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RENAL SEQUENCE
9/26 - 10/13
2008

Fall 2008

University of Michigan
Medical School

M2 DAILY SCHEDULE
FALL TERM 2008-09

	MONDAY 9/29/08	TUESDAY 9/30/08	WEDNESDAY 10/1/08	THURSDAY 10/2/08	FRIDAY 10/3/08
8:00	Proteinuria and Non-Inflammatory Diseases of the Glomerulus		Nephritis and Inflammatory Diseases of the Glomerulus	Diuretics	Mechanisms of Acute Renal Failure J. Weinberg
9:00		The Kidney and Systemic Disease - Hypertension C. Gulaghelo			Approach to the Patient with Acute Renal Failure J. Weinberg
10:00		Physiology of Water Metabolism M. Hennig	Potassium & Magnesium Homeostasis J. Weinberg	Acid Base Physiology F. Bevens	Electrolyte Review
11:00	The Kidney and Systemic Diseases - Diabetes F. Bevens	Approach to the Patient with Osteomyelitis/Dysuria M. Hennig	Approach to the Patient with Disorders of Potassium & Magnesium Levels J. Weinberg	Approach to the Patient with Acidosis or Alkalosis F. Bevens	J. Weinberg
1:00		CLINCOPATHOLOGICAL CORRELATION LABS **Nephrotic Syndrome** (1/2 class) - 3:3 PM	**Longitudinal Case Small Groups** Renal I (Attendance Required)	CLINCOPATHOLOGICAL CORRELATION LABS **Acute Glomerulonephritis** (1/2 class) - 1-3 PM	
2:00					
3:00		CLINCOPATHOLOGICAL CORRELATION LABS **Nephrotic Syndrome** (1/2 class) - 3:3 PM		CLINCOPATHOLOGICAL CORRELATION LABS **Acute Glomerulonephritis** (1/2 class) - 3:3 PM	
4:00					
5:00	**Male/Female Phys Exams** 1:00 PM - 5:00 PM Student Sign-up	**Male/Female Phys Exams** 1:00 PM - 5:00 PM Student Sign-up	**Male/Female Phys Exams** 3:00 PM - 5:00 PM Student Sign-up	**Male/Female Phys Exams** 1:00 PM - 5:00 PM Student Sign-up	**RENAL QUIZ** OPEN 5:00 PM, 10/3 CLOSE 11:59 PM, 10/5

Course Updates

1. Electrolyte review session on Friday, 10/3. Opportunity to have more interactive experience with fluid and electrolyte problems and answer any questions you have before the quiz about any material covered in the relevant lectures. You will benefit from working on these problems and the electrolyte problems on the web site before you take the quiz.

2. Quiz content:

Physiology of Volume Regulation/Heung
Approach to Edema and Hypovolemia/Heung
Physiology of Water Metabolism/Heung
Approach to Osmoregulatory Disorders/Heung
Holzman comments on fluid and electrolyte aspects of nephrotic syndrome in

"Proteinuria and Non-inflammatory Diseases of the Glomerulus" but NO GLOMERULAR PATHOLOGY.

Potassium and Magnesium Homeostasis
Approach to Patient with Potassium and Magnesium Disorders
Acid Base Physiology/Brosius
Approach to Patient with Acidosis or Aklalosis/Brosius
Diuretics/Shlafer
Fluid and Electrolyte Cases from old Shayman text on the web site.
Problems in the Electrolyte Review session.

Strategies for Mastering the Fluid and Electrolyte Material

1. Review the listed lectures in the course pack and your notes on them.
2. Do the electrolyte problems on the web site.
3. If you have questions, Email them to the instructors or to me. They will be answered promptly.
4. Read and answer the problems for the Friday review session before the session.
5. Come to the review session to hear the discussion of the best answers to that problem set and to the questions that are asked about those problems or any of the other fluid and electrolyte material.
6. Don't take the quiz until you have taken advantage of all these resources.
7. On the quiz, don't spend a large amount of of time on the extra credit questions until you are absolutely sure you have done your best on the required ones.

Potassium and Magnesium Homeostasis

Objectives

1. Understand the distribution of potassium within body fluid compartments and the relative roles of the kidney and extrarenal routes in potassium excretion.

2. Know how cellular redistribution buffers the body during acute potassium loads.

3. Identify the factors regulating the distribution of potassium between intracellular and extracellular compartments.

4. Understand how potassium is handled by different segments of the nephron.

5. Know the factors which regulate renal potassium excretion including aldosterone, plasma potassium concentration, tubular flow rate.

6. Understand the cellular actions of aldosterone and amiloride.

7. Understand how diuretics promote potassium wasting.

8, Appreciate how the kidney handles magnesium and the association between hypomagnesemia and other electrolyte disturbances.

Case 3: Life Threatening Hyperkalemia

A 35 y.o. female with 20 year history of Type I diabetes and hypertension is hospitalized for treatment of a cellulitis. Creatinine - 2.5 mg/dl, K^+ 4.8 mEq/L, BP 150/100. The intern starts enalapril (angiotensin converting enzyme inhibitor) and atenolol (beta-blocker).

Three days later, BP is well-controlled at 115/70, but morning chemistries return with a K^+ is 6.8 and EKG shows peaked T waves and widening of the QRS complex. Urgent treatment for hyperkalemia is started.

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Dx: Hyperkalemia secondary to inhibition of aldosterone production by angiotensin converting enzyme inhibitor and shift of potassium out of cells by beta-blocker in the setting of preexisting decrease of kidney clearance function and lack of insulin.

Why is K^+ important?

- Most abundant cation (58 mEq/kg), predominantly intracellular (98.5%). Only 1.4% of K^+ is in the extracellular fluid space.

- Distribution labile, dependent on active transport by Na^+,K^+-ATPase and the regulation of that process.

- Controls cardiac and neuromuscular excitability via membrane potential, which is a function of Ki/Ke.

Hyperkalemia – transient increase then decreased excitability due to closing of Na^+ channels.

Hypokalemia – decreased excitability

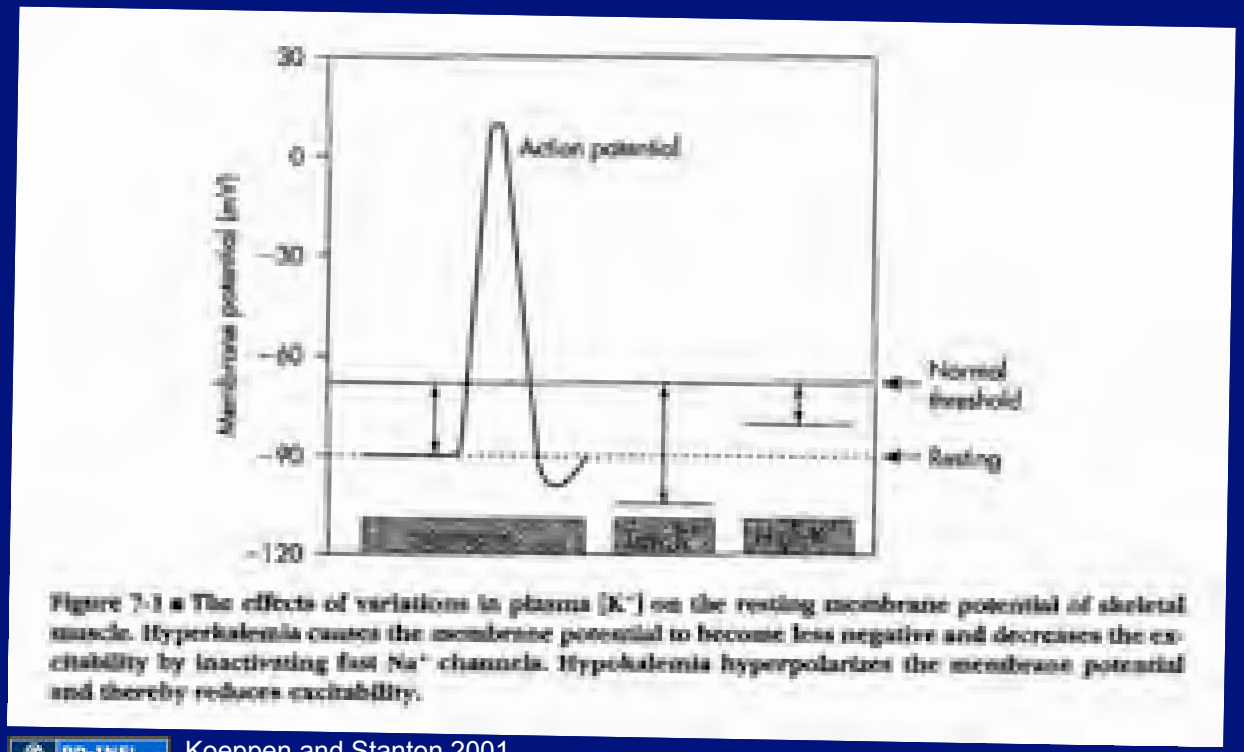


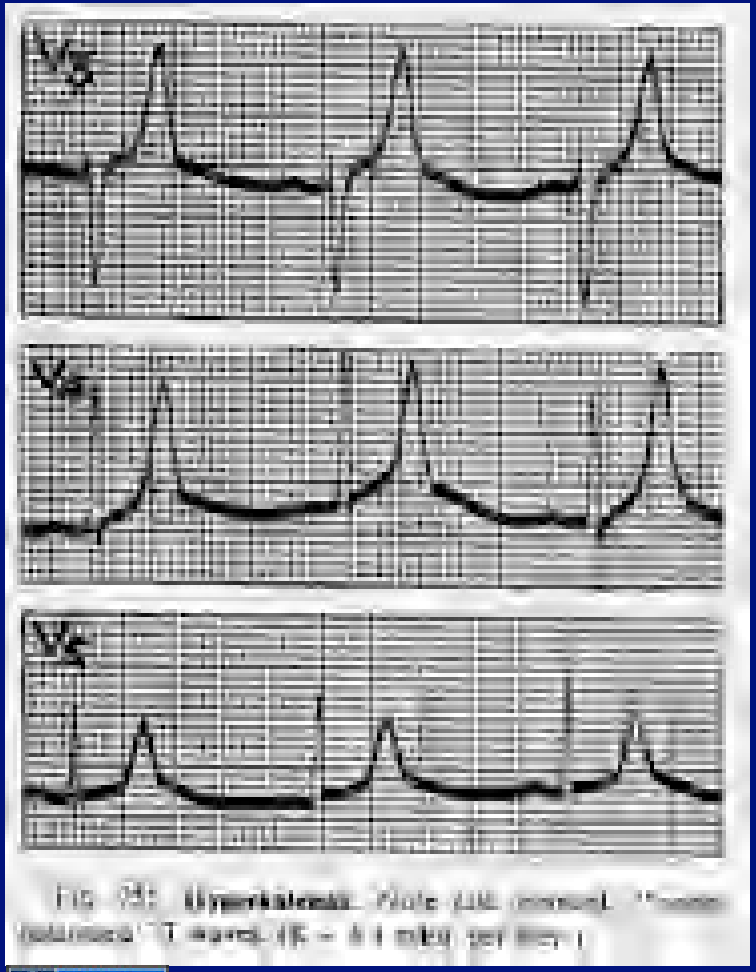
Figure 7-1 ■ The effects of variations in plasma [K^+] on the resting membrane potential of skeletal muscle. Hyperkalemia causes the membrane potential to become less negative and decreases the excitability by inactivating fast Na^+ channels. Hypokalemia hyperpolarizes the membrane potential and thereby reduces excitability.

PD-INEL Koeppen and Stanton 2001

	Intracellular fluid	Extracellular fluid
$[K^+]$	150 mEq/l	4.5 mEq/l
Volume	28 liters	14 liters
Total K^+	4200 mEq	63 mEq
Percent	98.53	1.47

If a 70 kg person ingests 2 cups of orange juice containing 20 mEq K^+ and all of it remains in the extracellular space, how much will serum K^+ increase?

60% of total body weight is water - 42 L
33% of total body water is extracellular - 14 L
Change serum K^+ is 20 mEq/14 L = 1.43 mEq/L
Serum K^+ increases from normal of 4.5 to hyperkalemic level of 5.9.



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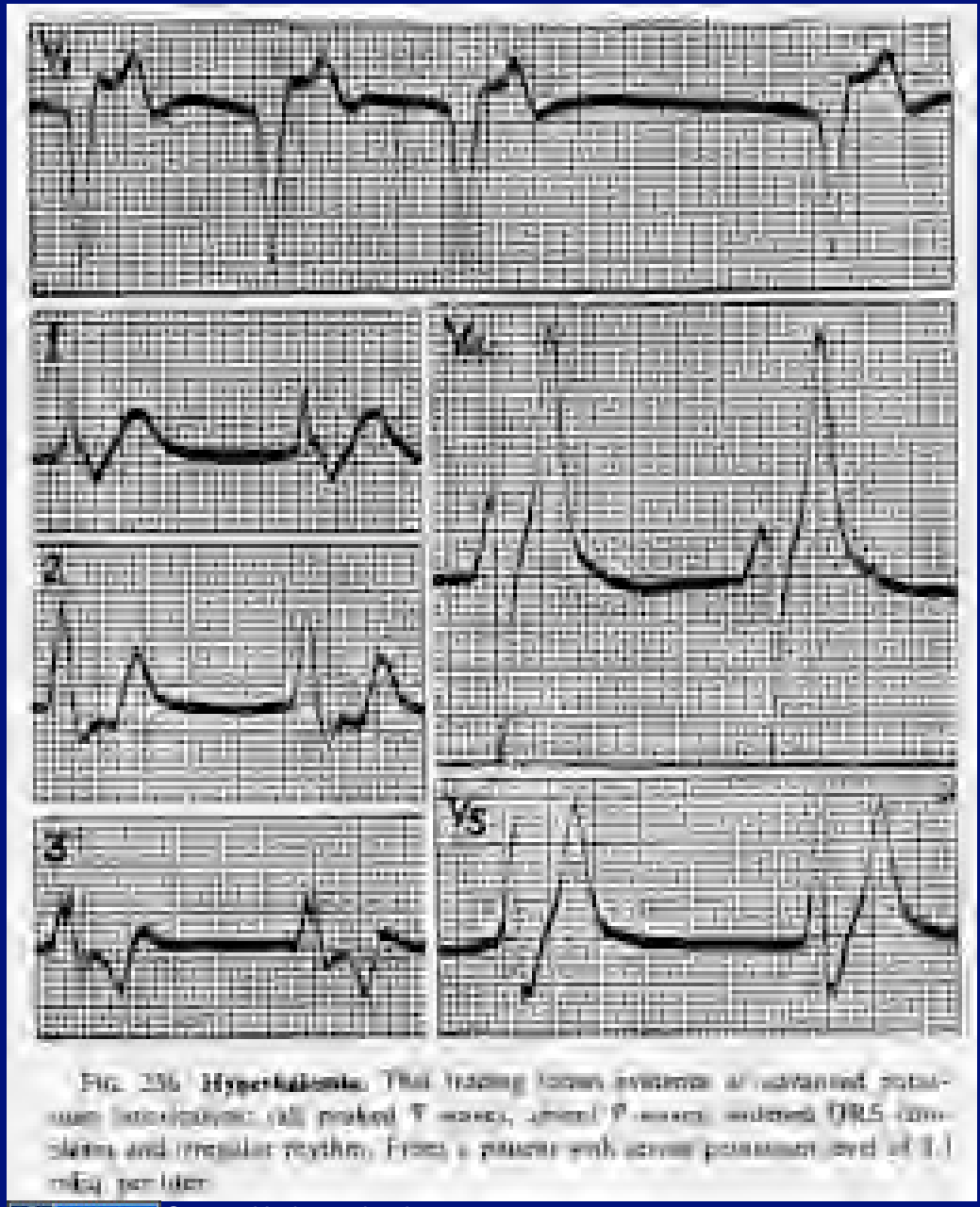

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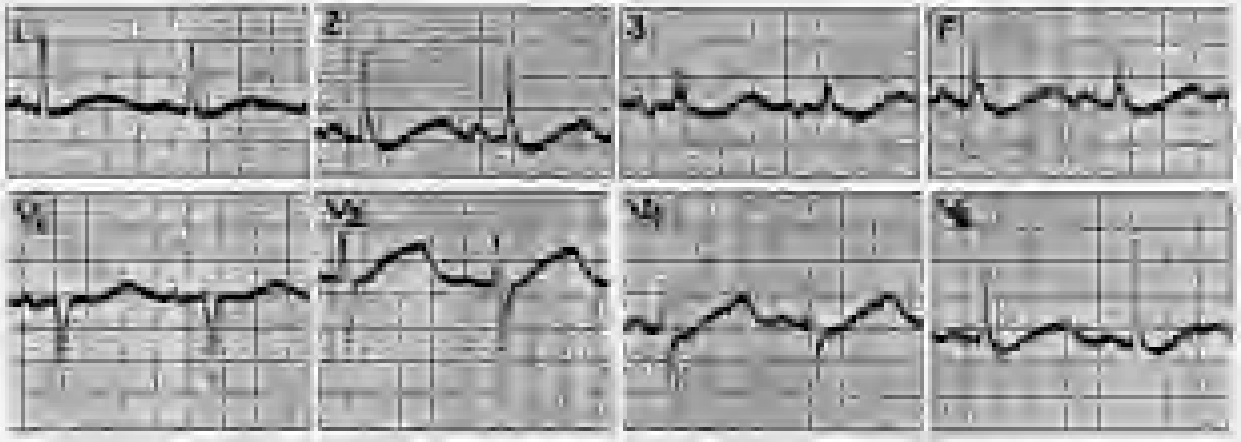


Fig. 251. **Hypokalemia.** Note characteristic pattern with ST depression and extremely prominent U waves.

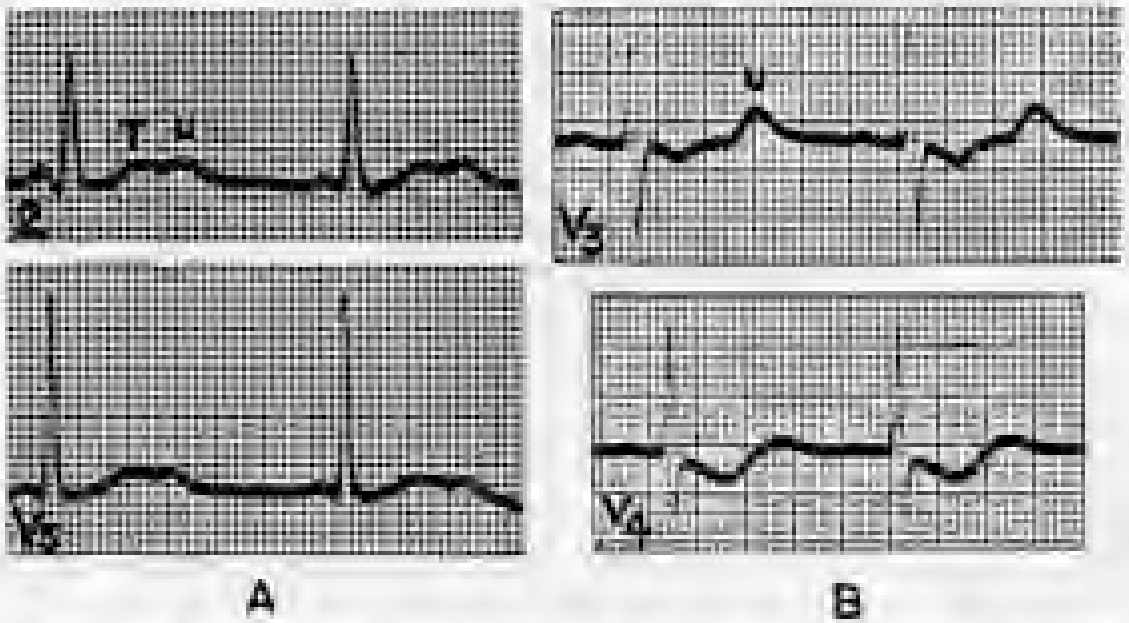
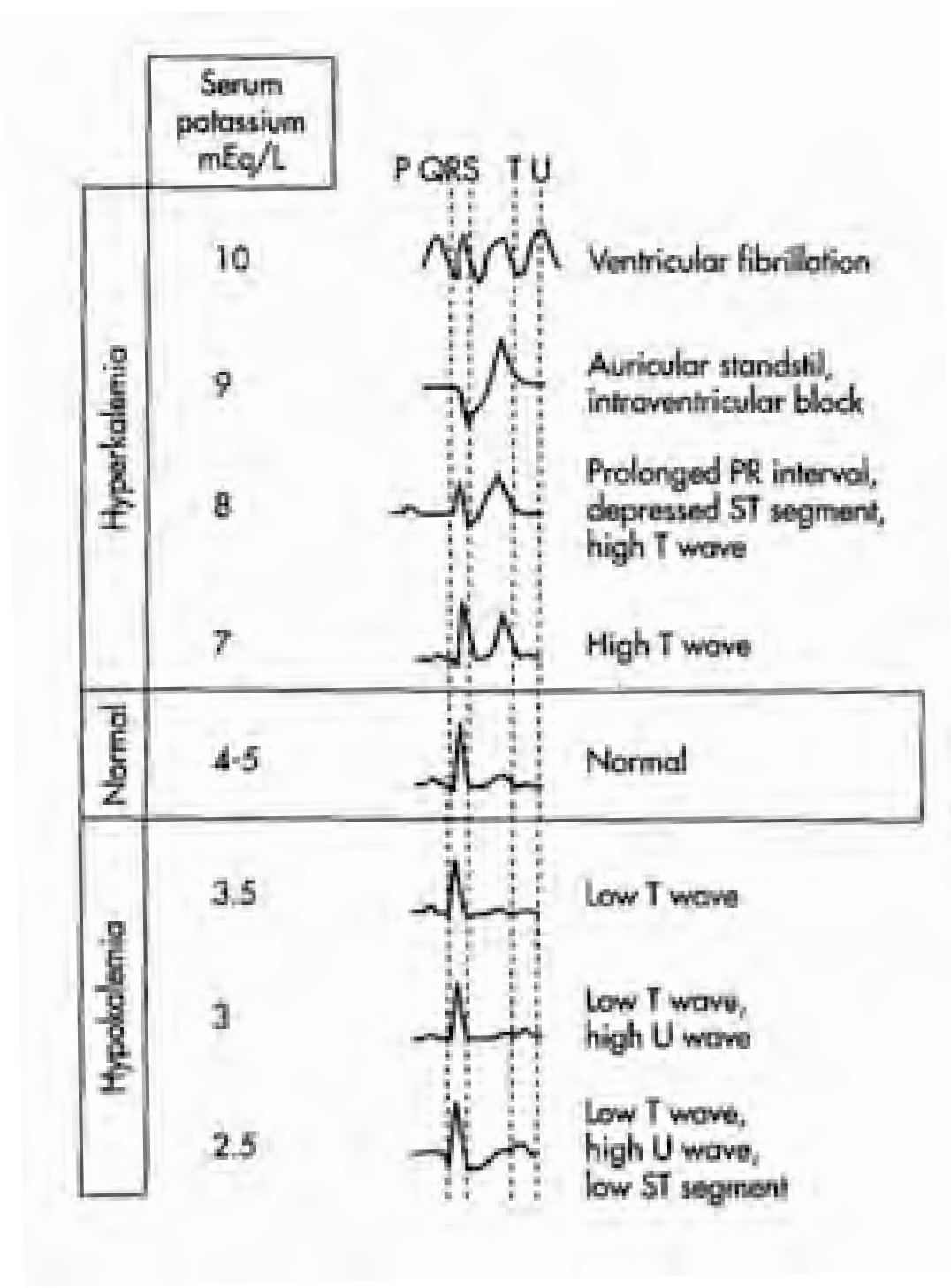
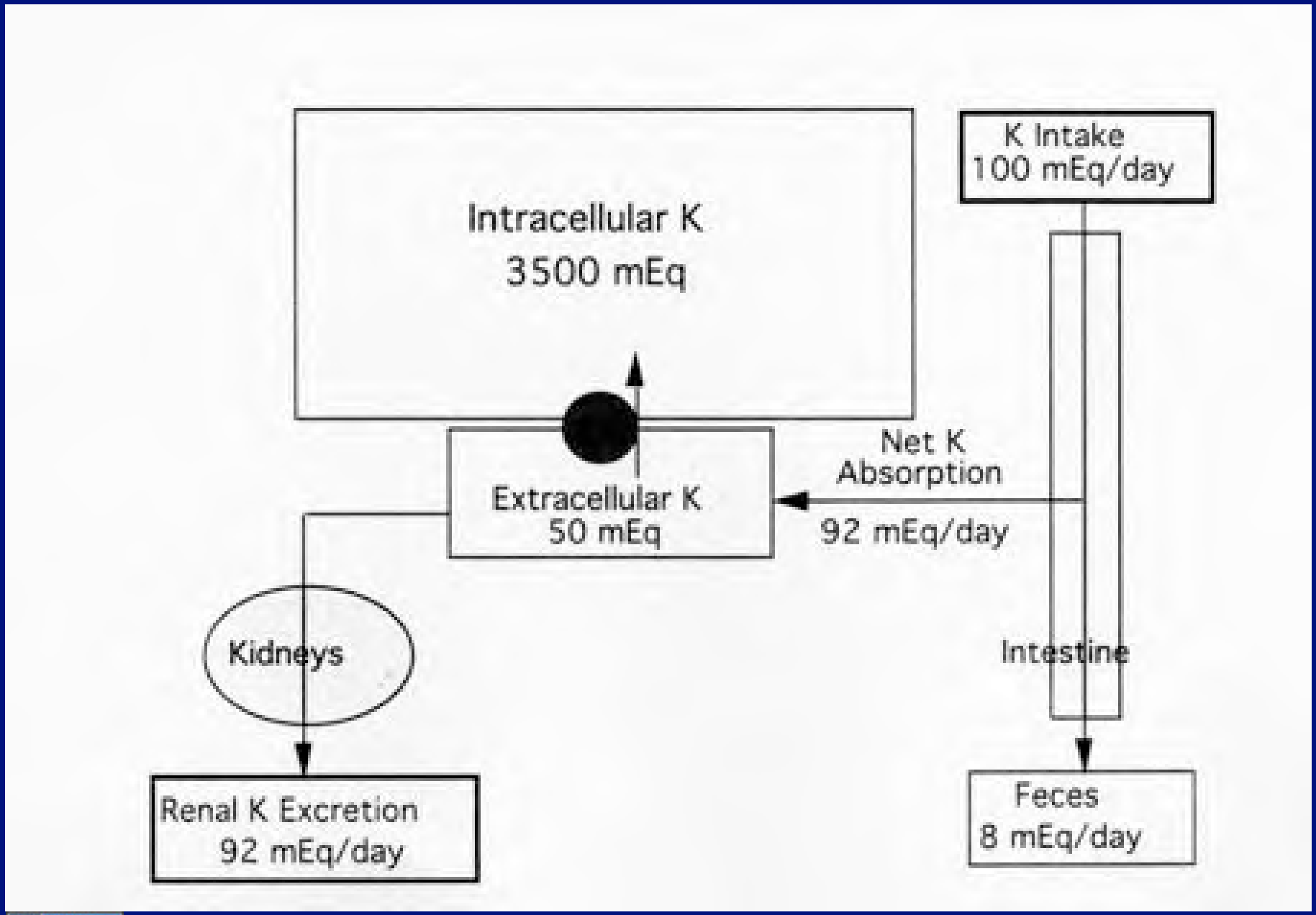
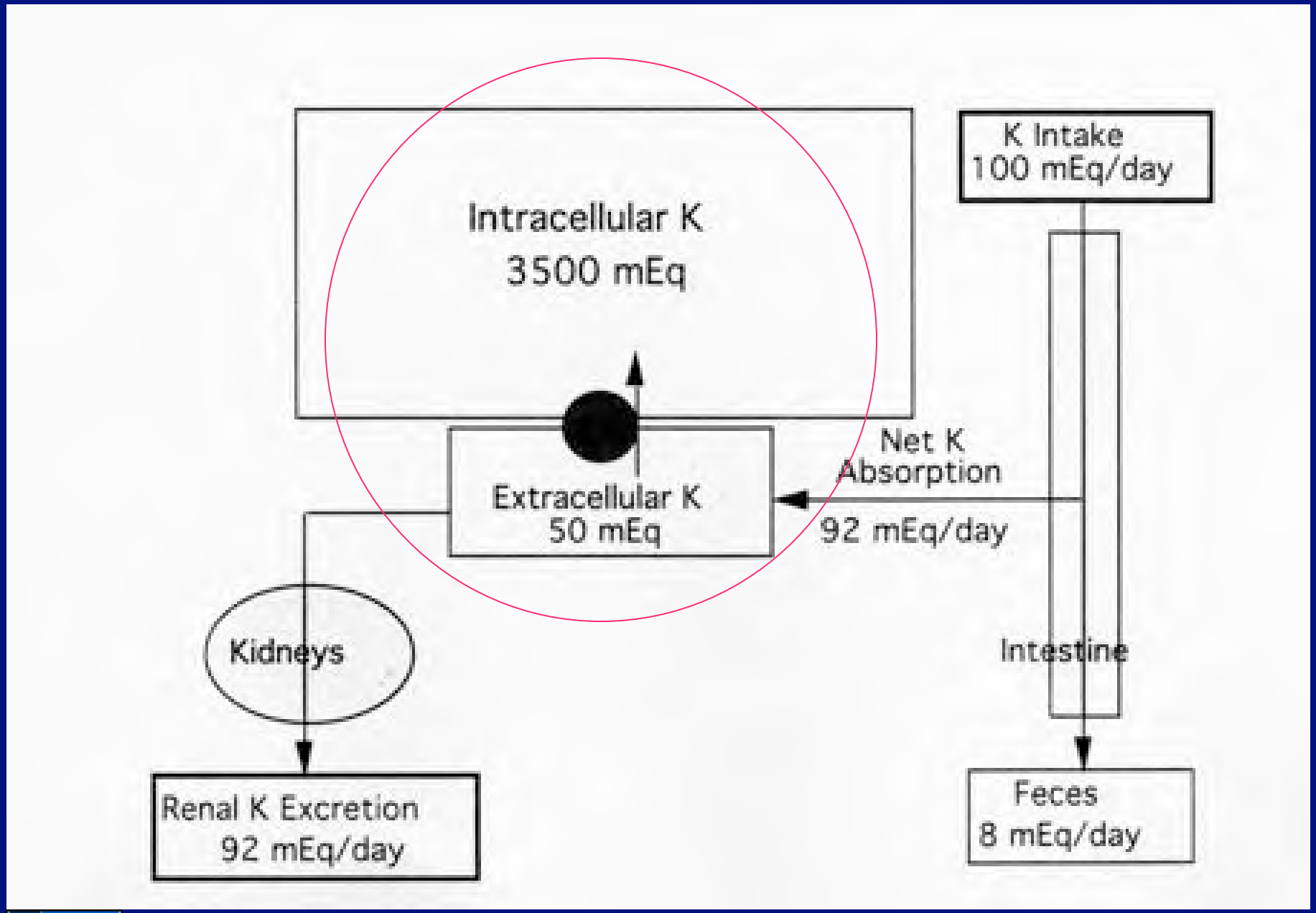


Fig. 252. **Hypokalemia.** Tracings A and B are from different patients. A shows early changes of hypokalemia with prominent U wave merging to form continuous undulating wave with T wave. B shows changes of advanced hypokalemia (1.8 mEq. per liter) in a patient with cirrhosis; note ST-T depression with very prominent U waves in V_4.




Intracellular K
3500 mEq
K Intake
100 mEq/day
Net K
Absorption
92 mEq/day
Extracellular K
50 mEq
Kidneys
Intestine
Renal K Excretion
92 mEq/day
Feces
8 mEq/day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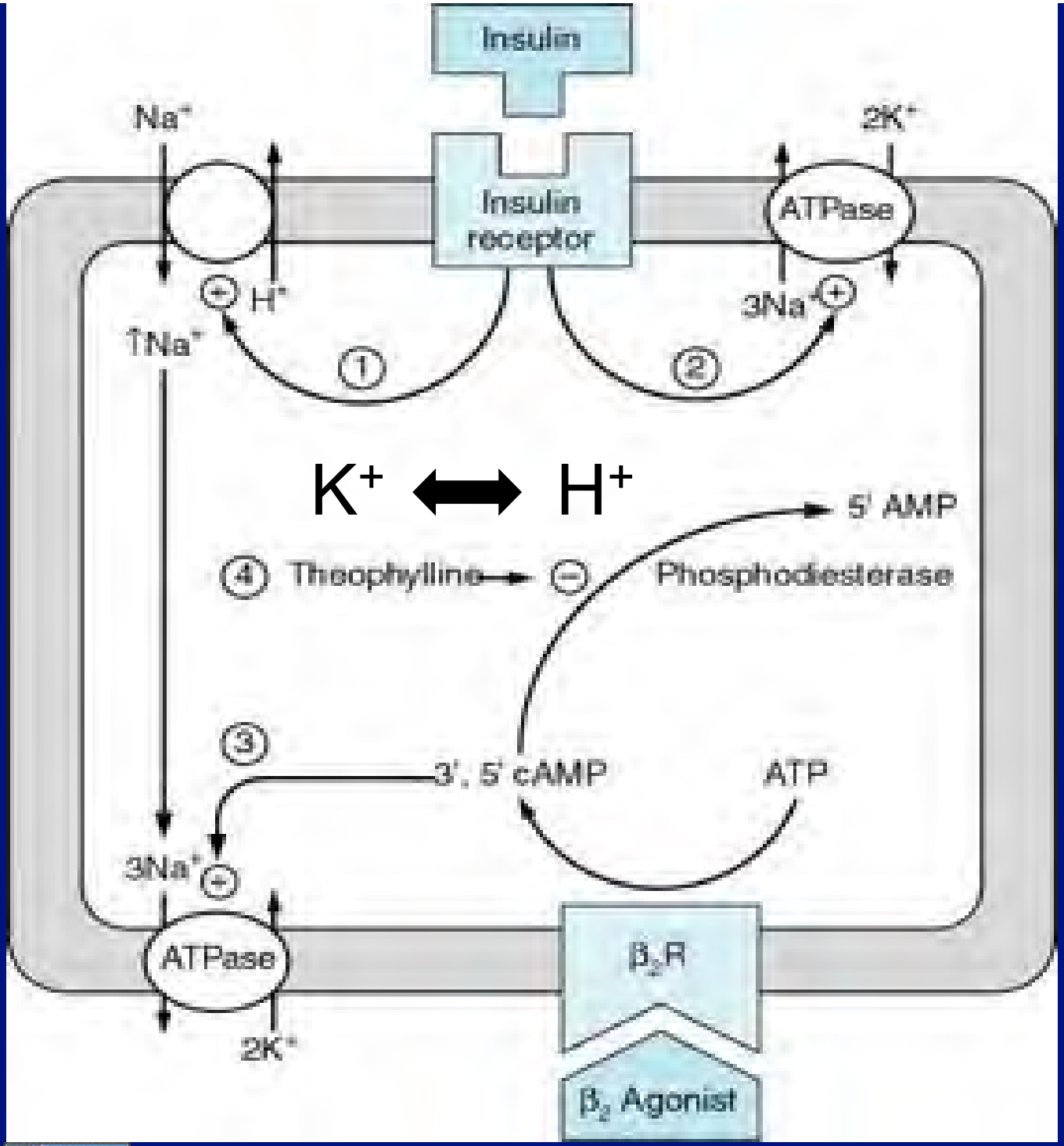
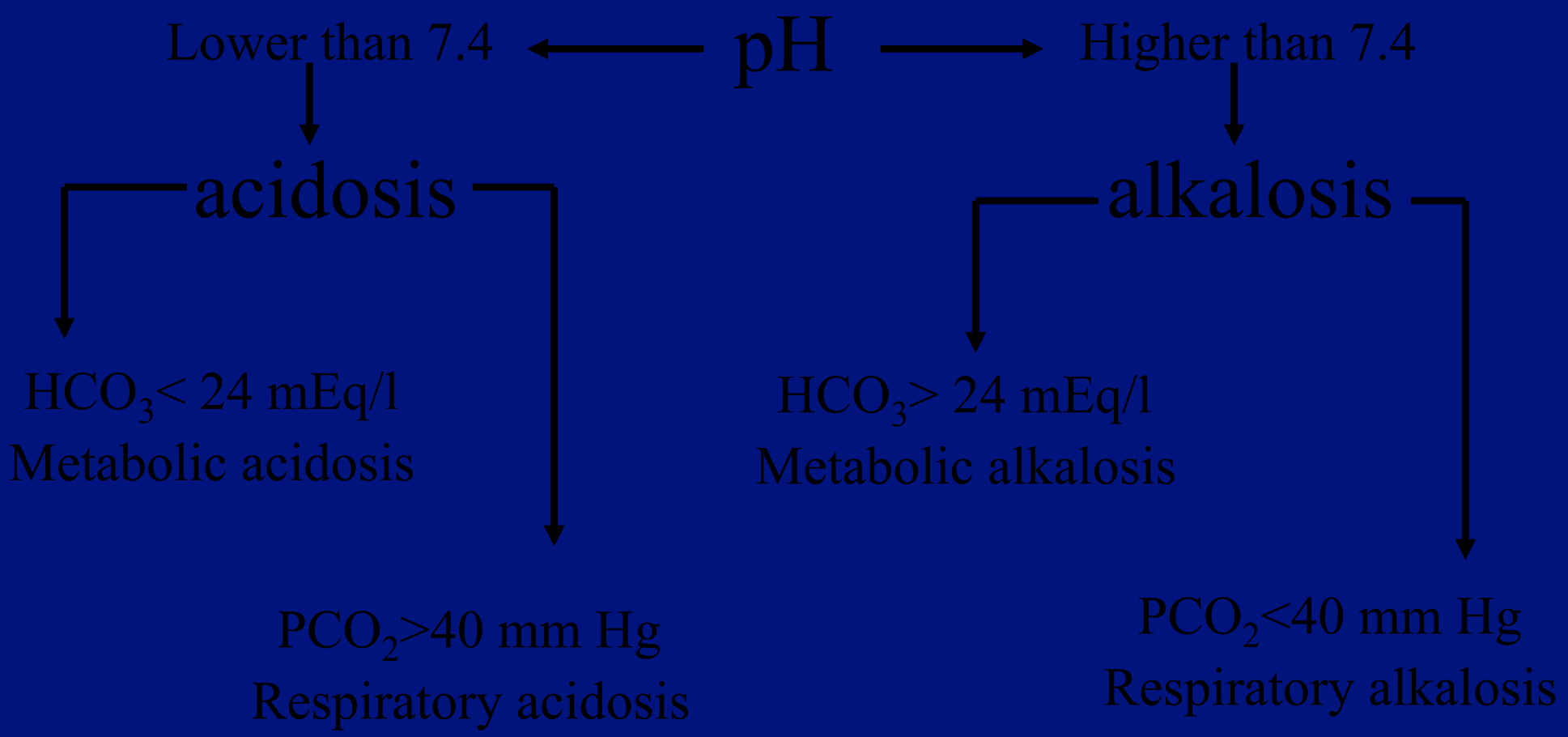


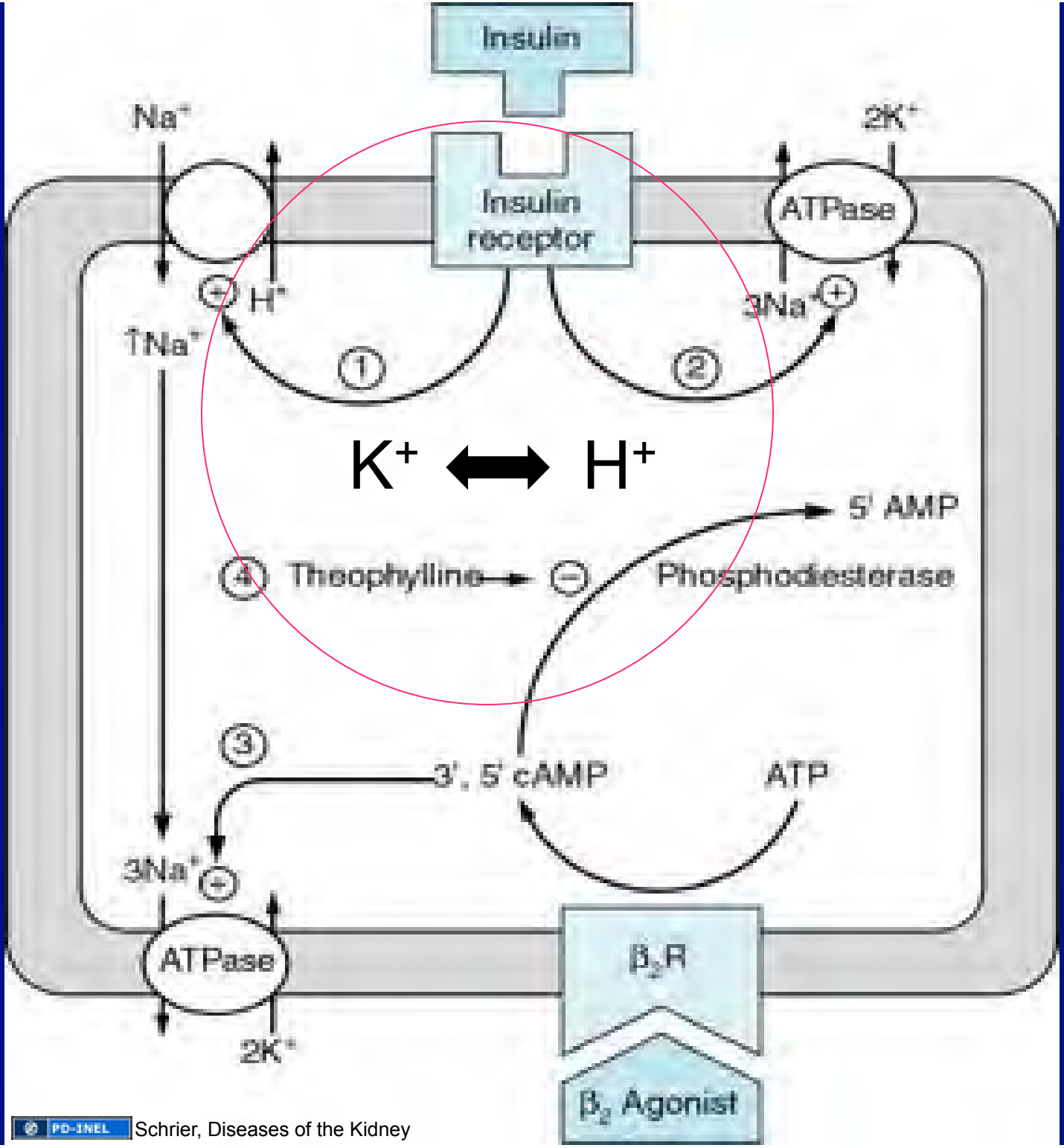
PD-INEL Schrier, Diseases of the Kidney

Diagnosis of acid base disorders

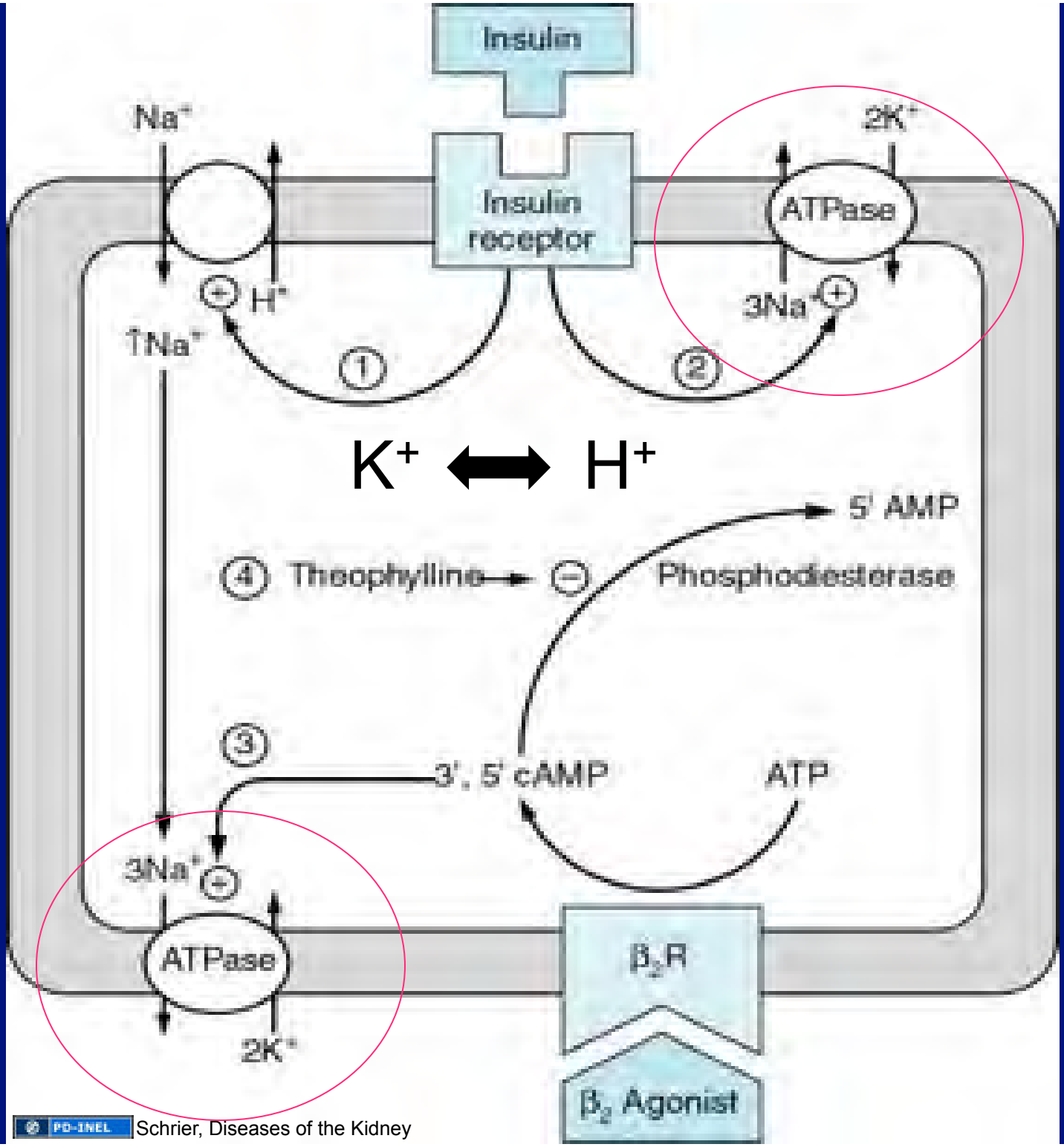


Evaluating Acid-Base Status

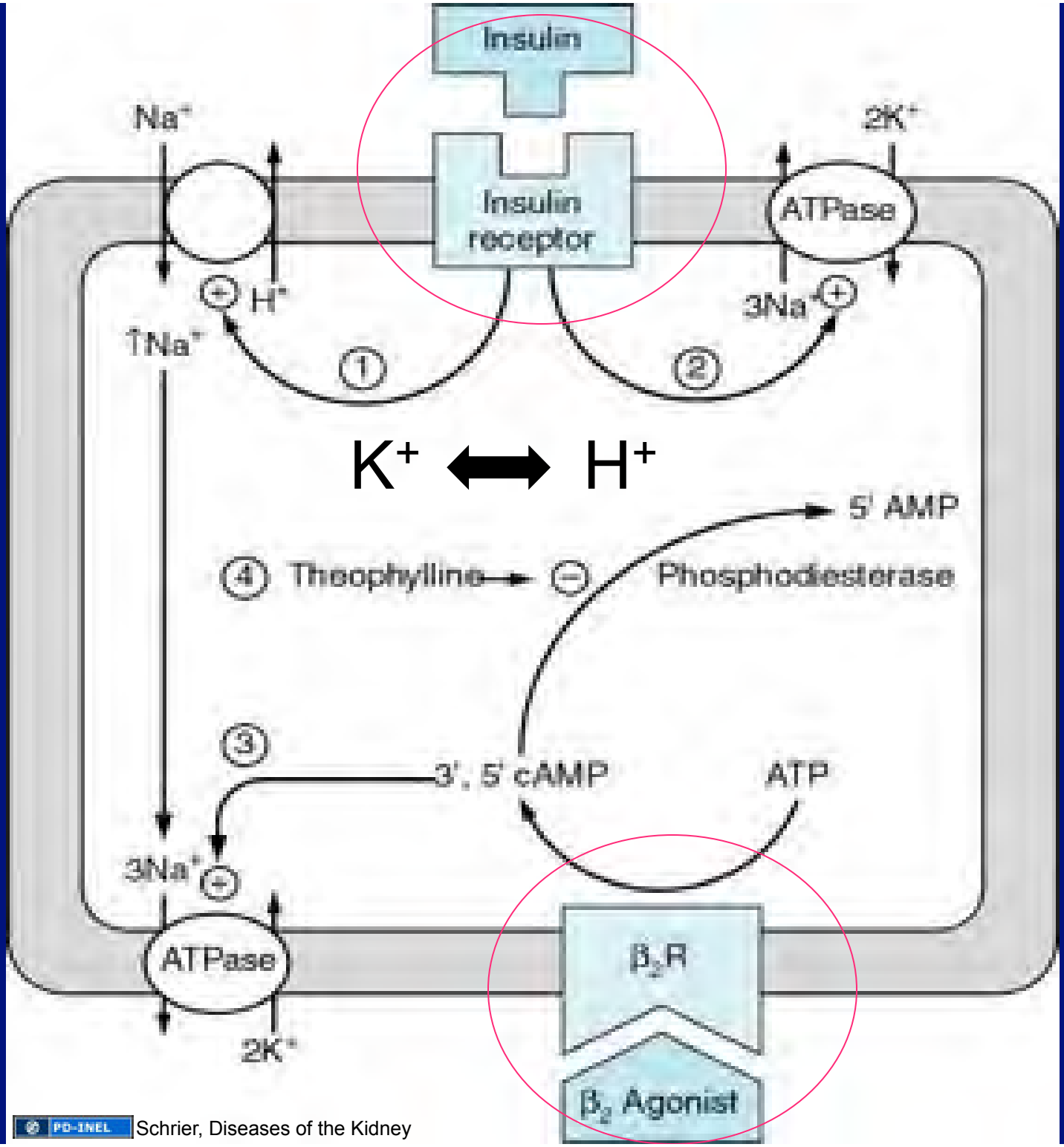
- Respiratory and renal function strive to keep pH = 7.4.
- Both metabolic and respiratory abnormalities can alter pH
- For our purposes, 3 questions:
  - Is the abnormality respiratory or metabolic?
  - If respiratory, is it acute or chronic?
  - If metabolic, is the respiratory system responding appropriately?



 Schrier, Diseases of the Kidney



PD-INEL Schrier, Diseases of the Kidney



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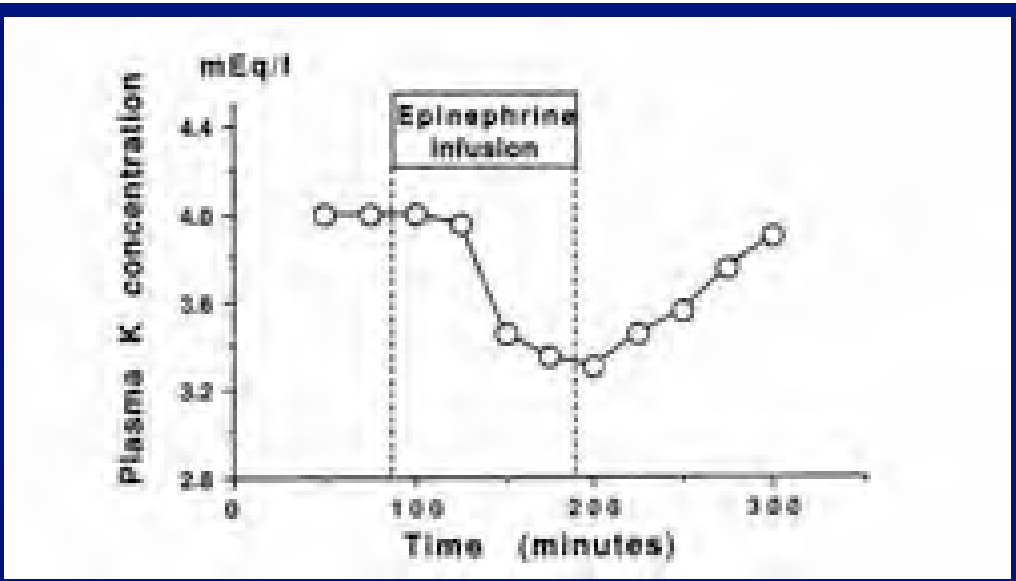
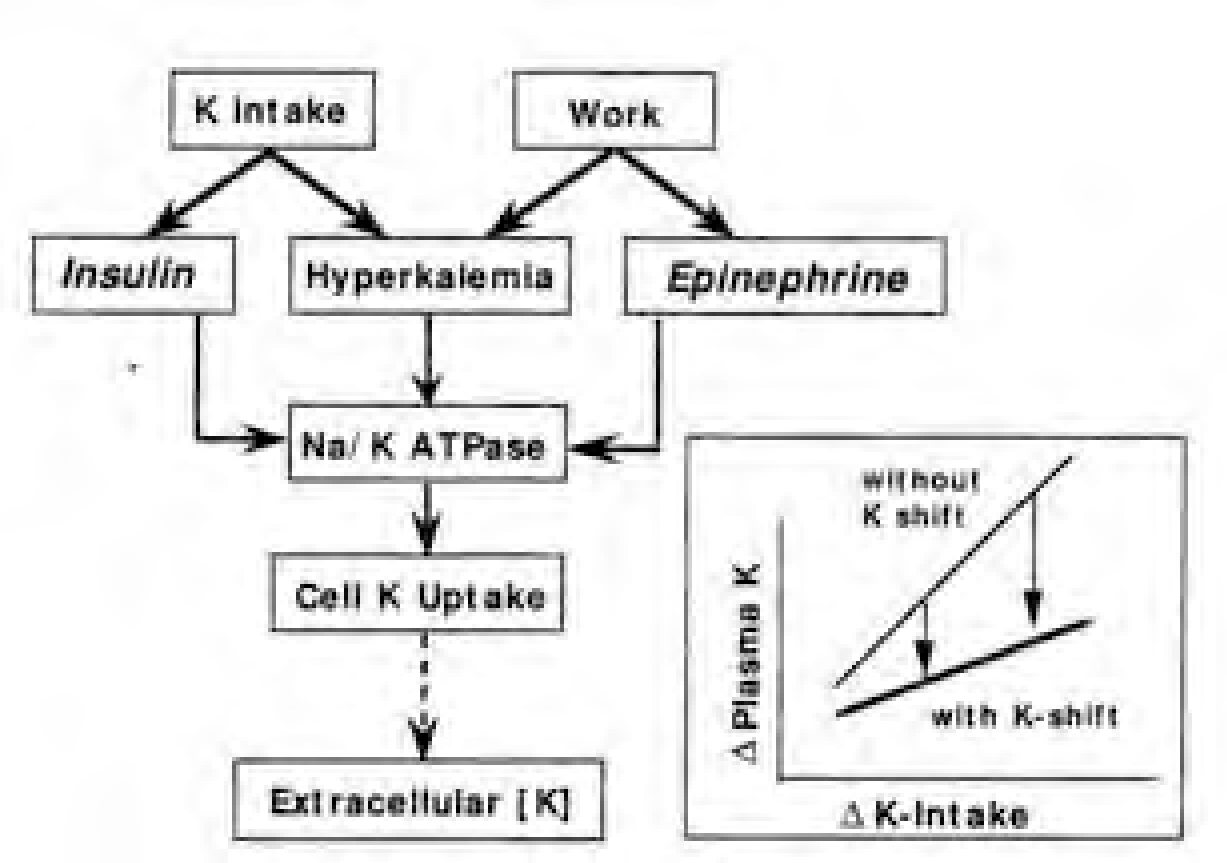


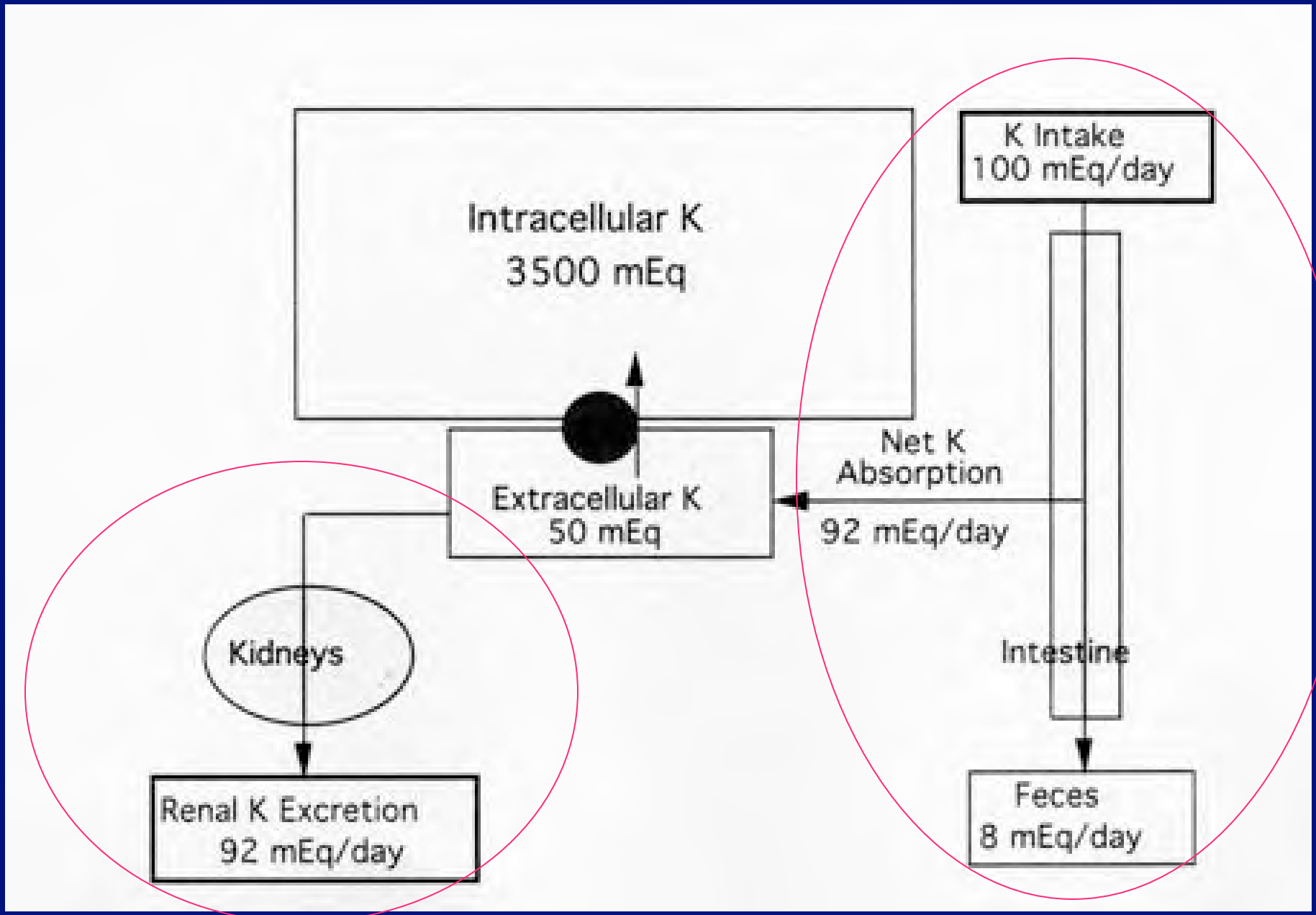


PD-INEL Schnerrman,Sayegh Kidney Physiology

Major modulators of systemic transcellular potassium movement

Physiologic
Insulin
Catecholamines

Pathophysiologic
Acid-base status
Osmolarity
Tissue integrity



 Schnerrman,Sayegh Kidney Physiology

Major routes of K^+ excretion

- Kidney > 85%

- GI tract < 15%

- Contribution of GI tract to renal excretion increases in CRF to > 30% of intake.

- Skin losses can be substantial under some circumstances.

Renal handling of K^+

- Glomerular filtration
- Early proximal reabsorption followed by secretion, then reabsorption in the TAL.
- Distal secretion predominantly by principal cells of the cortical collecting duct under control of multiple factors:

  Aldosterone
  Plasma K^+
  Flow rate/sodium delivery

  Anions
  pH
  ADH

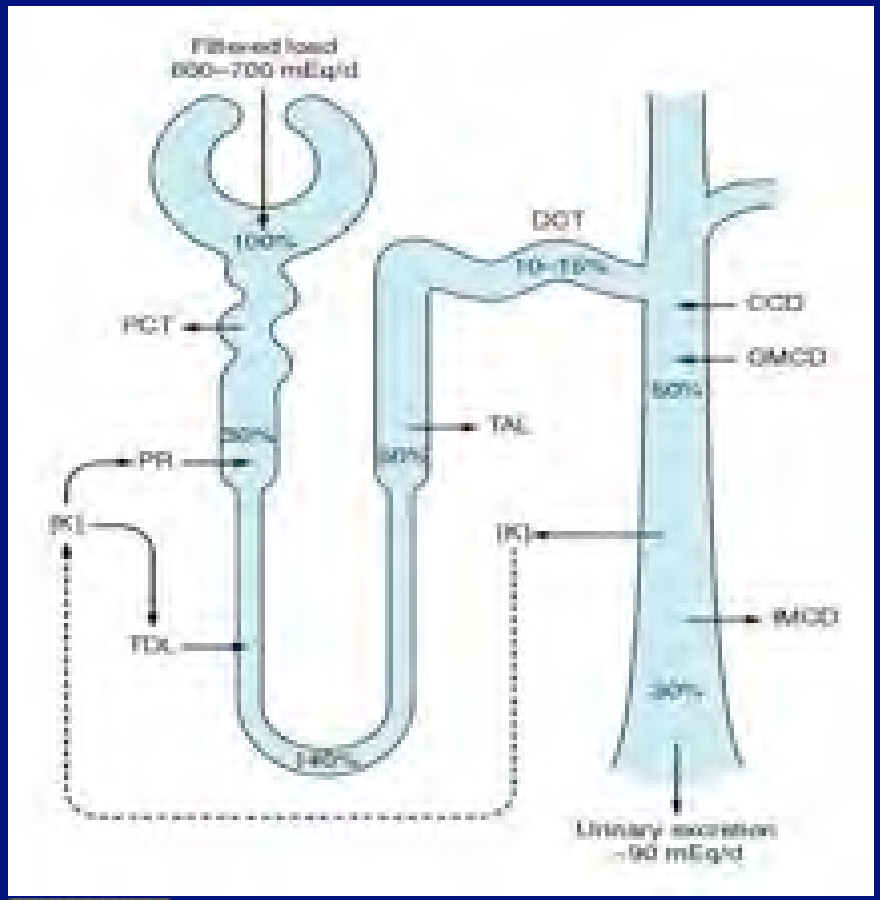
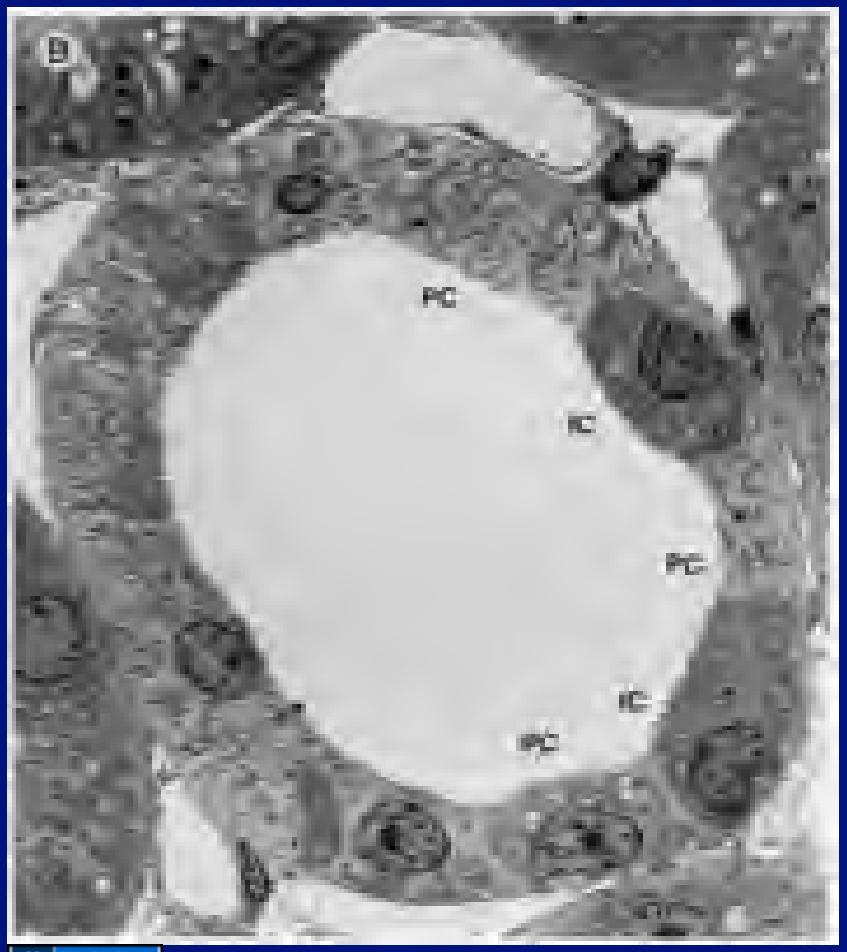


Image illustrating the difference between principal cells and intercalated cells in the collecting duct removed



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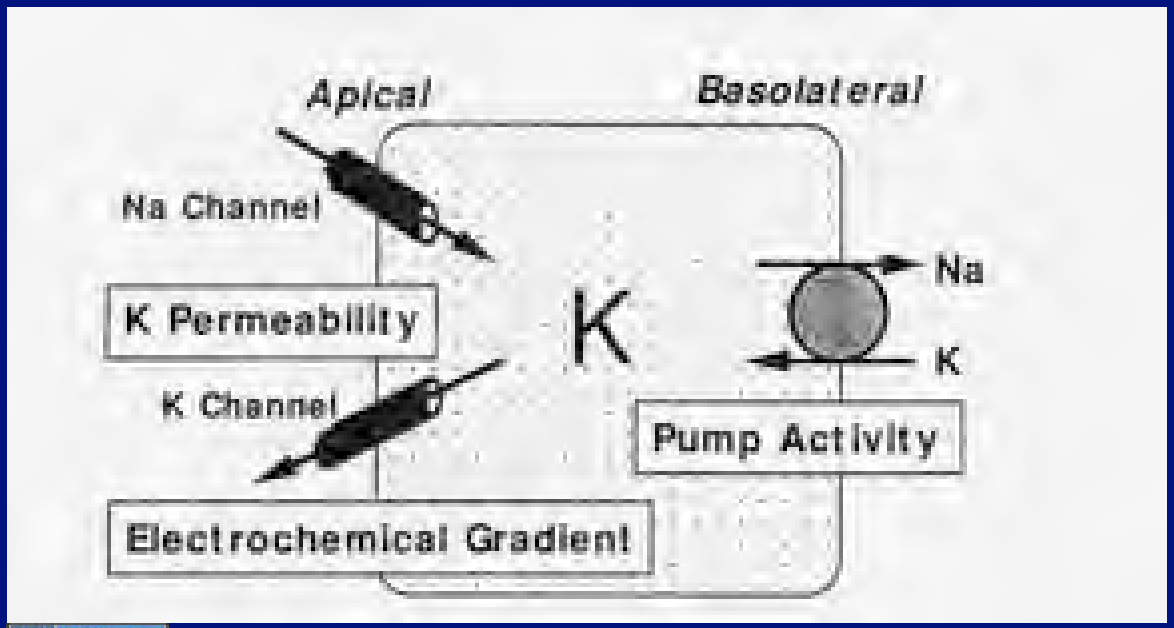
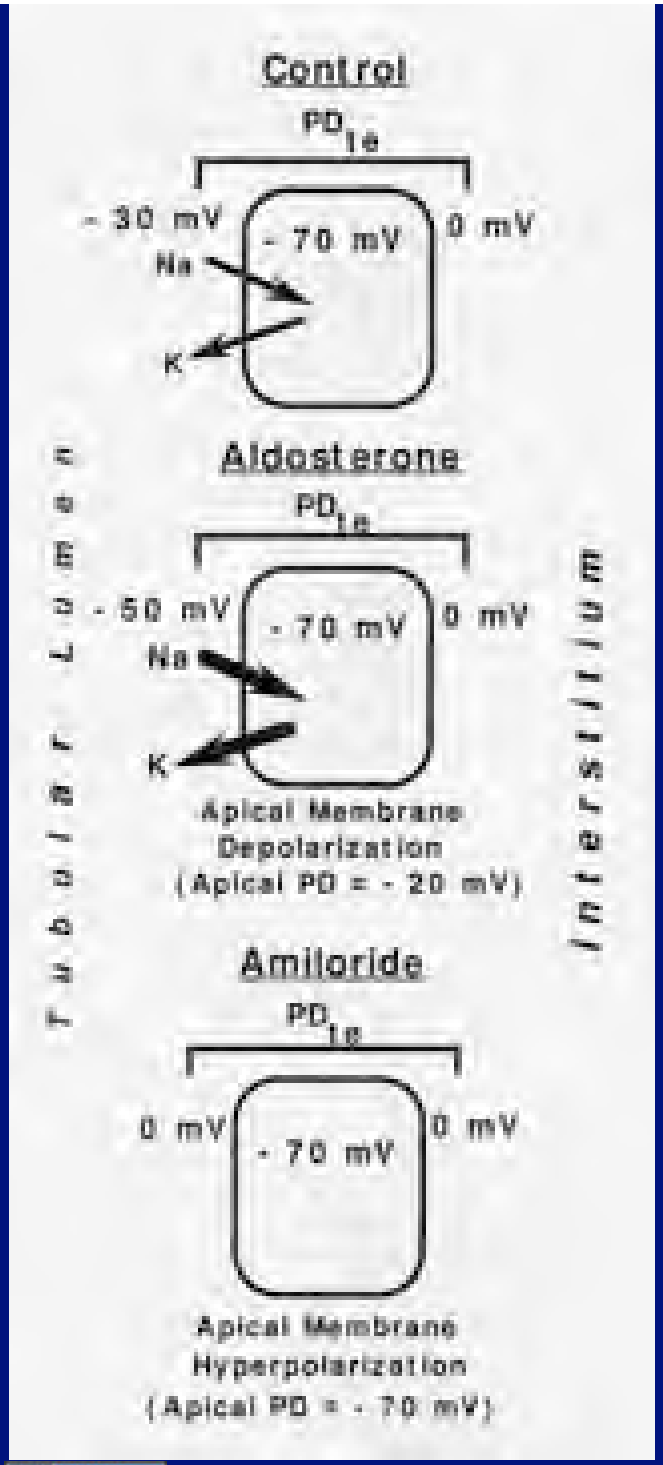
Collecting Duct



PD-INEL Schnerrman,Sayegh Kidney Physiology



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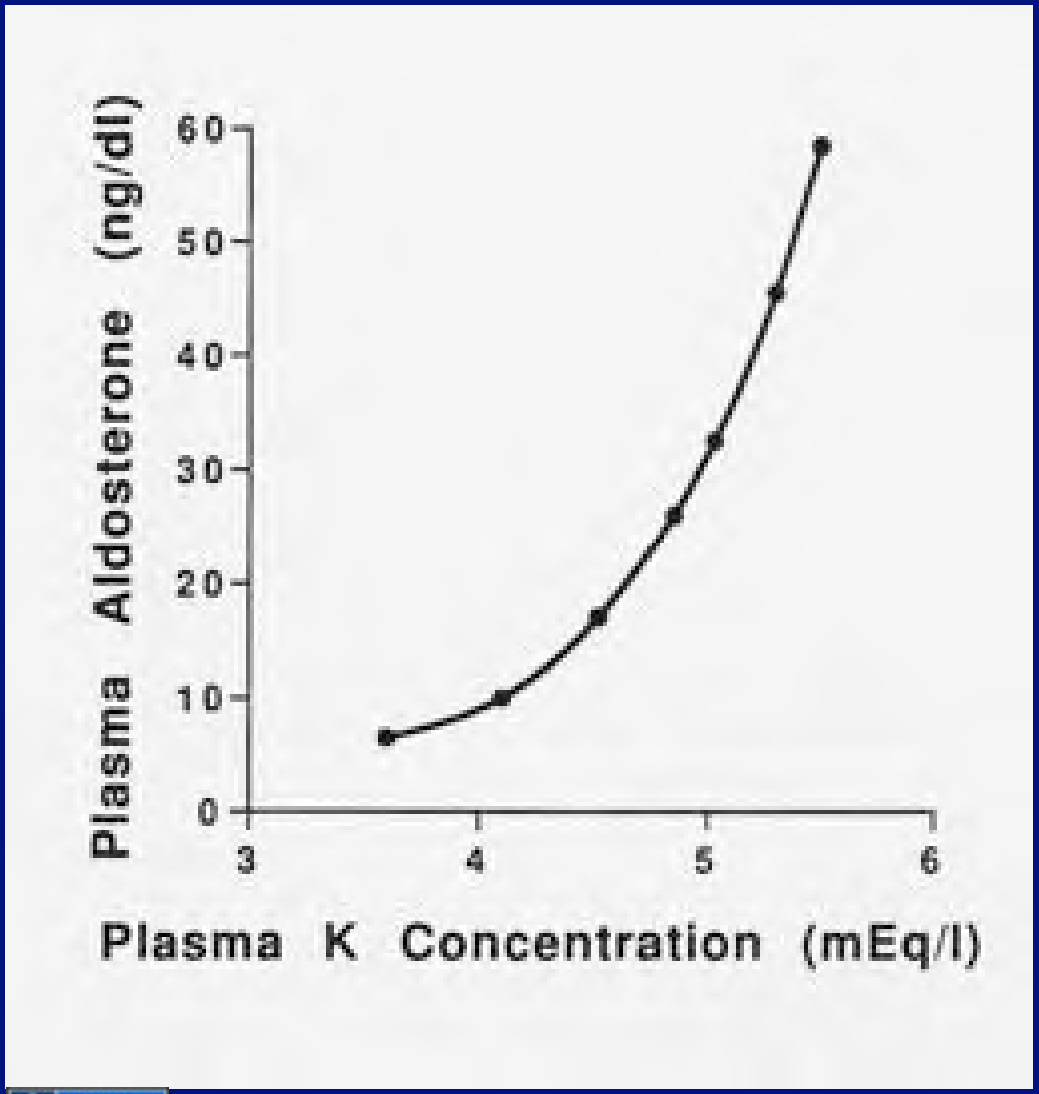
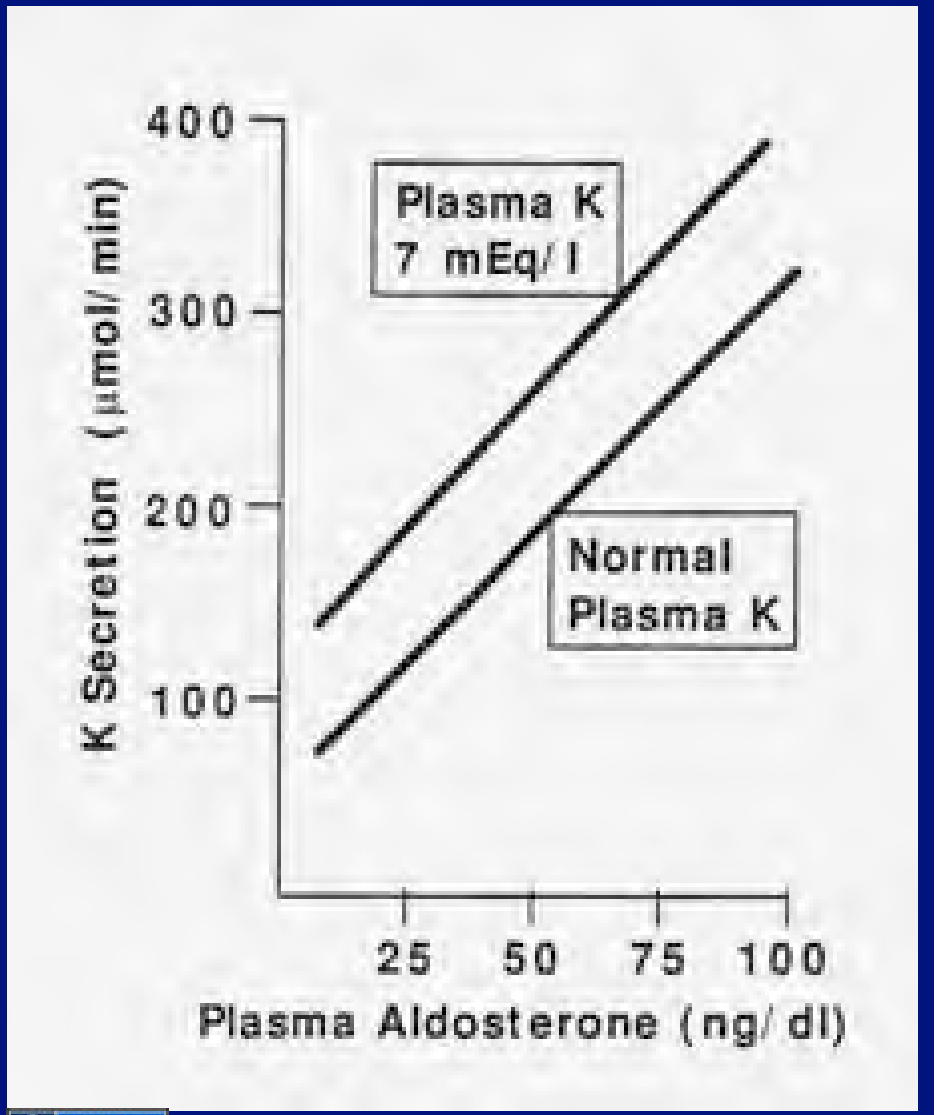
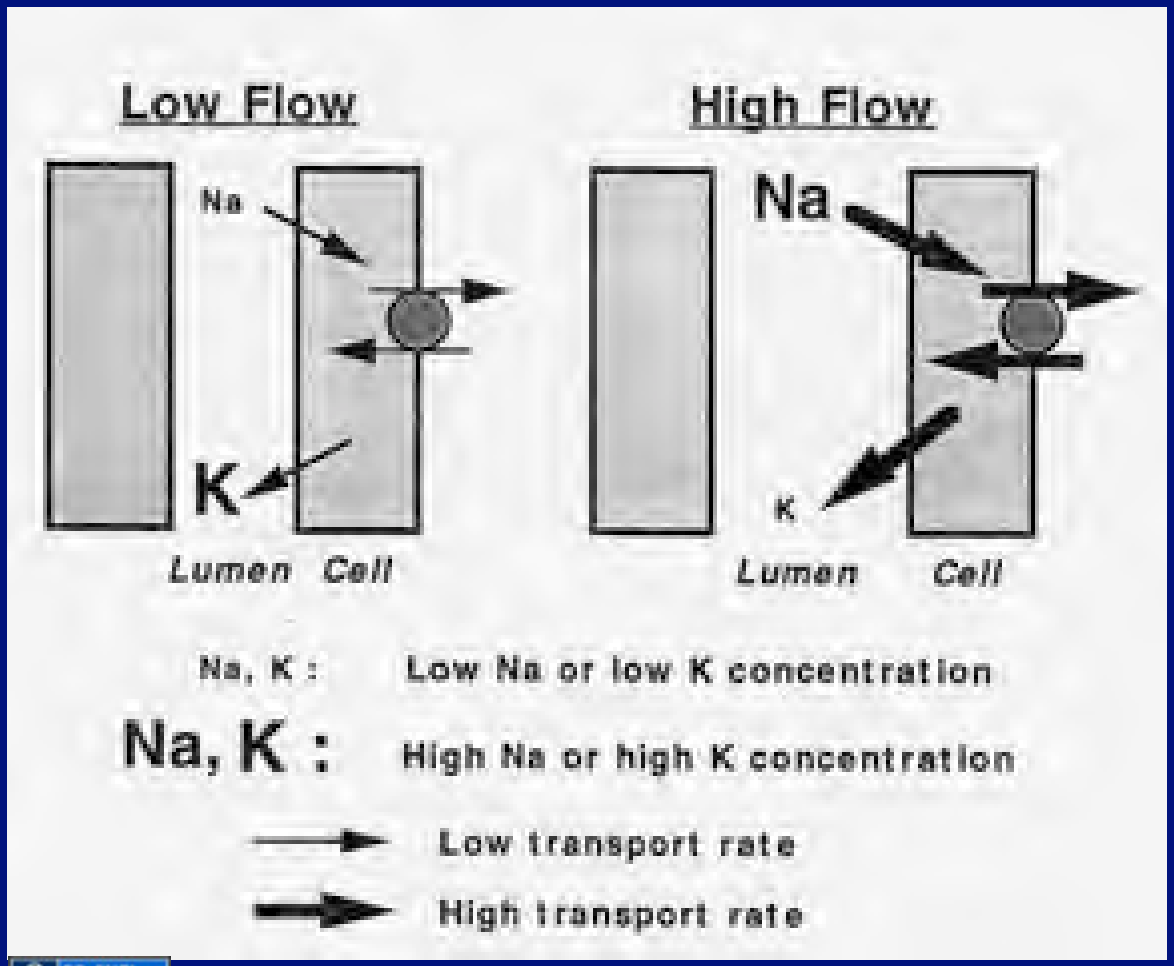


PD-INEL Schnerrman,Sayegh Kidney Physiology

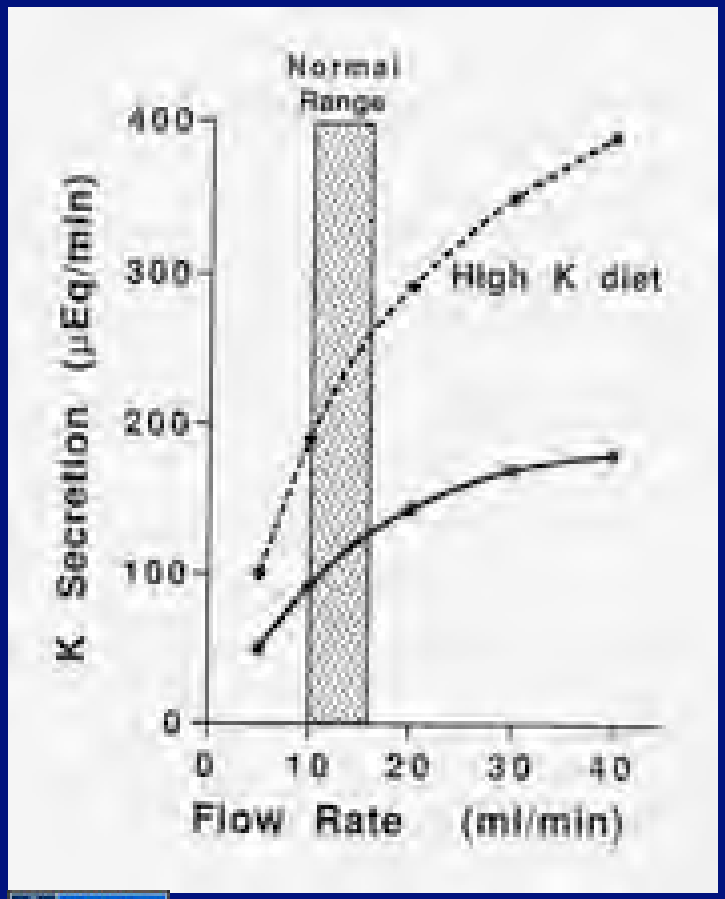


PD-INEL Schnerrman,Sayegh Kidney Physiology

Mechanisms for potassium adaptation. Sufficient to account for increase of K^+ excretion from 100 to 400 meq/day over 48 hours, while limiting extent of increased serum K+ from 3.8 to only 4.8.



PD-INEL Schnerrman,Sayegh Kidney Physiology



PD-INEL Schnerrman,Sayegh Kidney Physiology

Magnesium Homeostasis

- Second most abundant intracellular cation, next to K^+.

- Only 1-2% is in the extracellular space.

- 67% is in bone, only part of which is readily exchangable.

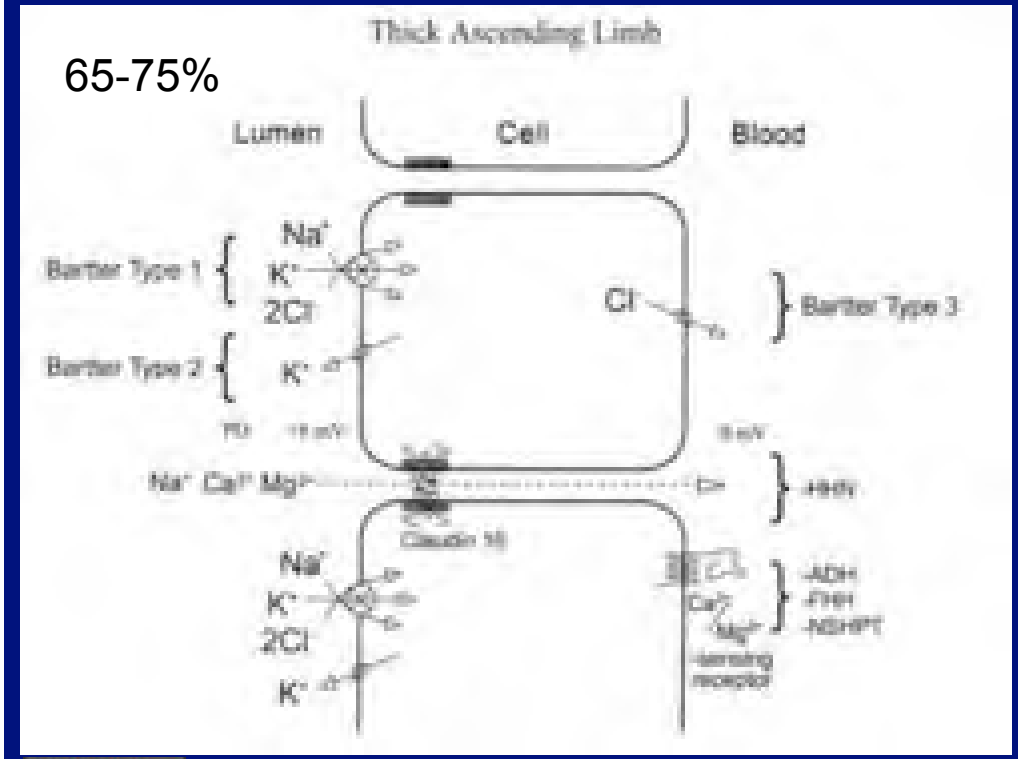
- In plasma, 60% is free, 40% is bound.

- Regulates multiple intracellular processes:

Enzyme activity and interaction with ATP
Control of ion channels

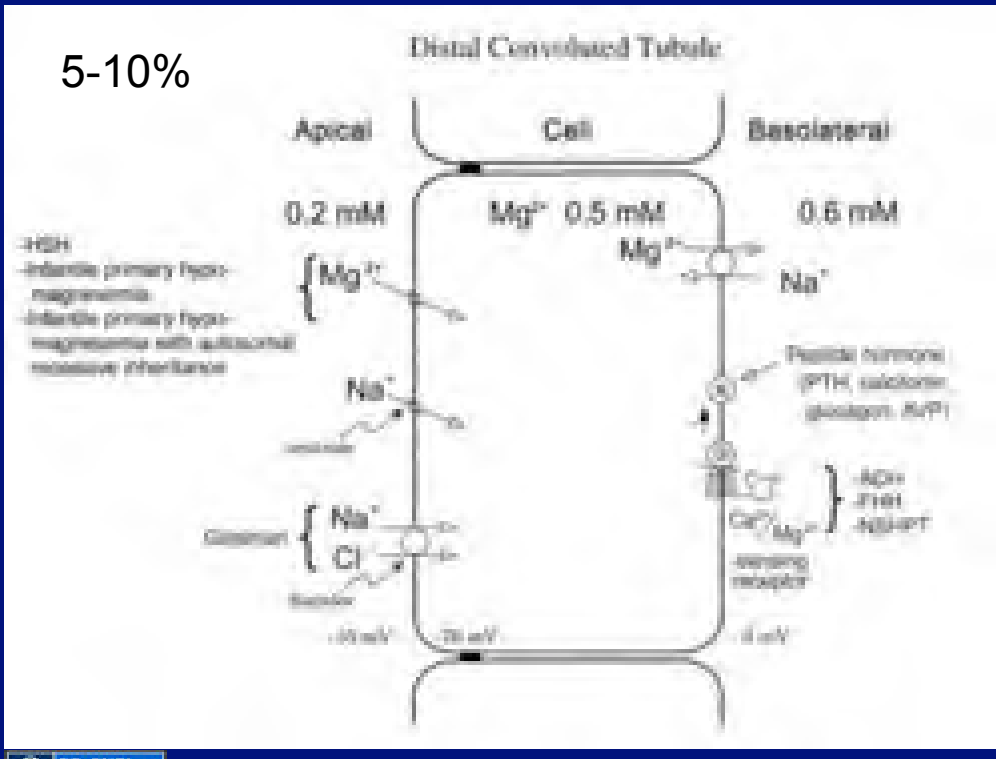
- Prominently affects:
Potassium metabolism
Calcium metabolism
Neuromuscular excitability via both its direct actions and its effects on potassium and calcium metabolism. Decreased magnesium increases irritability including promotion of cardiac arrhythmias, seizures, and muscle spasms.

65-75%



PD-INEL Cole, D.E. and Quamme, G.A.

5-10%



PD-INEL Cole, D.E. and Quamme, G.A.

Magnesium Balance and Renal Handling

At the important cortical thick ascending limb reabsorption site, most of the reabsorption is paracellular, driven by the positive lumen voltage created by flux through the Na/K/2Cl transporter. The major tight junction protein mediating this process, paracellin-1, has recently been identified by positional cloning of families with an autosomal recessive syndrome of profound renal Mg^{2+} wasting.

A more commonly manifested consequence of this mechanism for Mg^{2+} reabsorption is that anything that inhibits the Na/K/2Cl transporter, such as the commonly used loop diuretics, can lead to Mg^{2+} wasting, depletion, and resulting symptoms.

Approach to Disorders of Potassium and Magnesium

Objectives

1. Understand the basis and importance for the diagnosis of disorders of potassium balance.

2. Recognize the electrocardiographic patterns associated with hyper and hypokalemia.

3. Know the major etiologies for hyperkalemia arising from increased intake, cellular redistribution and decreased excretion and the basis for these.

4. Understand how the determinants of renal potassium excretion contribute to the development of hyperkalemia during common clinical states.

5. Know the major etiologies for hypokalemia and understand the associations between hypokalemia and metabolic alkalosis or acidosis and the use of urinary chloride in its diagnosis.

6. Know the treatment options for hyperkalemia and hypokalemia and the mechanism of action for each option.

7. Understand the clinical settings in which you need to be concerned about hypomagnesemia and hypermagnesemia.

Hyperkalemia

- Spurious

- True

Decreased excretion

+

Excess supply

Redistribution

Exogenous

Spurious Hyperkalemia

- Hemolysis

- Thrombocytosis, > 1,000,000

- Leukocytosis, > 200,000

- Abnormal erythrocytes
  hereditary spherocytosis
  familial pseudohyperkalemia
  (Temp dependent K^+ loss)

- Ischemic blood drawing
  fist clenching

Spurious Hyperkalemia

- Hemolysis

- Thrombocytosis, > 1,000,000

- Leukocytosis, > 200,000

- Abnormal erythrocytes
  hereditary spherocytosis
  familial pseudohyperkalemia
  (Temp dependent K^+ loss)

- Ischemic blood drawing
  fist clenching

THE EKG IS NORMAL

Sources of 'excess' K^+ to promote hyperkalemia

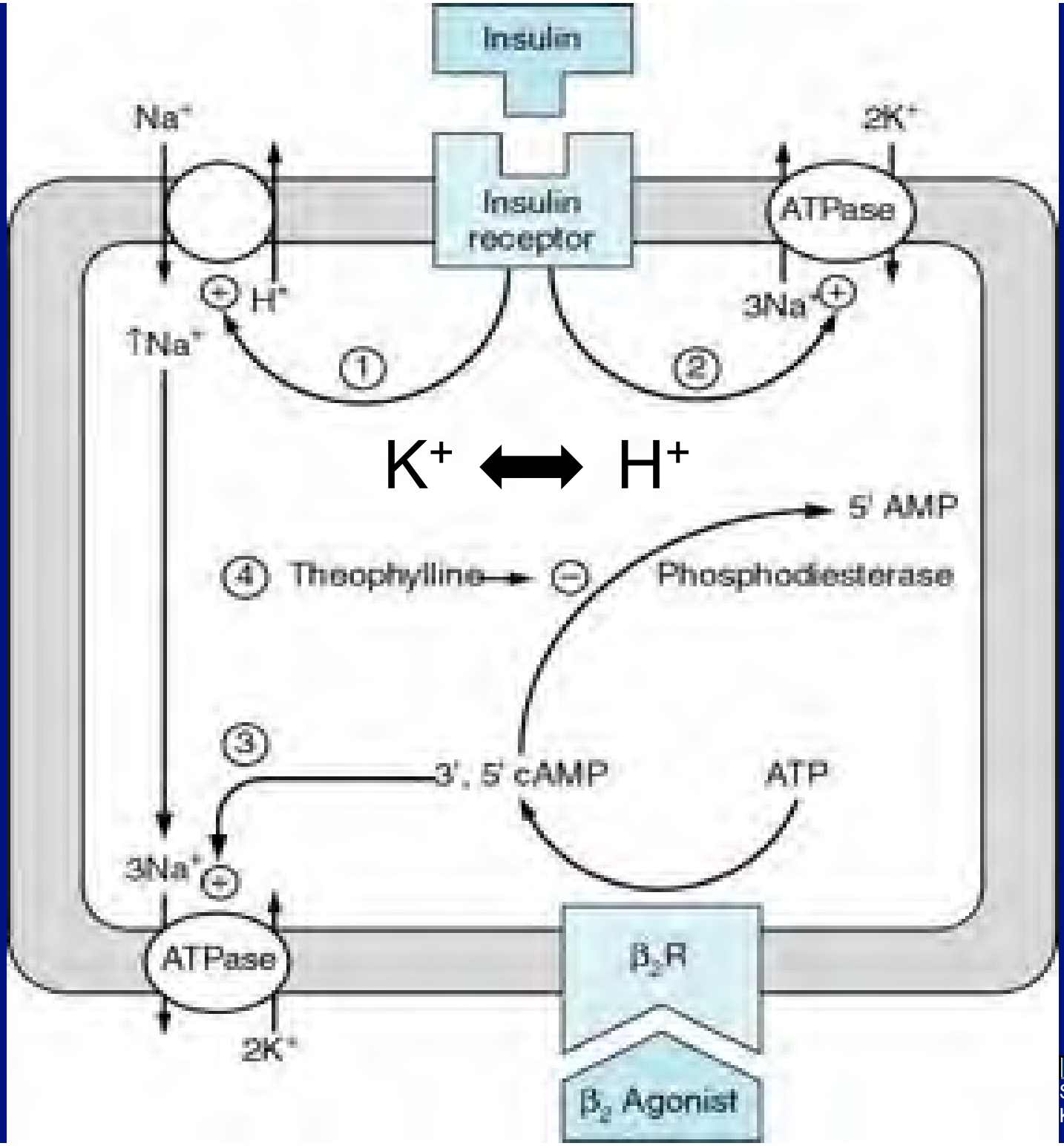
- Redistribution of endogenous, intracellular K^+

- Exogenous K^+
  - Diet
  - Iatrogenic

Major modulators of systemic transcellular potassium movement

Physiologic
Insulin
Catecholamines

Pathophysiologic
Acid-base status
Osmolarity
Tissue integrity



Schrier, Diseases of the Kidney

Hyperkalemia due to redistribution

- Exercise (0.7-1.3 meq/l-moderate exertion)
- Diabetes – insulin lack
- Hyperosmolar states: hyperglycemia, mannitol
- Acidosis
- Cytolysis
    - Tissue necrosis
    - Tumor lysis
    - Hematoma dissolution
    - Massive intravascular hemolysis
- Catabolic states
- Drugs
    - Beta blockers
    - Digitalis intoxication

Hyperkalemia due to excess exogenous K^+

- Increased intake - only produces hyperkalemia if excretory mechanisms are also impaired

Normal intake 50-100 meq/d but can be as high as 500-700 meq/d.
Minimum to maintain K^+ - 20-30 meq/d

Especially rich dietary K^+ sources
Most fruits and vegetables
Coffee, tea, milk

High potassium foods

Be sure to limit or avoid high potassium foods.

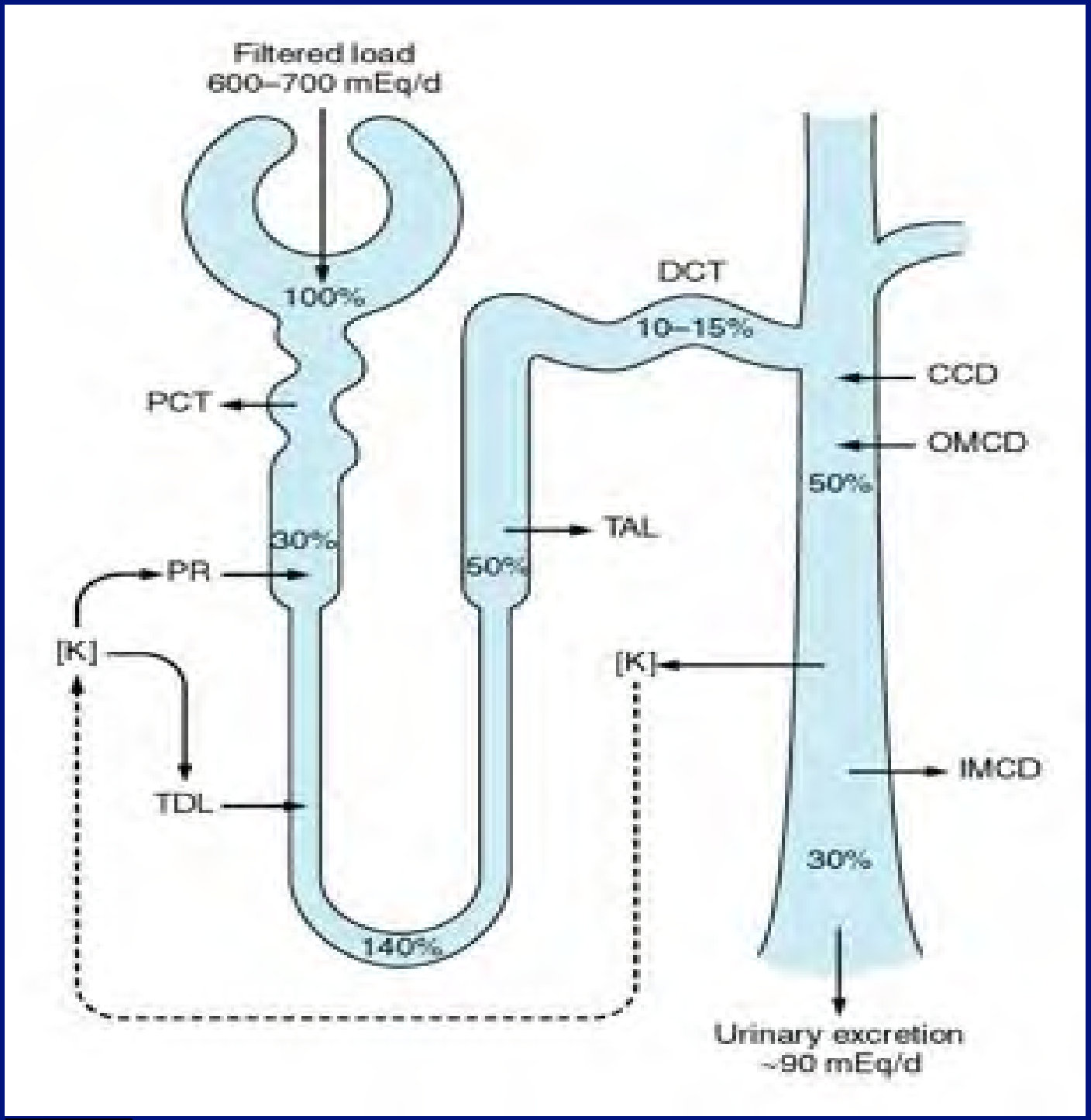
Food type	High potassium foods	
Fruits	• Avocados	• Kiwi
	• Bananas	• Mangos
	• Cantaloupe	• Oranges & orange juice
	• Dried fruits	• Papaya
	• Honeydew	• Prune juice
Vegetables	• Artichoke	• Sweet potatoes
	• Dried beans & peas	• Tomatoes, tomato sauce
	• Pumpkin	• Vegetable juices
	• Potatoes, French fries	• Winter squash
	• Spinach (cooked)	
Dairy	• Milk	• Ice cream
	• Yogurt	
Miscellaneous	• Chocolate	• Salt substitute
	• Molasses	• Seeds and nuts

Disclaimer: The above list does not include all foods high in potassium. Portion size also plays a role in the amount of potassium you get from the foods you eat. Consult your dietitian and doctor about what to eat based on your individual requirements.

Hyperkalemia due to excess exogenous K^+

'Hidden' exogenous sources

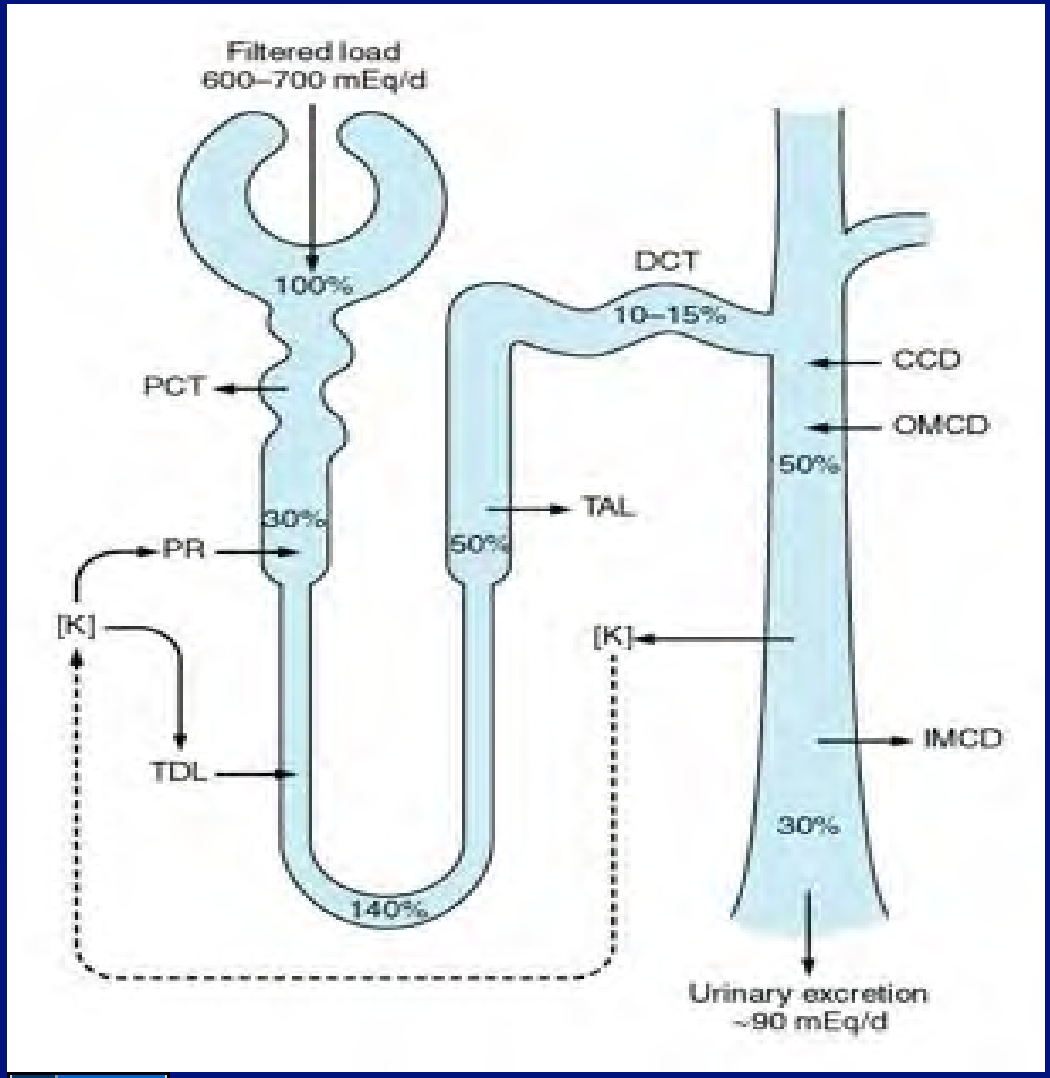
- Salt substitutes



Schrier, Diseases of the Kidney

Hyperkalemia due to decreased K^+ excretion

- Renal insufficiency due to decreased number of functioning nephrons for any reason.



Schrier, Diseases of the Kidney

Hyperkalemia due to decreased K^+ excretion

-Damage to collecting tubules of still functioning nephrons

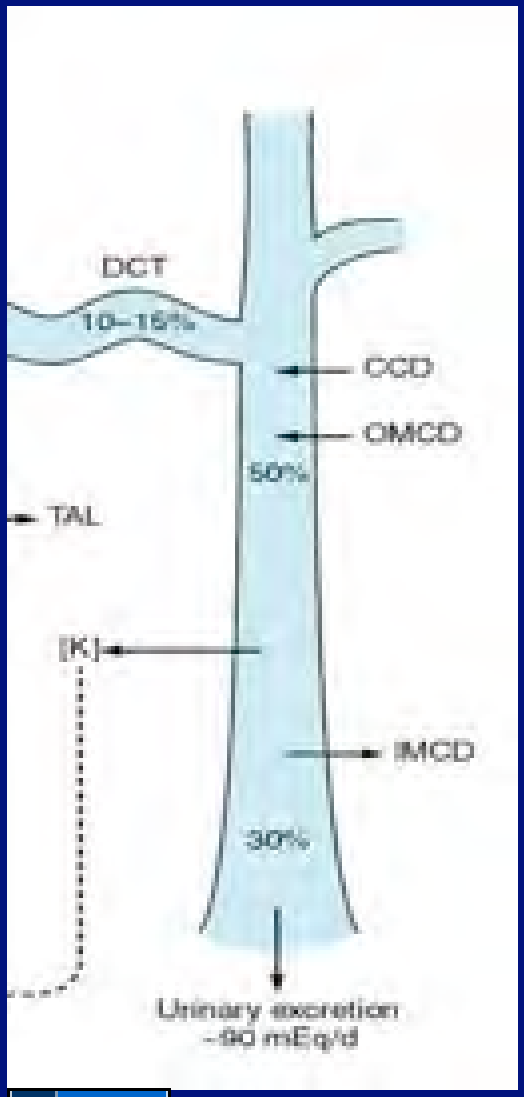
Obstruction

Interstitial nephritis

-Drug-induced inhibition of principal cell transport mechanisms

Na^+ channel blockers:

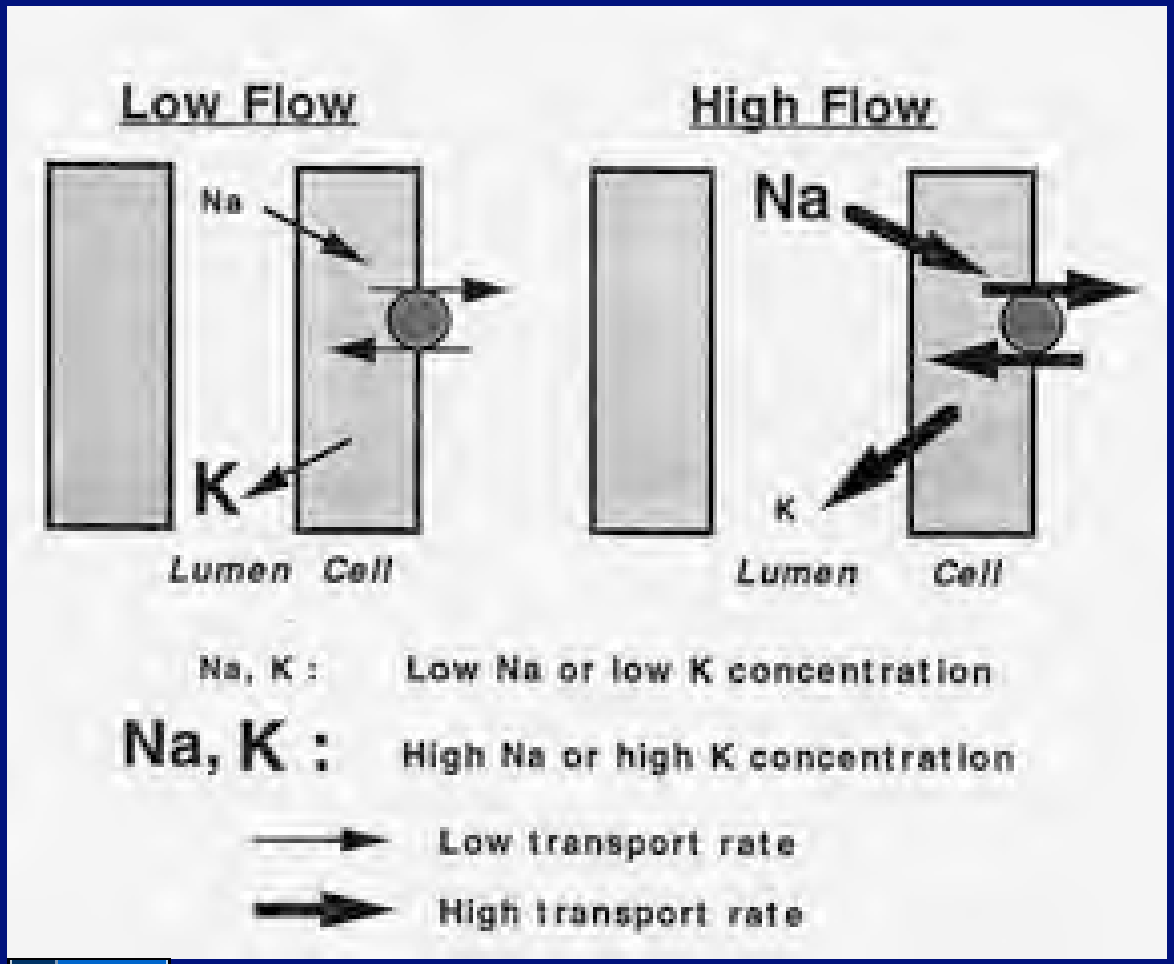
amiloride, triamterene, pentamidine, trimethoprim



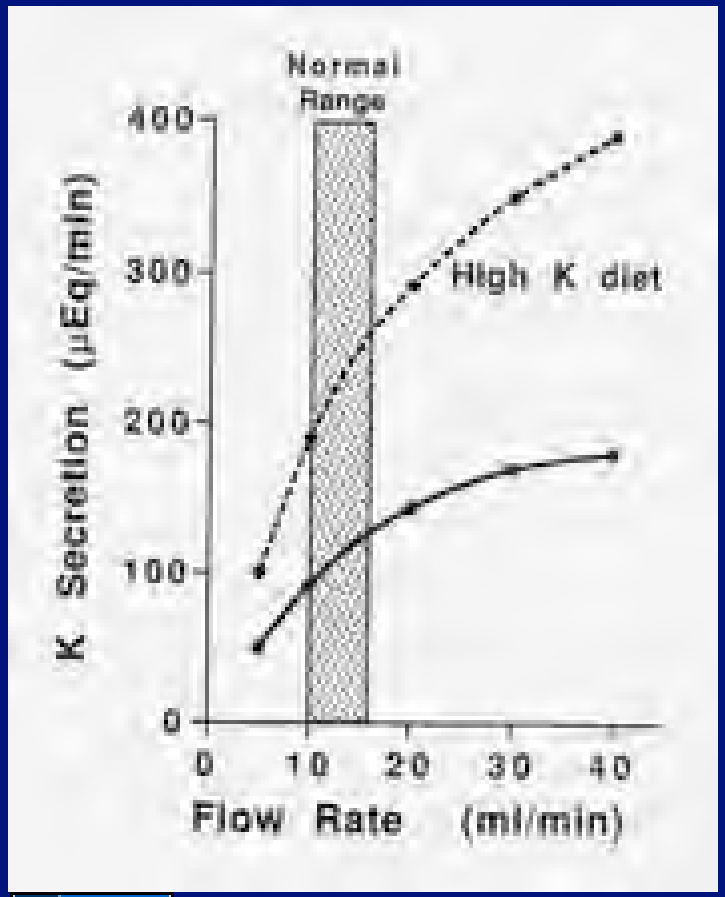
Schrier, Diseases of the Kidney

Hyperkalemia due to decreased K^+ excretion

- Reduced solute delivery to collecting tubule sites of K^+ secretion:
  - Volume depletion
  - NSAIDs



Schnerrman,Sayegh Kidney Physiology



Schnerrman,Sayegh Kidney Physiology

Hyperkalemia due to decreased K^+ excretion

- Impaired aldosterone availability or action:

Primary adrenal disease - normal or increased renin

Addison's disease

Hyporeninemic hypoaldosteronism

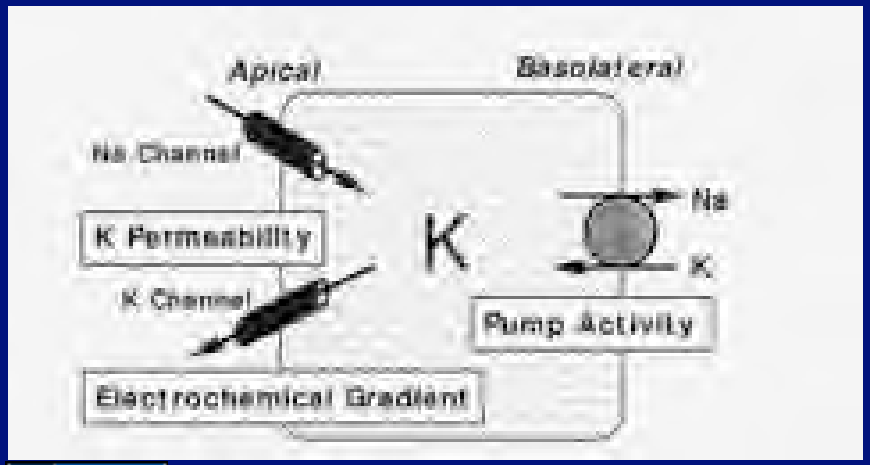
Diabetes mellitus

Virtually all other forms of moderate renal insufficiency

Drugs

Decrease aldosterone production - ACEI, A2 receptor blockers, heparin

Antagonize aldosterone action - spironolactone



PD-INEL Schnerrman,Sayegh Kidney Physiology

Summary of drug effects promoting hyperkalemia

- Redistribution from intracellular to extracellular space:
  - Beta blockers
  - Digitalis intoxication

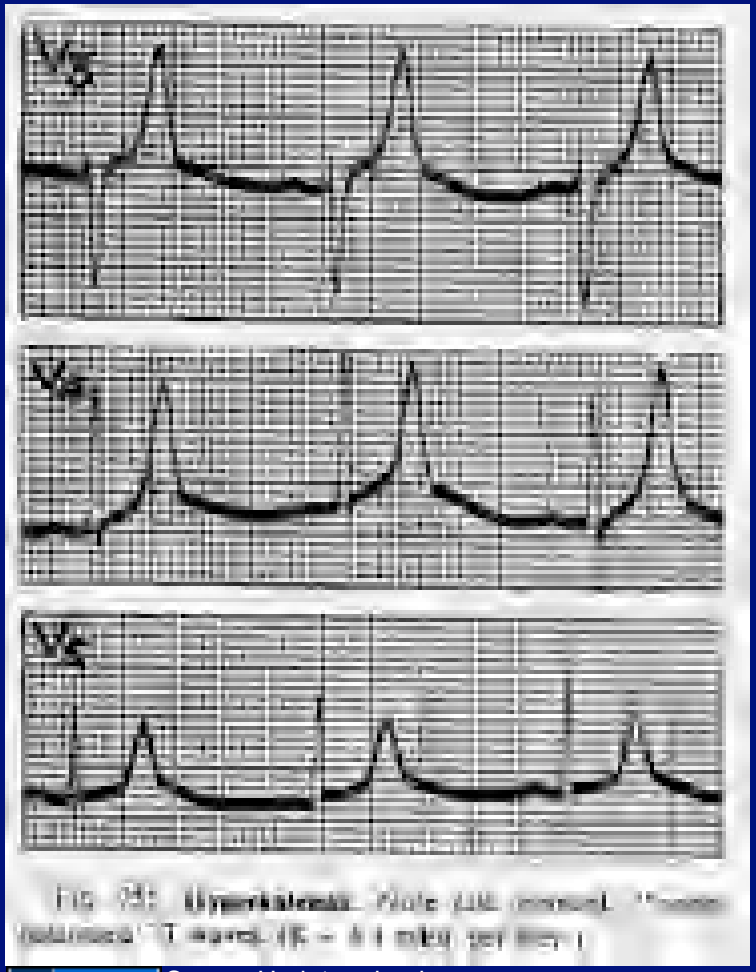
- Inhibition of principal cell transport Na^+ channels:
  - amiloride, triamterene, pentamidine, trimethoprim

- Reduced solute delivery to collecting tubule sites of K^+ secretion:
  - NSAIDs

- Impaired aldosterone availability or action:
  - Decrease aldosterone production - ACEI, A2 receptor blockers, heparin
  - Antagonize aldosterone action - spironolactone

Manifestations of hyperkalemia

- Cardiac arrhythmias



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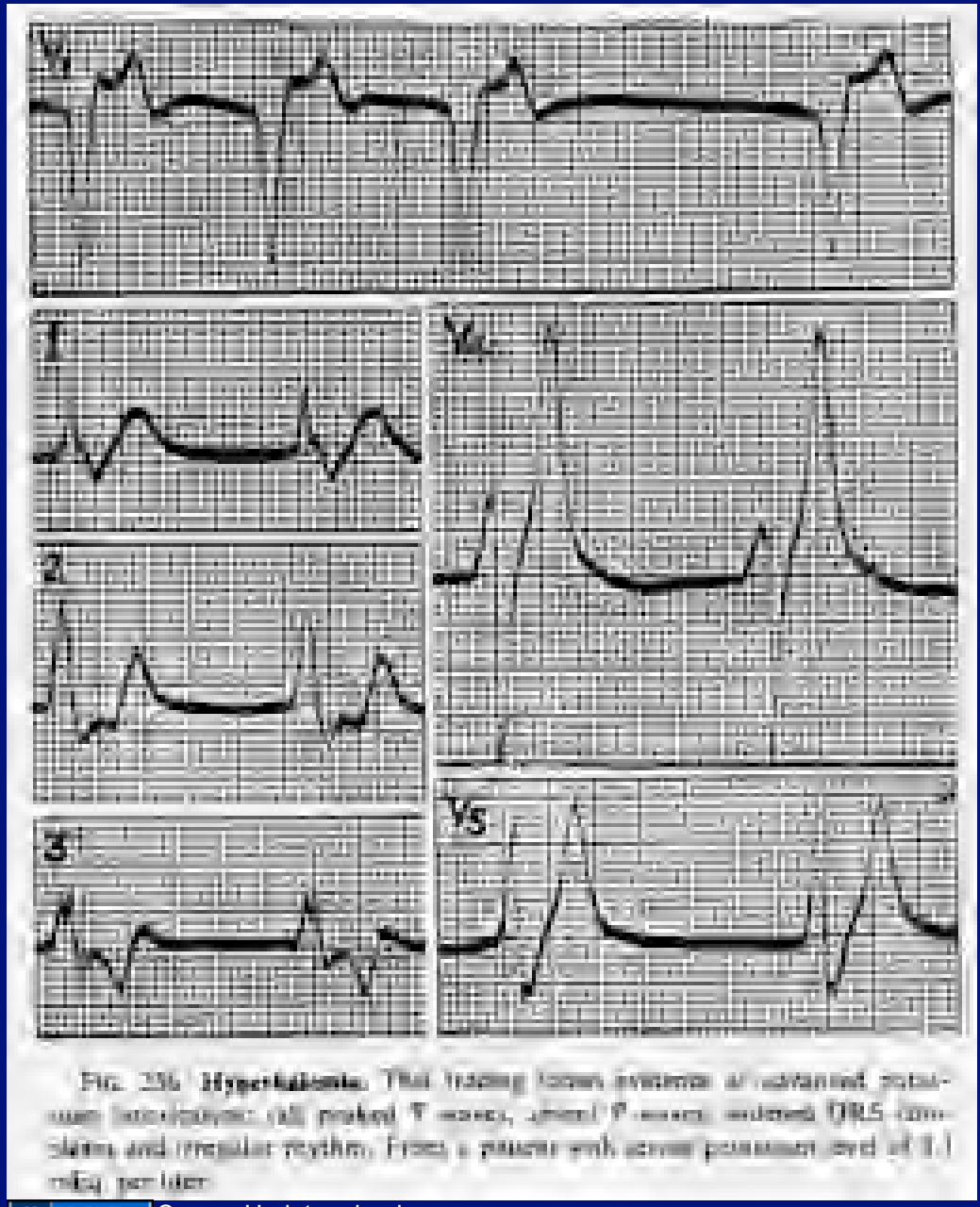

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Manifestations of hyperkalemia

- Cardiac arrhythmias

- Neuromuscular
- Decreased renal ammonia production, which can predispose to metabolic acidosis
- Decreased plasma renin, increased aldosterone
- Increase insulin, glucagon, catecholamines
- Antihypertensive effect

Treatment of hyperkalemia

- Immediate measures
  - Restore excitability
  - Redistribute K^+ back within cells

- As soon as can be implemented
  - Effect net removal of K^+

- Chronic measures
  - Limit intake
  - Promote excretion

Restore excitability

Parenteral calcium
10 ml of 10% calcium gluconate, can repeat once.

Redistribute K^+ back within cells

- Sodium bicarbonate

- Insulin + glucose
  Use insulin alone if glucose already elevated.

- B_2 agonists - Albuterol nebulizer

Effect net removal of K^+

- Sodium polystyrene sulfonate (Kayexalate)

  Oral route is most effective and safe - onset 60 min. Enemas can rarely be dangerous (bowel necrosis) and are best avoided.

- Forced diuresis

  K^+ excretion is closely related to urine flow, irrespective of the level of GFR, so any unused urine output capacity can contribute to treating hyperkalemia.

  Furosemide is not as kaliuretic as thiazides or acetazolamide, but the larger volumes of urine produced (with adequate sodium replacement) are highly effective in promoting renal K^+ excretion where the potential exists.

- Dialysis

  Incrementally lower bath K^+, removes 25-30 mEq/hr

Chronic measures to treat hyperkalemia

- Diet

- Increased Na^+ intake (±bicarbonate)
  + diuretics

- Mineralocorticoids

- Sodium polystyrene sulfonate (Kayexalate)

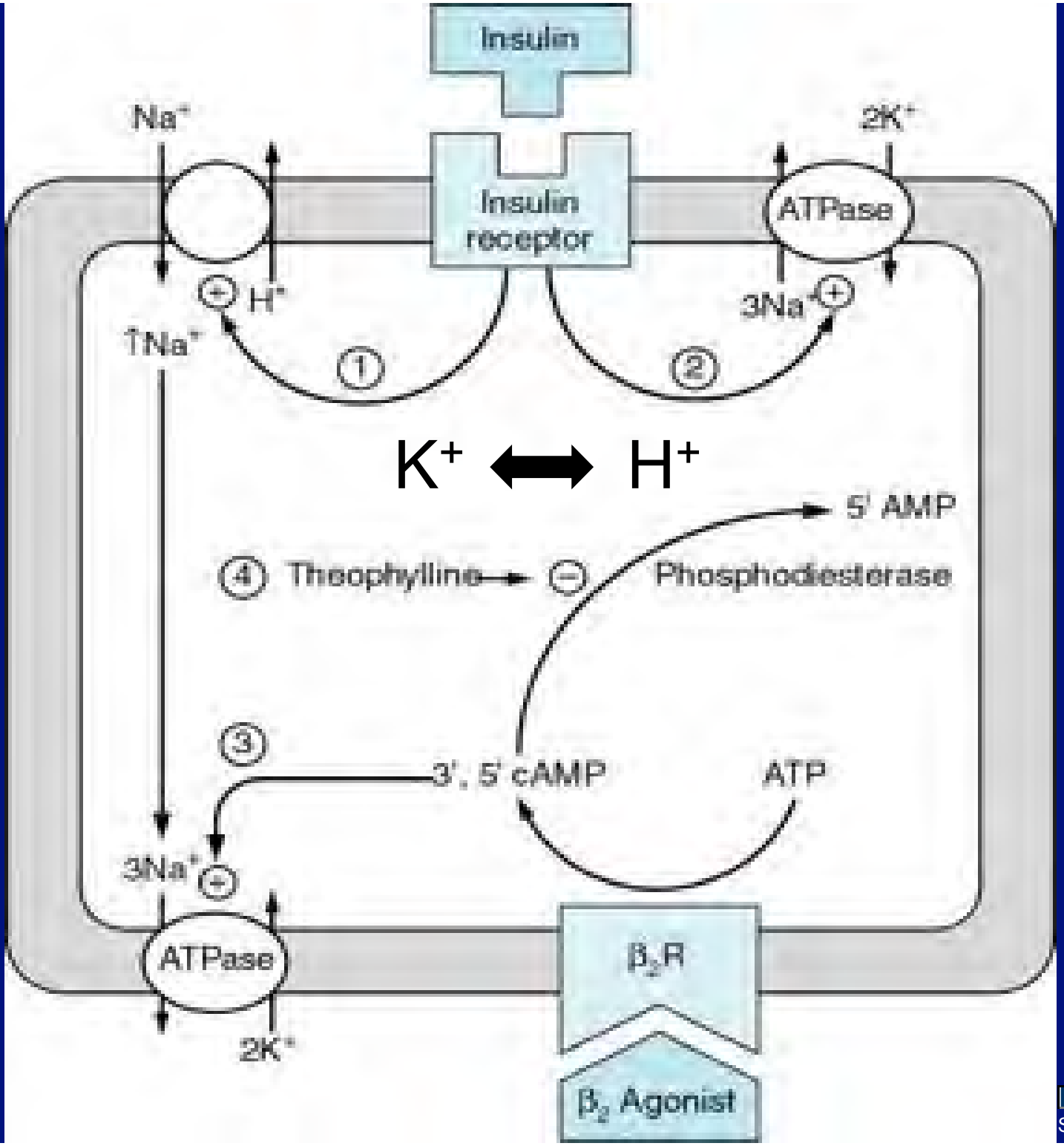
Hypokalemia

- Spurious
- Redistribution
- Inadequate intake
- Extrarenal losses
- Renal losses

Spurious

K^+ uptake in vitro after blood drawing
- Leukocytosis > 100,000
- Erythrocyte uptake when blood is drawn shortly after insulin administration.

MUCH LESS COMMON THAN SPURIOUS HYPERKALEMIA



Schrier, Diseases of the Kidney

Redistribution

- Alkalosis

- Hyperadrenergic states

- Insulin excess

  Insulin in diabetic

  Carbohydrate load in nondiabetic without K^+ replacement

- Drugs

  Beta adrenergic agonists: epinephrine, salbutamol, terbutaline, albuterol

  cAMP phosphodiesterase inhibitors - Theophylline

  Calcium channel blockers

  Barium, Toluene, Chloroquine

Inadequate intake leading to hypokalemia

- Normal intake is about 80-100 meq/day,

- Normal maintenance to replace obligate losses (5-25 meq/day). These are low enough so that decreased intake alone in someone on an oral diet is rarely enough to account for hypokalemia.

Excess losses leading to hypokalemia

-Renal - virtually always driven by increased aldosterone, which may be either secondary or primary

-Extrarenal - usually GI disorders, virtually always compounded by renal losses

Excess losses leading to hypokalemia

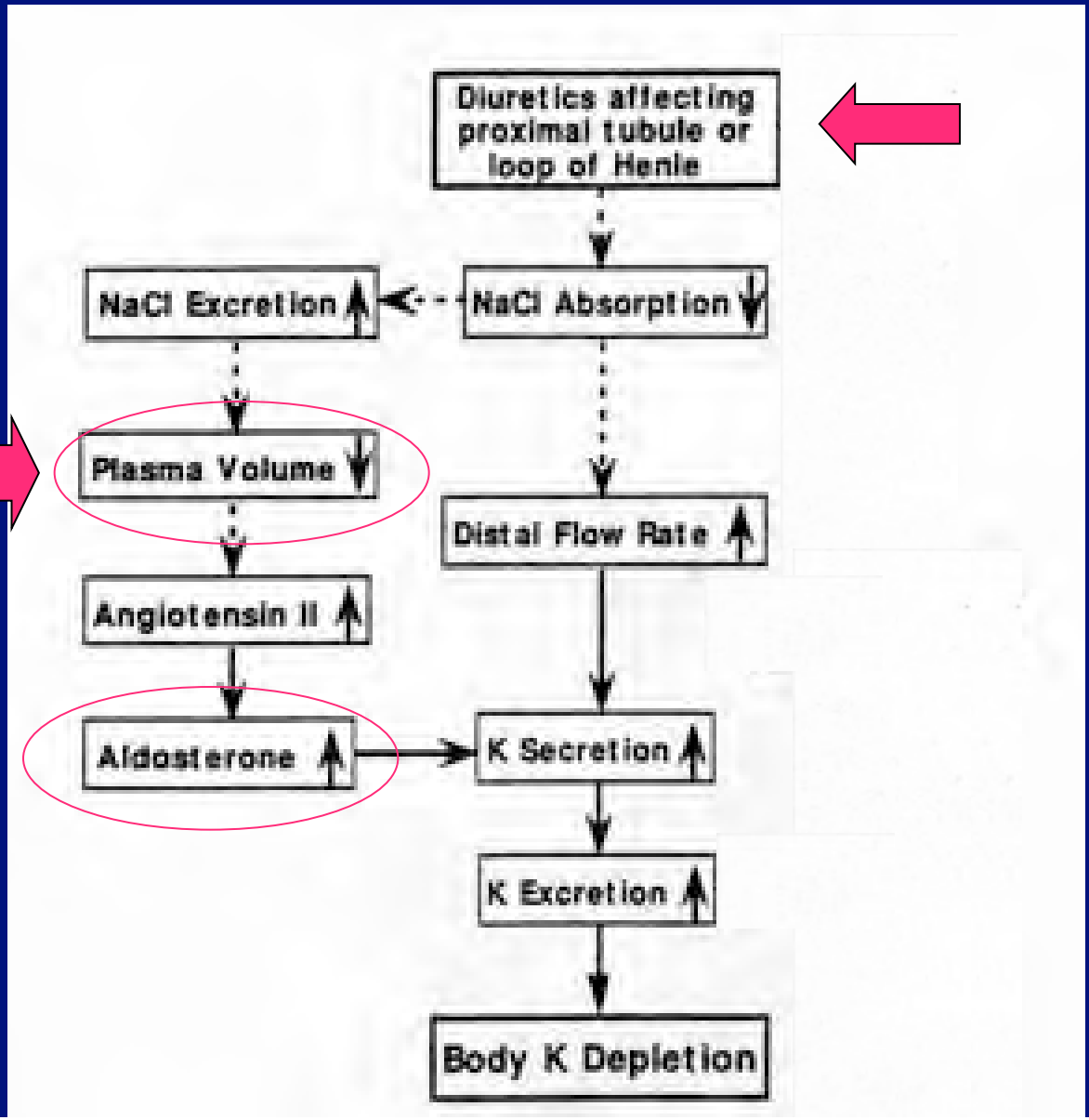
-Renal - virtually always driven by increased aldosterone, which may be either secondary or primary

-Extrarenal - usually GI disorders, virtually always compounded by renal losses

Renal etiologies of hypokalemia

Excess mineralocorticoid states

- Secondary hyperaldosteronism - Diuretics, GI fluid losses



Diuretic-Induced Hypokalemia

- Except for potassium-sparing agents all other classes of diuretics produce hypokalemia - carbonic anhydrase inhibitors (proximal tubule), loop, and thiazide (distal convoluted tubule).

-Increased distal flow and Na^+ delivery

- Activation of renin-angiotensin system with increased aldosterone

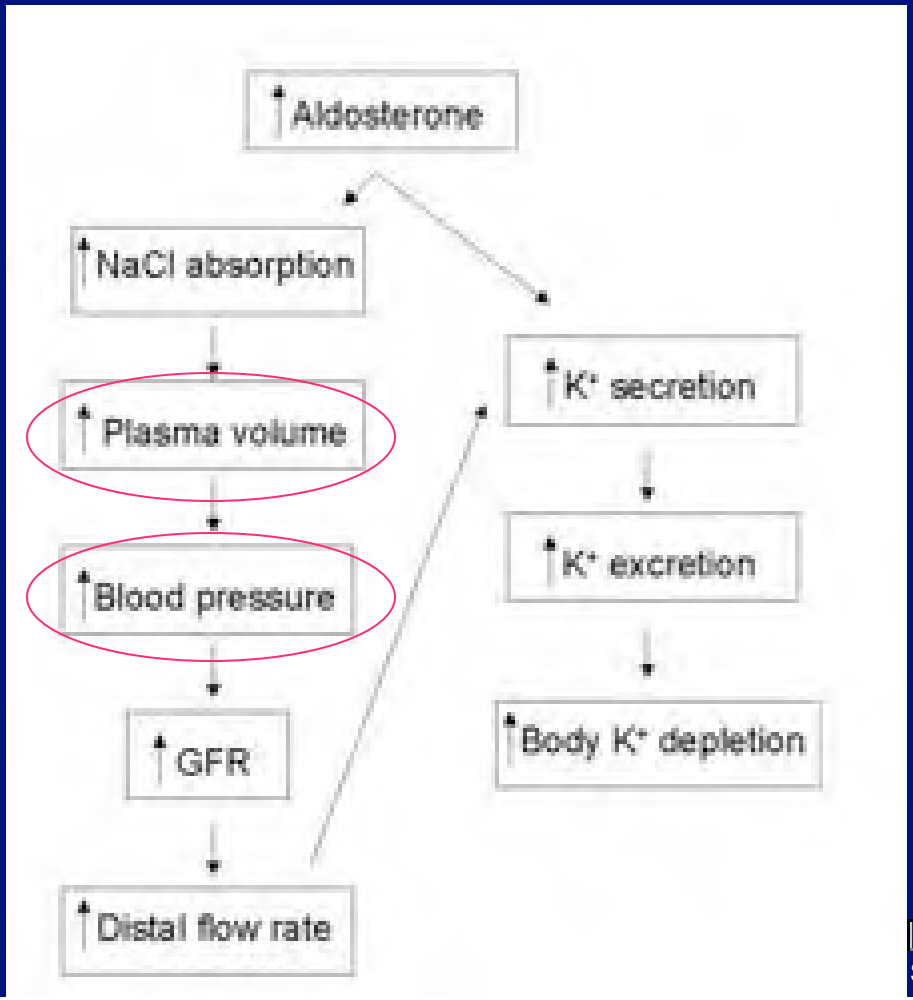
- Especially important to treat in:
  Patient receiving cardiac glycosides
  Acute myocardial infarction
  Chronic underlying heart disease

Renal etiologies of hypokalemia

Excess mineralocorticoid states

- Primary hyperaldosteronism syndrome - Characterized by hypertension

Licorice (glycyrrhetinic acid) - decreases activity of 11β - hydroxysteroid dehydrogenase allowing cortisol to act as a mineralocorticoid



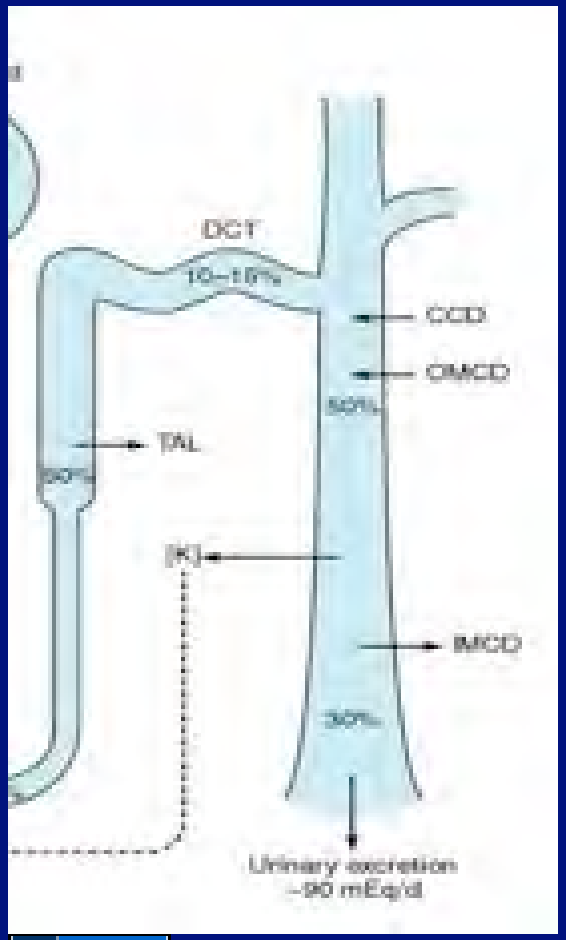
Renal etiologies of hypokalemia

Tubule function abnormalities

- Hypomagnesemia - increased K^+ loss via thick ascending limb and collecting tubule K^+ channels

- Type I renal tubular acidosis - impaired proton pumping by intercalated cells of collecting tubule.
  Characterized by metabolic acidosis.

- Bartter's syndrome
  mutation in TAL Na/2Cl transporter
- Gitelman's syndrome –
  mutation in DCT NaCl cotransporter
- Liddle's syndrome –
  mutation in CT Na^+ channel



PD-1NEL Schrier, Diseases of the Kidney

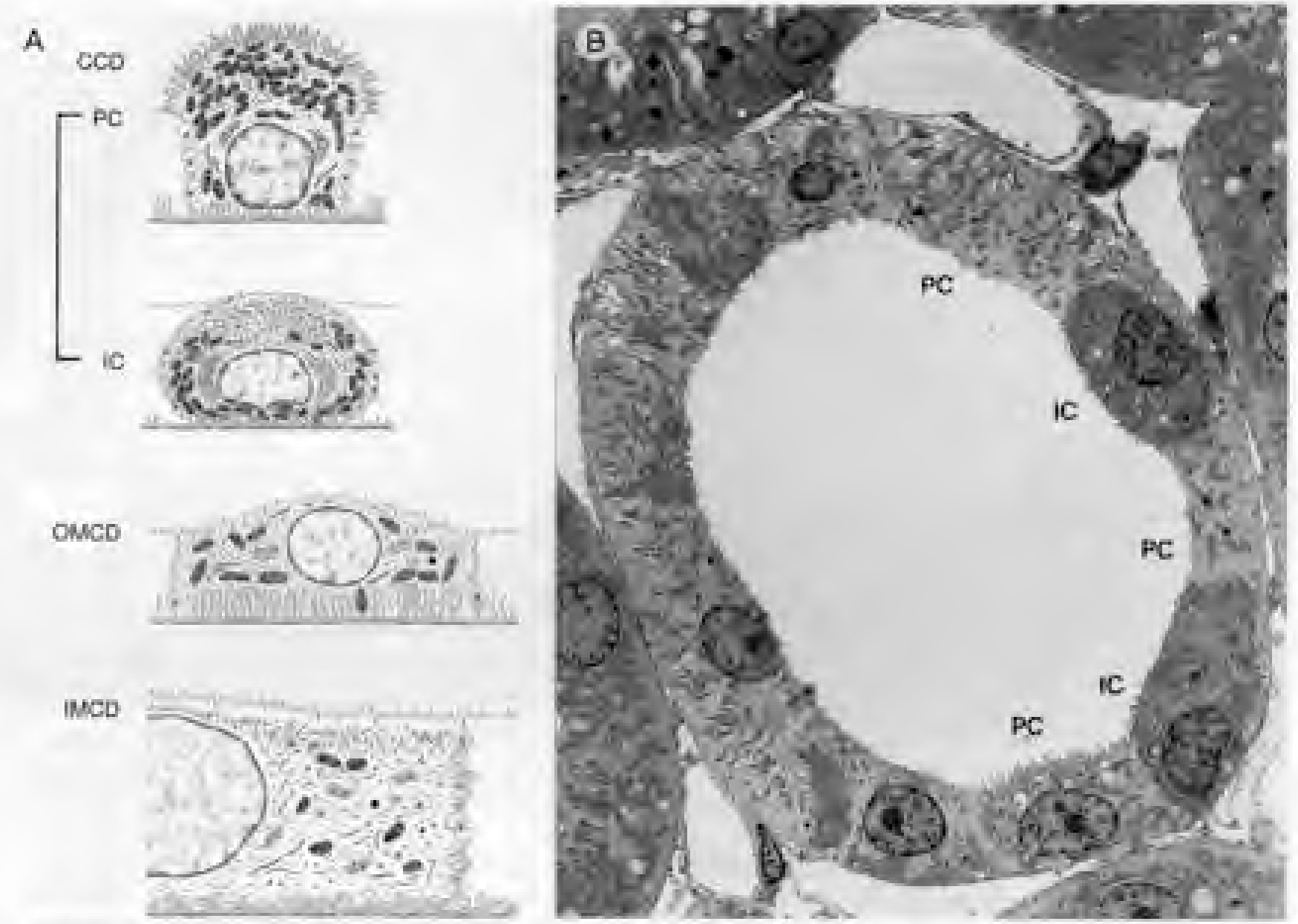


FIGURE 10 Collecting duct. The collecting duct changes its morphology as it travels from cortex to medulla. In the cortex there are two cell types—principal cells (PC) and intercalated cells (IC). Appearance is shown schematically on the left (A) and in cross section on the right (B).

Excess losses leading to hypokalemia

- Renal - virtually always driven by increased aldosterone, which may be either secondary or primary

- Extrarenal - usually GI disorders, virtually always compounded by renal losses

Extrarenal etiologies of hypokalemia (1)

Upper GI fluid losses from vomiting and gastric drainage

This form of hypokalemia is accompanied by a metabolic alkalosis because of the acid (HCl) content of gastric fluid. Moreover, as each becomes established, the hypokalemia and the metabolic alkalosis promote each other via their effects on kidney transport.

Extrarenal etiologies of hypokalemia (1)

Upper GI fluid losses from vomiting and gastric drainage

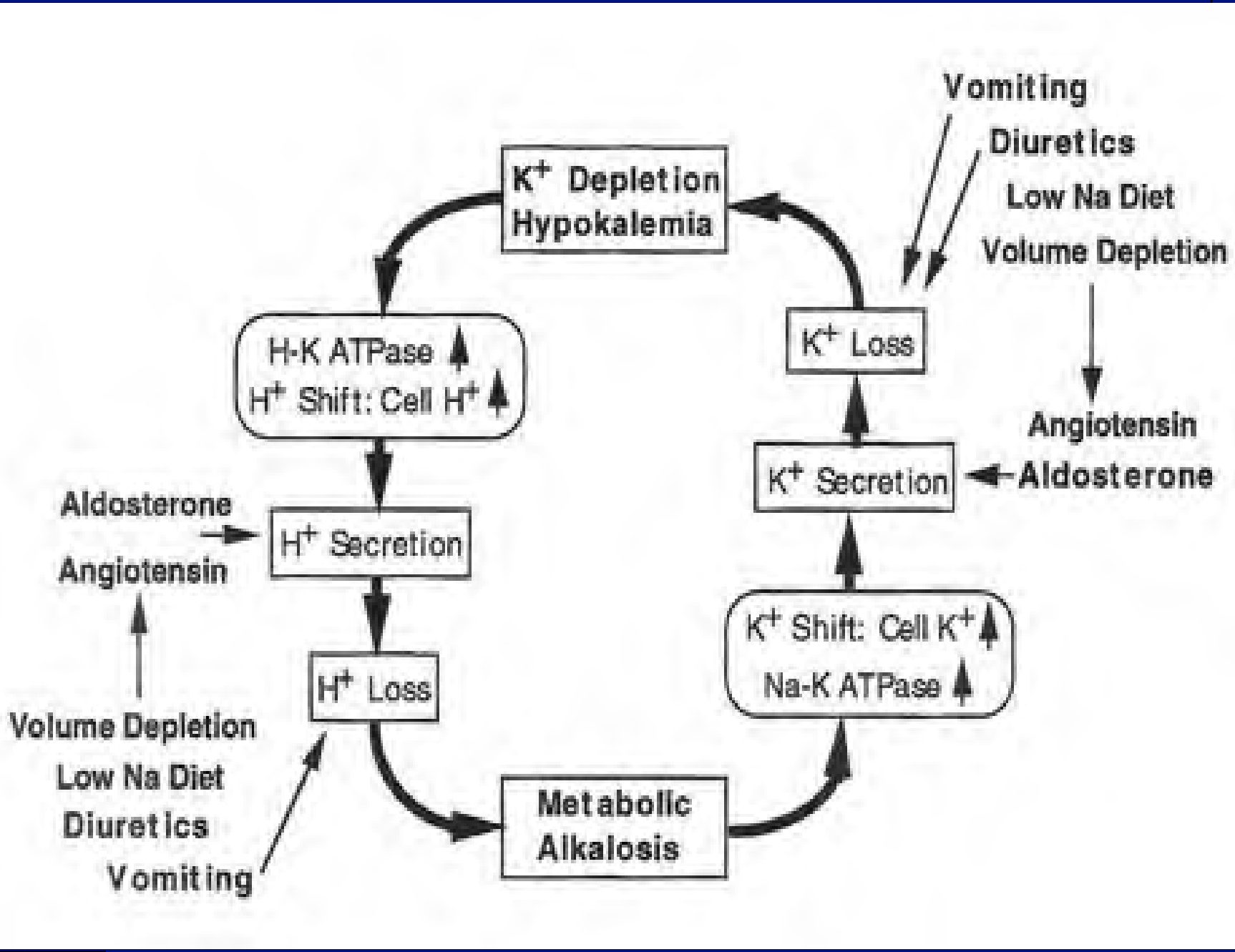
This form of hypokalemia is accompanied by a metabolic alkalosis because of the acid (HCl) content of gastric fluid. The hypokalemia and the metabolic alkalosis promote each other.

- Gastric fluid - 5-10 meq/l K^+ - this is not enough to account for most of the K^+ losses seen.

- Much of the potassium loss is explained by renal K^+ losses driven by two factors:
  1) volume depletion-induced stimulation of aldosterone secretion (secondary hyperaldosteronism)
  2) metabolic alkalosis promotes renal K^+ excretion

- Additional lowering of K^+ results from the systemic effects of metabolic alkalosis to promote redistribution of K^+ to the intracellular space.

Interrelationships between K^+ and H^+ handling



Extrarenal etiologies of hypokalemia (2)

Acute large volume diarrhea, fistulas and enterostomies

- Hypokalemia from these GI losses is accompanied by metabolic acidosis because of the high HCO_3^- concentration of the GI fluids lost and their large volume.

- K^+ content of these fluids is 20-50 meq/l K^+. This is sufficient to produce enough direct K^+ loss to account for hypokalemia, but renal losses as a result of the volume depletion and hypokalemia will also contribute.

Understand hypokalemia by the company it keeps

- Alkalosis (upper GI, diuretic) or acidosis (lower GI, renal tubular acidosis).

- Hypertension - primary mineralocorticoid excess

- Urine chloride

Use of urine chloride in the diagnosis of hypokalemia associated with metabolic alkalosis

- Typically, to help assess volume status we measure urine Na^+, low values being indicative of sodium conservation and volume depletion. However, in states of metabolic alkalosis, the increased bicarbonate content of the urine drags Na^+ with it for charge compensation, making the Na^+ a less reliable measure of volume. So, during metabolic alkalosis, we will often instead measure urine chloride.

- Volume depletion - Low urine chloride (< 10-20 meq/l) – "chloride sensitive alkalosis"
  - Vomiting/gastric drainage
  - Previous use of diuretics

Low urine chloride is both an index of the volume status in these conditions and predictor of the efficacy of chloride replacement in treating them. They are sometimes called "chloride-responsive" alkalosis.

- High urine chloride (> 20 meq/l) – "chloride-insensitive alkalosis"
  - Primary excess mineralocorticoid conditions - primary hyperaldosteronism. Accompanied by hypertension.

Use of urine chloride in the diagnosis of hypokalemia associated with metabolic alkalosis (2)

Why do the primary excess mineralocorticoid conditions have high urine chloride? Shouldn't the continued presence of increased aldosterone maintain increased Na^+ (and Cl^-) absorption and keep the urinary concentration of Cl^- low?

Use of urine chloride in the diagnosis of hypokalemia associated with metabolic alkalosis (2)

Why do the primary excess mineralocorticoid conditions have high urine chloride? Shouldn't the continued presence of increased aldosterone maintain increased Na^+ (and Cl^-) absorption and keep the urinary concentration of Cl^- low?

In primary hyperaldosteronism/Cushings disease and similar disorders, an additional phenomenon that explains this behavior occurs. After the first few days of elevated aldosterone levels during which urine chloride is low and ECF expands, the kidney "escapes" from the maximum aldosterone effect, so that chloride appears in the urine again and further volume expansion does not occur. The patient simply stays at a moderately increased volume and continues to be hypertensive. This also explains why primary hyperaldosteronism is not associated with edema. Causes of the escape are suppression of the renin-angiotensin system by the volume expansion, release of atrial natriuretic peptide, and, possibly release of a hypothalamic diuretic factor

Manifestations of hypokalemia

- Arrhythmias, potentiate digitalis toxicity

- Decreased insulin release-glucose intolerance

- Muscle weakness, ileus, rhabdomyolysis

- Renal dysfunction - concentrating deficit, increased ammonia production, promotion of metabolic alkalosis

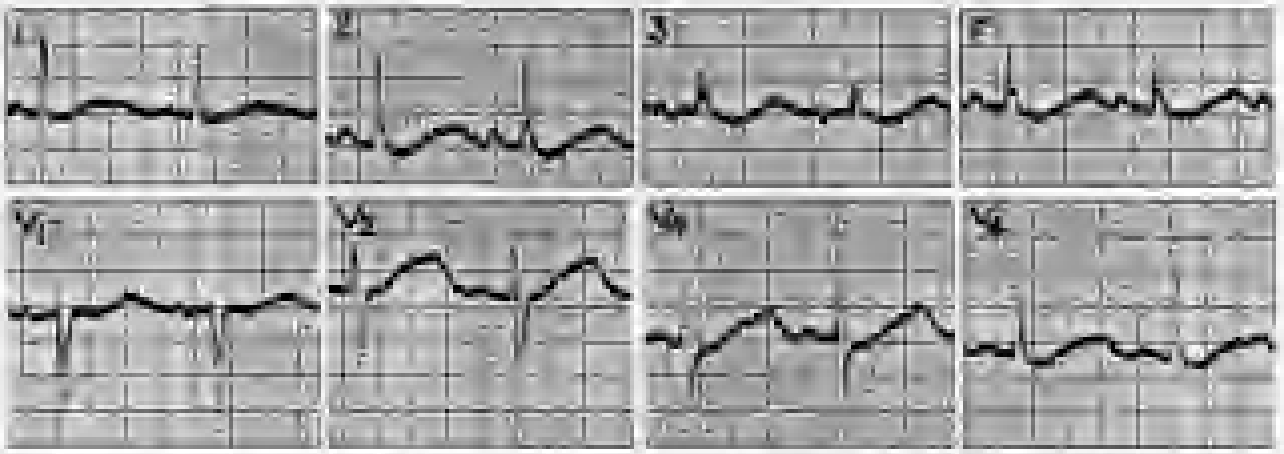


Fig. 251. **Hypokalemia.** Note characteristic pattern with ST depression and extremely prominent U waves.

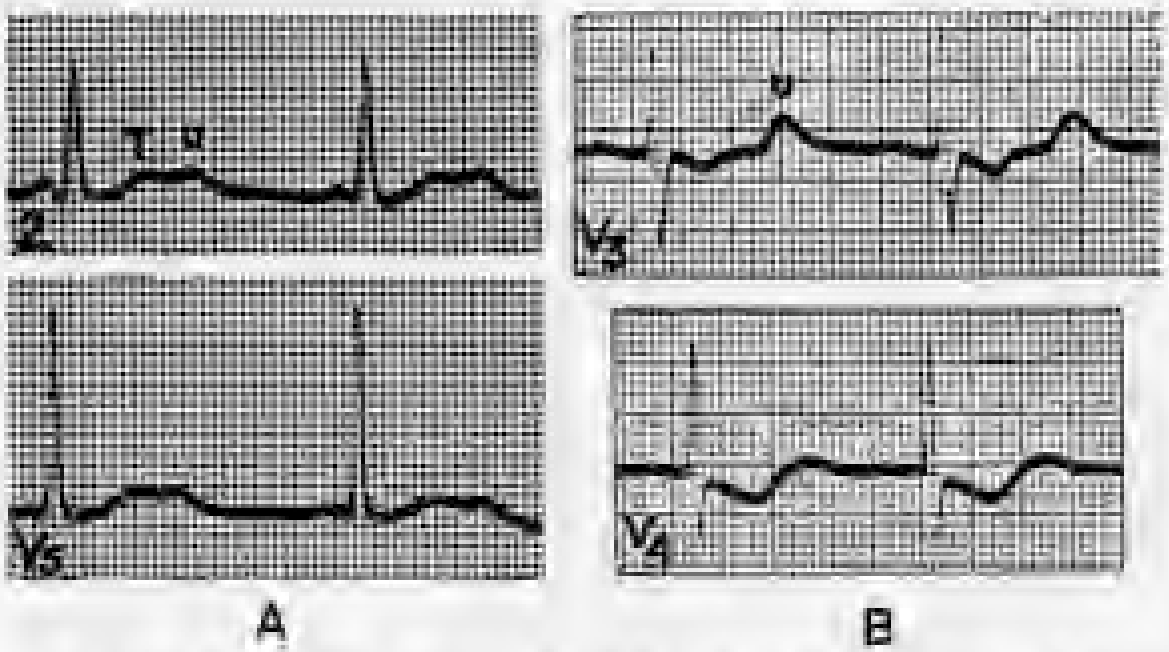
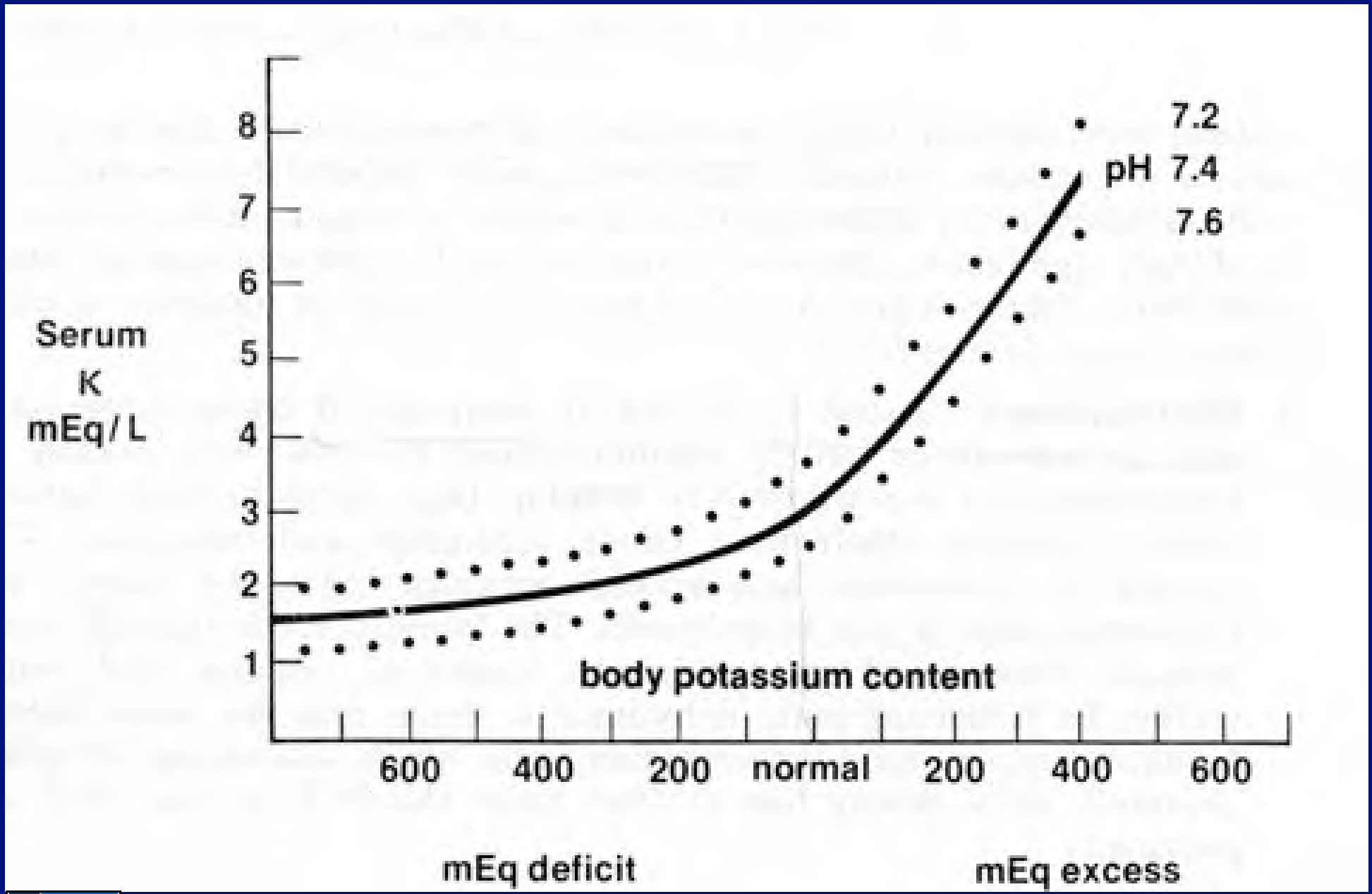


Fig. 252. **Hypokalemia.** Tracings A and B are from different patients. A shows early changes of hypokalemia with prominent U wave merging to form continuous undulating wave with T wave. B shows changes of advanced hypokalemia (1.8 mEq. per liter) in a patient with Cushing's disease. Note ST-T depression with very prominent U waves in V_4.

Treatment of hypokalemia

- Extent of deficit

Between serum K^+s of 4 and 2, each 0.27 mEq/l is equivalent to 100 mEq of total body K^+.


Serum
K
mEq/L
8
7
6
5
4
3
2
1
7.2
pH 7.4
7.6
body potassium content
600
400
200
normal
200
400
600
mEq deficit
mEq excess

Oral vs. intravenous replacement of K^+

- Oral route is safest and is highly effective

- K^+-sparing agents
  Amiloride, triamterene
  Spironolactone

- IV K^+ must be given carefully to avoid hyperkalemia
  For usual peripheral administration do not exceed 30-40 and 10 mEq/hr.
  For urgent replacement under very close monitoring can 10-20 mEq/100 cc. via infusion pump at up to 40 mEq/hr.

A 40 year old male seen for his annual physical has recently been having more headaches than usual. He is on no medications except aspirin for the headaches. Blood pressure is 170/110 with a pulse of 80. Physical examination is normal except for hypertensive retinopathy. There is no abdominal bruit or edema. Labs show:

Na^+ = 140 mEq/L (normal)
K^+ = 2.7 mEq/L (low)
Cl^- = 90 mEq/L (low)
HCO_3^- = 35 mEq/L (high)
Glucose = 90 mg/dL (normal)
BUN = 14 mg/dL (normal)
Creatinine = 1.0 mg/dL (normal)

After the basic chemistry profile returns, additional studies are obtained:
Plasma renin activity – 1 ng/ml/hr (low)
Plasma aldosterone – 700 ng/dL (high)
CT scan – 3 cm mass of right adrenal

A 40 year old male seen for his annual physical has recently been having more headaches than usual. He is on no medications except aspirin for the headaches. Blood pressure is 170/110 with a pulse of 80. Physical examination is normal except for hypertensive retinopathy. There is no abdominal bruit or edema. Labs show:

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After the basic chemistry profile returns, additional studies are obtained:
Plasma renin activity – 1 ng/ml/hr (low)
Plasma aldosterone – 700 ng/dL (high)
CT scan – 3 cm mass of right adrenal

Diagnosis: adrenal adenoma

Is the urine chloride high or low?

A 45 year old male presents with a blood pressure of 155/95 and a normal laboratory profile. He is started on a diuretic, hydrochlorthiazide, for the hypertension. Three weeks later he returns for a checkup. He has noted increased urination throughout the day. Blood pressure is 140/85. Laboratory studies show:

Na^+ = 136 mEq/L (normal)
K^+ = 3.2 mEq/L (low)
Cl^- = 95 mEq/L (low)
HCO_3^- = 29 mEq/L (high)
Glucose = 275 mg/dL (high)
BUN = 15 mg/dL (normal)
Creatinine = 1.1 mg/dL (normal)

A 45 year old male presents with a blood pressure of 155/95 and a normal laboratory profile. He is started on a diuretic, hydrochlorothiazide, for the hypertension. Three weeks later he returns for a checkup. He has noted increased urination throughout the day. Blood pressure is 140/85. Laboratory studies show:

Na^+ = 136 mEq/L (normal)
K^+ = 3.2 mEq/L (low)
Cl^- = 95 mEq/L (low)
HCO_3^- = 29 mEq/L (high)
Glucose = 275 mg/dL (high)
BUN = 15 mg/dL (normal)
Creatinine = 1.1 mg/dL (normal)

Diagnosis: Diuretic-induced hypokalemia complicated by hypokalemia-induced glucose intolerance.

Hypomagnesemia

- Inadequate supply

  Starvation, malnutrition, parenteral feeding without $Mg2^{+}$

- Decreased intestinal absorption

  Diarrhea and malabsorption, intestinal and biliary fistulas

  Small bowel resection

- Renal losses

  Diuretics

  Toxins - Aminglycosides, cis-platinum, amphotericin B

  cyclosporine

Hypermagnesemia

- Decreased renal excretion in chronic renal failure

- Rapid parenteral treatment (pregnancy)

Relations between magnesium balance and potassium and calcium handling

Hypokalemia occurs along with hypomagnesemia 40-60% of the time.

- Both share common causes - diuretics, diarrhea
- Primary renal K^+ wasting - the K^+ channels that mediate K^+ secretion from cells to lumen in both thick ascending limb and cortical collecting tubule are inhibited by ATP. Decreased Mg^{2+} may limit this inhibition. Mg^{2+} may also directly block the channels.
  - Hypokalemia does not fully correct with K^+ replacement until Mg^{2+} is also replaced.

Hypocalcemia virtually always accompanies severe hypomagnesemia (< 1 mEq/l).

- Hypomagnesemia suppresses parathyroid hormone secretion.
- Hypomagnesemia promotes resistance of bone to Ca^{2+}-mobilizing effects of PTH.

Hypomagnesemia = Hyperexcitability

- Cardiac arrhythmias

- Seizures

- Tetany, fasciculations

- Positive Chvostek's and Trousseau's signs (also related to the neuronal effects of the concomitant hypocalcemia)

- Weakness and anorexia

- Hypokalemia, hypocalcemia

- Treat with oral or parenteral Mg^{2+}, K^{+}, and Ca^{2+} replacement

Hypermagnesemia = Hypoexcitability

- Bradycardia
- Hypotension
- Muscle weakness, respiratory paralysis
- Decreased or absent deep tendon reflexes
- Sedation
- Treat with parenteral calcium, dialysis

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 10: Koeppen and Stanton 2001
Slide 13: Source Undetermined (Both Images)
Slide 14: Source Undetermined
Slide 15: Source Undetermined
Slide 16: Schnerrman,Sayegh Kidney Physiology. Lippincott-Raven, 1998.
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