DIURETICS

- ✓ Drugs inducing a state of increased urine flow are called diuretics.
- ✓ These agents are inhibitors of renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions, such as Cl^-, enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium.
- ✓ Diuretics, thus, increase the volume of urine and often change its pH as well as the ionic composition of the urine and blood.
- ✓ The efficacy of the different classes of diuretics varies considerably, with the increase in Na^+ secretion varying from less than 2 percent for the weak, potassium-sparing diuretics, to over 20 percent for the potent loop diuretics.
- ✓ In addition to these ion-transport inhibitors, there are osmotic diuretics that prevent water reabsorption as well as aldosterone antagonists and a carbonic anhydrase inhibitor.
- ✓ The major clinical uses of diuretics are in managing disorders involving abnormal fluid retention (edema) or treating hypertension in which their diuretic action causes an initial decreased blood volume followed by a lowering of the peripheral resistance, leading to reduced blood pressure.

Physiology of Urine Formation

- ✓ The Basic functional unit of kidney is a, 'Nephron'.
- ✓ There are about a million nephrons.
- ✓ Each nephron consist of:
  (1) Bowman's capsule with glomerulus
  (2) Proximal convoluted tubule
  (3) Loop of Henle with ascending and descending limbs
  (4) Distal convoluted tubule that finally opens into collecting tubule.

- ✓ Urine formation starts from glomerular filtration in prodigal way.
- ✓ Normally, about 180 L of fluid is filtrated everyday: all soluble constitutes of blood minus the plasma proteins and lipids are filtered at the glomerulus.
- ✓ More than 99 % of the glomerular filtrate is reabsorbed in the tubules; about 1.5 L urine is produced in 24 hours.
- ✓ The diurectics act primarily by inhibiting tubular reabsorption: just 1 % decrease in tubular reabsorption would more than double urine.

Proximal convoluted tubule

- ✓ In the extensively convoluted proximal tubule located in the cortex of the kidney, almost all the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed.
- ✓ Approximately two thirds of the Na^+ is also reabsorbed.
- ✓ Chloride enters the lumen of the tubule in exchange for an anion, such as oxalate, as well as paracellularly through the lumen.
- ✓ Water follows passively from the lumen to the blood to maintain osmolar equality.
- ✓ If not for the extensive reabsorption of solutes and water in the proximal tubule, the mammalian organism would rapidly become dehydrated and lose its normal osmolarity.

- ✓ The Na^+ that is reabsorbed is pumped into the interstitium by Na^+/K^+–adenosine triphosphatase (ATPase), thereby maintaining normal levels of Na^+ and K^+ in the cell.
- ✓ Carbonic anhydrase in the luminal membrane and cell of the proximal tubule modulates the reabsorption of bicarbonate.

Descending loop of Henle

- ✓ The remaining filtrate, which is isotonic, next enters the descending limb of the loop of Henle and passes into the medulla of the kidney.
- ✓ The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism that is responsible for water reabsorption.
- ✓ This results in a tubular fluid with a threefold increase in salt concentration.

Ascending loop of Henle

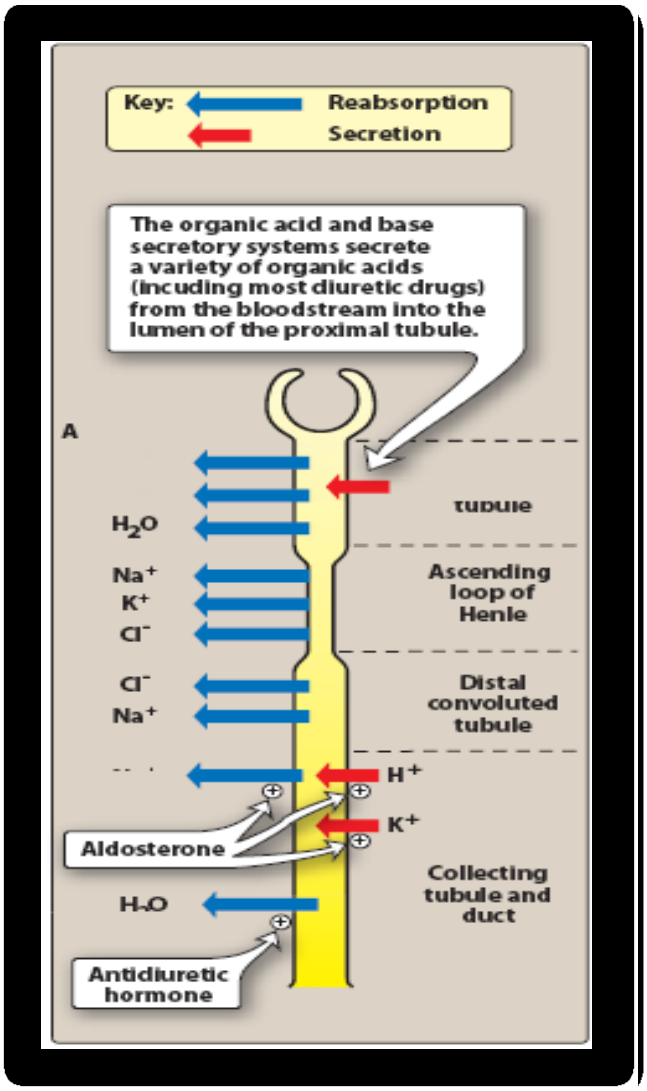
- ✓ The cells of the ascending tubular epithelium are unique in being impermeable to water.
- ✓ Active reabsorption of Na^+, K^+, and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter.
- ✓ Both Mg^{2+} and Ca^{2+} enter the interstitial fluid via the paracellular pathway.
- ✓ The ascending loop is, thus, a diluting region of the nephron.
- ✓ Approximately 25 to 30 percent of the tubular sodium chloride returns to the interstitial fluid, thereby helping to maintain the fluid's high osmolarity.
- ✓ Because the ascending loop of Henle is a major site for salt reabsorption,

Distal convoluted tubule

- ✓ The cells of the distal convoluted tubule are also impermeable to water.
- ✓ About 10 percent of the filtered sodium chloride is reabsorbed via a Na^+/Cl^- transporter that is sensitive to thiazide diuretics.
- ✓ Calcium reabsorption is mediated by passage through a channel and then transported by a Na^+/Ca^{2+}-exchanger into the interstitial fluid.
- ✓ The mechanism, thus, differs from that in the loop of Henle.
- ✓ Additionally, Ca^{2+} excretion is regulated by parathyroid hormone in this portion of the tubule.

Collecting tubule and duct

- ✓ The principal cells of the collecting tubule and duct are responsible for Na^+, K^+, and water transport, whereas the intercalated cells affect H^+ secretion.
- ✓ The sodium enters the principal cells through channels that are inhibited by *amiloride* and *triamterene*.
- ✓ Once inside the cell, sodium reabsorption relies on a Na^+/K^+-ATPase to be transported into the blood.
- ✓ Aldosterone receptors in the principal cells influence Na^+ reabsorption and K^+ secretion.
- ✓ Aldosterone increases the synthesis of Na^+ channels and of Na^+/K^+-ATPase, which when combined increase sodium reabsorption. Antidiuretic hormone (ADH; vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts.
- ✓ This action is mediated by cyclic adenosine monophosphate.



CLASSIFICATION OF DIURETICS

ACCORDING TO SITE OF ACTION:

1. **Drug increasing renal solute filtration:**
   - ✓ Cardiac glycosides: Digitalis
   - ✓ Xanthine alkaloids: Aminophylline, Caffines, Theophylline
   - ✓ Plasma expanders: Dextran, Water
   - ✓ Dopamine
2. **Drugs increasing renal solute excretion (Osmotic diuretics):**
   - ✓ Electrolytes like Sodium chloride, Potassium citrate, Potassium carbonate, Potassium acetate, and Potassium chloride
   - ✓ Non-electrolytes: Mannitol, Isosorbide, Sucrose, Urea, Glycerol
3. **Drugs which inhibit reabsorption of Na^+:**

- ✓ Marcurials: Mersalyl, Mercaptomerin, Meralluride, Chlormerodrin, Mercurous Chloride
- ✓ Thiazides: Bendrofluzide, Hydrochlothiazide, Chlorthalidone, Clopamide, Chloroxolone, Indapamide, polythiazide, Cyclopenthiazide
- ✓ Loop-diuretics: Furosemide, Ethacrinic, Bumetamide, Peretanide, Torasemide, Indacrinone

4. **Drugs which depress H^+ for Na^+ exchange:**
   - ✓ Carbonic anhydrase inhibitors: Acetazolamide, Dichlorphenamide, Ethozolamide, Methazolamide
   - ✓ Acidifying salts: Ammonium chloride, Arginine hydrochloride
5. **Potassium sparing diuretics:**
   - ✓ Spironolactone
   - ✓ Triamterene
   - ✓ Amiloride

ACCORDING TO POTENCY

A. Weak diuretics:

1. **Osmotic diuretics:**
   Electrolytes like Sodium chloride, Potassium citrate, Potassium carbonate, Potassium acetate, and Potassium chloride
   Non-electrolytes: Mannitol, Isosorbide, Sucrose, Urea, Glycerol
2. **Acidifying salts:**
   Ammonium chloride, Arginine hydrochloride
3. **Xanthine derivatives:**
   Aminophylline, Theophylline
4. **Carbonic-anhydrase inhibitors:**
   Acetazolamide, Dichlorphenamide, Ethozolamide, Methazolamide

B. Moderately potent diuretics:

Thiazide derivatives:
Bendrofluzide, Hydrochlothiazide, Chlorthalidone, Clopamide, Chloroxolone, Indapamide, polythiazide, Cyclopenthiazide

C. Very Potent diuretics:

Loop diuretics:
Furosemide, Ethacrinic, Bumetamide, Peretanide, Torasemide, Indacrinone

Mercurials:
Mersalyl, Mercaptomerin, Meralluride, Chlormerodrin, Mercurous Chloride

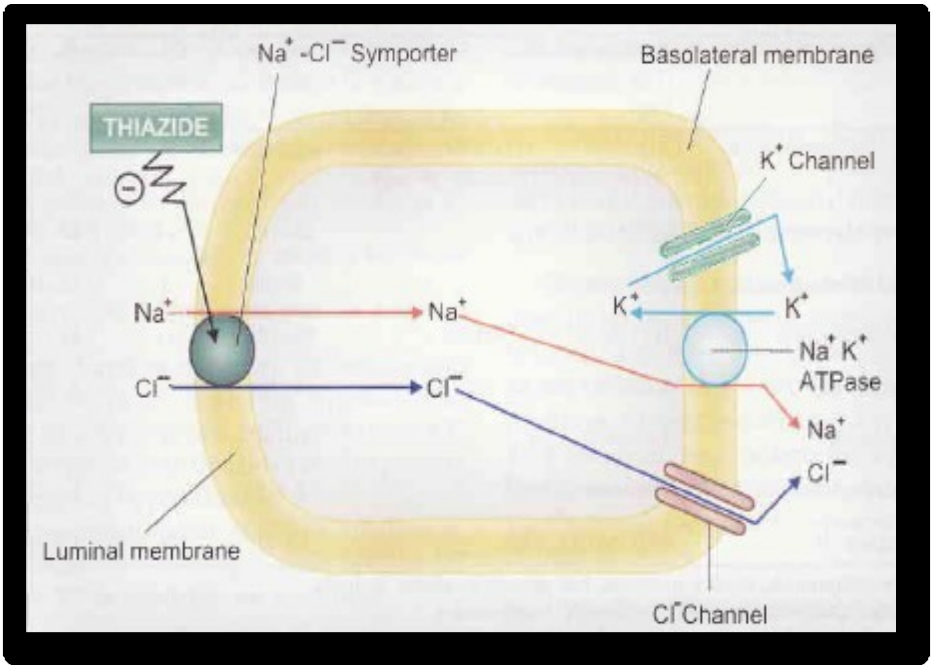
D. Potassium sparing diuretics:
Spironolactone, Triamterene, Amiloride

THIAZIDE DIURETICS

- ✓ The thiazides are the most widely used of the diuretic drugs.
- ✓ All thiazides affect the distal tubule, and all have equal maximum diuretic effects, differing only in potency.
- ✓ Chlorothiazide was the first modern diuretic that was active orally and was capable of affecting the severe edema of cirrhosis and heart failure with a minimum of side effects.
- ✓ Its properties are representative of the thiazide group, although newer derivatives,
- ✓ such as hydrochlorothiazide and chlorthalidone, are now used more commonly. Hydrochlorothiazide has far less ability to inhibit carbonic anhydrase compared to chlorothiazide. It is also more potent, so that the required dose is considerably lower than that of chlorothiazide. On the other hand, the efficacy is exactly the same as that of the parent drug. In all other aspects it resembles chlorothiazide.

Mechanism of action:

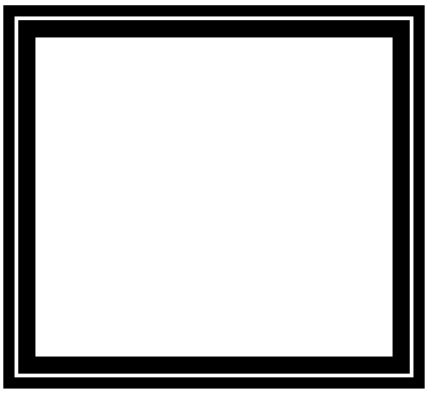
- ✓ The thiazide derivatives act mainly in the cortical region of the ascending loop of Henle and the distal tubule to decrease the reabsorption of Na^+, apparently by inhibition of a Na^+/Cl^- co-transporter on the luminal membrane of the tubules.
- ✓ They have a lesser effect in the proximal tubule.
- ✓ As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid.
- ✓ The acid-base balance is not usually affected.
- ✓ Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.



PHARMACOLOGICAL ACTIONS:

Increased excretion of Na^+ and Cl^-:

- ✓ Thiazide diuretics cause diuresis with increased Na^+ and Cl^- excretion, which can result
- ✓ in the excretion of a very hyperosmolar urine.
- ✓ This latter effect is unique, insofar as the other diuretic classes are unlikely to produce a hyperosmolar urine.
- ✓ The diuretic action is not affected by the acid-base status of the body, and hydrochlorothiazide
- ✓ does not change the acid-base status of the blood.
- ✓ The relative changes in the ionic composition of the urine during therapy with thiazide diuretics are given below.



Loss of K^+:

- ✓ Because thiazides increase the Na^+ in the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+, resulting in a continual loss of K^+ from the body with prolonged use of these drugs.
- ✓ Therefore, it is imperative to measure serum K^+ often (more frequently at the beginning of therapy) to assure that hypokalemia does not develop.

Loss of Mg^{2+}:

- ✓ Magnesium deficiency requiring supplementation can occur with chronic use of thiazide diuretics, particularly in elderly patients. The mechanism for the magnesuria is not understood.

Decreased urinary calcium excretion:

- ✓ Thiazide diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+}.
- ✓ This effect contrasts with the loop diuretics, which increase the Ca^{2+} concentration of the urine.
- ✓ **There is evidence from epidemiologic studies that use of thiazides preserves bone mineral density at the hip and spine and that the risk for hip fracture is reduced by a third.**

Reduced peripheral vascular resistance:

- ✓ An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output.
- ✓ With continued therapy, volume recovery occurs.
- ✓ However, there are continued hypotensive effects, resulting from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle.

THERAPEUTIC USES:

Hypertension:

- ✓ Clinically, the thiazides have long been the mainstay of antihypertensive medication, because they are inexpensive, convenient to administer, and well tolerated.
- ✓ They are effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension.
- ✓ With thiazides, the blood pressure stabilizes at a lower level and can be maintained indefinitely by a daily-dosage level of the drug, which causes lower peripheral resistance without having a major diuretic effect.
- ✓ Many patients can be continued for years on the thiazides alone, although a small percentage of patients require additional medication, such as adrenergic blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers.
- ✓ **The hypotensive actions of angiotensin-converting enzyme inhibitors are enhanced when given in combination with the thiazides.**

Heart failure:

- ✓ Loop diuretics are the diuretics of choice in reducing extracellular volume in heart failure.
- ✓ Thiazide diuretics may be added if additional diuresis is needed.

Hypercalciuria:

- ✓ The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary Ca^{2+} excretion.
- ✓ This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

Diabetes insipidus:

- ✓ Thiazides have the unique ability to produce a hyperosmolar urine.
- ✓ Thiazides can substitute for antidiuretic hormone in the treatment of nephrogenic diabetes insipidus.
- ✓ The urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with the drug.

PHARMACOKINETICS:

- ✓ The drugs are effective orally.
- ✓ Their action starts within 1 hr, but the duration varies from 8-48 hrs.
- ✓ The more lipid-soluble agents have larger volumes of distribution, lower rates of renal clearance and are longer acting.
- ✓ Most of the agents undergo little hepatic metabolism and are excreted as such.
- ✓ They are filtrated at the glomerulus as well as secreted in the Proximal Tubules by organic anion transport.
- ✓ Tubular reabsorption depends on lipid solubility: the more soluble ones are highly reabsorbed-prolinging duration of action.
- ✓ Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure, and they exhibit a prolonged biologic half-life.
- ✓ All thiazides are secreted by the organic acid secretory system of the kidney.

ADVERSE EFFECTS:

Most of the adverse effects involve problems in fluid and electrolyte balance.

Potassium depletion:

- ✓ Hypokalemia is the most frequent problem encountered with the thiazide diuretics, and it can predispose patients who are taking **digoxin** to ventricular arrhythmias.
- ✓ Often, K^+ can be supplemented by diet alone such as by increasing the intake of citrus fruits, bananas, and prunes. In some cases, K^+ salt supplementation may be necessary.
- ✓ Activation of the renin-angiotensin-aldosterone system by the decrease in intravascular volume contributes significantly to urinary K^+ losses.
- ✓ Under these circumstances, the K^+ deficiency can be overcome by **spironolactone,** which interferes with aldosterone action, or by administering **triamterene or amiloride**, which act to retain K^+.
- ✓ Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.

Hyponatremia:

- ✓ This serious adverse effect may develop due to elevation of ADH as a result of hypovolemia as well as diminished diluting capacity of the kidney and increased thirst.
- ✓ Limiting water intake and lowering the dose of diuretic can prevent this condition.

Hyperuricemia:

- ✓ Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system.
- ✓ Being insoluble, the uric acid deposits in the joints, and a full-blown attack of gout may result in individuals who are predisposed to gouty attacks.
- ✓ It is important, therefore, to perform **periodic blood tests** for uric acid levels.

Volume depletion:

- ✓ This can cause orthostatic hypotension, or light-headedness.

Hypercalcemia:

- ✓ The thiazides inhibit the secretion of Ca^{2+}, sometimes leading to elevated levels of Ca^{2+} in the blood.

Hyperglycemia:

- ✓ Patients with diabetes mellitus who are taking thiazides for hypertension may become hyperglycemic and have difficulty in maintaining appropriate blood sugar levels.
- ✓ This effect is due to impaired release of insulin and tissue uptake of glucose.

Hyperlipidemia:

- ✓ The thiazides can cause a 5 to 15-percent increase in serum cholesterol as well as increased serum low density lipoproteins.
- ✓ Lipid levels, however, may return to normal with long-term therapy.

Hypersensitivity:

- ✓ Bone marrow suppression, dermatitis, necrotizing vasculitis, and interstitial nephritis are very rare.
- ✓ Individuals who are hypersensitive to sulfa drugs may also be allergic to the thiazide diuretics.

THIAZIDE-LIKE ANALOGS

These compounds lack the thiazide structure, but, like the thiazides, they have the unsubstituted sulfonamide group and share their mechanism of action.

Chlorthalidone:

- ✓ Chlorthalidone is a nonthiazide derivative that behaves pharmacologically like hydrochlorothiazide.
- ✓ It has a very long duration of action and, therefore, is often used to treat hypertension.
- ✓ It is given once per day for this indication.

Metolazone:

- ✓ Metolazone is more potent than the thiazides and, unlike the thiazides, causes Na^+ excretion in advanced renal failure.

Indapamide:

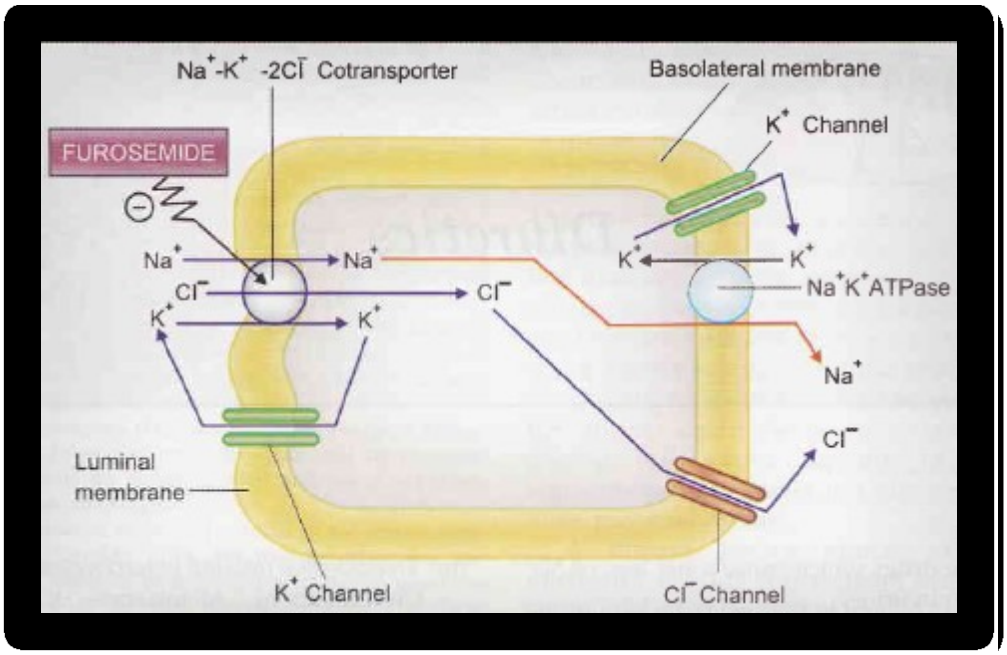
- ✓ Indapamide is a lipid-soluble, nonthiazide diuretic that has a long duration of action.
- ✓ At low doses, it shows significant antihypertensive action with minimal diuretic effects.
- ✓ Indapamide is metabolized and excreted by the gastrointestinal tract and the kidneys.
- ✓ It is, therefore, less likely to accumulate in patients with renal failure and may be useful in their treatment.

LOOP OR HIGH-CEILING DIURETICS

- ✓ The development of these orally and rapidly acting highly efficacious Diuretics was a breakthrough.
- ✓ The maximal natriuretic effect is much greater than that of other classes.
- ✓ The diuretic response gord on increasing with increasing dose: upto 10 L of urine may be produced in a day.
- ✓ Bumetanide, furosemide, torsemide, and ethacrynic acid are four diuretics that have their major action on the ascending limb of the loop of Henle.
- ✓ Compared to all other classes of diuretics, these drugs have the highest efficacy in mobilizing Na^+ and Cl^- from the body.
- ✓ They produce copious amounts of urine.
- ✓ Furosemide is the most commonly used of these drugs.
- ✓ Ethacrynic acid has a steeper dose-response curve than furosemide, but it shows greater side effects than those seen with the other loop diuretics, and its use is, therefore, limited.
- ✓ Bumetanide is much more potent than furosemide, and its use is increasing.

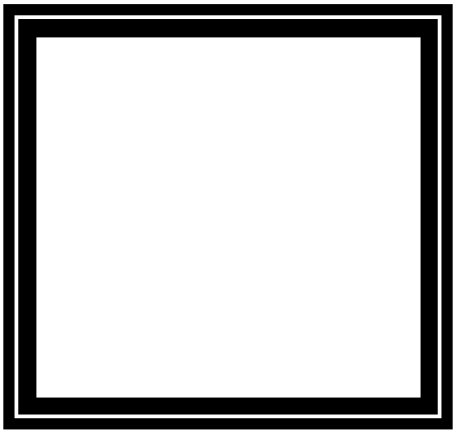
MECHANISM OF ACTION:

- ✓ Loop diuretics inhibit the cotransport of $Na^+/K^+/2Cl^-$ in the luminal membrane in the ascending limb of the loop of Henle.
- ✓ Therefore, reabsorption of these ions is decreased.
- ✓ The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25 to 30 percent of filtered NaCl, and downstream sites are not able to compensate for this increased Na^+ load.
- ✓ A minor component of action on proximal tubule has also been indicated.
- ✓ It is secreted in proximal tubule by organic anion transport and reaches Ascending Loop of Henle where it acts from luminal side of the membrane.
- ✓ It abolish the corticomedullary osmotic gradient and block positive as well as negative free water clearance.



PHARMACOLOGICAL ACTIONS:

- ✓ The loop diuretics act promptly, even among patients who have poor renal function or have not responded to thiazides or other diuretics.
- ✓ Changes in the composition of the urine induced by loop diuretics are as indicate in figure.



- ✓ **Loop diuretics increase the Ca^{2+} content of urine, whereas thiazide diuretics decrease the Ca^{2+} concentration of the urine. In patients with normal serum Ca^{2+} concentrations, hypocalcemia does not result, because Ca^{2+} is reabsorbed in the distal convoluted tubule. However, hypomagnesemia can occur due to loss of Mg^{2+}.**
- ✓ It tends to raise blood uric acid level by competing with its proximal tubular secretion as well as by increasing reabsorption in proximal tubule which is a consequence of reduced e.c.f. volume.
- ✓ The loop diuretics cause decreased renal vascular resistance and increased renal blood flow.
- ✓ In addition, loop diuretics increase prostaglandin synthesis.

- ✓ The prostaglandins have a role in their diuretic action, and NSAIDS such as indomethacin that interfere in prostaglandin synthesis can reduce the diuretic action of these agents.

THERAPEUTIC USES:

- ✓ The loop diuretics are the drugs of choice for reducing the **acute pulmonary edema** of heart failure.
- ✓ Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations, such as acute pulmonary edema, which calls for a rapid, intense diuresis.
- ✓ Loop diuretics (along with hydration) are also useful in treating **hypercalcemia**, because they stimulate tubular Ca^{2+} excretion.
- ✓ They also are useful in the treatment of hyperkalemia.
- ✓ Oedema due to cardiac failure, hepatic disease, nephritic syndrome etc
- ✓ Acute chronic renal failure

PHARMACOKINETICS:

- ✓ Loop diuretics are administered orally or parenterally.
- ✓ Their duration of action is relatively brief (2 to 4 hours).
- ✓ They are secreted into urine.

ADVERSE EFFECTS:

Ototoxicity:

- ✓ Hearing can be affected adversely by the loop diuretics, particularly when used in conjunction with the aminoglycoside antibiotics.
- ✓ Permanent damage may result with continued treatment.
- ✓ Ethacrynic acid is the most likely to cause deafness.
- ✓ Vestibular function is less likely to be disturbed, but it, too, may be affected by combined treatment with the antibiotic.

Hyperuricemia:

- ✓ Furosemide and ethacrynic acid compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and, in turn, causing or exacerbating gouty attacks.

Acute hypovolemia:

- ✓ Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.
- ✓ Hypercalcemia may occur under these conditions.

Potassium depletion:

- ✓ The heavy load of Na^+ presented to the collecting tubule results in increased exchange of tubular Na^+ for K^+, with the possibility of inducing hypokalemia.
- ✓ The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis.
- ✓ Potassium depletion can be averted by use of potassium-sparing diuretics or dietary supplementation with K^+.

Hypomagnesemia:

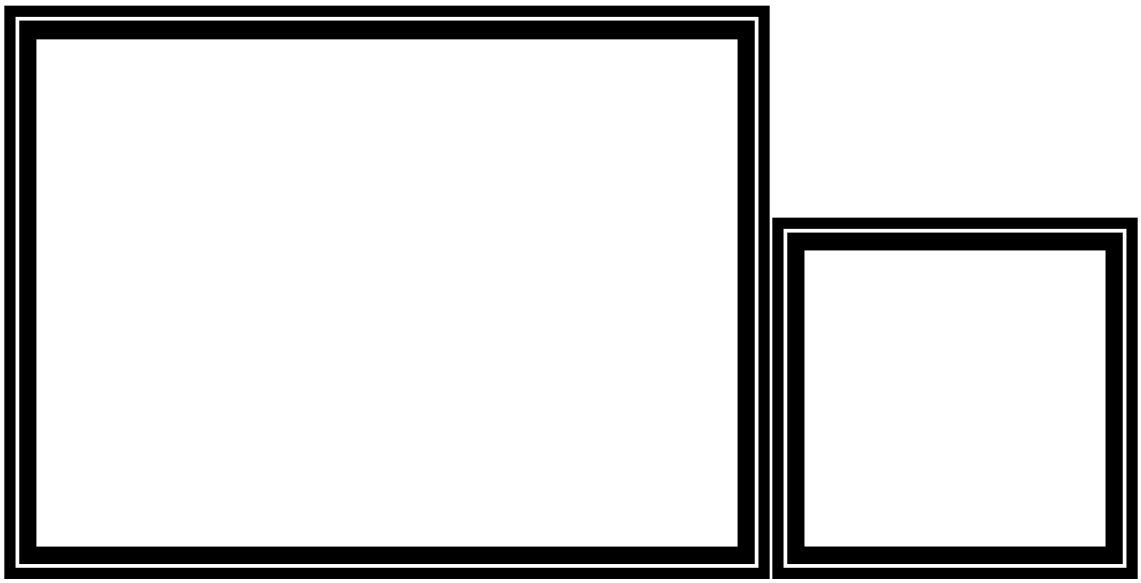
- ✓ A combination of chronic use of loop diuretics and low dietary intake of Mg^{2+} can lead to hypomagnesemia, particularly in the elderly.
- ✓ This can be corrected by oral supplementation.

POTASSIUM-SPARING DIURETICS

- ✓ Potassium-sparing diuretics act in the collecting tubule to inhibit Na+ reabsorption and K+ excretion.
- ✓ The major use of potassium-sparing agents is in the treatment of hypertension, most often in combination with a thiazide.
- ✓ It is extremely important that patients who are treated with any potassium-sparing diuretic be closely monitored for potassium levels.
- ✓ Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted.
- ✓ These drugs should be avoided in patients with renal dysfunction because of the increased risk of hyperkalemia.

MECHANISM OF ACTION:

- ✓ Spironolactone is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites.
- ✓ The spironolactone-receptor complex is inactive.
- ✓ That is, it prevents translocation of the receptor complex into the nucleus of the target cell and, therefore, it cannot bind to DNA.
- ✓ This results in a failure to produce proteins that are normally synthesized in response to aldosterone.
- ✓ These mediator proteins normally stimulate the Na^+/K^+-exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na^+ reabsorption and, therefore, K^+ and H^+ secretion.



MR: Mineralocorticoid receptor, AL: Aldosterone

PHARMACOLOGICAL ACTIONS:

- ✓ In most edematous states, blood levels of aldosterone are high, which is instrumental in retaining Na^+.
- ✓ When spironolactone is given to a patient with elevated circulating levels of aldosterone, the drug antagonizes the activity of the hormone, resulting in retention of K^+ and excretion of Na^+.

- ✓ In patients who have no significant circulating levels of aldosterone, such as those with Addison disease (primary adrenal insufficiency), no diuretic effect of the drug occurs.
- ✓ In common with the thiazides and loop diuretics, the effect of spironolactone depends on renal prostaglandin synthesis.
- ✓ Eplerenone is a new aldosterone-receptor antagonist, with actions comparable to those of spironolactone.
- ✓ Eplerenone may have less endocrine effects than spironolactone.

THERAPEUTIC USES:

Diuretic:

- ✓ Although spironolactone has a low efficacy in mobilizing Na^+ from the body in comparison with the other drugs, it has the useful property of causing the retention of K^+.
- ✓ Because of this latter action, spironolactone is often given in conjunction with a thiazide or loop diuretic to prevent the K^+ excretion that would otherwise occur with these drugs.
- ✓ It is the diuretic of choice in patients with hepatic cirrhosis.

Secondary hyperaldosteronism:

- ✓ Spironolactone is the only potassium-sparing diuretic that is routinely used alone to induce a net negative salt balance.
- ✓ It is particularly effective in clinical situations associated with secondary hyperaldosteronism.

Heart failure:

- ✓ Spironolactone prevents the remodeling that occurs as compensation for the progressive failure of the heart.
- ✓ Its use has shown to decrease mortality associated with heart failure.

Edema:

- ✓ It is more useful in cirrhotic and nephritic edema: aldosterone levels are high.
- ✓ It breaks the resistance to thiazide diuretics that develops due to secondary hyperaldosteronism and reestablishes the reaponse.
- ✓ Thus, it is particulary employed in refractory edema.

PHARMACOKINETICS:

- ✓ Spironolactone is completely absorbed orally and is strongly bound to proteins.
- ✓ It is rapidly converted to an active metabolite, canrenone.
- ✓ The action of spironolactone is largely due to the effect of canrenone, which has mineralocorticoid-blocking activity.
- ✓ Spironolactone induces hepatic cytochrome P450.

ADVERSE EFFECTS:

- ✓ Spironolactone frequently causes gastric upsets and can cause peptic ulcers because it chemically resembles some of the sex steroids
- ✓ Spironolactone may act at receptors in other organs to induce **gynecomastia** in male patients and **menstrual irregularities** in female patients. Therefore, the drug should not be given at high doses on a chronic basis.
- ✓ It is most effectively employed in mild edematous states, for which it is given for a few days at a time.
- ✓ At low doses, spironolactone can be used chronically with few side effects.
- ✓ Hyperkalemia, nausea, lethargy, and mental confusion can occur.

INTERACTION:

- ✓ Given with K^+ supplements- dangerous hyperkalaemia can occur.
- ✓ Aspirin blocks spironolactone action by inhibiting tubular secretion of canrenone.
- ✓ More pronounced hyperkalaemia can occur in patient's receiving ACE inhibitors/angiotensin receptor blockers.
- ✓ Spironolactone increase plasma digoxin concentration.

TRIAMTERENE AND AMILORIDE

- ✓ These are inhibitors of renal epithelial Na^+ channel.
- ✓ Their most imp effect is to decrease K^+ excretion, particularly when it is high due to large K^+ intake or use of a diuretic that enhance K^+ loss.
- ✓ This is accompanied by a small increase in Na^+ excretion.
- ✓ Their action is independent of aldesterone.

MECHANISM OF ACTION:

- ✓ The luminal membrane of late distal tubule and collecting duct cells express a distinct 'amiloride sensitive' or 'renal epithelial' Na^+ channel through which Na^+ enters the cell down its electrochemical gradient which is generated by Na^+/K^+ ATPase operating at the basolateral membrane.
- ✓ This Na^+ entry partially depolarizes the luminal membrane creating a -15 mV transepithelial potential difference which promotes secretion of K^+ into the lumen through K^+ channels.
- ✓ Though there is no direct coupling between Na^+ and K^+ channels, more the delivery of Na^+ to the distal nephron-greater is its entry through the Na^+ channel- luminal membrane is depolarized more-driving force for K^+ secretion is augmemted.
- ✓ As such, all diurrectics acting proximally promotes K^+ secretion.
- ✓ Amiloride and triamterene block the luminal Na+ channels-indirectly inhibit K^+ excretion, while the net excess loss of Na+ is minor.
- ✓ The intercalated cells in collecting duct possess an ATP driven H^+ pump which secretes H^+ ions into the lumen.
- ✓ This pump is facilitated by lumen negative potential, decrease H^+ ion secretion as well predispose to acidosis.
- ✓ Both triamterene and Amiloride are used conjunction with thiazide type or high celling diuretics: prevent hypokalaemia and slightly augment the natriuretic and antihypertensive response.

ADVERSE EFFECT

- ✓ Risk of hyperkalaemia
- ✓ **Triamterene;** Nausea, dizziness, muscle cramps, rise in blood urea.
  Impaired glucose tolerance and photosensitivity

INTERACTION:

- ✓ Given with K^+ supplements- dangerous hyperkalaemia can occur.
- ✓ Aspirin blocks spironolactone action by inhibiting tubular secretion of canrenone.
- ✓ More pronounced hyperkalaemia can occur in patients receiving ACE inhibitors/angiotensin receptor blockers.
- ✓ Spironolactone increase plasma digoxin concentration.

DIFFERENCE BEETWEN AMILORIDE AND TRIAMTERENE:

- ✓ Amiloride is 10 times more potent than triamterence.
- ✓ At higher dose also inhibits Na+ reabsorption in proximal tubule.
- ✓ It decreases Ca^{2+} excretion and increase urate excretion.
- ✓ Thus, hypercalcaemic action of thiazides is augmented but hyperuricaemic action is partly annulled.
- ✓ A mild antihypertensive action is also reported.
- ✓ It is not bound to plasma protein and not metabolized.
- ✓ Duration of action is longer than triamterene.
- ✓ Amiloride blocks entry of Li^+ through Na^+ channels in the Collecting Ducts cells and mitigates diabetes insipidus induced by lithium.

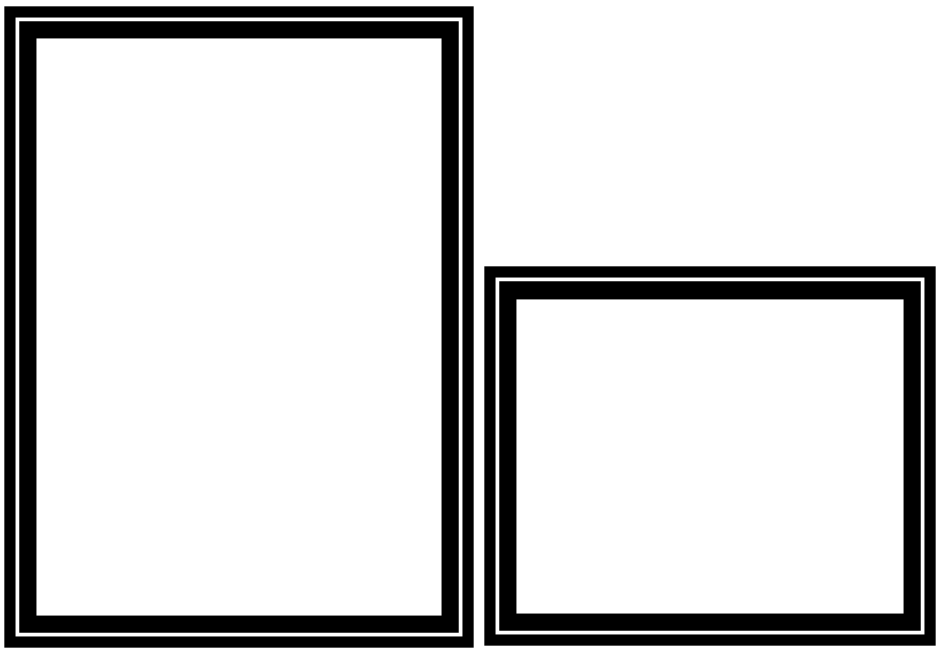
CARBONIC ANHYDRASE INHIBITOR

- ✓ Acetazolamide inhibits the enzyme carbonic anhydrase in the proximal tubular epithelial cells.
- ✓ Carbonic anhydrase inhibitors are more often used for their other pharmacologic actions rather than for their diuretic effect, because they are much less efficacious than the thiazides or loop diuretics.

ACETAZOLAMIDE

MECHANISM OF ACTION:

- ✓ Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O, leading to H_2CO_3, which spontaneously ionizes to H^+ and HCO_3^- (bicarbonate).
- ✓ H^+ secreted by the tubules for exchange with Na^+. Sodium thus pass back to blood to maintain conservation of sodium concentration of the body.
- ✓ Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.
- ✓ The decreased ability to exchange Na^+ for H^+ in the presence of acetazolamide results in a mild diuresis.
- ✓ Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH.
- ✓ The loss of HCO_3^- causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy.
- ✓ Changes in the composition of urinary electrolytes induced by acetazolamide are summarized in Figure.
- ✓ Phosphate excretion is increased by an unknown mechanism.
- ✓ Other action:
  1. Lowering of intraocular tension due to decreased formation of aqueous humour
  2. Decreased gastric HCL and pancreatic $NaHCO_3$ secretion: this action require very high dose so clinically not significant
  3. Raised level of CO_2 in brain and lowering of pH so sedation and elevation of seizure threshold
  4. Alteration of CO_2 transport in lungs and tissues: these actions are masked by compensatory mechanisms.



THERAPEUTIC USES:

Treatment of glaucoma:

- ✓ The most common use of acetazolamide is to reduce the elevated intraocular pressure of open-angle glaucoma.
- ✓ Acetazolamide decreases the production of aqueous humor, probably by blocking carbonic anhydrase in the ciliary body of the eye.
- ✓ It is useful in the chronic treatment of glaucoma but should not be used for an acute attack.
- ✓ Topical carbonic anhydrase inhibitors, such as dorzolamide and brinzolamide, have the advantage of not causing any systemic effects.

Mountain sickness:

- ✓ Less commonly, acetazolamide can be used in the prophylaxis of acute mountain sickness among healthy, physically active individuals who rapidly ascend above 10,000 feet.
- ✓ Acetazolamide given nightly for 5 days before the ascent prevents the weakness, breathlessness, dizziness, nausea, and cerebral as well as pulmonary edema characteristic of the syndrome.

Epilepsy:

- ✓ As a adjuvant in absence seizures when primary drugs are not fully effective

Periodic paralysis

PHARMACOKINETICS:

- ✓ Acetazolamide is given orally once to four times daily.
- ✓ It is secreted by the proximal tubule.

ADVERSE EFFECTS:

- ✓ Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur.
- ✓ Hypersensitivity reactions- fever, rashes.

- ✓ Bone marrow depression is rare but serious.
- ✓ The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+.

OSMOTIC DIURETICS

- ✓ Osmotic diuretics are solutes which have the following properties.
  - Pharmacologically inert
  - Generally non-metabolizable
  - Increased osmolality of plasma and tubular fluid
  - Freely filtrated at the glomerulus
  - Not significantly reabsorbed by the renal tubules.

MECHANISM OF ACTION:

- ✓ In the proximal tubule sodium is actively absorbed from tubular lumen, dragging water passively along with it.
- ✓ In the presence of a non-absorbable solute such as mannitol, diffusion of water is reduced relative to that of sodium.
- ✓ As a consequence the net absorption of sodium diminishes.
- ✓ There is an enhanced urine flow with a relatively smaller increase in the sodium excretion.
- ✓ However, this action is of secondary importance; the main site of action of the osmotic diuretics is the loop.
- ✓ They expand the ECF and increase the renal blood flow, thereby reducing the medullary tonicity, which inhibits water extraction from the descending limb.
- ✓ This limits the passive reabsorption of sodium from the ascending limb.
- ✓ The other osmotically active solutes are urea, glucose, isosorbid, and urographic and angiographic contrast agents.
- ✓ In case of glucose, this mechanism becomes operative when the tubular maximum for reasorption of glucose is exceeded because of hyperglycemia.
- ✓ When GFR is acutely reduced, solutes undergo more complete reabsorption in the proximal tubule, so that there is a marked fall in the urine flow and solute excretion.
- ✓ Diuretics that act by directly inhibiting tubular resorption may also be ineffective in these circumstances.
- ✓ However, the osmotic diuretics retain their effectiveness.
- ✓ Although the GFR is reduced, a substance like mannitol is filtrated at the glomerulus and is excreted in the voided urine, dragging water with it.

MANNITOL

- ✓ It is a sugar which, when injected IV, is not metabolized and is rapidly filtered by the glomeruli.
- ✓ Being nonreabsorbable, it exerts marked osmotic activity, causing osmotic dieresis.
- ✓ It increases excretion of all the electrolytes including magnesium and calcium.
- ✓ To be effective mannitol has to be administered in sufficiently larger doses.
- ✓ It is not a suitable diuretic to treat cardiac edema with sodium retention.
- ✓ This is because administration of mannitol increases the ECF volume by extracting water from the cells, thus increasing further the load on the already decompensated heart.

- ✓ When the renal tubules are damaged in addition to reduction in GRF they become permeable to mannitol, which then loses its capacity to induce dieresis.

ADVERSE REACTION

- ✓ It can cause headache, nausea, chills, polydipsia, confusion and pain in the chest.
- ✓ Excessive amounts or rapid infusion of mannitol can cause cellular dehydration; pulmonary edema in patients with CHF and hyponatremia.
- ✓ Extravasation of mannitol may cause thrombophlebitis.
- ✓ It can cross the blood brain barrier, though less readily than urea, and may occasionally cause rise in intracranial tension.
- ✓ Mannitol should not be mixed with whole blood because agglutination and irreversible crenation of RBCs may occur.

CONTRAINDICATION:

- ✓ Pulmonary congestion/edema
- ✓ Intracranial bleeding, except during craniotomy
- ✓ Congestive heart failure
- ✓ Metabolic edema with abnormal capillary fragility
- ✓ Established acute renal failure with anuria.

THERAPEUTIC USES

- ✓ Barbiturate poisoning
- ✓ Acute renal failure
- ✓ Raised intraocular pressure
- ✓ Cerebral edema
- ✓ During rapid dialysis

XANTHINE DIURETICS

- ✓ Xanthine derivatives might increase the renal blood flow by virtue of their cardiac stimulant property and vasodilator action which promote filtration of fluid by the glomeruli.
- ✓ They also produce dieresis by diminishing the tubular reabsorption of water.
- ✓ The chief mechanism seems to be the interference in tubular reabsorption of Na^+ and Cl^- perhaps by acting on the enzyme concerned with the transport of these ions.
- ✓ This eventually leads to less absorption of water and favours its excretion.
- ✓ The xanthine diuretics are not preferable to other diuretics, since they lack in prompt and uniform action.
- ✓ They are used in edema of the heart and kidneys associated with renal insufficiency.

ACIDIFYING DIURETICS

- ✓ Ammonium chloride, Ammonium nitrate and calcium chloride are used as acidotic diuretics.
- ✓ Ammonium chloride gives out ammonium ions.
- ✓ Liver converts ammonium ion to urea which acts as diuretic.
- ✓ The chloride ions obtained in the process from HCL acid reacts with HCO_3 of blood, and as a result the alkali reserve of the body gets depleted.
- ✓ The excess acid is therefore, excreted in urine to make the urine acidic.

- ✓ With increase in acidity of urine, ammonium ions are secreted by the tubules so as to exchange with sodium.
- ✓ Sodium ions thus return to the body and ammonium chloride or ammonium nitrate which is excreted, take equivalent amount of water.
- ✓ Hence the action of acidifying diuretics is self limiting.
- ✓ However, if the kidney function is impaired, no effective secretion of ammonium ion results and acidosis of urine take place.
- ✓ Because of the irritating action of acidotic diuretics on gastric mucosa, they are given in enteric coated tables to avoid sensation of nausea and vomiting.
- ✓ These agents are useful to correct metabolic alkalosis caused by mercurials.

AMMONIUM CHLORIDE:

- ✓ It is given orally in divided doses.
- ✓ Large doses cause gastric irritation and diarrhoea.
- ✓ It is contraindicated in renal insufficiency.

AMMONIUM NITRATE:

- ✓ It is given in divided doses.
- ✓ Actions are similar to those described for ammonium chloride.

POTASSIUM NITRATE:

- ✓ It is given orally in divided doses.
- ✓ In renal insufficiency, potassium retention may produce toxicity.

MERCURIAL DIURETICS

- ✓ The mechanism whereby these agents induce dieresis is ascribed to their diminishing tubular reabsorption of water.
- ✓ Marked increase in chloride excretion occurs after treatment with mercurial compounds which is also accompanied by increased amount of sodium in the urine.
- ✓ Site of action is in the proximal convoluted tubule.
- ✓ As the mercuric ion combine with the sulphydryl enzymes which are associatd with the metabolic process, it is presumed that the mercurials might act on the sulph-hydryl enzymes of the proximal tubule to suppress the reabsorption.
- ✓ Organic mercurial compounds are very potent diuretics.
- ✓ Their action is increased when given together with xanthine diuretics.
- ✓ They are used in edema associated with cardiac decompensation, nephotic edema, ascites of liver and subacute and chronic nephritis.
- ✓ Mercurial compounds partially affect the functional activity of kidneys and decrease the reabsorption of electrolytes, chloride and sodium.

TOXICITY:

- ✓ They are contraindicated in acute nephritis since they can paralyze the kidneys.
- ✓ They may cause irritation of the mouth and stomach with digestive disturbances.
- ✓ Albuminuria, hematuria, dizziness and skin rashed may be seen as a result of toxicity brought about by these compounds.