Medical Grand Rounds

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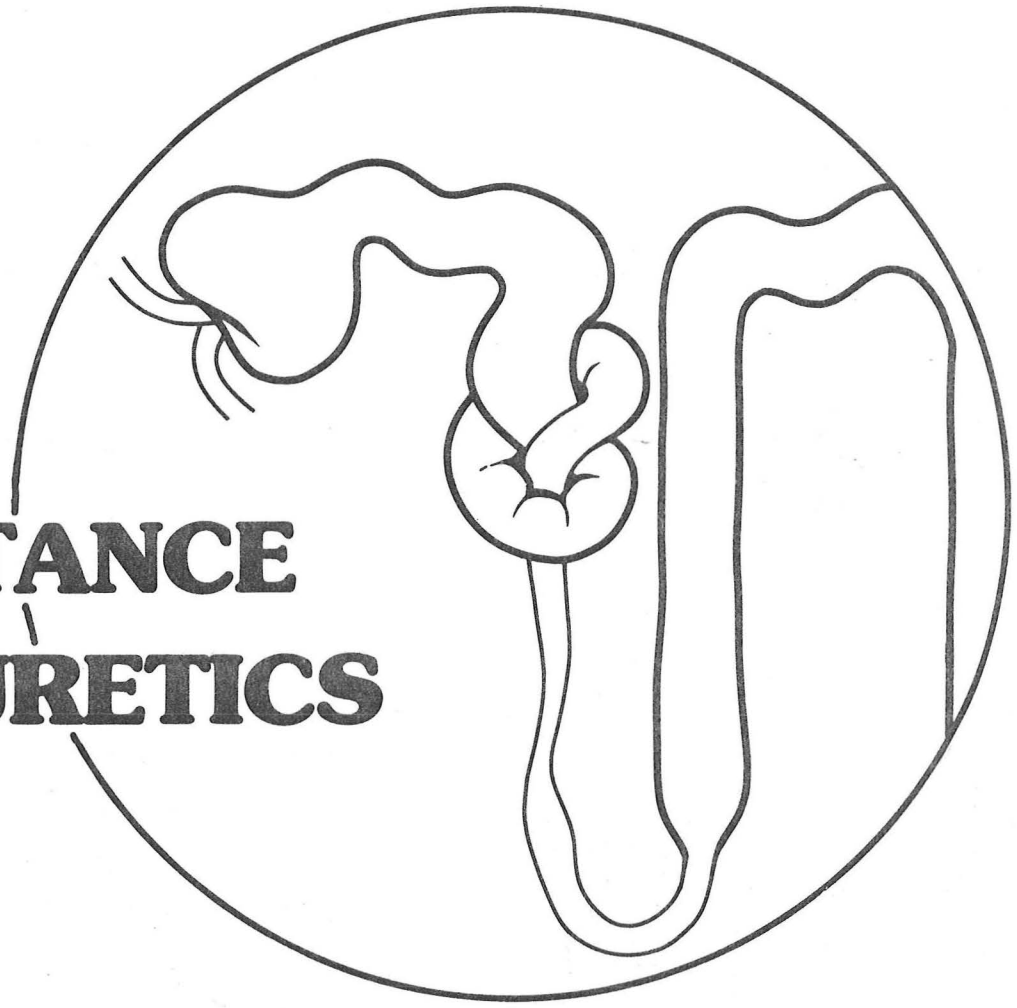

RESISTANCE TO DIURETICS

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INTRODUCTION

Many patients manifest resistance to diuretics. This term, resistance, is difficult to quantify, for it implies a diminished response in individual patients compared to that of a "normal subject", and response among "normals" is highly variable. Clearly, however, at one end of the spectrum some patients require exceedingly large doses of potent diuretics to manifest a small response. The other end of the scale encompasses a "gray zone" in which resistance is difficult to define and more specific criteria for which will be proposed later in this review.

The most commonly encountered clinical conditions in which resistance to diuretics occurs include the azotemic patient, the edematous disorders of congestive heart failure, liver disease and nephrotic syndrome and of less practical but of mechanistic importance, the patient administered inhibitors of prostaglandin synthesis. Each of these clinical states will be addressed and the mechanisms of resistance considered. To do so, requires an understanding of the pathophysiology of salt and water handling in these clinical conditions which, in turn, requires an understanding of normal solute and water homeostasis. Obviously, one must also understand the detailed pharmacology of diuretics. This review will focus upon the pharmacologic aspect of diuretic resistance and will tend to be more general in providing background for the pathophysiology of solute handling in the aforementioned states.

PATHOPHYSIOLOGY

Physiology Of Renal Handling Of Sodium (for review, see 1,2)

Glomerular Filtration (for review, see 3)

The amount of sodium appearing in the urine represents the cumulative amount of sodium that is filtered less that reabsorbed along the nephron plus any small component which might be secreted into the tubular lumen. The amount of any ion filtered is a function of the glomerular filtration rate and the concentration in serum of the ion in question which is unbound to serum components and therefore able to pass through the glomerular sieve. Since sodium is not bound to protein (in contrast to calcium, for example), the amount filtered per unit time is equal to the concentration in plasma times glomerular filtration rate. As will be discussed subsequently, in most clinical states excluding end stage renal failure, filtration of sodium does not contribute importantly to sodium retention and/or resistance to diuretics.

Proximal Tubule (for review, see 4-8)

The proximal tubule isotonically reabsorbs approximately 65% of filtered sodium. The mechanisms of sodium reabsorption in the proximal tubule are several, (Figure 1) and include that which passively follows the active reabsorption of organic solutes such as glucose and amino acids (9,10), that which is reabsorbed with bicarbonate under the influence of carbonic anhydrase (11), and that which is reabsorbed by other mechanisms, one of which may include the passive following of

chloride down an electrochemical gradient that has been established by the reabsorption of bicarbonate earlier in the nephron and one of which may be an active reabsorption of sodium (12).

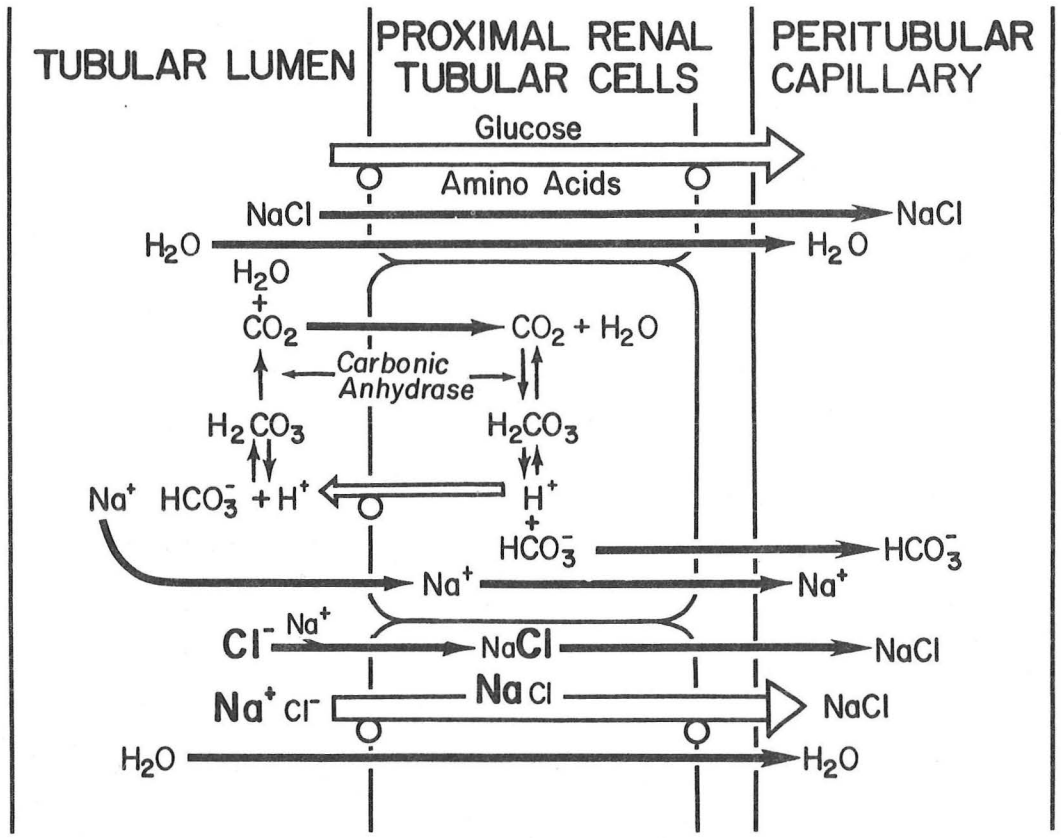

Figure 1: *Schematic diagram of sodium reabsorption by the proximal tubule.*

In addition to these forces moving sodium and water out of the proximal tubule and into the blood, there is a component of backleak into the proximal nephron. Consequently, net reabsorption in the proximal tubule includes that amount reabsorbed less that amount that leaks back into the tubular lumen. The amount of backleak is influenced by the peritubular osmotic pressure which in turn is determined by the relationship between glomerular filtration rate and renal blood flow; namely the filtration fraction, which is equal to GFR divided by RBF:

$$FF = \frac{GFR}{RBF} \quad (13\text{-}17).$$

If filtration fraction decreases, a smaller fraction of blood flowing to the kidney is filtered causing the protein in the peritubular fluid to be less concentrated; the lower osmotic force maintains less of the

reabsorbed solute outside of the lumen and as a consequence more back-leak occurs. As a consequence, net reabsorption decreases. In contrast, if filtration fraction increases, the fraction of blood flowing to the kidney that is filtered has increased, increasing osmotic pressure in the peritubular vascular space and facilitating reabsorption by diminishing backleak. As a consequence, net reabsorption of solute will be greater when filtration fraction has increased (Figure 2). It is important to note that changes in filtration fraction can occur either by changes in glomerular filtration rate, changes in renal blood flow or by changes in both. It is the net effect on the ratio of the two which is of over-riding importance.

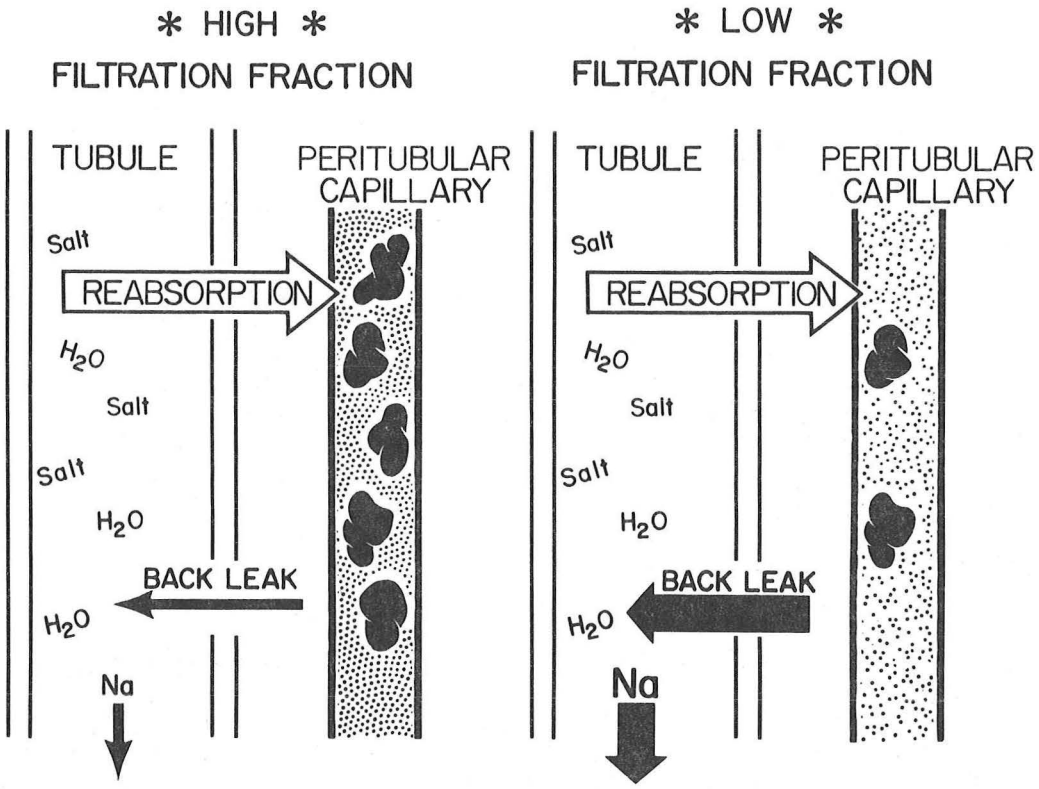

Figure 2: *Schematic diagram of the effect of filtration fraction on peritubular osmotic pressure, back leak, and net reabsorption by the proximal tubule.*

The role of intrarenal distribution of blood flow in sodium homeostasis is unclear. Exploring this parameter has been fraught with methodologic problems which to this date have not been resolved (18).

As will be discussed in more detail subsequently, edematous states have been associated with increased reabsorption of sodium by the proximal tubule. Clearly, increases in filtration fraction occur and may be contributory. Whether increased reabsorption by the proximal nephron occurs by other mechanisms is unclear.

Loop of Henle (for review, see 19)

Water alone is reabsorbed from the thin descending limb of the loop of Henle, but at the thick ascending limb of the loop of Henle, solute reabsorption again occurs. This segment of the nephron is impermeable to water and actively reabsorbs chloride with sodium following passively, removing 25-30% of filtered solute under normal conditions (Figure 3). However, the capacity of this segment of the nephron is great, and under conditions in which solute delivery to this segment is increased the amount of solute reabsorbed also increases. As a consequence, rejection of solute by the proximal nephron may be compensated for by the capacity of the thick ascending limb to increase its contribution to overall solute reabsorption. Recent evidence suggests that this segment of the nephron may contribute to the increased sodium reabsorption of edematous states by unknown mechanisms.

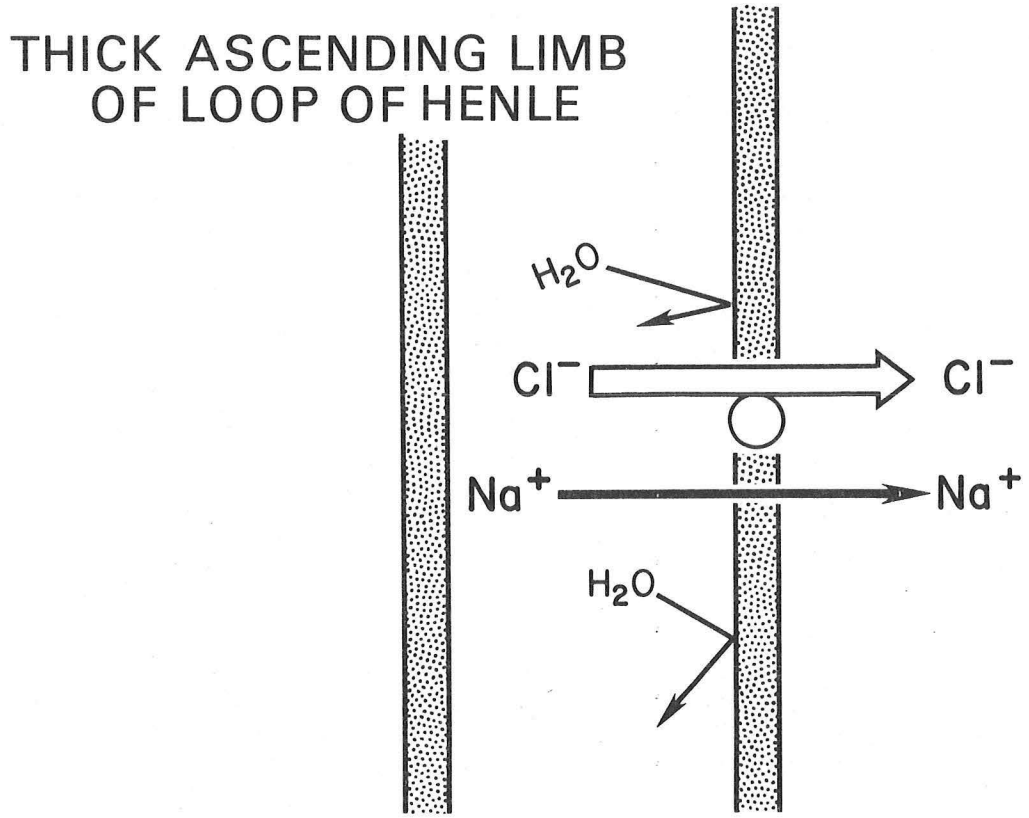

Figure 3: *Schematic diagram of sodium reabsorption by the thick ascending limb of the loop of Henle.*

Distal Nephron (for review, see 20)

The distal tubule and collecting duct reabsorb sodium in exchange for either potassium or hydrogen by both aldosterone dependent and independent mechanisms (Figure 4). It is important to note that in all other segments of the nephron, sodium and potassium move in parallel, while in this segment of the nephron, though not necessarily in a one to one stoichiometric relationship, sodium and potassium move in opposite directions.

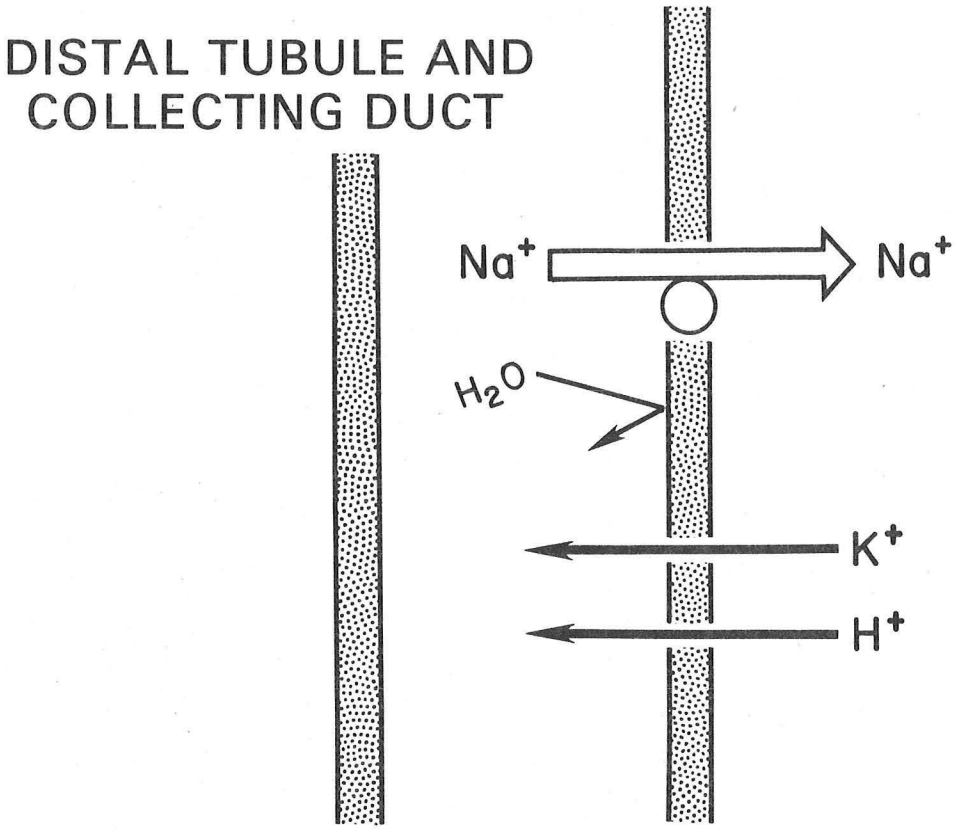

Figure 4: *Schematic diagram of sodium reabsorption by the distal tubule and collecting duct.*

PATHOPHYSIOLOGY

Pathophysiology of Sodium Retention (for review, see 21-26)

Glomerular Filtration (27-33)

As noted in the previous section, glomerular filtration determines the amount of sodium reaching the tubular lumen and can be a determinant of the final amount of solute in the urine. Theoretically, increases in glomerular filtration rate might increase urinary sodium excretion while decreases could decrease the amount of solute appearing in the urine. Vasodilators such as aminophyllin, when administered parenterally, cause a diuresis and natriuresis which has been attributed to their effects to increase glomerular filtration. However, it is more likely that these diuretic effects are due to an additional, disproportionate increase of renal blood flow, thereby decreasing filtration fraction with its resultant effects to increase backleak and decrease the net reabsorption of solute in the proximal tubule. At the other end of the scale, decrements in glomerular filtration rate cause sodium retention only at severe degrees of renal impairment. It is not until glomerular filtration rate becomes less than approximately 10 ml/min that GFR is limiting.

In edematous disorders and during inhibition of prostaglandin synthesis, changes in filtration do not correlate with sodium handling or with response to diuretics. Though some patients may have diminished glomerular filtration rates, natriuresis may occur without a change in filtration. For example, after a LeVeen shunt, cirrhotic patients diurese in excess of changes in glomerular filtration rate or with no change in filtration. Similarly, many patients with, and experimental models of, sodium retention have normal glomerular filtration rates.

Proximal Tubule

Early studies demonstrated an increased reabsorption of sodium by the proximal tubule in patients with congestive heart failure, cirrhotic liver disease and nephrotic syndrome, and in a variety of animal models of edema formation (34-47). As a consequence, considerable data support the hypothesis that sodium retention in the above disease states is related to a change in proximal tubule homeostasis such that greater than normal amounts of sodium are reabsorbed. The mechanisms of this reported avidity of the proximal nephron have not been clarified.

Disease-induced changes in distribution of blood flow to different segments of the nephron have been advocated as etiologic to the increased sodium reabsorption. Shunting of blood flow from cortical to juxtamedullary nephrons has been found with reversal of this distribution by potent diuretics (48-52). However, as noted previously, the pathophysiologic role of intrarenal distribution of blood flow is unclear, and sodium retention occurs without changes in distribution (18).

The role for changes in filtration fraction in patients with congestive heart failure, cirrhotic liver disease and nephrosis is more

clear. Many patients have decreased renal blood flow in excess of decrimants in glomerular filtration rate, increasing filtration fraction which should decrease backleak in the proximal nephron and thereby increase net proximal tubular reabsorption (53-63). Renal vasodilatation, particularly while increasing systemic blood pressure, reverses this effect and causes a natriuresis (57,61). It has been hypothesized that decreased cardiac output and/or "effective circulating volume" causes release of vasoactive mediators, in turn, causing the effects on renal hemodynamics.

Loop of Henle

More recent data in man but mainly from animal models of edema-forming states which avoid some of the pitfalls of studies deriving data on proximal tubular function, indicate that increased solute reabsorption occurs in the ascending limb of the loop of Henle (39,60-65). Some studies purport to show normal function of the proximal tubule while most implicate both the proximal nephron and the ascending limb as sites of increased sodium reabsorption. Similar to the situation with studies of the proximal tubule, mechanisms for this avidity by the loop of Henle are unclear.

Distal Nephron

The distal tubule and collecting duct, particularly via aldosterone-mediated sodium reabsorption, were early favorites for the site of the nephron responsible for sodium retention in the edema-forming states. In cirrhosis in particular, circulating concentrations of aldosterone are greatly elevated in many patients. A variety of studies have been performed in man and experimental animals, some of which indicate that aldosterone at most is important for the genesis of edema, but that it plays little if any role in the maintenance of the edematous state (32,66-78). It appears that if aldosterone plays any role in the pathogenesis of sodium retention in these disease states, it is minor.

PHARMACOLOGY OF DIURETIC AGENTS (for review, see 79-82)

Sites of Action

To understand resistance to diuretics one must have a working knowledge and familiarity with sites of diuretic action (Figure 5), with the determinants of access of diuretics to their sites of action, and with the determinants of response to the diuretic once it reaches its site of effect.

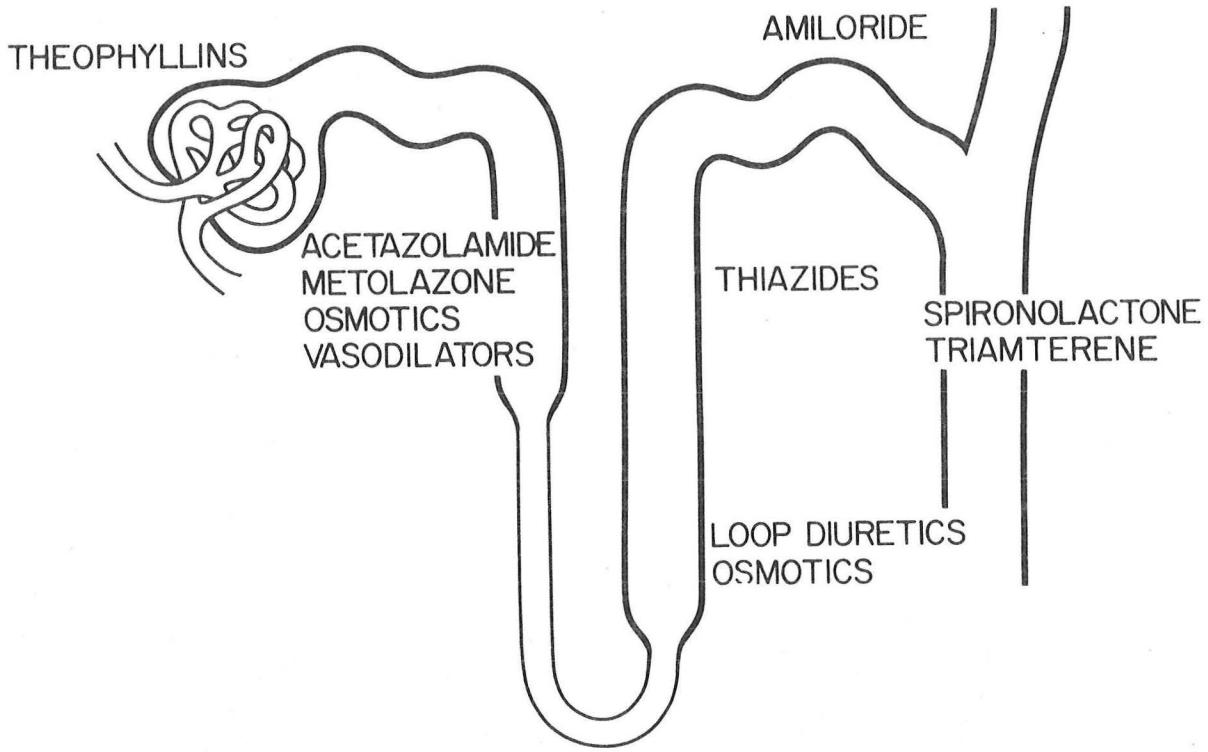

Figure 5: *Schematized renal tubule depicting tubular sites of action of diuretics.*

Glomerular Filtration

As noted previously, some agents such as the theophyllins have been considered to have a diuretic effect by increasing the glomerular filtration of solute. However, this effect is probably more likely due to effects of these compounds on filtration fraction with the increase in renal blood flow greater than the relative increase in glomerular filtration rate causing a decrease in filtration fraction which, in turn, increases backleak and causes decreased net reabsorption of solute by the proximal tubule.

Proximal Nephron

Several diuretics can affect proximal tubular reabsorption of solute. Acetazolamide, the classic inhibitor of carbonic anhydrase, has its predominant effect at this site, causing rejection of sodium bicarbonate by the proximal tubule and a sodium bicarbonate diuresis (83-85). Metolazone, a newer diuretic, has a distal effect similar to the thiazides, but additionally decreases reabsorption in the proximal tubule by an unclear mechanism, which is exclusive of inhibition of carbonic anydrase (86,87).

As noted previously, various vasodilators, particularly the theophyllin compounds, by increasing renal blood flow, and decreasing filtration fraction, increase rejection of solute from the proximal tubule. It is important to note that all of the loop diuretics described to date possess this capacity to increase renal blood flow without affecting glomerular filtration rate, particularly when they are administered intravenously (48,50,52,88,89). This vasodilator effect is similar in time course to the effects of parenterally administered loop diuretics on venous capacitance (90). This increase in venous capacitance caused by venodilation decreases preload and thereby decreases left ventricular end diastolic pressure and pulmonary congestion in patients with acute pulmonary edema. This effect occurs prior to any diuretic effect and requires intact kidneys. It has been hypothesized that the diuretic causes release of some vasoactive component from the kidney, causing the venodilation (91). A leading candidate for the vasoactive substance is one or another of the prostaglandins, particularly prostacyclin, PGI_2, for parenterally administered loop diuretics cause release of prostaglandins by the kidney (92-97). Consequently, a component of the diuretic effect caused by loop diuretics when administered parenterally may be a result of this hemodynamic component to increase renal blood flow. Therefore, it is possible that resistance to diuretics could occur if this hemodynamic component were absent in the disease states noted previously. Though evidence is only fragmentary, it does appear that these diuretics maintain their capacity to effect renal blood flow. Whether this effect on renal blood flow in resistant states is quantitatively diminished is unknown.

Loop of Henle

Loop and thiazide diuretics block chloride reabsorption by the thick ascending limb of the loop of Henle (for review, see 98). The loop diuretics affect both the medullary and cortical segments of this segment of the nephron (99-102) while the thiazide diuretics affect only the cortical segment (103-106). Since the medullary segment is responsible for generating the concentrated medullary interstitium which, in turn, provides the driving force for reabsorption of water under the influence of antidiuretic hormone, this segment of the nephron is responsible for the capacity of the kidney to concentrate the urine and interference with its function affects concentrating ability. Similarly, the cortical segment of the thick ascending limb of the loop of Henle is responsible for dilution of the urine and interference with its function decreases the ability to form a dilute urine.

Distal Nephron (for review, see 107,108)

Amiloride blocks solute reabsorption in the distal convoluted tubule, an effect which is aldosterone-independent. Triamterene has a similar effect in the collecting duct. Spironolactone also affects the collecting duct, but its effect is dependent upon aldosterone since it is a competitive blocker of the renal tubular receptor for aldosterone. Since these diuretics reverse exchange of sodium for potassium, they are commonly referred to as potassium sparing. They are relatively weak diuretics unless increased aldosterone is an important component of the sodium retention in an individual patient. Though effective in many patients with cirrhotic liver disease, numerous studies cited previously have demonstrated aldosterone not to be the primary determinant of sodium retention in these patients.

Determinants of Access of Diuretic to its Site of Action

In addition to understanding the site at which diuretics have their predominant effect, it is also important to understand how diuretics reach their site of action, for resistance to a diuretic might occur if the disease state prevents the diuretic from reaching this site. All diuretics except those acting on the distal tubule and collecting duct must reach the tubular lumen to be effective. These diuretics, excluding osmotic agents, are all organic acids and are highly bound to serum proteins. As a consequence, they cannot reach the tubular lumen by glomerular filtration for only a small fraction of the total drug in serum is free in the circulation and can be sieved through the glomerulus. These drugs reach the luminal compartment by being actively secreted from the blood into the urine at the organic acid transport pathway of the straight segment of the proximal tubule (Figure 6) (109,110). Blocking this pathway can block access of these diuretics to their site of action and can diminish response, an effect which occurs with co-administration of probenecid (111) or in azotemia as will be discussed subsequently.

For a diuretic to reach the tubular lumen, it obviously must gain access to the systemic circulation. Orally administered drug in edematous states, theoretically might be incompletely absorbed because of an edematous bowel wall. Consequently, a possible mechanism of diuretic resistance which must be explored, includes malabsorption of orally administered drug.

Determinants of Response

Once the diuretic reaches its site of action, one must then examine the determinants of response. Since the diuretics in questios act from the luminal surface of the nephron, one might predict that amounts of drug in the urine are more reflective of that drug reaching the site of action than are concentrations in the serum. This hypothesis has been proven by our group in man with furosemide and by other groups performing similar studies with a variety of diuretics in animal models (109-111). Consequently, we have attempted to assess the determinants of response to diuretics by measuring urinary amounts of furosemide and relating these measures to response. We assume that general concepts derived

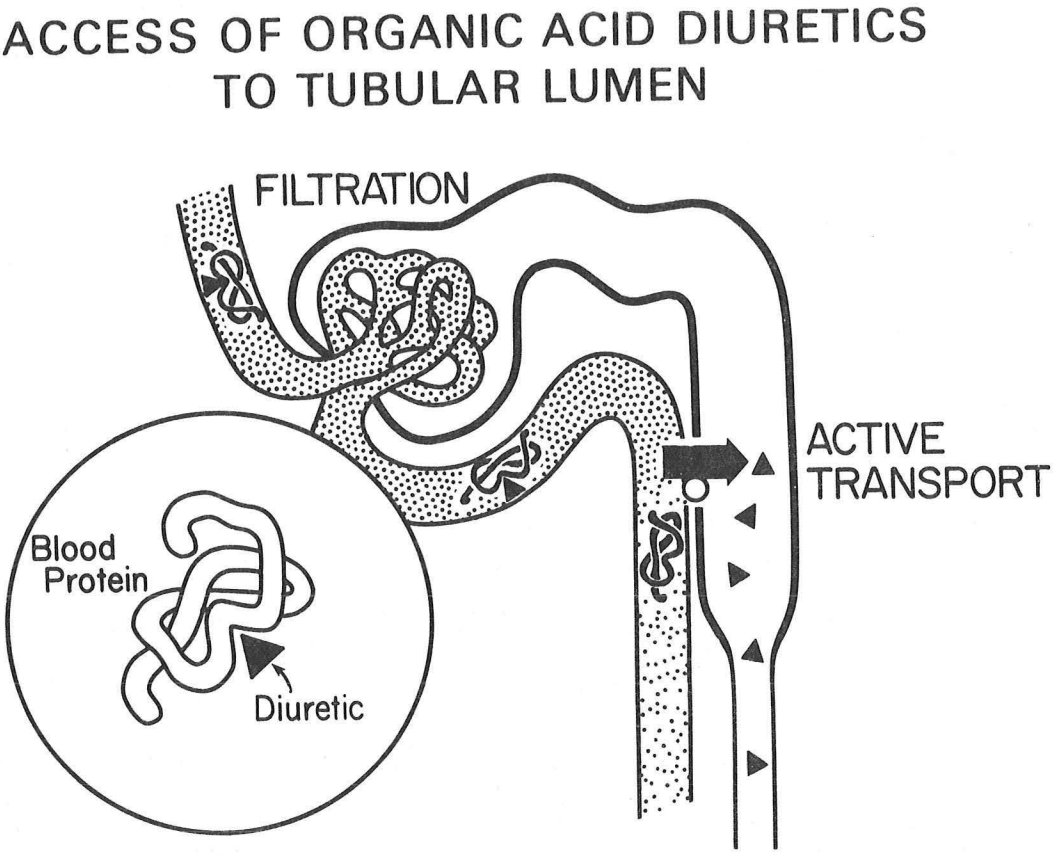

Figure 6: *Schematized illustration of route of access to the tubular lumen of a protein bound organic acid diuretic.*

from the furosemide data can be extrapolated to other organic acid diuretics.

We have performed a number of studies in normal volunteers to assess the determinants of response. Clearly the total amount of drug delivered to the urine relates to response. A 40mg dose of fursoemide results in twice the amount of drug reaching the urine as does a 20mg dose, and one observes an appropriate increase in response until the upper plateau of the dose response curve is attained in an individual subject.

In addition to the importance of the total amount of drug delivered into the urine, the time course of that delivery can also importantly affect total overall response. In studies we performed in normal human subjects administered probenecid in addition to furosemide, probenecid

altered the time course of delivery of furosemide without altering the total amount of drug delivered. In this particular case the overall response was increased (Figure 7) (111,112). A similar phenomenon has been observed with chlorothiazide and presumably applies to other diuretics (113). One should not get the impression that this is a drug interaction with potential clinical importance for it is not clear that this combination would have the same effect in patients with disease or that the increment in total response is sufficient to be important. Consequently, the main importance of this drug interaction is to define the role of the time course of delivery in addition to the importance of total delivery of drug into the urine.

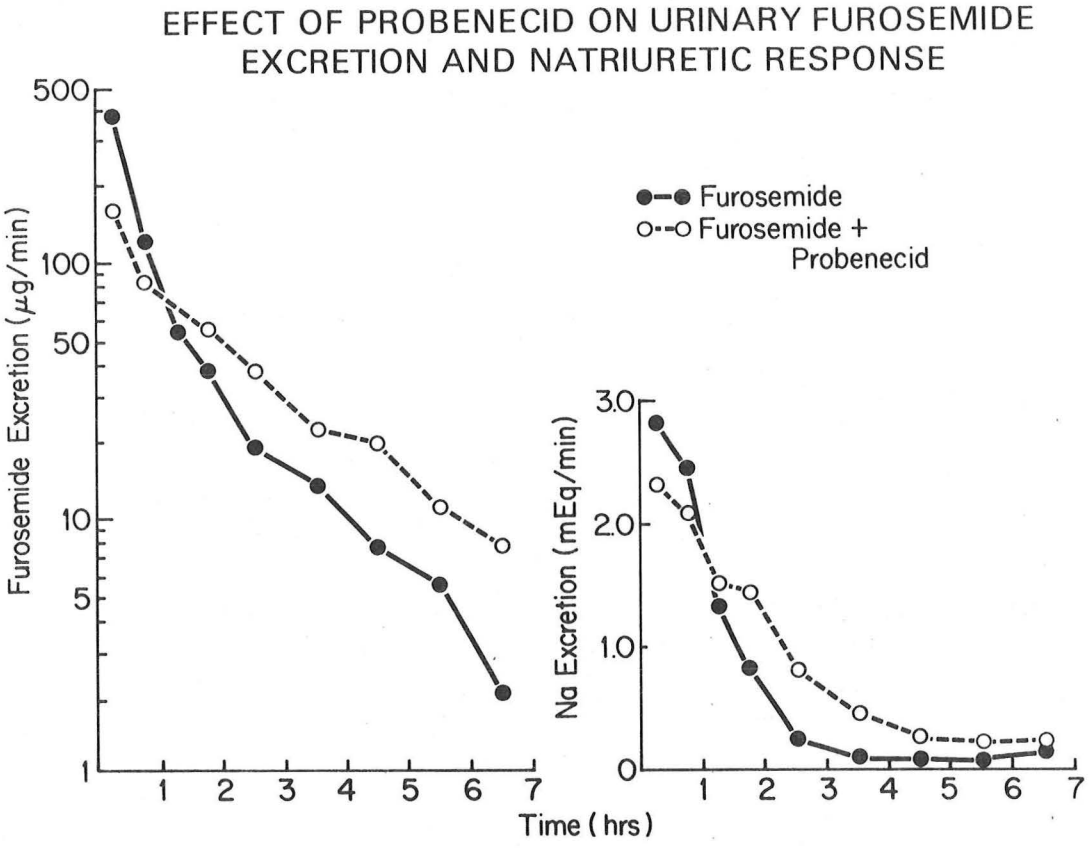

Figure 7: *Effect of probenecid on the time course of excretion of furosemide and on response. Though the total amount of furosemide excreted was unchanged, overall response increased.*

Once the drug reaches its active site there is a characteristic dose response relationship which describes the magnitude of response related to the amount of drug at the active site (Figure 8). As in most pharmacologic systems the characteristics of this relationship are a sigmoid curve when one plots the logarithm of the dose versus response.

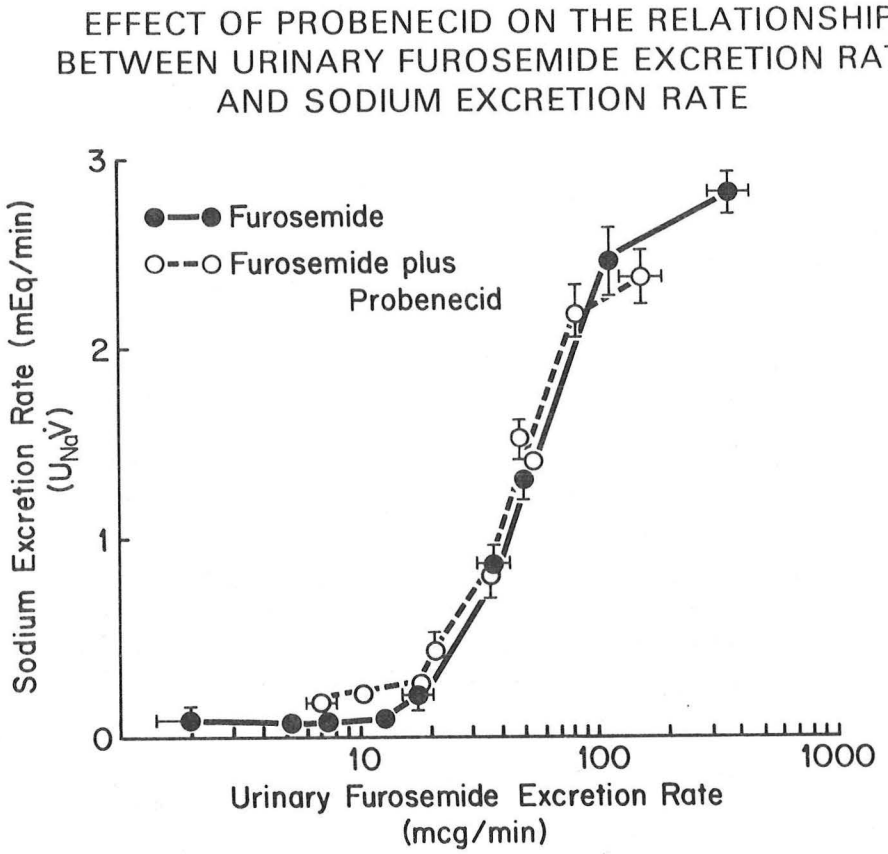

Figure 8: *Sigmoid dose-response curve relating urinary furosemide excretion rate to natriuretic response.*

Because all three of the above discussed aspects of delivery are important to response, to assess diuretic resistance one must assess the total amount of drug delivered into the urine, the time course of that delivery and the dynamics of the dose-response relationship once drug reaches its site of action. To date, very few studies have been performed assessing all of these determinants of diuretic response.

MECHANISMS OF RESISTANCE IN SELECTED CLINICAL CONDITIONS

Azotemia

The patient with azotemia often requires large doses of potent diuretics to achieve a response. One might think that the diuretic resistance in these patients occurs because of decreased glomerular filtration of solute. However, a series of studies have demonstrated that the primary cause of diuretic resistance in patients short of end stage renal failure is that accumulated endogenous organic acids of uremia block the active transport pathway for organic acid diuretics, preventing access to their site of action (114-116). As a consequence, exceedingly large doses are required to achieve enough diuretic within the tubular lumen to manifest a response. Needless to say, this tactic is at the expense of very high serum concentrations of potentially toxic diuretics, accounting for the increased incidence of ototoxicity in such patients. No studies have been performed that assess the changes in time course of drug delivery in patients with azotemia or which assess the dose response relationship in such patients. It is tantalizing to hypothesize that a diuretic which gained access to the tubular lumen by a route other than the organic acid pathway might continue to be efficacious until decrements in glomerular function in which filtration of solute becomes limiting.

Inhibition of Prostaglandin Synthesis

Administration of inhibitors of prostaglandin synthesis to normal subjects and patients with a variety of disease states diminishes basal solute and water excretion and diminishes the response to diuretics (117-122). These findings have been cited to implicate prostaglandins as potential mediators of the effects of diuretics. It is important to note that the various inhibitors of prostaglandin synthesis are also organic acids and potentially could block transport of organic acid diuretics to their site of action. We have performed a series of studies in normal subjects probing the mechanism of effect of indomethacin to decrease the response to intravenously-administered furosemide by assessing the determinants of response noted previously. Indomethacin decreased the response to both 20 and 40mg doses of furosemide without affecting the total amount of furosemide delivered into the urine or the time course of drug delivery, data similar to that from studies in dogs (Table 1, Figure 9)(123,124).

EFFECT OF INDOMETHACIN ON TOTAL URINARY EXCRETION OF FUROSEMIDE

	24 hr urinary furosemide (mg)	
	40 mg dose	20 mg dose
Furosemide alone	19.7 ±2.2	9.3 ±1.4
Furosemide + Indomethacin	18.8 ±1.7	9.4 ±0.4

TABLE 1

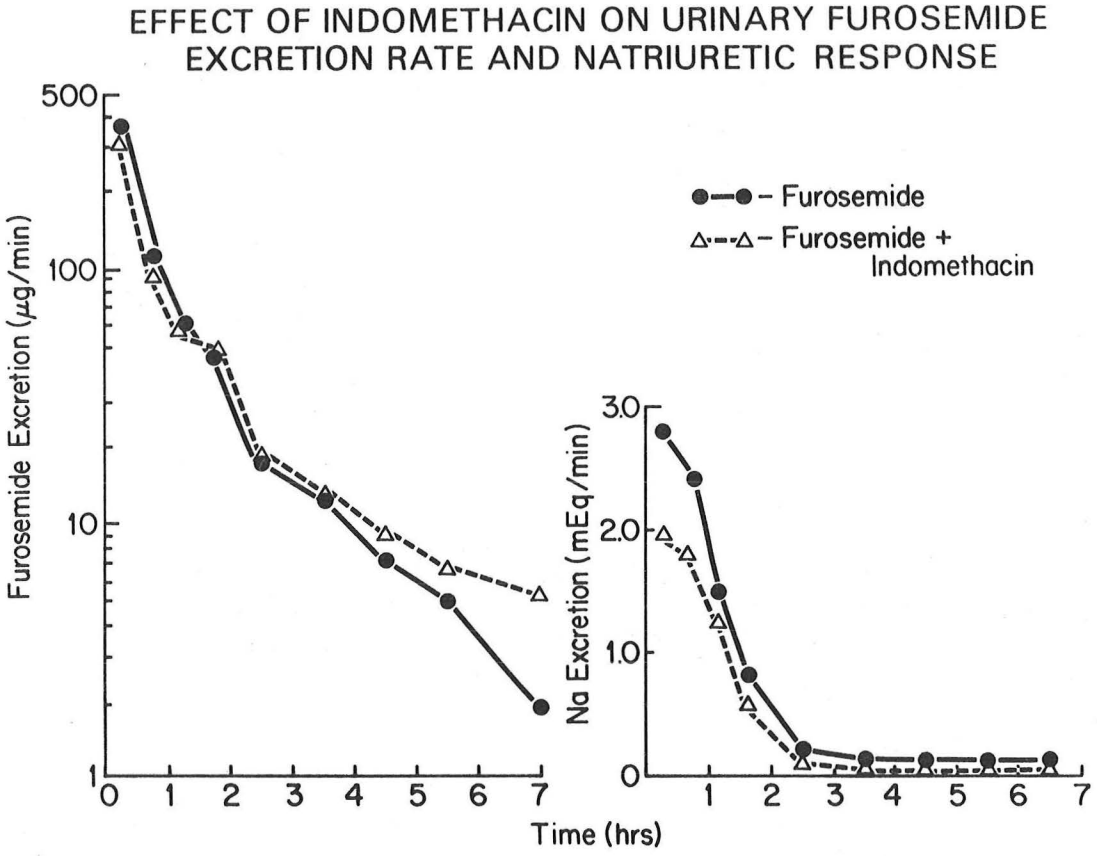

Figure 9: *Effect of indomethacin on the time course of excretion of furosemide and on response.*

Assessed as the effect on the dose response relationship, however, indomethacin changed the dose response characteristics in a manner similar to that of a non-competitive inhibitor (Figure 10).

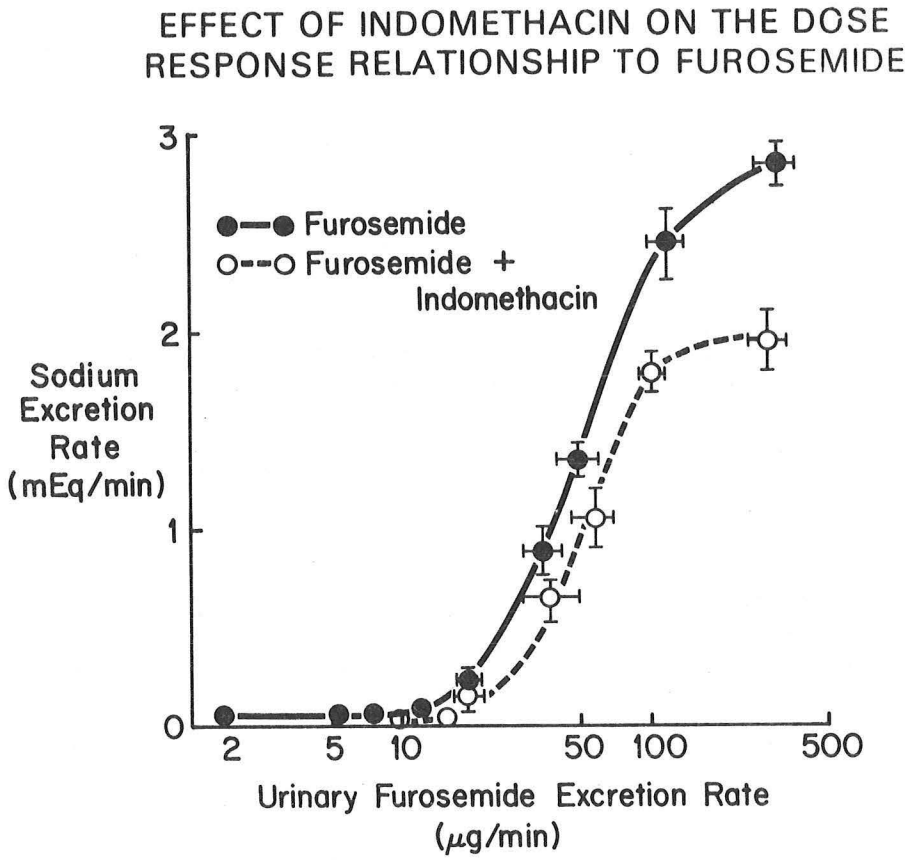

Figure 10: *Effect of indomethacin on the dose-response relationship to furosemide.*

This effect was associated with a decrease in furosemide-stimulated prostaglandin release by the kidney (125). The shift in the dose response curve caused by indomethacin could be caused by a number of mechanisms. Studies in which dogs have been instrumented for monitoring a variety of hemodynamic parameters have demonstrated that indomethacin decreases the hemodynamic effects of furosemide (126-130). Whether or not there is an additional inhibition of the tubular effect of the diuretic is unclear. The change in the dose response relationship of furosemide by indomethacin demonstrated in man may well occur because indomethacin decreases the usual effects of parenterally administered furosemide to increase renal blood flow, thereby blocking the decrease in filtration fraction, thereby decreasing backleak and decreasing rejection of solute by the proximal tubule. In this manner, indomethacin's effect could solely be a hemodynamic interaction with furosemide without affecting the tubular responsiveness to furosemide and yet manifest as the change in the dose response relationship as has been demonstrated. On the other hand, an additional tubular effect may also occur. Its elucidation will require further study.

Edematous States

Our laboratory has similarly studied the determinants of response to diuretics in several edematous states, including congestive heart failure, cirrhotic liver disease, and nephrotic syndrome. Each of these groups of patients manifested a spectrum of severity of disease. We demonstrated that the total amount of drug delivered into the urine was the same in these subjects as in normal volunteers (Table 2). Additionally, the bioavailability or the absorption of furosemide was unchanged in this group of edematous subjects. In some patients with decreased renal function, there was a change in the time course of drug delivery into the urine, though this change was slight. In patients with relatively normal renal function there was no difference in the time course of drug delivery (Figure 11).

FRACTION OF FUROSEMIDE EXCRETED UNCHANGED AFTER ADMINISTRATION OF DIFFERENT DOSES

	Dose of Furosemide		
	20mg	40mg	80mg
Intravenous administration			
Normal	0.475 ± 0.026	0.492 ± 0.156	0.591 ± 0.094
CHF		0.440 ± 0.194	
Oral administration			
Normal		0.125 ± 0.105	0.144 ± 0.029
CHF		0.124 ± 0.075	

TABLE 2

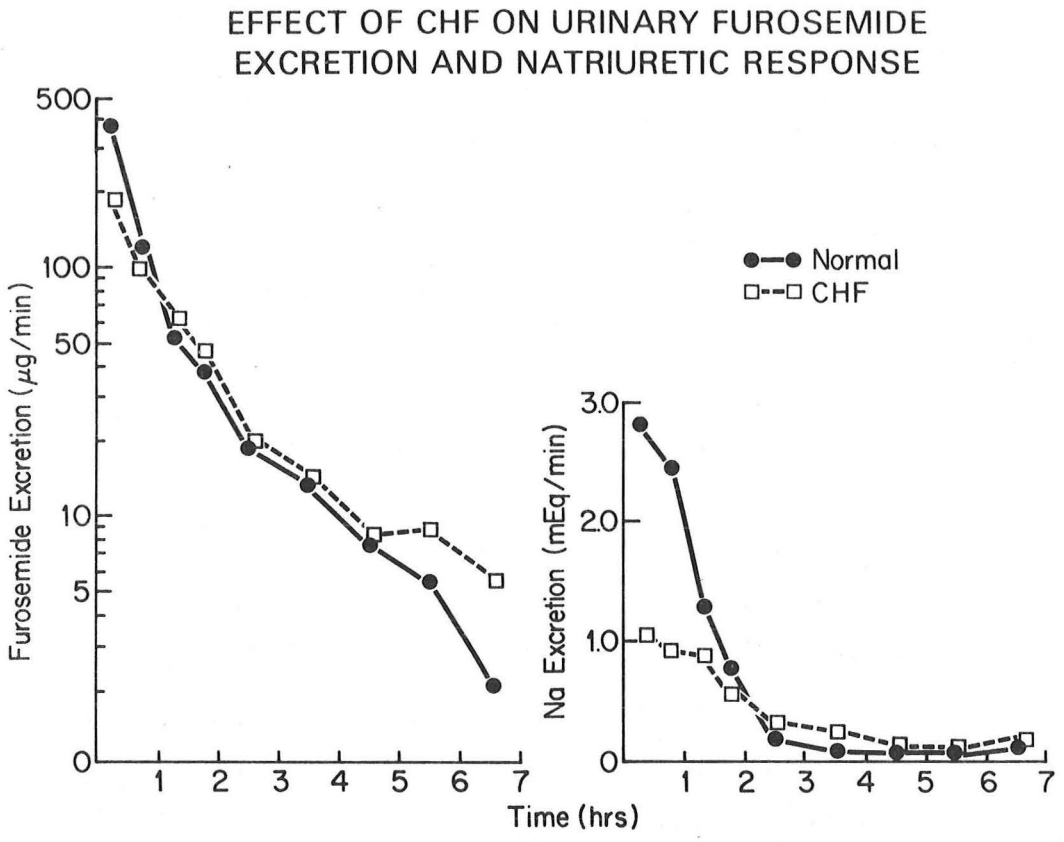

Figure 11: *Time course of excretion of furosemide and of response in patients with congestive heart failure.*

The dose response relationship, however, was markedly changed (Figure 12) (131).

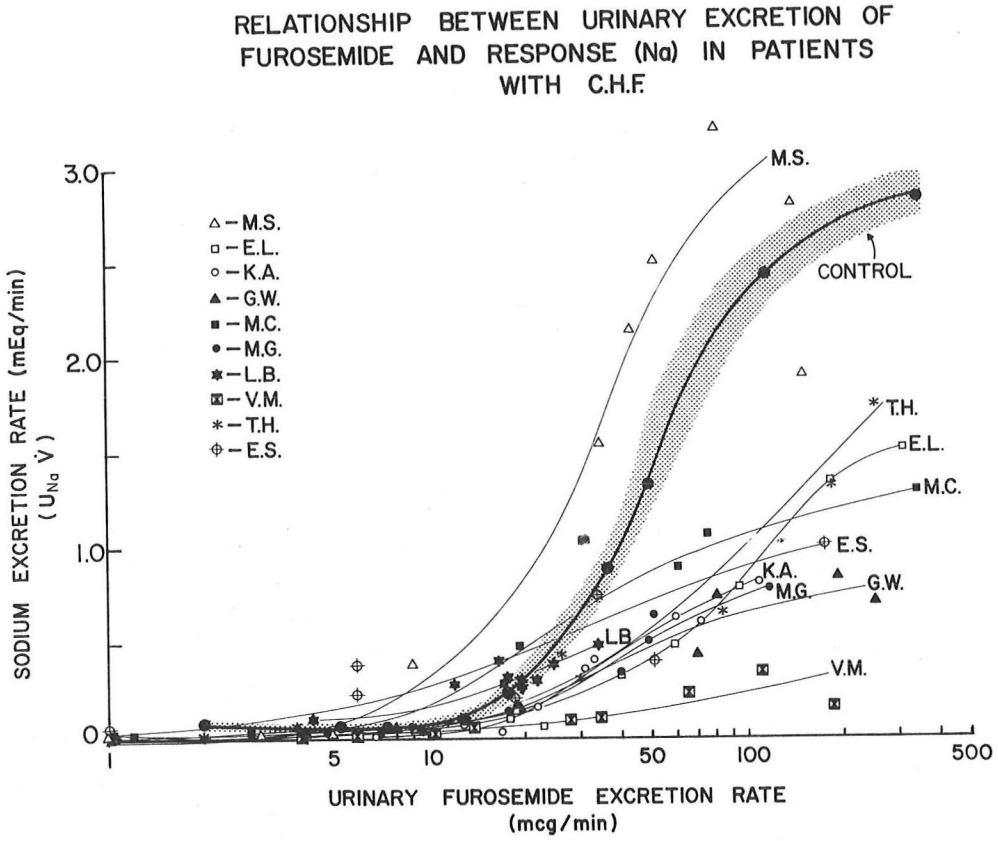

Table 12: *Dose response relationship to furosemide in patients with congestive heart failure.*

In these patients with a variety of diseases, no clear-cut pattern of change emerged when assessing all of the different patients we have studied. It was clear that the dose response relationship was shifted to the right, but in addition the contour of the dose response relationship was changed. Possible mechanisms for this effect are many, and essentially encompass the potential pathophysiologic mechanisms of sodium retention in these disease states. It is unlikely that decrements in glomerular

filtration play a predominant role, for most of these patients had near normal glomerular filtration rates and for reasons cited in the previous discussion of pathophysiology. Increases in proximal reabsorption of solute either through changes in hemodynamics or through changes in avidity for solute could affect response and might be responsible for these shifts in the dose response relationship. Similarly, the changes in solute handling by the ascending limb of the loop of Henle could well be responsible for the observed shifts in the dose response relationship. This possibility is especially intriguing since furosemide's site of action is the ascending limb of the loop of Henle. It is unlikely that aldosterone excess accounts for the changes observed in these patients for the sodium to potassium ratio in the urine was no different from that of normal subjects. The mechanisms of this shift require further elucidation.

A shift in the dose response relationship is the most specific means for defining diuretic resistance and in addition might be used as a probe to explore the pathophysiology of solute handling in such disease states. For example, if increased proximal reabsorption of solute caused the abnormal dose response relationship, one might expect co-administration of an agent inhibiting proximal reabsorption to shift the dose response relationship more towards normal. In the few patients in which the effects of concomitantly administered acetazolamide were studied only a parallel shift upward of the abnormal curve occurred (Figure 13).

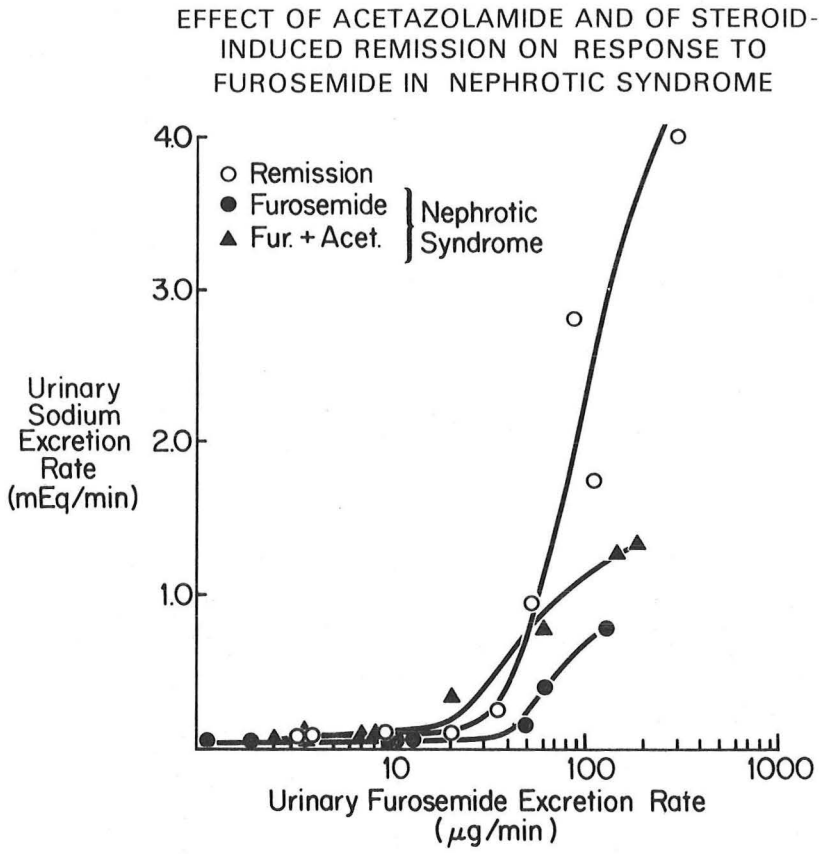

Figure 13: *Dose response relationship to furosemide in one patient during remission and during an exacerbation of the nephrotic syndrome with and without coadministration of acetazolamide.*

Additionally, to support the hypothesis that glomerular filtration rate is not the determinant of this changed dose response curve, we studied one patient who received a LeVeen shunt for cirrhotic ascites. Before the shunt this patient had a markedly diminished response to furosemide with a flattened dose response relationship. After the shunt, this patient's glomerular filtration rate increased dramatically with a decrease in her serum creatinine from approximately 3 to less than 1. Her dose-response relationship after the shunt, however, was still considerably abnormal (Figure 14).

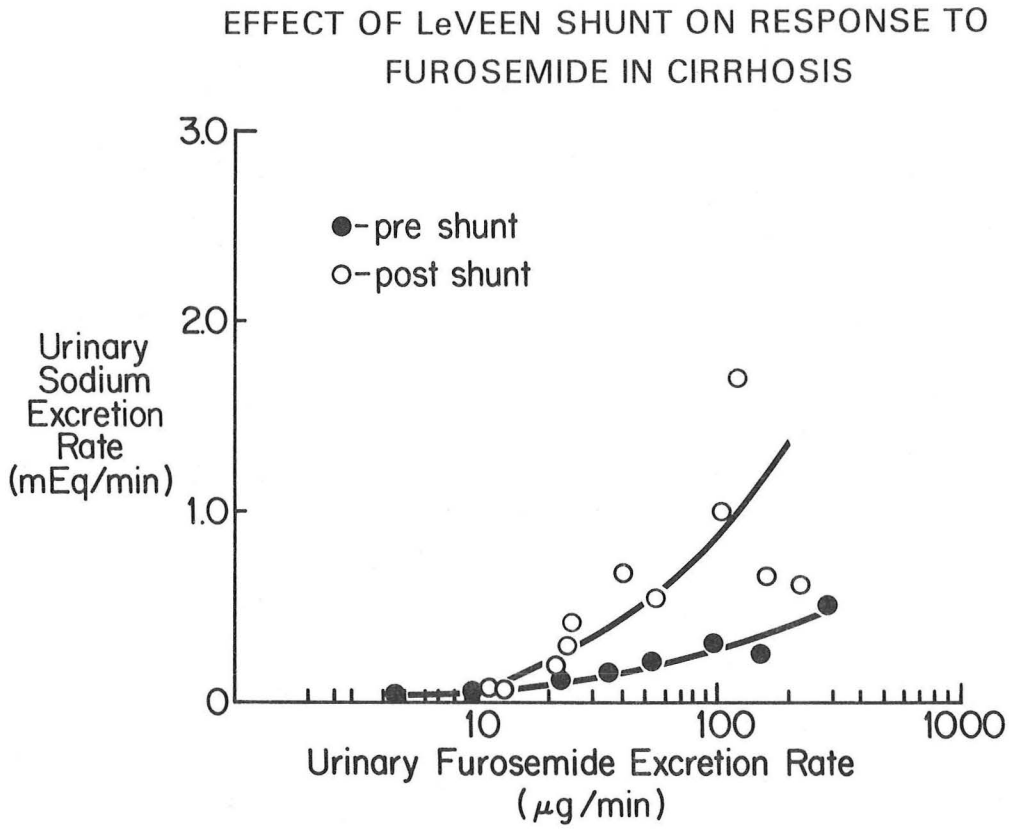

Figure 14: *Dose response relationship to furosemide in one patient before and after a LeVeen shunt.*

Consequently, it is clear that changes in the dose response relationship to furosemide, and presumably to other diuretics, occur through as yet undefined mechanisms. Preliminary results indicate that changes in glomerular filtration rate or increased proximal reabsorption of solute are not responsible for the observed changes. Similarly, it is unlikely that increased reabsorption of solute by the distal tubule under the influence of aldosterone is etiologic. Changes in handling of solute or activity of the chloride pump in the ascending limb of the loop of Henle is a candidate for the mechanism of this change. But additionally, disease-induced changes in the furosemide receptor-mediator-response relationship may well be implicated. Since prostaglandins have been proposed as potential mediators of the response to diuretics, it will be extremely important to assess their potential role in attempts to elucidate the mechanism(s) of change in response to diuretics in these various disease states.

CLINICAL RESPONSE TO RESISTANT STATES

In azotemic patients or patients with other disease states in whom glomerular filtration is diminished, the mechanism of resistance appears to be lack of delivery of diuretic into the tubular lumen because of competition for transport by accumulated endogenous organic acids. This blockade can be overcome to a degree by administration of greater amounts of drug, and such a maneuver can be attempted empirically. If one had the capacity to measure amounts of diuretic appearing in the urine, however, one might better be able to gauge what dose to attempt and whether or not other factors might additionally be responsible for the resistance to the diuretic in one's individual patient. For example, if one noted that adequate amounts of furosemide were attained in the urine by administration of a 200mg dose, little would be gained, other than the increased risk of toxicity, by increasing the dose to greater amounts. This tenant may be particularly important in subjects with acute renal failure in whom some physicians administer escalating doses of potent diuretics in an attempt to "open up" the kidney. It is conceivable that one might be able to define a dose of furosemide above which little is gained in terms of increased delivery into the urine, but at which more is at risk in terms of toxicity.

If there is sufficient delivery of drug into the urine, a next step to assess potential mechanisms of resistance is to measure urinary electrolytes. If the electrolyte pattern in the urine indicates secondary hyperaldosteronism, blockers of the renal effects of circulating aldosterone might be efficacious. However, as has been demonstrated in the previous discussion, the abnormality in dynamics of response in patients in whom delivery of drug is normal, relates more to the primary disease than to readily definable changes in renal function. One must attempt to treat the primary disease expecting the dynamics of response to return towards normal. It should be emphasized, however, that even though coadministration of diuretics that work at other segments of the renal tubule do not normalize the dynamics of response to diuretics, there is still an additive effect, and one may be able to attain a needed diuresis by logical addition of drugs such as acetazolimide or aminophyllin to a regimen of potent loop diuretics.

In summary, there are many candidates for mechanisms of resistance to diuretics, including changes in handling of the diuretics themselves in addition to the abnormalities in the dynamics of the response to diuretics which are part and parcel of the pathophysiology of the solute retention in the variety of disease states in which resistance to diuretics occurs. Much can be learned with future studies of this subject. Hopefully, a pharmcologic approach to diuretic resistance may shed some light on the mechanisms of edema formation and the changes in renal solute handling that occur in edematous disorders.

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