also can be influenced by other factors, including angiotensin II, norepinephrine, renal prostaglandins, atrial natriuretic peptide, endothelin, and tubuloglomerular feedback (see below).

Role of Other Starling's Forces

The other determinants of glomerular filtration in Eq. (2-2) are of much lesser importance in the physiologic regulation of the GFR. The permeability of the glomerular capillary wall, for example, remains relatively constant in most normal conditions.[110,111] Furthermore, *small changes in net permeability will not affect the GFR*, since the attainment of filtration equilibrium means that it is the rise in capillary oncotic pressure, not permeability, that limits the filtration of small solutes and water.[111] A variety of hormones, including angiotensin II, antidiuretic hormone, and prostaglandins, can affect the LpS.[89,116] However, the physiologic significance of these effects is uncertain, although high concentrations of angiotensin II can lead to a net decline in GFR in some settings.[89] Similarly, a reduction in LpS in disease states such as glomerulonephritis can contribute to the fall in GFR that is commonly observed; this problem is due primarily to a reduction in the surface area available for filtration.[117] The reduction in permeability becomes a limiting factor, because it is now severe enough to prevent filtration equilibrium from being reached.

Alterations in P_{bs} or the plasma oncotic pressure also affect the GFR only in disease states.[111] As an example, ureteral or intratubular obstruction leads to an increase in P_{bs}, thereby reducing the hemodynamic gradient favoring glomerular filtration.[118] On the other hand, volume depletion due to vomiting or diarrhea can result in hemoconcentration and a rise in the plasma protein concentration. This increases π_p, contributing to the decrease in GFR that may be seen in this setting.

REGULATION OF GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW

Regulation of renal hemodynamics is primarily achieved via changes in arteriolar resistance, which can affect both RPF [from Eq. (2-3)] and GFR (by altering P_{gc} and RPF). In normal subjects, for example, changes in posture or diet can produce alterations in renal perfusion pressure. In this setting, two closely related *intrarenal* phenomena, autoregulation, and tubuloglomerular feedback, interact to maintain the GFR and RPF at a relatively constant level.[119] In comparison, pathophysiologic states, such as volume depletion, can lead to activation of systemic neurohumoral factors that can override these intrarenal effects.

Autoregulation

Since P_{gc} is an important determinant of GFR, it might be expected that small variations in arterial pressure could induce large changes in GFR. However, the GFR and RPF remain roughly constant over a wide range of arterial pressures (Fig. 2-8).[120,121] This phenomenon, which is also present in other capillaries,[122] is intrinsic to the kidney, occurring in denervated, perfused kidneys, and has been termed *autoregulation.*

Since the GFR and RPF are maintained in parallel, autoregulation must be mediated in part by changes in afferent arteriolar resistance (Fig. 2-7).[119,123] As systemic pressure rises, for example, an increase in afferent arteriolar tone prevents the elevation in pressure from being transmitted to the glomerulus, allowing P_{gc} and GFR to remain unchanged.[123] The enhanced arteriolar resistance also increases total renal vascular resistance, and, from Eq. (2-3), this increase in vascular tone balances the rise in pressure and minimizes any change in RPF.

Conversely, as blood pressure decreases, *afferent arteriolar dilation* will initially protect both GFR and RPF. However, the ability to maintain renal hemodynamics becomes impaired at mean arterial pressures below 70 mmHg. In this setting, GFR and RPF fall in proportion to the drop in blood pressure, and the GFR ceases when the systemic pressure reaches 40 to 50 mmHg.

The mechanism by which autoregulation is mediated is incompletely understood. The simplest hypothesis is that myogenic stretch receptors in the wall of the afferent arteriole are of primary importance, similar to the role of the precapillary sphincterin the muscle capillary.[122] An elevation in renal perfusion pressure, for example, will increase the degree of stretch, which will then promote arteriolar constriction;[123] this effect is mediated in part by increased cell entry of calcium.[124]

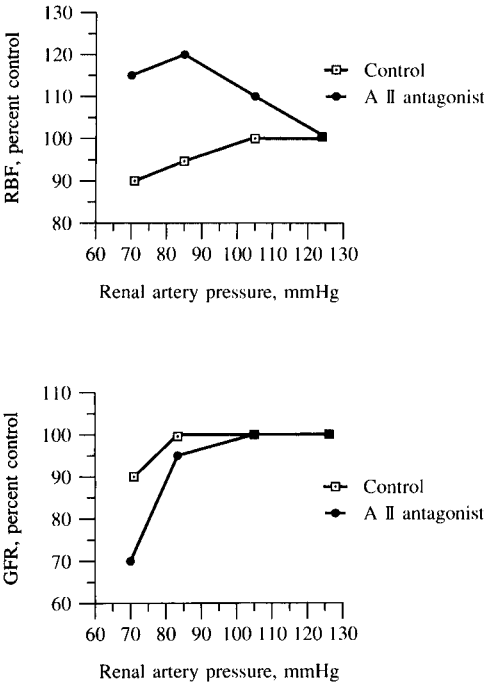

Figure 2-8 Effect of reducing renal artery pressure (from a baseline value of about 125 mmHg) on renal blood flow (RBF) and GFR, expressed as a percentage of control values in dogs fed a normal-sodium diet. The open squares represent control animals in which both RBF and GFR were maintained until the pressure was markedly reduced. The closed symbols represent animals given an intrarenal infusion of an angiotensin II antagonist; autoregulation of RBF was maintained (with an increase in the baseline level because of the fall in renal vascular resistance), but the GFR was less well regulated. Although not shown, autoregulation also applies when the renal artery pressure is initially raised. (*Adapted from Hall JE, Guyton AC, Jackson TE, et al,* Am J Physiol *233:F366, 1977. Used with permission.*)

The efferent arterioles, in comparison, have different characteristics: They do not seem to respond directly to changes in stretch and therefore do not contribute directly to the myogenic response.[125] Why this occurs is not clear, but the apparent absence of voltage-gated Ca^{2+} channels in the efferent arterioles may play a contributory role.[126]

However, autoregulation of GFR is mediated by more than myogenic responses, as both angiotensin II (when the renal perfusion pressure is reduced) and tubuloglomerular feedback (especially when renal perfusion pressure is increased; see below) can play an important role.[121,127] Other regulators of renal vascular resistance, such as the vasodilator nitric oxide (endothelium-dependent relaxing factor), do not appear to participate in autoregulation.[128]

As illustrated in Fig. 2-8, for example, the administration of an angiotensin II antagonist results in the dissociation of the autoregulation of RPF and GFR.[121] As described above, the renin-angiotensin system is activated as renal perfusion pressure is lowered, resulting in both local and systemic generation of angiotensin II.[129] The preferential increase in efferent arteriolar resistance induced by angiotensin II contributes to autoregulation of GFR by preventing any fall in P_{gc}; consequently, infusion of an angiotensin II antagonist or an ACE inhibitor leads to less effective maintenance of the GFR. This *angiotensin II dependence is most prominent when the renal perfusion pressure is substantially reduced* (Fig. 2-8). Autoregulation of GFR with the initial decrease in renal artery pressure is primarily mediated by TGF and the stretch receptors.[127]

Clinical Implications Patients with bilateral renal artery stenosis, due most often to atherosclerotic lesions, have an elevated pressure proximal to the stenosis but a normal or reduced pressure distal to the stenosis. As a result, the administration of antihypertensive therapy to lower the systemic blood pressure is likely to diminish the distal renal artery pressure (which includes that perfusing the glomeruli) to a level that is below normal. In this setting, autoregulation plays an important role in maintaining P_{gc} and GFR, a response that can be partially impaired by diminishing the production of angiotensin II with an ACE inhibitor. Up to one-half of such patients given an ACE inhibitor will have a usually mild decline in GFR, although severe (and reversible) renal failure can occur.[130,131] Diuretic-induced volume depletion appears to be an important risk factor for this problem, since it makes maintenance of the GFR even more angiotensin II–dependent.[121,132]

A similar decline in GFR can occur in the affected kidney in *unilateral* renal artery stenosis.[133] a change that can lead to eventual ischemic atrophy.[134] This is not easy to detect clinically, however, since the presence of the contralateral nonstenotic kidney prevents the development of acute renal failure (as would be evidenced by a rise in the plasma creatinine concentration; see below).

Other medications are less likely to produce this problem, since they do not interfere with autoregulation.[130,135] However, the ability of autoregulation to protect the GFR is impaired if the perfusion pressure is markedly reduced (Fig. 2-8). Thus, any antihypertensive agent can produce acute renal failure when there are *severe and bilateral* renovascular lesions (or a marked unilateral lesion in a solitary kidney).[135]

The risk of acute renal failure after ACE inhibition is not limited to renovascular disease, but can occur in any condition in which renal perfusion pressure is reduced. As an example, ACE inhibitors are standard therapy in heart failure, leading to increases in cardiac output, patient survival, and renal blood flow, as well as an improvement in functional status. Despite all of these beneficial changes, the GFR falls in about one-third of cases, presumably due to a reduction in P_{gc} induced by efferent arteriolar dilation.[136,137] This is most likely to occur in patients with a diastolic pressure below 70 mmHg who are being treated with high doses of diuretics.

Although the autoregulatory changes in arterial and arteriolar resistance are reversed when the renal perfusion pressure is elevated, angiotensin II levels are low in the basal state and it is unlikely that any further reduction is responsible for the maintenance of GFR. There is, however, substantial evidence for the role of tubuloglomerular feedback in this setting.

Tubuloglomerular Feedback

Tubuloglomerular feedback (TGF) refers to the alterations in GFR that can be induced by changes in tubular flow rate (Fig. 2-9). This phenomenon is mediated

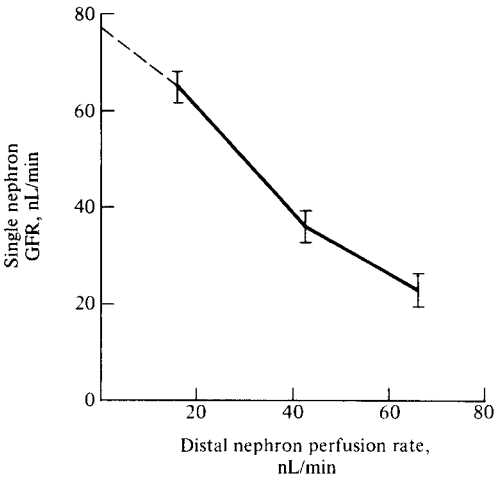

Figure 2-9 Relationship of single nephron GFR to distal nephron (macula densa) perfusion rate in dogs. As the perfusion rate increases (via the insertion of a micropipette into the late proximal tubule), there is a progressive reduction in GFR to a minimum of about one-half the basal level. (*From Navar LG*, Am J Physiol *234:F357, 1978. Used with permission.*)

by the specialized cells in the *macula densa* segment at the end of the cortical thick ascending limb of the loop of Henle; these cells sense changes in the delivery and subsequent reabsorption of chloride.[94,99,100] The importance of chloride is, as described previously, probably related to the chloride dependence of the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane that promotes the entry of these ions into the cell (see Fig. 4-3).[94,99,100]

TGF plays an important role in autoregulation.[127,141] An elevation in renal perfusion pressure can activate TGF via an initial rise in GFR; the ensuing increase in macula densa chloride delivery will then initiate a response that *returns both GFR and macula densa flow toward normal* (Fig. 2-9). This effect is mediated primarily by afferent arteriolar constriction, thereby decreasing the intraglomerular hydraulic pressure.[123,142]

If, on the other hand, the Na^+-K^+-$2Cl^-$ cotransporter in a single nephron is inhibited by a loop diuretic (such as furosemide), there is a marked impairment in autoregulation as renal perfusion pressure is increased.[142] That part of the autoregulatory response that persists has been thought to reflect myogenic, stretch-induced vasoconstriction.[124,142] There is, however, an alternative possibility: *cooperativity* among adjacent nephrons supplied by a common arterial branch.[143] The afferent vasoconstriction occurring in one nephron may be transmitted back up the artery and lead to vasoconstriction in adjacent nephrons. Thus, the in vivo effect of increasing distal Cl^- delivery in all nephrons will lead to a greater degree of afferent vasoconstriction in a single nephron than is induced by the macula densa in that nephron.

Mediators The factors that mediate TGF are incompletely understood.[140] The afferent site of constriction seen with increased distal flow involves the cells of the juxtaglomerular apparatus that are responsible for renin secretion.[123] Although this observation suggests an important role for angiotensin II in tubuloglomerular

feedback, this hormone appears to play a permissive role, perhaps by sensitizing the afferent arteriole to the true mediator.[144] This action of angiotensin II appears to be relatively specific, since other vasopressors such as norepinephrine and antidiuretic hormone (ADH) do not have a similar effect.[145]

The sensitizing action on TGF is essential if angiotensin II is to contribute to maintenance of the effective circulating volume by decreasing Na^+ excretion (see above).[146] The angiotensin II–mediated increase in proximal reabsorption will diminish distal flow, which should, via a decrease in the TGF signal, raise the GFR to return distal delivery to the baseline level. This response is minimized by the associated increase in sensitivity of the afferent arteriole to the mediator of TGF, thereby permitting the desired reduction in Na^+ excretion.[146]

Despite its modulating effect, angiotensin II is not the primary mediator of TGF, since changes in renin release do not correlate with TGF. As an example, increasing distal NaCl delivery will activate TGF at the same time that macula densa–mediated renin release is diminished.

There is suggestive evidence that the changes in arteriolar resistance associated with TGF may be mediated by alterations in the local release of *adenosine*,[102] which can induce the observed constriction of the afferent arteriole.[147] The TGF response to increased NaCl delivery is largely inhibited by blockade of the adenosine receptor and/or adenosine formation.[148,149] How adenosine secretion might be regulated in this setting is unknown. One possibility is that raising the GFR will increase sequentially the filtered Na^+ load, tubular sodium reabsorption, and the utilization of ATP, which results in the generation of adenosine.[102]

The adenosine hypothesis can also explain how the macula densa can concurrently perform two functions: regulating TGF and renin secretion. The increase in adenosine release with volume expansion can both activate TGF[148] and inhibit renin release.[102,103]

Another vasoconstrictor that may participate in TGF is thromboxane. Thromboxane production is increased when TGF is activated, the administration of a thromboxane mimetic increases the sensitivity of TGF, and the TGF response is blunted by a thromboxane antagonist.[151] ATP itself is also a constrictor of the afferent arteriole that may contribute to TGF.[152]

Vasodilator responses in TGF occur when macula densa flow is reduced. This may be mediated in part by reduced availability of the above vasoconstrictors.[153]

An additional significant regulator of TGF is *nitric oxide* (NO). NO, a molecular gas synthesized by cells in the macula densa, *blunts* the TGF response to increase sodium chloride delivery.[154]

NO release from the macula densa is increased in this setting, thereby countering the afferent arteriole constriction elicited in the TGF response. Thus, changes in macula densa NO production may underlie the resetting of TGF that occurs when salt intake is varied; the response is appropriately blunted with a high-salt diet, as maintenance of glomerular filtration promotes excretion of the excess salt.[155]

An alternative hypothesis suggests that changes in *interstitial Cl^- concentration or osmolality* constitute the signal for alterations in arteriolar resistance. The interstitial region bordered by the early distal tubule (including the macula densa) and the glomerular arterioles (see Fig. 1-4) is poorly perfused; as a result, solutes transported into this area from the luminal fluid are removed slowly, because they must diffuse over a relatively long distance before they can enter the peritubular capillaries.

Direct measurements in this region have demonstrated that, as distal flow rate and therefore macula densa Cl^- reabsorption are progressively increased, there is a rise in the local interstitial Cl^- concentration from about 150 meq/L (similar to that in plasma) to *over 600 meq/L.*[156] This increase in solute concentration or in osmolality may then directly increase afferent arteriolar tone.[150] In comparison, the interstitial Cl^- concentration remains relatively constant in areas that are further away from the juxtaglomerular region.[156] These sites are better perfused, and reabsorbed NaCl is rapidly removed by the peritubular capillaries.

Functions A major function of autoregulation and TGF is to *prevent excessive salt and water losses.* To understand this concept, it is important to appreciate the differences in function between the proximal and distal segments of the nephron. The bulk of the filtrate (about 90 percent) is reabsorbed in the proximal tubule and loop of Henle, with the final *qualitative* changes in urinary excretion (such as hydrogen and potassium secretion and maximum sodium and water reabsorption) being made in the distal nephron, particularly in the collecting tubules. The collecting tubules, however, have a relatively limited *total* reabsorptive capacity. Thus, the ability of the macula densa to decrease the GFR when distal delivery is enhanced prevents distal reabsorptive capacity from being overwhelmed, which could lead to potentially life-threatening losses of sodium and water. Viewed in this light, it may be that it is *macula densa flow itself, not the GFR*, that is being maintained by autoregulation and TGF.[157]

A possible clinical example of TGF is the fall in GFR seen in acute tubular necrosis, the most common form of acute renal failure developing in the hospital. In this disorder, proximal and loop sodium reabsorption are impaired by ischemic or toxic tubular damage. Thus, the reduction of GFR (which is not easily explained by any histologic abnormality) may in part represent an *appropriate* TGF response to maintain sodium balance.[138,158] Similarly, TGF also mediates the reduction in GFR that occurs when proximal reabsorption is partially impaired by the administration of the carbonic anhydrase inhibitor acetazolamide, a proximally acting diuretic that can be useful in patients with edema and metabolic alkalosis (see page 451).[159]

On the other hand, glucosuria seems to *impair* TGF by an unknown mechanism that is in part mediated by the increase in tubular fluid glucose concentration.[138] This may play an important role in the marked fluid losses typically seen in diabetic ketoacidosis or nonketotic hyperglycemia (see Chap. 25). The osmotic diuresis induced by glucose reduces sodium and water transport in the proximal tubule and loop of Henle.[160] If TGF were normally active, the

ensuing increase in delivery to the macula densa would diminish the GFR, thereby minimizing the degree of fluid loss.

Neurohumoral Influences

The intrarenal effects of autoregulation and TGF are likely to be most important in the day-to-day regulation of renal hemodynamics in normal subjects. Autoregulation also may help to maintain the GFR in patients with hypertension or with *selective* renal ischemia, as with bilateral renal artery stenosis. In fact, many of the experimental studies of autoregulation have been performed by using a suprarenal aortic clamp to selectively alter renal perfusion pressure.[121,127]

In patients, however, renal artery pressure is most often reduced because of effective circulating volume depletion (as with true volume depletion, heart failure, or cirrhosis; see Chap. 8). In these disorders, there is marked stimulation of the vasoconstrictor sympathetic nervous and renin-angiotensin systems.[76,161] As described previously, angiotensin II increases the resistance in the efferent and to a lesser degree the afferent arteriole.[80,82] In comparison, norepinephrine (either circulating or released from the renal sympathetic nerves) directly increases afferent tone and indirectly, via stimulation of the release of renin and angiotensin II, enhances efferent resistance.[80,162]

Thus, a reduction in systemic prefusion pressure is associated with renal neurohumorally mediated vasoconstriction rather than autoregulation and TGF-induced vasodilatation. The effect of these changes varies with the degree of neurohumoral activation. A relatively mild increase in renal sympathetic tone may produce no change in baseline renal perfusion, but may be sufficient to impair autoregulation (and therefore maintenance of GFR) as renal perfusion pressure is reduced.[163] In comparison, patients with advanced heart failure or severe volume depletion have more marked increments in norepinephrine and angiotensin II. In this setting, RPF is reduced at rest with a lesser fall or no change in GFR, since efferent constriction increases the P_{gc}.[80,162] This is a very effective adaptation because it preferentially shunts perfusion to the critical coronary and cerebral circulations while maintaining GFR and therefore excretory capacity.

Renal vasodilator prostaglandins play an important role in modifying these vasoconstrictive effects. Both angiotensin II and norepinephrine stimulate glomerular prostaglandin production.[86,164] The ensuing attenuation in the degree of arteriolar constriction prevents *excessive* renal ischemia, which might otherwise be induced by the high local concentration of vasoconstrictors.[87,165] To a lesser degree, increased secretion of vasodilator kinins by the kidney also may act to preserve renal perfusion in this setting.[165]

Clinical Implications The clinical importance of these protective vasodilator responses has been amply demonstrated in humans by the administration of nonsteroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis.[167] These agents, which are widely used in the treatment of arthritis and other disorders, have little effect on renal function when given to normo-

volemic subjects in whom the baseline level of renal prostaglandin production is relatively low.

The nonsteroidal anti-inflammatory drugs can, however, produce an acute decline in GFR and renal plasma flow when given to patients with high angiotensin II and norepinephrine levels. This most often occurs with effective circulating volume depletion due, for example, to heart failure or cirrhosis. In these conditions, prostaglandin synthesis is appropriately enhanced, and administration of a nonsteroidal anti-inflammatory drug can lead to unopposed action of the vasoconstrictors and acute renal failure (Fig. 2-10).[167,168] Studies in animals indicate that both afferent and efferent resistance are increased in this setting; the ensuing reduction in renal perfusion leads to a fall in GFR which, as mentioned above, is flow-dependent.[165]

The decrease in renal perfusion seen with effective volume depletion is also typically associated with a marked alteration in the *distribution of intrarenal blood flow*. Under normal circumstances, approximately 80 percent of renal blood flow goes to the outer cortex (where most of the glomeruli are located), 10 to 15 percent to the inner cortex (the site of the juxtamedullary nephrons; see Fig. 1-3), and the remaining 5 to 10 percent to the medulla. With hypovolemia, however, there is a marked reduction in outer cortical flow, with a preferential increase in perfusion to the inner cortex.[168-171] The mechanism by which these changes occur is unknown; angiotensin II, catecholamines, and prostaglandins have all been implicated, but their role is unproven.[171]

The physiologic significance of this intrarenal shunting of renal blood flow is also uncertain. It has been postulated that increasing inner cortical flow might promote Na^+ retention in hypovolemic states because the juxtamedullary nephrons, with their long loops of Henle, have a greater reabsorptive surface

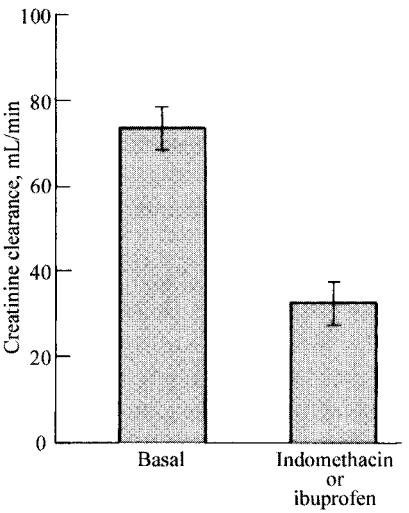

Figure 2-10 Reduction in GFR, as estimated from the creatinine clearance, from a mean of 73 mL/min down to 32 mL/min after the administration of a nonsteroidal anti-inflammatory drug (indomethacin or ibuprofen) to 12 patients with stable hepatic cirrhosis and ascites. Urinary prostaglandin E_2 excretion was substantially greater than normal in these subjects and was markedly reduced following therapy. (*From Zipse RD, Hoefs JC, Speckhart PF, et al*, J Clin Endocrinol Metab *48:895, 1979. Copyright by The Endocrine Society, 1979. Used with permission.*)

than those in the outer cortex. However, redistribution of blood flow is not necessarily associated with redistribution of glomerular filtration, making this hypothesis less likely.[172]

Volume expansion In contrast to these hormonal changes with volume depletion, volume expansion (as with a high-sodium diet) tends to be associated with increased renal perfusion and perhaps a mild rise in GFR.[54] Reduced secretion of angiotensin II and norepinephrine and enhanced release of dopamine and atrial natriuretic peptide all may contribute to this response (see Chap. 8).

- Dopamine dilates both the afferent and efferent arterioles,[119] thereby raising renal blood flow while producing a lesser increment or no change in GFR.
- Atrial natriuretic peptide, on the other hand, appears to produce the unusual combination of afferent dilation and efferent constriction, both of which will raise P_{gc} and therefore the GFR; there is a lesser alteration in RPF, since total renal vascular resistance is relatively unchanged.[173]

These hormonal alterations also facilitate excretion of the excess sodium: The release of those agents that enhance sodium reabsorption (angiotensin II, aldosterone, and norepinephrine) is diminished, whereas that of atrial natriuretic peptide and dopamine is enhanced.

Endothelin and nitric oxide Endothelin, released locally from endothelial cells, is another potent renal vasoconstrictor that affects both afferent and efferent glomerular arterioles, leading to reductions in renal blood flow and GFR.[174-176] As with the other renal vasoconstrictors, the degree of ischemia is minimized by endothelin-induced release of prostacyclin.[177]

Although endothelin is probably not an important regulator of renal hemodynamics in normal subjects, it may play a role in the reduction in GFR seen in postischemic acute renal failure. In this setting, endothelial injury may lead to the release of endothelin and subsequent renal vasoconstriction.[178] A similar mechanism may contribute to the decrease in renal perfusion induced by cyclosporine.[179,180]

Another vasoactive factor released from the endothelial cells (in addition to prostacyclin and endothelin) is nitric oxide. Nitric oxide appears to be released tonically in the renal circulation, thereby lowering renal vascular resistance (in contrast to the vasoconstrictive effect of endothelin).[174,181,182]

Glomerular hemodynamics and progressive renal failure Arteriolar resistance and renal hemodynamics also may play an important role in patients with underlying chronic renal disease. A large body of experimental and clinical evidence suggests that *intraglomerular hypertension* is partially responsible for the progression of many disorders to end-stage renal failure.[183,184]

According to this theory, the loss of nephrons (due to almost any renal disease) leads to a compensatory rise in filtration in the remaining more normal nephrons. This is an appropriate response in the short term, as it tends to maintain the total GFR. It is driven by afferent arteriolar dilatation, which leads to a rise in both P_{gc} and plasma flow. The elevation in intraglomerular pressure, however, appears to be maladaptive in the long term, since it tends to lead to progressive glomerular damage. Similar findings are seen in diabetic nephropathy, except that the renal vasodilatation is a primary event, induced in some way by hyperglycemia or insulin deficiency.[185,186]

These observations are of potentially great clinical importance, since treatment can be aimed at reversing the hemodynamic adaptations. Both dietary protein restriction and antihypertensive therapy, perhaps preferentially with an ACE inhibitor, can lower the intraglomerular pressure and diminish the degree of glomerular injury in experimental models of renal disease. Several clinical trials in chronic renal disease in humans suggest that administration of an ACE inhibitor can slow the rate of loss of GFR, particularly in diabetic nephropathy.[187-190] The efficacy of dietary protein restriction remains controversial,[191-193] with evidence of benefit being best in patients with diabetic nephropathy.[194]

The apparent preferential benefit of ACE inhibition compared to other antihypertensive drugs is thought to be related to reversal of angiotensin II–induced constriction of the efferent arteriole. Decreasing vascular resistance at this site will directly lower the intraglomerular pressure, independent of the reduction in the systemic blood pressure (Fig. 2-8).

Summary

The GFR is normally maintained within relatively narrow limits to prevent inappropriate fluctuations in solute and water excretion. Regulation of the GFR is primarily achieved by alterations in arteriolar tone that influence both the hydraulic pressure in the glomerular capillary and renal blood flow. In normal subjects, the GFR is maintained by autoregulation, a phenomenon that is mediated by at least three factors: stretch receptors in the afferent arteriole, angiotensin II, and tubuloglomerular feedback.[127] These responses, however, can be overridden by neurohumoral vasoconstiction in hypovolemic states, in an attempt to maximize coronary and cerebral perfusion.

CLINICAL EVALUATION OF RENAL CIRCULATION

Concept of Clearance and Measurement of GFR

Estimation of the GFR is an essential part of the evaluation of patients with renal disease. Since the total kidney GFR is equal to the sum of the filtration rates in each of the functioning nephrons, the total GFR can be used as an *index of functioning renal mass*. As an example, the loss of one-half of the functioning nephrons will lead to a significant decline in the GFR (which may be only 20 to

30 percent, not 50 percent, due to compensatory hyperfiltration in the remaining nephrons). At this time, fluid and electrolyte balance may still be maintained and the urinalysis may be normal. Thus, the fall in GFR may be the *earliest and only clinical sign of renal disease.*

Serial monitoring of the GFR can also be used to estimate the severity and to follow the course of kidney disease. A reduction in GFR implies either progression of the underlying disease or the development of a superimposed and potentially reversible problem, such as diminished renal perfusion due to volume depletion. An increase in GFR, on the other hand, indicates improvement or possibly hypertrophy in the remaining nephrons.

Measurement of the GFR is also helpful in determining the proper dosage of those drugs that are excreted by the kidney by glomerular filtration. When the GFR falls, drug excretion will be reduced, resulting in an increase in plasma drug levels and potential drug toxicity. To prevent this, drug dosage must be lowered in proportion to the decrease in GFR.

How can the GFR be measured? Consider a compound, such as the fructose polysaccharide inulin (not insulin), with the following properties:

1. Able to achieve a stable plasma concentration
2. Freely filtered at the glomerulus
3. Not reabsorbed, secreted, synthesized, or metabolized by the kidney

In this situation,

$$\text{Filtered inulin} = \text{excreted inulin}$$

The filtered inulin is equal to the GFR times the plasma inulin concentration (P_{in}), and the excreted inulin is equal to the product of the urine inulin concentration (U_{in}) and the urine volume (V, in milliliters per minute or liters per day). Therefore,

$$\text{GFR} \times P_{in} = U_{in} \times V \tag{2-4}$$

$$\text{GFR} = \frac{U_{in} \times V}{P_{in}} \tag{2-5}$$

The term $(U_{in} \times V)/P_{in}$ is called the clearance of inulin and is an accurate estimate of the GFR. The inulin clearance, in mL/min, refers to that volume of plasma cleared of inulin by renal excretion. If, for example, 1 mg of inulin is excreted per minute ($U_{in} \times V$) and the P_{in} is 1.0 mg/dL (or, to keep the units consistent, 0.01 mg/mL), then the clearance of inulin is 100 mL/min; that is, 100 mL of plasma has been cleared of the 1 mg of inulin that it contained.

Use and Limitations of Creatinine Clearance

Despite its accuracy, the inulin clearance is rarely performed clinically because it involves both an intravenous infusion of inulin and an assay for inulin that is not

available in most laboratories. The most widely used method to estimate the GFR is the endogenous *creatinine clearance.*[108,195]

Creatinine is derived from the metabolism of creatine in skeletal muscle and is released into the plasma at a relatively constant rate. As a result, the plasma creatinine concentration (P_{cr}) is very stable, varying less than 10 percent per day in serial observations in normal subjects.

Like inulin, creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, some creatinine enters the urine by tubular secretion via the organic cation secretory pump in the proximal tubule, resulting in creatinine excretion exceeding the amount filtered by 10 to 20 percent.[108] Thus, the creatinine clearance (C_{cr})

$$C_{cr} = \frac{U_{cr} \times V}{P_{cr}} \tag{2-6}$$

will tend to exceed the inulin clearance by 10 to 20 percent. Fortuitously, this is balanced by an error of almost equal magnitude in the measurement of the P_{cr}. One method involves a colorimetric reaction after the addition of alkaline picrate. The plasma, but not the urine, contains noncreatinine chromogens (acetone, proteins, ascorbic acid, pyruvate), which account for approximately 10 to 20 percent of the normal P_{cr}.[108] Since both the U_{cr} and the P_{cr} are elevated to roughly the same degree, the errors tend to cancel out and the creatinine clearance is a reasonably accurate estimate of the GFR, particularly in the patient with relatively normal renal function. The normal values of the creatinine clearance are approximately 95 ± 20 mL/min in women and 120 ± 25 mL/min in men.[108]

The creatinine clearance is usually determined in the following way. The plasma creatinine concentration is measured in a venous blood sample, and the $U_{cr} \times V$ is concomitantly measured with a 24-h urine collection, since shorter collections tend to give less reliable results. Suppose, for example, that a 30-year-old woman who weighs 60 kg is being evaluated for the possible presence of renal disease and the following results are obtained:

$$P_{cr} = 1.2 \text{ mg/dL}$$

$$U_{cr} = 100 \text{ mg/dL}$$

$$V = 1080 \text{ mL/day}$$

Since

$$1080 \text{ mL/day} \div 1440 \text{ min/day} = 0.75 \text{ mL/min}$$

$$C_{cr} = \frac{100 \times 0.75}{1.2} = 63 \text{ mL/min}$$

This finding suggests that the patient has lost about one-third of her GFR.

Limitations Although the creatinine clearance is widely used in clinical medicine, there are two major problems that limit its accuracy as an estimate of the GFR: an incomplete urine correction and increased tubular secretion of creatinine as renal

function declines. The relative constancy of creatinine production and subsequent excretion can be used to assess the completeness of the urine collection. In adults under the age of 50, daily creatinine excretion should be about 20 to 25 mg/kg lean body weight in men and 15 to 20 mg/kg in women. Between the ages of 50 and 90, there is a progressive 50 percent reduction in creatinine excretion (to about 10 mg/kg in men), due primarily to a decrease in skeletal muscle mass. These relationships can be expressed by the following equations, which estimate daily creatinine excretion in mg/kg per day:[195]

$$\text{Creatinine excretion} = 28 - (\text{age in years}/6) \quad \text{(in men)}$$

$$= 22 - (\text{age in years}/9) \quad \text{(in women)}$$

Creatinine excretion that is much below these expected values suggests an incomplete collection. In the above 30-year-old woman, for example, creatinine excretion is 18 mg/kg per day (1080 mg ÷ 60 kg), indicating that a complete collection has probably been obtained [22 − (30/9) = 18.7].

The second major error, enhanced creatinine secretion, begins early in the course of progressive renal disease. As the GFR falls, the initial rise in the plasma creatinine concentration enhances creatinine delivery to the proximal secretory pump. This leads to an elevation in creatinine secretion, since the pump is not yet saturated.[196] At a GFR of 40 to 80 mL/min, for example, the absolute amount of creatinine secreted may have risen by *more than 50 percent* with secretion accounting for as much as 35 percent of urinary creatinine.[196] As a result, the $U_{cr} \times V$ is much higher than it would be if creatinine were excreted only by glomerular filtration, resulting in a potentially marked *overestimation* of the true GFR.[196-198]

The net effect is that the creatinine clearance may be normal (> 90 mL/min) in about one-half of patients with a true GFR (as measured by inulin clearance) of 61 to 70 mL/min and one-quarter of those with a GFR of 51 to 60 mL/min.[197] This difference may become proportionately more prominent in patients with more advanced renal disease, in whom the creatinine clearance can, in some cases, exceed the GFR by more than twofold.[198]

Thus, the creatinine clearance is not a predictably accurate measure of the GFR; all that can be concluded is that the creatinine clearance (calculated from a complete urine collection) *represents an upper limit of what the true GFR may be.* Furthermore, the degree of creatinine secretion appears to vary with time, changing the creatinine clearance independent of alterations in the GFR.[195,199,200] In some cases, the change in creatinine clearance is discordant with the change in the GFR. As an example, the degree of creatinine secretion may fall (via an unknown mechanism) at a time when the GFR is actually increasing in treated patients with lupus nephritis; this improvement, however, may be masked by no change or even a reduction in the creatinine clearance if the decrease in secretion is proportionately greater than the increase in creatinine filtration.[199,200]

The only way to determine the GFR accurately is to measure the clearance of inulin or a radiolabeled compound such as iothalamate or DTPA.[195,201] Unfortunately, determination of the inulin or iothalamate clearance is not rou-

tinely available. There are, however, two alternatives that may provide a more accurate estimate of the GFR: averaging the creatinine and urea clearances (see below) and measurement of the creatinine clearance during the administration of the H_2 blocker cimetidine, which is another organic cation that competitively inhibits creatinine secretion.

Cimetidine must be given in relatively high dose to predictably inhibit creatinine secretion in most patients.[202,203] As an example, one regimen used a single oral dose of 1200 mg plus a water load with urine collected between 3 and 6 hours for both creatinine and inulin clearance. The ratio of the creatinine to inulin clearance at baseline was about 1.5 (range 1.14 to 2.27), indicating substantial creatinine secretion. The ratio fell to 1.02 in eight patients, but remained elevated (1.33) in the remaining patients, who had more efficient urinary cimetidine excretion.[202]

It is important to appreciate, however, that *exact knowledge of the GFR is not usually required*, particularly with the ability to measure plasma levels of many of those potentially toxic drugs that are normally excreted by the kidney (such as digoxin or an aminoglycoside antibiotic). What is important to know is whether the GFR is changing (which can usually be determined from the plasma creatinine concentration alone) and whether the GFR is reduced in a patient with kidney disease who has a normal or high-normal plasma creatinine concentration (see below).

In addition to the potential errors involved in the use of the creatinine clearance, there is an additional problem: Progressive disease is not always associated with a significant reduction in GFR even if the latter is accurately measured. As noted above, nephron loss is generally associated with compensatory hypertrophy and hyperfiltration in the remaining normal or less affected nephrons. Thus, in a disease such as lupus nephritis, progressive glomerular scarring can occur during the healing phase with little reduction in the total GFR.[200,204] In this setting, the patient must also be monitored for other signs of disease progression, such as an increase in protein excretion or in the systemic blood pressure.

Plasma Creatinine and GFR

Changes in the GFR (rather than an exact measurement of the GFR) can generally be ascertained from measurement of the P_{cr}, a routine laboratory test. In a subject in the steady state,

$$\text{Creatinine excretion} = \text{creatinine production} \tag{2-7}$$

Creatinine excretion is roughly equal to the amount of creatinine filtered ($GFR \times P_{cr}$), whereas the rate of creatinine production is relatively constant. If these substitutions are made in Eq. (2-7), then

$$GFR \times P_{cr} = \text{constant} \tag{2-8}$$

Thus, the *plasma creatinine concentration varies inversely with the GFR*. If, for example, the GFR falls by 50 percent, creatinine excretion will also be reduced.

As a result, newly produced creatinine will accumulate in the plasma until the filtered load again equals the rate of production. Excluding changes in tubular secretion, this will occur when the P_{cr} has doubled:

$$GFR/2 \times 2P_{cr} = GFR \times P_{cr} = \text{constant}$$

In adults, the range for the normal P_{cr} is 0.8 to 1.3 mg/dL in men and 0.6 to 1.0 mg/dL in women.[108]

Creatinine production and the P_{cr} can be influenced by changes in diet. Creatinine production is determined by the total body creatine content, which itself is determined by the amount of creatine synthesized from amino acids and directly ingested in meat. As an example, creatine production can be enhanced by a high-protein or high-meat diet; this change, however, must persist over a period of weeks to months before creatinine production (and therefore the P_{cr}) is significantly enhanced, since only 1 to 2 percent of the extra creatine is converted to creatinine per day.[205] Furthermore, the increase in the P_{cr} may be less than the increment in production because a high-protein diet also tends to raise the GFR and therefore the rate of creatinine excretion.[206,207] On the other hand, switching to a meat-free diet can lower the P_{cr} by as much as 15 percent without any change in the true GFR.[208]

A more acute effect may be seen with the ingestion of cooked meat, since heating promotes the conversion of creatine to creatinine. As an example, eating a 4-oz hamburger can raise creatinine excretion by as much as 350 to 450 mg (a 20 to 30 percent increase) and can acutely elevate the P_{cr} by as much as 1 mg/dL.[205,209] Thus, the P_{cr} should optimally be measured when the patient is fasting.

The idealized reciprocal relationship between the GFR and the P_{cr} is depicted in Fig. 2-11. There are three important points to note about this relationship. First, this curve is *valid only in the steady state* when the P_{cr} is stable. If, for

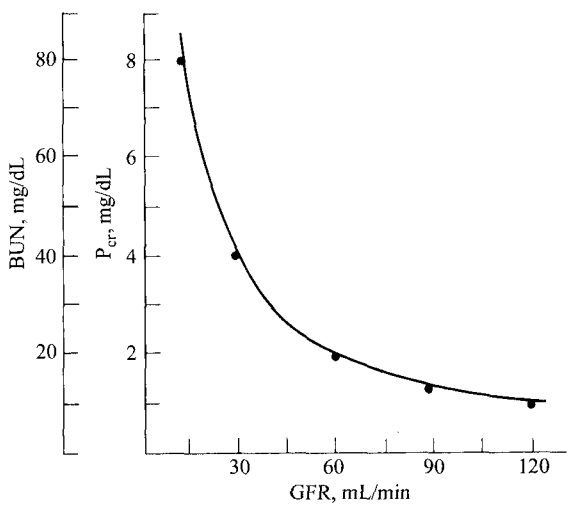

Figure 2-11 Idealized steady-state relationship between the plasma creatinine concentration (P_{cr}), blood urea nitrogen (BUN), and the GFR.

example, a patient develops acute renal failure with a sudden drop in the GFR from 120 to 12 mL/min, the P_{cr} on day 1 will be normal, since there will not have been time for creatinine to accumulate in the plasma. After 7 to 10 days, the P_{cr} will stabilize at roughly 10 mg/dL, a level consistent with the reduced GFR.

The steady state can be disturbed by changes in creatinine production as well as in urinary excretion. Thus, a malnourished patient with reduced creatinine production may have a stable P_{cr} despite a fall in GFR.

Second, it is important to appreciate the *shape* of the curve. In a patient with normal renal function, an apparently minor increase in the P_{cr} from 1.0 to 1.5 mg/dL can represent a marked fall in the GFR from 120 to 80 mL/min. In contrast, in a patient with advanced renal failure, a marked increase in the P_{cr} from 6.0 to 12.0 mg/dL reflects a relatively small reduction in the GFR from 20 to 10 mL/min. Thus, the *initial elevation in the P_{cr} represents the major loss in GFR.* Furthermore, progressive reductions in GFR in patients with advanced disease are more easy to detect by measurement of the P_{cr} (which may show a large increase) than by measurement of the GFR (which may fall by only a few mL/min, a change that may be less than the sensitivity of the assay).[195]

Third, the relationship between the GFR and the P_{cr} is dependent upon the rate of creatinine production, which is largely a function of muscle mass and meat and protein intake. In Fig. 2-11, a normal GFR of 120 mL/min is associated with a P_{cr} of 1.0 g/dL. Although this may be true for a 70-kg man, a similar GFR in a 50-kg woman might be associated with a P_{cr} of only 0.6 mg/dL. In this setting, a P_{cr} of 1.0 mg/dL is not normal and reflects a 40 percent fall in GFR.

To account for the effects of body weight, age, and sex on muscle mass, the following formula has been derived to estimate the creatinine clearance (in mL/min) from the P_{cr} in the steady state in adult men:[209,210]

$$C_{cr} = \frac{(140 - \text{age}) \times \text{lean body weight (in kg)}}{P_{cr} \times 72} \tag{2-9}$$

This value should be multiplied by 0.85 in women, since a lower fraction of the body weight is composed of muscle.

The results obtained with this formula appear to correlate fairly well with a simultaneously measured creatinine clearance. Its usefulness can be illustrated by the observation that a P_{cr} of 1.4 mg/dL represents a creatinine clearance of 101 mL/min in an 85-kg, 20-year-old man:

$$C_{cr} = \frac{(140 - 20) \times 85}{1.4 \times 72}$$

but a creatinine clearance of only 20 mL/min in a 40-kg, 80-year-old woman:

$$C_{cr} = \frac{(140 - 80) \times 40 \times 0.85}{1.4 \times 72}$$

The latter example calls attention to the danger of overdosing elderly patients who have seriously impaired renal function despite a relatively normal P_{cr}. The use of this simple formula can help to avoid this problem but should not replace monitoring of plasma drug levels when potentially toxic agents are given.

A similar decline in creatinine production can occur in malnourished patients, such as those with cirrhosis. In addition to the loss of muscle mass, decreased meat intake and perhaps decreased hepatic production of creatine, the precursor of creatinine, can also play a contributory role. The net effect is that some cirrhotic patients with an apparently "normal" P_{cr} of 1 to 1.3 mg/dL have a GFR (as measured by inulin clearance) that can range from as low as 20 to 60 mL/min to a clearly normal value above 100 mL/min.[211,212] The low protein intake and decreased production of urea (due to the hepatic disease) also limit the rise in blood urea nitrogen (BUN) that should occur as the GFR falls (Fig. 2-11).

Thus, the presence of substantial renal dysfunction may be masked in cirrhotic patients if only the BUN and P_{cr} are measured. Calculation of the creatinine clearance will partially overcome this problem, since the reduction in creatinine production will be accounted for by a decline in creatinine excretion. However, because of increased creatinine secretion, the clearance value obtained may overestimate the true GFR by as much as 40 percent or more in patients with renal insufficiency.[212]

In summary, the P_{cr} tends to vary inversely with the GFR in the steady state. Because of this relationship, serial measurements of the P_{cr} are typically used to monitor patients with kidney dysfunction. A rise in P_{cr} indicates disease progression, whereas a fall in P_{cr} suggests recovery of renal function (if muscle mass and meat intake are relatively constant). It is also presumed that a stable P_{cr} means stable disease, although this may not be an accurate assumption.

Limitations It is now clear that significant disease progression can occur with *little or no change in the P_{cr}* in patients with a normal or near-normal GFR (> 60 mL/min). Three factors can contribute to this problem, two of which prevent or minimize any fall in true GFR and one of which (increased creatinine secretion) can limit the rise in P_{cr} when the GFR does fall:

1. Loss of nephrons leads to compensatory hyperfiltration in the remaining more normal nephrons, thereby maintaining the total GFR despite continued disease activity.[184] As described above, in lupus nephritis, for example, progressive glomerular scarring may be associated with no detectable change in glomerular filtration due to hypertrophy in normal or less affected glomeruli.[204]
2. Glomerular diseases damage the glomerular basement membrane, tending to lower the GFR by diminishing the effective surface area available for filtration. This effect, however, is counteracted by a rise in glomerular capillary pressure (P_{gc}) that tends to maintain the GFR despite progressive glomerular injury.[117] The mechanism by which this occurs is not well understood; an initial reduction in GFR due to the fall in surface area could lead to diminished macula densa flow and activation of TGF, which could then raise the GFR back to the baseline level.
3. When the GFR does begin to fall, the rise in the P_{cr} is lessened or prevented by an increase in tubular secretion, as described previously.[196] The potential

result of this adaption is illustrated in Fig. 2-12. Although a fall in GFR from 120 to 60 mL/min should ideally induce a doubling of the P_{cr}, many patients have only a small increase in the P_{cr} (of as little as 0.1 to 0.2 mg/dL) because of enhanced tubular secretion. With more advanced disease (P_{cr} > 1.5 to 2 mg/dL), the P_{cr} rises as expected, presumably due to saturation of the secretory mechanism.

The major clinical implication of these findings is that, in a patient with known renal disease, *a P_{cr} that is stable at a level under 1.5 mg/dL does not necessarily reflect stable disease.* As a result, it is important to look for other signs of disease progression, such as increased proteinuria, a more active urine sediment, or an elevation in the systemic blood pressure. In addition, variations in the degree

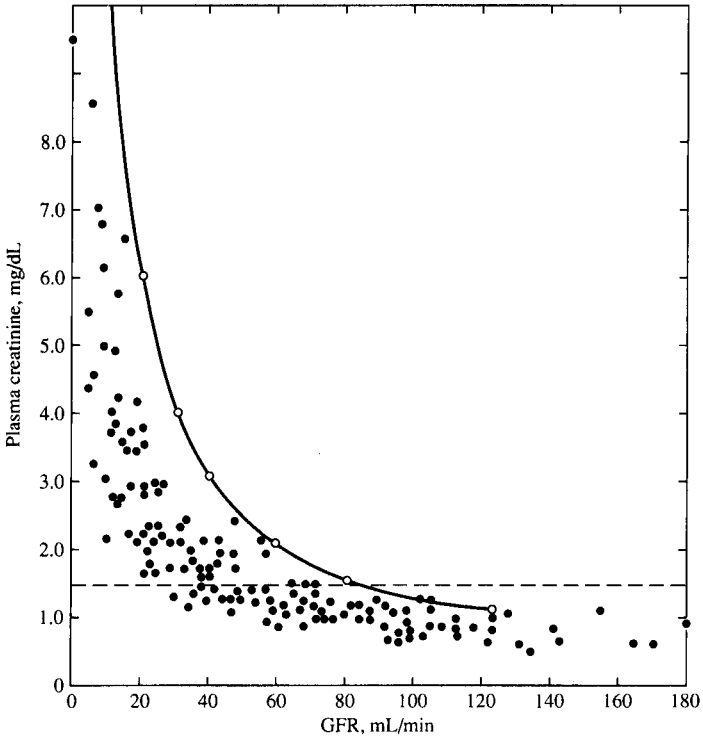

Figure 2-12 Relationship between the P_{cr} and the true GFR (as measured by the inulin clearance) in 171 patients with glomerular disease. The open circles joined by a continuous line represent the idealized relationship between these parameters if creatinine were excreted solely by glomerular filtration (see Fig. 2-11); the dotted line represents the upper limit of "normal" for the P_{cr} of 1.4 mg/dL. With the GFR varying between 120 and 60 mL/min in different patients, there is often little elevation in the P_{cr} due primarily to enhanced tubular secretion. Once the P_{cr} is above 1.5 to 2 mg/dL (132 to 176 μmol/L), tubular secretion becomes saturated and the P_{cr} rises as expected with further reductions in GFR. (*From Shemesh O, Golbetz H, Kriss JP, Myers BD*, Kidney Int *28:830, 1985. Used with permission from* Kidney International.)

of creatinine secretion can cause the P_{cr} to vary independent of the GFR.[199,200] Thus, an increase in GFR may not lead to a reduction in the P_{cr} if it is associated with a proportionate decline in creatinine secretion.[200]

Less commonly, an error arises due to an elevation in the measured P_{cr} without any change in the GFR (or BUN). This is most often due to a large meat meal,[208] ketoacidosis (in which acetoacetate can raise the P_{cr} by 0.5 to 2 mg/dL or more because it is measured as a noncreatinine chromogen),[213] or the administration of cimetidine or the antimicrobial trimethoprim (which is most often given in combination with sulfamethoxazole), both of which competitively inhibit creatinine secretion.[203,214,215]. In the last setting, the P_{cr} may increase by as much as 0.4 to 0.5 mg/dL.[215] Ranitidine, another commonly used H_2 blocker, has a less prominent effect on creatinine handling than cimetidine because it is given in much lower doses.[214]

Because of the variability in creatinine secretion and production, other endogenous markers, such as cystatin C, have been evaluated for the estimation of GFR. Cystatin C is a low-molecular-weight protein that is a member of the cystatin superfamily of cysteine protease inhibitors. It is produced by all nucleated cells, and its rate of production is relatively constant, being unaltered by inflammatory conditions or changes in diet. Preliminary studies suggest that the plasma cystatin C concentration correlates more closely with the GFR than the plasma creatinine concentration.[217] Whether the measurement of cystatin C levels will become available clinically is at present unknown.

Blood Urea Nitrogen and GFR

Changes in the GFR also can be detected by changes in the concentration of urea in the blood, measured as the BUN. Like creatinine, urea is excreted primarily by glomerular filtration, and the BUN tends to vary inversely with the GFR (Fig. 2-11).

However, two factors can alter the BUN without change in the GFR or P_{cr}: changes in urea production and tubular urea reabsorption. Urea is formed by the hepatic metabolism of amino acids that are not utilized for protein synthesis. As amino acids are deaminated, ammonia is produced. The development of toxic levels of ammonia in the blood is prevented by the conversion of ammonia (NH_3) into urea in a reaction that can be summarized by the following equation:

$$2NH_3 + CO_2 \rightarrow H_2N{-}CO{-}NH_2 + H_2O$$

Thus, urea production and the BUN are increased when more amino acids are metabolized in the liver. This may occur with a high-protein diet, enhanced tissue breakdown (due to trauma, gastrointestinal bleeding, or the administration of corticosteroids), or decreased tissue anabolism (due to tetracycline).[217] On the other hand, urea production and the BUN are reduced by severe liver disease or a low protein intake.

The second factor is that urea excretion is not determined solely by glomerular filtration. Approximately 40 to 50 percent of the filtered urea is normally reab-

sorbed by the tubules. This process is passive, being driven by the rise in tubular fluid urea concentration that results from the reabsorption of sodium and water. Thus, urea transport is enhanced in hypovolemic states due to the increase in sodium reabsorption. The net result is reduced urea excretion and an elevation in the BUN that is not due to a fall in GFR and therefore is not associated with a rise in the P_{cr}.[217] Under most conditions, the ratio of the BUN to the P_{cr} is 10 to 15:1. When this ratio exceeds 20:1, one of the conditions associated with enhanced urea production or effective circulating volume depletion should be suspected.[217]

In summary, a reduction in the GFR results in elevation in both the BUN and the P_{cr}. Because of the variability in urea production and reabsorption, the P_{cr} is a more reliable reflection of the GFR. For similar reasons, the urea clearance is not an accurate estimate of the GFR. Since urea is reabsorbed and the degree of reabsorption is variable, the quantity of urea excreted is much less than the amount filtered. As a result, the urea clearance is only 50 to 70 percent that of inulin.[218]

The overestimation of the GFR with the creatinine clearance and the underestimation with the urea clearance has led to the suggestion that the average of these two values should be used:

$$\text{GFR} = \frac{C_{cr} + C_{urea}}{2} \tag{2-10}$$

This equation may be most accurate in patients with moderate to advanced renal disease ($P_{cr} > 2.5\,\text{mg/dL}$).[219]

Change in GFR with Aging

An association between age and decreasing GFR, via several hypothetical but unproven mechanisms, has been suggested by several studies.[220] In the Baltimore Longitudinal study, for example, the mean rate of decline in creatinine clearance was found to be 0.75 mL/min per year.[221] However, this and other studies may be flawed because of their reliance upon endogenous creatinine clearance measurements and the presence of possible confounding conditions.

In an effort to obtain a more reliable correlation between GFR and age, another study, which examined the GFR as measured via inulin clearance, found that a majority of elderly patients with normal cardiac function had measured clearances within the normal range.[222] Thus, although the elderly appear to have lower clearance rates, comorbid conditions may significantly affect measurements of renal function among such patients, and increased age is not invariably associated with a decreased GFR.[223]

Summary

Estimation of the GFR remains an important method of monitoring patients with renal disease. There is, however, no easily available way to do this accurately. The

increase in tubular secretion of creatinine as the GFR begins to fall seriously limits the validity of the creatinine clearance. Since this test can overestimate the GFR by twofold or more in patients with moderate to advanced renal disease,[198] it is best used as an *upper limit* of what the true GFR may be. The P_{cr}, on the other hand, is helpful in following the course of the disease, since the P_{cr} tends to vary inversely with the GFR (as long as muscle mass and meat intake are relatively constant). However, enhanced creatinine secretion can minimize any rise in the P_{cr} as the GFR falls from the normal level of 120 mL/min down to 60 to 80 mL/min.

Thus, a stable P_{cr} that is below 1.5 mg/dL does not necessarily mean that the renal disease is stable. In this setting, increases in systemic blood pressure and/or the activity on the urinalysis may be the only clues to progressive disease (unless an inulin or iothalamate clearance can be measured).[199] Once the P_{cr} is above 1.5 to 2 mg/dL, however, tubular secretion is saturated, and a stable P_{cr} makes it unlikely that progressive renal damage is occurring.

Variability in the production and tubular reabsorption of urea makes the BUN a less useful reflection of the GFR than the P_{cr}. The main clinical use of the BUN is in the calculation of the BUN-to-P_{cr} ratio, which, if elevated, suggests that diminished renal perfusion contributes to the renal disease (assuming that none of the causes of increased urea production is present).[217]

Measurement of Renal Plasma Flow

The principles of clearance have also been used to measure the RPF in experimental conditions; this test has little clinical utility. Paraaminohippurate (PAH) is an easily measured indicator that enters the urine by glomerular filtration and by the organic anion secretory pathway in the proximal tubule. The combination of filtration and secretion results in the almost complete removal of PAH from the plasma in a single pass through the kidney. Therefore,

$$\begin{aligned} \text{PAH delivery to kidney} &= \text{PAH excretion} \\ \text{RPF} \times P_{PAH} &= U_{PAH} \times V \\ \text{RPF} &= \frac{U_{PAH} \times V}{P_{PAH}} = C_{PAH} \end{aligned} \tag{2-11}$$

If the hematocrit (Hct) is known, then the renal blood flow (RBF) can be calculated from

$$\text{RBF} = \frac{C_{PAH}}{1 - \text{Hct}} \tag{2-12}$$

The normal RPF and RBF in humans are roughly 625 mL/min and 110 mL/min, respectively. Since only 85 to 90 percent of the PAH actually is removed from the circulation in a single pass, the PAH clearance will underestimate both RPF and RBF by 10 to 15 percent.

PROBLEMS

2-1 A 68-year-old man is admitted to the hospital with acute renal failure. The following plasma creatinine concentrations are obtained:

Day	Plasma creatinine, mg/dL
1	1.0
2	3.0
3	4.9

If the patient weighs 70 kg, what would you estimate the GFR to be on day 2?

2-2 Dopamine dilates both the afferent and efferent arterioles. What effect will this have on
(a) Renal blood flow
(b) GFR (in relation to the change in renal blood flow)
(c) The filtration fraction
(d) The concentration of albumin in the peritubular capillary

2-3 A patient with diabetic nephropathy has chronic renal failure (plasma creatinine concentration equals 2.1 mg/dL) and hypertension. He can be treated with an ACE inhibitor, which primarily dilates the efferent arteriole, or with other antihypertensive agents, which primarily dilate the afferent arteriole. Assuming that each form of therapy is equally effective in lowering the systemic blood pressure:
(a) Compare the likely effects of the two regimens on the glomerular capillary hydraulic pressure, P_{gc}.
(b) Could this difference be clinically important?

2-4 A creatinine clearance test is performed in an 80-kg man. The following results are obtained:

$$P_{cr} = 3.5 \text{ mg/dL}$$

$$\text{24-h urine volume} = 800 \text{ mL}$$

$$U_{cr} = 125 \text{ mg/dL}$$

(a) Calculate the creatinine clearance.
(b) Is this an accurate estimate of the GFR?

REFERENCES

1. Beeuwkes R, Bonventre JV. Tubular organization and vascular-tubular relations in the dog kidney. *Am J Physiol* 229:695, 1975.
2. Abrahamson DR. Structure and development of the glomerular capillary wall and basement membrane. *Am J Physiol* 253:F783, 1987.
3. Reiser J, Kriz W, Kretzler M, Mundel P. The glomerular slit diaphragm is a modified adherens junction. *J Am Soc Nephrol* 11:2000, 1999.
4. Weber M. Basement membrane proteins. *Kidney Int* 41:620, 1992.
5. Natori Y, O'Meara YM, Manning EC, et al. Production and polarized secretion of basement membrane components by glomerular epithelial cells. *Am J Physiol* 262:R131, 1992.
6. Groffen AJ, Veerkamp JH, Monnens LA, van den Heuvel LP. Recent insights into the structure and functions of heparan sulfate proteoglycans in the human glomerular basement membrane. *Nephrol Dial Transplant* 14:2119, 1999.
7. Kashtan CE. Alport syndrome and thin glomerular basement membrane disease. *J Am Soc Nephrol* 9:1736, 1998.
8. Harvey SJ, Zheng K, Sado Y, et al. Role of distinct type IV collagen networks in glomerular development and function. *Kidney Int* 54:1857, 1998.

9. Ding J, Stitzel J, Berry P, et al. Autosomal recessive Alport syndrome: Mutation in the COL4A3 gene in a woman with Alport syndrome and posttransplant antiglomerular basement membrane nephritis. *J Am Soc Nephrol* 5:1714, 1995.
10. Brenner BM, Hostetter TH, Humes HD. Molecular basis of proteinuria of glomerular origin. *N Engl J Med* 298:826, 1978.
11. Kanwar YS, Liu ZZ, Kashihara N, Wallner EI. Current status of the structural and functional basis of glomerular filtration and proteinuria. *Semin Nephrol* 11:390, 1991.
12. Fujigaki Y, Nagase M, Kobayasi S, et al. Intra-GBM site of the functional filtration barrier for endogenous proteins in rats. *Kidney Int* 43:567, 1993.
13. Blantz RC, Gabbai FB, Peterson O, et al. Water and protein permeability is regulated by glomerular slit diaphragm. *J Am Soc Nephrol* 4:1957, 1994.
14. Daniels BS, Deen WM, Mayer G, et al. Glomerular permeability barrier in the rat. Functional assessment by in vitro methods. *J Clin Invest* 92:929, 1993.
15. Kerjaschki D. Dysfunction of cell biological mechanisms of visceral epithelial cells (podocytes) in glomerular diseases. *Kidney Int* 45:300, 1994.
16. Ruotsalainen V, Ljungberg P, Wartiovaara J, et al. Nephrin is specifically located at the slit diaphragm of glomerular podocytes. *Proc Natl Acad Sci U S A* 96:7962, 1999.
17. Oliver JD III, Anderson S, Troy JL, et al. Determination of glomerular size-selectivity in the normal rat with ficoll. *J Am Soc Nephrol* 3:214, 1992.
18. Deen WM, Bridges CR, Brenner BM, Myers BD. Heteroporous model of glomerular size selectivity: Application to normal and nephrotic humans. *Am J Physiol* 249:F374, 1985.
19. Latta H. An approach to the structure and function of the mesangium. *J Am Soc Nephrol* 2 (suppl):S65, 1992.
20. Scandling JD, Black VM, Deen WM, Myers BD. Gomerular permselectivity in healthy and nephrotic humans. *Adv Nephrol* 21:159, 1992.
21. Groggel GC, Stevenson J, Hovingh P, et al. Changes in heparan sulfate correlate with increased glomerular permeability. *Kidney Int* 33:517, 1988.
22. Sawada H, Stukenbrok H, Kerjaschki D, Farquhar MG. Epithelial polyanion (podocalyxin) is found in the sides but not the soles of the foot processes of the glomerular epithelium. *Am J Pathol* 125:309, 1986.
23. Comper WD, Glasgow EF. Charge selectivity in kidney ultrafiltration. *Kidney Int* 47:1242, 1995.
24. Osicka TM, Comper WD. Glomerular charge selectivity for anionic and neutral horseradish peroxidase. *Kidney Int* 42:1630, 1995.
25. Guasch A, Deen WM, Myers BD. Charge selectivity of the glomerular filtration barrier in healthy and nephrotic humans. *J Clin Invest* 92:2274, 1993.
26. Ota Z, Shikata K, Ota K. Nephrotic tunnels in glomerular basement membrane as revealed by a new electron microscopic method. *J Am Soc Nephrol* 4:1965, 1994.
27. Shemesh O, Ross JC, Deen WM, et al. Nature of the glomerular capillary injury in human membranous nephropathy. *J Clin Invest* 77:868, 1986.
28. Shemesh O, Ross JC, Deen WM, et al. Nature of the glomerular capillary injury in human membranous glomerulopathy. *J Clin Invest* 77:868, 1986.
29. Golbetz H, Black V, Shemesh O, Myers BD. Mechanism of the antiproteinuric effect of indomethacin in nephrotic humans. *Am J Physiol* 256:F44, 1989.
30. Sharon Z, Schwartz MM, Pauli BU, Lewis EJ. Kinetics of glomerular visceral epithelial cell phagocytosis. *Kidney Int* 14:526, 1978.
31. Savage CO. The biology of the glomerulus: Endothelial cells. *Kidney Int* 45:314, 1994.
32. Ishino T, Kobayashi R, Wakui H, et al. Biochemical characterization of contractile proteins of rat cultured mesangial cells. *Kidney Int* 39:1118, 1991.
33. Davies M. The mesangial cell: A tissue culture view. *Kidney Int* 45:320, 1994.
34. Hugo C, Shankland SJ, Bowen-Pope DF, et al. Extraglomerular origin of the mesangial cell after injury. A new role of the juxtaglomerular apparatus. *J Clin Invest* 100:786, 1997.
35. Striker GE, Striker LJ. Glomerular cell culture. *Lab Invest* 53:122, 1985.
36. Moriyama T, Fujibayashi M, Fujiwara Y, et al. Angiotensin II stimulates interleukin-6 release from cultured mouse mesangial cells. *J Am Soc Nephrol* 6:95, 1995.

37. Kusner DJ, Luebbers EL, Nowinski RJ, et al. Cytokine- and LPS-induced synthesis of interleukin-8 from human mesangial cells. *Kidney Int* 39:1240, 1991.
38. Schreiner GF. The mesangial phagocyte and its regulation of contractile biology. *J Am Soc Nephrol* 2(suppl):S74, 1992.
39. Skott O, Jensen BL. Cellular and intrarenal control of renin secretion. *Clin Sci* 84:1, 1993.
40. Toffelmire EB, Slater K, Corvol P, et al. Response of prorenin and active renin to chronic and acute alterations of renin secretion in normal humans. Studies using a direct immunoradiometric assay. *J Clin Invest* 83:679, 1989.
41. Gomez RA, Chevalier RL, Everett AD. Recruitment of renin gene-expressing cells in adult rat kidney. *Am J Physiol* 259:F660, 1990.
42. Hosoi M, Kim S, Takada T, et al. Effects of prorenin on blood pressure and plasma renin concentrations in stroke-prone spontaneously hypertensive rats. *Am J Physiol* 262:E234, 1992.
43. Shaw KJ, Do YS, Kjos S, et al. Human decidua is a major source of renin. *J Clin Invest* 83:2085, 1989.
44. Nushiro N, Ito S, Carretero OA. Renin release from microdissected superficial, midcortical, and juxtamedullary afferent arterioles in rabbits. *Kidney Int* 38:426, 1990.
45. Naftilan AJ, Zuo WM, Ingelfinger J, et al. Localization and differential regulation of angiotensinogen mRNA expression in the vessel wall. *J Clin Invest* 88:1300, 1991.
46. Schunkert H, Ingelfinger JR, Hirsch AT, et al. Evidence for tissue specific activation of renal angiotensinogen mRNA expression in chronic stable experimental heart failure. *J Clin Invest* 90:1523, 1992.
47. Dzau, VJ. Tissue renin-angiotensin system in myocardial hypertrophy and failure. *Arch Intern Med* 153:937, 1993.
48. Kifor I, Moore TJ, Fallo F, et al. Potassium-stimulated angiotensin release from superfused adrenal capsules and enzymatically digested cells of the zona glomerulosa. *Endocrinology* 129:823, 1991.
49. Wagner C, Jensen BL, Kramer BK, Kurtz A. Control of the renal renin system by local factors. *Kidney Int* 54(suppl 67):S-78, 1998.
50. Wilkes BM, Mento PF, Pearl AR, et al. Plasma angiotensins in anephric humans: Evidence for an extrarenal angiotensin system. *J Cardiovasc Pharmacol* 17:419, 1991.
51. Ingelfinger JR, Zuo WM, Fon EA, et al. In situ hybridization evidence for angiotensinogen messenger RNA in the rat proximal tubule. An hypothesis for the intrarenal renin angiotensin system. *J Clin Invest* 85:417, 1990.
52. Yanagawa N. Potential role of local luminal angiotensin II in proximal tubule sodium transport. *Kidney Int* 39(suppl 32):S-33, 1991.
53. Seikaly MG, Arant BS Jr, Seney FD Jr. Endogenous angiotensin concentrations in specific intrarenal fluid compartments of the rat. *J Clin Invest* 86:1352, 1990.
54. Redgrave J, Rabinowe S, Hollenberg NK, Williams GH. Correction of abnormal renal blood flow response to angiotensin II by converting enzyme inhibition in essential hypertension. *J Clin Invest* 75:1285, 1985.
55. Oliver JA, Sciacca RR. Local generation of angiotensin II as a mechanism of regulation of peripheral vascular tone in the rat. *J Clin Invest* 74:1247, 1984.
56. Wenting GJ, DeBruyn HB, Man in't Veld AJ, et al. Hemodynamic effects of captopril in essential hypertension, renovascular hypertension and cardiac failure: Correlations with short- and long-term effects on plasma renin. *Am J Cardiol* 49:1453, 1982.
57. Bader M, Zhao Y, Sander M, et al. Role of tissue renin in the pathophysiology of hypertension in TGR(mREN2) 27 rats. *Hypertension* 19:681, 1992.
58. Hilgers KF, Peters J, Veelken R, et al. Increased vascular angiotensin formation in female rats harboring the mouse *Ren-2* gene. *Hypertension* 19:687, 1992.
59. Hall JE. Intrarenal actions of converting enzyme inhibitors. *Am J Hypertens* 2:875, 1989.
60. Ischikawa I, Harris RC. Angiotensin actions in the kidney: Renewed insight into the old hormone. *Kidney Int* 40:583, 1991.
61. Goodfriend TL, Elliot ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 334:1649, 1996.

62. Murphy TJ, Alexander RW, Griendling KK, et al. Isolation of a cDNA encoding the vascular type-1 angiotensin II receptor. *Nature* 351:233, 1991.
63. Stoll M, Steckelingd UM, Paul M, et al. The angiotensin AT_2-receptor mediates inhibition of cell proliferation in coronary endothelial cells. *J Clin Invest* 95:651, 1995.
64. Quan A, Baum M. Effect of luminal angiotensin II receptor antagonists on proximal tubule transport. *Am J Hypertens* 12:499, 1999.
65. Cogan MG. Angiotensin II: A potent controller of sodium transport in the early proximal tubule. *Hypertension* 15:451, 1990.
66. Quan A, Baum M. Regulation of proximal tubule transport by angiotensin II. *Semin Nephrol* 17:423, 1997.
67. Liu F-Y, Cogan MG. Angiotensin II stimulates early proximal bicarbonate absorption in the rat by decreasing cyclic adenosine monophosphate. *J Clin Invest* 84:83, 1989.
68. Liu-F-Y, Cogan MG. Role of protein kinase C in proximal bicarbonate absorption and angiotensin signalling. *Am J Physiol* 258:F927, 1990.
69. Geigel J, Giebisch G, Boron WF. Angiotensin II stimulates both Na^+-H^+ exchange and Na^+/HCO_3^- cotransport in the rabbit proximal tubule. *Proc Natl Acad Sci U S A* 87:7917, 1990.
70. Cogan MG, Xie M-H, Liu F-Y, et al. Effects of DuP 753 on proximal nephron and renal transport. *Am J Hypertens* 4:315s, 1991.
71. Scholz H, Kurtz A. Role of protein kinase C in renal vasoconstriction caused by angiotensin II. *Am J Physiol* 259:C421, 1990.
72. Zimmerman JB, Robertson D, Jackson EK. Angiotensin II-noradrenergic interactions in renovascular hypertensive rats. *J Clin Invest* 80:443, 1987.
73. Purdy RE, Weber MA. Angiotensin II amplification of α-adrenergic vasoconstriction: Role of receptor reserve. *Circ Res* 63:748, 1988.
74. Clemson B, Gaul L, Gubin SS, et al. Prejunctional angiotensin II receptors. Facilitation of norepinephrine release in the human forearm. *J Clin Invest* 93:684, 1994.
75. Watkins L Jr, Burton JA, Haber E, et al. The renin-angiotensin-aldosterone system in congestive failure in conscious dogs. *J Clin Invest* 57:1606, 1976.
76. Dzau VJ. Renal and circulatory mechanisms in congestive heart failure. *Kidney Int* 31:1402, 1987.
77. Schroeder ET, Anderson JH, Goldman SH, Streeten DHP. Effect of blockade of angiotensin II on blood pressure, renin and aldosterone in cirrhosis. *Kidney Int* 9:511, 1976.
78. Rasmussen H. The calcium messenger system. *N Engl J Med* 314:1164, 1986.
79. Stern N, Golub M, Novawa K, et al. Selective inhibition of angiotensin II-mediated vasoconstriction by lipoxygenase blockade. *Am J Physiol* 257:H434, 1989.
80. Myers BD, Deen WM, Brenner BM. Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in the rat. *Circ Res* 37:101, 1975.
81. Yuan BH, Robinette JB, Conger JD. Effect of angiotensin II and norepinephrine on isolated rat afferent and efferent arterioles. *Am J Physiol* 258:F741, 1990.
82. Hegeraas KJ, Aukland K. Interlobular arterial resistance: Influence of renal arterial pressure and angiotensin II. *Kidney Int* 31:1291, 1987.
83. Wilcox CS, Welch WJ, Snellen H. Thromboxane mediates renal hemodynamic response to infused angiotensin II. *Kidney Int* 40:1090, 1991.
84. Denton KM, Fennessy PA, Alcorn D, Anderson WP. Morphometric analysis of the actions of angiotensin II on renal arterioles and glomeruli. *Am J Physiol* 262:F367, 1992.
85. Carmines PK, Mitchell KD, Navar LG. Effect of calcium antagonists on renal hemodynamics and glomerular function. *Kidney Int* 41(suppl 36):S-43, 1992.
86. Stahl RAK, Paravicini M, Schollmeyer P. Angiotensin II stimulation of prostaglandin E_2 and 6-keto-$F_{1\alpha}$ formation by isolated human glomeruli. *Kidney Int* 26:30, 1984.
87. Oliver JA, Pinto J, Sciacca RR, Cannon PJ. Increased renal secretion of norepinephrine and prostaglandin E2 during sodium depletion in the dog. *J Clin Invest* 66:748, 1980.
88. Vallotton M, Gerber C, Dolci W, Wüthrich RP. Interaction of vasopressin and angiotensin II in stimulation of prostacyclin synthesis in vascular smooth muscle cells. *Am J Physiol* 257:E617, 1989.

89. Ichikawa I, Pfeffer JM, Pfeffer MA, et al. Role of angiotensin II in the altered renal function of congestive heart failure. *Circ Res* 55:669, 1984.
90. Ingelfinger JR, Pratt RE, Ellison K, Dzau V. Sodium regulation of angiotensinogen mRNA expression in rat kidney cortex and medulla. *J Clin Invest* 78:1311, 1986.
91. Bock HA, Hermle M, Brunner FP, Thiel G. Pressure dependent modulation of renin release in isolated perfused glomeruli. *Kidney Int* 41:275, 1992.
92. Freeman RH, Davis JO, Villareal D. Role of renal prostaglandins in the control of renin release. *Circ Res* 54:1, 1984.
93. Kopp U, DiBona GF. Interaction of renal β_1-adrenoreceptors and prostaglandins in reflex renin release. *Am J Physiol* 244:F418, 1983.
94. Lorenz JN, Weihprecht H, Schnermann J, et al. Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. *Am J Physiol* 260:F486, 1991.
95. Kotchen TA, Luke RG, Ott CE, et al. Effect of chloride on renal and blood pressure responses to sodium chloride. *Ann Intern Med* 98(part 2):817, 1983.
96. Jones-Dombi T, Churchill P. The baroreceptor mechanism for controlling renin secretion: Effect of calcium channel blockers. *J Pharmacol Exp Ther* 266:274, 1993.
97. Ho S, Carretero OA, Abe K, et al. Effect of prostanoids on renin release from rabbit afferent arterioles with and without macula densa. *Kidney Int* 35:1138, 1989.
98. Data JL, Berber JG, Crump WJ, et al. The prostaglandin system: A role in canine baroreceptor control of renin release. *Circ Res* 42:454, 1978.
99. Lapointe J-Y, Bell PD, Cardinal J. Direct evidence for apical Na^+:$2Cl^-$:K^+ cotransport in macula densa cells. *Am J Physiol* 258:F1466, 1990.
100. Schlatter E, Salomonsson M, Persson AEG, Greger R. Macula densa cells sense luminal NaCl concentration via furosemide sensitive Na^+-$2Cl^-$-K^+ cotransport. *Pfluegers Arch* 414:286, 1989.
101. Martinez-Maldonado M, Gely R, Tapia E, Benabe JE. Role of macula densa in diuretic-induced renin release. *Hypertension* 16:261, 1990.
102. Spielman WS, Arend JS. Adenosine receptors and signalling in the kidney. *Hypertension* 17:117, 1991.
103. Weinprecht H, Lorenz JN, Schnermann J, et al. Effect of adenosine$_1$-receptor blockade on renin release from rabbit isolated perfused juxtaglomerular apparatus. *J Clin Invest* 85:1622, 1990.
104. Greenberg SG, Lorenz JN, He X, et al. Effect of prostaglandin synthesis inhibition on macula densa-stimulated renin secretion. *Am J Physiol* 265:F578, 1993.
105. Traynor TR, Smart A, Briggs JP, Schnermann J. Inhibition of macula densa-stimulated renin secretion by pharmacological blockade of cyclooxygenase-2. *Am J Physiol* 277:F706, 1999.
106. Henrich WL, Schrier RW, Berl T. Mechanisms of renin secretion during hemorrhage in the dog. *J Clin Invest* 64:1, 1979.
107. Cuneo RC, Espiner EA, Nicholls G, et al. Effect of physiological levels of atrial natriuretic peptide on hormone secretion: Inhibition of angiotensin-induced aldosterone secretion and renin release in normal man. *J Clin Endocrinol Metab* 65:765, 1987.
108. Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. *Am J Med* 32:65, 1962.
109. Guyton AC. *Textbook of Medical Physiology*, 8th ed. Saunders, Philadelphia, 1991, chap. 16.
110. Maddox DA, Deen WM, Brenner BM. Dynamics of glomerular ultrafiltration. VI. Studies in the primate. *Kidney Int* 5:271, 1974.
111. Brenner BM, Humes HD. Mechanics of glomerular ultrafiltration. *N Engl J Med* 297:148, 1977.
112. Arendshorst W, Gottschalk CW. Glomerular ultrafiltration dynamics: Historical perspective. *Am J Physiol* 248:F163, 1985.
113. Savin VJ. Ultrafiltration in single isolated human glomeruli. *Kidney Int* 24:748, 1983.
114. Brenner BM, Troy JL, Daugharty TM, et al. Dynamics of glomerular ultrafiltration in the rat. II. Plasma-flow dependence of GFR. *Am J Physiol* 223:1184, 1972.
115. Renkin E, Robinson R. Glomerular filtration. *N Engl J Med* 290:785, 1974.

116. Dworkin LD, Ichikawa I, Brenner BM. Hormonal modulation of glomerular function. *Am J Physiol* 244:F95, 1983.
117. Kaizu K, Marsh D, Zipser R, Glassock RJ. Roles of prostaglandins and angiotensin II in experimental glomerulonephritis. *Kidney Int* 28:629, 1985.
118. Yarger WE, Aynedjian HS, Bank N. A micropuncture study of postobstructive diuresis in the rat. *J Clin Invest* 51:625, 1972.
119. Steinhausen M, Endlich K, Wiegman DL. Glomerular blood flow. *Kidney Int* 38:769, 1990.
120. Navar LG. Renal autoregulation: Perspectives from whole kidney and single nephron studies. *Am J Physiol* 234:F357, 1978.
121. Hall JE, Guyton AC, Jackson TE, et al. Control of glomerular filtration rate by renin-angiotensin system. *Am J Physiol* 233:F366, 1977.
122. Johnson PC. Autoregulation of blood flow. *Circ Res* 59:483, 1986.
123. Casellas D, Moore LC. Autoregulation and tubuloglomerular feedback in juxtaglomerular arterioles. *Am J Physiol* 258:F660, 1990.
124. Harder DR, Gilbert R, Lombard JH. Vascular muscle cell depolarization and activation in renal arteries on elevation on transmural pressure. *Am J Physiol* 253:F778, 1987.
125. Hayashi K, Epstein M, Loutzenheiser R. Pressure-induced vasoconstriction of renal microvessels in normotensive and hypertensive rats: Studies in isolated perfused hydronephrotic kidney. *Circ Res* 65:1475, 1989.
126. Carmines PK, Fowler BC, Bell PD. Segmentally distinct effects of depolarization on intracellular [Ca^{2+}] in renal arterioles. *Am J Physiol* 265:F677, 1993.
127. Schnermann J, Briggs JP, Weber PC. Tubuloglomerular feedback, prostaglandins, and angiotensin in the autoregulation of glomerular filtration rate. *Kidney Int* 25:53, 1984.
128. Beierwaltes WH, Sigmon DH, Carretero OA. Endothelium modulates renal blood flow but not autoregulation. *Am J Physiol* 262:F943, 1992.
129. Kastner PR, Hall JE, Guyton AC. Control of glomerular filtration rate: Role of intrarenally formed angiotensin II. *Am J Physiol* 246:F897, 1984.
130. Hricik DE, Dunn MJ. Angiotensin-converting-enzyme inhibitor-induced renal failure: Causes, consequences, and diagnostic uses. *J Am Soc Nephrol* 1:845, 1990.
131. Jackson B, Matthews PG, McGrath BP, Johnston CI. Angiotensin converting enzyme inhibition in renovascular hypertension: Frequency of reversible renal failure. *Lancet* 1:225, 1984.
132. Hricik DE. Captopril induced renal insufficiency and the role of sodium balance. *Ann Intern Med* 103:222, 1985.
133. Wenting GJ, Tan-Tjiong HL, Derkx FHM, et al. Split renal function after captopril in unilateral renal artery stenosis. *Br Med J* 288:886, 1984.
134. Michel J-B, Dussaule J-C, Choudat L, et al. Effect of antihypertensive treatment in one-clip, two kidney hypertension in rats. *Kidney Int* 29:1011, 1986.
135. Textor SE, Novick A, Tarazi RC, et al. Critical renal perfusion pressure for renal function in patients with bilateral atherosclerotic renal vascular disease. *Ann Intern Med* 102:308, 1985.
136. Packer M, Lee WH, Medina N, et al. Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 106:346, 1987.
137. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] trial). *Am J Cardiol* 70:492, 1992.
138. Blantz RC, Pelayo JC. A functional role for the tubuloglomerular feedback mechanism. *Kidney Int* 25:739, 1984.
139. Briggs JP, Schnermann J. The tubuloglomerular feedback mechanism: Functional and biochemical aspects. *Ann Rev Physiol* 49:251, 1987.
140. Schnermann J, Traynor T, Yang T, et al. Tubuloglomerular feedback: New concepts and developments. *Kidney Int* 54(suppl 67):S-40, 1998.
141. Moore LC. Tubuloglomerular feedback and SNGFR autoregulation in the rat. *Am J Physiol* 247:F267, 1984.
142. Moore LC, Casellas D. Tubuloglomerular feedback dependence of autoregulation in rat juxtaglomerular afferent arterioles. *Kidney Int* 37:1402, 1990.

143. Kallskog O, Marsh DJ. Tubuloglomerular feedback-initiated vascular interactions between adjacent nephrons in the rat kidney. *Am J Physiol* 259:F60, 1990.
144. Schnermann J, Briggs JP. Restoration of tubuloglomerular feedback in volume-expanded rats by angiotensin II. *Am J Physiol* 259:F565, 1990.
145. Schnermann J, Briggs JP. Effect of angiotensin and other pressor agents on tubuloglomerular feedback responses. *Kidney Int* 38(suppl 30): S-77, 1990.
146. Navar LG, Saccomani G, Mitchell KD. Synergistic intrarenal actions of angiotensin on tubular reabsorption and renal hemodynamics. *Am J Hypertens* 4:90, 1991.
147. Weihprecht H, Lorenz JN, Briggs JO, Schnermann J. Vasomotor effects of purinergic agonists in isolated rabbit afferent arterioles. *Am J Physiol* 263:F1026, 1992.
148. Schnermann J, Weihprecht H, Briggs JP. Inhibition of tubuloglomerular feedback by adenosine$_1$ receptor blockade. *Am J Physiol* 258:F553, 1990.
149. Thomson S, Bao D, Deng A, Vallon V. Adenosine formed by 5′-nucleotidase mediates tubuloglomerular feedback. *J Clin Invest* 106:289, 2000.
150. Navar LG, Inscho EW, Ibarrola M, Carminès PK. Communication between the macula densa cells and the afferent arteriole. *Kidney Int* 39(suppl 32):S-78, 1991.
151. Welch WJ, Wilcox CS. Potentiation of tubuloglomerular feedback in the rat by thromboxane mimetic. *J Clin Invest* 89:1857, 1992.
152. Navar LG. Integrating multiple paracrine regulators of renal microvascular dynamics. *Am J Physiol* 274:F433, 1998.
153. Thompson SC, Bachmann S, Bostanjoglo M, et al. Temporal adjustment of the juxtaglomerular apparatus during sustained inhibition of proximal reabsorption. *J Clin Invest* 104:1149, 1999.
154. Welch WJ, Wilcox CS, Thomson SC. Nitric oxide and tubuloglomerular feedback. *Semin Nephrol* 19:25, 1999.
155. Wilcox CS, Welch WJ. TGF and nitric oxide: Effects of salt intake and salt-sensitive hypertension. *Kidney Int* 55(suppl 55): S–9, 1996.
156. Persson B-E, Sakai T, Marsh DJ. Juxtaglomerular hypertonicity in *Amphiuma*: Tubular origin—TGF signal. *Am J Physiol* 254:F445, 1988.
157. Moore LC. Interaction of tubuloglomerular feedback and proximal nephron reabsorption in autoregulation. *Kidney Int* 22(suppl 12):S-173, 1982.
158. Thurau K. Acute renal success: The unexpected logic of oliguria in acute renal failure. *Am J Med* 61:308, 1976.
159. Leyssac PP, Karlsen FM, Skott O. Dynamics of intrarenal pressures and glomerular filtration rate after acetazolamide. *Am J Physiol* 261:F169, 1991.
160. Seely JF, Dirks JH. Micropuncture study of hypertonic mannitol diuresis in the proximal and distal tubule of the dog kidney. *J Clin Invest* 48:2330, 1969.
161. Henriksen JH, Bendtsen F, Gerbes AL, et al. Estimated central blood volume in cirrhosis: Relationship to sympathetic nervous activity, β-adrenergic blockade and atrial natriuretic factor. *Hepatology* 16:1163, 1992.
162. Tucker BJ, Mundy CA, Blantz RC. Adrenergic and angiotensin II influences on renal vascular tone in chronic sodium depletion. *Am J Physiol* 252:F811, 1987.
163. Persson PB, Ehmke H, Nafz B, Kircheim HR. Sympathetic modulation of renal autoregulation by carotid occlusion in conscious dogs. *Am J Physiol* 258:F364, 1990.
164. Bonvalet J-P, Pradelles P, Farman N. Segmental synthesis and actions of prostaglandins along the nephron. *Am J Physiol* 253:F377, 1987.
165. Schor N, Ichikawa I, Brenner BM. Glomerular adaptations to chronic dietary salt restriction or excess. *Am J Physiol* 238:F428, 1980.
166. Johnston PA, Bernard DB, Perrin NS, et al. Control of rat renal vascular resistance during alterations in sodium balance. *Circ Res* 48:728, 1981.
167. Oates JA, Fitzgerald GA, Branch RA, et al. Clinical implications of prostaglandin and thromboxane A_2 formation. *N Engl J Med* 319:761, 1988.
168. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. *Kidney Int* 32:1, 1987.

169. Kilcoyne MM, Schmidt DH, Cannon PJ. Intrarenal blood flow in congestive heart failure. *Circulation* 47:786, 1973.
170. Epstein M, Berk DP, Hollenberg NK, et al. Renal failure in patients with cirrhosis. *Am J Med* 49:175, 1970.
171. Stein JH, Boonjarern S, Maux RC, Ferris TF. Mechanism of the redistribution of renal cortical blood flow during hemorrhagic hypotension in the dog. *J Clin Invest* 52:39, 1973.
172. Bruns FJ, Alexander EA, Riley AL, Levinsky NG. Superficial and juxtamedullary nephron function during saline loading in the dog. *J Clin Invest* 53:971, 1974.
173. Weidmann P, Hasler, L, Gnadinger MP, et al. Blood levels and renal effects of atrial natriuretic peptide in normal man. *J Clin Invest* 77:734, 1986.
174. Lüscher TF, Bock HA, Yang Z, Diederich D. Endothelium-derived relaxing and contracting factors: Perspectives in nephrology. *Kidney Int* 39:575, 1991.
175. Edwards RM, Trizna W, Ohlstein EH. Renal microvascular effects of endothelin. *Am J Physiol* 259:F217, 1990.
176. Kohan DE. Endothelins in the normal and diseased kidney. *Am J Kidney Dis* 29:2, 1997.
177. Chou S-Y, Dahnan A, Porush JG. Renal actions of endothelin: Interaction with prostacyclin. *Am J Physiol* 259:F645, 1990.
178. Kon V, Yoshioka T, Fogo A, Ichikawa I. Glomerular actions of endothelin in vivo. *J Clin Invest* 83:1762, 1989.
179. Kon V, Sugiura M, Inagami T, et al. Role of endothelin in cyclosporine-induced glomerular dysfunction. *Kidney Int* 37:1487, 1990.
180. Lanese DM, Conger JD. Effects of endothelin receptor antagonist on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. *J Clin Invest* 91:2144, 1993.
181. Rademacher J, Forstermann U, Frohlich JC. Endothelium-derived relaxing factor influences renal vascular resistance. *Am J Physiol* 259:F9, 1990.
182. Berthold H, Just A, Kirchheim HR, et al. Interaction between nitric oxide and endogenous vasoconstrictors in control of blood flow. *Hypertension* 34:1254, 1999.
183. Jacobson HR, Klahr S. Chronic renal failure: Pathophysiology; Management. *Lancet* 338:419,423, 1991.
184. Olson JL, Heptinstall RM. Nonimmunologic mechanisms of glomerular injury. *Lab Invest* 1988, 59:564, 1988.
185. Anderson S, Rennke HG, Garcia DL, Brenner BM. Short and long term effects of antihypertensive therapy in the diabetic rat. *Kidney Int* 36:526, 1989.
186. Zatz R, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic nephropathy. *Proc Natl Acad Sci U S A* 82:5963, 1985.
187. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 334:939, 1996.
188. Ruggenenti P, Perna A, Gherardi G, et al. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 352:1252, 1998.
189. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456, 1993.
190. Wilmer WA, Hebert LA, Lewis EJ, et al. Remission of nephrotic syndrome in type 1 diabetes: Long-term follow-up of patients in the Captopril study. *Am J Kidney Dis* 34:308, 1999.
191. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 330:877, 1994.
192. Levy AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: What have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study Group. *J Am Soc Nephrol* 10:2426, 1999.
193. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 31:954, 1998.

194. Zeller K, Whittaker E, Sullivan L, et al. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 324:78, 1991.
195. Levey AS. Measurement of renal function in chronic renal disease. *Kidney Int* 38:167, 1990.
196. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration market in glomerulopathic patients. *Kidney Int* 28:830, 1985.
197. Kim KE, Onesti G, Ramirez O, et al. Creatinine clearance in renal disease. A reappraisal. *Br Med J* 4:11, 1969.
198. Bauer JH, Brooks CS, Burch RN. Clinical appraisal of creatinine clearance as a measurement of glomerular filtration rate. *Am J Kidney Dis* 2:337, 1982.
199. Petri M, Bockenstedt L, Colman J, et al. Serial assessment of glomerular filtration rate in lupus nephropathy. *Kidney Int* 34:832, 1988.
200. Myers BD, Chagnac A, Golbetz H, et al. Extent of glomerular injury in active and resolving lupus nephritis: A theoretical analysis. *Am J Physiol* 260:F717, 1991.
201. Perrone RD, Steinman TI, Beck GJ, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: Simultaneous comparison of ^{125}l-iothalamate, ^{169}Yb-DTPA, ^{99m}Tc-DTPA, and inulin. *Am J Kidney Dis* 16:224, 1990.
202. van Acker BAC, Koomen GCM, Koopman MG, et al. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 340:1326, 1992.
203. Hilbrands LB, Artz MA, Wetzels JFM, Koene RAP. Cimetidine improves the reliability of creatinine as a marker of glomerular filtration. *Kidney Int* 40:1171, 1991.
204. Chagnac A, Kiberd BA, Farinas MC, et al. Outcome of the acute glomerular injury in proliferative lupus nephritis. *J Clin Invest* 84:922, 1989.
205. Levey AS, Berg RL, Gassman JJ, et al. Modification of Diet in Renal Disease (MDRD) Study Group. Creatinine filtration, secretion and excretion during progressive renal disease. *Kidney Int* 36(suppl 27):S-73, 1989.
206. Castellino P, Levin R, Shohat J, DeFronzo RA. Effect of specific amino acid groups on renal hemodynamics in humans. *Am J Physiol* 258:F992, 1990.
207. Kontessis P, Jones S, Dodds R, et al. Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. *Kidney Int* 38:136, 1990.
208. Payne RB. Creatinine clearance: A redundant clinical investigation. *Ann Clin Biochem* 23:243, 1986.
209. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 16:13, 1976.
210. Gault MH, Longerich LL, Harnett JD, Weslowski C. Predicting glomerular function from adjusted serum creatinine. *Nephron* 62:249, 1992.
211. Papadakis MA, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Prospective study. *Am J Med* 82:945, 1987.
212. Caregaro L, Menon F, Angeli P, et al. Limitation of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. *Arch Intern Med* 154:201, 1994.
213. Molitch ME, Rodman E, Hirsch CA, Dubinsky E. Spurious creatinine elevations in ketoacidosis. *Ann Intern Med* 93:2800, 1980.
214. Rocci ML Jr, Vlasses PH, Ferguson RK. Creatinine serum concentrations and H_2-receptor antagonists. *Clin Nephrol* 22:814, 1984.
215. Berg KJ, Gjellestad A, Nordby G, et al. Renal effects of trimethoprim in cyclosporin- and azathioprine-treated kidney allografted patients. *Nephron* 43:218, 1989.
216. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 47:312, 1995.
217. Dossetor JB. Creatininemia versus uremia: The relative significance of blood urea nitrogen and serum creatinine concentrations in azotemia. *Ann Intern Med* 65:1287, 1966.
218. Smith HW, Goldring W, Chasis H. The measurement of the tubular excretory mass, effective blood flow and filtration rate in the normal human kidney. *J Clin Invest* 17:263, 1938.

219. Lubowitz H, Slatopolsky E, Shankel S, et al. Glomerular filtration rate determination in patients with chronic renal disease *JAMA* 199:252, 1967.
220. Rodriguez-Puyol D. The aging kidney. *Kidney Int* 54:2247, 1998.
221. Lindeman RD, Tobin J, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 26:861, 1984.
222. Fliser D, Franek E, Joest M. Renal function in the elderly: Impact of hypertension and cardiac function. *Kidney Int* 51:1196, 1997.
223. Fliser D, Franek E, Ritz E. Renal function in the elderly—Is the dogma of an inexorable decline of renal function correct (editorial)? *Nephrol Dial Transplant* 12:1553, 1997.