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Renal Physiology

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INTRODUCTION

Although the kidneys receive 20% of the cardiac output, they constitute only one half of 1% of the total body mass. The 180 L of glomerular filtrate produced each day are finely processed to maintain the internal milieu with exquisite precision.

The nephron, the functional unit of the kidney, consists of a glomerular capillary network, a proximal convoluted tubule, a loop of Henle, a distal convoluted tubule, and a collecting duct. There are approximately two to three million nephrons within two adult human kidneys; at rest only one tenth of this amount is required to maintain homeostasis. Therefore, a large reserve exists. The precise quantification of this reserve enables decisions regarding therapy to be made when renal dysfunction occurs. This chapter will review normal renal physiology and will examine the impact of alterations in renal function on urology. We will also discuss the limitations of various quantitative methods, while presenting several "bedside techniques" for the assessment of renal function.

DEVELOPMENTAL PHYSIOLOGY

Three bilateral excretory systems develop during embryologic growth. The earliest is the *pronephros*, which is composed of approximately 7 tubules. The proximal ends of these tubules form nephrostomes

which enter into the coelomic cavity, while the distal ends coalesce to form the pronephric duct which empties into the cloaca. The pronephros appears to be nonfunctional in mammals. At about the fourth week of development, the second system, the *mesonephros*, develops caudal to the first. The mesonephros consists of a glomerular structure, a proximal tubular segment, and a distal tubular segment. This structure produces some tubular fluid, at least transiently. In the female this structure regresses by the third month of gestation. In the male, the mesonephric tubules and duct (the former pronephric duct) develop into the efferent ductules of the epididymis, the duct of the epididymis, the ductus deferens, the seminal vesicle, and the ejaculatory duct. The third system, the *metanephros*, originates from two different embryologic tissues at about the eighth week of fetal life¹: the glomerulus and tubules arise from the mesenchyme of the nephrogenic ridge.² The excretory portion (collecting duct, calyces, pelvis, and ureter) arise from a specialized structure of the mesonephric duct, the ureteric bud. The nephrons in the metanephros appear to be functional as early as the 11th to 12th week of fetal life. It appears that morphologic and functional maturation of nephrons starts in the deep nephrons and then extends to the superficial nephrons.

The morphologic and functional effects

of renal senescence begin in the cortical regions and progress toward the medullary portions of the kidney—the opposite of nephron maturation. In humans, the kidney loses over 20% of its weight between the 4th and 8th decade. While the greatest loss occurs in the cortex, the medullary portion is also involved, and displays a generalized fibrosis similar to that seen with chronic hypertension. However, even without hypertension, arteriolar hyalinization and glomerular sclerosis results in the loss of 50% of glomeruli by the eighth decade.¹

RENAL HEMODYNAMICS

Functional Organization of the Renal Circulation

The renal circulation is designed to simultaneously accomplish bulk filtration, reabsorption, and precise selective regulation of the constituents of normal urine. From an enormous blood flow of about a liter per minute, only about 1 mL of urine is formed per minute. The energy requirement of this process is about 10% of basal oxygen consumption, yet the efficiency of the kidney is reflected in its low arteriovenous oxygen difference.²

Originally, the renal circulation was quantified by clearance techniques measuring total renal blood flow. More recently, micropuncture and microangiographic techniques have advanced the understanding of the renal microcirculation.^{3,4} It is now known that the kidney is not composed of a single homogeneous circulation but is rather made up of several distinct microvascular networks. These include the glomerular microcirculation, the cortical peritubular microcirculation, and the microcirculation that nourishes and drains the inner and outer medulla.²

The gross anatomy of the renal vasculature has previously been described. The interlobular arteries taper as they pass through almost the entire renal cortex, and each gives rise to about 20 afferent glomerular arterioles that supply one or more of the 1.5 million glomeruli of the human kidney. The vascular pathways in the glomerulus change under different physiologic

conditions, and there is intermittent flow within glomeruli which may play a role in regulation of glomerular filtration rate (GFR). The discovery that the glomerular mesangium contains contractile elements that respond to angiotensin II (AII) and other vasoactive substances supports this hypothesis.⁵ As they extend beyond the glomerulus the efferent arterioles form dense peritubular capillary plexuses that nourish the proximal or distal convoluted tubules situated in the cortex. Alternatively the arterioles pass into the medulla (especially from juxtamedullary glomeruli) and divide into bundles of vasa recta that parallel medullary rays.⁴ Microdissection and injection studies have recently shown that, except for the initial portion of the peritubular capillaries in the outer cortex, the efferent peritubular capillary network and the nephron arising from each glomerulus are dissociated.⁶ There are distinct outer and inner medullary capillary networks. In the inner medulla, the degree of organization of vascular-tubular relations correlates with concentrating ability.⁷

The major changes in hydraulic pressure across the renal vascular bed are shown in Figure 1. The role of physical factors in the regulation of GFR will be discussed later.

Measurement of Renal Blood Flow. Measurements of the clearance of organic iodides, Diodrast, and para-aminohippurate (PAH) are used to estimate renal blood flow (RBF), and are based on application of the Fick principle. At low plasma concentrations these substances are almost totally secreted by the renal tubules; there is no extrarenal metabolism, storage, or production. Accurate utilization of the technique requires normal renal function and extraction, and assumes a renal venous concentration approaching zero. Since the extraction is probably never complete, the term “effective renal plasma flow” (ERPF) has been used. In disease states, venous sampling with actual determination of PAH extraction (E_{pah}) is required to calculate true renal plasma flow.

Accordingly, clearance of PAH (C_{pah}) is calculated by the formula $U_i \times Q_u =$

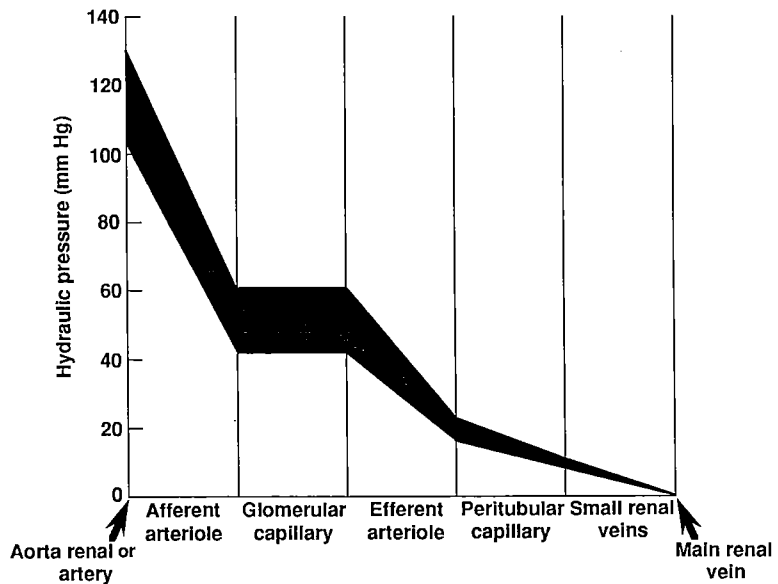


Fig 1. Diagram showing changes in the magnitude of intravascular hydraulic pressure from renal artery to renal vein in the Munich-Wistar rat. Steepest axial hydraulic pressure drops occur along the afferent and efferent arterioles; no significant pressure drop has been detected along glomerular capillary vessels. Thus, the cortical capillary exchange beds of the glomerular and peritubular networks operate at markedly different hydraulic pressures. Since the transglomerular hydraulic pressure difference exceeds the local oncotic pressure difference, fluid is lost from these capillaries by filtration. In the peritubular network, the transcapillary oncotic pressure difference exceeds the prevailing hydraulic pressure difference, thereby favoring fluid absorption into these capillaries.

$(A_i - V_i) \times \text{RPF}$ where:

U_i = concentration of indicator in urine (mg/mL)

Q_u = urine flow rate (mL/min)

A_i = concentration of indicator in arterial plasma (mg/mL)

V_i = concentration of indicator in venous plasma (mg/mL)

RPF = renal plasma flow rate (mL/min)

Rewriting this equation,

$$\text{RPF} = \frac{U_i Q_u}{A_i - V_i}$$

Since extraction is assumed to be almost complete in the clinical setting (that is, $V_i = 0$) and A_i is kept constant, the equation for C_{pah} becomes:

$$\text{RPF} = \frac{U_i Q_u}{A_i} \text{ or } \frac{U_{\text{pah}} \times V}{P_{\text{pah}}}$$

where U_{pah} = urine concentration of PAH and P_{pah} = plasma concentration of PAH.

Of note, $U_i Q_u$ = excreted load of the indicator (mg/min) and $V = Q_u$ (urine flowrate).

The conversion of renal plasma flow rate to blood flow is achieved by dividing RPF by the plasma fraction of whole blood as estimated by the hematocrit (HCT).

$$\text{RBF} = \frac{\text{RPF}}{1 - \text{HCT}}$$

The complexity of determination of RBF by the C_{pah} technique and the requirement of normal renal function have led to a search for alternative techniques. Single-injection techniques using a variety of radioisotopes followed by measurement of the rate of disappearance of the isotope tag from the blood or by noninvasive moni-

toring are discussed elsewhere (Volume 1, Chapter 6). Radionuclide monitoring techniques allow calculation of differential RBF from each kidney, which often provides critical clinical information.

Distribution of Renal Blood Flow. Total RBF estimated by C_{pah} technique is 1200 mL/min/1.73 m²; this value has been confirmed by a variety of methods. In infants up to 1 year of age, RBF is about one half of the adult flow; it reaches the adult level at about 3 years of age.⁸ RBF falls after age 30, and has declined to about one half of maximum by age 90.⁹ When related to renal mass, RBF is remarkably similar in various species, and is usually about 4 mL/g/min.

Although it is well documented that the perfusion rate in different regions of the kidney is not uniform, there remains considerable disagreement about regional blood flow measurements obtained by different methods under differing experimental conditions. Moreover, no clear correlation exists between distribution of renal blood flow and renal function. The utilization of inert gas washout, radioactive microspheres, or nondiffusible indicators is beyond the scope of this review.^{3,10} This area remains under investigation and may be relevant to the understanding of the pathophysiology of acute renal failure.¹¹ The attractive hypothesis that there is a causal relationship between the distribution of RBF and sodium handling awaits confirmation.

The renal cortex receives about 90% of the total renal blood flow (5 to 6 mL/min in the outer cortex), while flow in the outer medullary is only about 1 mL/min. However, medullary flow, "sluggish" relative to the cortex, is still greater per gram than flow to the liver, brain, or resting muscle.

Glomerular Filtration Rate

The elaboration of urine begins at the glomerulus with the formation of a nearly protein-free ultrafiltrate of plasma which enters Bowman's space. As the filtrate passes through the tubules, substances may be removed (reabsorption) or added (secretion). Clearance is "a quantitative de-

scription of the rate at which the kidney excretes various substances relative to their concentration in plasma."¹² It is calculated as follows:

U_x = concentration of x in a timed urine collection (mg/mL)

V = volume of urine per unit time (mL/min)

P_x = concentration of x in plasma (mg/mL)

$U_x V$ = rate of urinary excretion of x = excreted load (mg/min)

$C_x = U_x V / P_x$ = the (plasma) clearance of x (mL/min)

C_x is the volume of plasma containing x that would have to be completely cleared of x per unit time to supply an amount of x for urinary excretion at the measured rate. Clearance does not necessarily mean that an *actual* volume of plasma is, in fact, completely cleared of x. Rather, it refers to a "virtual volume" of plasma that would provide the measured amount of x.

A substance that is freely filtered and undergoes neither reabsorption nor secretion will have a clearance equal to the GFR. The clearance of inulin, a carbohydrate polymer of fructose, measured during a constant infusion, is the standard for measurement of GFR. A clearance greater than that of inulin indicates that a substance also undergoes tubular *secretion*; a clearance less than that of inulin implies tubular *reabsorption*.

Rewriting the clearance equation for x = inulin, we have:

$$C_{\text{inulin}} = U_{\text{inulin}} V / P_{\text{inulin}}$$

Because of the difficulty in measuring inulin clearance, the clearance of endogenous creatinine is used for clinical purposes as an estimate of GFR. Its plasma concentration remains stable during a 24-hour period, and its rate of excretion does not vary with urine flow. Thus, creatinine clearance (C_{cr}) can be calculated during a 24-hour collection of urine, with a plasma sample obtained at any time during the collection period. In normal man, filtered creatinine does not undergo tubular reabsorption; some tubular secretion does occur. At the plasma creatinine concentration that pre-

vails at normal GFR, the ratio C_{cr}/C_{inulin} is close to 1, implying negligible secretion. At progressively lower GFRs, however, tubular secretion plays an increasingly important part in creatinine excretion. At GFRs below 30 mL/min, C_{cr} may overestimate C_{inulin} by 50% to 80%. Because this represents small absolute differences at low GFRs, C_{cr} is satisfactory as an estimate of GFR in patients with chronic renal insufficiency.

Kidney weight is more closely correlated with body surface area than with either height or weight. In order to compare renal function in persons of different sizes, GFR is frequently described per standard unit of body surface area, 1.73 m^2 .¹²

Often the need arises to accurately predict C_{cr} without waiting for the results of 24-hour urine testing. For example, the dose of various potentially toxic drugs may need to be quickly adjusted when beginning therapy. Several investigators have devised formula to predict C_{cr} utilizing serum creatinine, body weight, age, and sex as variables. The most widely used of these is that described by Crockcroft and Gault.¹³ Estimated GFR is given by the following equation:

$$\frac{(140-\text{age})(\text{weight})}{72 S_{cr}} \text{ mL/min}$$

(multiply the equation by 0.85 for women)
where:

1. S_{cr} is serum creatinine (mg/dL)
2. Age is in years
3. Weight is in kg

The major prerequisite for use of this formula is that renal function be at steady state (as defined by a stable serum creatinine). The group studied by Crockcroft and Gault consisted of 249 patients ranging in age from 18 to 92 years old whose measured mean C_{cr} ranged from 37.4 to 114.9 mL/min. The correlation coefficient between measured and calculated C_{cr} was 0.84; this value is not significantly different than the correlation between two consecutive measurements of C_{cr} obtained from the same individual.

Factors Affecting Glomerular Filtration. Micropuncture studies of individual nephrons in the Munich-Wistar rat and the squirrel monkey, which possess glomeruli on the renal cortical surface, have permitted direct measurement of the factors that determine single-nephron glomerular filtration rate (SNGFR).¹⁴⁻¹⁶ Assuming that all nephrons behave in a manner similar to those accessible to micropuncture, the regulation of whole-kidney GFR can be understood in terms of changes in one or more of the forces that regulate SNGFR. The symbols designating these forces, used in the following discussion, are summarized in Table 1.

The principal driving force for glomerular filtration is the hydrostatic pressure at the glomerular capillary (P_{gc}). This pressure is a consequence of the forces that maintain systemic blood pressure—cardiac output and systemic vascular resistance. P_{gc} , which favors ultrafiltration, is opposed by the hydrostatic pressure in Bowman's space of the renal tubule (P_t). The differ-

TABLE 1. Factors Governing SNGFR

P_{gc}	Hydrostatic pressure in the glomerular capillary
P_t	Hydrostatic pressure in the tubule (and its proximal extension, Bowman's space)
ΔP	Net transglomerular hydrostatic pressure
π_{gc}	Oncotic pressure of glomerular capillary plasma
π_t	Oncotic pressure of tubular fluid
$\Delta \pi$	Net transglomerular oncotic pressure
P_{uf}	Effective ultrafiltration pressure ($\Delta P - \Delta \pi$)
k_f or L_p	Hydraulic permeability of glomerular capillary
A	Glomerular surface area available for ultrafiltration
K_f or L_{pa}	Glomerular ultrafiltration coefficient

ence between these values is the transmembrane hydraulic pressure gradient (ΔP):

$$\Delta P = P_{gc} - P_t$$

Complementing these hydrostatic forces are the osmotic pressures exerted by plasma proteins, known as colloid osmotic pressure or oncotic pressure. The oncotic pressure of glomerular capillary plasma (π_{gc}) tends to oppose transcapillary fluid movement; the oncotic pressure of tubular fluid (π_t) tends to favor it. The difference between these two forces at any point is the transmembrane oncotic pressure ($\Delta\pi$):

$$\Delta\pi = \pi_{gc} - \pi_t$$

Under normal circumstances, filtration of plasma proteins is negligible and π_t is essentially zero. At any point along the length of the capillary, the effective filtration pressure (P_{uf}) can be calculated as follows:

$$P_{uf} = \Delta P - \Delta\pi$$

As filtration proceeds along the length of the glomerular capillary, the concentration of protein, and hence π_{gc} , rises. By the time the plasma reaches the efferent arteriole, π_{gc} has risen to a value equal to ΔP . This local equality of ΔP and π_{gc} is known as filtration pressure equilibrium (FPE). Precisely where along the length of the capillary FPE occurs cannot be determined, but at this point SNGFR becomes zero. FPE occurs in the surface glomeruli of the Munich-Wistar rat under hydropenic conditions. Whether FPE occurs in human glomeruli remain uncertain. In addition to P_{uf} , SNGFR is determined by both the hydraulic permeability of the glomerular capillary (k_f or L_p) and the total surface area available for ultrafiltration (A). The hydraulic permeability of the glomerular capillary is much greater than that of capillaries in nonrenal tissues. Because k_f and A cannot at present be independently measured, they are considered together as their product, the glomerular ultrafiltration coefficient, K_f or $L_p A$:

$$K_f = k_f \times A$$

The factors that determine SNGFR can thus be summarized by any of the following

equations:

$$\text{SNGFR} = K_f(P_{uf})$$

$$\text{SNGFR} = K_f(\Delta P - \Delta\pi)$$

$$\text{SNGFR} = K_f [(P_{gc} - P_t) - (\pi_{gc} - \pi_t)]$$

The actions of these forces are illustrated in Figure 2.

Changes in any of the foregoing variables in health or disease will have predictable effects on SNGFR.^{17,18}

Autoregulation of Glomerular Filtration Rate and Renal Blood Flow. Autoregulation of GFR and RBF is believed to occur mainly through variations in afferent arteriolar resistance. Parallel regulation of GFR and RBF result in response to changes in arterial pressure (Fig 3). There is less than 10% change in RBF or GFR over a wide range of perfusion pressure, from 80 to 180 mm Hg. This phenomenon was described as early as 1947, and appears to be a critical mechanism controlling renal homeostasis.¹⁹ Only at very low arterial perfusion pressure does an increase in efferent arteriolar resistance contribute to the maintenance of P_{gc} , sustaining SNGFR at reduced RBF.²⁰

The mechanism of autoregulation remains incompletely defined. Autoregulation is not unique to the kidney, but is most efficient in the renal and cerebral circulations. Since it is present in innervated, denervated, and isolated kidneys, it is assumed to be mediated by events intrinsic to the kidney—hence the term “autoregulation.” At present it appears that more than one proposed mechanism of autoregulation—namely, myogenic, metabolic, tubuloglomerular feedback, and/or humoral systems—may be causative. There is particular interest in a juxtaglomerular apparatus, which may play a critical role, although data from experiments utilizing a variety of angiotensin and prostaglandin blockers are conflicting.²¹

Evidence from micropuncture studies supports the hypothesis that changes in the rate of fluid flow in the distal tubule elicit changes in glomerular arteriolar resistance. This phenomenon is known as *distal tub-*

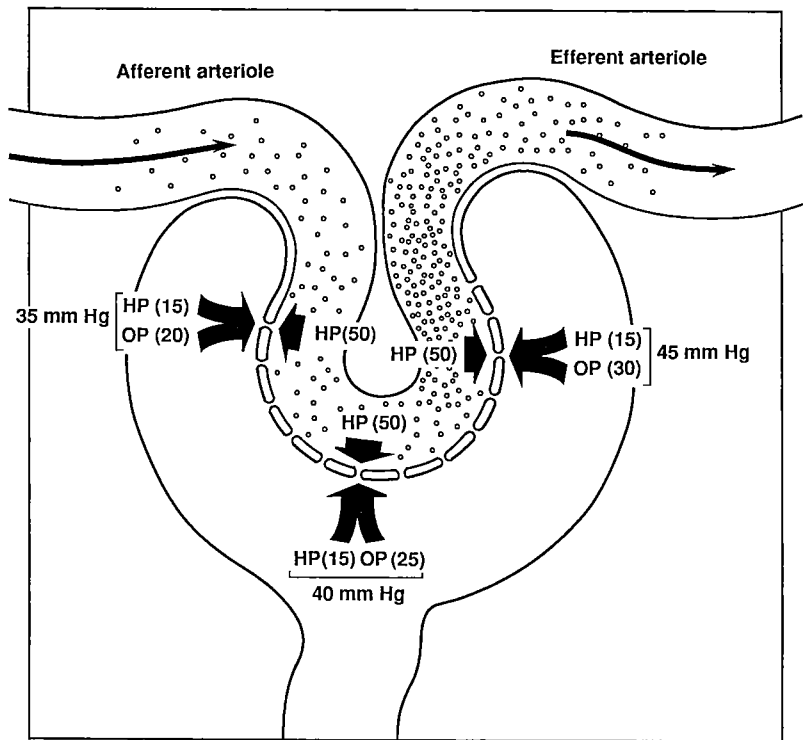


Fig 2. Starling forces regulating glomerular filtration. Net filtration pressure is the result of opposing hydrostatic pressure (HP) in the glomerular capillary and of the sum of hydrostatic pressure in Bowman's space and plasma oncotic pressure (OP). Net filtration pressure is maximal at the afferent arteriolar site of the capillary and approaches zero toward the efferent arteriolar site, because of increasing plasma oncotic pressure as a direct consequence of ultrafiltration.

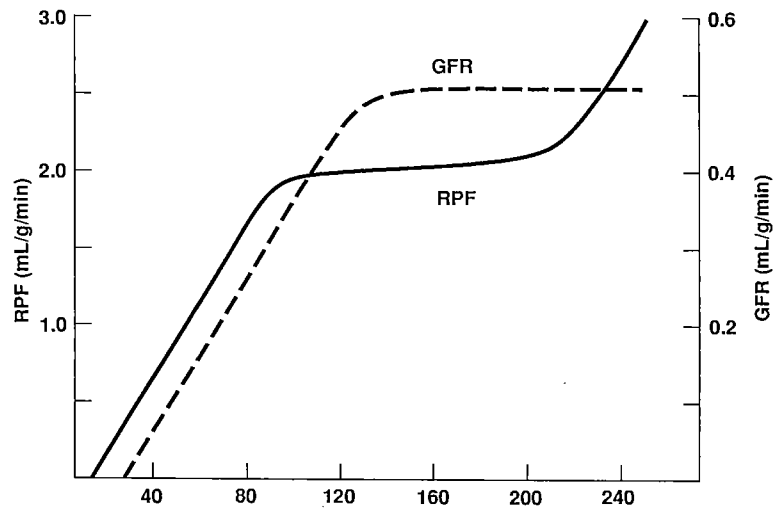


Fig 3. Autoregulation of renal plasma flow (RPF) and stability of glomerular filtration rate (GFR) over a similar range of mean arterial pressures. [Adapted from Shipley RE, Study RS, Changes in renal blood flow, extraction of inulin, glomerular filtration rate, tissue pressure and urine flow with acute alterations of renal artery blood pressure, *Am J Physiol* (1951;167:676), with permission.]

uloglomerular feedback. The morphologic association of the macula densa portion of the distal tubule and the afferent arteriole of the same nephron suggests that these structures are involved in the autoregulatory response. Considerable controversy persists, however, over (1) what aspect of distal tubular flow is perceived as the signal that engages autoregulation and (2) what are the mechanisms and sites of changes in arteriolar resistance. The initiating signal appears to be tubular-fluid chloride and its reabsorptive transport by cells of the macula densa.^{22,23} Many recent studies have indicated that chloride might not be the only signal.^{24,25}

Increases in distal fluid osmolality appear to result in an increase in intracellular free calcium concentration ($\{Ca^{2+}\}_i$). This increase in $\{Ca^{2+}\}_i$ might have two separate and opposite effects. First, it may enhance contraction of both the afferent and efferent arterioles. This would result in a decreased SNGFR and prevent an acute loss of fluid and electrolytes. Second, however, an increased $\{Ca^{2+}\}_i$ results in a decrease in renin release from the granules of the juxtaglomerular cells of the afferent arteriole. In the face of a continued stimulus, such as volume expansion, this would reduce local angiotensin II production and increase SNGFR, resulting in an increased excretion rate.

An alternative theory first proposed by Bayliss explains autoregulation as a consequence of variations in afferent arteriolar tone that occur as a direct result of changes in arterial blood pressure (*myogenic theory*).²⁶ An increase in pressure stretches the arteriolar smooth muscle and elicits contraction of the muscle layer, thus increasing afferent arteriolar resistance and regulating both GFR and RBF.¹⁸

The *metabolic theory* predicts that vasodilatory metabolites accumulate with a decrease in organ perfusion which results in a return to baseline blood flow rates. The major objection to this theory results from the well-known relationship between renal blood flow and renal metabolism.²⁷ Renal metabolism is primarily determined by the rate of sodium reabsorption, which in turn is directly related to GFR. Since GFR is

known to vary with RBF, it would follow that an increase in metabolism would produce an increase of the putative vasodilator and thus RBF. This would make autoregulation by vasodilatory metabolites impossible.

Autoregulatory factors, including vasodilatory prostaglandins, kinins, adenosine, and the renin-angiotensin system have been implicated in the autoregulation of RBF and GFR.²⁷⁻³² However, controversy persists, and the role of these *humoral factors* needs better definition.

It is most likely that all of these systems contribute, in part, to the phenomenon of renal autoregulation, and future studies will probably delineate the relative contribution of each.

Glomerular Permeability. The fluid entering Bowman's space is nearly free of albumin and larger molecules. Restriction to glomerular filtration of certain molecules is known as glomerular permselectivity. The determinants of glomerular permselectivity include effective glomerular "pore" size and the electrostatic charge on the glomerular filtration barrier. The degree of filtration of a molecule is thus determined by its size, shape, and charge. Filtration of macromolecules such as albumin may also be affected by renal hemodynamics.

The filtration of molecules larger than inulin (molecular radius = 14 Å) is progressively restricted, and approaches zero at molecular radii of about 40 Å.¹⁴ The molecular radius of albumin is 36 Å.

The glomerular filtration barrier is covered by sialoproteins that bear fixed negative charges. Albumin is a polyanion at physiologic pH. Hence, it is also restricted from glomerular filtration by the interaction of similar electrostatic charges. Neutral dextran, which has a molecular radius equal to that of albumin but which lacks a net negative charge, is filtered more than 100 times as easily as albumin.³³ In certain forms of renal disease, diminution in the glomerular charge barrier may increase glomerular permeability to albumin, resulting in proteinuria.

The glomerular filtration of albumin may

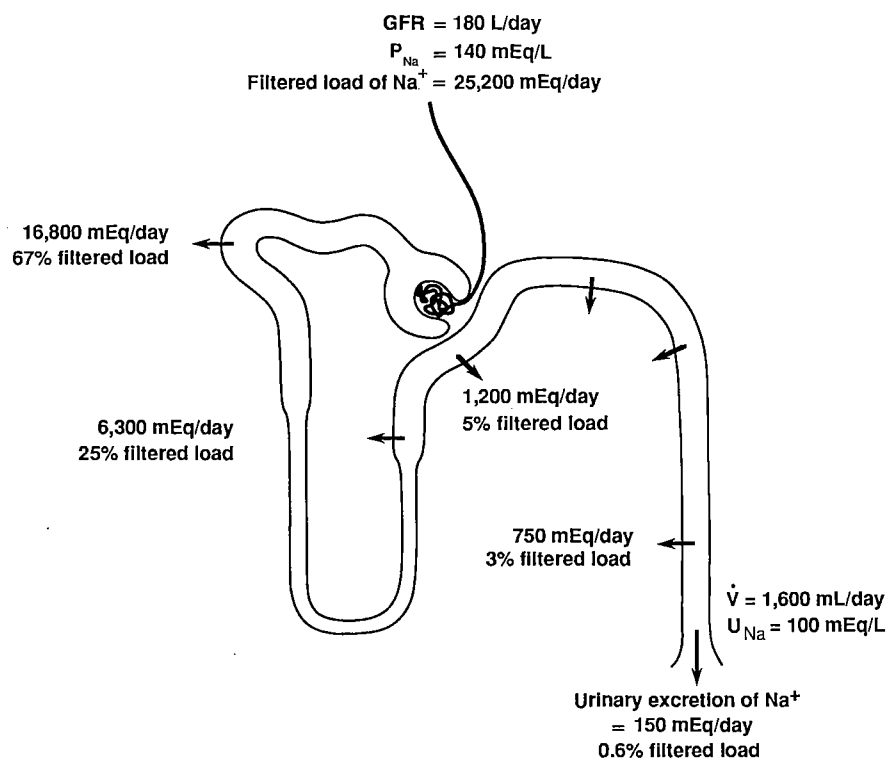


Fig 4. Daily renal turnover of Na^+ in a normal adult human. The diagram of the nephron represents the composite of the roughly 2 million nephrons of both kidneys. In steady state (equilibrium), the organism is, by definition, in balance. For Na^+ , this means that the daily output of Na^+ equals the daily intake. Obviously, Na^+ is excreted mainly by the kidneys; the difference between the rate of urinary excretion of Na^+ and the daily intake is made up by extrarenal routes of excretion, such as sweat, saliva, and other gastrointestinal secretions. Under normal circumstances the extrarenal losses of Na^+ are negligible. GFR = glomerular filtration rate; P_{Na} and U_{Na} = plasma and urinary concentration of sodium, respectively.

also be increased by a reduction in renal plasma flow unaccompanied by a change in glomerular filtration rate. Such an increase in "filtration fraction" (the ratio of GFR/RPF) may lead to an increase in the concentration of albumin in the glomerular capillaries and thereby augment the gradient favoring albumin diffusion into the filtrate.

SALT AND WATER HANDLING

Sodium (Na) and its associated anions (mostly chloride and bicarbonate) are confined to the extracellular fluid (ECF) compartment and are the principal determinants of ECF osmolality. Because water moves freely across cell membranes, and because

the osmolality of ECF is kept constant, it follows that the volume of ECF is directly related to the total body content of sodium. Renal tubular reabsorption of sodium and water preserves ECF volume despite glomerular filtration of large volumes of plasma. Changes in tubular sodium reabsorption defend ECF volume against changes in the filtered sodium load produced by changes in GFR. In addition, changes in excretion maintain sodium balance at varying levels of intake. The handling of sodium by the nephron is summarized in Figure 4.

The reabsorption of sodium ion takes place against electrical and chemical (concentration) gradients and requires expenditure of metabolic energy. Such a process

is described as active transport. The energy for the bulk of sodium reabsorption derives from aerobic metabolism. There is a direct, linear relationship between the rate of sodium reabsorption and oxygen consumption by the kidney.³⁴

The exact mechanisms of sodium transport throughout the nephron continue to be investigated. In the proximal tubule, sodium in the tubular lumen travels down its concentration gradient, across the luminal (apical) membrane, into the tubular epithelial cell. Within the cell, the concentration is kept low by pumps in the basal and lateral membranes that extrude sodium into the peritubular space, from which it can enter the peritubular capillaries. These pumps, involving the enzyme Na,K-ATPase, represent the "active" (energy-consuming) component of sodium transport. For the most part, chloride reabsorption follows sodium extrusion as a consequence of the negative luminal potential created by outward sodium movement.

Water is reabsorbed "passively," by moving down a gradient of osmolality between tubular fluid (lower) and peritubular (higher). This gradient is established by the reabsorption of sodium and its attendant anions. Because the water permeability of the proximal tubule is high, only a small osmotic gradient is required to effect water movement.

Similar sodium-reabsorptive processes probably operate in the distal tubules and collecting ducts. Unlike these other segments, however, the thick ascending limb of the loop of Henle has a positive luminal potential. Among the mechanisms proposed to account for this is active transport of chlorine with secondary, passive sodium reabsorption.^{35,36}

Regulation of Sodium Excretion

Defense mechanisms ensure that the bulk of filtered sodium is reabsorbed in the proximal nephron segments. Renal autoregulation keeps GFR, and hence the filtered sodium load, constant. If a hemodynamic disturbance that changes GFR occurs, the filtered load of sodium changes. The prox-

imal tubule alters its absolute rate of sodium reabsorption in parallel, so that the fractional sodium reabsorption remains constant. This phenomenon, termed glomerular-tubular balance, prevents loss or accumulation of large amounts of sodium. The mechanism by which glomerular-tubular balance is achieved remains uncertain. One hypothesis stresses the importance of physical factors.³⁷ Because the transglomerular passage of plasma protein is restricted, a change of GFR produces a parallel change in the protein concentration in the glomerular capillaries. This fluid passes into the efferent arteriole and thence to the peritubular capillaries. Thus, a rise in GFR would result in an increase in peritubular oncotic pressure. This tends to favor net sodium reabsorption. Decrements in peritubular oncotic pressure would have the opposite effect. The importance of peritubular protein concentration in the regulation of proximal sodium reabsorption has been challenged.³⁸ An alternative theory suggests that the glomerular filtrate itself contains a substance that stimulates its own reabsorption.³⁹ The identity of this substance is unknown.

Like with chronic dietary changes, comparatively small changes in sodium intake produce changes in urinary sodium excretion via changes in the handling of this ion by the collecting ducts. Except with extreme changes in ECF volume, such as can be produced by parenteral infusions, chronic sodium loading is usually not associated with changes in proximal reabsorption. Reabsorption by the collecting ducts is stimulated by aldosterone, the secretion of which is regulated, in part, by ECF volume through the activity of the renin-angiotensin system. Other humoral factors may also regulate sodium excretion, including substances whose production in the kidney is related to the sodium balance, such as prostaglandins, angiotensin II, dopamine, and bradykinin.

The existence of one or more "natriuretic hormones," thought to be produced in the central nervous system or at other sites in response to sodium loading, has also been proposed.^{40,41} Natriuretic hormones may act on the collecting duct to

inhibit reabsorption, perhaps by inhibition of Na, K-ATPase. There is growing evidence that an atrial natriuretic factor (ANF) may play a physiologic role in the regulation of salt and water balance in humans.⁴²⁻⁴⁶ ANF is secreted principally by atrial myocytes in response to increased intravascular volume. It acts in concert on the veins, the kidneys, and the adrenal glands to reduce systemic blood pressure and intravascular volume, chronically as well as acutely.⁴⁷ The reduction in systemic blood pressure is the result of a reduced peripheral vascular resistance, diminished cardiac output and decreased intravascular volume. In the kidney, ANF acts on specific receptors to induce hyperfiltration, inhibition of Na⁺ transport, and suppression of renin release. These actions result in a natriuresis, diuresis, and lowering of arterial blood pressure.⁴⁸ ANF also inhibits aldosterone biosynthesis both by inhibiting renin secretion from the renal juxtaglomerular apparatus and, more directly, by a receptor-mediated effect on adrenal glomerulosa cells. These actions also tend to lower arterial blood pressure and intravascular volume.

Changes in peritubular hydrostatic pressure in the renal interstitium can alter handling by the proximal tubule, the loop of Henle, and possibly by the collecting duct.^{38,49,50} An increase in interstitial pressure resulting from a rise in arterial pressure, renal vasodilation, or alterations in filtration fraction (resulting from changes in filtration dynamics at the glomerular tuft) can increase renal Na excretion acutely. Whether such physical factors influence tubular function directly or through resultant changes in the levels of intrarenal hormones remains undetermined. Stimulation of the adrenergic innervation to the kidney increases tubular Na reabsorption, independent of changes in GFR or renal plasma flow.⁵¹ The site at which sympathetic stimulation acts appears to be the proximal tubule.

The rate of sodium excretion is of diagnostic importance in determining the cause of oliguria. With prerenal azotemia, sodium excretion is usually less than 15 mmol/L, whereas sodium excretion is usu-

ally higher with renal causes (eg, acute tubular necrosis). However, prerenal factors often coexist with renal disease, thus there is considerable overlap in the urine sodium concentration (U_{Na}) in these two situations.⁵² Therefore, only values that are clearly abnormally high or low are diagnostic. The fractional excretion of sodium ($FE_{Na}\%$), obtained by dividing the clearance of sodium by the clearance of creatinine, provides a much better index by which to differentiate renal from prerenal causes. $FE_{Na}\%$ is calculated by the following formula:

$$FE_{Na}\% = (U_{Na} * P_{Cr} * 100) / (P_{Na} * U_{Cr}) \\ = (C_{Na} / C_{Cr}) * 100$$

where:

U_{Na} = urine sodium concentration

P_{Cr} = plasma creatinine concentration

U_{Cr} = urine creatinine concentration

C_{Na} = clearance of sodium

C_{Cr} = clearance of creatinine

A value lower than 1% favors a prerenal etiology while a value greater than 1% favors a renal cause. Although fairly sensitive and specific, $FE_{Na}\%$ values of less than 1% have been reported in patients with a variety of causes of acute renal failure other than prerenal disease (eg, myoglobinuria or hemoglobinuria, radiocontrast nephropathy, renal azotemia superimposed on chronic prerenal failure as in hepatic cirrhosis).⁵³

Urinary Dilution and Concentration

In the proximal tubule, where some two thirds of the glomerular filtrate is reabsorbed, water follows NaCl reabsorption, and the tubular fluid remains isotonic to plasma (normally 270 to 285 mOsm/kg). Separation of NaCl from water reabsorption occurs in the loop of Henle, by a mechanism that generates tubular fluid that is hypotonic (dilute) as compared with plasma. In the absence of vasopressin (ADH), the final urine remains dilute, permitting the excretion of a water load. The

loop of Henle also helps generate a hypertonic medullary interstitial environment. Under conditions of water deprivation (hydropenia), ADH causes fluid in the collecting ducts to equilibrate osmotically with the medullary interstitium. This results in hypertonic (concentrated) urine, and conserves water. Urine osmolality may vary normally from 50 mOsm/kg to approximately 1200 mOsm/kg.

The excretion of water relative to solute may be described quantitatively as free water clearance (C_{H_2O}). Not a true clearance in the sense of inulin or creatinine, C_{H_2O} is the difference between the measured urinary flow rate and the "osmolar clearance," ie, the rate of urine formation that would be necessary to excrete the measured urinary osmolar load at a tonicity equal to that of plasma. The calculation of C_{H_2O} is summarized below.

$$C_{H_2O} = V - C_{osm}$$

V = urine flow rate (mL/min)

$$C_{osm} = \text{osmolar clearance (mL/min)} \\ = (U_{osm} \times V) / P_{osm}$$

U_{osm} = urine osmolality (mOsm/kg)

P_{osm} = plasma osmolality (mOsm/kg)

$U_{osm} \times V$ = urinary osmolar load (mOsm/min)

$$C_{H_2O} = V - [(U_{osm} \times V) / P_{osm}]$$

$$C_{H_2O} = V [1 - (U_{osm} / P_{osm})] (\text{mL/min})$$

When dilute urine is produced, $U_{osm} < P_{osm}$, and C_{H_2O} is positive, implying net free water excretion. When concentrated urine is produced, $U_{osm} > P_{osm}$, and C_{H_2O} has a negative value, implying net free water conservation. Negative free water clearance ($-C_{H_2O}$) is symbolized as $T_{C_{H_2O}}$.

The formation of hypotonic tubular fluid occurs in the thick ascending limb of the loop of Henle. This segment is impermeable to water. The reabsorption of Cl and Na separates solute from water and reduces the osmolality of fluid leaving this segment to approximately 100 mOsm/kg. This pro-

cess occurs irrespective of external water balance. Administration of a water load reduces systemic extracellular fluid tonicity and inhibits ADH secretion. In the absence of ADH, the cortical and medullary portions of the collecting duct remain impermeable to water. Because NaCl reabsorption can continue in these segments, urine osmolality may be further reduced to the minimum of 50 mOsm/kg. The excretion of dilute urine maintains ECF tonicity in response to a water load.

Concentrated urine is elaborated in response to hydropenia, which raises ECF osmolality and stimulates ADH secretion. In man, ADH binds to receptors on the basolateral membrane of collecting duct epithelial cells. This activates the enzyme adenylate cyclase, which catalyzes intracellular cyclic AMP (cAMP) formation. cAMP—via a cAMP-dependent protein kinase—facilitates phosphorylation of a component of the apical membrane. Through a process that also involves cel-

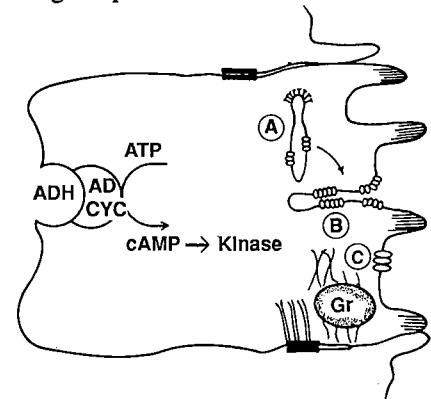


Fig 5. Diagrammatic view of the intercellular action of antidiuretic hormone (ADH). The hormone is bound to receptors on the basolateral membrane of the receptor cell and activates adenylate cyclase, increasing the intracellular concentration of cAMP. A series of intermediate steps take place (ADCYC), including activation of a cAMP-dependent protein kinase. Cytoplasmic tubular structures (aggrephores, A) are induced to fuse with the lumina membrane (B), and aggregates of water conducting particles are delivered to the membrane (C). Gr = subluminal granule; ATP = adenosine triphosphate. [Adapted from Hays RM, Franki N, Ding G, Effects of antidiuretic hormone on the collecting duct, *Kidney Int* (1987;31:530), with permission.]

lular microtubules, this increases the permeability of the collecting tubule of water (Fig 5). Urea permeability is also increased in the medullary portion. During hyponatremia, most water reabsorption occurs in the cortical collecting tubule, where hypotonic luminal fluid leaving the loop of Henle equilibrates with the isotonic interstitium of the cortex. The isotonic fluid in the cortical collecting tubule subsequently becomes hypertonic in the medullary collecting duct, by osmotic equilibration with the hypertonic medullary interstitium.

The kidney generates medullary hypertonicity by means of the loop of Henle. According to the "countercurrent hypothesis," reabsorption of NaCl without water in the ascending limb, and its deposition in the interstitium, creates a local (horizontal) osmotic gradient. The increase in medullary tonicity causes water to leave the descending limb, raising its tonicity. The proximity of the descending and ascending limbs of the same tubules (arranged in hairpin curves) causes a constant

gradient of tonicity at any given horizontal level to be multiplied along the vertical axis, creating high tonicities at the bend of the loop. This creates the progressive gradient of medullary tissue osmolality from corticomedullary junction to the papillary tip (Fig 6). Modification of the countercurrent hypothesis has been proposed to account for the importance of urea in augmenting urinary concentration.^{54,55} According to the modified hypothesis, the process of urinary concentration begins with active chloride transport in the ascending thick limb. Urea and water (to which this segment is impermeable) remain behind in the hypotonic fluid. In the cortical and outer medullary collecting tubules, ADH augments water but not urea permeability. Water leaves these segments, raising the luminal concentration of urea. In the inner medullary collecting duct, ADH enhances urea permeability as well. Urea thus leaves the tubule and accumulates in the interstitium. This action raises medullary tonicity and causes water to

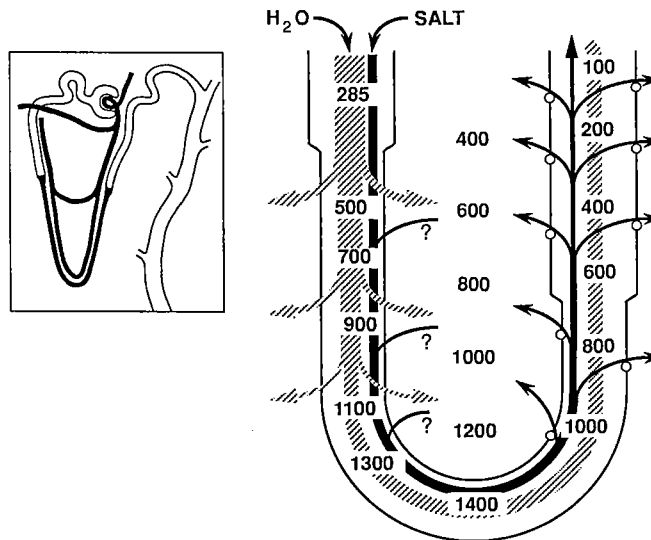


Fig 6. The loop of Henle, the "countercurrent multiplier." The numbers indicate the osmotic concentration in mOsm/kg H₂O of the tubular fluid and the interstitial fluid. The active transport of salt, without water, out of the ascending limb increases the osmotic concentration of the medullary interstitium. The small horizontal gradient is multiplied vertically by countercurrent flow. Water is reabsorbed from the descending limb by this osmotic force. Note that tubular fluid flows out of the loop at an osmotic concentration lower than that of the entering fluid. Fractionally more solute than water has been lost to the medullary interstitium.

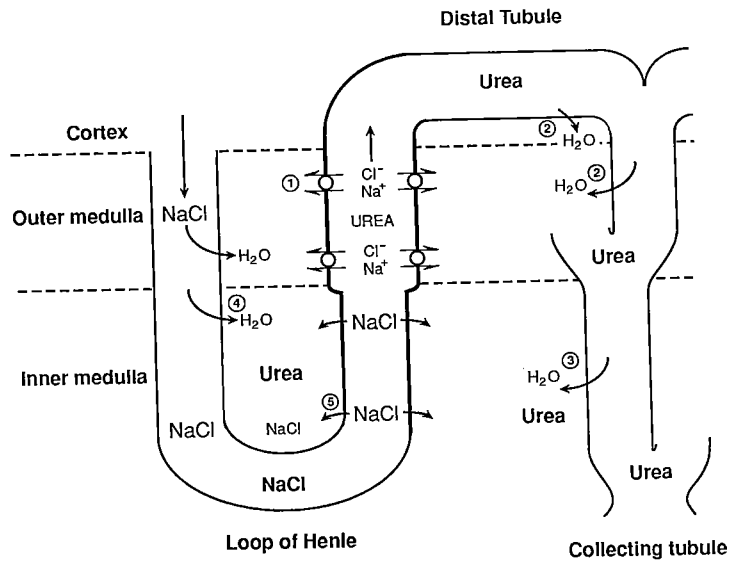


Fig 7. Recent modifications of the countercurrent hypothesis by Stephenson, Kokko, and Rector. Both the thin ascending limb in the inner medulla and the thick distal tubule are impermeable to water, as indicated by the thickened lining. In the thick ascending limb, active chloride reabsorption, accompanied by passive sodium movement (1), renders the tubule fluid dilute and the outer medullary interstitium hyperosmotic. In the last part of the distal tubule and in the collecting tubule in the cortex and outer medulla, water is reabsorbed down its osmotic gradient (2), increasing the concentration of urea that remains behind. In the inner medulla, both water and urea are reabsorbed from the collecting duct (3). Some urea reenters the loop of Henle (not shown). This medullary recycling of urea, in addition to trapping of urea by countercurrent exchange in the vasa recta (not shown), causes urea to accumulate in large quantities in the medullary interstitium (indicated by large type), where it osmotically extracts water from the descending limb (4) and thereby concentrates sodium chloride in descending limb fluid. When the fluid rich in sodium chloride enters the sodium chloride-permeable (but water-impermeable) thin ascending limb, sodium chloride moves passively down its concentration gradient (5), rendering the tubule fluid relatively hypoosmotic to the surrounding interstitium.

leave the descending limb of Henle's loop, which is permeable to water but not to NaCl or urea. The raises the NaCl concentration of fluid reaching the hairpin turn. The ascending thin limb is impermeable to water but not to NaCl or urea. In this segment, NaCl diffuses down its concentration gradient, into the interstitium. Urea diffuses in, but at a slower rate, leading to progressive reduction of luminal tonicity in the segment. The osmotic gradients that are established are multiplied by the countercurrent mechanism. An additional effect of this mechanism is to cause some urea to remain in the medulla, where it recycles between the collecting duct, the interstitium, and the loop of Henle. This mechanism is summarized in Figure 7.

Acid-Base Balance

To maintain the acid-base balance of the ECF, the kidney must excrete net acid at a rate equal to the rate of extrarenal net acid production (approximately 0.3 to 1.0 mEq/kg day). The kidney maintains the pH of the ECF by regulating the plasma bicarbonate HCO_3^- concentration. It does so by two processes: (1) reclamation of filtered HCO_3^- and (2) generation of new HCO_3^- by means of net acid excretion. The proximal tubule lowers the luminal pH from 7.3 to approximately 6.7, and thus reabsorbs the major portion of HCO_3^- . The collecting tubule provides the final urinary acidification with titration of ammonia, phosphate, and other titratable buffers.⁵⁶

The normal filtered load of HCO_3^- is about 4500 mEq/day. Less than 0.1% of filtered HCO_3^- appears in the final urine; approximately 80% of filtered HCO_3^- is reclaimed by the proximal tubule. Although the net result of this process is referred to as HCO_3^- reabsorption, the HCO_3^- in tubular fluid is not directly reabsorbed as such. Instead, the tubular epithelial cells add HCO_3^- to peritubular blood as a consequence of proton (H^+) secretion. The enzyme carbonic anhydrase, with then-tubular epithelial cells, catalyzes the hydration of carbon dioxide (CO_2) to form carbonic acid (H_2CO_3). Dissociation of H_2CO_3 yields H^+ and HCO_3^- . The H^+ is secreted into the tubular lumen, where it combines with filtered HCO_3^- to form H_2CO_3 . Carbonic anhydrase is also present in the brush border, where it catalyzes the dehydration of luminal H_2CO_3 to CO_2 and water. The CO_2 can diffuse back into the cell, where it may be hydrated to form additional H_2CO_3 . The HCO_3^- generated within the cell diffuses into peritubular blood, possibly via specific pathways.⁵⁷ The bulk of H^+ secretion by the proximal tubule appears to be coupled to sodium reabsorption by a direct-exchange mechanism.⁵⁷

The factors that can affect proximal HCO_3^- reabsorption include (1) *extracellular fluid volume*—decrements in absolute or effective volume enhance HCO_3^- reabsorption, whereas increments have the opposite effect; (2) *arterial P_{CO_2}* —hypercapnia stimulates HCO_3^- reabsorption, whereas hypocapnia inhibits; (3) *body potassium stores*—there is a slight stimulation of proximal HCO_3^- reabsorption by prior potassium depletion; (4) *parathormone*—inhibits reabsorption; and (5) phosphate depletion—inhibits reabsorption.

The kidney adds new HCO_3^- to blood by secreting H^+ in excess of that which is necessary to reclaim filtered HCO_3^- . This process results in net acid excretion. Under normal circumstances, net acid secretion replaces the HCO_3^- consumed in buffering the strong acid by-products of metabolism, mainly sulfuric and phosphoric acids. Depending on diet, some 40 to 70 mEq of H^+ derived from such acids are produced daily.

Net acid excretion may also increase in response to the addition of ketoacids or lactic acid in disease states, or to compensate for hypercapnia. The secreted H^+ is taken up by urinary buffers, principally monohydrogen phosphate (HPO_4^-) and ammonia (NH_3), which are converted to H_2PO_4^- and NH_4^+ . Net acid excretion is equal to the sum of H_2PO_4^- and NH_4^+ excretion, minus any HCO_3^- that escapes reabsorption. The H_2PO_4^- is also referred to as titratable acid. This term denotes the amount of strong base required to titrate urine back to pH 7.4. A comparatively small proportion of secreted H^+ is unbound to buffers; it is this component that can result in a minimum urinary pH of about 4.4.

Most net acid excretion occurs in the collecting ducts, where H^+ is secreted by pumps that are not directly coupled to sodium reabsorption. This process also depends on intracellular carbonic anhydrase. There is no brush border carbonic anhydrase in the collecting ducts. The rate of net acid excretion can be modified by (1) *the electrical gradient between the tubule cell and the lumen*— Na^+ reabsorption in the collecting ducts creates a negative intraluminal potential; this favors H^+ secretion. The gradient is augmented by increased sodium delivery and reabsorption, especially when Na^+ is accompanied by a poorly reabsorbed anion. This enhancement of H^+ secretion by Na^+ reabsorption brings about an indirect coupling of these processes; (2) *mineralocorticoids*—aldosterone can directly stimulate the capacity of the H^+ pump.⁵⁸ In addition, by stimulating Na^+ reabsorption in the collecting duct, aldosterone enhances the electrical gradient that favors H^+ secretion; (3) *buffer availability*— NH_3 is produced in the kidney from glutamine. It gains access to the tubular fluid in both the proximal and the distal nephron by nonionic diffusion. Acidosis increases renal NH_3 production. Increased buffer availability, by taking up free H^+ , reduces the chemical gradient against which H^+ is pumped; this stimulates H^+ secretion. The mechanism by which a change in systemic pH affects ammoniogenesis remains undefined. Ammoniogenesis can also be stimulated by

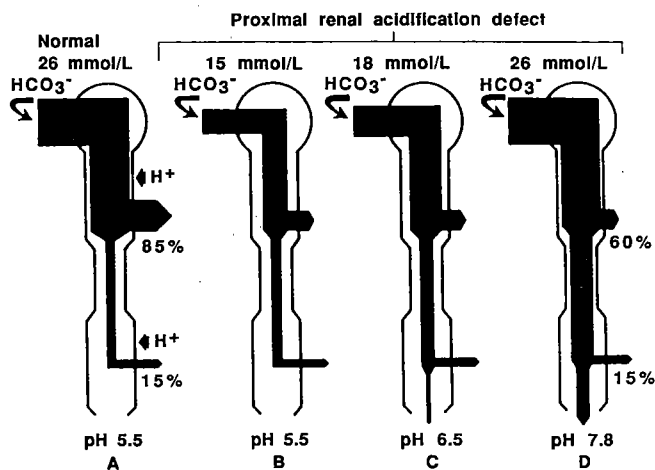


Fig 8. Schematic representation of the proximal renal acidification defect in Type II RTA. Effect of changes in plasma bicarbonate concentration on the delivery of bicarbonate to the distal nephron and as a consequence, on urinary pH and on excretion of bicarbonate. A, In normal subjects, at normal plasma bicarbonate concentrations, approximately 15% of the filtered bicarbonate load escapes reabsorption in the proximal tubule and is reabsorbed in the distal nephron; urinary bicarbonate excretion is nil, urinary pH is appropriately low, and net acid excretion is normal. B, In patients with Type II RTA, bicarbonate excretion might also be nil, urinary pH may be appropriately low, and net acid excretion may not be diminished at reduced plasma bicarbonate concentration (metabolic acidosis). This is because the amount of HCO_3^- escaping reabsorption proximally and delivered to the distal nephron is not supranormal when the amount of bicarbonate presented to the proximal tubule for reabsorption is significantly reduced. C, When, however, metabolic acidosis is somewhat mitigated (by administration of NaHCO_3), supranormal amounts of bicarbonate are delivered out of the proximal tubule because the defective proximal tubule cannot reabsorb the modest increase in filtered load of HCO_3^- . As a consequence, bicarbonate escapes reabsorption in the distal nephron, urinary pH becomes inappropriately high, and net acid excretion is reduced. D, If the plasma bicarbonate concentration and filtered bicarbonate load are increased to normal levels, the amount of bicarbonate escaping reabsorption proximally greatly exceeds the resorptive capacity of the normal distal nephron, and massive bicarbonaturia occurs. In the illustration of Type II RTA, renal tubule reabsorption of bicarbonate ($T_{\text{HCO}_3^-}$) at normal plasma bicarbonate concentration (26 mmol/L) is reduced by 25%. [Adapted from Morris RC, Sebastian A, McSherry E, The symposium on acid-base homeostasis, *Kidney Int* (1972;1:322), with permission.]

potassium depletion and inhibited by potassium loading. An adaptive increase in ammoniogenesis is the principal mechanism for the excretion of increased acid loads.⁵⁹

Defective Tubular Hydrogen Ion Secretion. Defects in renal tubular hydrogen ion secretion, also termed renal tubular acidosis (RTA), may occur either in the proximal tubule (RTA type 2) or in the distal tubule (RTA type 1).⁶⁰

Proximal RTA (Type 2). Three major processes occur in the nephron to rid the

body of excess acid: sodium bicarbonate reabsorption, ammonia trapping, and titratable acid formation. Unlike in the distal tubule, in the proximal tubule the formation of titratable acid and NH_4^+ is negligible. The major function of the proximal tubule is the reabsorption of bicarbonate. One bicarbonate ion is reabsorbed for each hydrogen ion excreted. The proximal tubule has a high-capacity bicarbonate transport system, and it reabsorbs approximately 80% of filtered bicarbonate. In proximal RTA defects, the reabsorptive threshold (T_m) for bicarbonate is thought to be lowered (Fig 8).⁶¹ This results in the delivery

of large amounts of sodium bicarbonate to the distal kidney. The distal tubule has a relatively low capacity for bicarbonate reabsorption (however, it is a "high-gradient system" and is able to secrete hydrogen ions across a large gradient). Thus, the hydrogen ions secreted distally primarily absorb free bicarbonate producing little NH_4^+ bonding and titratable acid secretion. This results in an alkaline, bicarbonate-rich urine. Extracellular volume contraction occurs secondarily to this massive anion (HCO_3^-) loss. In an attempt to compensate for this extracellular volume contraction, chloride reabsorption is increased, resulting in a hyperchloremic metabolic acidosis. As systemic acidosis progresses, the filtered load of sodium bicarbonate diminishes, allowing only small amounts of bicarbonate to be delivered distally. Thus, below this lowered bicarbonate reabsorptive threshold (T_m), distal acidification processes can compensate for defective proximal acidification. This results in more complete bicarbonate reabsorption distally with titratable acid and NH_4^+ production and urine with a pH of 5.0 or less. However, the amount of bicarbonate required to maintain a normal serum level is massive, since it must equal the amount of bicarbonate excretion. In proximal RTA, potassium and calcium excretion are increased. However, since citrate excretion is relatively normal, nephrocalcinosis and renal calculi formation are rare. Clinically, the effects on children include: osteomalacia, rickets, abnormal gut calcium absorption, decreased phosphorus, and abnormal vitamin D metabolism.

Distal RTA (Type 1). In distal RTA defects, the distal tubule is unable to secrete hydrogen ions against a large gradient and is thus unable to produce a urine pH of less than 5.4 even when challenged.⁶¹ Minimal urine pH in distal RTA ranges from 5.4 to 6.5, depending on the severity of the transport defect. The distal tubule normally accounts for, at most, 15% of total bicarbonate reabsorption. Since proximal reabsorption is not affected in distal RTA, the urinary bicarbonate concentration is only 5 mEq/L, even at a urine pH of 6.5.

Thus daily excretion of bicarbonate is not usually greater than 10 to 15 mEq/day in patients with distal RTA.

Therefore, the acidosis of distal RTA is more easily controlled than is the acidosis of proximal RTA. Systemic acidosis results in increased bone reabsorption and, in turn, increased urinary calcium. In addition, the urine is mildly alkaline (unlike proximal RTA that maintain an almost normal urine pH) and nephrocalcinosis is common in distal RTA secondary to low solubility of the excess calcium in a mildly alkaline urine with a decreased citrate content.

Two subsets of patients with RTA have been described. The first group presents with *complete RTA* (cRTA); these patients comprise the majority of those with RTA. The patients are acidotic and usually present with the known renal manifestations of the disease (eg, nephrocalcinosis). Another group of patients presents with *incomplete RTA* (iRTA). Patients with iRTA are nonacidotic and present with nephrocalcinosis. Like patients with cRTA, these patients are also unable to increase the urinary excretion of titratable acid to a normal maxima when presented with an acid load.⁶² These patients are considered to have a "milder" form of the disease. Functional renal mass and GFR is relatively well maintained, and excretion of NH_4^+ is sufficient to prevent frank acidosis.⁶³

The acidosis of RTA is non-anion gap acidosis (anion gap being defined as the difference between the major intravascular cations, sodium and potassium minus the sum of the major anions, chloride and bicarbonate; normally between 12 and 16) associated with *hyperchloremia* and *hypokalemia* in contradistinction to the acidosis associated with ATN or reduced GFR (a hypochloremic and hyperkalemic acidosis). The hyperchloremia results from increased NaCl reabsorption stimulated by volume contraction secondary to sodium bicarbonate loss in the urine. The hypokalemia results from stimulation of the renin-angiotensin-aldosterone (secondary to volume contraction) axis as well as increased distal Na-K exchange occurring with the increased distal delivery of NaHCO_3 .

Potassium

Over 90% of plasma potassium undergoes glomerular filtration. Most of it is reabsorbed in the proximal tubule and the loop of Henle. The bulk of potassium in the final urine is added to tubular fluid by secretion in the late distal tubule and cortical collecting duct. Tubular epithelial cells in these segments take up potassium from peritubular fluid by a mechanism involving Na,K-ATPase.⁶⁴ This gives rise to an intracellular transport pool of potassium. Potassium secretion is favored by the negative intratubular potential created by distal Na reabsorption, and by the concentration gradient between intracellular potassium and tubular fluid. In addition to these passive forces that influence potassium secretion, an active transport mechanism may exist.⁶⁵ There is no evidence either for a coupled exchange between Na⁺ absorption and K⁺ secretion or for competition between intracellular K⁺ and H⁺ for tubular secretory pathways.

Potassium excretion is augmented by an increase in distal tubular fluid flow rate (as with saline or osmotic diuresis, diuretic drugs, or postobstructive diuresis). This promotes potassium secretion by maintaining a steep potassium concentration gradient between the cell and the tubular fluid. In addition, increased quantities of sodium are presented to distal reabsorptive sites. The negative intratubular potential created by increased sodium reabsorption also promotes potassium secretion.

Mineralocorticoids stimulate potassium secretion, possibly by stimulating Na,K-ATPase in the basolateral membrane.⁶⁵ This would increase potassium uptake and raise intracellular potassium concentration, thereby enhancing potassium secretion.

Calcium

Only that portion of plasma calcium that is not bound to plasma proteins is filtered at the glomerulus. Ultrafilterable calcium (Ca) represents about 60% of total plasma calcium. There is subsequent tubular reabsorption of 96% to 98% of this filtered load. The bulk of calcium reabsorption occurs in the proximal tubule and the ascend-

ing limb of the loop of Henle. Additional reabsorption occurs in the distal convoluted tubule and cortical collecting duct.⁶⁶ Calcium movement along the nephron appears to be subject to two transepithelial transport processes. One is a paracellular and gradient-dependent (concentration) process that predominates in most segments of the nephron. The other is a transcellular, energy-dependent process that characterizes calcium transport in the distal nephron.⁶⁷ Recent investigations have focused on the role of a cytosolic calcium binding protein (CaBP_r) located in the distal tubule that might modulate calcium transport in this nephron segment.^{68,69} Regulation of calcium by several known factors (eg, vitamin D, parathyroid hormone [PTH]) might be due to their effect on production of CaBP_r in the distal tubule.

Calcium reabsorption in the proximal tubule occurs parallel with sodium reabsorption, with a component of calcium absorption being directly sodium-dependent.⁷⁰ Calcium reabsorption in the proximal tubule is inhibited by PTH, cyclic AMP, acetazolamide, exogenous sodium loading, and phosphate depletion. The effect on urinary calcium, however, depends on the behavior of more distal nephron sites. In the loop of Henle (as well as the distal convoluted tubule and collecting duct), calcium reabsorption is stimulated by PTH. This accounts for the hypocalciuric effect of this hormone despite its inhibition of proximal calcium absorption. Calcium reabsorption in the loop of Henle is inhibited by furosemide. When diuretic-induced extracellular volume depletion is prevented by replacement of salt and water losses, furosemide causes an increase in urinary calcium excretion.⁷¹ This accounts for the efficacy of furosemide in the emergency treatment of hypercalcemia. Final modulation of urinary calcium excretion occurs in the distal tubule and collecting ducts. In these segments, active transport of calcium occurs, which can be dissociated from sodium reabsorption. Thus, chlorthiazide, which inhibits distal tubular sodium transport, also directly stimulates calcium absorption in this segment.⁷² This may be the major explanation for the reduction in uri-

nary calcium excretion with chronic administration of thiazides. An additional hypocalciuric effect of thiazide diuretics may result from extracellular fluid volume contraction, with consequent stimulation of calcium reabsorption in the proximal tubule.

Other factors that stimulate calcium reabsorption between the late proximal tubule and the early distal convoluted tubule include hypocalcemia, metabolic alkalosis (increased tubular HCO_3^-), vitamin D, and phosphate loading. Reabsorption is inhibited by hypercalcemia, metabolic acidosis, hypermagnesemia, and phosphate depletion.⁶⁶

Phosphate

Plasma inorganic phosphate, existing as a mixture of HPO_4^- and H_2PO_4^- , is 80% to 90% ultrafilterable at the glomerulus. Of the filtered load, 80% to 97% is reabsorbed. The tubular reabsorption of phosphate can increase to nearly 100% in response to phosphorus deprivation. Most phosphate reabsorption occurs in the proximal tubule. The existence of a distal site of phosphate transport is also suspected.^{73,74} PTH inhibits phosphate reabsorption in the proximal tubule and increases urinary phosphate. This effect is associated with increased urinary excretion of nephrogenous cyclic AMP.

EXCRETION OF ORGANIC SOLUTES

Urea

Urea is the major end product of protein catabolism in man. It is freely filtered at the glomerulus. Water reabsorption increases the urea concentration in tubular fluid, with subsequent urea diffusion out of the tubule. At typical urine flow rates of 1 mL/min, 30% to 40% of filtered urea is reabsorbed in the proximal tubule. The medullary collecting ducts are also permeable to urea, and their permeability is enhanced by vasopressin. Reabsorption of urea in the collecting duct is enhanced by antidiuresis and inhibited by water diuresis.

Urea reabsorbed in the collecting ducts contributes to the hypertonicity of medullary interstitial fluid and plays an important role in urinary concentration.

The rate of urea reabsorption is inversely related to tubular fluid flow rate. At urine flow rate of about 2 mL/min, during water diuresis, 60% to 70% of filtered urea is excreted, ie, urea clearance is 60% to 70% of the GFR. At low urine flow rates, during antidiuresis or reductions in renal blood flow, urea clearance may fall to 10% to 20% of the GFR. This accounts for the disproportionate increase in BUN compared with serum creatinine in states of "prerenal azotemia."

Uric Acid

Uric acid is the end product of purine catabolism in man. On a low-purine diet, uric acid production from endogenous sources is about 700 mg per day. Two thirds of the uric acid load is excreted by the kidneys. Intestinal excretion, with degradation by bacterial enzymes, accounts for the rest. Because of its low pKa (5.75), it exists in plasma almost entirely as urate. The low pH attained in urine in the distal nephron favors the formation of uric acid, which is of limited solubility in water.

Current evidence favors a four-component model for renal handling of urate⁷⁵: (1) plasma urate is freely filtered at the glomerulus; (2) filtered urate undergoes nearly complete tubular reabsorption; (3) approximately 50% of this reabsorbed urate is secreted into tubular fluid; and (4) postsecretory reabsorption reclaims about 80% of the secreted urate. Antiuricosuric agents such as pyrazinoic acid (the metabolite of the antituberculous agent pyrazinamide) inhibit the tubular secretory mechanism. Probenecid, a uricosuric agent, acts by inhibiting postsecretory reabsorption.⁷⁶ The majority of patients with gout appear to have an impairment in renal uric acid excretion, which is incompletely characterized.⁷⁷

Urate secretion is accomplished by organic anion secretory mechanisms located in the proximal tubule. A variety of other substances share and mutually compete for

this mechanism. They include oxalate, lactate, hippurate, penicillins, cephalosporins, thiazides, furosemide, and ethacrynic acid. A separate organic cation-secretory mechanism also exists. Among the substances transported by this system are creatinine, cimetidine, and trimethoprim.

Glucose

Although glucose is freely filtered at the glomerulus, it undergoes essentially complete reabsorption in the early portion of the proximal tubule, so that urine is normally glucose-free. With progressively higher filtered loads (at higher plasma glucose concentrations), reabsorption increased, until a tubular maximum glucose reabsorption rate (TmG) is attained. Filtered glucose in excess of the TmG appears in the urine.¹²

Glucose transport is linked to proximal sodium reabsorption. When the latter is inhibited, as by ECF volume expansion, the TmG falls. These observations have given rise to the following model: Glucose in tubular fluid interacts with a carrier mechanism in the luminal membrane of the tubular epithelial cell. This carrier, which exhibits saturation kinetics, facilitates the entry of glucose into the tubular epithelial cell. Sodium is required for glucose-carrier interaction. Once transported into the cell, glucose may diffuse down its own concentration gradient from tubular epithelial cell to peritubular blood.

Amino Acids

Circulating amino acids readily cross the glomerular filter and undergo nearly complete reabsorption by proximal tubular cells. This occurs via mechanisms in the brush border membrane. As in the case of glucose, this process appears to be carrier-mediated, Na-dependent, and energy-requiring.⁷⁸ Separate transport mechanisms in the basolateral membrane also mediate cellular uptake of amino acids from peritubular fluids.

Much attention has been focused on the tubular transport mechanisms for cystine and the cationic (dibasic) amino acids: arginine, lysine, and ornithine. Reabsorption

of these amino acids is defective in classic cystinuria. Because of the insolubility of cystine, urinary stones are formed. A model for tubular handling of these amino acids must account for the following observations: (1) whereas patients with classic cystinuria have excessive excretion of all four amino acids, patients have been described with either isolated cystinuria or hyperdibasic aminoaciduria (arginine, lysine, ornithine) without cystinuria. (2) In cystinuric patients, the clearance of cystine can exceed creatinine clearance, implying tubular secretion of cystine. (3) Renal cortical tissue slices from cystinuric patients may show no defect in taking up cystine from bathing medium, compared with slices from normal subjects.

According to the currently favored model, there are separate transport systems in the basolateral and brush border membranes. In the basolateral membrane are two uptake mechanisms—one for cystine and another for arginine, lysine, and ornithine. Amino acids that accumulate within the cell may be secreted into tubular fluid. In the brush border are three separate reabsorptive mechanisms. One is shared by all four amino acids; the second is for arginine, ornithine, and lysine only; and the third is for cystine alone.⁷⁹

Citrate

Urinary citrate may help prevent calcium nephrolithiasis by chelating urinary calcium. Plasma citrate, present at concentrations of 0.05 mMol to 0.3 mMol, undergoes glomerular filtration and subsequent proximal tubular reabsorption. Citrate excretion in man ranges between 10% and 35% of the filtered load.⁸⁰ In addition, some of the citrate that escapes filtration is taken up by the tubular cells from postglomerular blood. Citrate that enters the cell is metabolized via the citric acid cycle to CO₂ and water.

Citrate excretion is profoundly influenced by systemic acid-base balance, through consequent changes in tubular cell pH. Metabolic alkalosis increases citrate excretion. A rise in cellular pH inhibits citrate metabolism, leading to a rise in in-

tracellular citrate concentration. The latter tends to inhibit citrate reabsorption. Metabolic acidosis has the opposite effect. Distal renal tubular acidosis and administration of acetazolamide are associated with hypocitruria and relatively alkaline urine. Both conditions predispose to calcium nephrolithiasis and nephrocalcinosis.

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