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CLINICAL USE OF DIURETICS

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Introduction:

Diuretics are pharmacologically active compounds which increase net excretion of solute and water. A clinical discussion on the use of these agents can be divided into two fundamentally different parts. The first section of this presentation will review the recent physiological findings pertinent to understanding the mechanisms by which diuretics exert their effect. The second and the major section discusses each of the major families of diuretics separately with special emphasis on: mechanism of action; complications; advantages; disadvantages, and the clinical indication of that particular group of diuretics.

Physiological Background:

Numerous exciting discoveries have recently been made which have clarified our understanding of the specific functions of the various segments of the renal tubules. It would be a gross oversimplification to attribute the degree of diuresis simply to inhibition of these transport processes, however, a review of these recent advantages does provide for a convenient beginning by which to consider the mechanism of action of the diuretics. The knowledge of the transport properties will contribute to a more rationale approach to patients who are in fluid-electrolyte imbalance states, or to those patients who have proven renal disease.

In Figure 1 are shown the schematics of various segments of mammalian nephron. These divisions are made principally on functional basis. Each segment has uniquely different properties. A detailed description of these various transport functions is beyond the scope of this presentation, however, Figure 2 does identify the general transport processes of these segments which can be influenced by the various pharmacological agents. As can be seen, each segment has a fundamentally different active transport system. It is interesting to speculate that it is this difference in the basic properties of the different nephron segments which account for localized action of the various diuretics. For example, as will be shown later, a drug which specifically inhibits chloride transport would not be expected to inhibit transport processes anywhere else except the thick ascending limb while a specific inhibitor of aldosterone would only act in the distal tubule.

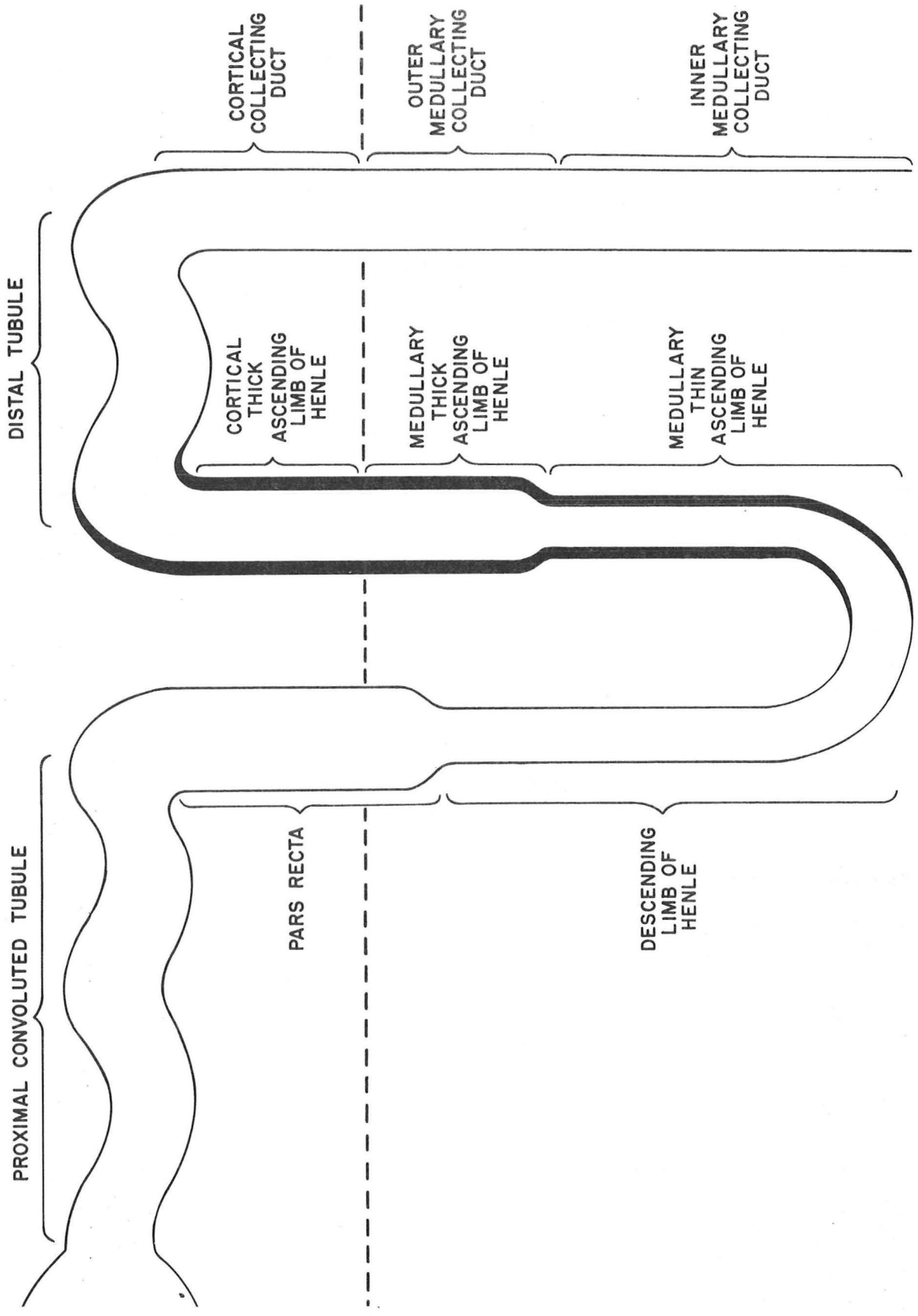

Figure 1: Various anatomical segments of the mammalian nephron.

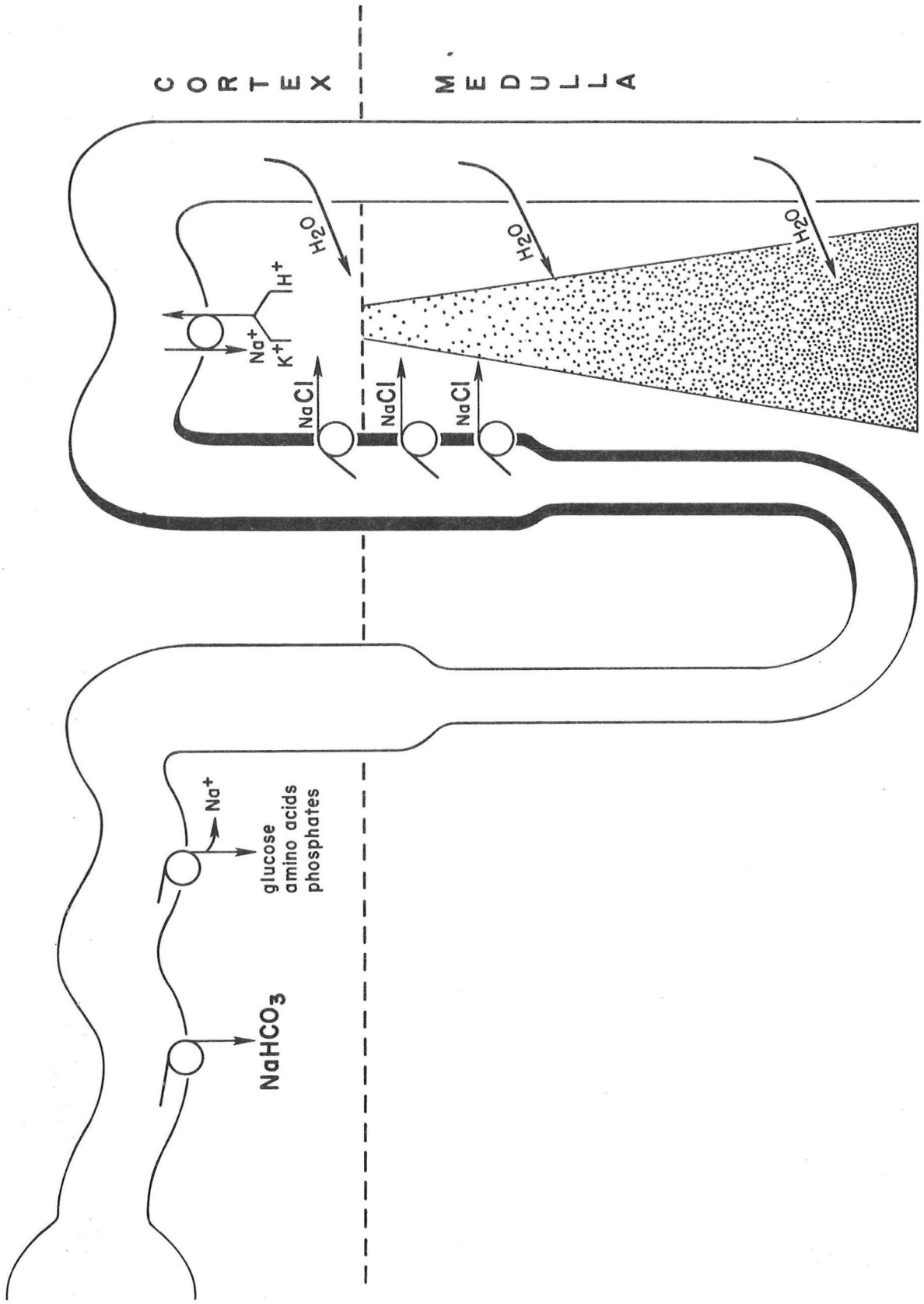

Figure 2: Major transport processes influencing net transport of solute and/or water out of various nephron segments.

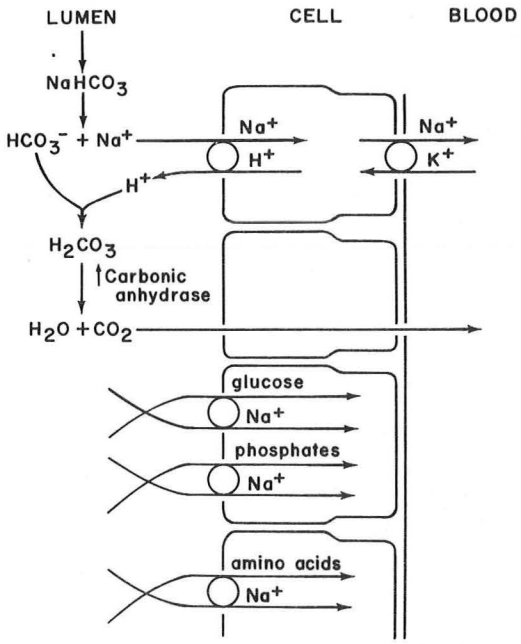

Figure 3: Schematics of transport processes in the proximal convoluted tubule.

Net transport of fluid out of the proximal tubule can be considered the sum of three components: 1) active outward transport of solute; 2) passive outward transport of solute; and 3) back-leak of reabsorbate. To our knowledge, diuretics do not directly effect the back-leak of reabsorbate. It is for this reason that only the first two components of transport will be considered in this presentation. Figure 3 demonstrates the schematics of those active outward transport processes existing in the proximal convoluted tubule. Of these, the outward transport of sodium bicarbonate provides the principal driving force for net efflux of fluid.

Of more minor significance is the active outward transport of glucose, amino acids and phosphates to which sodium seems to be coupled by passive mechansisms which have not been completely elucidated.

The movement of water is coupled passively to the above mentioned processes. The net effect of active solute and fluid transport is the concentration of the residual intraluminal constituents. The major electrolyte gradient which is developed by this process is elevation of intraluminal chloride to concentrations higher than on the blood side. Conditions have thus been generated which allow sodium chloride (with its osmolal complement of water) to passively diffuse down its concentration gradient. Currently there is no evidence to suggest that active sodium chloride transport plays any major role in abstraction of fluid out of the proximal convoluted tubule.

Under normal circumstances the proximal convoluted tubule reabsorbs some 50-75% of glomerular filtrate. Since the normal filtration rate is

about 180 liters/day this means that roughly 100 liters of filtrate are reabsorbed in the proximal tubule. Thus at first glance one might expect an increase in urine flow up to 30 liters/day with a 30% inhibition of net proximal transport as can be accomplished with carbonic anhydrase inhibitors. However, this is not the case and in fact urine flow is rarely increased more than 4 times the control values with acetazolamide (Diamox). The reason for this is that the tubules distal to the proximal tubule have a very high reserve capacity to reabsorb more sodium chloride than under normal conditions. In general, inhibition of the distal transport processes (thick ascending limb of Henle) will give a more effective diuresis than can be accomplished with pure proximal inhibitors.

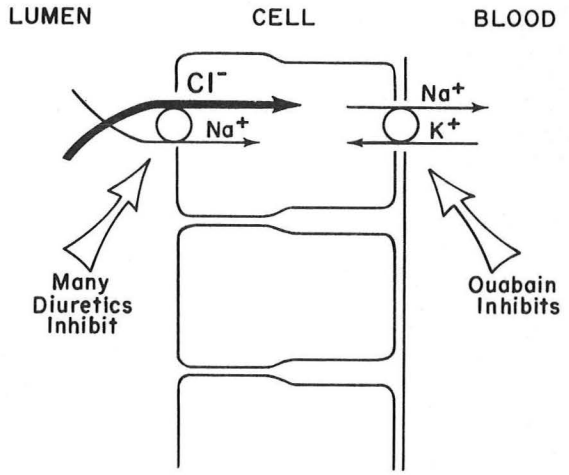

Figure 4: Active chloride transport in the thick ascending limb of Henle.

Figure 4 depicts schematically the electrogenic chloride pump which we have recently identified in the thick ascending limb of Henle. In these studies it was further shown that sodium transport is primarily a passive process coupled to active transport of chloride. In addition, this segment was found to be completely water impermeable. The combination of these trasnport processes allows for generation of luminal fluid which is less concentrated than adjacent interstitium by pumping out more solute than water. The same fundamental process is present in both the medullary and cortical thick ascending limb of Henle. However it must be emphasized that the inhibitor or stimulation of these two segments will have entirely different physiological consequences with respect to the clinical fluid balance states.

It is now well established that the kidney can excrete urine either less or more concentrated than plasma depending on the homeostasis of a given patient. The generation of dilute urine is basically a function of the cortical thick ascending limb of Henle. It is this segment which forms a free water, C_{H_2O}. (Free water is that amount of water which can be removed from urine and leave the residual iso-osmolar with respect to plasma, usually expressed in ml/min.) Thus inhibition of cortical thick ascending limb of Henle would impair the ability to form maximum dilute urine, while increased delivery of salt from the proximal tubule to the cortical thick ascending limb of Henle would allow for greater excretion of free water.

This latter consequence would be especially beneficial to patients with hyponatremia and associated expanded extracellular fluid compartment. In the volume expanded patient the inhibition of free water clearance may be associated with even a further decrease in plasma solute concentrations. On the other hand, in contrast with the cortical thick ascending limb of Henle, the medullary thick ascending limb of Henle is responsible for generation of concentrated urine by pumping more solute than water into the interstitium. As the fluid courses through the collecting duct it will osmotically equilibrate with the hypertonic medullary interstitium and form concentrated urine under the influence of antidiuretic hormone When the urine is more concentrated than plasma, negative free water ($T^{c}_{H_2O}$) has been formed (that amount of water that must be added to the urine to make it isotonic with respect to plasma, ml/min). Thus inhibition of medullary thick ascending limb of Henle would lead to an inability to make maximally concentrated urine.

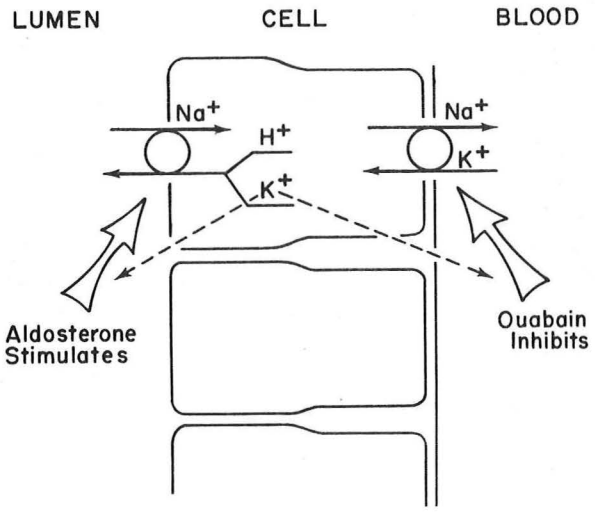

Figure 5: Schematics of active transport processes across the distal convoluted tubule. The broken line from intracellular potassium shows its passive diffusion down concentrating gradient.

Figure 5 depicts the superficial features of the transport mechanisms existing in the distal convoluted tubule. The most important process in this segment is the cation exchange pump existing presumably at the luminal surface. This pump can be stimulated by aldosterone. In this segment each time a sodium ion is reabsorbed a cation (either hydrogen or potassium) would be secreted. Though this coupling may not be rigorously one to one, it is convenient to think of distal tubular function in these terms. Whether potassium or hydrogen is secreted for each absorbed sodium would partly be dictated by the acid-base balance of a patient, and probably by the serum concentration of potassium. For illustrative purposes it is convenient to think that a "regulatory gait" swings to shut off hydrogen secretion allowing for potassium exchange during metabolic alkalosis. Inhibition of this pump would lead to conservation of hydrogen and potassium while resulting in greater fractional loss of sodium while stimulation of the pump, either by primary or secondary aldosteronism, would lead to hypokalemic alkalosis.

DIURETICS

As stated in the introduction diuretics are a group of compounds which increase urine flow by varying renal tubular mechanisms. A number of different classification systems have been published. For purposes of this discussion the diuretics are grouped into 6 different families. The generic and trade preparations are listed in the appendix with appropriate doses to be administered.

Mercurials:

Mechanism of action - A number of previous publications have focused their attention on two different aspects by which organic mercurials exert their diuretic effect: 1) nephron localization, and 2) intracellular mechanism of action. Diuresis secondary to mercurials does not begin until after a 30-60 minute delay after intramuscular injection with peak diuresis effect not occurring until 2-3 hours after administration. The reason for this delay is that the mercurial diuretics are bound to plasma proteins with only a small fraction existing either in the free form or complexed to small molecular weight compounds such as cysteine. These small complexes or the free diuretics are then either secreted by the pars recta or filtered through the glomerulus. Nevertheless the mercurial ion binds to sulfhydryl groups of the intracellular protein. The main physiological effect of these events is exerted in the cortical and medullary thick ascending limb of Henle. Though the mercurials bind nonspecifically to most sulfhydryl containing proteins, the specific effects of these diuretics are thought to be mediated primarily by their inhibition of the chloride pump in the thick ascending limb of Henle. To a lesser extent the cation exchange pump within the distal tubule also seems to be inhibited. The mercurial diuretics inhibit the maximal diluting and concentrating capacity of the kidney since they act in the cortical and medullary thick ascending limb of Henle.

Complications - Mercurials as a family are relatively safe diuretics. Under normal usage the complications secondary to mercurials are mainly due to their diuretic effects. Since the chloride pump is specifically inhibited, there is a disproportionately large increase in chloride excretion leading to hypochloremic alkalosis. Mercurials should not be used repeatedly in states with low filtration rates (i.e. contra-indicated in most types of renal disease) since this may lead to mercurial toxicity. Various types of hypersensitivity reactions have been described, but these are relatively rare.

Advantages - Mercurials offer relatively predictable diuresis without the degree of kaliuresis as with the more potent diuretics, ethacrynic

acid and furosemide. A minor advantage arises in treatment of congestive heart failure on an out-patient basis in a population that cannot be relied on to take their medications as prescribed. With the intramuscular injection of mercurials one is assured that the patient in fact has received the diuretic.

Disadvantages - A number of disadvantages are associated with the use of mercurials: 1) the degree of diuresis in congestive heart failure is not as large as with furosemide or ethacrynic acid; 2) it must be given intramuscularly; and, 3) mercurials are not effective in metabolic alkalosis.

Use - Mercurials may be used in most cases with increased extracellular fluid volumes providing that the renal function is normal; however, mercurials offer limited, if any, advantage over furosemide. It is well suited for out-patient treatment of congestive heart failure giving mild and predictable diuresis without the same danger of hypokalemia as with the thiazides or with the more potent diuretics.

Benzothiazides:

Mechanism of action - Thiazides have two basic sites of action within the nephron. Its principal diuretic effect is derived from inhibition of the cortical thick ascending limb of Henle as evidenced from decrease in free water formation. Thiazides also have a proximal effect mediated through the carbonic anhydrase inhibitory powers, but this effect is clearly of minimal significance clinically. The ability to make $T^{C}_{H_2O}$ does not seem to be affected during thiazide-induced diuresis.

Complications - The benzothiazide group of diuretics are associated with great variety of reported complications, however many of these are based on reports of single or small number of cases. For this reason the evidence for causal relationship is tenuous for such events as hepatitis, pancreatitis or cutaneous vasculitis. A macular papular skin rash seems to be more common with the thiazides than with the other diuretics but its occurrence also is relatively rare. The more established complications include: hypokalemic alkalosis; occasional production of hyperglycemia; increase in serum uric acid; and decrease in glomerular filtration rate with increased BUN. The hypokalemic alkalosis is secondary to increased delivery of sodium to the distal tubule. Since diuretics are mainly administered in conditions with increase in extracellular fluid volume (such as congestive heart failure and ascites with liver disease) there exists concommitant secondary hyperaldosteronism leaving the distal tubule more sensitive to increased sodium delivery. With increase reabsorption of sodium there is an increase excretion of hydrogen and potassium via

the cation exchange pump, Figure 5. The resultant hypokalemia increases proximal reabsorption of the bicarbonate thus aggravating existing alkalosis. In addition, contraction alkalosis secondary to increase excretion of water plays a role in development and/or maintenance of alkalosis secondary to thiazides. The hyperglycemia is of two origins: 1) insensitivity of the beta cells of pancreas to normal stimulation to release of insulin and 2) decrease peripheral utilization of glucose. Both of these may be mediated in large part through hypokalemia and only to minor extents (if at all) secondary to thiazides themselves. Increase levels of serum uric acid is mainly due to volume contraction leading to increased proximal reabsorption of uric acid; however, other factors (which are of more minor significance) probably also are responsible such as increase in uric acid production and/or inhibition of uric acid secretion. The rise in BUN which often is seen with patients on thiazides results principally from contraction of effective arterial volume with resultant decrease in glomerular filtration rate. Mild elevation of serum calcium occurs in almost all of the patients who are put on thiazides (intact parathyroid glands are not necessary); however, development of clinically significant hypercalcemia is rare.

Advantages - Thiazides may be administered orally and have a prolonged effect. This results in a diuresis which is steadier than can be obtained with the more potent short-acting diuretics. Thiazides are more effective antihypertensive agents than furosemide and ethacrynic acid when equal volume contractions have been achieved. This probably is mediated by inhibition of vasopressor actions of various substances by the thiazides.

Disadvantages - Besides the obvious disadvantages listed under complications, thiazides are more refractory in dilutional hyponatremia than furosemide and ethacrynic acid.

Use - Thiazides are especially useful in those patients who require an antihypertensive effect together with a mild diuresis. Thus thiazides are indicated in many patients with congestive heart failure and a mild degree of hypertension secondary to arteriosclerotic cardiovascular disease.

Furosemide and Ethacrynic Acid:

Mechanism of action - Furosemide and ethacrynic acid are not similar in chemical structure; however, they may be considered together because of the similarity in physiological action. Currently we do not know whether these two diuretics exert their effect identically at the molecular level, but the patient's overall diuretic response to these two drugs is comparable. Both are extremely potent diuretics. In each the principal diuretic response arises from inhibition of both the medullary and cortical thick

ascending limb of Henle (both inhibit the maximal diluting and concentrating ability of the kidney). With both diuretics the mean sodium excretion increases more than with the thiazides or mercurials whereas the mean values for potassium output are less. Furosemide, in addition to the ascending limb affect, also has a mild carbonic anhydrase inhibitory power. Currently it is not clear whether the proximal inhibition by furosemide is of clinical significance. Both drugs potentiate maximal diuresis produced by thiazides, but reportedly thiazides have no effect on the pattern of water or electrolyte excretion when given to an animal or man undergoing diuresis with furosemide or ethacrynic acid. (In unconfirmed reports from Duke it is claimed that some patients with anasarca who are receiving maximum doses of furosemide and are refractory will increase their urine output when thiazides are given in addition to furosemide.) Both diuretics have their onset of action almost immediately when given intravenously, and have a much shorter duration of action than mercurial or thiazide diuretics.

Complications - Ethacrynic acid and furosemide both may predispose a patient to ototoxicity. This complication has been associated much more frequently with large doses of these diuretics in a setting of low creatinine clearance. The mediating mechanism is not clear, however, it has been argued that the drugs acutely change the electrolyte compositions of the endolymph in the inner ear leading to secondary changes in the outer hair cells. If this were the mechanism then furosemide and ethacrynic acid should have the same degree of ototoxicity. It is difficult to be certain the exact incidence of ototoxicity since most of the reports are single cases or based on a small number of cases. However, I feel that ethacrynic acid probably is associated with a greater incidence. In each case the ototoxicity usually is acute and transient, but with both drugs permanent loss of hearing has been reported. To date there has been a much greater number of permanent hearing losses attributed to ethacrynic acid than to furosemide. Whether this will be confirmed in the future in large prospective groups remains to be seen, however, I currently would favor furosemide over ethacrynic acid. However, this point is not well anchored and case reports have appeared in which transient hearing loss occurred with one diuretic only to recur when challenged with the other. There are other complications of furosemide and ethacrynic acid which are similar to those of chlorothiazides and secondary to their potent diuretic effect. For example, both drugs may produce significant rise in BUN and serum creatinine due to a fall in glomerular filtration rate associated with a contraction of the effective arterial circulatory state. This seems to be especially a worrisome feature in those patients who are in a tenuous low cardiac output state. The serum uric acid levels also are increased acutely when furosemide and ethacrynic acid are administered. This may be secondary to volume contraction. These diuretics probably do not influence carbohydrate metabolism in similar fashion to

thiazides. Most of the larger well controlled studies, as well as our own experience, have failed to demonstrate any increase in the fasting blood sugar, glucose tolerance curves, nor do they seem to precipitate frank diabetes. There are few case reports supporting the view that carbohydrate metabolism in fact is affected, however, the incidence must be significantly less than with the thiazides. The lack of effect on carbohydrate metabolism may be because the urine sodium/potassium excretion rates are much higher with furosemide and ethacrynic acid than with the thiazides, thus resulting in less potassium deficiency for the same degree of volume contraction. As with many other drugs, various idiosyncrotic reactions have been reported. In addition, furosemide increases urinary excretion of calcium, and may rarely produce tetany. Also, furosemide may cause salicylate intoxication in some patients receiving high doses of aspirin.

Advantages - These two drugs are extremely potent and rapid in onset. In spite of the remarks in previous paragraphs, the complications due to these drugs are relatively rate, and principally secondary to overly rapid diuresis. Both of these drugs are relatively effective regardless of the underlying fluid-electrolyte or acid-base balance state of the patient. Thus diuresis can be expected with patients in metabolic or respiratory acidosis or in patients with hyponatremia, hypokalemia, or hypochloremia. There appears to be no increase in renal toxicity with a compromise in glomerular filtration rate.

Disadvantages - There are essentially no disadvantages. Patients should be followed at regular intervals with monitoring of serum electrolytes and periodic checks of liver function studies.

Use - Ethacrynic acid and furosemide may be used in most cases where diuresis alone is indicated. If a hypotensive affect is desired in addition to minimal diuretic demands, then benzothiasides should be used on outpatient basis in place of ethacrynic acid or furosemide. It is not necessary to start potassium supplements with ethacrynic acid and furosemide on a routine basis. Distinct minority of patients will develop hypokalemia with these and the thiazide diuretics, however, great majority of the patients will not. It is advisable to check the patients serum potassium approximately one to two weeks after these drugs are first started. In on this or subsequent checks the serum potassium is low, then supplementation with potassium chloride is indicated or triampterene may be added to the diuretic regime in reliable patients to control the serum potassium concentration.

Carbonic Anhydrase Inhibitors:

Mechanism of action - The diuretic effect of these compounds arises principally from the proximal inhibition of carbonic anhydrase. This leads

to an increase in bicarbonate excretion and increase in free water formation. In the distal tubular cell there is less hydrogen ion formation with inhibition of carbonic anhydrase. With decrease hydrogen ion formation (and consequent decrease in bicarbonate regeneration) there is increase loss of potassium into the distal tubule. Thus the initial effect on urine is increased output of water, bicarbonate and potassium with minimal if any effect on chloride or sodium excretion.

Complications - Acetazolamide is a remarkably nontoxic agent in both animals and man. At doses greater than 1 gm/day patients frequently complain of drowsiness with numbness and tingling of fingers. However, this is an unreasonably high dose to administer since if a patient does not respond to 0.5 gm/day, generally they will not respond to higher doses.

Advantages - Currently carbonic anhydrase do not possess any well established advantages over other diuretics at the clinical level. These compounds may improve metabolic alkalosis by promoting increase excretion of bicarbonate.

Disadvantages - Carbonic anhydrase inhibitors as a group are relatively ineffective in the seriously edematous patient, though may be quite useful in minimally expanded states.

Use - These drugs may be used as an adjunct in treatment of hemopoietic neoplasms where high uric acid excretion rates may be anticipated. Alkaline urine would be of protective benefit from uric acid crystallization.

Aldosterone Inhibitors and Triamterene:

Mechanism of action - Spironolactone, specific antagonist of aldosterone, and triamterene both produce a similar change in urinary volumes and electrolyte excretory patterns. Both increase sodium excretion minimally (not over 2-3% of filtered load) while causing an associated conservation of potassium and hydrogen. Both are felt to inhibit the cation exchange pump of the distal tubule, see Figure 5. It is for this reason that these two diuretics will be considered together. However, that these two compounds are not identical can be shown in adrenalectomized animals. Spironolactone is without effect in animals and humans with previous adrenalectomies, whereas triamterene is equally effective whether the adrenal glands are present or absent. In addition, when triamterene is given to patients undergoing spironolactone diuresis, the degree of diuresis is potentiated. Thus the two drugs do not act through the same exact mechanism, but similar pumps must exist in the distal tubule which are specifically sensitive to inhibition by spironolactones or triamterene.

Complications - The principal complication with these two agents is the possibility of hyperkalemia. This can be of life threatening degree especially in patient with compromised renal function. Potassium supplementation should not be given with these two agents except under extremely rare and specific circumstances.

Advantages - Principal advantage of both of these diuretics is that they conserve potassium. Both drugs may potentiate the degree of diuresis obtained by other diuretics.

Disadvantages - Neither spironolactone nor triamterene are potent diuretics when used alone.

Use - Spironolactones are especially useful alone or in combinations with other diuretics in those clinical states with secondary aldosteronism. Patients with cirrhosis and ascites who are especially susceptible to complications of other diuretics can be treated with spironolactone with relatively minimal risk of worsening their underlying electrolyte balance. Triamterene is specifically indicated in rare patients with pseudo-aldosteronism. Triamterene may be used conveniently with other diuretics to prevent the degree of kaliuresis otherwise seen. However, it must be emphasized that use of triamterene is not indicated in that group of patients who cannot be relied on for periodic checks of serum potassium levels.

Osmotic Diuretics:

Mechanism of action - Mannitol is the prototype of the osmotic diuretics. Under normal physiological conditions the principal site of action of mannitol is the proximal tubule where it osmotically prevents the absorption of normal amounts of filtrate. With the nonspecific inhibition of the proximal tubule reabsorption there is greater delivery of sodium chloride to the loop of Henle thus allowing for increased generation of both $T^{C}_{H_2O}$ and C_{H_2O}. However, under the circumstances in which mannitol usually is used (low perfusion states) an extratubular mechanism is at least as important as the tubular effect in maintaining adequate urine output. It has been convincingly demonstrated that mannitol can re-establish glomerular filtration rates in animals in which glomerular filtration was previously stopped by lowering renal artery pressure to less than 50 mmHg. This latter effect is probably mediated by decreasing the afferent arteriole resistance, thus increasing the effective hydrostatic perfusion pressure within the glomerulus.

Complications - There are no specific complications associated with osmotic diuretics with the exception of the necessary expansion of the intravascular space attendant with the administration of these compounds.

Advantages - This group of diuretics are the most effective (if not the only) in restoring glomerular filtration rates during and after transient hypotension.

Disadvantages - Mannitol must be given intravenously. In cases of anurea which cannot be reversed with mannitol, there is a danger of over-expansion of the extracellular fluid compartment with resultant hyponatremia.

Use - Osmotic diuretics have proven to be useful in those cases where renal shutdown (with development of acute tubular necrosis) may be anticipated. In this category belong those patients with severe hypotension whether secondary to hemorrhage or other causes. Mannitol is especially useful as a prophylactic measure during induction phases of anesthesia where sudden drops of blood pressure may be expected during extensive surgical procedures. The approximate dose is 25 to 50 grams given as a 20% solution. This amount should be administered as a single bolus. If the urine flow does not increase within 10 minutes, then further doses of mannitol are contraindicated. In those patients who do respond favorably, then a continuous infusion (10-12% solution) may be started and continued as long as deemed necessary.

APPENDIX

COMMON DIURETICS

* Preparations Stocked at PMH Pharmacy

Generic Name	Commercial Preparations	Active Dose
I. Mercurials:		
* Meralluride	Mercuhydrin (130 mg/1 cc)	1-2 cc IM
Mercurophylin	Mercuzanthin (100 mg/1 cc)	1-2 cc IM
Mercaptomerin	Thiomerin (130 mg/1 cc)	1-2 cc IM
Chlormerodrin	Neohydrin (18.3 mg/tab)	3-6 tabs qd
onset: 1 hr.		
maximum: 2-3 hrs.		
duration: 18-24 hrs.		
II. Thiazides:		
Chlorothiazide	Diuril Chlotride	250-2000 mg qd
* Hydrochlorothiazide	Esidrix Hydro-Diuril Oretic Dichlotride	25-150 mg qd
* Trichlormethiazide	Naqua Metahydrin Depleil	2-4 mg qd (up to 16 mg qd)
Hydroflumethiazide	Saluron Hydrenox Leodrine	25-150 mg qd
Benzydroflumethiazide	Naturetin	5-20 mg qd
Methyclothiazide	Enduron	2-10 mg qd
Polythiazide	Renese	1-4 mg qd
Cyclopenthiazide	Navidrex	0.5-2 mg qd
Cyclothiazide	Anhydron	1-2 mg qd
onset: 30 min (po)		
maximum: 2-4 hrs. (po)		
duration: 2 hrs. (IV) 24 hrs (po)		

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* Preparations Stocked at PMH Pharmacy

	Generic Name	Commercial Preparations	Active Dose
III.	Furosemide:		
	* Furosemide	Lasix	40-80 mg qd
	onset:	1 min. (IV) < 30 min. (po)	
	maximum:	5-10 min. (IV) 1 hr. (po)	
	duration:	4 hrs 8 hrs.	
IV.	Ethacrynic Acid:		
	* Ethacrynic acid	Edecrin	50-100 mg qd
	onset and duration similar to Furosemide		
V.	Carbonic Anhydrase Inhibitors:		
	* Acetazoleamide	Diamox	250-500 mg qd
	Methazoleamide	Neptazane	100-300 mg qd
	onset:	(Diamox) 30 min. (po) 1 min. (IV)	
	maximum:	2 hrs.	
	duration:	8-12 hrs.	
VI.	Aldosterone Inhibitors (and Triamterene:		
	* Spironolactone	Aldactone	100-200 mg qd
	* Triamterene	Dyrenium	100-200 mg qd
	onset:	2-3 hrs.	
	maximum:	several days	
	duration:	12-18 hrs. (Spironolactone)	
		8-16 hrs. (Triampterene)	
VII.	Osmotic Diuretics:		
	* Mannitol	Osmitrol	25-100 gms (20% solution)
	onset:	immediate	
	maximum:	immediate	
	duration:	as long as infusion kept up	

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