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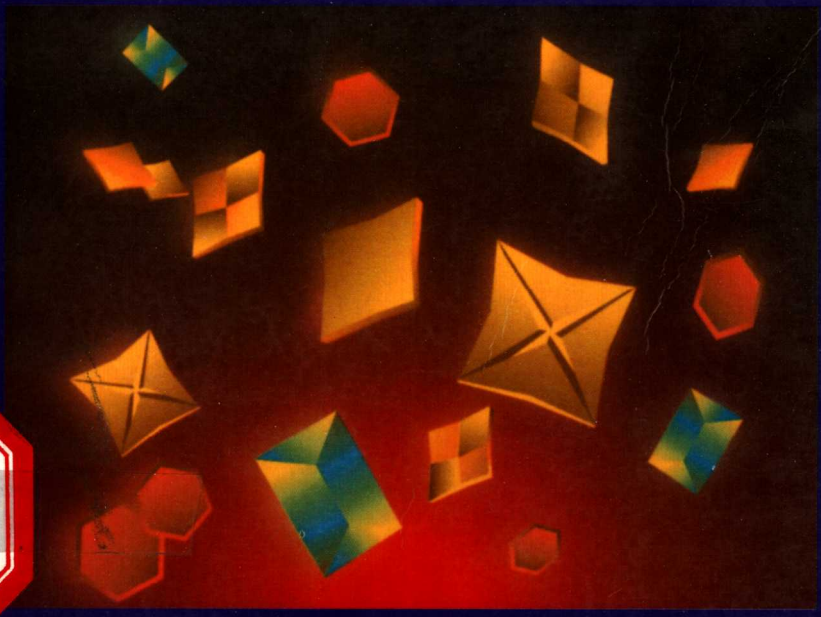
Manual of Nephrology

Fifth Edition

配英汉索引

肾病学手册

Edited by
Robert W. Schrier



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Manual of Nephrology

Fifth Edition

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Preface

The fifth edition of the *Manual of Nephrology* has been substantially updated with new authors in 10 of the 15 chapters. The focus of the manual continues to be primary care physicians, medical students, nephrology fellows, and house staff. The manual provides a practical approach to the diagnosis and treatment of acute and chronic renal diseases; fluid, electrolyte, and acid-base disorders; urinary tract infections; renal stones; and hypertensive disorders. Renal imaging approaches and recommendations for different renal disorders are discussed by Ronald R. Townsend and Robert A. Older. The diagnostic value of a careful urinalysis is again presented by Sharon G. Adler and Kenneth Fairley.

David H. Ellison has coauthored the chapter on edematous disorders and brings his expertise in diuretics to this important area. Similarly, Tomas Berl has strengthened the chapter on hyponatremia and hypernatremia with his vast experience in disorders of renal water excretion. William D. Kaehny and Stuart L. Linas have lent their extraordinary teaching talents to the respective chapters on disorders of acid-base and potassium. Robert F. Reilly has expertly dealt with disorders of calcium and phosphorus metabolism as well as renal calculi in a practical, elegant, and up-to-date manner. Jay Redington has joined L. Barth Reller to present the most recent information about the diagnosis of and preferred antibiotic regimens for treatment of infection of the upper and lower urinary tract. Charles L. Edelstein has joined Robert E. Cronin in writing the chapter on acute renal failure. They have applied their substantial experience and knowledge in elucidating this important area. Bruce J. Fisch and David M. Spiegel have presented excellent chapters on chronic renal failure and renal replacement therapy, respectively. The general approach to drug dosing patients with renal failure, including specific recommendations for some 500 medications, has been expertly presented by George R. Aronoff. Phyllis August has updated her chapter on kidney disease and pregnancy, along with Adrian I. Katz and Marshall D. Lindheimer, and Charles R. Nolan has expertly dealt with the diagnosis and treatment of hypertensive disorders, including both primary and secondary hypertension.

All of these contributing authors were selected for their ability to use their extraordinary scientific knowledge in a practical way, allowing for focused and cost-effective plans of diagnosis and treatment in the best interest of patients. In this same spirit, the *Manual of Nephrology* is dedicated to Professor Hugh de Wardener, physician, scientist, and educator, who has made remarkable contributions to medical science and to his patients for more than 50 years.

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1 The Edematous Patient: Cardiac Failure, Cirrhosis, and Nephrotic Syndrome

David H. Ellison and
Robert W. Schrier

I. **Body fluid distribution.** Of the total fluid in the human body, two-thirds resides inside the cell (i.e., intracellular fluid), and one-third resides outside the cell [i.e., extracellular fluid (ECF)]. The patient with generalized edema has an excess of ECF. ECF resides in two locations: in the vascular compartment (plasma fluid) and between the cells of the body but outside of the vascular compartment (interstitial fluid). In the vascular compartment, approximately 85% of the fluid resides on the venous side of the circulation and 15% on the arterial side (Table 1-1). An excess of interstitial fluid constitutes edema. On applying digital pressure, interstitial fluid can generally be moved from the area of pressure, leaving an indentation; this is described as *pitting*. This demonstrates that the excess interstitial fluid can move freely within its space between the body's cells. If digital pressure does not cause pitting in the edematous patient, then free movement of the interstitial fluid is not present. Such nonpitting edema can occur with lymphatic obstruction (i.e., lymphedema) or regional fibrosis of subcutaneous tissue, which may occur with chronic venous stasis.

Although generalized edema always signifies an excess of ECF, specifically in the interstitial compartment, the intravascular volume may be decreased, normal, or increased. Because two-thirds of ECF resides in the interstitial space and only one-third in the intravascular compartment, a rise in total ECF volume may occur as a consequence of excess interstitial fluid (i.e., generalized edema) even though intravascular volume is decreased.

A. **Starling's law** states that the rate of fluid movement across a capillary wall is proportional to the hydraulic permeability of the capillary, the transcapillary hydrostatic pressure difference, and the transcapillary oncotic pressure difference. As shown in Figure 1-1, under normal conditions fluid leaves the capillary at the arterial end, because the transcapillary hydrostatic pressure difference favoring transudation exceeds the transcapillary oncotic pressure difference, which favors fluid reabsorption. In contrast, fluid returns to the capillary at the venous end because the transcapillary oncotic pressure difference exceeds the hydrostatic pressure difference. Because serum albumin is the major determinant of capillary oncotic pressure, which acts to maintain fluid in the capillary, hypoalbuminemia can lead to excess transudation of fluid from the vascular to the interstitial compartment. Although hypoalbuminemia might be expected to lead commonly to edema, several factors act to buffer the effects of hypoalbuminemia on fluid transudation. First, an increase in transudation tends to dilute interstitial fluid, reducing the interstitial protein concentration. Second, increases in interstitial fluid volume increase interstitial hydrostatic pressure. Third, the lymphatic flow into the jugular veins, which return transudated fluid to the circulation, increases. In fact, in cirrhosis, where hepatic fibrosis causes high capillary hydrostatic pressures in association with hypoalbuminemia, the lymphatic flow can increase 20-fold, to 20 L per day, attenuating the tendency to accumulate interstitial fluid. When these

Table 1-1. Body fluid distribution

Compartment	Amount	Volume in 70-kg man
Total body fluid	60% of body weight	42 L
Intracellular fluid	40% of body weight	28 L
Extracellular fluid (ECF)	20% of body weight	14 L
Interstitial fluid	Two-thirds of ECF	9.4 L
Plasma fluid	One-third of ECF	4.6 L
Venous fluid	85% of plasma fluid	3.9 L
Arterial fluid	15% of plasma fluid	0.7 L

safety factors are overwhelmed, interstitial fluid accumulation can lead to edema. Another factor that must be borne in mind as a cause of edema is an increase in fluid permeability of the capillary wall (an increase in hydraulic conductivity). This increase is the cause of edema associated with hypersensitivity reactions and angioneurotic edema, and it may be a factor in edema associated with diabetes mellitus and in idiopathic cyclic edema.

B. These comments refer to **generalized edema** (i.e., an increase in total body interstitial fluid), but it should be noted that such edema may have a **predilection for specific areas** of the body for various reasons. The formation of ascites because of portal hypertension has already been mentioned. With the normal hours of upright posture, accumulation of the edema fluid in the dependent parts of the body should be expected, whereas excessive hours at bed rest in the supine position will predispose to edema accumulation in the sacral and periorbital areas of the body. The physician must also be aware of the potential presence of localized edema, which must be differentiated from generalized edema.

C. Although generalized edema may have a predilection for certain body sites, it is nevertheless a **total-body phenomenon** of excessive interstitial fluid. Localized edema, on the other hand, is caused by local factors and therefore is not a total-body phenomenon. Venous obstruction, as can occur with thrombophlebitis, may cause localized edema of one lower extremity. Lymphatic obstruction (e.g., from malignancy) can also cause excessive accumulation of interstitial fluid and, thus, edema. The physical examination of a patient with ankle edema should, therefore, include a search for venous incompetence (e.g., varicose veins) and for evidence of lymphatic disease. It should be recognized, however, that deep venous disease may not be detectable on physical examination and therefore may necessitate other diagnostic approaches (e.g., venography). Thus, if the venous disease is bilateral, the physician may mistakenly search for causes of generalized edema (e.g., cardiac failure and cirrhosis), when indeed the bilateral ankle edema is caused by local factors. Pelvic lymphatic obstruction (e.g., malignancy) can also cause bilateral lower-extremity edema and thereby mimic generalized edema. Trauma, burns, inflammation, cellulitis, and angioedema are other causes of localized edema.

II. Body fluid volume regulation. The edematous patient has long presented a challenge in the understanding of body fluid volume regulation. In the normal subject, if ECF is expanded by the administration of isotonic saline, the kidney excretes the excess amount of sodium and water in the urine, thus returning ECF volume to normal. The important role of the kidney in volume regulation has been recognized for many years. What has not been understood, however, is why the kidneys continue to retain sodium and water in the edematous patient. It is understandable that when kidney disease is present and renal function is markedly impaired (i.e., in acute or chronic renal failure), the kidney continues to retain sodium and water, even to a degree causing hypertension and pulmonary edema. Much more perplexing are those circumstances in which the kidneys are known to be

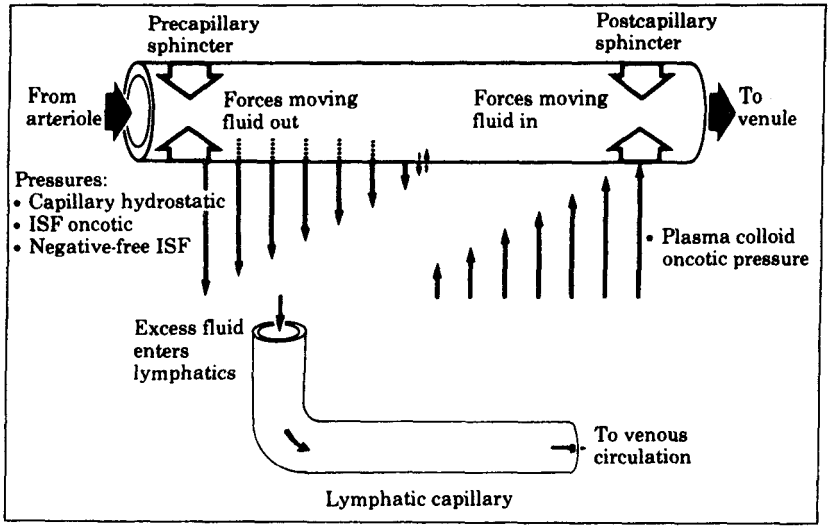

Figure 1-1. Effect of Starling forces on fluid movement across capillary wall. (ISF, interstitial fluid.)

normal and yet continue to retain sodium and water in spite of expansion of ECF and edema formation (*e.g., cirrhosis, congestive heart failure*). For example, if the kidneys of a cirrhotic patient are transplanted to a patient without liver disease, excessive renal sodium and water retention no longer occur. The conclusion has emerged, therefore, that neither total ECF nor its interstitial component, both of which are expanded in the patient with generalized edema, is the modulator of renal sodium and water excretion. Rather, as Peters suggested in the 1950s, some body fluid compartment other than total ECF or interstitial fluid volume must be the regulator of renal sodium and water excretion.

A. The term **effective blood volume** was coined to describe this undefined, enigmatic body fluid compartment that signals the kidney, through unknown pathways, to retain sodium and water in spite of expansion of total ECF. That the kidney must be responding to cardiac output was suggested, providing an explanation for sodium and water retention in low-output cardiac failure. This idea, however, did not provide a universal explanation for generalized edema, because many patients with decompensated cirrhosis who were avidly retaining sodium and water were found to have normal or elevated cardiac outputs.

B. **Total plasma or blood volume** was then considered as a possible candidate for the effective modulator of renal sodium and water excretion. However, it was soon apparent that expanded plasma and blood volumes were frequently present in renal sodium- and water-retaining states such as congestive heart failure and cirrhosis. The venous component of plasma in the circulation has also been proposed as the modulator of renal sodium and water excretion and thus of volume regulation, because a rise in the left atrial pressure is known to cause a water diuresis and natriuresis, mediated in part by a suppression of vasopressin and a decrease in neurally mediated renal vascular resistance. A rise in right and left atrial pressure has also been found to cause a rise in atrial natriuretic peptide. However, in spite of these effects on the low-pressure venous side of the circulation, renal sodium and water retention

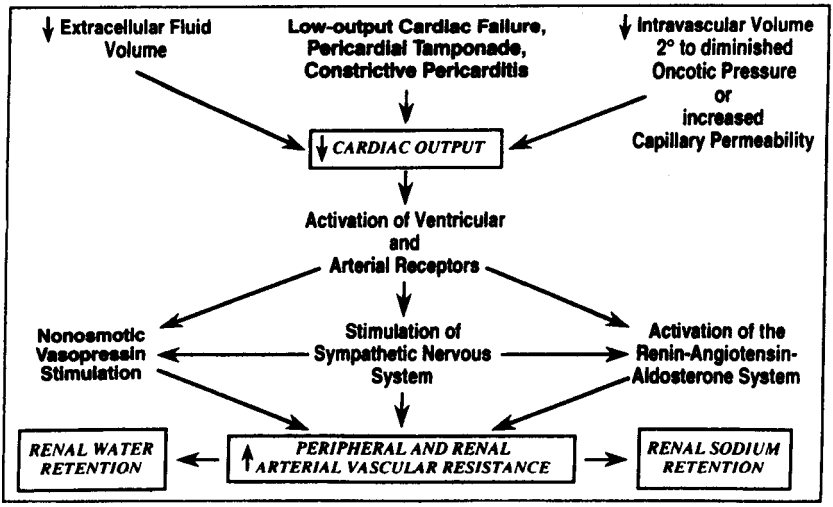

Figure 1-2. Decreased cardiac output as the initiator of arterial underfilling. (From Schrier RW. A unifying hypothesis of body fluid volume regulation. *J R Coll Physicians Lond* 1992;26:296. Reprinted with permission.)

are hallmarks of congestive heart failure, a situation in which pressures in the atria and venous component of the circulation are routinely increased.

C. The **arterial portion of body fluids** (see Table 1-1) is the remaining compartment that may be pivotal in regulation of renal sodium and water excretion. More recently, the relationship between cardiac output and peripheral arterial resistance [the effective arterial blood volume (EABV)] has been proposed as a regulator of renal sodium and water reabsorption. This relationship establishes the "fullness" of the arterial vascular tree. In this context, a primary decrease in cardiac output, peripheral arterial vasodilation, or a combination thereof may cause arterial underfilling and thereby initiate and sustain a sodium- and water-retaining state, which leads to edema. The sodium- and water-retaining states that are initiated by a fall in cardiac output are shown in Figure 1-2 and include (a) ECF volume depletion (e.g., diarrhea, vomiting, hemorrhage); (b) low-output cardiac failure, pericardial tamponade, and constrictive pericarditis; and (c) intravascular volume depletion secondary to protein loss and hypoalbuminemia (e.g., nephrotic syndrome, burns or other protein-losing dermopathies, protein-losing enteropathy); and increased capillary permeability (capillary leak syndrome). The causes of increased renal sodium and water retention leading to edema that are initiated by primary peripheral arterial vasodilation are equally numerous and are shown in Figure 1-3. Severe anemia, beri-beri, Paget's disease, and thyrotoxicosis are causes of high-output cardiac failure that may lead to sodium and water retention. A wide-open arteriovenous fistula, hepatic cirrhosis, sepsis, pregnancy, and vasodilating drugs (e.g., minoxidil, hydralazine, and prazosin) are other causes of peripheral arterial vasodilation that decrease renal sodium and water excretion.

D. Two major **compensatory processes** protect against arterial underfilling, as defined by the interrelationship of cardiac output and peripheral arterial vascular resistance. One compensatory process is very rapid and consists of a neurohumoral and systemic hemodynamic response,

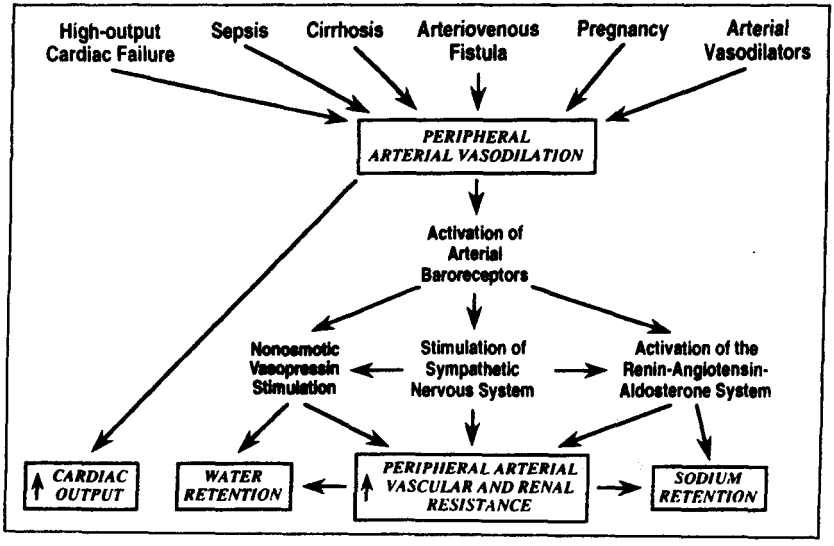

Figure 1-3. Peripheral arterial vasodilation as the initiator of arterial underfilling. (From Schrier RW. A unifying hypothesis of body fluid volume regulation. *J R Coll Physicians Lond* 1992;26:297. Reprinted with permission.)

whereas the other is slower and involves renal sodium and water retention. In edematous patients, these compensatory responses occur to varying degrees depending on the point in the clinical course at which the patient is seen. Because of the occurrence of these compensatory processes, mean arterial pressure is a poor index of the integrity of the arterial circulation. Whether a primary fall in cardiac output or peripheral arterial vasodilation is the initiator of arterial underfilling, the compensatory responses are quite similar. As depicted in Figures 1-2 and 1-3, the common neurohumoral response to arterial underfilling involves the stimulation of three vasoconstrictor pathways, namely, the sympathetic nervous system, angiotensin, and vasopressin. In addition to direct effects, the sympathetic nervous system increases angiotensin and vasopressin because increases in central sympathetic hypothalamic input and beta-adrenergic stimulation via renal nerves are important components of increased nonosmotic vasopressin release and stimulation of renin secretion, respectively. With a primary fall in cardiac output or with peripheral arterial vasodilation, increases in peripheral arterial vascular resistance or cardiac output, respectively, occur to maintain arterial pressure acutely. This rapid compensation allows time for the slower renal sodium and water retention to occur and further restore arterial circulatory integrity. With a decrease in ECF volume such as occurs with acute gastrointestinal losses, sufficient sodium and water can be retained to restore cardiac output to normal and terminate renal sodium and water retention before edema forms. Such may not be the case with low-output cardiac failure, because even these compensatory responses may not restore cardiac output to normal.

1. Thus, the **neurohumoral** and **renal sodium- and water-retaining mechanisms** persist as important compensatory processes in maintaining arterial circulatory integrity. Specifically, neither the acute nor the chronic compensatory mechanisms are successful in restoring cardiac contractility or in reversing cardiac tamponade or constrictive pericar-

dial tamponade. Compensatory renal sodium and water retention occurs with expansion of the venous side of the circulation as arterial vascular filling improves but does not return to normal. The resultant rise in venous pressure enhances capillary hydrostatic pressure and thus transudation of fluid into the interstitial fluid with resultant edema formation. With hypoalbuminemia and the capillary leak syndrome, excessive transudation of fluid occurs across the capillary bed and also prevents restoration of cardiac output; thus, continuous renal sodium and water retention occurs and causes edema formation.

2. **Peripheral arterial vasodilation,** the other major initiator of arterial underfilling, also generally cannot be totally reversed by compensatory mechanisms and thus may lead to edema formation. Peripheral arterial vasodilation results in dilatation of precapillary arteriolar sphincters, increasing capillary hydrostatic pressure and probably capillary surface area. A larger proportion of retained sodium and water is transudated across the capillary bed into the interstitium in these edematous disorders (see Fig. 1-3).

E. Another reason that low cardiac output or peripheral arterial vasodilation may lead to edema formation is the inability of patients with these disorders, as compared with normal subjects, to escape from the **sodium-retaining effect of aldosterone** (Fig. 1-4). In the normal subject receiving large exogenous doses of aldosterone or another mineralocorticoid hormone, a rise in glomerular filtration rate and a decrease in proximal tubular sodium and water reabsorption lead to an increase in sodium and water delivery to the distal nephron site of aldosterone action. This increase in distal sodium delivery is the major mediator of escape from the sodium-retaining effect of mineralocorticoids in normal subjects, thus avoiding edema formation. In contrast, the renal vasoconstriction that accompanies the compensatory neurohumoral response to arterial underfilling is associated with a decrease in sodium and water delivery to the distal nephron site of aldosterone action. This diminution in distal delivery, which occurs primarily because of a fall in glomerular filtration rate and an increase in proximal tubular sodium reabsorption, results in a failure to escape from aldosterone and, therefore, causes edema formation. The importance of renal hemodynamics, particularly glomerular filtration rate, in the aldosterone escape phenomenon is emphasized by the observation that in pregnancy, a state of primary arterial vasodilation, aldosterone escape occurs in spite of arterial underfilling because of an associated 30% to 50% increase in glomerular filtration rate. It still remains to be determined why pregnancy is associated with this large increase in glomerular filtration rate, which occurs within 2 to 4 weeks of conception. The increase in filtration rate cannot be due to plasma volume expansion, because this does not occur until several weeks after conception. The higher filtered load of sodium, and thus distal sodium load in pregnancy, no doubt allows the escape from the sodium-retaining effect of aldosterone. The occurrence of aldosterone escape in pregnancy attenuates edema formation compared with other edematous disorders.

III. Dietary and diuretic treatment of edema: general principles. The daily intake of sodium in this country is typically 4 to 6 g [1 g of sodium contains 43 mEq; 1 g of sodium chloride (NaCl) contains 17 mEq of sodium]. By not using added salt at meals, the daily sodium intake can be reduced to 4 g (172 mEq), whereas a typical "low-salt" diet contains 2 g (86 mEq). Diets that are lower in NaCl content can be prescribed, but many individuals find them unpalatable. If salt substitutes are used, it is important to remember that these contain potassium chloride; therefore, potassium-sparing diuretics (i.e., spironolactone, triamterene, amiloride) should not be used with salt substitutes. Other drugs that increase serum potassium concentration must also be used with caution in the presence of salt substitute intake [e.g., converting enzyme inhibitors, beta blockers, and nonsteroidal antiinflammatory drugs (NSAIDs)]. When prescribing dietary

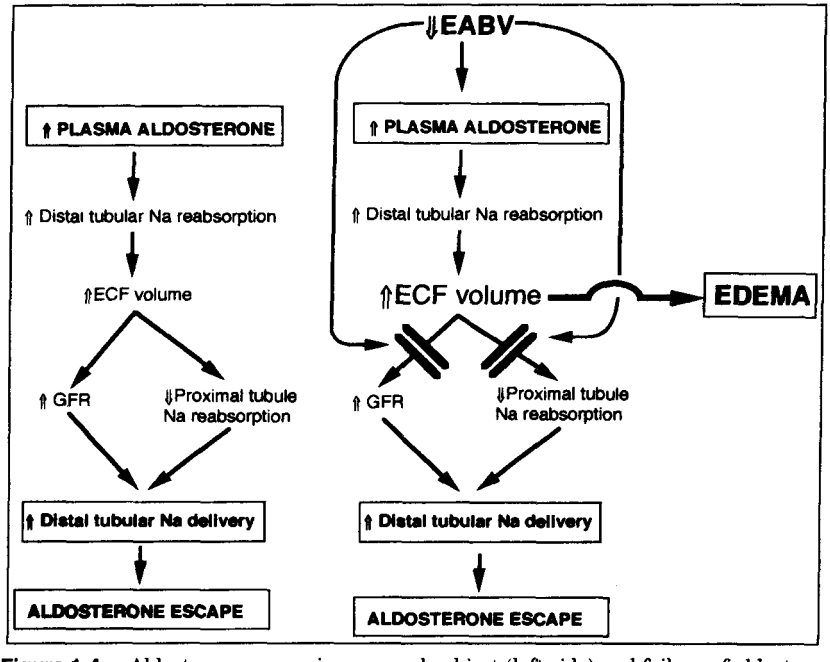

Figure 1-4. Aldosterone escape in a normal subject (left side) and failure of aldosterone escape in patients with arterial underfilling (right side). (EABV, effective arterial blood volume; ECF, extracellular fluid; GFR, glomerular filtration rate.) (From Schrier RW. Body fluid regulation in health and disease: a unifying hypothesis. *Ann Intern Med* 1990;113:155–159. Adapted with permission.)

therapy for an edematous patient it is important to emphasize that NaCl restriction is required, even if diuretic drugs are used. The therapeutic potency of diuretic drugs varies inversely with dietary salt intake.

All commonly used **diuretic drugs** act by increasing urinary sodium excretion. They can be divided into five classes, based on the predominant site of action along the nephron (Table 1-2). Osmotic diuretics (e.g., mannitol) and proximal diuretics (e.g., acetazolamide) are not employed as primary agents to treat edematous disorders. Loop diuretics (e.g., furosemide), distal convoluted tubule (DCT) diuretics (e.g., hydrochlorothiazide), and collecting duct diuretics (e.g., spironolactone), however, all play important but distinct roles in treating edematous patients. The goal of diuretic treatment of edema is to reduce ECF volume and maintain it at the reduced level. This requires an initial period of natriuresis, but, at steady state, urinary NaCl excretion returns close to baseline despite continued diuretic administration. Importantly, the presence of an initial natriuresis does *not* establish therapeutic efficacy if ECF volume does not decline. Conversely, the return to "basal" levels of urinary sodium excretion does not indicate diuretic resistance. The continued efficacy of diuretic therapy is documented by the rapid return to ECF volume expansion that occurs if the diuretic is discontinued.

A. When a **diuretic drug is administered by mouth,** the magnitude of the natriuretic response is determined by the intrinsic potency of the drug, its bioavailability, the dose, the amount delivered to the kidney, the amount that enters the tubule fluid (most diuretics act from the luminal side), and the physiologic state of the individual. Except for proximal diuretics, the maximal natriuretic potency of a diuretic can be predicted from its site of

Table 1-2. Physiologic classification of diuretic drugs

Osmotic diuretics
Proximal diuretics
Carbonic anhydrase inhibitors
Acetazolamide
Loop diuretics (maximal FE_{Na} = 30%)
Na-K-2Cl inhibitors
Furosemide
Bumetanide
Torsemide
Ethacrynic acid
Distal convoluted tubule diuretics (maximal FE_{Na} = 9%)
Na-Cl inhibitors
Chlorothiazide
Hydrochlorothiazide
Metolazone
Chlorthalidone
Indapamide*
Many others
Collecting duct diuretics (maximal FE_{Na} = 3%)
Na channel blockers
Amiloride
Triamterene
Aldosterone antagonists
Spironolactone

FE_{Na}, fractional sodium excretion.
*Indapamide may have other actions as well.

action. Table 1-2 shows that loop diuretics can increase fractional sodium excretion to 30%, DCT diuretics can increase it to 9%, and sodium channel blockers can increase it to 3%. The intrinsic potency of a diuretic is defined by its dose response curve, which is generally sigmoid. The steep sigmoid relation is the reason that loop diuretic drugs are often described as "threshold drugs." When starting loop diuretic treatment, ensuring that each dose reaches the steep part of the dose-response curve before the dose frequency is adjusted is important. Recommended maximum doses of loop diuretics are given in Table 1-3. Because loop diuretics are rapid-acting, many patients note an increase in urine output within several hours of taking the drug; this can be helpful in establishing that an adequate dose has been reached. Because loop diuretics are short-acting, any increase in urine output more than 6 hours after a dose is unrelated to drug effects. Using diuretic drugs b.i.d. or t.i.d. is rational only if each dose exceeds the diuretic threshold.

B. The **bioavailability of diuretic drugs** varies widely between classes of drugs, between different drugs of the same class, and even within drugs. The bioavailability of loop diuretics ranges from 10% to 100% (mean, 50% for furosemide; 80% to 100% for bumetanide and torsemide). Limited bioavailability can usually be overcome by appropriate dosing, but some drugs, such as furosemide, are variably absorbed by the same patient on different days, making precise titration difficult. Doubling the furosemide dose when changing from intravenous to oral therapy is customary, but the relation between intravenous and oral dose may vary. For example, the amount of sodium excreted during 24 hours is similar whether furosemide is administered to a normal individual by mouth or by vein,