PRINCIPLES OF DIURETIC THERAPY
IN EDEMATOUS CONDITIONS

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The clinical use of diuretics should be based on a good understanding of the pathophysiology of edema and the disease being treated, the pharmacology of the diuretics and their reported side effects. This knowledge allows one the best opportunity to effectively and safely match the mechanism of action of the diuretic to the altered physiology caused by the disease. The major clinical conditions for which diuretics have been used in the treatment of edema are shown in Table 1. It is generally agreed that, whatever the pathophysiology of the primary disease, the retention of sodium by the kidney ultimately determines the magnitude of the fluid overload and consequent edema formation. Thus, an understanding of normal salt and water handling by the kidney is essential.

SALT AND WATER HANDLING BY THE KIDNEY

Regulators of Salt and Water Handling (1-4)

The amount of sodium excreted into the urine is equal to the filtered load at the level of the glomerulus minus the sodium reabsorbed as the filtrate passes down the tubule. At least three factors are known to regulate sodium balance within the kidney. Glomerular filtration rate (first factor) has been most extensively studied and therefore the best understood. However, the overall roles of aldosterone (second factor) and the third factor(s) remain controversial. The mean glomerular filtration rate (GFR) in man is 125 milliliters per minute per 1.73 meters squared. Each day, the kidneys produce approximately 180 liters of glomerular filtrate containing about 25,000 mEq's of sodium. Ninety-nine point 5 percent of the filtered sodium load is reabsorbed along
Table 1. Clinical Conditions Associated with Edema

<table>
<thead>
<tr>
<th>Renal Failure, acute and chronic</th>
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<tr>
<td>Nephrotic Syndrome</td>
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<td>Congestive Heart Failure</td>
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<tr>
<td>Hepatic Failure and Cirrhosis</td>
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<td>Protein Losing Enteropathy</td>
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the nephron, yielding an average of 125 mEq sodium excreted in the urine. The amount of sodium filtered is directly proportional to the GFR, and if only GFR were involved, a 1% change in the GFR would result in changes of as much as 250 mEq sodium excreted in the urine. These large changes in the amount of filtered sodium are modified by a corresponding decrease or increase in tubular reabsorption of sodium. This cooperative working relationship between GFR (first factor) and tubular reabsorption is called glomerulotubular balance.

Aldosterone (second factor) is the most potent of the mineralocorticoids in sodium reabsorption. The principal site of action is in the collecting duct where sodium is reabsorbed in association with but not directly dependent upon the secretion of potassium and hydrogen ions. Since only one percent of the filtered sodium load reaches the collecting duct, aldosterone would have a relatively small effect on sodium excretion. Aldosterone requires 30-60 minutes to induce the intracellular or membrane-bound proteins which allow for potassium secretion and subsequent sodium reabsorption, and thus could not participate in minute to minute control of sodium reabsorption. Chronic administration of mineralocorticoids causes only a transient salt retention after which sodium balance is restored. This phenomenon called "DOCA release" mitigates against aldosterone's relative importance as a regulator of sodium balance.

Because of such circumstantial evidence, factors other than GFR and aldosterone have been hypothesized to explain minute to minute control of the concentration and volume of the extracellular fluid. Direct evidence for the existence of additional factor(s) was first established by de Wardener (5). While maintaining GFR and aldosterone concentration constant, he was able to demonstrate in the dog a brisk diuresis and natriuresis in response to an intravenous saline infusion. Because neither the first nor second factor could account for the diuresis, he postulated the existence of a natriuretic or third factor(s). In two decades since de Wardener's original work, several hypotheses have been proposed to explain the mechanism(s) by which third factor(s) participates in glomerulotubular balance. A circulating substance of hormonal nature (6,7), changes in the peritubular physical