CHAPTER 36

Physiology and Pathophysiology of Sodium Retention and Wastage

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INTRODUCTION

Extracellular fluid (ECF) volume is determined by the balance between sodium intake and renal excretion of sodium. Under normal circumstances, wide variations in salt intake lead to parallel changes in renal salt excretion, such that ECF volume is maintained within narrow limits. This relative constancy of ECF volume is achieved by a series of afferent sensing systems, central integrative pathways, and renal and extrarenal effector mechanisms acting in concert to modulate sodium excretion by the kidney.

In the major edematous states, effector mechanisms responsible for sodium retention behave in a more or less nonsuppressible manner, resulting in either subtle or overt expansion of ECF volume. In some instances, an intrinsic abnormality of the kidney leads to primary retention of sodium, resulting in expansion of ECF volume. In other instances, the kidney retains sodium secondarily as a result of an actual or sensed reduction in effective circulatory volume.

Renal sodium wastage can be defined as the inability of the kidney to conserve sodium to such an extent that continued loss of sodium into the urine leads to contraction of intravascular volume and hypotension. Renal sodium wastage occurs in circumstances where renal sodium transport is pharmacologically interrupted (administration of diuretics), where the integrity of renal tubular function is breached (tubulointerstitial renal disease), or when mineralocorticoid activity or tubular responsiveness are diminished or absent.

SODIUM INTAKE AND SODIUM BALANCE

Under normal circumstances, renal excretion of sodium is regulated so that balance is maintained between intake and output and ECF volume is stabilized. A subject maintained on a normal sodium diet is in balance when body weight is constant and sodium intake and output are equal. When the diet is abruptly decreased, a transient negative sodium balance ensues. A slight contraction of ECF volume signals activation of sodium-conserving mechanisms, which lead to decreases in urinary sodium excretion. After a few days, sodium balance is achieved and ECF volume and weight are stabilized, albeit at a lower value. If sodium intake is increased to the previous normal values, transient positive sodium balance leads to expansion of ECF volume, thereby suppressing those mechanisms that enhanced sodium reabsorption. A new steady state is reached when ECF volume has risen sufficiently so that sodium excretion now equals intake. In both directions a steady state is achieved whereby sodium intake equals output, while ECF volume is expanded during salt loads and shrunken during salt restriction. The kidney behaves as though ECF volume is the major regulatory element modulating sodium excretion.

The major edematous states—congestive heart failure, cirrhosis of the liver, and nephrotic syndrome—depart strikingly from those constraints. These states are characterized by persistent renal salt retention despite progressive expansion of ECF volume. Unrelenting sodium reabsorption is not the result of diminished sodium intake or even in most cases diminished plasma volume, as dietary salt is adequate and total ECF and plasma volumes are expanded. Renal sodium excretion no longer parallels changes in ECF volume; rather, the kidney behaves as if sensing a persistent low-volume stimulus. Some critical component of ECF volume remains underfilled.

PRIMARY AND SECONDARY EDEMA

A common feature of the major edematous states is persistent renal salt retention despite progressive expansion of both plasma and ECF volume. Two themes have been proposed to explain the persistent salt retention that characterizes the major edematous states: salt retention may be a primary abnormality of the kidney or a secondary response to some disturbance in circulation.

Primary edema (overflow, overfill, nephritic) refers to expansion of ECF volume and subsequent edema formation consequent to a primary defect in renal sodium excretion. Increased ECF volume and expansion of its subcompartments

result in manifestations of a well-filled circulation. Hypertension and increased cardiac output are commonly present. The mechanisms normally elicited in response to an underfilled circulation are suppressed (↓ renin-angiotensin-aldosterone, ↓ antidiuretic hormone (ADH), ↓ activity of sympathetic nerves, ↓ circulating catecholamines). Acute poststreptococcal glomerulonephritis and acute or advanced chronic renal failure are examples of primary edema.

Secondary edema (underfill) results from the response of normal kidneys to actual or sensed underfilling of the circulation. In this form of edema, a primary disturbance within the circulation secondarily triggers renal mechanisms for sodium retention. Those systems that normally serve to defend the circulation are activated (↑ renin-angiotensin-aldosterone, ↑ ADH, ↑ activity of sympathetic nerves, ↑ circulating catecholamines). The renal response in underfill edema is similar to that in normal subjects placed on a low-salt diet, that is, low fractional excretion of sodium, increased filtration fraction, and prerenal azotemia. Despite these similarities, a number of critical features distinguish these two states: (1) sodium balance is positive in underfill edema while salt-restricted normal subjects are in balance; and (2) administration of salt to sodium-restricted normals transiently expands ECF volume, after which sodium excretion equals intake, whereas in underfill edema, ECF volume expands progressively consequent to unyielding salt retention; and features of an underfilled circulation persist in underfill edema, while the circulation is normalized in normals.

The circulatory compartment that signals persistent activation of sodium-conserving mechanisms in secondary edema is not readily identifiable. Cardiac output may be high (arteriovenous shunts) or low (congestive heart failure). Similarly, plasma volume may be increased (arteriovenous shunts and heart failure) or decreased (some cases of nephrotic syndrome). The body fluid compartment ultimately responsible for signaling a volume-regulatory reflex leading to renal sodium retention is effective arterial blood volume (EABV). EABV identifies that critical component of arterial blood volume, actual or sensed, that regulates sodium reabsorption by the kidney. In both normal circumstances and the major edematous states, the magnitude of EABV is the major determinant of renal salt and water handling.

CONCEPT OF EFFECTIVE ARTERIAL BLOOD VOLUME

In order to explain adequately persistent sodium retention in underfill edema, two cardinal features must exist. First, there must be a persistent low-volume stimulus sensed by the kidney that is then translated into persistent, indeed often unrelenting, retention of sodium despite adequate salt intake and overexpansion of ECF volume. Second, there must be a disturbance in those forces that partition retained fluid into the various subcompartments of the ECF space, resulting in an inability to terminate the low-volume stimulus. The first feature can be ascribed to a shrunken EABV, a feature common to all major edematous states. The second feature can be attributed to a disruption in Starling forces, which normally dictate the distribution of fluid within the extracellular compartment. A disturbance in the circulation exists such that retained fluid is unable to restore EABV but rather is sequestered, resulting in edema formation.

Fluctuations in EABV are modulated by two key determinants: (1) filling of the arterial tree (normally determined by venous return and cardiac output), and (2) peripheral resistance (a factor influenced by compliance of the vasculature and degree of arteriolar runoff). A reduction in EABV can be the result of decreased arterial blood volume owing to low cardiac output as in congestive heart failure. Conversely, EABV can be reduced in the face of increased arterial blood volume when there is excessive peripheral runoff as seen in arteriovenous shunting and vasodilation. Increased compliance of the arterial vasculature in which arterial blood volume is reduced relative to the holding capacity of the vascular tree, results in decreased EABV. For example, administration of salt to a subject with a highly compliant or "slack" circulation (as in pregnancy) results in a sluggish natriuretic response, in contrast to a high resistance or "tight" circulation (as in primary aldosteronism or accelerated hypertension) in which salt administration causes prompt natriuresis.

Under normal circumstances, EABV is well correlated with ECF volume. Figure 1 depicts the relationship between subcompartments of ECF volume and renal sodium excretion in both normal and edematous states. Under normal circumstances, subcompartments of ECF volume freely communicate in response to changes in dietary sodium, such that expansion or shrinkage of these compartments occurs in concert (Fig. 1, states 1A and 1B). In steady-state conditions, sodium intake and output are in balance; the set point at which balance is attained is dictated by salt intake.

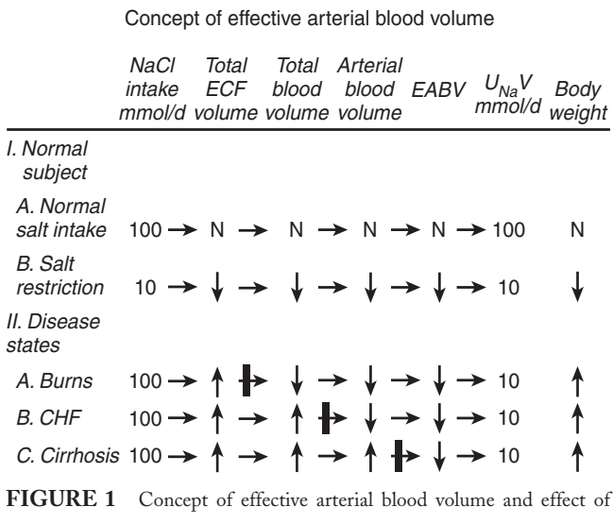

FIGURE 1 Concept of effective arterial blood volume and effect of fluid distributory disturbances on sodium balance and sodium excretion.

By contrast, major edematous states are characterized by a shrunken EABV, which cannot be filled despite expansion of one or more subcompartments. No longer is EABV well correlated with total ECF volume and salt intake. Due to a disturbance in the forces that normally partition fluid into the various subcompartments of ECF space, EABV remains contracted even though total ECF volume is greatly expanded. Activation of sodium-conserving mechanisms persist despite plentiful salt intake. Such derangements in fluid distribution can be categorized as to disturbances in Starling forces within the interstitial space, between interstitial space and vascular tree, and disturbances within the circulation. Types of disturbance are summarized next.

1. *Trapped fluid (Fig. 1, state 2A).* In the first type of disturbance, fluid is trapped within a pathologic compartment such that it cannot contribute to effective extracellular volume, that is, volume capable of filling interstitial and vascular spaces. Decrease in effective extracellular volume leads to decreases in total blood volume, arterial blood volume, and EABV, and renal sodium retention is stimulated. Retention of salt and water cannot reexpand effective extracellular volume as fluid is sequestered into an abnormal fluid compartment behind the "Starling block" within the interstitial space. Such third spacing of fluid into inflamed tissue, vesicles and bullae, peritonitis, necrotizing pancreatitis, rhabdomyolysis, and burns functionally behaves as if lost from the body.
2. *Reduced oncotic pressure.* A reduction in the circulating level of albumin can lead to a second type of fluid maldistribution. Decreased plasma oncotic pressure allows fluid to translocate from the vascular compartment to the interstitial space. Reductions in total blood volume, arterial blood volume, and EABV lead to sodium retention. The retained salt and water, owing to a "Starling block" across the capillary bed, leak into the interstitial space.
3. *Vascular disturbances (Fig. 1, states 2B and 2C).* A third type of fluid distributory disturbance results from abnormalities within the circulation and can be of two types. The prototypical example of the first type is congestive heart failure. A failing ventricle results in decreased cardiac output and high diastolic intraventricular pressures. Venous return is impeded with consequent reductions in arterial blood volume and EABV. Sodium retention is stimulated but arterial blood volume and EABV remain contracted due to a circulatory block across the heart. In consequence, venous volume expands and leads to transudation of fluid into the interstitial space.

The second type of circulatory abnormality that leads to fluid maldistribution is exemplified by arteriovenous shunting (e.g., Paget's disease, beriberi, thyrotoxicosis, anemia, cirrhosis). Widespread shunting through multiple small arteriovenous communications results in increased venous return, thereby augmenting cardiac output and arterial filling. However, arterial runoff and vasodilation lead to underperfusion of some critical area in the microcirculation. The circulatory block lies between the arterial blood volume and EABV.

What distinguishes secondary edematous states from the normal circumstance is an inability to expand EABV owing to Starling or circulatory blocks within the extracellular space. Normally, the system of volume regulation behaves as an open system, such that fluctuations in one compartment are quickly translated into parallel changes in other compartments; total ECF volume and EABV are closely related. In contrast, volume regulation in underfill edema can be regarded as clamped; EABV remains shrunken despite expansion of the subcompartments of the extracellular space. EABV becomes dissociated from total ECF volume; salt retention becomes unrelenting and salt administration cannot reexpand the contracted EABV.

AFFERENT LIMB VOLUME CONTROL

The regulation of extracellular volume by the kidney requires the existence of sensing mechanisms capable of detecting changes in both dietary salt intake and cardiovascular performance (Table 1).

Low-Pressure Baroreceptors

A considerable body of evidence supports the existence of volume receptors located centrally within the thorax, on the venous side of the circulation, capable of sensing contraction and expansion of ECF volume. The great veins and atria are ideally suited for providing a sensitive mechanism to monitor plasma volume by virtue of large capacitance and distensibility. Small changes in central venous pressure lead to large changes in size and wall tension, which are registered by a variety of neural receptors capable of responding to mechanical stretch or transmural pressure. Two such receptors, type A and B, are found in both atria and consist of unencapsulated fibers that run within the vagus nerve (243). Type A receptors may respond to changes in atrial tension but are uninfluenced by atrial volume. In contrast, activity of type B receptors correlates well with atrial size

TABLE 1 Afferent Sensing Mechanisms Involved in Control of Extracellular Fluid Volume

Low-pressure baroreceptors in great veins, atria, lungs
Arterial (high-pressure) baroreceptors in aorta and carotid sinus
Intrarenal sensors
Cortical mechanoreceptors
Cortical chemoreceptors
Myogenic reflex in afferent arteriole
Tubuloglomerular feedback mechanism
Juxtaglomerular apparatus
Hepatic volume receptors—osmoreceptors, ionic receptors, baroreceptors
Central nervous system volume sensors—ionic receptors, osmoreceptors

(243). Afferent impulses originating in these low-pressure baroreceptors travel along the vagus nerve and exert a tonic inhibitory effect on central integrative centers in the hypothalamus and medulla, which in turn modulate sympathetic outflow. Diminished atrial distention reduces afferent fiber discharge so that tonic inhibition of the integrative centers is reduced and sympathetic outflow is stimulated (240). Conversely, atrial distention increases afferent impulse trafficking, thereby augmenting inhibition of sympathetic outflow. In addition, changes in atrial distention, probably through similar neural mechanisms, have been shown to alter plasma ADH and renin levels in a direction that parallels sympathetic outflow.

In addition to the atria, there are also receptors with vagal afferents in the lungs, great veins and both ventricles that exert a tonic inhibitory influence over central sympathetic outflow that may play a role in sensing volume. The widespread distribution of these receptors provides for considerable redundancy in the vagal cardiopulmonary reflex such that receptors from one region can likely compensate for the loss of afferent input from another region.

A number of observations suggest that changes in atrial distention can alter urinary sodium excretion through mechanisms that are independent of neural pathways. For example, interruption of the vagus nerve or complete cardiac denervation would be expected to eliminate the renal response to changes in atrial distention. Although such lesions eliminate the diuretic and natriuretic response to atrial balloon inflation or reversible mitral stenosis, they do not eliminate the natriuretic response to volume expansion (147). Similarly, bilateral cervical vagotomy in nonhuman primates, and denervated cardiac allografts in humans fail to alter the normal diuretic and natriuretic response to head-out water immersion (225). Such observations lead to the discovery of natriuretic peptides that are synthesized in the heart and respond to the fullness of the circulation. Atrial natriuretic peptide (ANP) is a peptide synthesized and stored in the cardiac atria. The primary stimulus for its release is atrial distention. Since administration of ANP to human volunteers has been shown to increase the renal excretion of sodium and water, release of this factor is an additional mechanism by which ECF volume is regulated. Maneuvers that lead to distention of the atria and are associated with increased plasma levels of ANP include isotonic volume expansion, head out body water immersion and administration of mineralocorticoids. By contrast, maneuvers that decrease central blood volume such as diuretic administration and lower body negative pressure are associated with a decline in plasma ANP levels.

The cardiac atria are also a source of brain natriuretic peptide (BNP). BNP shares with ANP a high degree of structural homology and biologic activities including vasorelaxation and natriuresis (142). Unlike ANP, however, brain natriuretic peptide is synthesized in and secreted primarily from ventricular myocytes in response to myocardial stretch. In fact, plasma levels of BNP may be used as a marker of the degree of left ventricular dysfunction (226). The mechanism by which ANP and BNP increase renal salt and water excretion is discussed in the section focused on effector mechanisms.

While sensing mechanisms on the venous side of the circulation clearly play a role in sensing volume in subjects with a normal circulation, they cannot be a major determinant in those edematous states characterized by central venous engorgement in which avid sodium retention persists despite high central venous pressures. In these states, some other component of the circulation is signaling the kidney to retain sodium in a manner that input from the venous side of the circulation is overridden. Analysis of EABV suggests that this sensing system is on the arterial side of the circulation.

Arterial (High-Pressure) Baroreceptors

Baroreceptors in the aorta and carotid sinus participate in the maintenance of ECF volume. In response to changes in arterial pressure, pulse pressure profile, or vascular capacitance, afferent impulses travel along the glossopharyngeal and vagus nerve to an integrative site within the medulla, where central sympathetic outflow is tonically inhibited (195, 264). Reduction in systemic arterial pressure increases sympathetic outflow and results in renal sodium retention. Conversely, increased arterial pressure reduces sympathetic outflow and urinary sodium excretion increases. The renal response to occlusion of an established arteriovenous fistula supports an important role for arterial baroreceptors in modulating renal sodium excretion (91). Closure of a large fistula decreases the runoff of arterial blood into the venous circulation. As a result, diastolic arterial pressure increases. These changes are associated with a prompt increase in renal sodium excretion while renal blood flow and glomerular filtration rate remain constant. By contrast, unloading of the arterial baroreceptors results in activation of several effector mechanisms that lead to renal sodium retention. In humans subjected to lower-body negative pressure sufficient to narrow the pulse pressure, there is activation of the sympathetic nervous system and the renin-angiotensin system as well as increased release of AVP (132). In addition, vascular resistance increases in the forearm, splanchnic, and the renal circulation.

While abundant evidence exists to support an important role for high-pressure baroreceptors in the regulation of ECF volume, some observations suggest that these sensors are not the ultimate determinant of ECF volume. For example, arterial baroreceptor denervation does not diminish the diuretic and natriuretic response to volume expansion. In addition, edematous states can be characterized by persistent renal salt retention even in the setting of increased arterial pressure and increased cardiac output. In these settings, a shrunken EABV must be registered by receptors elsewhere in the arterial circulation.

Intrarenal Sensing Mechanisms

The kidney contains several types of sensing mechanisms capable of detecting alterations in ECF volume. The first type of sensor relates to the rich concentration of sensory neurons in renal cortical structures (223). Using neurophysiologic techniques, two major classes of neural sensory receptors have been identified in the kidney. The first type of receptor is a mechanoreceptor that monitors changes in hydrostatic pressure in the kidney. This receptor is sensitive to changes in arterial perfusion as well as changes in venous and ureteral pressure. The second type of receptor is a chemoreceptor that is responsive to renal ischemia and/or changes in the chemical environment of the renal interstitium. Information registered by both types of receptors is transmitted to the spinal cord and then on to central integrative centers. In this manner, immediate feedback on the function and status of each kidney can be centrally integrated with input from other volume sensors so that body fluid homeostasis can be more precisely regulated.

Renal afferent nerves in one kidney can influence the efferent sympathetic activity in the other kidney in the form of a renalrenal reflex (162). These reflexes have been demonstrated at the ganglionic, spinal and supraspinal level. The nature of the reflex exhibits species difference. In the dog, stimulation of renal mechanoreceptors leads to increased activity of sympathetic nerves in the contralateral kidney resulting in a fall in renal blood flow and urinary sodium excretion (164). By contrast, renal mechanoreceptor or chemoreceptor stimulation in the rat causes a sympathoinhibitory response in the contralateral kidney causing a diuresis and natriuresis (164). In both species, the change in contralateral renal function occurs in the absence of a change in systemic hemodynamics. Further studies in the rat have shown that increasing levels of baseline efferent sympathetic nerve activity exert a facilitory effect on the renalrenal reflex (163). By contrast, inhibition of prostaglandin synthesis, blockade of substance P, and hypoxia all attenuate the reflex (166).

Intrarenal sensing mechanisms enable the kidney to maintain blood flow relatively constant in the setting of varying arterial pressures, a process referred to as autoregulation. Renal autoregulation is accomplished by two mechanisms intrinsic to the kidney: (1) a myogenic reflex intrinsic to the afferent arteriole and (2) tubuloglomerular feedback (TGF). The myogenic reflex describes the ability of the afferent arteriole to either constrict or dilate in response to changes in perfusion pressure. A reduction in pressure elicits a vasodilatory response, while an increase in pressure results in vasoconstriction. The myogenic response is located diffusely within the preglomerular circulation and provides a mechanism to buffer the glomerular capillaries from sudden changes in arterial pressure.

TGF is a second component of renal autoregulation that serves to reinforce the myogenic reflex by responding to changes in distal NaCl concentration (303). The anatomic basis for TGF lies in the juxtaposition of the macula densa cells in the distal nephron to smooth muscle cells in the afferent arteriole. The macula densa cells respond to changes in luminal NaCl concentration by way of a Na,K-2Cl cotransporter located on the apical membrane. A decrease in perfusion pressure causes an initial decline in intraglomerular pressure and glomerular filtration rate resulting in decreased distal delivery of NaCl. The decrease in NaCl concentration is sensed by the macula densa causing a vasodilatory signal to be sent to the afferent arteriole. As a result, intraglomerular pressure and glomerular filtration rate are returned toward normal and distal NaCl delivery increases. The net effect is to stabilize the sodium chloride concentration entering the distal nephron.

A second component of tubuloglomerular feedback is called into play when changes in distal sodium chloride delivery are more pronounced or sustained as occurs when extracellular fluid volume is altered. This component either activates or suppresses renin release from the juxtaglomerular cells. A persistent decrease in delivery of sodium chloride to the macula densa as when ECF volume is contracted stimulates renin release. The subsequent formation of angiotensin II and aldosterone cause renal sodium retention leading to correction of the volume contracted state. A persistent increase in distal sodium chloride delivery reflecting expansion of extracellular fluid volume has the opposite effect. Renin release is also influenced by changes in perfusion pressure at the level of the juxtaglomerular apparatus. Under conditions of decreased renal perfusion, renin release is stimulated independently of any change in glomerular filtration rate or distal sodium delivery. Sympathetic nerve activity is a third mechanism involved in the regulation of renin release. Renal nerve stimulation via activation of beta-adrenergic nerves directly stimulates renin release and this effect can be disassociated from major changes in renal hemodynamics.

Thus, the myogenic reflex and the tubuloglomerular feedback system are components of a sensing mechanism within the kidney that enable changes in volume to be registered. As discussed in more detail below, these systems can alter glomerular hemodynamics in a manner that contributes to the maintenance of a normal ECF volume.

Hepatic and Intestinal Volume Receptors

Several lines of evidence suggest that intrahepatic mechanisms may contribute to the afferent limb of volume control. Located in the portal system, the liver is ideally positioned to monitor dietary sodium intake (168, 222, 233). In this regard, oral sodium loads or infusion of either isotonic or hypertonic saline into the portal vein results in an increase in urinary sodium excretion. The natriuretic response to the intraportal infusion is quantitatively greater than the natriuretic response observed with peripheral infusions. This natriuretic response may be initiated by either osmoreceptors or sodium chloride–sensitive receptors known to be

present within the liver. Activation of these receptors leads to decreased renal sympathetic nerve activity, which in turn accounts for the natriuretic response. The afferent limb of this hepatorenal reflex terminates centrally within the nucleus of the solitary tract (222). This reflex can be blocked by hepatic denervation or prior vagotomy. Stimulation of one or both of these receptors may also account for the increased release of plasma AVP from the hypothalamus known to occur with increased concentrations of sodium in the portal circulation. In turn, AVP may play a role in mediating the decrease in renal sympathetic nerve activity at the level of the area postrema (233). A hepatic baroreceptor mechanism has also been identified that can reflexively alter renal sympathetic nerve activity (168). In contrast to stimulation of osmoreceptors and ionic receptors, activation of hepatic baroreceptors leads to increased renal sympathetic nerve activity.

Hepatic and or portal sensing mechanisms can also influence intestinal salt reabsorption through what has been described as a hepatointestinal reflex. The afferent limb of this reflex travels through the vagus nerve and into the nucleus tractus solitarius. Infusion of 9% saline into the portal circulation has been shown to depress jejunal Na absorption through this pathway (222).

A more recently described mechanism by which orally administered Na loads can lead to adjustments in urine Na excretion is through the intestinal release of peptides that regulate cyclic guanosine monophosphate (51, 106). Guanylin and uroguanylin are peptides found throughout the intestine and are released from epithelial cells into both the lumen and the systemic circulation. These peptides exert a natriuretic effect when administered intravenously raising the possibility that they play a physiologic role in adjusting urinary sodium excretion in response to changes in dietary salt intake. The role of hepatic and intestinal sensing mechanisms in the day-to-day regulation of sodium chloride balance remains to be defined.

Central Nervous System Afferent Sensing Mechanisms

While the existence of intracerebral receptors sensitive to changes in osmolality is indisputable, a similar afferent mechanism responsive to changes in sodium balance may also be present. Several lines of evidence suggest the presence of cerebral sodium sensors. For example, infusion of hypertonic saline into the carotid artery results in a quantitatively greater natriuretic effect than that observed with a systemic infusion (313). A natriuretic response is also observed with injection of hypertonic saline into the cerebral ventricles. This later response appears specific to increasing concentrations of sodium chloride rather than increased osmolality since intraventricular infusions of mannitol exert no effect on urinary sodium excretion (65, 206). Other manifestations of central administration of hypertonic saline include a dipsogenic effect, pressor response, increased release of AVP, and reduction in renin release and renal sympathetic nerve activity. These effects are similar to the pattern of responses elicited by central administration of angiotensin II suggesting that similar neural pathways are involved. In support of this possibility, administration of an angiotensin receptor blocker has been shown to block the pressor response and the natriuresis following the intraventricular infusion of hypertonic saline (206). In addition, receptor blockade significantly reduces the fall in renal sympathetic nerve activity. The role that this sodium sensing system plays in the steady-state control of sodium balance remains to be determined.

RENAL MECHANISMS FOR SODIUM RETENTION

In secondary edema or any state where EABV is consistently contracted, the persistent stimulation of the afferent volume-sensing system described previously leads to the activation of efferent pathways, which signal the kidney to conserve salt. The shrunken EABV promotes the release of catecholamines, activates the renin-angiotensin-aldosterone and sympathetic nervous systems, and stimulates the secretion of ADH. These defenses usually fail to normalize the circulation and renal underperfusion persists. This state of renal underperfusion is characterized by humoral secretions and neurocirculatory reflexes that alter the glomerular and postglomerular circulation and activate various transport systems throughout the nephron (Table 2). The mechanisms of renal sodium handling will now be discussed followed by a discussion of the effector systems that regulate renal salt handling.

Glomerular Filtration Rate

The renal excretion of sodium is ultimately a function of filtered load (calculated as glomerular filtration rate [GFR] times plasma Na concentration) minus the quantity reabsorbed into the peritubular circulation and returned to the systemic circu-

TABLE 2 Effector Mechanisms Regulating Extracellular Fluid Volume

Renal mechanisms for Na retention
Sympathetic nervous system
Renin-angiotensin-aldosterone system
Prostaglandins
Kallikrein-kinin system
Antidiuretic hormone
Endothelin
Nitric oxide
Natriuretic compounds
Atrial natriuretic peptide
Brain natriuretic peptide
C-type natriuretic peptide
Urodilatin
Guanylin and uroguanylin

lation. Isolated fluctuations in GFR and hence filtered load of sodium are accompanied by only minor changes in urinary sodium excretion, arguing against a primary role of filtration rate as a regulator of sodium excretion. For example, when GFR is increased by maneuvers other than volume expansion (glucocorticoids, high protein feeding) little change in fractional sodium excretion occurs. Conversely, when the filtered load of sodium is held constant or even reduced, a persistent natriuresis accompanies volume expansion. Near constancy in fractional excretion of sodium in the setting of increases or decreases in GFR is known as glomerular-tubular balance. Changes in GFR are buffered by parallel adaptations in sodium reabsorption by the proximal tubule such that large changes in filtered load of sodium result in only small changes in distal sodium delivery. Given the constraints of glomerulotubular balance, it follows that physiologic control of Na excretion involves effector mechanisms operative at the level of the renal tubule.

Proximal Tubule

The proximal tubule reabsorbs approximately 50% of the filtered NaCl, 70%–90% of filtered $NaHCO_3$, and close to 100% of filtered organic solutes. Absorption of these solutes involves both transcellular and paracellular processes. Because the proximal tubule is a very leaky epithelium, paracellular transport occurring by both diffusion and/or convective mechanisms can be significant.

Transcellular Solute Transport

To effect $NaHCO_3$ absorption, H ions are secreted from cell to luminal fluid by an apical-membrane amiloride-sensitive Na/H antiporter and a H ion translocating ATPase. Approximately two-thirds of HCO_3 absorption is mediated by the antiporter, while the remainder is accounted for by the H ion pump (266). The energy for H extrusion by the antiporter is derived from the low intracellular Na concentration resulting from the activity of a basolateral Na,K-ATPase. The majority of the base generated in the cell by H efflux exits across the basolateral membrane on the $Na/3HCO_3$ (or equivalently $Na/HCO_3/CO_3$) cotransporter (7). The net result of these processes is high rates of acid transport from the peritubular interstitium and blood into the lumen of the proximal tubule. This leads to high rates of $NaHCO_3$ absorption that causes luminal fluid HCO_3 concentration to decrease by 60%–80% in the midproximal tubule.

Transcellular NaCl absorption is also mediated by the Na/H antiporter, functioning in parallel with Cl/base exchangers (262). Secretion of H and a negatively charged base at equal rates leads to generation of the neutral acid, HB, which is lipophilic and is thought to recycle across the apical membrane. The nature of the base exchanged with Cl is not totally settled but appears to include OH^-, $formate^-$, and $oxalate^-$ (259). With this mode of transport there is no net H secretion and thus no luminal acidification or bicarbonate absorption. Na and Cl enter the cell across the apical membrane at equal rates. The Na exits the cell on the basolateral Na,K-ATPase, while the Cl can exit the cell by one of several possible mechanisms.

Well defined transport systems exist on the apical membrane of the proximal tubule that allow for sodium-coupled transport of a variety of solutes including glucose, amino acids, and inorganic and organic ions. Once again, the driving force for these transporters is a low intracellular Na concentration resulting from the activity of a basolateral Na,K-ATPase. Most of these solutes then exit the basolateral membrane by facilitated diffusion.

Paracellular Solute Transport

Solutes can also cross the proximal tubule across the paracellular pathway. In general, the major barrier to paracellular solute movement is the tight junction, which in the proximal tubule is highly permeable such that passive fluxes can be significant.

In the early part of the proximal tubule, Na is preferentially reabsorbed with bicarbonate and other nonchloride solutes by transcellular processes. As a result, the concentrations of HCO_3 and these other solutes progressively fall along the length of the proximal tubule. Analysis of the fluid in the mid- to late proximal tubule shows a HCO_3 concentration of 5–10 mEq/L and virtually no organic solutes. At the same time the chloride concentration progressively increases along the length of the tubule. At the end of the proximal tubule the Cl concentration is 20–40 mEq/L higher than plasma Cl concentrations. The net result of these changes is that driving forces are present for passive paracellular diffusion.

While the driving forces for organic solutes favors back diffusion from the blood and peritubular interstitium into the lumen, the permeability of the late proximal tubule to these solutes is low. As a result, the rates of back diffusion are relatively small. Similarly, the driving force for $NaHCO_3$ favors back diffusion into the proximal tubule lumen. Because of a higher permeability, this back diffusion can be significant, with two-thirds of active HCO_3 absorption negated by passive HCO_3 back leak in the late proximal tubule (8). Lastly, the high luminal Cl concentration provides a driving force for passive diffusive Cl absorption. Because of the high permeability of the proximal tubule to Cl, fluxes can be large (262). This large paracellular Cl flux generates a lumen-positive voltage in the late proximal tubule that can then provide a driving force for passive Na absorption. Most studies have estimated that one- to two-thirds of NaCl absorption in the late proximal tubule occurs by passive mechanisms (6, 297).

Role of Peritubular Starling Forces in Regulation of Proximal Tubular Solute Transport

At any given plasma protein concentration, the magnitude of the protein oncotic force acting along the peritubular capillary will be a function of filtration fraction, that

is, fraction of plasma water extracted by the process of glomerular filtration. In turn, filtration fraction is importantly influenced by efferent arteriolar tone. This resistance vessel interposed between the glomerular and peritubular capillary networks importantly influences both glomerular and downstream peritubular hydrostatic pressure.

When a normal individual ingests a high-salt diet, expansion of plasma volume and EABV occurs. As a result, plasma protein concentration is reduced because of hemodilution. In response to expanded EABV, renal plasma flow increases while glomerular filtration rate remains constant or rises only slightly, resulting in decreased filtration fraction. The decline in filtration fraction results in a lower percentage of protein-free ultrafiltrate formation at the glomerulus so that the normal rise in postglomerular protein concentration is less. Peritubular oncotic pressure falls consequent to both systemic dilution and reduced fraction of blood flow undergoing ultrafiltration at the glomerulus. In addition, the lower efferent resistance leads to increased peritubular hydrostatic pressure. Reductions in peritubular colloid osmotic pressure and increases in peritubular hydrostatic pressure lead to decreased uptake of reabsorbate into the peritubular capillary bed. The accumulation of reabsorbate leads to an increase in interstitial pressure, which in turn has been demonstrated to decrease solute and volume absorption across the proximal tubule.

By contrast, salt restriction results in contraction of plasma volume and EABV. Despite the reduction in renal plasma flow, GFR is maintained near normal owing to efferent arteriolar constriction. Filtration fraction increases as a normal amount of protein-free ultrafiltrate is now removed from a decreased volume of blood. The increased fraction of blood flow undergoing ultrafiltration and systemic concentration of albumin lead to a higher concentration of protein in blood leaving the glomerulus and entering the peritubular capillaries. In addition, an increase in efferent arteriolar tone lowers peritubular capillary hydrostatic pressure. Increased peritubular oncotic pressure and decreased peritubular hydrostatic pressure enhance the movement of reabsorbate into peritubular capillaries. Interstitial pressure declines, resulting in less back leak of reabsorbate into the tubular lumen.

Loop of Henle

Mechanisms responsible for regulating renal salt excretion also exist within the loop of Henle. The anatomy of this nephron segment differs according to the originating glomerulus. Superficial glomeruli give rise to loops that are composed of a thin descending limb that extends to the junction of inner and outer medulla and culminates with a thick ascending portion. Glomeruli residing in deeper portions of the renal cortex give rise to a thin descending limb that extends deeper into the inner medulla. From here and in distinction to superficial loops, deep loops possess a thin ascending limb that extends from the bend of Henle's loop to the junction of inner and outer medulla, where the thick ascending limb arises. The thin descending limb is impermeable to NaCl but has high water permeability. In contrast, the thin ascending limb is impermeable to water but highly permeable to NaCl. The thick ascending limb is also impermeable to water and is characterized by active NaCl reabsorption.

Differential permeabilities for salt and water of each segment within the long loops of Henle provide a mechanism for regulating salt excretion. As water is reabsorbed from the thin descending limb in response to high medullary urea and salt concentrations, the NaCl concentration of fluid entering the thin ascending limb exceeds that within the interstitium. As a consequence, a driving force exists for passive NaCl reabsorption. Conditions that increase medullary blood flow (volume expansion, water diuresis, prostaglandins, ANP) will lead to "washout" of the medullary osmotic gradient and secondarily decrease the driving force for passive NaCl reabsorption. Lower interstitial urea and NaCl concentrations lead to less water extraction from the thin descending limb, resulting in a lower concentration of NaCl entering the thin ascending limb. As a result, NaCl reabsorption is diminished in the thin and thick ascending limbs. The superficial nephron has only a short transit time through the medulla and does not possess a thin ascending limb; thus changes in medullary tonicity have a lesser impact on passive salt efflux in this segment.

The thick ascending limb plays an important role in the regulation of ECF volume by providing mechanisms for the reabsorption of NaCl and $NaHCO_3$. NaCl is transported across the apical membrane by the Na/K/2Cl cotransporter, while a Na/H antiporter initiates the reabsorption of $NaHCO_3$. Salt reabsorption in this segment is regulated by several factors. Prostaglandins have been shown to exert an inhibitory effect on salt absorption in this segment that may be important in the natriuretic response to volume expansion (131). In this setting, enhanced prostaglandin production leads to increased medullary blood flow and a decrease in the medullary interstitial osmolality. As a result, the driving force for passive NaCl absorption is diminished. In addition, micropuncture as well as microperfusion studies have shown that prostaglandins have a direct inhibitory effect on chloride transport in the medullary thick ascending limb (131). In the setting of volume contraction, salt absorption is increased in this segment. This effect is mediated by factors known to be activated in the setting of volume depletion to include renal nerves and AVP.

Cortical Collecting Tubule

The cortical collecting tubule is a low-capacity nephron segment capable of reabsorbing NaCl against steep gradients. As discussed below the principal regulator of Na reabsorption in this segment is aldosterone. Changes in ECF volume through the renin-angiotensin system lead to reciprocal changes in circulating aldosterone levels. Aldosterone stimulates sodium reabsorption by increasing the permea-

bility of the luminal membrane. Both enhanced sodium entry and aldosterone lead to increased Na,K-ATPase activity on the basolateral membrane. Reabsorption of sodium increases the degree of luminal electronegativity that secondarily stimulates chloride reabsorption through the paracellular pathway. AVP has also been shown to increase Na transport in this segment. By contrast, PGE2 and bradykinin inhibit sodium reabsorption in this segment. ANP and brain natriuretic peptide inhibit Na transport in the inner medullary collecting duct.

EFFECTOR MECHANISM REGULATING RENAL SODIUM HANDLING

Sympathetic Nervous System

Postganglionic sympathetic axons originating in the prevertebral celiac and paravertebral ganglia of T6-L4 have been found to innervate cells of afferent and efferent arterioles, the juxtaglomerular apparatus, and the renal tubules. A number of observations suggest that this extensive renal innervation provides the anatomic basis for sympathetic nerves to play an important role in ECF volume regulation (Fig. 2).

Bilateral renal denervation in both anesthetized and conscious animals leads to rapid increases in urinary sodium excretion (31, 277). Conversely, electrical stimulation of renal nerves promptly decreases urinary sodium excretion without alterations in GFR or renal plasma flow (40). Renal nerves also contribute to a reflex arc whereby alterations in sodium handling by one kidney can be adjusted for by the opposite kidney (77).

Sympathetic nerves alter renal salt and water handling by direct and indirect mechanisms. Increased nerve activity indirectly influences proximal sodium reabsorption by altering preglomerular and postglomerular arteriolar tone, thereby effecting changes in filtration fraction. The subsequent alterations in peritubular hydrostatic and oncotic forces lead to changes in proximal sodium reabsorption. Renal nerves directly stimulate proximal tubular fluid reabsorption through receptors located on the basolateral membrane of proximal tubular cells (22). In the rabbit proximal tubule, stimulation is mediated by β-adrenergic receptors (22), while in the rat proximal tubule both α- and β-adrenergic receptors play a role (331). Stimulation of α1 and α2 receptors has been shown to increase the activity of the Na/H antiporter (112, 113) and the Na,K-ATPase providing a mechanism by which proximal tubule transport is stimulated. Renal nerve activity also stimulates sodium chloride reabsorption in the loop of Henle and early distal tubule. These indirect and direct effects on renal Na handling are further amplified by the ability of sympathetic nerves to stimulate renin release leading to the formation of angiotensin II and aldosterone.

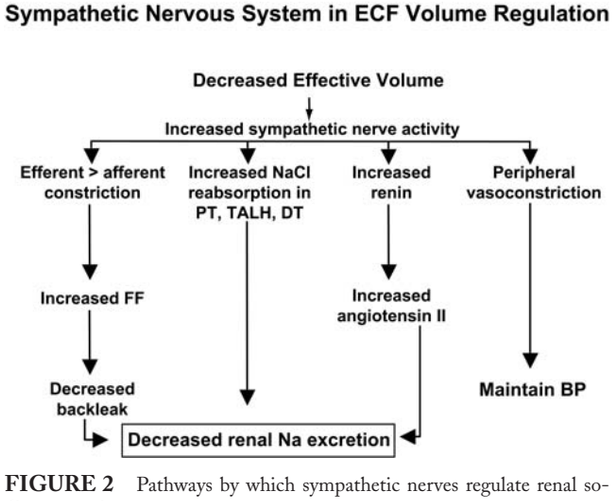

FIGURE 2 Pathways by which sympathetic nerves regulate renal sodium excretion.

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system is an important effector mechanism in the control of ECF balance. Physiologic control of this system involves a complex interaction between neural, humoral, and baroreceptor stimuli.

Decreases in renal perfusion provide a direct stimulatory effect for renin release from the juxtaglomerular cells in the afferent arteriole. This baroreceptor-mediated mechanism has been demonstrated in the nonfiltering kidney under conditions of hemorrhagic hypotension or aortic constriction (37). The relationship between changes in perfusion pressure and renin release is defined by a nonlinear curve. Renin release remains relatively constant until pressure falls to a threshold value of 80–90 mm Hg, below which renin release increases in an exponential fashion (153).

Increased sympathetic nerve activity directly stimulates the release of renin from juxtaglomerular cells via activation of renal β1 adrenoreceptors. Sympathetic nerves also have an effect of a modulating baroreceptor-mediated mechanism of renin release by shifting the threshold for renin release to a higher perfusion pressure.

Locally produced prostaglandins stimulate the release of renin. In fact, baroreceptor-stimulated renin release is mediated in part by prostaglandins especially within the autoregulatory range (27). β-adrenergic stimulation of renin release, however, is not mediated by prostaglandins.

Renin release is also influenced by distal tubular sodium chloride concentration by way of the tubuloglomerular feedback mechanism. Sustained increases in delivery of sodium chloride to the macula densa whether from increased single-nephron GFR or decreased absorption of filtrate at more proximal nephron segments suppresses renin release from the juxtaglomerular apparatus. Sustained decreases in distal sodium chloride delivery have the opposite effect. The formation of renin leads to increased circulating angiotensin II (Ang II), which in turn directly affects multiple organ systems involved in blood pressure and volume homeostasis. Ang II

serves an important role in stabilizing the circulation by its direct vasoconstrictor activity and by potentiating the vasoconstrictive effects of sympathetic nerves on peripheral neuroeffector junctions. In addition, Ang II is capable of altering renal sodium handling at several sites along the nephron and does so by both indirect and direct mechanisms (Fig. 3).

Ang II preferentially increases the tone of the efferent arteriole so that under conditions of a decreased EABV renal blood flow falls to a greater extent than GFR and filtration fraction increases. As discussed previously, these changes lead to alterations in peritubular Starling forces that favor proximal sodium reabsorption.

Ang II also affects renal Na handling by modulating sympathetic nerve activity. Ang II is capable of increasing sympathetic neurotransmission by facilitating the release of norepinephrine through interactions at the presynaptic junction as well as having stimulatory effects within the central nervous system (69). Ang II also affects sodium balance by enhancing the efficiency of the tubuloglomerular feedback mechanism (214). Increased Ang II levels heighten the responsiveness of the tubuloglomerular mechanism to any given signal delivered by the macula densa.

In addition to these indirect mechanisms, Ang II has direct effects on renal sodium handling. Addition of Ang II to the peritubular capillary has been shown to enhance the rate of volume absorption in the proximal tubule, measured by the split droplet technique (128). In these studies, low concentrations of Ang II stimulate volume absorption, while high concentrations have an inhibitory effect. Similar results have been found in the in vitro perfused proximal convoluted tubule (295). Ang II stimulates HCO_3 absorption in the very early S1 proximal tubule with a lesser effect in the later proximal tubule. This corresponds with the distribution of Ang II receptors in the proximal tubule (82). Ang II has been shown to stimulate the proximal tubule apical membrane Na/H antiporter, and the basolateral membrane $Na/3HCO_3$ symporter in parallel (221). Activation of these transport mechanisms explains the observed increase in $NaHCO_3$ absorption induced by Ang II. Renal sodium handling can be altered by Ang II produced systemically or by Ang II synthesized locally within the kidney. The proximal tubule possesses all the machinery required for local production of Ang II (215). Indeed, measurement of luminal Ang II concentration have been in the range of 10^{-8} M, which can be compared to systemic concentrations of 10^{-11} to 10^{-10} M (42). These high renal concentrations may allow Ang II to function as an autocrine/paracrine factor. In fact, regulation of renal function by Ang II may be more dependent on regulation of local production than on regulation of systemic production (251, 268).

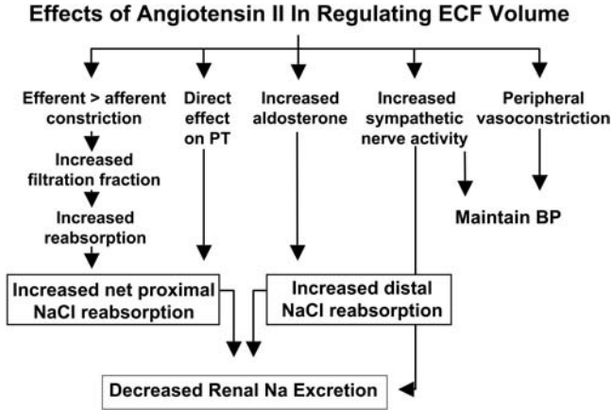

FIGURE 3 Pathways by which angiotensin II regulates renal sodium excretion.

In addition to effects on the proximal nephron, Ang II enhances distal sodium absorption primarily by stimulating aldosterone release from the adrenal zona glomerulosa. Aldosterone, in turn, increases sodium reabsorption in the cortical collecting tubule. Aldosterone importantly regulates potassium secretion in this nephron segment as well. Enhanced activity of Na,K-ATPase and generation of luminal electronegativity via sodium reabsorption provide a favorable electrochemical gradient for potassium secretion into the tubular lumen. Under conditions in which sodium is reabsorbed more proximally (decreased EABV), however, high levels of aldosterone do not result in potassium loss. Similarly, when distal sodium delivery is plentiful and aldosterone is suppressed (ECF volume expansion) potassium loss is not accelerated. The dependence of K secretion on distal delivery of sodium and aldosterone levels helps to make K excretion independent of changes in extracellular fluid volume.

Prostaglandins

Prostaglandins are compounds derived from metabolism of arachidonic acid that influence both renal blood flow and sodium handling within the kidney. PGI2, synthesized by vascular endothelial cells predominantly within the renal cortex, mediates baroreceptor but not β-adrenergic stimulation of renin release (27). PGE2, produced by interstitial and collecting duct epithelial cells predominantly within the renal medulla, is stimulated by Ang II and has vasodilatory properties. PGF2a is a prostaglandin with vasoconstrictor activity produced from PGE2 by the enzyme PGE2-9-ketoreductase. The activity of this enzyme varies according to salt intake, thus allowing relatively more vasodilation or vasoconstriction depending on the given level of salt balance in the animal.

Under baseline euvolemic conditions prostaglandin synthesis is negligible and as a result these compounds play little to no role in the minute-to-minute maintenance of renal function. Where these compounds come to serve a major role is in the setting of a systemic or intrarenal circulatory disturbance. This interaction is best illustrated when examining renal function under conditions of actual or perceived volume depletion. In this setting, renal blood flow is decreased, and sodium reabsorption, renin release, and urinary concentrating ability are increased. To a large extent, these findings are mediated by the effects of increased circu-

lating levels of Ang II, arginine vasopressin (AVP), and catecholamines. At the same time, these hormones stimulate the synthesis of renal prostaglandins, which in turn act to dilate the renal vasculature, inhibit salt and water reabsorption, and further stimulate renin release. Prostaglandin release under these conditions serves to dampen and counterbalance the physiologic effects of the hormones that elicit their production. As a result, renal function is maintained near normal despite the systemic circulation being clamped down. Predictably, inhibition of prostaglandin synthesis will lead to unopposed activity of these hormonal systems resulting in exaggerated renal vasoconstriction and magnified antinatriuretic and antidiuretic effects. In fact, many of the renal syndromes that are associated with the use of NSAIDs can be explained by the predictions of this model.

Prostaglandins predominately exert a natriuretic effect in the kidney. These compounds increase urinary sodium excretion by both indirect and direct mechanisms (Fig. 4). Through their activity as renal vasodilators, prostaglandins may cause an increase in the filtered load of sodium. In addition, these compounds preferentially shunt blood flow to the inner cortical and medullary regions of the kidney. As a result of increased medullary blood flow, there is a fall in the medullary interstitial solute concentration. Processes that reduce the degree of medullary hypertonicity lead to a concomitant reduction in the osmotic withdrawal of water from the normally sodium impermeable thin descending limb of Henle. This, in turn, decreases the sodium concentration of fluid at the hairpin turn. The net effect is less passive reabsorption of sodium across the normally water impermeable thin ascending limb of Henle. Consistent with this mechanism, infusion of PGE1 lowers, and prostaglandin synthesis inhibition raises, sodium chloride and total solute concentration in the medulla (131).

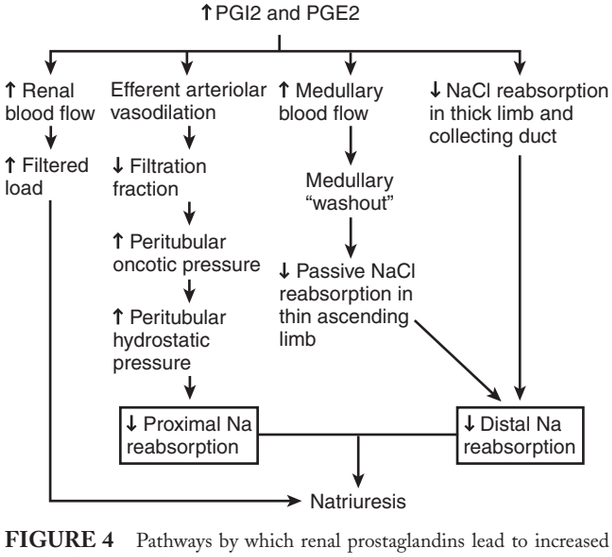

FIGURE 4 Pathways by which renal prostaglandins lead to increased renal sodium excretion.

Prostaglandins can also affect sodium reabsorption in the proximal tubule by virtue of their ability to influence the tone of the efferent arteriole. As discussed previously, changes in the tone of this vessel play a central role in determining the Starling forces that govern fluid reabsorption in this nephron segment. By lessening the degree to which the efferent arteriole is constricted, prostaglandins can alter peritubular Starling forces in a manner that leads to a decrease in proximal tubular sodium reabsorption. In a model of high circulating levels of Ang II induced by suprarenal aortic constriction, inhibition of prostaglandin synthesis was found to increase efferent arteriole oncotic pressure and decrease peritubular hydrostatic pressure resulting in a significant increase in proximal fluid reabsorption (244).

In addition to these hemodynamically mediated changes in renal sodium handling, prostaglandins have direct effects on tubular sodium transport. In the isolated perfused tubule, PGE2 has been shown to inhibit sodium transport in the cortical and outer medullary collecting duct (309). Using the same technique, PGE2 has also been shown to decrease NaCl transport in the thick ascending limb of Henle. In vivo studies also support a direct inhibitory effect of prostaglandins on sodium transport in the loop of Henle, distal nephron, and collecting duct (131). The mechanism of this direct inhibitory effect is unclear, but may involve decreased activity of the Na,K-ATPase.

It would at first seem paradoxical that under conditions of volume depletion the kidney would elaborate a compound that has further natriuretic properties. The role of prostaglandins in this setting, however, is to moderate the avid salt retention that would otherwise occur in the setting of unopposed activation of the renin-angiotensin-aldosterone and adrenergic systems. By virtue of their natriuretic properties, prostaglandins play a role in ensuring adequate delivery of filtrate to more distal nephron segments under conditions in which distal delivery is threatened (e.g., renal ischemia, hypovolemia). In addition, diminished NaCl reabsorption in the thick ascending limb of Henle reduces the energy requirements of this segment. This reduction in thick limb workload in conjunction with a prostaglandin-mediated reallocation in renal blood flow help to maintain an adequate oxygen tension in the medulla under conditions that could otherwise have resulted in substantial hypoxic injury.

Kallikrein-Kinin System

Kinins are potent vasodilator peptides found within the kidney but whose physiologic role has yet to be fully defined. Renal kallikrein is a serine protease of high molecular weight produced in the distal tubule. This protease uses the peptide kininogen as a substrate to produce two kinins: bradykinin and lysylbradykinin (also known as kallikrein). These kinins are degraded in the kidney by the same enzyme responsible for conversion of Ang I to Ang II, namely, kininase II (also called angiotensin converting enzyme) (50). Renal kallikrein activity is increased by

mineralocorticoids, Ang II, and PGE2 (50). In turn, kinins stimulate renin release and PGE2 production.

Intrarenal infusion of bradykinin increases renal blood flow and sodium excretion without a change in GFR (193). In addition, urinary excretion of bradykinin varies inversely with salt intake (17). Localization of kallikrein in the distal tubule as well as the presence of high-affinity binding sites for bradykinin in the thick ascending limb and cortical and outer medullary collecting ducts support the distal nephron as the site in which kinins affect sodium transport (64). Bradykinin has been found to inhibit net sodium absorption in the in vitro microperfused thick ascending limb and cortical collecting duct (122). In addition, kinins may increase urinary Na excretion by increasing medullary blood flow resulting in a washout of the medullary interstitium (284). Bradykinin can increase renal blood flow either directly or by stimulating the release of vasodilatory prostaglandins (284).

Antidiuretic Hormone

In addition to the well-defined system for osmotic control of vasopressin release, ADH is regulated by an anatomically separate pathway sensitive to changes in EABV. Afferent impulses originating from both low- and high-pressure baroreceptors travel via the vagus nerve to a central integrating center, which modulates ADH release in response to nonosmotic stimuli. Maneuvers that increase pressure in the cardiac atria have a suppressive effect on the release of ADH, while decreased pressure has the opposite effect. A similar relationship exists between ADH release and changes in pressure in the high-pressure baroreceptors located in the carotid artery (292). Baroreceptor-stimulated ADH release leads to increased water absorption by the kidney and in high concentrations may exert a systemic vasoconstrictive effect. ADH can also affect renal sodium handling. Pressor doses of arginine vasopressin have been shown to increase filtration fraction, an effect that secondarily would lead to enhanced proximal NaCl reabsorption. In addition, AVP has a direct tubular effect on solute transport in the thick ascending limb of Henle and the collecting duct. The release of ADH in response to a diminished EABV, along with activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, provides a marker of an underfilled circulation even when edema is widespread.

Endothelin

The endothelins are autocrine/paracrine factors that regulate blood pressure and renal function and may play a role in the regulation of ECF volume. This family of peptides consists of three members called endothelin-1, endothelin-2, and endothelin-3 (ET1, ET2, ET3) (140). These peptides can interact with one of two receptors, termed ETa and ETb. The ETa receptor binds ET1 and ET2 but not ET3, while the ETb receptor can bind all three endothelins with high affinity. Radiolabeled binding and mRNA expression studies suggest that the ETa receptor is primarily expressed in vascular structures, while the ETb receptor is the predominant receptor expressed in the renal tubules both in the proximal and distal nephron. Both ET1 and ET3 are produced locally by kidney tubules and are in an ideal location to bind to ETb receptors located along the nephron.

The effects of endothelin on proximal tubule function have been examined by adding ET1 to the basolateral side of the in vitro perfused proximal straight tubule (107). Low concentrations of ET1–stimulated rates of volume and presumably sodium transport, while high concentrations inhibited transport. The mechanism of this stimulatory effect appears to be mediated by activation of the apical Na/H antiporter through stimulation of the ETb receptor (125).

Nitric Oxide

Nitric oxide is an endothelial derived factor that can function as an effector in the regulation of ECF volume. In particular, nitric oxide has been shown to participate in the natriuretic response to increases in blood pressure or intravenous expansion of ECF volume. An acute increase in arterial pressure normally leads to a natriuretic response, a relationship referred to as pressure natriuresis. Although the exact mechanism of pressure natriuresis is not fully understood, evidence suggests that an increase in renal interstitial hydrostatic pressure and alterations in medullary blood flow may participate in this response. Under conditions of nitric oxide inhibition, an increase in perfusion pressure fails to increase renal interstitial hydrostatic pressure and the natriuretic response is blunted (227). Similarly, inhibition of nitric oxide has been shown to blunt the natriuretic response to intravenous volume expansion (258). These observations suggest that nitric oxide may play a role in augmenting urinary sodium excretion under conditions of volume expansion.

Atrial Natriuretic Peptide and Other Natriuretic Peptides

The synthesis and release of ANP provide a mechanism whereby cardiac atria serve both an afferent and an efferent function in control of ECF volume. This peptide is synthesized by atrial myocytes and is stored as an inactive high-molecular-weight form in granules. Presumably through atrial distention, maneuvers that increase atrial pressure cause release of the active low-molecular-weight form of ANP (78). Acute volume expansion, water immersion, postural changes, and salt feeding all result in increased plasma ANP concentration. Systemic infusion of ANP increases GFR and filtration fraction despite a fall in mean arterial pressure. The increase in GFR may be mediated by increased glomerular capillary hydrostatic pressure resulting from afferent arteriolar dilation and concurrent efferent arteriolar constriction (236). Continuous infusion or bolus injection of ANP produces dramatic increases in renal salt

and water excretion. While increased GFR may contribute to increased urinary sodium excretion at high levels of ANP, physiologic concentrations elicit a natriuretic response without a change in GFR, suggesting additional mechanisms whereby sodium excretion is augmented. In this regard, ANP has been found to inhibit sodium reabsorption in the cortical collecting tubule and inner medullary collecting duct (306). In addition, ANP decreases the medullary solute gradient such that passive sodium chloride reabsorption in the thin ascending limb is decreased (63). Finally, ANP reduces renin secretion, blocks aldosterone secretion, and opposes the vasoconstrictive effect of Ang II (Fig. 5).

With the recent discovery of other natriuretic peptides, ANP now appears to be only one member of a family of homologous polypeptide hormones that stimulate diuresis, natriuresis, and vasorelaxation. ANP and brain natriuretic peptide (BNP) are circulating hormones that are primarily synthesized in the cardiac atria and ventricles respectively. C-type natriuretic peptide (CNP) is mainly produced by the vascular endothelium and is thought to act as a local paracrine factor in the control of vascular tone. Studies examining the renal effects of CNP have produced conflicting results but it appears that this peptide is only weakly natriuretic (18, 142, 260). All of the natriuretic peptides mediate their biologic effects through a family of particulate guanylyl cyclase receptors (NPR-A and NPR-B). The affinity of ANP and BNP is greatest for NPR-A, while that of CNP is much higher for NPR-B. All three natriuretic peptides bind to a third receptor (NPR-C), which does not contain guanylyl cyclase and functions predominately as a clearance receptor. Urodilatin is a NH_2 terminal extended form of circulating ANP. However, unlike ANP, this peptide is not found in the systemic circulation, but rather is synthesized in the kidney where it acts as a paracrine factor. Similar to ANP, this peptide exerts a natriuretic effect and presumably participates in the regulation of natriuresis under physiologic conditions (211).

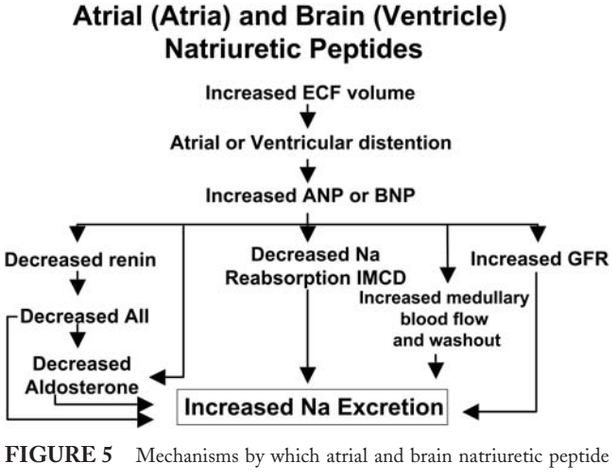

FIGURE 5 Mechanisms by which atrial and brain natriuretic peptide regulate renal sodium excretion.

CONGESTIVE HEART FAILURE

The fundamental abnormality underlying congestive heart failure is an inability of the heart to maintain its function as a pump. As a result, a series of complex compensatory reflexes are initiated that serve to defend the circulation. The renal response to a failing myocardium is retention of salt and water resulting in expansion of ECF volume. If myocardial dysfunction is mild, expansion of ECF volume leads to increased left ventricular end-diastolic volume, which raises cardiac output according to the dictates of the Frank-Starling principle. In this state of compensated congestive heart failure, salt intake and output come into balance but at the expense of an expanded ECF volume. Further deterioration in ventricular function leads to further renal retention of salt and water. There is progressive expansion of ECF volume and features of a congested circulation become manifest: peripheral edema, engorged neck veins, and pulmonary edema. Despite massive overexpansion of ECF volume, the kidneys behave as though they were responding to a low-volume stimulus.

In subsequent sections, a detailed analysis of the afferent and efferent regulatory limbs in congestive heart failure will be provided.

Afferent Sensing Mechanisms in Congestive Heart Failure

Low-Pressure Baroreceptors

A characteristic feature in many forms of congestive heart failure is increased stretch and transmural pressure within the cardiac atria. These alterations would normally provide afferent signals that suppress sympathetic outflow and decrease the release of renin and ADH and ultimately result in a diuretic and natriuretic response. In congestive heart failure, this afferent signaling mechanism is markedly perturbed. Despite the presence of venous congestion and elevated cardiac filling pressures sympathetic nervous activity and serum concentrations of renin and ADH are increased and urinary salt excretion is blunted. Several clinical and experimental studies have shown that the responsiveness of the low-pressure baroreflex is diminished.

Greenberg et al. (121) measured afferent signals from pressure-sensitive atrial (type B) receptors in dogs with chronic congestive heart failure induced by tricuspid regurgitation or pulmonary stenosis. In response to saline infusion, receptor firing was markedly decreased as compared to the control dogs. A similar decrease in activity of atrial type B receptors was found in dogs with chronic volume overload and increased cardiac output due to an aortocaval fistula (348). This decrease in sensitivity of atrial mechanoreceptors contributes to the increased and altered regulation of efferent renal sympathetic nerve activity that has been observed in congestive heart failure. Dibner-Dunlap and Thames (66) examined the response of renal sympathetic nerve activity to increases in atrial pressure in a dog model of low-output

heart failure induced by rapid ventricular pacing. As compared to controls, there was a markedly impaired reflex reduction of renal sympathetic nerve activity in the heart failure animals when atrial pressure was increased by either volume expansion or by balloon inflation. A similar impairment in atrial mechanoreceptor modulation of renal nerve activity has been described in a rat model of low cardiac–output congestive heart failure (73). In this model, the baroreflex defect was localized to the periphery at the level of the receptor and not the central nervous system (70, 73). In this regard, morphological changes consisting of nerve fiber arborization have been described in the atria of dogs with congestive heart failure (348). Studies in human subjects also suggest that cardiopulmonary mechanoreflexes are impaired in congestive heart failure (216).

High-Pressure Baroreceptors

The increase in renal sympathetic nerve activity in cardiac failure has also been attributed to impaired arterial baroreceptor function. High-pressure baroreceptors in the carotid sinus and aortic arch normally exert a tonic inhibitory effect on central nervous system sympathetic outflow. A reduction in cardiac output severe enough to reduce mean arterial pressure could lead to reduced activity of the arterial baroreceptors and therefore explain the augmentation in CNS sympathetic outflow and renal salt retention. Although the precise mechanism for the sympathoexcitation is not known, a sustained reduction in arterial pressure is unlikely to be the sole explanation. First, arterial pressure is usually normal in congestive heart failure. Second, arterial baroreceptors adapt to sustained changes in arterial pressure so that afferent activity normalizes despite continued alterations in arterial pressure. Rather, there appears to be an intrinsic abnormality that develops in arterial baroreflex regulation in congestive heart failure (74). Sympathetic function becomes insensitive to manipulations that normally suppress or enhance its activity. For example, infusion of nitroprusside increases both the heart rate and the circulating norepinephrine levels in normal subjects, whereas equivalent hypotensive doses in subjects with congestive heart failure elicit a blunted response (237). Similarly, patients with heart failure show less bradycardia when arterial pressure is raised by infusion of phenylephrine. Such alterations in baroreflex function may result from abnormalities peripherally or alterations in central autonomic regulatory centers.

Several observations suggest that Ang II may contribute to the depressed baroreflex sensitivity in heart failure. As discussed below the renin-angiotensin system is activated in the setting of congestive heart failure. Ang II has been shown to upwardly reset the arterial baroreflex control of heart rate in the rabbit independent of a change in arterial pressure (43). In the rat, increased levels of endogenous Ang II produced by changes in dietary salt intake, tonically increase the basal level of renal sympathetic nerve activity and upwardly reset the arterial baroreflex control of renal sympathetic nerve activity (69). Administration of an Ang II receptor blocker can reverse these changes in proportion to the degree of activation of the renin-angiotensin system. In a rabbit model of congestive heart failure, administration of an Ang II receptor blocker has been shown to improve the baroreflex control of sympathetic outflow (224). DiBona et al. (68) found that administration of an Ang II receptor blocker decreased efferent renal sympathetic nerve activity and improved the sensitivity of the arterial baroreflex mechanism in rats with congestive heart failure. This improvement was evident when the blocker was administered intravenously or when given directly into the cerebral ventricles. In a subsequent study, these same investigators found that the improved baroreflex regulation of renal sympathetic nerve activity was associated with an improved ability of the kidney to excrete both an acute and a chronic sodium load (71). Interestingly, captopril administered to patients with congestive heart failure restores the normal hemodynamic response to postural tilt and infusion of vasoconstrictive agents (60).

Cardiac Output

A reduction in cardiac output has been suggested as the afferent signal that leads to Na retention in heart failure. When cardiac output is reduced by constriction of the abdominal or thoracic vena cava, urinary sodium excretion is typically decreased (267, 294). Restoring cardiac output to normal by autologous blood transfusion ameliorated renal salt retention despite the fact that venous and hepatic pressures were persistently elevated (267). However, other observations question the importance of cardiac output alone as a key sensing mechanism in signaling renal salt retention. For example, using other means to reduce cardiac output comparable to that seen with constriction of the vena cava does not necessarily decrease renal sodium excretion (212). Rats with small to moderate myocardial infarctions have normal capacities to increase cardiac output in response to volume loads but the sodium excretory response in these animals remains blunted. Even when cardiac output is increased above normal as with the creation of an arteriovenous fistula in dogs clinical findings of ascites and peripheral and pulmonary edema develop (348). Despite increased cardiac output, levels of renin, aldosterone, and ANP are high (324). Thus, it is evident that the initiating signal for salt retention in congestive heart failure cannot originate solely from a decrease in cardiac output.

Other Sensors

Other afferent sensing mechanisms potentially active in congestive heart failure include intrahepatic baroreceptors (the evidence for these is controversial) and mechanoreceptors within the kidney. Chemosensitive receptors have been identified within skeletal muscle, heart, and kidney, which by responding to changing levels of metabolic breakdown products may participate in sensing of ECF volume. One such sensing mechanism may relate to the cardiac sympathetic afferent reflex. The reflex begins with sympathetic afferent fibers that respond to changes in cardiac pressure

and dimension or substances that may accumulate in ischemia or heart failure. The reflex is excitatory in nature such that activation of the afferent fibers leads to increased central sympathetic outflow. As with the arterial baroreceptor reflex, there is evidence that Ang II plays a modulating role in this reflex (197). Ma et al. (197) found that the cardiac sympathetic afferent reflex is activated in dogs with congestive heart failure and that central Ang II can enhance the degree to which sympathetic outflow is enhanced.

In summary, a contracted EABV serves as the afferent signal that elicits activation of effector mechanisms resulting in sodium retention. As with other edematous disorders, the exact volume compartment that comprises EABV has not been elucidated (Fig. 6).

Effector Mechanisms in Congestive Heart Failure

Nephron Sites of Renal Sodium Retention

Renal sodium handling in the setting of congestive heart failure is similar to that which occurs in an otherwise normal individual who is volume depleted. Activation of effector mechanisms lead to alterations in renal hemodynamics and tubular transport mechanisms that culminate in renal salt retention.

Renal hemodynamics in congestive heart failure are characterized by reduced renal plasma flow and a well-preserved glomerular filtration rate such that filtration fraction is typically increased. In a rat model of myocardial infarction, Hostetter et al. (135) found a positive correlation between the decline in renal plasma flow and the degree to which left ventricular function was impaired. The glomerular filtration rate remained well preserved as a result of an increased filtration fraction except in the animals with a severely compromised left ventricle. When examined at the level of the single nephron, these hemodynamic changes were found to be the result of a disproportionate increase in efferent arteriolar vasoconstriction and increased glomerular capillary hydraulic pressure (137). Treatment with an angiotensin-converting enzyme inhibitor caused a decline in filtration fraction and efferent arteriolar resistance suggesting an important role for Ang II in mediating efferent arteriolar constriction. In this regard, changes in glomerular and proximal tubular function seen in states of heart failure are similar to those that result from infusion of Ang II or norepinephrine. Ang II, catecholamines, and renal nerves are all capable of increasing both the afferent and the efferent arteriolar tone but predominantly act on the latter. These changes in glomerular hemodynamics serve to maintain glomerular filtration rate near normal as renal plasma flow declines secondary to impaired cardiac function. As cardiac function progressively declines and the reduction in renal plasma flow becomes severe, the glomerular filtration rate will begin to fall. At this point there is an inadequate rise in filtration fraction because efferent arteriolar vasoconstriction can no longer offset the intense afferent arteriolar constriction. Higher plasma catecholamines and further increases in sympathetic nerve activity acting to provide circulatory stability result in greater constriction of the afferent arteriole such that glomerular plasma flow and transcapillary hydraulic pressure are reduced. In this setting, the glomerular filtration rate becomes dependent on afferent arteriolar flow.

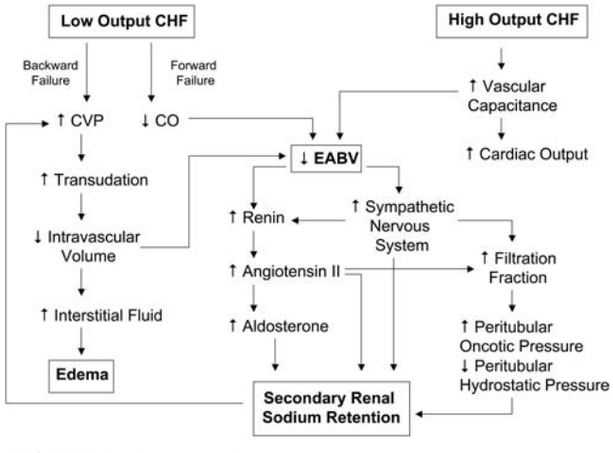

FIGURE 6 Summary of pathways leading to renal sodium retention in low- and high-output congestive heart failure. CO, cardiac output; EABV, effective arterial blood volume; CVP, central venous pressure.

These predictions are consistent with what has been observed in human subjects with varying degrees of left ventricular function (187). As left ventricular function declines, the glomerular filtration rate is initially maintained by an increased filtration fraction. However, in patients with severely depressed left ventricular function a progressive decline in renal blood flow becomes associated with a fall in glomerular filtration rate due to an inadequate rise in filtration fraction. In these patients, administration of an ACE inhibitor can result in a further lowering of the glomerular filtration rate even though systemic arterial pressure remains fairly constant (241).

Both experimental and clinical studies support the proximal nephron as a major site of increased sodium reabsorption in the setting of congestive heart failure. In human subjects, clearance techniques have primarily been employed to demonstrate the contribution of the proximal nephron. For example, infusion of mannitol was shown to increase free-water excretion to a greater extent in patients with congestive heart failure as compared to normal controls. Since mannitol inhibits fluid reabsorption proximal to the diluting segment, it was inferred that enhanced free-water clearance was reflective of augmented delivery of Na to the diluting segment from the proximal tubule (21). A similar conclusion was reached utilizing clearance techniques in the setting of pharmacologic blockade of distal nephron sites (23). In dogs with an arteriovenous fistula, there is a failure to escape from the Na-retaining effects of deoxycorticosterone acetate. In addition, these animals do not develop hypokalemia in contrast to normal controls (144). The failure to develop hypokalemia in the setting of mineralocorticoid excess is best explained by decreased delivery of Na to the distal nephron

as a result of enhanced proximal Na reabsorption. Alterations in peritubular hydrostatic and oncotic forces as well as direct effects of various neurohormonal effectors account for enhanced proximal sodium and water absorption in this setting (137).

The distal tubule may also importantly contribute to enhanced sodium reabsorption in states of congestive heart failure. Clearance and micropuncture studies have documented enhanced distal nephron sodium reabsorption in various experimental models of heart failure, including arteriovenous fistulas, chronic pericarditis, and chronic partial thoracic vena cava obstruction (14). In dogs with chronic vena cava obstruction (179) and rats with an arteriovenous fistula (310), the loop of Henle was localized as a site of enhanced sodium reabsorption. Similar to the proximal nephron, physical factors influenced by alterations in renal hemodynamics may account for augmented sodium reabsorption in this segment (179).

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system is activated when the heart fails as a pump (210). Components of this system serve to compensate for decreased cardiac output by stabilizing the circulation and expanding ECF volume.

Several mechanisms known to mediate release of renin are operative in the setting of a failing myocardium. Diminished pressure within the afferent arteriole leads to enhanced renin release via a baroreceptor mechanism, the sensitivity of which is heightened consequent to augmented baseline sympathetic nerve activity (153). Enhanced salt and water reabsorption in the proximal tubule and loop of Henle diminishes sodium chloride concentration at the macula densa providing a stimulatory signal for renin release by way of the tubuloglomerular feedback mechanism. Finally, increased sympathetic nerve activity directly enhances renin release via stimulation of β-adrenergic receptors.

Renin acts on angiotensinogen synthesized in the liver and elsewhere to produce the decapeptide, angiotensin I. Angiotensin I is converted to Ang II by the angiotensin converting enzyme present in the lungs, kidney, and blood vessels throughout the circulation.

Ang II plays a pivotal role in glomerular and proximal tubule function that characterizes most models of congestive heart failure. By selectively increasing efferent arteriolar tone, adjustments in the glomerular and postglomerular circulatory network favor net reabsorption in the proximal tubule. Increased filtration fraction leads to increased peritubular oncotic pressure and in combination with decreased peritubular hydrostatic pressure net sodium reabsorption is enhanced. Ang II also stimulates proximal tubule salt and water reabsorption by a direct mechanism (128, 295). In addition, increased efferent arteriolar resistance tends to increase glomerular capillary hydrostatic pressure, thereby mitigating any fall in GFR that would otherwise occur from decreased renal blood flow. In clinical as well as experimental models of heart failure, administration of ACE inhibitors improves renal blood flow and increases urinary sodium excretion consistent with important Ang II-mediated effects on the renal microvasculature (85).

Ang II also contributes to renal salt and water retention through effects that lead to increased renal sympathetic nerve activity. Ang II has been shown to depress the sensitivity of the baroreflex mechanism such that a higher pressure is required to decrease central sympathetic outflow. In addition, Ang II directly stimulates sympathetic outflow at the level of the central nervous system. The chronic administration of an ACE inhibitor to patients with congestive heart failure leads to a reduction in central sympathetic outflow and improves the sympathoinhibitory response to baroreflex stimulation (119). Ang II affects renal salt and water handling in the distal nephron through stimulation of aldosterone release by the adrenal gland. Aldosterone acts primarily on the collecting duct to promote tubular reabsorption of sodium. Aldosterone-stimulated sodium reabsorption generates a luminal negative voltage that secondarily enhances excretion of hydrogen and potassium ions. The magnitude of potassium secretion will depend on the volume and composition of filtrate reaching the collecting duct. In this regard, patients with heart failure rarely manifest hypokalemia and alkalosis despite oversecretion of mineralocorticoid unless distal sodium delivery is increased by use of a diuretic. Effector mechanisms acting proximally, including Ang II, sympathetic nerves, and peritubular physical factors, serve to diminish distal delivery of sodium. Thus, although plasma renin and aldosterone levels are frequently elevated in heart failure, there is conflicting data as to the importance of aldosterone in mediating renal salt retention (84, 129, 329).

The conflicting data regarding the importance of the renin-angiotensin-aldosterone system in the generation of cardiac edema is best resolved when analyzed with respect to severity of heart failure. The initial response to constriction of the pulmonary artery or thoracic inferior vena cava in dogs is a reduction in blood pressure and increases in renin and aldosterone levels. These changes are accompanied by nearly complete renal sodium retention (329). Administration of a converting enzyme inhibitor during this acute phase lowers blood pressure further, consistent with an important role of circulating Ang II in the maintenance of blood pressure. Over several days plasma volume and body weight increase, while renin, aldosterone, and sodium balance return to control values. In contrast to the acute setting, administration of a converting enzyme inhibitor during this chronic phase results in no significant hypotension. Animals with more severe impairment of cardiac output have plasma renin and aldosterone levels that remain elevated and these animals remain sensitive to the hypotensive effects of converting enzyme inhibition.

Similar changes in the activation of the renin-angiotensin-aldosterone axis are seen in dogs with an arteriovenous fistula (324). In the early phase of this high-output cardiac failure model, significant elevations in renin and aldosterone levels occur and renal sodium retention is marked. Several days later,

after development of peripheral edema and ascites, renin and aldosterone levels returned to baseline and daily sodium excretion begins to match dietary intake.

Studies in humans have shown a similar relationship between the renin-angiotensin-aldosterone system and stage and severity of congestive heart failure (84). This relationship may explain why renal function improves in some patients treated with ACE inhibitors whereas renal function deteriorates in others. Systemic hemodynamcis and plasma renin activity have been compared in such patients (242). In subjects whose renal function worsens after administration of the drug, there is a greater fall in mean right atrial pressure, left ventricular filling pressure, mean arterial pressure, and systemic vascular resistance. In addition, plasma renin activity increases to a greater extent. These changes suggest a more contracted EABV and greater dependency of systemic vascular resistance on circulating Ang II in patients with ACE inhibitor induced renal dysfunction. Maintenance of GFR is critically dependent on Ang II-mediated efferent arteriolar constriction causing an adequate increase in glomerular capillary hydrostatic pressure in order to counterbalances the decrease in renal perfusion.

In summary, during severe decompensated left ventricular failure, decreased EABV elicits release of renin with consequent activation of Ang II and aldosterone. Acutely, increased circulating levels of Ang II serve to maintain systemic blood pressure and contribute to augmented sodium reabsorption through hemodynamic and direct effects on the proximal tubule and enhanced distal sodium reabsorption by stimulating aldosterone release. As ECF volume expands, renin, Ang II, and aldosterone become suppressed, although not necessarily to normal. At this stage, maintenance of systemic blood pressure is more dependent on volume rather than Ang II. Sodium balance is now achieved but at the expense of increased steady-state ECF volume. With further deterioration in cardiac function, persistent activation of the renin-angiotensin-aldosterone system may result, such that systemic blood pressure remains dependent on circulating Ang II despite expansion of ECF volume. In order to predict net renal and hemodynamic effects of converting enzyme inhibition, one has to consider this sequential change in renin to volume dependency of mean arterial blood pressure (311).

Sympathetic Nervous System

The sympathetic nervous system is activated in congestive heart failure. Plasma norepinephrine levels are elevated and concentrations correlate with degree of left ventricular dysfunction (178). In addition, direct nerve recordings have verified that central sympathetic nerve outflow is increased and this outflow correlates with left ventricular filling pressures (176).

Increased sympathetic tone influences renal reabsorption of salt and water by indirect as well as direct mechanisms. Glomerular hemodynamics are affected in a similar manner to that produced by Ang II. A preferential increase in efferent arteriolar resistance results in increased filtration fraction in patients with decompensated heart failure. Peritubular Starling forces are altered in a manner that enhances proximal salt and water absorption. In addition, sympathetic nerves directly stimulate tubular reabsorption of salt and water in both the proximal and the distal nephron.

Increased sympathetic nerve activity directly stimulates the release of renin from the juxtaglomerular cells and sensitizes the baroreceptor-mediated mechanism of renin release (153). The subsequent formation of Ang II provides a positive feed back loop leading to further increases in sympathetic nerve activity. Increased circulating Ang II sensitizes tissues to the actions of catecholamines and acts synergistically with renal nerves in modulating renal blood flow (248).

The observation that α-adrenergic antagonists and ganglionic blockers abolish sodium retention in dogs with thoracic vena cava constriction supports an important role for renal nerves in mediating salt retention in heart failure (293). In the rat model of cardiac failure due to myocardial infarction, it has been demonstrated that increased activity of renal sympathetic nerves mediates a significant portion of the abnormal renal salt and water retention (72). These animals have an impaired diuretic and natriuretic response to intravenous saline volume loading that is associated with an attenuated inhibition of efferent renal sympathetic nerve activity. The impaired renal excretory response is normalized by prior renal denervation. Renal denervation also normalizes the attenuated diuretic and natriuretic response to ANP in these rats. A similar role for renal nerves in mediating abnormal renal salt and water retention has been shown in a dog model of compensated high-output heart failure (325).

Prostaglandins

Increased production of prostaglandins plays an important role in maintaining circulatory homeostasis in congestive heart failure. In response to decreases in cardiac output, neurohumoral vasoconstrictor forces (i.e., the renin-angiotensin-aldosterone system, the neurosympathoadrenal axis) participate in the maintenance of systemic arterial pressure and result in increased total peripheral vascular resistance. These same vasoconstrictors stimulate the renal production of vasodilatory prostaglandins such that the rise in renal vascular resistance is less than that seen in the periphery. Vasodilatory prostaglandins function in a counterregulatory role, attenuating the fall in renal blood flow and glomerular filtration rate that would otherwise occur if vasoconstrictor forces were left unopposed (244).

The delicate balance between constrictor and dilator forces upon the renal vasculature is best demonstrated when inhibitors of the cyclooxygenase pathway are given. In a model of congestive heart failure produced by inflation of a balloon in the thoracic inferior vena cava, there is a reduction in cardiac output that is accompanied by a significant rise in systemic vascular resistance, plasma renin activity, and the concentration of norepinephrine. Despite the increase in peripheral vascular resistance, renal vascular resistance does

not change and there is only a slight fall in renal blood flow. Administration of indomethacin or meclofenamate in this setting results in a marked decrease in renal blood flow and an increase in renal vascular resistance, suggesting that renal prostaglandins play an important role in the maintenance of renal blood flow under conditions of decreased cardiac output (238).

Renal prostaglandins are also important in moderating the salt and water retention that would otherwise occur in the setting of unopposed activation of effector mechanisms such as angiotensin II, aldosterone, renal sympathetic nerves, and ADH (244). In dogs with chronic pericardial tamponade, the increase in urinary sodium excretion normally seen after pericardiocentesis is attenuated by indomethacin and augmented by infusion of arachidonic acid. Similarly, in humans with decompensated cardiac failure, infusion of prostaglandin E2 results in increased fractional excretion of sodium. In hyponatremic heart-failure patients, administration of indomethacin leads to a decrease in cardiac output and increase in systemic vascular resistance. Prostaglandins play an increasingly important role in modulating renal hemodynamics, sodium excretion, and circulatory homeostasis as the degree of heart failure worsens.

Natriuretic Peptides

Circulating levels of ANP are elevated in humans and experimental animals with heart failure. These levels correlate with the severity of disease (59, 271). In patients with varying New York Heart Association functional classes, those of class IV have significantly higher levels than those of class I and class II. These levels vary inversely with left ventricular ejection fraction and decrease as ejection fraction improves during the course of treatment. Since the predominant stimulus for ANP release is atrial stretch, it is noteworthy that both the plasma level and the magnitude of step up across the heart correlates best with atrial pressure (271).

The natriuretic and vasodilatory properties of ANP suggest that this peptide plays an important counterregulatory role in congestive heart failure. In a rat model of heart failure, administration of a monoclonal ANP antibody was found to increase cardiac filling pressure and systemic vascular resistance (81). In this same model, renal blood flow and GFR decreased following the administration of a natriuretic peptide receptor blocker. These hemodynamic changes were accompanied by a reduction in urine flow and urine sodium excretion (203).

Attempts to use ANP therapeutically in congestive heart failure have produced disappointing results (59, 154). ANP infused in patients with heart failure causes only a minimal change in fractional sodium excretion and urine flow rates as compared to the robust response in normal controls (59). The diminished renal responsiveness to ANP is pronounced when considering that baseline endogenous plasma ANP levels are often already elevated five- to sevenfold in heart failure patients. Similarly, inhibition of renin release by ANP is attenuated in heart-failure patients (59).

The mechanism of renal nonresponsiveness in heart failure is not entirely clear. A downregulation of receptors due to sustained exposure to high levels of ANP or altered intrarenal hemodynamics are possibilities. The renal tubules appear to be responsive to ANP since urinary cGMP levels are increased in patients with congestive heart failure (4). One attractive explanation for ANP resistance is decreased delivery of sodium to the distal nephron, that portion of the nephron where ANP normally exerts its direct natriuretic effect. In this regard, administration of an Ang II receptor antagonist, an intervention that would increase distal sodium delivery, can restore the renal responsiveness to ANP (3). Thus, while ANP levels are uniformly elevated in congestive heart failure, potentially beneficial natriuretic properties are overwhelmed by more powerful antinatriuretic effector mechanisms.

Other natriuretic factors have been tested therapeutically in congestive heart failure with mixed results (26). In a double-blind, placebo-controlled trial, infusion of brain natriuretic peptide was associated with a significant reduction in pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure and mean arterial pressure as well as an increase in cardiac index. These hemodynamic benefits were accompanied by a significant increase in urinary volume as well as sodium excretion (201). In a preliminary report, infusion of brain natriuretic peptide was found to have a similar benefit on cardiac filling pressures and systemic vascular resistance, however, in this study only a few patients exhibited an increase in urinary sodium excretion (203). Urodilatin has also been tested in patients with congestive heart failure. A prolonged infusion of this natriuretic factor in 12 patients was reported to lower cardiac preload and to significantly increase urinary sodium excretion (90).

Endothelin and Nitric Oxide

Circulating levels of endothelin are increased in the setting of congestive heart failure. These levels have been shown to correlate positively with various indices of cardiac dysfunction. Studies in which endothelin antagonists have been administered suggest a possible role for endothelin in the pathophysiology of cardiac failure. In a randomized, double-blind study of human subjects with heart failure, infusion of an ETa and ETb receptor blocker (bosentan) was associated with a reduction in right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and mean arterial pressure (152). The effects of administering an antagonist specific for either the ETa or ETb receptor was recently reported in a dog model of congestive heart failure (327). In these animals, ETa blockade alone lead to a reduction in cardiac filling pressures and increased cardiac output. These hemodynamic changes were associated with an increase in GFR and renal plasma flow as well as increased urinary sodium excretion. By contrast, administration of an ETb receptor blocker resulted in an increase in cardiac filling pressures and a decrease in cardiac output. There was no change in GFR however renal plasma flow fell. It was concluded that

endogenous endothelins adversely effect cardiac hemodynamics and cause fluid retention primarily through ETa receptors.

Nitric oxide production is increased in congestive heart failure (333). Increased release of nitric oxide from resistance vessels may partly antagonize neurohumoral vasoconstrictor forces. Inhibiting nitric oxide production in heart failure patients causes a significant increase in pulmonary and systemic vascular resistance as well as decline in cardiac output. In the renal vasculature, nitric oxide production is also increased; however, the renal vasodilatory response to nitric oxide is impaired (2). In part, this defect is due to the effects of Ang II since administration of an angiotensin receptor antagonist can restore nitric oxide-mediated renal vasodilation.

Arginine Vasopressin

Increased circulating levels of AVP is a characteristic finding in patients with congestive heart failure. The nonosmotic release of AVP plays an important role in the development of hyponatremia, which in turn is a well-defined predictor of mortality in heart failure patients. In experimental heart failure, there is upregulation of the mRNA for vasopressin in the hypothalamus (151). In addition, there is increased expression of the mRNA and the protein for the aquaporin-2 water channel (342). In a rat model of heart failure, selective antagonism of the V-2 receptor is associated with a significant improvement in free water clearance (342). Use of a V-2 receptor antagonist to treat hyponatremia in human subjects with heart failure is currently being investigated.

CIRRHOSIS

Renal sodium excretion is normally regulated so that extracellular fluid (ECF) volume is maintained within normal limits. Any maneuver that increases ECF volume will lead to a prompt and sustained natriuresis until the volume returns to normal. In patients with cirrhosis, this homeostatic mechanism becomes deranged such that large increases in ECF volume are accompanied by continued renal salt retention resulting in edema and ascites formation.

Presinusoidal versus Postsinusoidal Obstruction and Ascites Formation

In patients with cirrhosis, the kidneys are normal but are signaled to retain salt in an unrelenting manner. The critical event in the generation of this signal is development of hepatic venous outflow obstruction. In the normal state, the portal circulation is characterized by high flow, low pressure, and low resistance. The imposition of a resistance into this high-flow vasculature will uniformly raise portal pressure, but development of ascites is critically dependent on location of the resistance. Conditions associated with presinusoidal vascular obstruction such as portal vein thrombosis and schistosomiasis raise portal pressure but are not generally associated with ascites. By contrast, hepatic diseases such as Laennec's cirrhosis and Budd Chiari syndrome cause early postsinusoidal vascular obstruction and are associated with marked degrees of salt retention, anasarca, and ascites. Thus, during the development of the cirrhotic process, ascites will accumulate primarily when the pathologic process is associated with hepatic venous outflow obstruction and sinusoidal hypertension.

This distinction between presinusoidal and postsinusoidal obstruction can best be explained by comparing the characteristics of fluid exchange in capillaries of the splanchnic bed versus those in the hepatic sinusoids. The intestinal capillaries are similar to those in the peripheral tissues in that they have continuous membranes with small pores such that a barrier exists preventing plasma proteins from moving into the interstitial space. An increase in capillary hydrostatic pressure will cause the movement of a protein poor fluid to enter the interstitial compartment and decrease the interstitial protein concentration. Interstitial protein concentration is further reduced by an acceleration in lymph flow that is stimulated by the fluid movement. As a result, the interstitial oncotic pressure falls and the plasma oncotic pressure remains unchanged. The net oncotic force therefore rises and offsets the increase in hydrostatic force providing a buffer against excessive fluid filtration. The fall in intestinal lymph protein concentration is maximal at relatively low pressures and is much greater than that observed from the cirrhotic liver (19, 336). Thus, the increase in net oncotic force associated with dilution of the interstitial protein and accelerated lymph flow contribute to the protection against ascites in patients whose only abnormality is portal hypertension.

The situation across the liver sinusoids is quite different. Hepatic sinusoids, unlike capillaries elsewhere in the body, are extremely permeable to protein. As a result, colloid osmotic pressure exerts little influence on movement of fluid. Rather, direction of fluid movement is determined almost entirely by changes in sinusoidal hydraulic pressure. Thus, efflux of protein-rich filtrate into the space of Disse is critically dependent on hepatic venous pressures. Obstruction to hepatic venous outflow will lead to large increments in formation of hepatic lymph and flow through the thoracic duct. Unlike the intestinal capillaries, there is little to no restriction in the movement of protein into the interstitium such that the protein concentration of hepatic lymph will quickly approach that of plasma (118). As a result, no significant oncotic gradient develops between plasma and the interstitium at high sinusoidal pressures and flow.

When sinusoidal pressure increases to such a degree that hepatic lymph formation exceeds the capacity of the thoracic duct to return fluid to the circulation, interstitial fluid weeps off the liver into the peritoneal space and forms ascites. Lymph formation in the setting of cirrhosis can be more than 20-fold greater than that which occurs under normal circumstances (336). Whereas in normal humans

1–1.5 liters/day of lymph are returned to the circulation, subjects with cirrhosis even without ascites may have lymph flow through the thoracic duct as high as 15–20 liters/day (335). The predominance of hepatically produced lymph to overall lymph production is illustrated by studies in experimental animals with cirrhosis. Barrowman and Granger (19) found a 29-fold increase in hepatic lymph flow, while only a threefold increase was noted in the splanchnic lymphatics. Eleven of 19 animals had normal flows of intestinal lymph, while all the cirrhotic animals had increased flows in liver lymph.

Conditions associated with the rapid onset of postsinusoidal obstruction such as acute right sided congestive heart failure and Budd–Chiari syndrome initially give rise to ascitic fluid that has a high protein concentration that may even approach that of plasma. This high protein concentration is reflective of the liver being the predominant source of the ascitic fluid. However, over time the protein content of ascites in these conditions begins to decrease. Witte et al. (337) measured the total protein in ascitic, pleural, and peripheral edema fluid in acute and chronic heart failure patients. In the setting of acute heart failure, the mean concentration of protein in ascitic fluid was approximately 5 g/dl. By contrast, the protein concentration in ascitic fluid of chronic congestive heart failure patients was 2.7 g/dl. A lower protein concentration is also typical of conditions such as Laennec's cirrhosis in which postsinusoidal obstruction develops slowly.

Two phenomena contribute to this change in ascitic fluid protein concentration. If the hepatic sinusoids are subjected to an increased hydrostatic pressure for a long period of time they begin to assume the anatomic and functional characteristics of capillaries found elsewhere in the body, a process referred to as capillarization (289). This change leads to a decrease in albumin permeability such that oncotic forces begin to play some role in hepatic lymph formation. At the same time hypoalbuminemia develops secondary to decreased hepatic synthesis as well as dilution secondary to ECF volume expansion. As a result, the protein content of hepatic lymph, although still high, falls to approximately 50%–55% of plasma values (336).

The second factor contributing to the lower ascitic protein concentration is the superimposition of portal hypertension. Early in the development of portal hypertension when plasma protein concentration is normal only minimal amounts of ascitic fluid is derived from the splanchnic bed due to the buffering effect of increased net oncotic force opposing fluid filtration. Extremely high hydrostatic pressures are required to produce significant amounts of ascitic fluid in the setting of normal plasma protein concentrations. By contrast, less and less hydrostatic pressure is required for the formation of ascitic fluid as the plasma albumin concentration decreases and the net osmotic force declines. In this setting, there is a large contribution of the splanchnic bed to the generation of ascites and the fluid is characterized by a low protein concentration.

The development of portal hypertension is also associated with changes in the splanchnic circulation that secondarily lead to increased lymph production in the splanchnic bed. The importance of the splanchnic lymphatic pool in the generation of ascites is reflected by the fact that in most instances ascitic fluid is transudative and characterized by a protein concentration of <2.5 g/dl. Classically, portal hypertension was considered to be the sole result of increased resistance to portal venous flow. However, studies in experimental models suggest that increased portal venous flow resulting from generalized splanchnic arteriolar vasodilation also plays a role in the genesis of increased portal pressure (40, 326). This vasodilation leads to changes in the splanchnic microcirculation that may predispose to increased filtration of fluid. For example, an acute elevation of venous pressure in the intestine normally elicits a myogenic response that leads to a reduction in blood flow. This decrease in flow is thought to serve a protective role against the development of bowel edema. However, in chronic portal hypertension this myogenic response is no longer present. In this setting, arteriolar resistance is reduced such that capillary pressure and filtration are increased (24). The loss of this autoregulatory mechanism may account for the greater increase in intestinal capillary pressure and lymph flow seen under conditions of chronic portal hypertension when compared to acute increases in portal pressure of the same magnitude (167). The potential causes of splanchnic arteriolar vasodilation are discussed below.

The importance of portal hypertension in the pathogenesis of ascites is highlighted by several observations. First, patients with ascites have significantly higher portal pressures as compared to those without ascites (220). Although the threshold for ascites development is not clearly defined it is unusual for ascites to develop with a pressure below 12 mm Hg. Gines found that only 4 of 99 cirrhotic patients with ascites had a portal pressure <12 mm Hg as estimated by hepatic venous wedged pressure (117). Second, portal pressure correlates inversely with urinary sodium excretion (220). Third, maneuvers designed to reduce portal pressure are known to have a favorable effect on the development of ascites. For example, surgical portosystemic shunts used in the treatment of variceal bleeding reduce portal pressure and are associated with a lower probability of developing ascites during follow up (59). Both side-to-side and end-to-side portocaval anastomosis have been shown effective in the management of refractory ascites in cirrhosis. Recent studies also suggest that reducing portal pressure with a transjugular intrahepatic portasystemic shunt has a beneficial effect on ascites (235).

In summary, ascites develops when the production of lymph from either or both the hepatic sinusoids and the splanchnic circulation exceeds the transport capacity of the lymphatics. In this setting, fluid will begin to weep from the surface of the liver and the splanchnic capillary bed and accumulate as ascites. The final protein concentration measured in the peritoneal fluid is determined by the sum of

the two contributing pools of fluid; one relatively high in protein originating in the liver and the other, a low protein filtered across splanchnic capillaries. Hepatic venous outflow obstruction leading to increased sinusoidal pressure and portal hypertension are the major determinants as to whether lymph production will be of a magnitude sufficient for ascitic fluid to accumulate. Increased sinusoidal pressure is also related to the subsequent development of renal salt retention. The mechanism by which sinusoidal hypertension signals the kidney to retain sodium is discussed in the following section.

Afferent Limb of Sodium Retention: Overfill versus Underfill Mechanisms

Classical Underfill Mechanism for Renal Salt Retention

The mechanism by which hepatic venous outflow obstruction leads to sufficiently high sinusoidal pressures for ascites formation is controversial. The classical (underfill) theory predicts that the degree of hepatic venous outflow obstruction is sufficient in the presence of normal splanchnic perfusion to perturb the balance between rates of hepatic lymph formation and thoracic duct flow, thereby resulting in formation of ascites. Both increased sinusoidal and portal venous pressures in conjunction with hypoalbuminemia cause formation of ascites in the presence of normal splanchnic perfusion. The formation of ascites, however, occurs at the expense of decreased intravascular volume. In consequence, a low venous filling pressure and a low cardiac output activate baroreceptor mechanisms, resulting in renal salt retention. According to this formulation, development of ascites is the primary event that leads to an underfilled circulation and subsequent renal salt retention.

The failure of measured hemodynamic parameters to satisfy predictions of the classical theory has raised questions regarding its validity. As originally conceived, it was predicted that extrasplanchnic plasma volume would be decreased and that cardiac output would be low. When measured, however, these values have rarely been low. In fact, measurements have indicated that total plasma volume is usually elevated in cirrhotic patients. Similarly, cardiac output is rarely low but tends to vary from normal to very high. In addition, studies performed in animal models of cirrhosis have found that sodium retention precedes the formation of ascites, suggesting that salt retention is a cause and not a consequence of ascites formation.

Overfill Mechanism for Renal Salt Retention

The incompatibility of measured hemodynamic parameters and timing of renal salt retention with the classical theory of ascites has led others to propose the overflow theory (186). Once again, hepatic disease with venous outflow obstruction is viewed as a prerequisite for development of increased sinusoidal and portal pressures. In contrast to the classical theory, however, normal splanchnic perfusion fails to raise sinusoidal pressure sufficiently to cause ascites formation. Rather, venous outflow obstruction signals renal sodium retention independent of diminished intravascular volume. Salt retention, in turn, increases plasma volume, cardiac output, and splanchnic perfusion, thus raising sinusoidal and portal pressures sufficiently to culminate in translocation of fluid into the interstitial space and eventually the peritoneum. The combination of portal hypertension and increased arterial volume would lead to overflow ascites formation. This hypothesis is supported by the positive correlation between plasma volume and hepatic venous pressure and the persistence of increased plasma volume after portacaval anastomosis. Moreover, patients with ascites have significantly higher portal pressure than patients without ascites, and portal pressure correlates inversely with urinary sodium excretion (117).

Additional evidence linking hepatic venous outflow obstruction directly to renal sodium retention comes from studies performed in dogs fed the potent hepatotoxin dimethylnitrosamine (183–185). The pathophysiologic disturbances and histologic changes that develop over a 6–8-week period are similar in nature to those seen in Laennec's cirrhosis. In this model, sodium retention and increases in plasma volume precede formation of ascites by about 10 days (183). In order to exclude the possibility that the increase in plasma volume was solely due to an increased splanchnic plasma volume, repeat measurements were obtained after ligation of the superior and inferior mesenteric arteries, the celiac axis, and portal vein. In this way, any contribution of the splanchnic circulation could be excluded. These studies clearly showed that extrasplanchnic plasma volume was elevated at a time when dogs were in positive sodium balance. To further prove that extrasplanchnic plasma volume was increased, end-to-side portacaval shunts were placed prior to inducing cirrhosis (185). This maneuver was designed to prevent any increase in splanchnic plasma volume. In these studies, evidence of salt retention preceded the formation of ascites and was accompanied by a parallel increase in plasma volume.

In another series of studies using this same model, hemodynamic parameters were monitored during control, precirrhotic, and postcirrhotic sodium balance periods (184). Sodium retention was found to precede any detectable change in cardiac output or peripheral vascular resistance. Once ascites developed, plasma volume increased further and this was associated with increased cardiac output and a fall in peripheral vascular resistance. It was concluded that initiation of sodium retention and plasma volume expansion was not dependent on alterations in systemic hemodynamics. This conclusion has been corroborated in the canine model of hepatic cirrhosis induced by bile duct ligation (318) as well as in rats made cirrhotic with carbon tetrachloride inhalation and oral phenobarbital (191).

The pathway by which primary renal sodium retention would be linked to venous outflow obstruction in the overfill theory is not clear. Convincing evidence does exist for the

presence of an intrahepatic sensory network composed of osmoreceptors, ionic receptors, and baroreceptors. Studies in which hepatic venous pressure is raised have demonstrated increases in hepatic afferent nerve activity (180, 182, 318). Furthermore, a neural reflex pathway linking hepatic venous congestion and augmented sympathetic nerve activity has been identified (168). In addition, acute constriction of the portal vein in dogs results in renal sodium and water retention in the innervated unilateral kidney, while these effects are abolished in the contralateral denervated kidney (9). In addition to a neural mechanism, there may also be a hormonal system by which the liver and kidney can communicate. Bankir et al. (16) recently suggested that hepatically produced cAMP may be one such hormone. Circulating cAMP is known to inhibit proximal salt and water absorption as well as contribute to the regulation of glomerular filtration rate. According to this hypothesis, decreased circulating cAMP levels as a result of liver disease could secondarily lead to renal salt retention and impaired renal function.

In summary, the overfill hypothesis is supported by a number of observations that indicate sodium retention precedes development of ascites in the absence of hemodynamic factors known to lead to salt retention. Moreover, high cardiac output coupled with increased plasma volume argue strongly for increased arterial blood volume, a finding seemingly incompatible with the underfill theory. Against such an analysis, however, is that mechanisms that sense arterial volume physiologically may be more sensitive than methods used to measure it. It should be noted that while statistically insignificant, there was a fall in blood pressure at the time of positive sodium balance in the dimethylnitrosamine model. This decrease may have been of sufficient magnitude to signal renal salt retention (184). Since cardiac output was unchanged, total peripheral resistance may have decreased. Similarly, patients with hepatic cirrhosis and ascites behave as if they are effectively volume depleted. Despite an increase in cardiac output and plasma volume arterial pressure is typically low. This fall in systemic blood pressure is consistent with an underfilled arterial vascular compartment. Thus, the distinction between classical and overflow theories better rests on the measurement of effective arterial blood volume (EABV).

Use of EABV to Distinguish Underfill and Overfill Mechanisms of Renal Salt Retention

The classical (underfill) theory predicts that EABV is low in patients with ascites and is the afferent mechanism signaling renal salt retention. The overflow theory predicts that EABV is expanded due to primary salt retention. While EABV cannot be measured directly, assessing the level of activation of neurohumoral effectors known to be regulated by EABV can be considered a measure of it. In this regard, levels of renin, aldosterone, ADH, and norepinephrine can serve as markers reflective of the magnitude of the EABV.

When renin and aldosterone values have been measured in patients with cirrhosis, values have varied from low to high. It is important, however, to consider these levels in the context of whether ascites is present or not. In the absence of ascites, subjects are in sodium balance and renin and aldosterone levels are normal (274). In the presence of ascites, mean renin and aldosterone levels are elevated, but individual values are often still normal (12, 117). This observation seems in conflict with the classical theory as all patients with ascites who are in positive sodium balance should have decreased EABV and high aldosterone levels. However, not all patients with ascites are retaining sodium. In fact, some patients are in balance such that sodium intake equals output. Thus, in examining the mechanism of sodium retention in cirrhosis with ascites, renin and aldosterone levels should be considered with respect to the rate of sodium excretion.

When examined in this fashion, a significant inverse relationship is found between urinary sodium excretion and plasma aldosterone (12, 117). In subjects with ascites who excrete 50–100 mEq of sodium per day, plasma aldosterone concentration is normal (12). As predicted by the classical theory, these patients have normal EABV and thus normal plasma aldosterone concentration. In patients with low rates of urinary sodium excretion, increased plasma aldosterone concentrations are reflective of a contracted EABV. Since aldosterone metabolism is impaired in liver disease, increased plasma concentrations could result from decreased hepatic clearance. When studied, however, increased secretion rate and not impaired metabolism is found to be the major cause of elevated aldosterone levels (279).

Measurement of plasma catecholamines to assess the level of activity of the sympathetic nervous system has been performed in subjects with cirrhosis. Similar to aldosterone, results of these measurements have been conflicting. However, when examined as a function of urinary sodium excretion rate, plasma norepinephrine and urinary sodium excretion are found to vary inversely (36). In addition, plasma norepinephrine is positively correlated with arginine vasopressin (AVP) and plasma renin activity.

Studies have also been performed in which humoral markers reflective of EABV were examined with respect to the ability to excrete water loads (35, 36). In those subjects who excreted less than 80% of a water load over a 5-hour period, plasma concentrations of AVP, renin, aldosterone, and norepinephrine were higher in comparison to those who were able to excrete greater than 80% of the water load (35, 36). In a similar study, cirrhotic patients unable to elaborate a positive free-water clearance after administration of a water load were also shown to have higher levels of AVP, norepinephrine, and plasma renin activity. Furthermore, the impairment in water excretion was found to parallel the clinical severity of disease (228). Thus, in patients with a low urinary sodium concentration or an impaired ability to excrete water loads, measurement of neurohumoral markers suggests the presence of a contracted EABV.

Placement of a peritoneovenous shunt results in a natriuretic response in patients with cirrhosis. This procedure creates direct route for replenishing the intravascular space through mobilization of ascitic fluid. The decrease in plasma renin activity and serum aldosterone levels after peritoneovenous shunting lends further support for a contracted EABV in these patients (39). Similar benefits have been reported in cirrhotic patients treated with the transjugular intrahepatic portal-systemic shunt (235, 269). The observation that large-volume paracentesis without intravenous albumin increases plasma renin activity and impairs renal function in most cirrhotic patients also argues against the overflow theory of ascites (116).

One component of the circulation that appears to be contributing to the overall decrease in EABV is the central circulation. Indirect measurements demonstrate that central blood volume is reduced while noncentral blood volume is expanded (218). In fact, the size of central and arterial blood volume is inversely correlated with sympathetic nervous system activity suggesting that unloading of central arterial baroreceptors is responsible for enhanced sympathetic activity. This conclusion is supported by studies using the technique of head-out water immersion (HWI) (92, 93). In this technique, subjects are seated and immersed in a water bath up to their necks. This technique results in redistribution of ECF volume from the interstitial space into the vasculature with a sustained increase in central blood volume. The central volume expansion is comparable to that induced by infusion of 2 liters of isotonic saline (93). Such a maneuver would be expected to raise both the EABV and the hepatic sinusoidal pressure. The classical theory would predict that HWI would lead to decreases in renin, aldosterone, ADH, and norepinephrine concentrations in response to expansion of EABV. Since renin levels correlate with wedged hepatic vein pressures, the overfill theory would predict further rises in renin and other hormonal systems consequent to initiation of a sinusoidal pressure-sensitive hepatorenal reflex. When HWI was performed in a heterogeneous group of patients with cirrhosis, the natriuretic response was variable, but suppression of renin and aldosterone levels was uniform (97). In a more homogenous group of patients characterized by impaired ability to excrete water and sodium, HWI was shown consistently to suppress plasma AVP, renin, aldosterone, and norepinephrine as well as to increase sodium and water excretion (34, 230).

Taken together, the multiplicity of data support the presence of decreased EABV in patients with decompensated cirrhosis and is most consistent with an underfill mechanism of renal salt retention (Fig. 7). Since blockade of endogenous vasoconstrictor systems in patients with cirrhosis and ascites leads to marked arterial hypotension, activation of these systems function to contribute to the maintenance of arterial pressure. At least one component of the decrease in EABV may be due to an underfilled central circulation. As discussed in the following paragraphs, increased perfusion of arteriovenous communications, systemic vasodilation, and

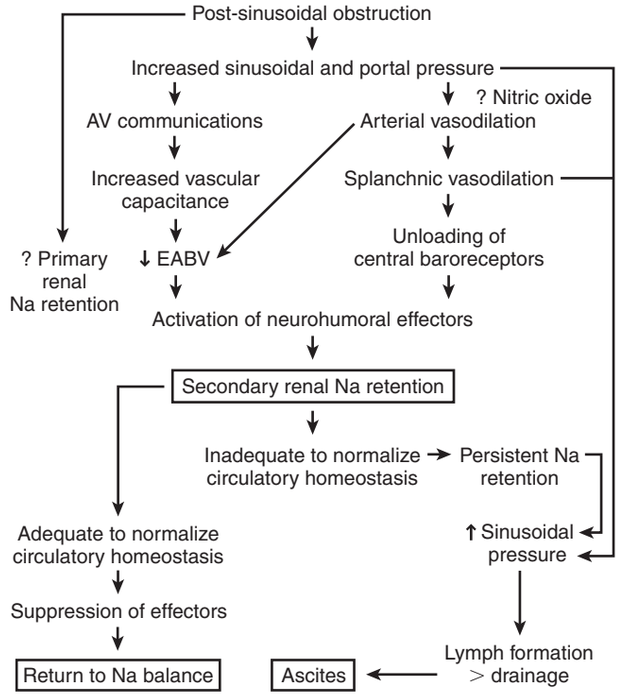

FIGURE 7 Unified theory of ascites formation: a modified underfill mechanism.

increased perfusion of the splanchnic bed are important factors in the genesis of an underfilled circulation. In addition, these factors play a major role in the hyperdynamic circulation that is typical of patients with chronic liver disease.

Hyperdynamic Circulation in Cirrhosis

Arteriovenous Communications

The characteristic circulatory changes observed in animal as well as clinical studies of cirrhosis consist of increased cardiac output, low mean arterial pressures, and low peripheral vascular resistance. The most attractive explanation for a contracted EABV in the setting of such a hyperdynamic circulation assigns a pivotal role to increased vascular capacitance. An increased vascular holding capacity out of proportion to plasma volume results in an underfilled circulation and decreased EABV. One factor that may account for increased vascular capacitance and a hyperdynamic circulation is the formation of widespread arteriovenous communications (32). In cirrhotics, arteriovenous fistula formation has been identified in the pulmonary, mesenteric, and upper and lower extremity circulations. In addition, increased blood flow has been measured in muscle and skin of the upper extremity not attributable to increased oxygen consumption, anemia, or thiamine deficiency (156). Postmortem injection demonstrated intense proliferation of small arteries in the splenic vasculature of patients with cirrhosis (200).

The hemodynamic changes and salt retention that occur with an arteriovenous fistula are reminiscent of what occurs in cirrhotic humans (91). With an open fistula, peripheral vascular resistance falls, cardiac output increases, and diastolic and mean blood pressures fall. The proportionately greater increase in vascular capacitance over cardiac output results in a contracted EABV. Consequent sodium retention expands ECF volume, raises venous filling pressure, and further increases cardiac output until balance is achieved between cardiac output and lowered peripheral resistance. At this point, sodium intake equals excretion, EABV is normalized, and the patient is in balance.

In cirrhosis, a similar imbalance occurs between plasma volume and vascular capacitance such that EABV remains contracted and renal sodium retention is stimulated. In contrast to a simple arteriovenous fistula, however, several factors are present in cirrhosis that makes sodium balance more difficult to achieve. First, these patients often have impaired cardiovascular function (32). Diminished venous return consequent to tense ascites or cardiomyopathy from alcohol or malnutrition may limit increases in cardiac output. Furthermore, depression of left ventricular function in response to increased afterload suggests subclinical cardiac disease despite elevated forward output (188). Second, retained sodium does not remain in the vascular space and lead to increased venous return. Rather, retained sodium becomes sequestered within the abdomen as ascites. Third, increased vascular permeability may further impair ability of retained sodium to expand EABV. Peripheral arterial vasodilation in cirrhotic rats is associated with increased vasopermeability to albumin, electrolytes, and water (49). Examination of interstitial fluid dynamics by means of a subcutaneous plastic capsule reveals substantial increases in interstitial fluid volume early in cirrhosis before appearance of ascites or peripheral edema (287). Such capillary leakage impedes filling of the intravascular compartment and prevents replenishment of a contracted EABV.

Primary Arterial Vasodilation

Arteriovenous fistulas and formation or hyperdynamic perfusion of preexisting capillary beds are changes that develop as cirrhosis progresses. Nevertheless, salt retention occurs early in the cirrhotic process before these anatomic changes are fully established. Since sodium retention antedates the formation of overt ascites and portosystemic shunting, peripheral arterial vasodilation has been proposed to be a primary event in the initiation of sodium and water retention in cirrhosis (291). In this manner, a decreased EABV and increased vascular capacitance could still be the signal for renal salt retention even in the earliest stages of liver injury. The peripheral arterial vasodilation hypothesis is supported by several studies in animal models. In rats with partial ligation of the portal vein, evidence of a reduced systemic vascular resistance precedes the onset of renal salt retention (5). In addition, a direct correlation has been found between the onset of decreased arterial pressure and renal sodium retention in the spontaneously hypertensive rats with experimental cirrhosis (191). As opposed to the classical underfilling theory, the arterial vascular underfilling would not be the result of a reduction in plasma volume, which in fact is increased, but rather to a disproportionate enlargement of the arterial tree secondary to arterial vasodilation. In the rat with carbon tetrachloride–induced cirrhosis, the fall in peripheral vascular resistance and hyperdynamic circulatory state precede ascites formation suggesting that generalized vasodilation is indeed an early finding with hepatic injury (103).

Perhaps the best evidence to date in support of an underfilled circulation due to arterial vasodilation comes from human studies of HWI accompanied by infusion of a vasoconstrictor. HWI is associated with increased perfusion of the central circulation, however, urinary excretion rates of salt and water improve but do not normalize with this procedure alone (Fig. 4) (34). Since systemic vascular resistance falls during HWI, it was proposed that further vasodilation may prevent complete restoration of EABV in subjects already peripherally vasodilated. Infusion of a vasoconstrictor will increase peripheral vascular resistance but will do little to improve an underfilled central circulation. Predictably, infusion of norepinephrine alone into cirrhotic subjects fails to significantly increase urinary sodium excretion (299). By contrast, when norepinephrine is infused during HWI so as to increase central perfusion and at the same time attenuate the fall in systemic vascular resistance, sodium excretion increases significantly. In six subjects with decompensated cirrhosis, this combined maneuver was found to increase urinary sodium excretion to an amount that when extrapolated over a 24-hr period was greater than sodium intake (299). These results are consistent with the hypothesis that arterial vasodilation causes an abnormal distribution of the total blood volume such that effective central blood volume is reduced.

Splanchnic Arterial Vasodilation As alluded to earlier, arterial vasodilation is particularly marked in the splanchnic arteriolar bed (141, 288, 326). Increasing degrees of splanchnic vasodilation contribute to the fall in mean arterial pressure and unloading of baroreceptors in the central circulation (62). As a result, central afferent sensors signal the activation of neurohumoral effectors, which in turn decrease perfusion of other organs but in particular the kidney. The importance of splanchnic vasodilation in the genesis of renal ischemia has been indirectly illustrated by the response to ornipressin, an analog of AVP that is a preferential splanchnic vasoconstrictor (124, 177). The administration of ornipressin to patients with advanced cirrhosis leads to correction of many of the systemic and renal hemodynamic abnormalities that are present. These include an elevation in mean arterial pressure, reductions in plasma renin activity and norepinephrine concentration, and increases in renal blood flow, glomerular filtration rate, and urinary sodium excretion and volume. Similar benefits have been reported with the combined use of octreotide and midodrine (148).

Role of Nitric Oxide in Arterial Vasodilation The underlying cause of arterial vasodilation particularly in the early stages of cirrhosis has not been fully elucidated but a great deal of attention has been focused on humoral factors. Table 3 lists several vasodilators that have been proposed to play a role in the hyperdynamic circulation of cirrhosis. Of these, there is an increasing body of experimental and preliminary human evidence suggesting that increased nitric oxide production may be an important factor in this process. In both experimental models and in human subjects with cirrhosis, increased production of nitric oxide can be demonstrated (278, 304, 330). In the cirrhotic rat, evidence of increased production is already present when the animals begin to retain sodium and antedates the appearance of ascites (23). Administration of nitric oxide synthase inhibitor L-NMMA to cirrhotic human subjects improves the vasoconstrictor response to noradrenaline suggesting that overproduction of nitric oxide is an important mediator of the impaired responsiveness of the vasculature to circulating vasoconstrictors (48). In addition, this same inhibitor administered in low doses has been shown to correct the hyperdynamic circulation in cirrhotic rats (232). In a more recent study utilizing this same model, normalization of nitric oxide production was associated with a marked natriuretic and diuretic response as well as a reduction in the degree of ascites in cirrhotic rats (202).

The precise mechanism for increased nitric oxide production in cirrhosis is not known but may be mediated at least in part via the release of tumor necrosis factor-alpha (189). In experimental models of hepatic disease, for example, the administration of anti-TNF-alpha antibodies or an inhibitor of nitric oxide synthesis results in increases in splanchnic and total vascular resistance, an elevation in the mean arterial pressure, and a reduction in cardiac output toward or, with nitric oxide inhibition, to normal (189, 232). Similarly, blocking the signaling events induced by TNF and nitric oxide production, via inhibition of protein tyrosine kinase, ameliorates the hyperdynamic abnormalities in rats with cirrhosis and portal hypertension (190). Studies in cirrhotic humans with an increased cardiac output and systemic vasodilatation have shown evidence of enhanced nitric oxide production, a finding compatible with the experimental observations.

In patients with cirrhosis, portosystemic shunts and decreased reticuloendothelial cell function allow intestinal bacteria and endotoxin to enter the systemic circulation. Increased circulating endotoxin levels could be a potential stimulus for tumor necrosis factor-alpha and/or nitric oxide production. To test this possibility, Chin-Dusting et al. (54) examined the effect of administering a fluoroquinolone antibiotic on hemodynamics in a group of well-compensated human cirrhotic patients. It was postulated that the antibiotic would decrease the level of circulating endotoxin and nitric oxide and improve peripheral hemodynamics. At baseline patients with cirrhosis had increased basal forearm blood flow as compared to normal controls. Administration of the nitric oxide inhibitor, N^G-monomethyl-L-arginine decreased forearm blood flow both in normals and in cirrhotic patients, but the effect was greater in patients with cirrhosis. This increased response suggested that nitric oxide was responsible for peripheral vasodilation in the cirrhotic patients. Administration of the antibiotic to cirrhotic patients was found to normalize basal forearm blood flow as well as the response to N^G-monomethyl-L-arginine. This study is consistent with the notion that bacterial endotoxin originating in the intestine is an important factor in stimulating nitric oxide production, which in turn contributes to the arteriolar vasodilation in patients with cirrhosis.

It is not yet known with certainty whether the endothelial (eNOS) or the inducible (iNOS) isoform is primarily responsible for increased production of nitric oxide. It has been suggested that the hyperdynamic circulatory state of cirrhosis may increase shear stress and thereby provide a stimulus for the upregulation of eNOS (204, 330). Increased activity of nitric oxide synthase in polymorphonuclear cells and monocytes (cells that primarily contain iNOS) described in cirrhotic human subjects suggest that the inducible isoform may also play a role in increased production (204).

In summary, an underfill mechanism appears to explain the bulk of experimental as well as clinical findings in established cirrhosis (Fig. 7). Less certain are mechanisms responsible for sodium retention that precede the development of ascites. The overfill theory invokes the presence of a hepatorenal reflex sensitive to subtle rises in intrahepatic pressure mediating initiation of renal salt retention. However, the finding of decreased peripheral vascular resistance even at this early stage suggests diminished arterial filling (184). Early peripheral arterial vasodilation and later formation of anatomic shunts lead to disproportionate increases in vascular capacitance with subsequent contraction of EABV, thereby signaling renal salt retention. While it is conceivable that both overfill mechanisms and underfill mechanisms may be operative at different stages of disease, the multiplicity of data both clinical and experimental can be assimilated into an underfill theory.

TABLE 3 Potential Vasodilators in Cirrhosis

Nitric oxide
Glucagon
Calcitonin gene-related peptide
Atrial natriuretic peptide
Brain natriuretic peptide
Prostaglandins
Substance P
Adrenomedullin

Concept of Balance in Cirrhosis

In the earliest stages of cirrhosis when arterial vasodilation is moderate and the lymphatic system is able to return increased lymph production to the systemic circulation, renal

sodium and water retention are sufficient to restore EABV and thereby suppress neurohumoral effectors. Balance is reestablished such that sodium intake equals sodium excretion but at the expense of an increased ECF volume. As liver disease progresses this sequence of arterial underfilling followed by renal salt retention is repeated. As long as the EABV can be restored to near normal levels the activation of effector mechanisms will be moderated and balance will be achieved albeit at ever-increasing levels of ECF volume (Fig. 5). Eventually lymph production will begin to exceed the drainage capacity of the lymphatic system. At this stage of the disease renal salt retention becomes less efficient at restoring EABV as retained fluid is sequestered in the peritoneal cavity as ascites. At the same time arterial underfilling is more pronounced, particularly as splanchnic arteriolar vasodilation becomes more prominent. Activation of neurohumoral effectors is magnified resulting in more intense renal salt retention. Even at this stage of the disease cirrhotic patients with ascites eventually reestablish salt balance. The terminal stages of the cirrhotic process are characterized by extreme arterial underfilling. At this time there is intense and sustained activation of neurohumoral effectors. As a result, renal salt retention is nearly complete as the urine becomes virtually devoid of sodium. The vasoconstrictor input focused in on the kidney is of such a degree that renal failure begins to develop.

Effector Mechanisms in Cirrhosis

Nephron Sites of Renal Sodium Retention

Salt retention and impaired free-water clearance are characteristic disturbances in renal function in cirrhotic patients. Evidence is available to support an important role for proximal and distal nephron segments in mediating enhanced sodium reabsorption.

Proximal Nephron Indirect evidence supporting enhanced proximal salt reabsorption comes from studies in human cirrhotic subjects in which infusion of mannitol or saline improves free-water clearance (57, 290). Increased proximal tubular salt reabsorption leads to decreased delivery of filtrate to the distal diluting segments, thereby impairing free-water formation. Presumably, by restoring distal delivery of filtrate, mannitol and saline infusions result in increased solute free-water formation. Similar increases in free-water clearance occur when central hypervolemia is induced by HWI. The increase in urine Na is accompanied by increased K excretion, suggesting enhanced distal delivery of sodium. Increased water excretion seen in response to HWI combined with simultaneous infusion of norepinephrine is also consistent with baseline enhanced proximal sodium reabsorption in decompensated cirrhotics (299). Since plasma ADH fell to the same extent in both the combined maneuver and the HWI alone, it was concluded that augmented water excretion during the combined maneuver was attributable to increased distal delivery.

Renal sodium handling has also been assessed in cirrhotic patients with no peripheral edema or ascites (340). Proximal fractional reabsorption of sodium was estimated using clearance techniques in the presence of a hypotonic diuresis. In these patients, proximal fractional sodium reabsorption failed to decrease in response to saline loading. Similar findings were found in studies examining the magnitude of renal sodium absorption that remained after ethacrynic acid and chlorothiazide therapy (86). Diuretic-resistant sodium reabsorption was found to be greater in cirrhotic patients as compared to normal controls, suggesting stimulated proximal salt absorption.

Experimental models of cirrhosis have provided more direct assessment of nephron function. Micropuncture studies in rats made cirrhotic by ligation of the common bile duct demonstrated increases in both the proximal tubule solute reabsorption and the filtration fraction (15). Enhanced proximal reabsorption was attributed to increased peritubular oncotic pressure. The importance of renal hemodynamic factors in abnormal renal handling of salt and water is further highlighted in studies of dogs made cirrhotic by a similar mechanism (207). In those animals chronically ligated, intrarenal administration of the vasodilator acetylcholine was found to ameliorate the blunted natriuretic response to saline infusion. In this model, sodium reabsorption was enhanced in both the proximal and the diluting segments of the nephron (33).

Distal Nephron Clinical and experimental evidence also supports an important role for distal nephron sodium retention in cirrhosis. During hypotonic saline-induced diuresis, renal sodium excretion and solute free-water clearance were measured in order to estimate distal sodium load and distal tubular sodium reabsorption (55). When compared to controls, cirrhotic patients with ascites had similar distal sodium delivery but increased distal fractional sodium reabsorption. In cirrhotic patients manifesting a sluggish natriuretic response to HWI, phosphate clearance was found similar to a group who demonstrated an appropriate increase in urinary sodium excretion (100). Since phosphate clearance was used as a marker of proximal sodium reabsorption, it was concluded that distal sodium reabsorption contributed importantly to renal sodium retention in patients with a sluggish natriuretic response. The results of a prospective, double-blind study comparing the diuretic response of furosemide to spironolactone in cirrhotic patients with ascites suggest that salt absorption in the cortical collecting tubule is enhanced (253). When administered furosemide, only 11 of 21 patients exhibited a diuresis, while 18 of 19 patients responded to spironolactone. Furthermore, 10 patients who failed to respond to furosemide demonstrated a diuretic response to spironolactone. Furosemide inhibits sodium reabsorption in the loop of Henle, thereby increasing delivery to the collecting duct. All patients treated with furosemide had increases in the rate of potassium excretion including the 11 patients who failed to increase urinary sodium excretion. These results, combined with the clinical effectiveness of

spironolactone in treatment of cirrhotic ascites, suggest enhanced salt absorption in the aldosterone-sensitive cortical collecting tubule.

In summary, clinical and experimental studies suggest an important role for proximal as well as distal nephron sites mediating renal salt retention in cirrhosis. The relative contribution of different nephron sites to impaired salt and water excretion may depend on the degree to which systemic hemodynamics are altered. With each stage of advancing liver disease there becomes a greater contraction of the EABV. In the earliest stages of liver disease, enhanced proximal reabsorption limits distal delivery of solute in a manner analogous to a nonedematous subject with intravascular volume depletion. If distal delivery can be normalized at this early stage, distal nephron sites may continue to reabsorb sodium avidly and therefore appear as the primary site responsible for ECF volume expansion. With severe reductions in EABV, presumably the proximal nephron becomes the dominate site of fluid reabsorption such that the contribution of the distal nephron becomes much less apparent.

Sympathetic Nervous System

The sympathetic nervous system has been shown to importantly contribute to abnormalities in body fluid homeostasis in cirrhosis. Studies in rats made cirrhotic by ligating the common bile duct suggest that increased renal nerve activity is a major factor in the progressive salt retention that occurs in these animals (67, 72). In this model, baseline renal nerve activity is increased and fails to decrease appropriately in response to intravenous saline. Renal denervation significantly improves the impaired ability to excrete an oral or intravenous salt load. In addition, renal denervation has been shown to normalize the attenuated diuretic and natriuretic response to the intravenous administration of ANP (155). In chronic metabolic studies, renal denervation also leads to a significant improvement in the positive cumulative sodium balance. The cause of the increased renal nerve activity is multifactorial. Recent studies have demonstrated an impairment in aortic and cardiopulmonary baroreceptor regulation of efferent renal nerve activity (276). In dogs with chronic bile duct ligation, renal nerve activity fails to decrease in response to high NaCl food intake (205). This defect has been attributed to abnormalities in hepatic NaCl-sensitive receptors or their immediate intrahepatic afferent connections.

Studies in human cirrhotic subjects are more indirect but also suggest an important role for the sympathetic nervous system. Levels of norepinephrine in patients with cirrhosis vary from normal to elevated. When measured in decompensated cirrhosis, levels are high and are inversely correlated with urinary sodium excretion (36). Confirming that plasma norepinephrine levels are in fact an index of sympathetic activity and not simply the result of impaired clearance, measurement of hepatic extraction of norepinephrine has been found normal in decompensated cirrhosis (230). In addition, direct measurement of peripheral nerve firing rates show evidence of increased central sympathetic activity. Patients characterized by impaired ability to excrete water loads have plasma levels of norepinephrine that correlate positively with levels of ADH, aldosterone, and plasma renin activity (36). Decreased EABV leads to baroreceptor-mediated activation of sympathetic nerve activity with subsequent enhancement of proximal salt reabsorption. Renal nerve-mediated decrease in sodium delivery to the diluting segment in addition to nonosmotic release of ADH contributes to the inability to maximally excrete water loads. Furthermore, increased renal nerve activity can indirectly enhance distal sodium reabsorption by stimulating renin release with subsequent formation of aldosterone. If baroreceptor-mediated increases in adrenergic activity are triggered by diminished EABV, then expansion of central blood volume should have a favorable effect in lowering plasma norepinephrine. In addition, decreased levels of norepinephrine should be associated with an improvement in renal salt and water excretion. In this regard, cirrhotic patients subjected to HWI demonstrate significant suppression of plasma norepinephrine levels (230). Moreover, during HWI there is a significant correlation between right atrial pressure, the decrement in plasma norepinephrine, and increase in fractional excretion of sodium (34).

However, other studies have not found a clear cut association between decreased circulating catecholamines and an improved renal excretory response. In a study of patients with decompensated cirrhosis subjected to HWI, there was a striking increase in creatinine clearance and a variable natriuresis that occurred independently of changes in plasma norepinephrine levels (95). Similarly, administration of the α_2 agonist, clonidine, inhibited renal sympathetic nerve activity and increased GFR and urine flow, but did not increase urinary sodium excretion (101). In another study of cirrhotic patients, clonidine was found to decrease the concentration of norepinephrine in the right renal vein but did not change GFR or urinary sodium excretion (280). These studies suggest that while sympathetic nerve activity is increased in cirrhosis, it is not the sole mechanism responsible for impaired salt and water excretion.

In addition to stimulating renal salt and water retention, increased sympathetic tone may also contribute to the renal vasoconstriction that characterizes the cirrhotic state (76, 275). Renal nerves are also likely to be one of several factors responsible for the intense vasoconstriction that characterizes the hepatorenal syndrome (20). Activation of the sympathetic nervous system may serve as a compensatory response to cirrhosis-induced vasodilation. In cirrhotic patients, infusion of the adrenergic blocking agent phentolamine into the renal artery resulted in systemic hypotension (94). The heightened sensitivity of blood pressure to phentolamine infusion is consistent with an important role of sympathetic nerves in maintaining vascular tone.

In summary, the sympathetic nervous system is activated under conditions of decompensated cirrhosis. Overactivity of this system is the result of a contracted EABV.

In addition, there is impaired regulation of sympathetic outflow due to abnormalities in several afferent sensing mechanisms. Increased renal nerve activity contributes to the cumulative salt retention that accompanies advancing liver disease. In addition, activation of sympathetic outflow plays an important compensatory role in maintaining vascular tone in the setting of decreased vascular resistance.

Aldosterone

In patients with cirrhosis and ascites, plasma concentrations of aldosterone are frequently elevated. Although aldosterone metabolism is impaired in liver disease, secretion rates are greatly elevated and are the major cause of elevated levels (279). The relationship between hyperaldosteronism and sodium retention is not entirely clear. Several studies have provided evidence that argues against an important role of aldosterone in mediating salt retention in cirrhosis. For example, patients treated with an aldosterone synthesis inhibitor do not necessarily exhibit a natriuretic response (279). In one study, renal salt excretion and changes in plasma renin and aldosterone levels were examined in 11 patients with ascites subjected to 5 days of high-salt intake. In patients with normal suppression of renin and aldosterone, salt retention and weight gain occurred to the same extent as patients who had persistent hypersecretion of renin and aldosterone (58). In addition, cirrhotic patients in positive sodium balance as compared to controls with matched sodium excretion have increased fractional distal sodium reabsorption despite lower plasma aldosterone levels. In 16 cirrhotic patients subjected to HWI, plasma renin activity and plasma aldosterone levels were found to decrease promptly. Despite suppression of the hormones, however, half of the patients manifested a blunted or absent natriuretic response (97). In another group of cirrhotic patients with ascites and edema, HWI induced a significant natriuresis despite acute administration of desoxycorticosterone, suggesting that enhanced sodium reabsorption can occur independently of increased mineralocorticoid activity.

In contrast, a number of observations support aldosterone as an important factor in the pathogenesis of sodium retention in patients with cirrhosis. For example, adrenalectomy or administration of a competitive inhibitor of aldosterone increases urinary sodium excretion (87). Patients who fail to manifest a diuretic response to furosemide tend to have higher renin and aldosterone levels and lower urinary sodium concentrations prior to treatment (33). Inability of furosemide to increase urinary sodium in these patients may result from reabsorption of delivered sodium in the collecting tubule under the influence of aldosterone. Similarly, patients with the highest renin and aldosterone levels are those who fail to diurese in response to HWI (97, 228). In order to more clearly define the relationship between sodium excretion and plasma aldosterone levels, patients with decompensated cirrhosis were subjected to HWI in combination with infused norepinephrine (229). It was hypothesized that in the setting of decreased EABV, inability to escape from the sodium-retaining effects of aldosterone results from enhanced proximal sodium reabsorption and therefore decreased distal sodium delivery. Use of HWI combined with norepinephrine so as to maintain peripheral vascular resistance provides the most effective means of increasing central blood volume and restoring EABV (299). In this study, the combined maneuver resulted in the largest negative sodium balance and suppressed plasma renin activity and aldosterone levels to a greater extent than HWI or norepinephrine alone.

As with the conflicting data regarding the role of the proximal and distal nephron in salt retention discussed previously, the degree to which systemic hemodynamics and EABV are impaired may explain some of the conflicting data noted above. It is possible that in patients with the greatest contraction of EABV intense proximal sodium reabsorption limits distal delivery to such an extent that the contribution of aldosterone to increase salt absorption is difficult to detect. By contrast, with less impairment of the EABV, distal delivery is better maintained such that the aldosterone-mediated sodium reabsorption becomes more obvious. In this regard, aldosterone has been shown to contribute to the exaggerated salt retention that occurs in the upright position in patients with early cirrhosis without ascites (30).

Prostaglandins

The observation that nonsteroidal anti-inflammatory drugs decrease GFR, renal blood flow, and sodium excretion in cirrhotics suggests that prostaglandins may serve a protective role. Ligation of the common bile duct in dogs results in enhanced synthesis of vasodilatory prostaglandins. When prostaglandin synthesis is inhibited with indomethacin, renal blood flow and GFR are reduced significantly (344). A similar protective effect may be present in cirrhotic humans (41). Administration of indomethacin to patients with alcoholic liver disease results in reduced effective renal plasma flow and creatinine clearance. These parameters were corrected when prostaglandin E1 was infused intravenously (41).

Prostaglandins may also importantly influence renal salt and water handling in cirrhosis. Patients pretreated with indomethacin exhibit a blunted natriuretic response to diuretics known to increase renal prostaglandin synthesis (213). In comparison to normal controls, patients with decompensated cirrhosis subjected to HWI demonstrate a threefold greater increase in PGE excretion, which is accompanied by increased creatinine clearance and sodium excretion (98). In subjects with ascites, impaired ability to clear free water is associated with lower urinary PGE2. Intravenous infusion of lysine acetylsalicylate reduced the clearance of free water, while GFR was variably affected. Diminished synthesis of prostaglandins may leave vasopressin-stimulated water reabsorption unopposed, thereby reducing free-water clearance. Prostaglandins may also participate in blood pressure homeostasis. In cirrhotic patients, the pressor response to infused Ang II is impaired. Administration of either indomethacin or ibuprofen results in significant decreases in renin

and aldosterone levels and restores pressor sensitivity to infused Ang II (347).

In summary, prostaglandins function in a protective role in decompensated cirrhosis. Similar to other hypovolemic states, prostaglandins act to maintain renal blood flow and GFR by ameliorating pressor effects of Ang II and sympathetic nerves (244). These agents may also serve to mitigate the impairment in free-water clearance that would otherwise occur from unopposed activity of AVP. Administration of prostaglandin inhibitors can partially correct excessive hyperreninemia and hyperaldosteronism and restore the pressor response to Ang II.

Kallikrein-Kinin System

Urinary kallikrein activity is increased in cirrhotic patients with ascites and preserved GFR, while urinary activity decreases in association with impaired renal function (252). The correlation between renal plasma flow and GFR suggests that the renal kallikrein-kinin system may contribute to maintenance of renal hemodynamics in cirrhosis.

At the level of the renal tubule bradykinin has been shown to exhibit a natriuretic effect. However, bradykinin also is a potent peripheral vasodilator and can cause microvascular leakage. In cirrhosis, these later effects could exacerbate an already contracted EABV and cause further salt retention. MacGilchrist et al. (198) studied the effects of kinin inhibition by systemically infusing aprotinin (a strong inhibitor of tissue kallikrein) into a group of patients with cirrhosis. This infusion was associated with a doubling of urinary sodium excretion and an increase in renal plasma flow and GFR. This beneficial effect on renal function in the setting of kinin inhibition was attributed to an improvement in systemic hemodynamics as systemic vascular resistance increased. Similarly, administration of a bradykinin β_2 receptor antagonist to cirrhotic rats normalized renal sodium retention and reduced the activity of the renin-angiotensin-aldosterone system (334). Inhibiting bradykinin-induced microvascular leakage and lessening the degree of vascular underfilling was felt to be the mechanism of the beneficial effect.

Natriuretic Peptides

The role of ANP in the pathogenesis of edema in hepatic cirrhosis remains undefined. While atrial ANP content was reduced in cirrhotic rats, most data indicate ANP levels are either normal or elevated in cirrhotic humans (143, 301). Elevated levels are the result of increase cardiac release rather than just impaired clearance. The cause of the high levels is not understood, because atrial pressure is normal and central blood volume is reduced. Stimulating the endogenous release of ANP induces a natriuretic response in some patients with cirrhosis, while other patients are insensitive (301). However, both groups of patients exhibited an increase in urinary cGMP suggesting that the kidney is still capable of responding to ANP even in the absence of a natriuretic effect (301).

Several potential mechanisms may account for ANP resistance in cirrhosis. This resistance could be the result of a defect intrinsic to the kidney or could be the result of altered systemic hemodynamics leading to activation of more potent sodium-retaining mechanisms (199). With regards to the first possibility an altered density of glomerular ANP binding sites has been demonstrated in the bile duct-ligated rat model of cirrhosis (111). In addition, ANP resistance was found in the isolated perfused kidney taken from sodium avid rats with cirrhosis induced by carbon tetrachloride (247). This preparation allows systemic and hormonal factors to be excluded. In the chronic caval dog model of cirrhosis, intrarenal infusion of bradykinin restored ANP responsiveness to previously resistant animals suggesting that an intrarenal deficiency of kinins could be a contributing factor (175).

Other studies have focused on systemic hemodynamics as a cause of ANP resistance. With each stage of advancing liver disease there becomes a greater reduction in EABV. Since ANP resistance tends to occur with more severe and advanced disease it is possible that ANP resistance is directly related to the impairment in EABV. Decreased EABV is associated with enhanced proximal reabsorption of solute. As a result, ANP resistance may be due to decreased delivery of salt to the site where ANP exerts its natriuretic effect. In support of this possibility, ANP resistance could be restored in cirrhotic rats by infusions of vasopressors so as to normalize arterial pressure and presumably improve the decrease in EABV (192). In human cirrhotics, ANP responsiveness can be markedly improved when distal sodium delivery is increased by administration of mannitol (220).

Circulating brain natriuretic peptide (BNP) levels are also increased in patients with cirrhosis (173). Infusion of BNP at a dose that elicits an increase in GFR, renal plasma flow, and urinary sodium excretion in normal controls has no effect in cirrhotic humans. The infusion is associated with an increase in urinary cGMP as well as a fall in plasma aldosterone levels suggesting that the peptide is capable of interacting with its receptor in these patients. As with ANP, the lack of natriuretic response to BNP may be due to overactivity of other antinatriuretic factors as well as decreased delivery of sodium to its tubular site of action.

Adrenomedullin is a peptide with vasodilatory properties that is highly expressed in cardiovascular tissues. Increased circulating levels that correlate with severity of disease have been described in patients with cirrhosis (104). Urodilatin is a natriuretic factor that is exclusively synthesized within the kidney. Unlike other natriuretic factors, levels are not increased in patients with cirrhosis (285).

Endothelin

Increased circulating levels of endothelin have been reported in cirrhosis (219). The stimulus and pathophysiologic significance of these levels is not known with certainty. The peptide may play a role in the renal vasoconstriction seen in the hepatorenal syndrome (117, 219).

Therapeutic Implications for Treatment of Salt Retention in Cirrhosis

Renal salt retention is the most common abnormality of renal function in chronic liver disease. Whenever urinary sodium excretion falls to an amount less than dietary salt intake ECF volume will begin to expand and eventually lead to the development of ascites and peripheral edema. The approach to the treatment of the cirrhotic patient with ascites is to alter sodium balance in such a way that urinary sodium excretion exceeds dietary salt intake. In this manner, ECF volume will contract. The ultimate goal is to reestablish salt balance at an ECF volume that is clinically associated with the absence of ascites and peripheral edema. The initial step in achieving this goal is to restrict dietary sodium intake. A reasonable starting point is a 88 mEq (2 g) sodium diet (281). Such a regimen can lead to negative salt balance in patients with high levels of baseline urinary sodium excretion (at least >90–100 mEq/day). In such patients, salt restriction alone may lead to resolution of ascites.

Diuretic Therapy

In patients with a low level of baseline urinary sodium excretion, dietary salt restriction alone is usually not sufficient to induce negative salt balance. In this situation, diuretic therapy is indicated. Spironolactone is the most commonly used first-line agent for several reasons. First, while normally considered a weak diuretic, spironolactone is oftentimes found to be more clinically effective that loop diuretics in some patients with advanced disease. Under normal circumstances, loop and thiazide diuretics are secreted into the proximal tubular lumen where they travel down stream and exert their natriuretic effect. In the setting of cirrhosis, decreased renal blood flow can limit delivery of these agents to the site of secretion in the proximal nephron. In addition, accumulation of compounds such as bile salts may compete or directly impair the secretory process. The net effect is that there is less delivery of the diuretic to its site of action and the natriuretic effect is limited. By contrast, spironolactone does not require tubular secretion. Rather, this agent enters the cells of the collecting tubule from the blood side. As a result, the efficacy of spironolactone is not impaired with cirrhosis. Second, spironolactone is a potassium sparing diuretic and therefore unlike loop or thiazide diuretics does not cause hypokalemia. The avoidance of hypokalemia is important in the management of cirrhotic patients as potassium depletion can contribute to the development of hepatic encephalopathy. Hypokalemia can lead to increased blood ammonia levels as a result of a stimulatory effect on renal ammonia synthesis as well as increased gastrointestinal absorption of nitrogen secondary to decreased bowel motility.

In patients who fail to develop a significant diuretic response to spironolactone alone, a thiazide diuretic can be added, the dose being determined by the level of renal function. If diuresis is still inadequate, a loop diuretic such as furosemide can be given in combination with the thiazide and spironolactone.

When attempting to initiate diuresis, caution is necessary to avoid excessive volume removal. The rate at which fluid can safely be removed in cirrhosis is dependent upon the presence or absence of peripheral edema. When a diuresis is induced, the fluid is initially lost from the vascular space; the ensuing fall in intravascular pressure then allows the edema fluid to be mobilized to replete the plasma volume. Edema mobilization is relatively rate-unlimited in patients with peripheral edema (263). In comparison, patients who only have ascites can mobilize edema fluid solely via the peritoneal capillaries. The maximum rate at which this can occur is only 300 to 500 ml/day; more rapid fluid removal in the absence of peripheral edema can lead to plasma volume depletion and azotemia.

Diuretic-Resistant Patients

Large-Volume Paracentesis Patients who fail to respond to a combination of dietary salt restriction and diuretic therapy are said to be diuretic resistant. These patients are in a state of persistent positive sodium balance and require a more invasive intervention in order to achieve negative salt balance. Large volume paracentesis is a procedure in which negative salt balance is established acutely by removing some or the entire volume of ascitic fluid. In patients with virtually no sodium in the urine and who are consuming 88 mEq of sodium per day, tense ascites can be avoided in most patients by removing approximately 8 liters of fluid every 2 weeks (282, 283). With some urinary sodium present the time interval required for repeat paracentesis can be extended, while excessive dietary sodium intake will tend to shorten the time interval between procedures.

Large volume paracentesis has been proven to be a safe and effective means to manage cirrhotic patients with tense ascites. In addition to cosmetic and symptomatic benefits, removal of ascites lowers intraabdominal pressure (265). Intrathoracic pressure also falls as a result of increased mobility of the diaphragm. These changes are associated with a reduction in portal pressure, increased cardiac output, decreased activation of neurohumoral effector mechanisms, and a slight improvement in the serum creatinine concentration (194, 265). These effects are transient in nature returning to baseline values by 6 days. Large volume paracentesis has also been shown to reduce intravariceal pressure and variceal wall tension (169).

The need to administer albumin in conjunction with large-volume paracentesis is controversial. The rational for administering albumin would be to minimize effective intravascular volume depletion and renal impairment that could potentially develop as ascitic fluid reaccumulates. Gines et al. (116) studied 105 patients with tense ascites undergoing large-volume paracentesis and randomized the subjects to receive albumin (10 g/liter of ascites removed) or no albumin. Patients not receiving albumin were more likely to show signs of hemodynamic deterioration including an increase in

the plasma renin activity; these patients were also much more likely to develop worsening renal function and/or severe hyponatremia (116). More recently, Gines et al. performed total paracentesis in 280 patients with tense ascites and randomized the subjects to replacement with different types of colloid to include albumin, dextran 70, or polygeline (115). Postparacentesis circulatory dysfunction (defined as a >50% increase in plasma renin activity 6 days after the procedure) developed in 85 patients. Of the various replacement fluids, postparacentesis circulatory dysfunction was much less common with albumin administration (19% vs 34% and 38%, respectively). This benefit was limited to patients in whom at least 5 liters of ascitic fluid was removed.

Other studies have shown that large-volume paracentesis can be performed without a deleterious effect on systemic or renal hemodynamics even though albumin has not been given (250, 261). In addition, there is no direct evidence that such replacement therapy impacts on the long term morbidity and mortality of patients with cirrhosis and ascites (217, 282, 283).

Peritoneovenous Shunting Peritoneovenous shunting has been used in the treatment of diuretic-resistant ascites. This procedure allows for ascites to be reinfused into the vascular space by way of the internal jugular vein. In patients with refractory ascites and renal failure due to the hepatorenal syndrome, peritoneovenous shunting has been associated with increased urinary sodium excretion and improved renal function (96, 314). However, the procedure is now rarely performed due to a high complication rate and the lack of survival advantage when compared to medical therapy (114, 308).

Transjugular Intrahepatic Portosystemic Shunt Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is a procedure that lowers intrahepatic and portal pressure. TIPS has primarily been employed as a treatment to control variceal bleeding but also appears to be an effective therapy in refractory ascites. In uncontrolled studies, TIPS has been shown to exert a diuretic effect sufficient enough to reduce and in some cases eliminate the presence of ascites (235, 305). In patients who respond, the dose of diuretics subsequently needed to control ascites can be markedly reduced (235, 305). The maximal benefit on renal function and urinary sodium excretion is often not seen for several weeks following the procedure (338). This delayed natriuretic effect may be related to the increased systemic vasodilation that typically develops immediately after insertion of the shunt (338, 339). This vasodilatory response may be due to increased delivery of vasodilators such as nitric oxide from the splanchnic circulation to the systemic circulation (339). In a small series of patients with hepatorenal syndrome, TIPS was found to improve renal function and reduce the activity of several vasoconstrictor systems (123). Despite the apparent benefit, a recently published randomized controlled trial comparing TIPS to paracentesis found that patient mortality was higher in the TIPS group, particularly in patients with Child-Pugh class C (174). In addition, TIPS placement is associated with a variety of complications that include encephalopathy and stent thrombosis or stenosis (286).

Summary

The sequence in which the various therapies discussed above are instituted can be viewed as a continuum that parallels the severity of the underlying cirrhotic state (Fig. 8). In the earliest stages of the disease, urinary sodium excretion is plentiful and negative salt balance can be achieved by simply

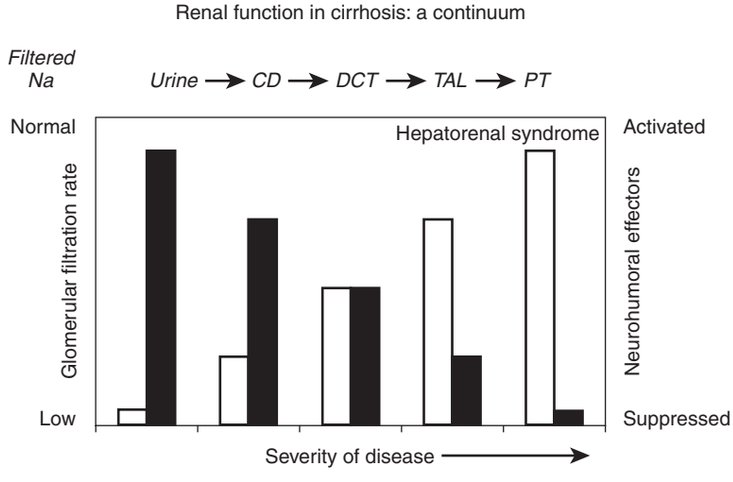

FIGURE 8 The fall in glomerular filtration rate (*solid bars*) and activation of neurohumoral effectors (*open bars*) can be viewed as a continuum that varies according to severity of the underlying cirrhotic process. As the disease advances, the urinary Na concentration falls. The filtered load of Na is completely reabsorbed at progressively more proximal sites along the nephron. A patient with hepatorenal syndrome is merely at the end of this continuum when the glomerular filtration rate has fallen sufficiently to cause significant azotemnia.

lowering dietary sodium intake. As the disease advances neurohumoral effectors become more activated initially resulting in more intense renal salt retention and later in a progressive decline in renal function. Eventually the filtered load of sodium becomes completely reabsorbed by the tubule such that the final urine becomes virtually devoid of salt. If some component of the filtered load reaches the collecting duct or beyond, spironolactone will be effective in increasing urinary sodium excretion. Once sodium reabsorption is complete proximal to the collecting duct then thiazides and later loop diuretics will have to be added to spironolactone in order to increase urinary sodium excretion. Eventually the filtered load is completely reabsorbed proximal to the thick ascending loop of Henle. At this point the patient is resistant to the effects of diuretics and requires more invasive procedures such as repetitive large-volume paracentesis in order to remain in salt balance. In the terminal stages of the disease, the glomerular filtration rate falls to such a degree that oliguria, azotemia, and eventually uremia are present and the patient is clinically diagnosed with hepatorenal syndrome. Vasoconstrictive input focused on the kidney is severe. The renal failure is functional in nature, however, since restoration of near normal renal function can be obtained following a liver transplant.

NEPHROTIC SYNDROME

The development of edema is one of the cardinal features of nephrotic syndrome. The mechanism of its formation is not entirely understood. The classical view of edema formation in the nephrotic syndrome describes the process as an underfill mechanism. According to this theory, urinary loss of protein results in hypoalbuminemia and decreased plasma oncotic pressure. As a result, plasma water translocates from the intravascular space into the interstitial space. When the magnitude of this transudation is sufficiently great, clinically detectable edema develops. Reduction in intravascular volume elicits activation of effector mechanisms that signal renal salt and water retention in an attempt to restore plasma volume. The renal response leads to further dilution of plasma protein concentration thereby exaggerating the already reduced plasma oncotic pressure and further enhancing edema formation. In order for this formulation of edema genesis to be true, three critical predictions must be satisfied: (1) blood and plasma volume must be reduced during accumulation of edema; (2) measurement of neurohumoral effectors should reflect activation consequent to contraction of effective arterial blood volume; and (3) maneuvers that increase plasma volume into the normal range should result in a natriuretic response. As discussed below, these predictions are satisfied in some patients, especially those with minimal-change nephrotic syndrome, whereas the majority of nephrotic patients fail to conform to this conceptual model.

Blood and Plasma Volume in Nephrotic Syndrome

The classical view of edema formation assigns a pivotal role to decreased plasma volume serving as the afferent mechanism signaling renal salt and water retention. When measured directly plasma volume has indeed been low in a variable proportion of patients with nephrotic syndrome (171, 209, 319). Even in patients judged to be normovolemic, an exaggerated fall in plasma volume has been observed when nephrotic patients go from the recumbent to standing position (88, 146). This orthostatic reduction in plasma volume can be profound and may, in part, explain the development of acute oliguric renal failure and hypovolemic shock that has been reported in patients with nephrotic syndrome (302).

Most studies, however, have failed to find a consistent reduction in blood and plasma volume in patients with nephrotic syndrome (79, 89, 110, 160). In a survey of 10 studies, plasma volume measurements were analyzed in 217 nephrotic patients (80). In only one-third of patients was plasma volume reduced, whereas it was normal in 42% and increased in 25%. It has been suggested that conflicting measurements of plasma volume in patients with nephrotic syndrome can be reconciled by separating patients according to histologic class (208). In this regard, one study compared the volume status of four patients with minimal change disease to that in five patients with membranous or membranoproliferative lesions (208). In patients with minimal change disease, plasma volume was decreased and plasma renin activity and aldosterone levels were increased. By contrast, plasma volume was either normal or increased and plasma renin activity was suppressed in the latter group. These authors concluded that edema formation in minimal change disease was primarily the result of decreased effective circulatory volume inciting secondary renal salt retention. By contrast, patients with more distorted glomerular architecture were felt to have a primary defect in renal salt excretion leading secondarily to an expanded plasma volume and eventually formation of edema.

Other studies have failed to find such a correlation between histology and plasma volume measurements. Even in patients with untreated minimal change disease, plasma volume has been found to be increased (80). In order to avoid potential methodologic problems, a recent study first established a reference frame for blood volume that was normalized to lean body mass and measured directly from plasma volume and red cell volume in otherwise normal children (328). Blood volume measurements in children with nephrotic syndrome due to minimal change disease as well as other histologic lesions were all found to be within this defined normal range. Following successful therapy with steroids, patients with minimal change disease demonstrate a fall in plasma volume and blood pressure and an increase in plasma renin activity (80). These changes are exactly the opposite of what one would expect if arterial underfilling were the proximate cause of renal salt retention. Finally, a

large study of nephrotic patients, including 35 patients with minimal change disease, found virtually all patients have normal or increased plasma and blood volume (109).

Neurohumoral Markers of Effective Circulatory Volume

Measurements of plasma renin activity and aldosterone concentration have been utilized as a method to indirectly differentiate primary sodium retention from an underfill mechanism of edema formation in nephrotic patients. Elevated values would be expected if blood volume was decreased, while suppressed values would occur in the setting of primary renal sodium retention and blood volume expansion. In this regard, plasma renin activity values collated from nine studies were found to be normal or low in 64 of 123 patients investigated (79). Plasma aldosterone levels were also decreased in the majority of these patients. When measured with respect to salt intake or urinary sodium excretion no consistent relationship was found. While some studies have found elevated plasma renin activity and aldosterone concentrations in patients with minimal change diseases others have not (127, 208). In a study examining plasma renin activity with respect to blood volume, no relationship was found in either patients with minimal change disease or those with histologic lesions on light microscopy (110). Although a higher proportion of patients with minimal change disease have elevated plasma renin and aldosterone levels as compared to those with histologic glomerular lesions these values tend to overlap (110, 127). Thus, measurement of various elements of the renin-angiotensin-aldosterone axis suggests that an underfill mechanism may mediate renal sodium retention in some but not all patients with nephrotic syndrome.

Effects of Manipulations to Expand Central Blood Volume

Another approach utilized to investigate the pathogenesis of sodium retention in the nephrotic syndrome has been to examine renal sodium handling and hormonal indices of effective circulatory volume in response to expansion of the intravascular blood volume. This has been primarily achieved by infusing albumin or expanding central blood volume by head-out body water immersion (HWI). The classical view of nephrotic edema would predict that expansion of the intravascular volume should correct renal salt and water retention. In children with minimal change disease, infusion of albumin has been reported to decrease plasma renin activity, arginine vasopressin (AVP), aldosterone, and catecholamines (272, 316). In association with these hormonal changes, there was a significant increase in the glomerular filtration rate, urine flow, and sodium excretion. In a less homogenous group of adult patients with nephrotic syndrome, baseline blood volumes were found to be low when expressed per kilogram wet weight (320). Plasma AVP was inversely correlated with blood volume and failed to decrease in response to a water load. When blood volume was expanded with 20% albumin, plasma levels of AVP fell accompanied by an augmented water diuresis. It was concluded that a contracted blood volume was responsible for the nonosmotic release of AVP. By contrast, other studies have found either no or only a minimal increase in urinary sodium excretion in response to infusion of albumin. In one study, infusion of hyperoncotic albumin in quantities sufficient to expand blood volume by 35% resulted in only a modest natriuretic response (160). In order to exclude the possibility that the blunted natriuretic response was due to an increase in peritubular colloid osmotic pressure, similar studies have been performed utilizing a prolonged infusion of iso-oncotic albumin. This maneuver was similarly accompanied by only a modest increase in sodium excretion such that the patients remained in positive salt balance (270). Studies utilizing HWI to expand blood volume have likewise produced conflicting results. Expansion of central blood volume by HWI in children with minimal change disease resulted in decreased levels of AVP, aldosterone, noradrenaline and plasma renin activity (272, 273). These changes were accompanied by significant increases in urine flow and sodium excretion. Similarly, adult patients with a variety of histologic lesions subjected to HWI were found to have significant increases in urinary sodium excretion (28, 170). By contrast, a more recent study in 10 patients with a variety of underlying glomerular diseases found only a blunted natriuretic response to HWI (257). While ANP levels rose to the same extent in control and nephrotic subjects suggesting equivalent degrees of volume expansion, peak urinary sodium excretion and urine flow in the nephrotic patients were one-third that in the control group.

A number of other observations also question the pivotal role assigned to hypoalbuminemia and reduced plasma oncotic pressure in the initiation of edema formation (10, 145, 146). For example, reducing plasma protein concentration in humans (10) or experimental animals (145, 146) with plasmapheresis results in either no change or actually increases plasma volume. In addition, patients with congenital analbuminemia demonstrate no disturbance in water and electrolyte balance and do not necessarily develop edema. Despite the reduction in plasma oncotic pressure, these patients exhibit an exaggerated natriuretic response when administered isotonic saline.

In summary, available data would argue for a contracted plasma volume as the afferent mechanism initiating sodium retention in some but not all patients with nephrotic syndrome. Rather, some component of primary renal sodium retention appears to be operative in nephrotic syndrome with histologic glomerular lesions as well as in many patients with minimal change disease (Table 4). Although children with minimal change nephrotic syndrome more often have low blood volume and increased renin-aldosterone profiles, coexistence of a primary impairment in renal sodium excretion cannot be excluded. In this regard, the natriuresis seen in patients recovering from minimal change disease occurs

TABLE 4 Evidence for Primary Renal Sodium Retention in Nephrotic Syndrome

Blood volume is often normal or increased.
Blood pressure is often increased.
Renin activity and aldosterone levels are not uniformly increased.
Onset of natriuresis during recovery precedes rise in plasma protein concentration.
Sodium excretion is modest in response to head-out water immersion or albumin infusion.
Experimental models
Sodium retention in a unilateral nephrosis model is confined to the diseased kidney.
Kidneys taken from nephrotic animals and perfused in vitro retain Na.

concurrently with a rise in filtration fraction (157). If an underfill mechanism were operative, one would have expected the baseline filtration fraction to be increased and then to fall with successful treatment. In addition, resolution of salt retention in response to steroid treatment has been shown to occur in the setting of persistent hypoproteinemia (46). Furthermore, the natriuresis and correction of the antinatriuretic neurohumoral profile demonstrated in studies using albumin infusions and HWI may have resulted from central blood volume expansion of a sufficient degree necessary to overcome a primary salt retaining state. Studies in experimental animals are also consistent with a defect intrinsic to the nephrotic kidney as the mechanism responsible for salt retention in the nephrotic syndrome. In the rat model of unilateral proteinuric renal disease induced by infusing puromycin aminonucleoside (PAN) into one kidney, diminished urinary sodium excretion was confined to the proteinuric kidney despite the fact that each kidney shared the same systemic milieu (138). In kidneys taken from rats previously exposed to PAN and then perfused in vitro, less sodium was excreted as compared to kidneys taken from control rats. Utilizing this experimental design, the defect in renal salt excretion was found to be localized to the kidney as systemic and circulating factors were eliminated.

In some patients, both primary salt retention as well as underfill mechanisms of edema formation may coexist. For example, in the earliest stages of a glomerular disease salt retention by the kidney may be primary in origin. As hypoalbuminemia develops and becomes progressively severe, plasma volume may fall and result in an element of superimposed secondary salt retention. The coexistence of these two mechanisms may account for the lack of uniformity in hemodynamic as well as hormonal and neurocirculatory profiles in patients with nephrotic syndrome.

Peripheral Capillary Mechanisms of Edema Formation

The presence of normal or increased plasma volume in the setting of a decreased serum albumin concentration is difficult to reconcile with the classical view of edema formation in the nephrotic syndrome. These findings can best be explained by examining the alterations that are known to occur in transcapillary exchange mechanisms in the setting of hypoproteinemia.

Fluid movement within the capillary bed between intravascular and interstitial spaces is determined by the balance of Starling forces between these two compartments:

$$J_v = K_f[(P_c - P_i) - (\pi_c - \pi_i)]$$

where J_v is fluid flux along the length of a capillary, K_f is the ultrafiltration coefficient, P_c is capillary hydrostatic pressure, P_i is interstitial hydrostatic pressure, π_c is capillary oncotic pressure, and π_i is interstitial oncotic pressure. On the arterial side of the capillary, the net hydrostatic pressure gradient $P_c - P_i$ (P) exceeds the net colloid osmotic pressure gradient $\pi_c - \pi_i$ (π) resulting in net filtration of fluid into the interstitial space. Due to an axial fall in capillary hydrostatic pressure, the balance of Starling forces at the venous end of the capillary ($\pi > P$) favors net reabsorption of fluid back into the capillary. In some tissues, net hydrostatic pressure exceeds opposing net colloid osmotic pressure throughout the length of the capillary such that filtration occurs along its entire length. Net ultrafiltrate is returned to the circulation via lymphatic flow such that in steady-state conditions total body capillary flux is equal to lymph flow; interstitial and intravascular volume remain stable and edema formation does not occur.

Absence of compensatory mechanisms would predict that small changes in P, π, or K_f would lead to increased fluid transudation and result in clinically detectable edema. However, the poor correlation between plasma albumin concentration and the presence or absence of edema suggests that counterregulatory adjustments do occur in those forces that govern fluid exchange between the intravascular and interstitial space (Table 5). One such factor relates to compliance characteristics of the interstitium (126). Under normal circumstances interstitial pressure ranges from −6 mm Hg to 0 mm Hg. Due to the noncompliant nature of this compartment small increases in interstitial volume result in large increases in interstitial pressure. Such increases in P_i act to oppose further transudation of fluid and provide an initial defense against the formation of edema. Increased interstitial pressure leads to the development of a second factor that also protects against edema formation, namely, increased lymphatic flow. Lymph flow can increase many fold under conditions of augmented net capillary fluid filtration. In patients with edema resulting from heart failure or nephrosis, the disappearance rate of a subcutaneous injection of ^{131}I-albumin is markedly enhanced consistent with increased lymphatic flow (133).

TABLE 5 Edema Defense Mechanisms That Limit Excessive Capillary Fluid Filtration

↑ Interstitial hydrostatic pressure
↑ Lymph flow
↓ Interstitial oncotic pressure
↓ Permeability of the capillary to protein

A third factor that minimizes fluid filtration is a reduction in interstitial oncotic pressure (102). In normal human plasma, colloid oncotic pressure (COP) is about 24 mm Hg and interstitial COP is about 12 mm Hg creating a transcapillary COP gradient of about 12 mm Hg (146). Since transcapillary fluid flux consists primarily of a protein-free ultrafiltrate, interstitial protein concentration tends to become diluted. In addition, increased lymphatic flow removes fluid and protein from the interstitial space and returns both to the vascular compartment thereby further reducing interstitial oncotic pressure. Body albumin pools are redistributed such that a greater fraction than normal is located in the vascular compartment (146). As hypoalbuminemia develops in the nephrotic syndrome, the COP of the interstitial fluid space falls in parallel with the COP of plasma (134, 159, 161). Nephrotic patients studied both in remission and in relapse demonstrate almost equivalent changes in the COP of plasma and the interstitium at all levels of serum albumin (161). The maintenance of the net COP gradient within the normal range mitigates this potential driving force for transudation of fluid into the interstitial space. A final factor that favors decreased fluid filtration is a change in the permeability of the capillary. Under conditions of hypoalbuminemia, the intrinsic permeability of the capillary to protein tends to decrease thereby increasing π_c along the capillary (341).

In summary, the reduction in serum oncotic pressure that accompanies the nephrotic syndrome would be predicted to alter Starling forces in a direction favoring net flux of fluid across the capillary bed. Despite this alteration, however, fluid tends not to accumulate within the interstitium in response to hypoalbuminemia because of the activation of a series of defense mechanisms that serve to oppose those forces favoring fluid movement from the intravascular space. These edema-preventing factors include increased interstitial hydrostatic pressure, accelerated lymphatic flow, a parallel decline in plasma and interstitial oncotic pressure, and decreased capillary permeability to protein. However, in the setting of ongoing primary renal salt retention, these buffering mechanisms become exhausted and clinically apparent edema may become evident. This occurs because salt retention leads to increases in capillary hydrostatic pressure at the very time defense mechanisms normally employed to prevent edema have been maximized. In the hypoproteinemic patient without salt retention, edema-preventing factors may be sufficient to protect against the development of edema. Thus, edema formation in the nephrotic syndrome results from the combined effects of primary salt retention coupled with exhausted defenses against edema (Fig. 9).

The changes in mean arterial pressure and blood volume as a function of varying extracellular fluid volume in hypoalbuminemic nephrotic patients as compared to normoalbuminemic chronic renal-failure patients illustrates these principles (158). In hypoalbuminemic patients with nephrotic syndrome, expansion of the extracellular fluid volume leads to immediate translocation of fluid into the extravascular space as evidenced by little change in mean arterial pressure

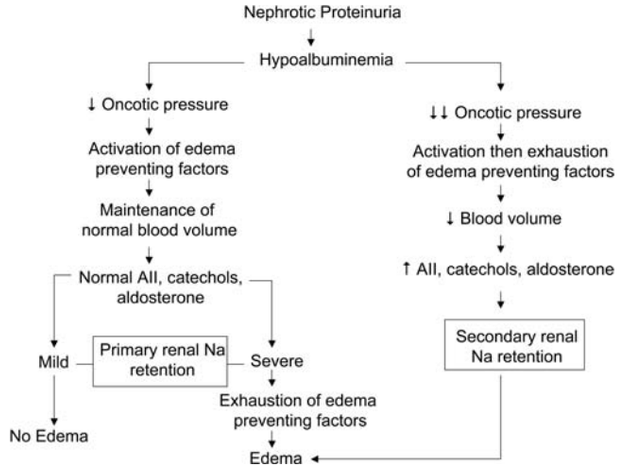

FIGURE 9 The left side of the figure depicts the mechanism of edema formation in most patients with nephrotic syndrome. An important variable that helps to explain the poor correlation between serum albumin concentration and the presence or absence of edema is the degree of primary renal Na retention. With severe Na retention by the kidney, edema-preventing factors become exhausted and edema becomes clinically apparent even when the serum albumin concentration is only mildly depressed. In the setting of mild renal Na retention, these factors remain adequate to prevent edema formation even in the presence of severe hypoalbuminemia. The right side of the figure depicts the classical view of edema formation in which low blood volume serves as the signal for secondary renal Na retention. This mechanism of edema formation is most commonly present in children with minimal change disease. In some patients, both mechanisms of edema formation may be operative. For example, early in the nephrotic syndrome, blood volume is normal and only primary renal Na retention is present. With worsening hypoalbuminemia, blood volume may begin to fall and result in a component of superimposed secondary renal Na retention.

or blood volume. Presumably, factors that serve to prevent edema are already maximized, and are overwhelmed by increases in capillary hydrostatic pressure that occur as a result of extracellular fluid volume expansion. By contrast, normoalbuminemic patients with chronic renal failure develop an increase in mean arterial pressure and blood volume as extracellular fluid volume expands. In these patients, more of the fluid is retained in the vascular tree due to activation of edema preventing factors. At some point of extracellular fluid volume expansion, these factors would also become overwhelmed and clinically detectable edema would develop.

Mechanism of Salt Retention in Nephrotic Syndrome

The intrarenal mechanism responsible for primary sodium retention in nephrotic syndrome has been examined in both experimental studies and clinical studies. A role for reduced GFR contributing to impaired sodium and water excretion was suggested in a study of nine adult patients with nephrotic syndrome due to various causes (298). Baseline inulin clearances were found to be lower in the subset of patients with an impaired capacity to excrete a water load. When these same subjects underwent HWI, increases in sodium and water excretion were found to be correlated with

increases in inulin clearance. This improvement was unassociated with a variety of other measured hemodynamic or neurohumoral factors suggesting an important role for GFR. However, other studies show that sodium excretion can be regulated independently from GFR in the nephrotic state. For example, in an animal model of nephrosis, administration of saralasin was found to increase GFR but did not enhance sodium excretion (138). In addition, many patients with nephrotic syndrome have normal or increased GFR and yet avidly retain sodium.

The bulk of experimental and clinical data implicate a tubular mechanism as the primary cause of salt retention in the nephrotic syndrome. Both experimental and clinical studies suggest that proximal reabsorption is decreased and implicate the distal nephron as the site responsible for sodium retention. Utilizing clearance techniques proximal sodium handling was assessed during diuretic-induced distal tubular blockade using chlorothiazide and ethacrynic acid (120). Nephrotic patients exhibited a greater natriuretic response than controls suggesting that distal nephron sites were responsible for enhanced sodium reabsorption. Measurement of tubular glucose handling has been used as a marker of proximal sodium reabsorption (319). In a group of nephrotic patients, glucose titration curves revealed a reduced threshold for glucose reabsorption further suggesting diminished proximal sodium reabsorption. In volume-expanded rats with autologous immune complex nephritis, a model that resembles membranous nephropathy, micropuncture and clearance methodology were used to study the site of sodium retention (29). Absolute proximal sodium reabsorption was decreased in nephrotic rats, while sodium delivery to the late distal tubule of superficial nephrons was comparable in control as well as nephrotic animals. Since fractional excretion of sodium was significantly lower in nephrotic versus control rats, the collecting duct was suggested as a possible site of altered handling of sodium. Enhanced sodium reabsorption in juxtamedullary nephrons not accessible to micropuncture could not be excluded. In the rat model of unilateral proteinuric renal disease induced by infusing PAN into one kidney, diminished urinary sodium excretion was confined to the proteinuric kidney (138). Since sodium delivery to the initial portion of the collecting duct was similar to the control kidney, increased sodium reabsorption at the collecting duct must have been the primary site of salt retention.

Neurohumoral Control of Enhanced Tubular Sodium Excretion

Renin-Angiotensin-Aldosterone

Studies demonstrating increased sodium retaining activity in the urine of nephrotic patients lead early investigators to suggest that aldosterone might play an important role in mediating sodium retention in the nephrotic syndrome (196). In rats made nephrotic with PAN, juxtaglomerular cell granularity was found to vary directly with the degree of sodium retention (315). In this same model, prior adrenalectomy prevented sodium retention that otherwise occurred in nephrotic controls with intact capacity to secrete aldosterone (149). When plasma renin activity and aldosterone concentrations were measured in a large group of nephrotic patients placed on a low sodium diet values varied widely although a negative correlation was found between urinary sodium and plasma aldosterone concentration (110). In a study of five nephrotic patients placed on a high salt diet for 8 days, plasma renin activity and plasma aldosterone levels were similar in both nephrotic subjects and control subjects (300). Administration of the aldosterone antagonist, spironolactone, on day 4 of the study resulted in an increase in urinary sodium excretion in the nephrotic patients, while no change was observed in the control group. Since aldosterone exerts salt-retaining effects on the distal nephron, a site implicated in formation of nephrotic edema, excess aldosterone activity is an attractive explanation for observed salt retention. Most data, however, fail to confirm an important role for aldosterone. In patients spontaneously retaining sodium, measurements of plasma renin activity and aldosterone concentration may be either low or high (44, 47). This disassociation is also seen during steroid-induced remission of nephrotic syndrome. In four patients with minimal change disease, plasma renin and aldosterone concentrations fell during steroid induced diuresis but once in remission these hormones returned to the same plasma concentrations observed when edema was present (208). Studies involving administration of either saralasin or converting enzyme inhibitors also fail to support an important role for the renin-angiotensin-aldosterone system in mediating salt retention (45, 47, 83). In nephrotic patients selected for high plasma renin activity, captopril administration also failed to prevent sodium retention despite producing marked reductions in plasma aldosterone (45). In the unilateral model of PAN-induced nephrosis, infusion of saralasin led to substantial increases in total kidney and single-nephron GFR of the perfused kidney, but urinary sodium excretion remained unchanged (138). This observation lends support for an intrarenal mechanism of salt retention independent of changes in GFR or activation of the renin-angiotensin-aldosterone system.

Sympathetic Nervous System

Increased plasma and urinary catecholamine concentrations have been found in patients with nephrotic syndrome (150, 239). The role of renal sympathetic nerve activity in mediating salt retention in nephrotic syndrome has been studied in rats made nephrotic by injection of adriamycin. An impaired ability to excrete an acute oral or intravenous isotonic saline load was improved by bilateral renal denervation (67). In response to acute infusion of saline, efferent renal sympathetic-nerve activity decreased to a lesser extent than that in control rats. Metabolic balance studies carried out over 26 days revealed an overall decrease in cumulative sodium balance only in those nephrotic rats with bilateral renal denervation (130). It was concluded that renal nerves

are an important effector mechanism in the chronic renal sodium retention that characterizes the nephrotic syndrome. Given the evidence for a distal nephron site of sodium reabsorption in nephrotic syndrome, it is noteworthy that beta-adrenergic stimulation of rabbit cortical collecting tubules enhances chloride transport (139). Other studies show that enhanced sodium retention in nephrotic syndrome cannot be entirely explained by sympathetic nervous system activity. In kidneys taken from rats previously exposed to puromycin aminonucleoside and perfused in vitro, less sodium is excreted as compared to kidneys taken from control animals (105). In this preparation, extrinsic neural factors are eliminated. In the adriamycin model of nephrosis, bilateral renal denervation similarly did not correct the blunted volume expansion natriuresis observed in nephrotic rats (322).

Atrial Natriuretic Peptide

Levels of ANP are reported to be normal or slightly elevated in patients with nephrotic syndrome (316). In animal models of the nephrotic syndrome, renal responsiveness to ANP has generally been found to be blunted (254). In contrast, infusion of synthetic human ANP to nephrotic patients results in increased sodium and water excretion similar to that in normal subjects (346). Infusion of albumin in children with nephrotic syndrome resulted in a rise in ANP levels that closely correlated with urinary sodium excretion. However, other studies have found a blunted natriuretic response to ANP in nephrotic patients (254). It has been proposed that enhanced distal sodium reabsorption in the nephrotic syndrome may, in part, be due to resistance of the collecting duct to the natriuretic actions of ANP (249, 255). The cellular basis of this resistance does not appear to be an abnormality in ANP binding to its receptor. Rather, the mechanism appears to be an inability to generate adequate amounts of the intracellular cGMP as a result of heightened activity of intracellular cGMP phosphodiesterase (323).

In summary, edema formation in the majority of patients with nephrotic syndrome can best be explained by an overfill mechanism. The maintenance of a normal plasma volume in the setting of hypoalbuminemia is the result of a series of edema preventing factors that act to both oppose fluid filtration across the capillary wall and to return fluid back into the vascular tree. The single most important variable in determining whether these factors are sufficient to prevent edema formation is the degree of renal salt retention. The variability in renal salt retention explains the poor correlation between the presence or absence of edema and the serum albumin concentration. In patients with severe hypoalbuminemia and no edema, renal salt retention is likely to be minimal such that edema preventing factors are sufficient in preventing excessive fluid filtration across the capillary wall. By contrast, edematous patients with near normal serum albumin concentration are more likely to have avid renal salt retention such that the factors opposing fluid filtration become exhausted. The defect in renal salt excretion has not been precisely localized but appears to reside in the distal nephron. The exact mechanism underlying this defect is unknown.

SODIUM WASTAGE

Renal salt wastage may be defined as persistent inappropriate renal loss of sodium from the body sufficient in magnitude to result in shrinkage of extracellular fluid volume causing azotemia, hypotension, and when extreme, circulatory collapse. When evaluating the relationship between urine sodium excretion and dietary intake the initial status of the extracellular fluid volume must be taken into consideration before concluding renal salt wasting is present. For example, renal salt wasting should not be considered present when urine sodium excretion greatly exceeds dietary intake in edematous patients placed on a low-salt diet. In this instance, negative salt balance is an appropriate response to correct the volume expanded state. As extracellular fluid volume normalizes the natriuresis will stop and sodium balance will be reestablished. By contrast, the imposition of a salt restricted diet to a euvolemic patient with chronic kidney disease may result in negative salt balance and contraction of extracellular fluid volume below normal limits. Even though the cumulative amount of sodium lost from the body may be far less than in the diuresing edematous patient, renal salt wasting is considered present since the reduction of extracellular fluid volume has fallen below normal. In this setting, worsening azotemia and hypotension may be present. The critical feature of renal salt wasting is the continued shrinkage of extracellular fluid volume below the lower limit of normal as a result of ongoing natriuresis. Disorders of renal salt wasting can be divided into intrinsic disorders of the kidney and disorders of efferent mechanisms that regulate renal sodium handling.

Intrinsic Renal Disease

Chronic Kidney Disease

Patients with advanced chronic kidney disease may exhibit mild renal salt wastage when subjected to rigid dietary sodium restriction. The pathogenesis of salt wastage is related to the adaptive increase in perfusion of remaining viable nephrons as total nephron mass progressively declines. Accompanying nephron hyperperfusion is a large increase in solute load. This solute load exceeds the reabsorptive capacity of remaining nephrons resulting in increased excretion of salt and water. The nephrons of patients with chronic kidney disease are continuously undergoing an osmotic diuresis of solutes including urea and the sodium salts of acids.

Studies by Coleman et al. (61), support an important role of osmotic diuresis in hyperfiltering nephrons in the genesis of salt wastage in chronic kidney disease. In these experiments, patients with chronic kidney disease are placed on a low sodium diet and then subjected to a water diuresis. As urine volume increases the urine sodium concentration falls

to a minimum value and thereafter remains fixed. At this point urine sodium excretion increases in parallel with further increases in urine flow rates. In salt-restricted normal participants subjected to a water diuresis combined with mannitol diuresis, the urine sodium concentration at which flow dependence of urine sodium excretion commences is greater as compared to the level during water diuresis alone. These data indicate that an osmotic diuresis is at least in part responsible for the mild salt wastage observed in patients with chronic kidney disease.

Clinical evidence of salt wastage in most patients with chronic kidney disease is typically only found when dietary salt restriction is extreme. Patients ingesting a dietary sodium of 10–15 mEq/day require a much longer period of time to establish salt balance as compared to normals and in many patients salt balance is never achieved. A persistent negative sodium balance leads to volume depletion, weight loss, relative hypotension, and worsening azotemia. In most instances, these findings are seen during the course of an intercurrent illness when salt intake is abruptly stopped or markedly reduced.

There are several reports in the literature in which renal salt wastage is more severe (53). Most of these cases have been described in patients with what appears to be chronic tubulointerstitial disease accompanied by cystic transformation of the renal medulla. In these unusual cases, urine sodium excretion is of such a magnitude that contraction of extracellular fluid volume develops in the setting of normal salt intake. Medullary cystic disease is an autosomal recessive disorder with cystic changes in corticomedullary and medullary regions of the kidney in which renal salt wastage can be severe.

Acute Renal Failure

Transient renal salt wastage is often seen in patients during the recovery phase of acute tubular necrosis. The magnitude of the natriuresis is a function of the amount of salt and water retained as the renal failure developed. Massive salt wasting leading to volume depletion and cardiovascular collapse is not a feature of this disorder. Some degree of salt wastage is often seen following the relief of urinary obstruction. The excretion of retained urea and other solutes contribute to an osmotic diuresis and account for the natriuresis. However, persistent salt wastage after these solutes are cleared does not typically occur.

Renal Tubular Disorders

Proximal or type II renal tubular acidosis is associated with renal salt wastage owing to the loss of sodium bicarbonate into the urine. Defective proximal acidification leads to a large increase in distal sodium bicarbonate delivery that is subsequently lost into the urine. The bicarbonaturic effect will continue until the serum bicarbonate concentration falls to a level that matches the reabsorptive capacity of the proximal nephron at which point sodium wastage will cease. As a result, salt wastage is transient in this disorder but nevertheless causes mild volume depletion from inappropriate renal salt loss.

Distal or type I renal tubular acidosis is also characterized by a mild form of renal salt wastage. The defect in distal acidification leads to the development of a hyperchloremic metabolic acidosis. Systemic acidosis impairs proximal salt reabsorption resulting in mild sodium wastage.

Bartter's and Gitelman's syndromes are characterized by renal salt wastage due to genetic defects in ion transporters involved in sodium reabsorption. In Bartter's syndrome impaired salt transport is localized to the thick ascending limb, while in Gitelman's syndrome the defect is localized to the distal convoluted tubule.

A variety of drugs can cause renal salt wastage as a result of tubular injury. This injury can be due to direct toxic effects of the drug as with Cis-platinum, aminoglycosides, and amphotericin B or be the result of acute tubulointerstitial nephritis as reported with methicillin and trimethoprim/sulfamethoxazole.

Disorders of Effector Mechanisms That Regulate Renal Sodium Transport

Decreased Mineralocorticoid Activity

Mineralocorticoid activity plays an important role in renal sodium conservation. Decreased activity and renal resistance to mineralocorticoids are causes of renal sodium wastage (345). The most clinically relevant form of mineralocorticoid deficiency results from primary diseases of the adrenal cortex. These diseases may either be acquired or congenital in origin. Subnormal aldosterone secretory rates leads to decreased reabsorption of sodium chloride in the cortical collecting tubule of the kidney. The kidney is fundamentally intact and the cortical collecting tubule cell responds normally to exogenously administered mineralocorticoids.

Renal salt wastage is a hallmark of Addison's disease in which patients may demonstrate severe volume depletion and cardiovascular collapse. Addison's disease results from progressive adrenocortical destruction leading to deficiencies in glucocorticoid and mineralocorticoid activity. These patients present with anorexia, vomiting, abdominal pain, weight loss, weakness, and salt craving. Physical examination reveals generalized hyperpigmentation particularly in skin folds and the axillae as well as bluish-grey hyperpigmentation of the lingual and buccal mucosa. Orthostatic hypotension is very common, indicative of volume depletion. Laboratory examination reveals an increased blood urea nitrogen to creatinine ratio characteristic of prerenal azotemia and elevated urinary sodium concentration. Hyponatremia, hyperkalemia and hyperchloremic metabolic acidosis are the characteristic electrolyte abnormalities.

Isolated aldosterone deficiency accompanied by normal glucocorticoid production occurs in association with hyporeninism, as an inherited biosynthetic defect, during protracted heparin administration, and postoperatively follow-

ing the removal of an aldosterone secreting adenoma. These patients have an inadequate ability to release aldosterone during salt restriction. In severe cases, salt wastage may be present on a normal salt intake.

Mineralocorticoid Unresponsiveness

Defective transport of sodium may also result from abnormalities in tubular responsiveness to aldosterone. Disorders in which there is a resistance to aldosterone have been localized to abnormalities in the mineralocorticoid receptor and to postreceptor defects in the epithelial sodium channel (ENaC) (345).

Pseudohypoaldosteronism type I is an inherited disorder of salt wasting that presents in infancy. The autosomal dominant form of this disease has been linked to functional mutations in the mineralocorticoid receptor. Renal salt wasting in these patients tends to be mild and spontaneously improves as patients age. A second form of the disease is inherited in an autosomal recessive fashion and is caused by inactivating mutations in either the alpha or beta subunits of the epithelial sodium channel in the collecting duct. The clinical manifestations are more severe in this form of the disease. Patients present in infancy with severe unrelenting salt wasting, hyperkalemia, and hyperchloremic metabolic acidosis, and a failure to survive syndrome. In addition to renal manifestations, patients also display frequent respiratory tract illnesses caused by an increase in the volume of airway secretions.

Cerebral Salt Wasting

The concept of a CSW syndrome was first introduced by Peters and colleagues in 1950 in a report describing three patients with neurological disorders who presented with hyponatremia, clinical evidence of volume depletion, and renal sodium wasting without an obvious disturbance in the pituitary-adrenal axis (256). These findings were subsequently confirmed in additional patients with widely varying forms of cerebral disease (332). In these initial reports, it was theorized that cerebral disease could lead to renal salt wastage and subsequent depletion of ECF volume by directly influencing nervous input into the kidneys. However, with the subsequent description of SIADH by Schwartz et al. (296), the clinical entity of CSW became viewed as either an extremely rare disorder or a misnomer for what was truly SIADH.

Only in recent years has CSW been thought of as a distinct entity. CSW should be considered in patients with central nervous system disease who develop hyponatremia and otherwise meet the clinical criteria for a diagnosis of SIADH but have a volume status that is inconsistent with that diagnosis. Unlike patients with SIADH who are volume expanded, patients with CSW show evidence of negative salt balance and reductions in plasma as well as total blood volume. The onset of this disorder is typically seen within the first 10 days following a neurosurgical procedure or after a definable event, such as a subarachnoid hemorrhage or stroke. CSW has been described in other intracranial disorders, such as carcinomatous or infectious meningitis and metastatic carcinoma.

The mechanism by which cerebral disease leads to renal salt wasting is poorly understood. The most probable process involves disruption of neural input into the kidney and/or central elaboration of a circulating natriuretic factor (Fig. 10). By either or both mechanisms, increased urinary sodium excretion would lead to a decrease in EABV and thus provide a baroreceptor stimulus for the release of AVP. In turn, increased AVP levels would impair the ability of the kidney to elaborate a dilute urine. In this setting, the release of AVP is an appropriate response to the volume depletion. By contrast, release of AVP in SIADH is truly inappropriate, because EABV is expanded.

A probable site for depressed renal sodium absorption in CSW is the proximal nephron. Because this segment normally reabsorbs the bulk of filtered sodium, a small decrease in its efficiency would result in the delivery of large amounts of sodium to the distal nephron and ultimately, into the final urine. Decreased sympathetic input to the kidney would be a probable explanation for impaired proximal reabsorption, because the sympathetic nervous system (SNS) has been shown to alter salt and water handling in this segment through various indirect and direct mechanisms. Because the SNS also plays an important role in the control of renin release, decreased sympathetic tone could explain the failure

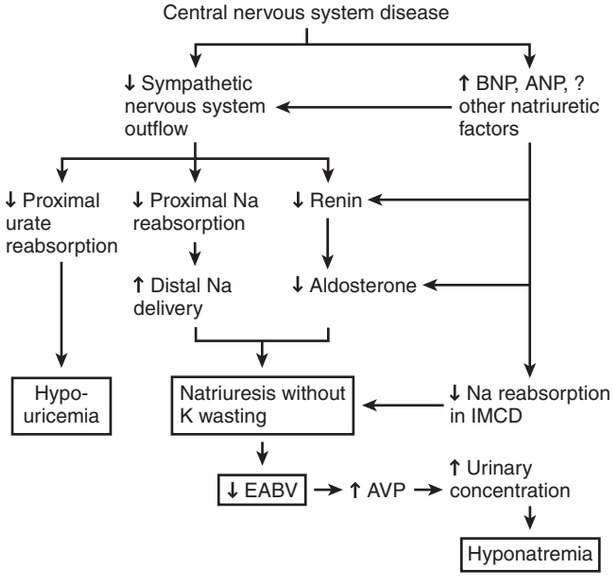

FIGURE 10 The pathophysiology of CSW. Conditions associated with increased urinary sodium excretion in the setting of volume contraction would be expected to result in renal potassium wasting because of increased delivery of sodium to the cortical collecting duct in the setting of increased aldosterone levels. The lack of renal potassium wasting in CSW can be accounted for by the failure of aldosterone to increase in spite of low extracellular fluid volume. ANP, atrial natriuretic peptide; AVP, arginine vasopressin; BNP, brain natriuretic peptide; CSW, cerebral salt wasting; EABV, effective arterial blood volume; IMCD, inner medullary collecting duct.

of circulating renin and aldosterone levels to rise in patients with CSW. The failure of serum aldosterone levels to rise in response to a decreased EABV can account for the lack of renal potassium wasting in spite of large increase in distal delivery of sodium. In this regard, hypokalemia has not been a feature of CSW.

In addition to decreased neural input to the kidney, release of one or more natriuretic factors could also play a role in the renal salt wasting observed in CSW. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have several effects that could lead to the clinical syndrome of CSW. For example, infusion of either of these peptides into normal human subjects results in a natriuretic response that is unrelated to changes in blood pressure. The ability of these compounds to increase glomerular filtration rate (GFR) accounts for some of the natriuresis; however, even in the absence of a change in GFR urinary sodium excretion increases because of a direct inhibitory effect on sodium transport in the inner medullary collecting duct. These peptides are also capable of increasing urinary sodium excretion without causing hypokalemia. For example, ANP and BNP are associated with decreased circulating levels of aldosterone because of direct inhibitory effects on renin release in the juxtaglomerular cells of the kidney as well as direct inhibitory effects on aldosterone release in the adrenal gland. In addition, inhibition of sodium reabsorption in the inner medullary collecting duct would not be expected to cause renal potassium wasting, because this segment is distal to the predominant potassium secretory site in the cortical collecting duct. As ECF volume becomes contracted proximal sodium reabsorption would increase resulting in less distal delivery of sodium to the collecting duct. Decreased sodium delivery protects against potassium wasting in the setting of high circulating levels of aldosterone.

ANP and BNP have also been shown to be capable of directly decreasing autonomic outflow through effects at the level of the brain stem. In this manner, natriuretic peptides can act synergistically with CNS disease to decrease neural input to the kidney. The evidence both for and against ANP as well as circulating ouabain-like factor as important factors in the development of CSW has been recently reviewed elsewhere.

For the various natriuretic compounds, Berendes et al. (25) have provided evidence to suggest that BNP might be the more probable candidate to mediate renal salt wasting. The authors compared 10 patients with subarachnoid hemorrhage who underwent clipping of an aneurysm to a control group comprising 10 patients who underwent craniotomy for resection of cerebral tumors. All patients with subarachnoid hemorrhage and none of the control group showed an increase in urine output accompanied by increased urinary sodium excretion that tended to peak 3–4 days following the procedure. Sodium and fluid loss in the urine was matched by intravenous replacement thus preventing the development of hyponatremia. As compared to the control group, significantly greater levels of BNP were found in the subarachnoid hemorrhage patients both before surgery and through postoperative day 8. The BNP concentration was significantly correlated with both urinary sodium excretion as well as intracranial pressure. By contrast, there were no differences in the circulating concentration of ANP or digoxin-like immunoreactive substances between the two groups. Plasma renin concentration was the same in both groups but plasma aldosterone concentrations were suppressed and varied in an opposite direction to that of BNP in the subarachnoid hemorrhage group.

BNP in humans is found primarily found in the cardiac ventricles, but also in the brain. It is not known whether brain or cardiac tissue or both contribute to the increased BNP concentration found in these patients with subarachnoid hemorrhage. Increased release of cardiac BNP could be part of a generalized stress response to the underlying illness, whereas increased intracranial pressure could provide a signal for brain BNP release. In this regard, one could speculate that the development of renal salt wasting and resultant volume depletion in the setting of intracranial disease is a protective measure limiting extreme rises in intracranial pressure. In addition, the vasodilatory properties of these natriuretic peptides might decrease the tendency for vasospasm in disorders such as subarachnoid hemorrhage.

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