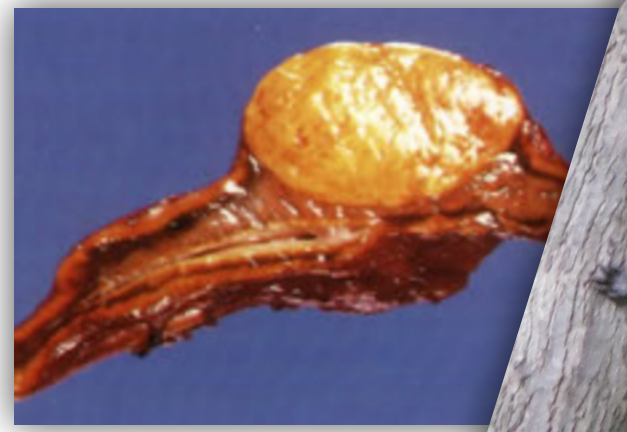
Hyperaldosteronism for the USMLE Step One Exam

Jerome W. Conn, MD



Howard J. Sachs, MD

Associate Professor of Medicine

University of Massachusetts Medical School

www.12DaysinMarch.com; Season III

E-mail: Howard@12daysinmarch.com

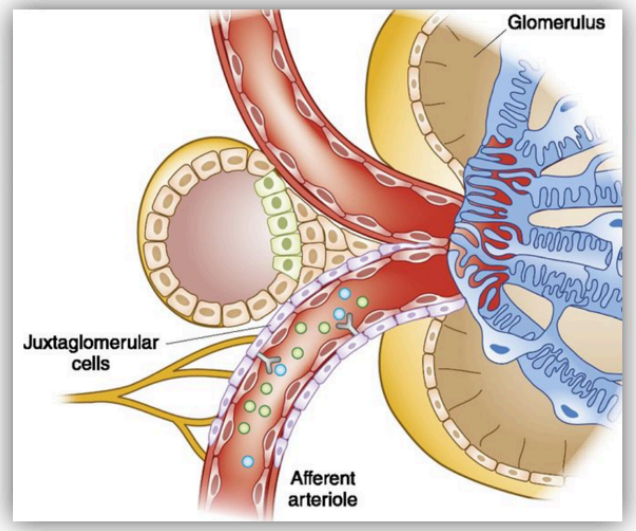
Hyperaldosteronism

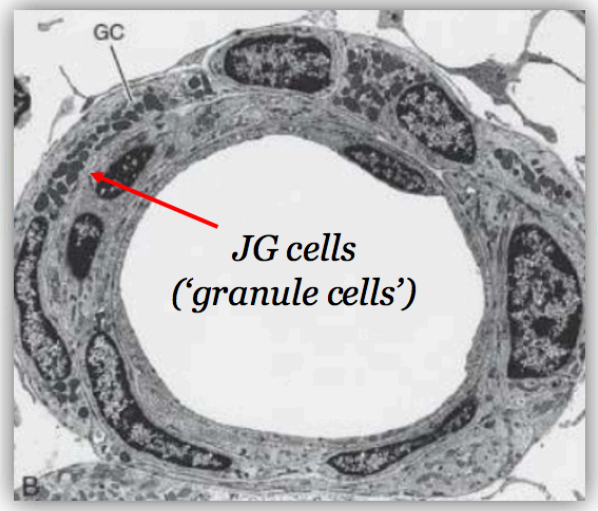
- Primary: Renin is suppressed
- Secondary: Renin is elevated

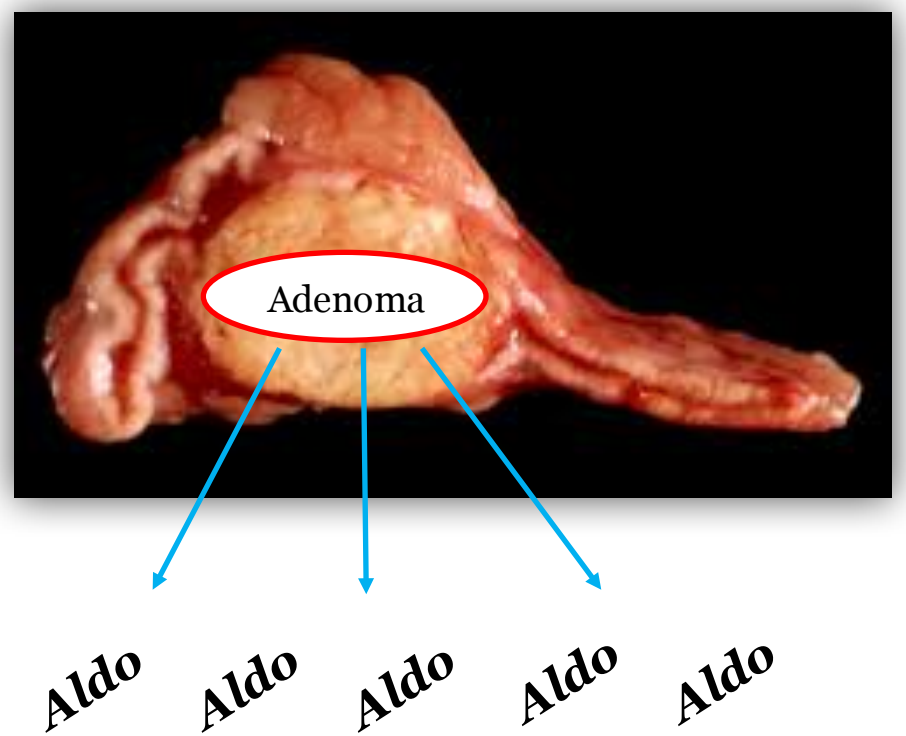
Introduction: General Approach

Hyperaldosteronism

- Secondary: Renin is elevated
- Primary: Renin is suppressed







Renin stimulated aldosterone production

Primary Hyperaldosteronism

- Primary: *Renin is suppressed*
  - HTN
    - Adrenal adenoma (*Conn's syndrome: autonomous secretion*)
    - Idiopathic adrenal hyperplasia
    - *Congenital adrenal hyperplasia (17-hydroxylase deficiency; not autonomous)*

- Secondary: *Renin is elevated*
  - *Appropriate: renal artery hypoperfusion*
  - *Inappropriate: reninoma*

Introduction: General Approach

Jerome W. Conn, MD

Secondary Hyperaldosteronism

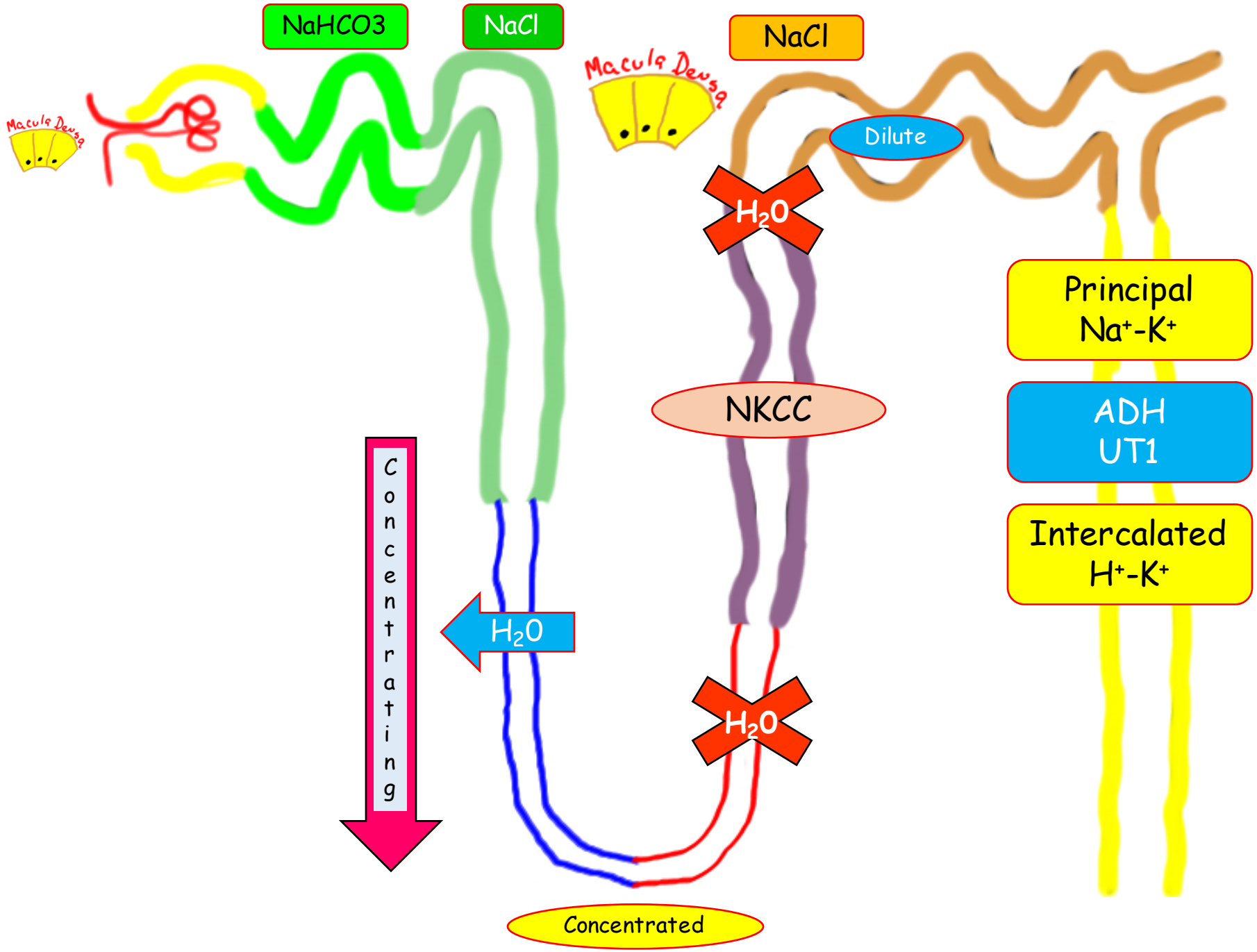
- Primary: *Renin is suppressed*
  - HTN
    - Adrenal adenoma (*Conn's syndrome, autonomous secretion*)
    - Idiopathic adrenal hyperplasia
    - Congenital adrenal hyperplasia (17-hydroxylase deficiency)

- Secondary: *Renin is elevated*
  - <u>Appropriate</u>: renal artery hypoperfusion
    - Systemic blood pressure **elevated** (e.g. *renal artery stenosis*)
    - Systemic blood pressure **low or normal** (e.g. *decreased effective circulating volume*)
  - <u>Inappropriate</u>: *reninoma* (e.g. *autonomous secretion, benign tumor*)
    - Systemic blood pressure **elevated**

Primary Hyperaldosteronism:
Adrenal Adenoma (Conn's Syndrome)

- Physiology
  - The Basics ➛ *Clinical Manifestations*
  - Regulatory Systems ➛ *Aldosterone Escape*
- Diagnostics
  - *Functional*
  - Anatomic
- Therapeutics
  - Aldosterone Antagonists
- Loose Associations
  - Hyperkalemia
  - Hypercortisolism
  - Adrenal failure

Jerome W. Conn, MD


NaHCO3
NaCl
NaCl
Macula Densa
Macula Densa
Dilute
H2O
Principal
Na+-K+
NKCC
ADH
UT1
Intercalated
H+-K+
Concentrating
H2O
H2O
Concentrated

Collecting tubules join to form collecting duct

Principal
Na^+-K^+

ADH
UT1

Intercalated
H^+-K^+

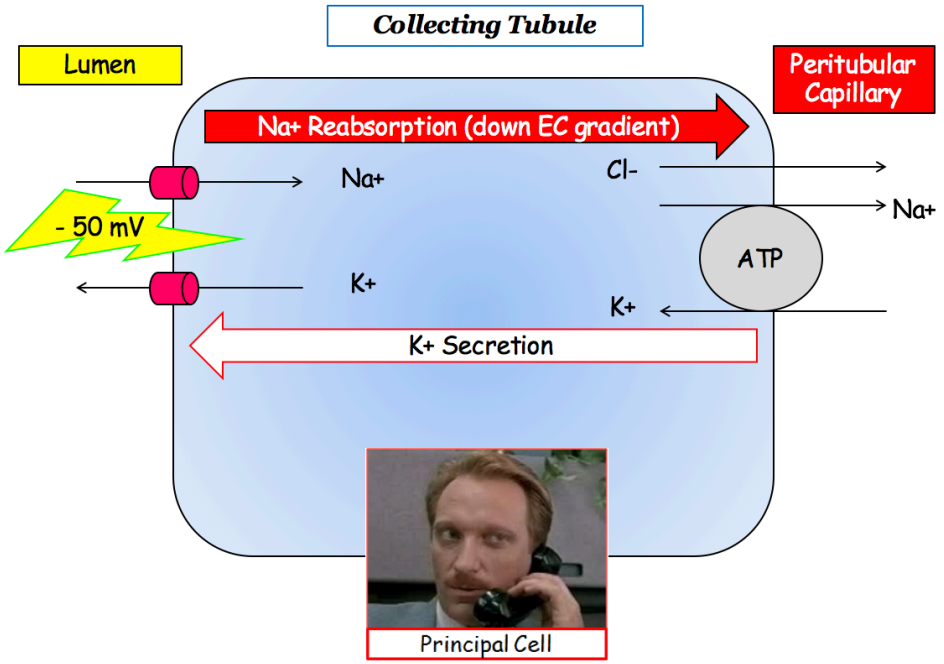
↑Na^+ absorption

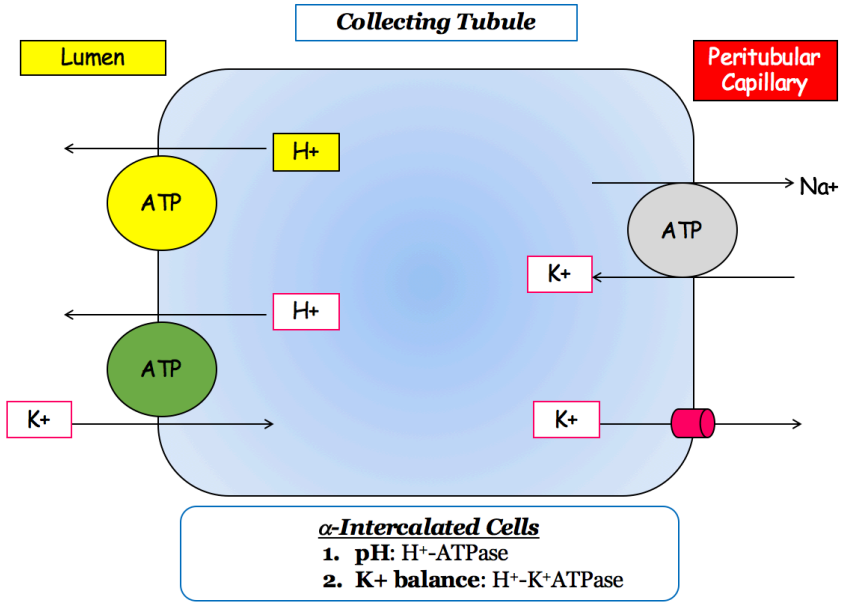
Aldosterone

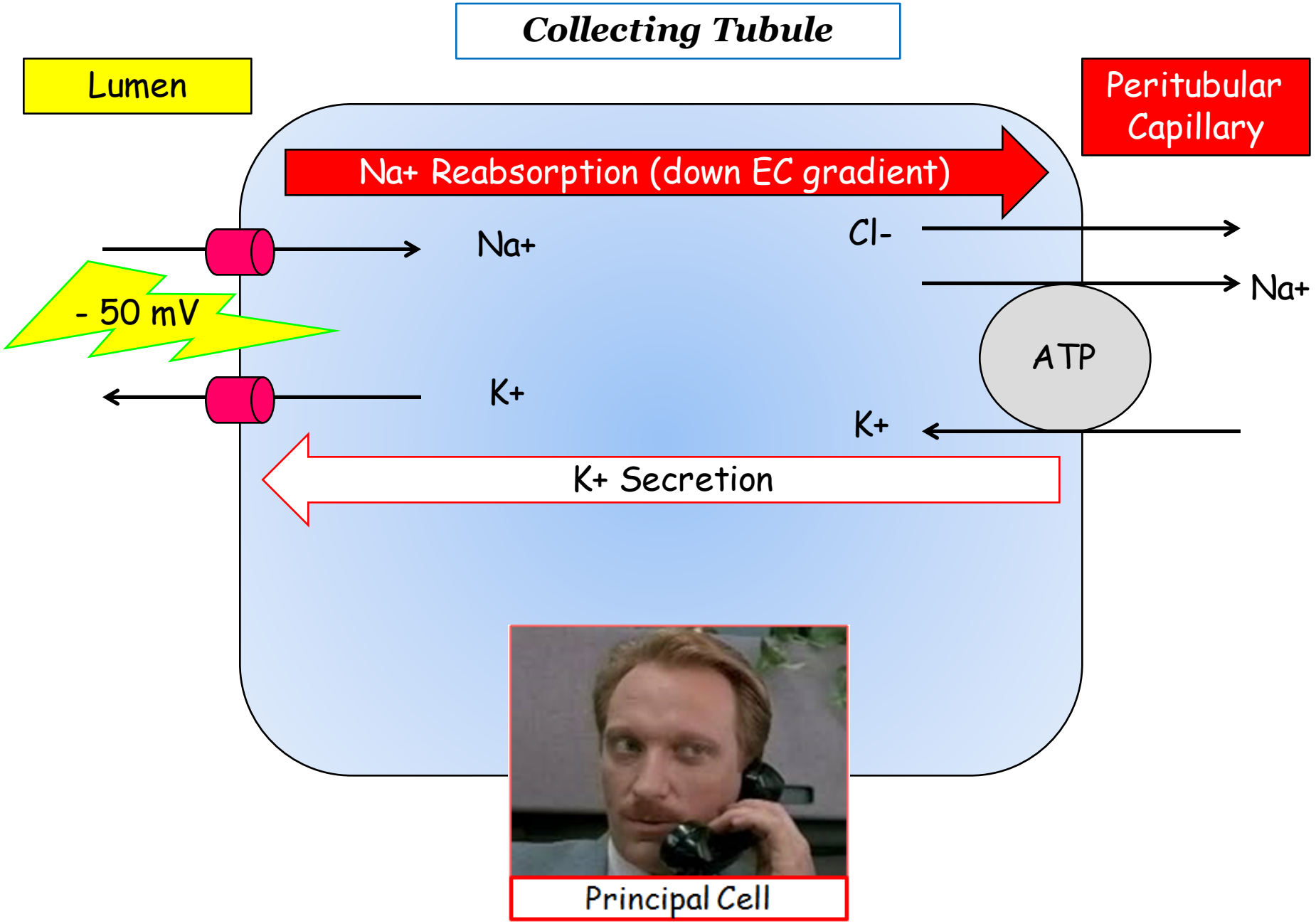
↓K^+

Aldosterone

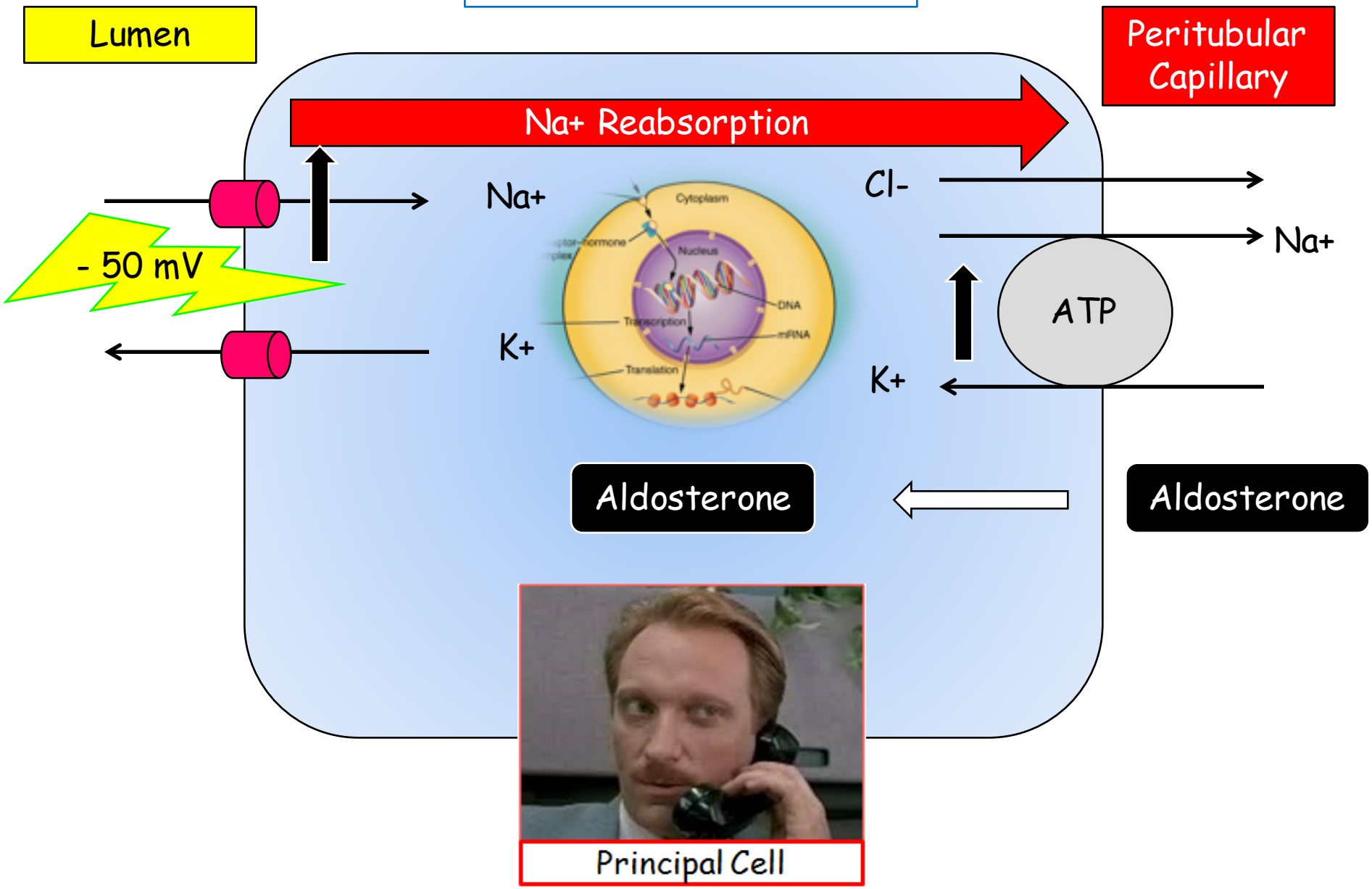
↓H^+

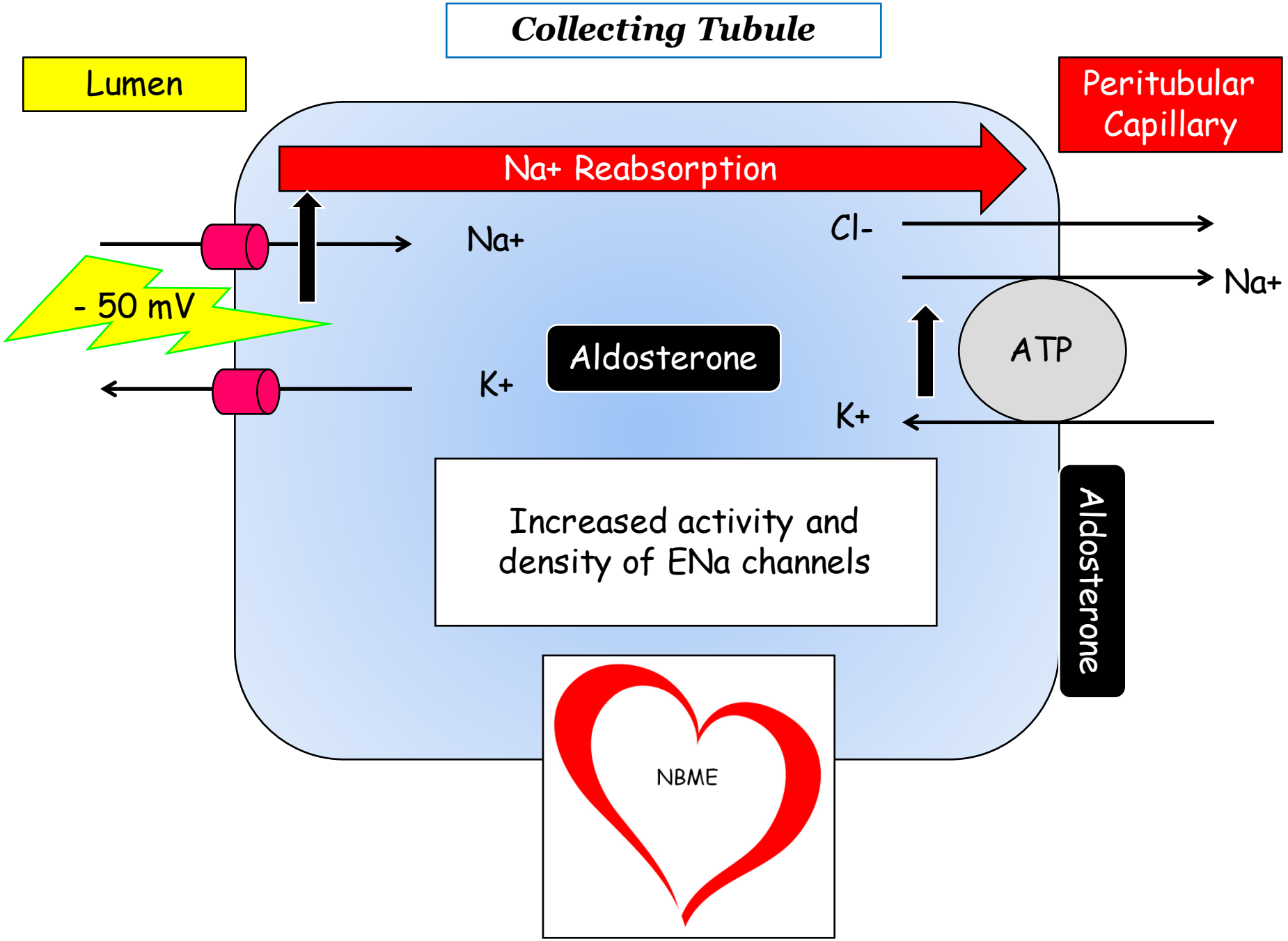


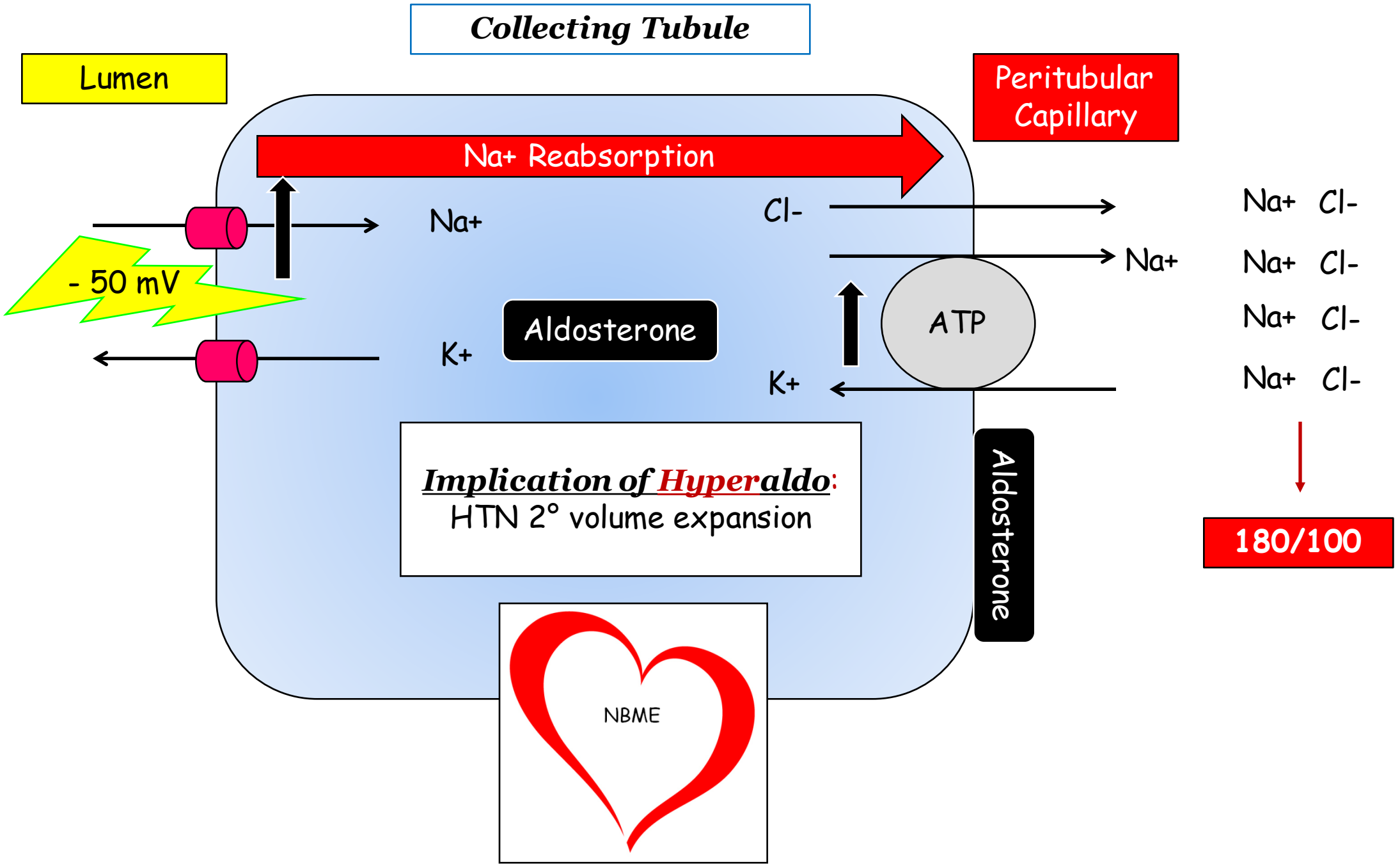


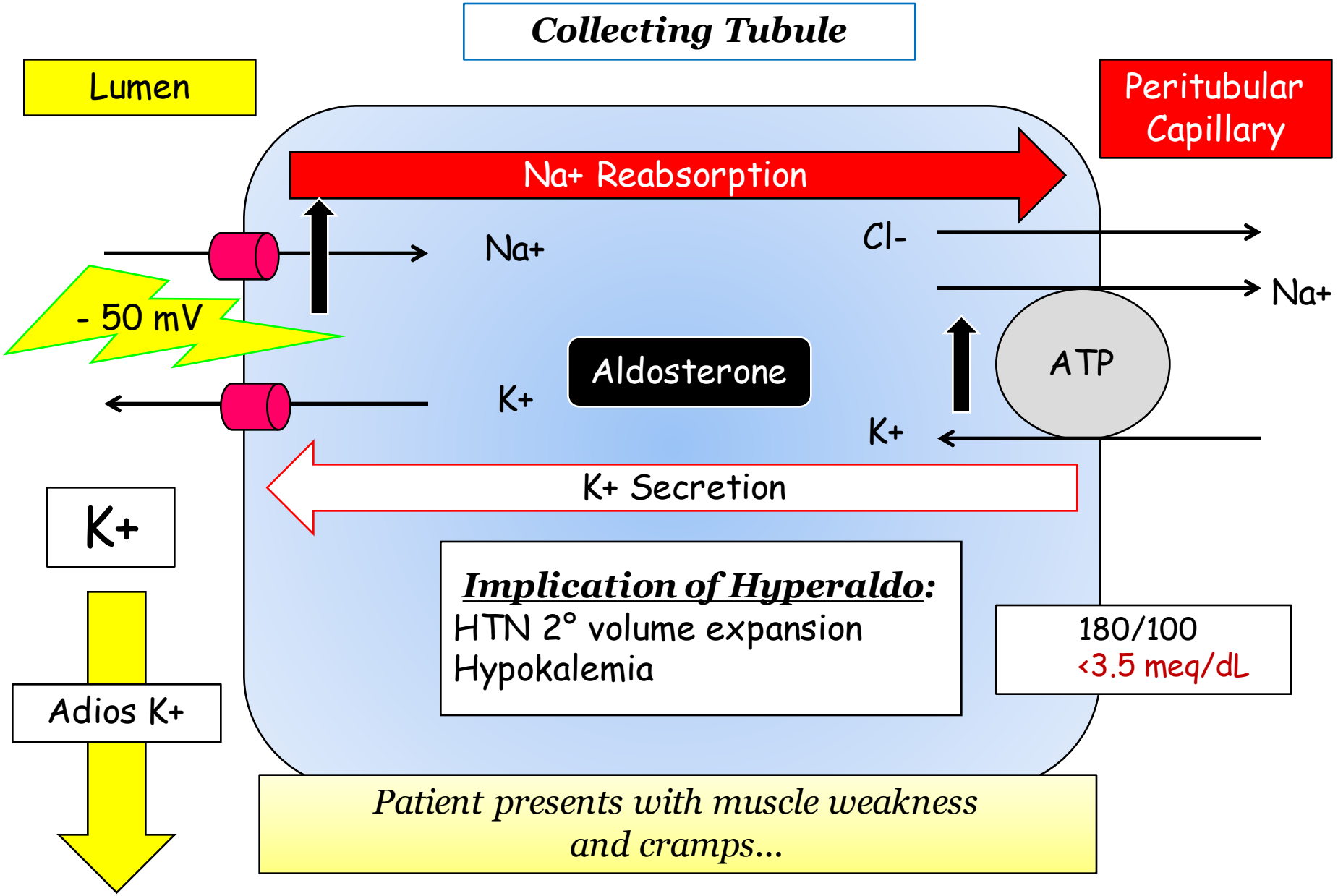

Collecting Tubule
Lumen
Peritubular Capillary
Na+ Reabsorption (down EC gradient)
Na+
Cl-
Na+
- 50 mV
ATP
K+
K+
K+ Secretion
Principal Cell

Collecting Tubule

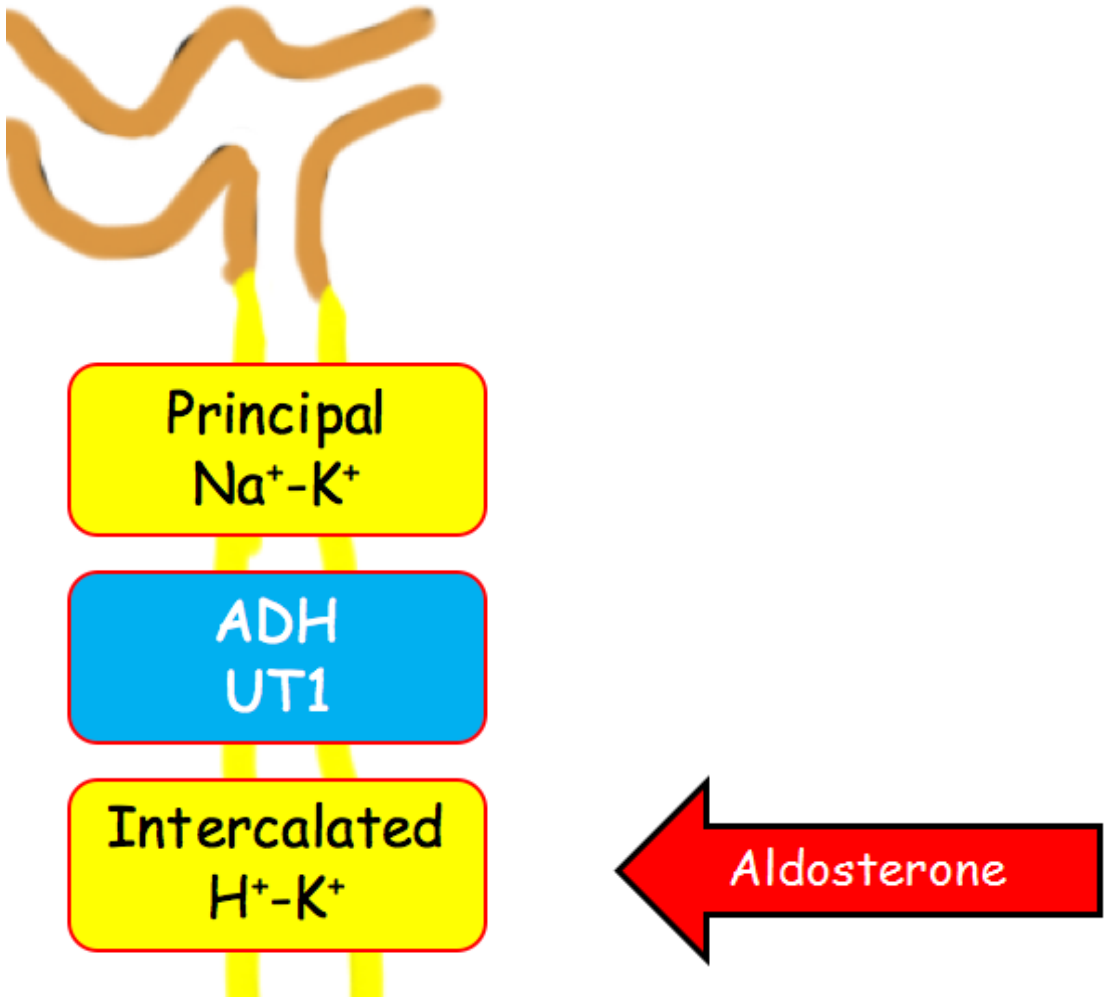


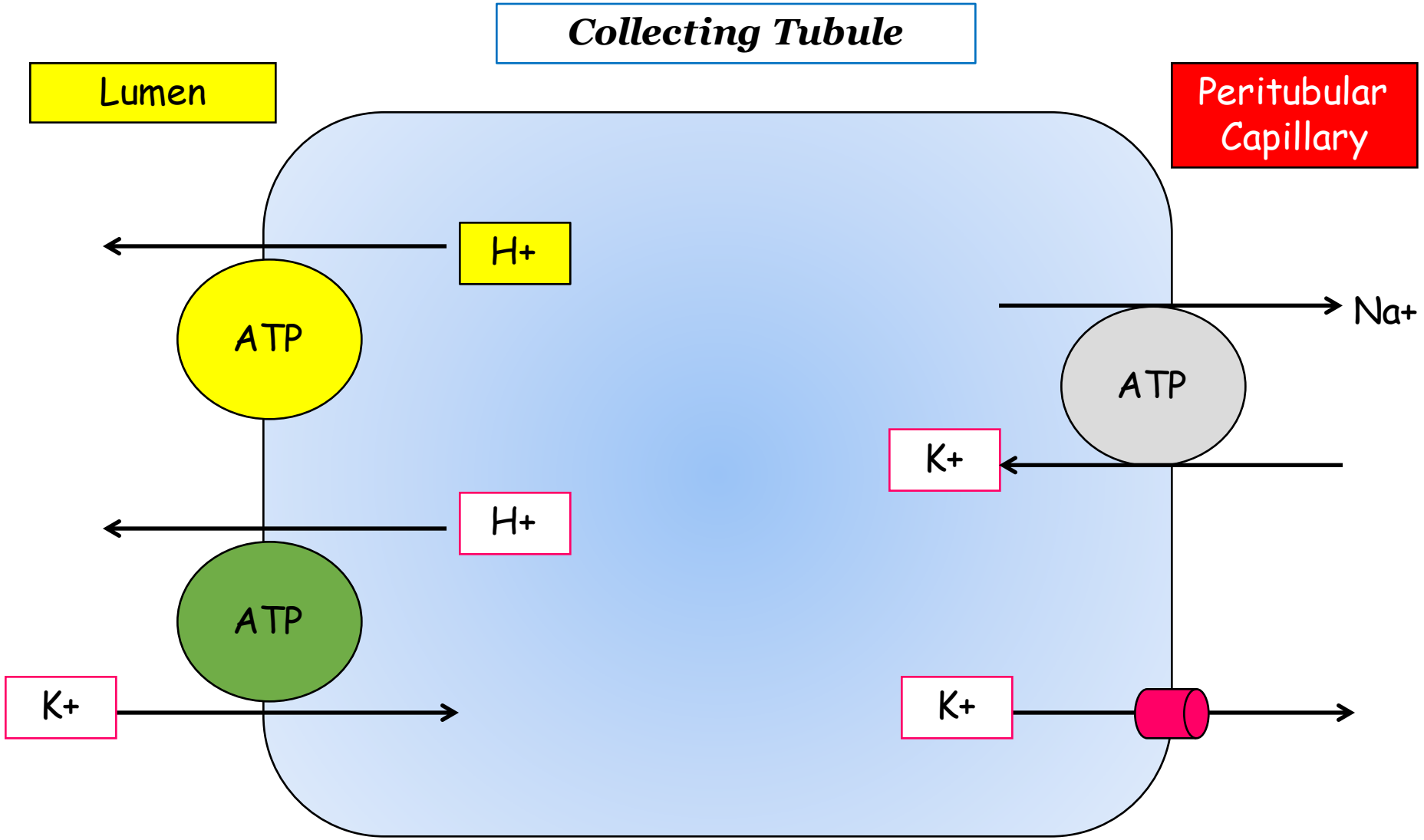

Collecting Tubule
Lumen
Peritubular Capillary
Na+ Reabsorption
Na+
Cl-
Na+
- 50 mV
Aldosterone
ATP
K+
K+
Increased activity and density of ENa channels
Aldosterone
NBME


Collecting Tubule
Lumen
Peritubular Capillary
Na+ Reabsorption
Na+
Cl-
- 50 mV
Aldosterone
K+
ATP
K+
Implication of Hyperaldo:
HTN 2° volume expansion
Aldosterone
Na+ Cl-
Na+
Na+ Cl-
Na+ Cl-
Na+ Cl-
180/100
NBME


Collecting Tubule
Lumen
Peritubular Capillary
Na+ Reabsorption
Na+
Cl-
Na+
- 50 mV
Aldosterone
ATP
K+
K+
K+ Secretion
K+
Adios K+
Implication of Hyperaldo:
HTN 2° volume expansion
Hypokalemia
180/100
<3.5 meq/dL
Patient presents with muscle weakness and cramps…

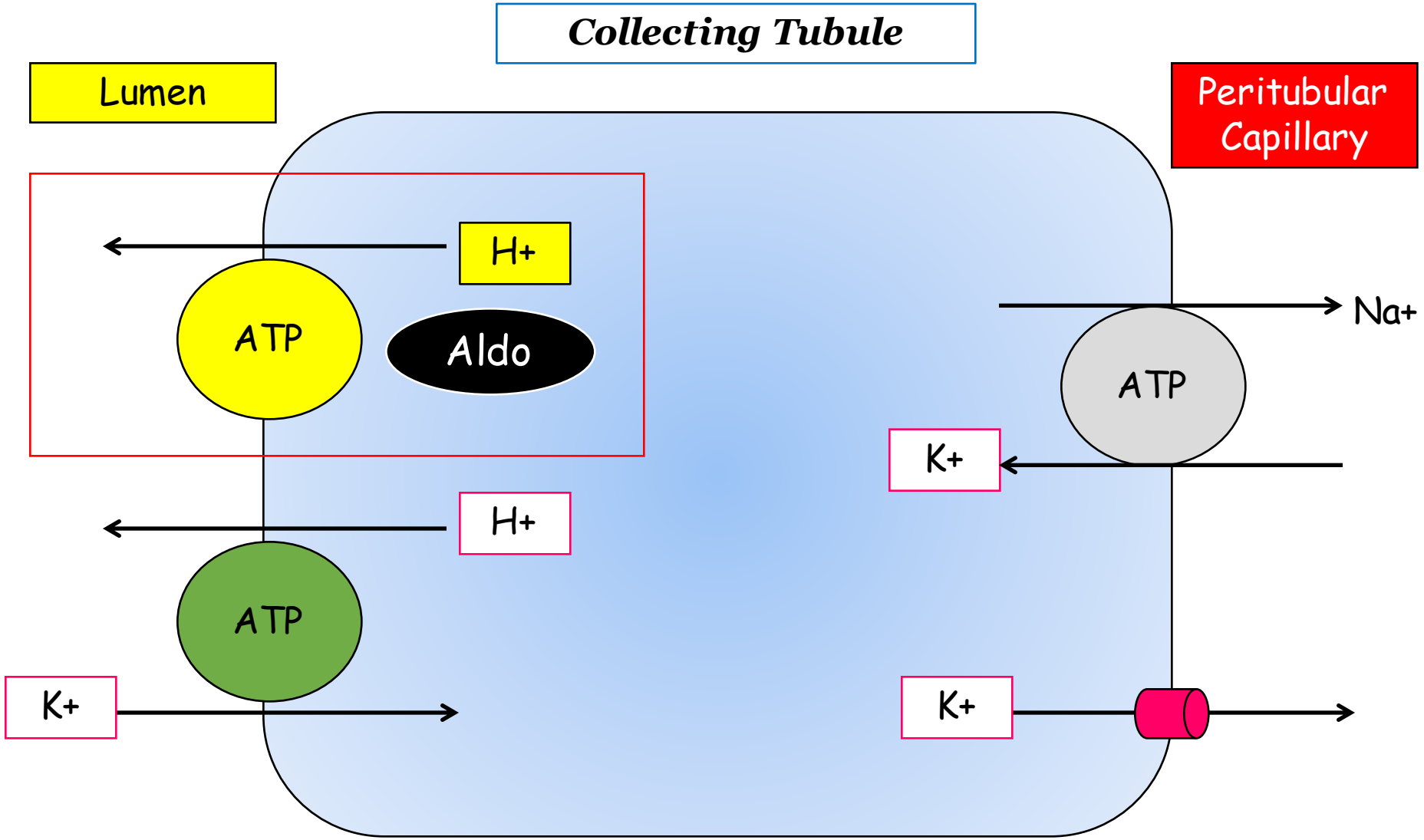
Collecting tubules join to form collecting duct

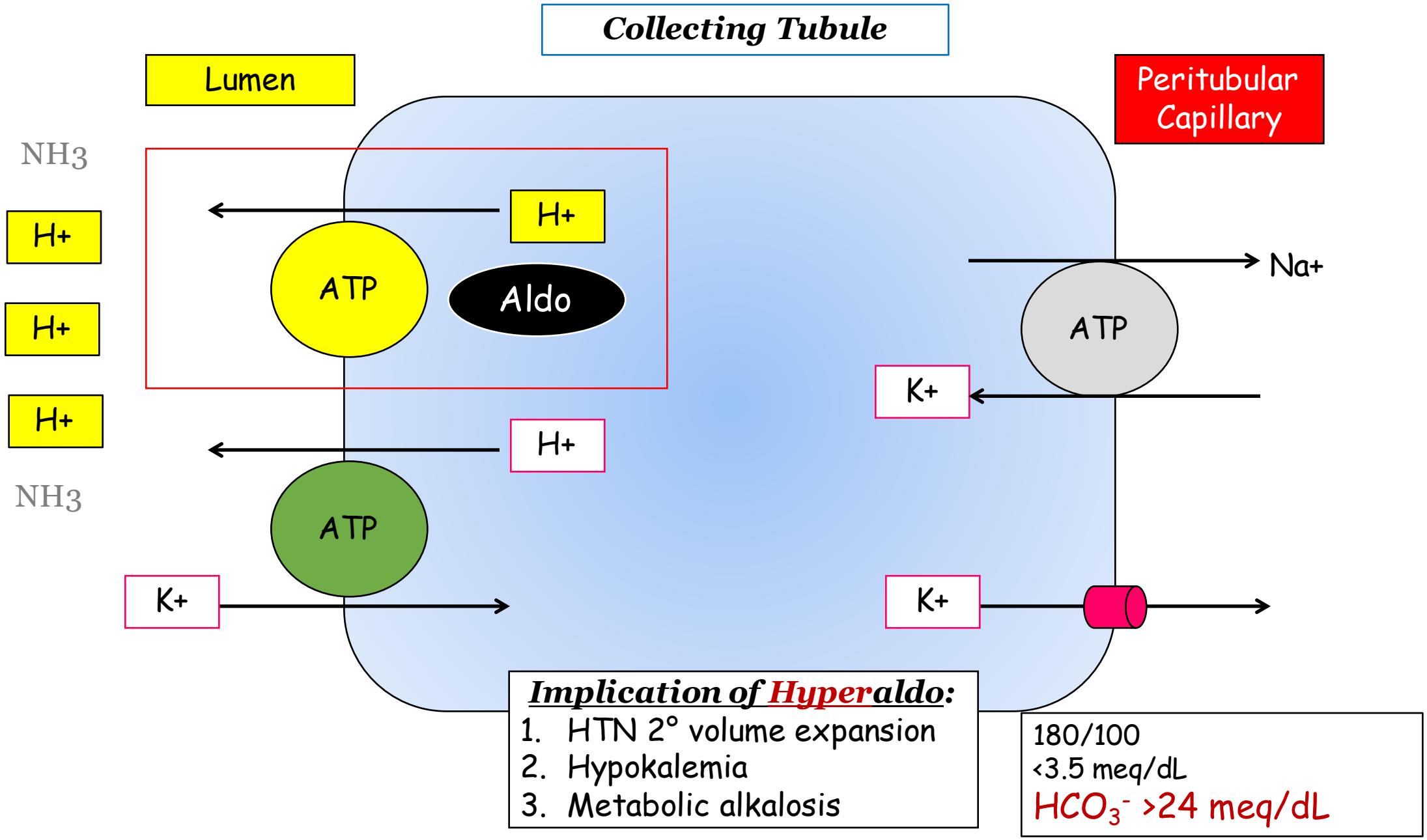


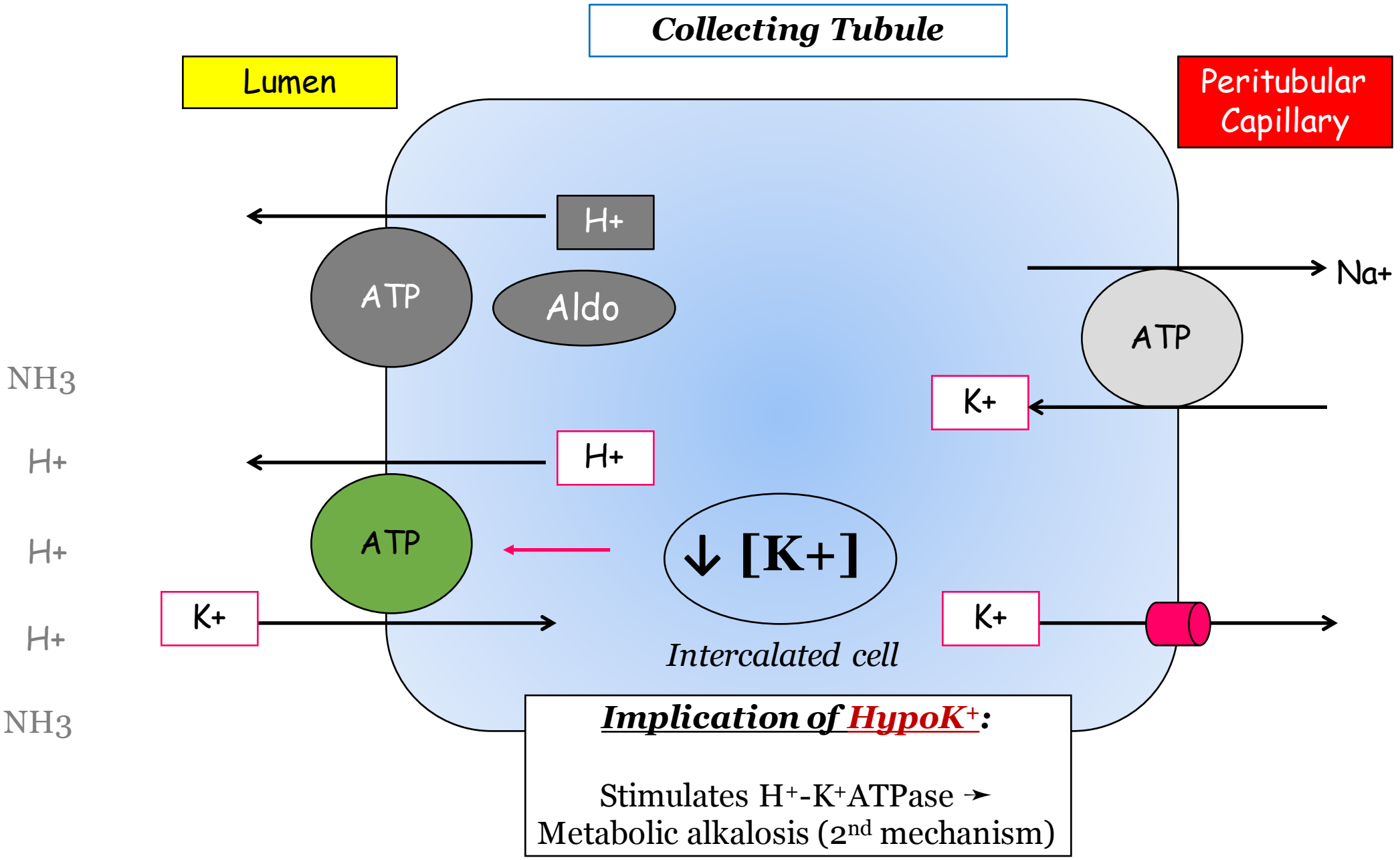


α-Intercalated Cells

1. **pH**: H^+-ATPase
2. **K+ balance**: H^+-K^+ATPase


Collecting Tubule
Lumen
Peritubular Capillary
H+
ATP
Aldo
Na+
ATP
K+
H+
ATP
K+
K+


Collecting Tubule
Lumen
Peritubular Capillary
NH3
H+
H+
H+
NH3
H+
ATP
Aldo
H+
ATP
K+
Na+
ATP
K+
K+
Implication of Hyperaldo:
1. HTN 2° volume expansion
2. Hypokalemia
3. Metabolic alkalosis
180/100
<3.5 meq/dL
HCO3- >24 meq/dL



Implication of HypoK⁺:

Stimulates H⁺-K⁺ATPase ➛
Metabolic alkalosis (2nd mechanism)

Hyperaldo: the Trifecta

Implication of Hyperaldo:

HTN 2° volume expansion
Hypokalemia
Metabolic alkalosis

Primary Hyperaldosteronism:
Adrenal Adenoma (Conn's Syndrome)

- Physiology
  - The basics ➛ *clinical manifestations*
    1. *Increases Na^+ (and Cl^-) absorption in principal cell (collecting duct):* HTN
    2. *K^+ wasting (maintain electrochemical gradient):* Hypokalemia
    3. *Stimulates H+-ATPase pump with H+ wasting:* Metabolic alkalosis
  - Regulatory Systems ➛ *aldosterone escape*

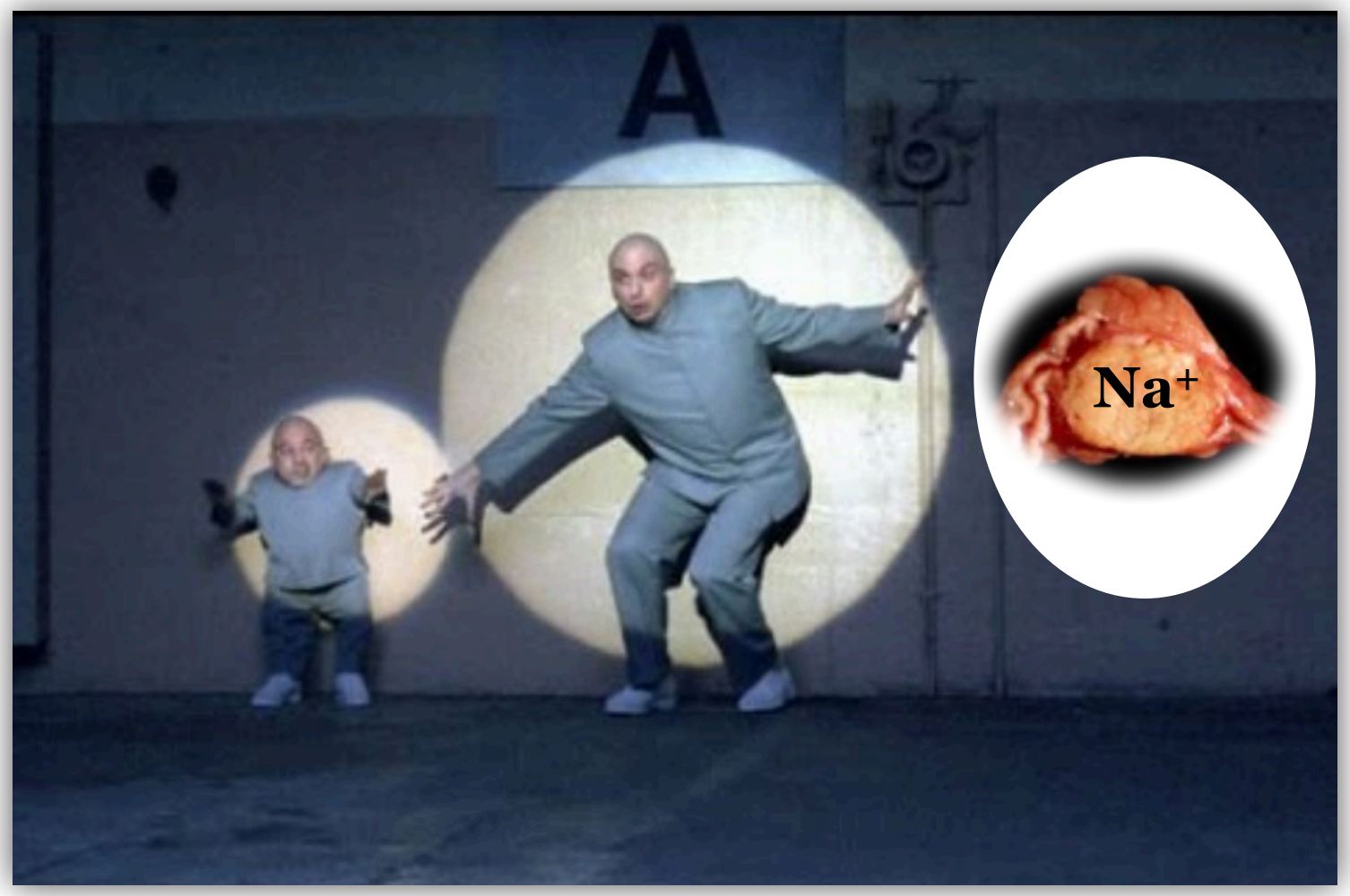
the Trifecta: what don't you see?

Implication of Hyperaldo:

HTN 2° volume expansion
Hypokalemia
Metabolic alkalosis

the Trifecta: what don't you see?

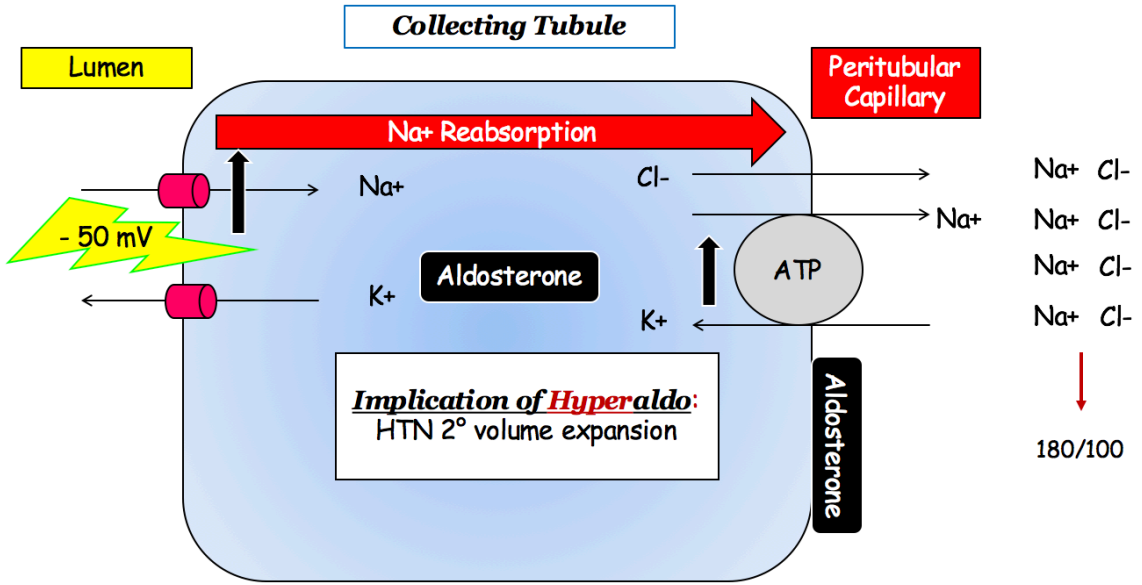
HyperNa$^+$ (P_{osm}): ***Aldosterone Escape***



Eunatremia: *Aldosterone Escape*

1. Pressure natriuresis (↑ Intraglomerular mm Hg)
2. ADH (maintains normal osms)
3. ANP (released in response to atrial stretch)

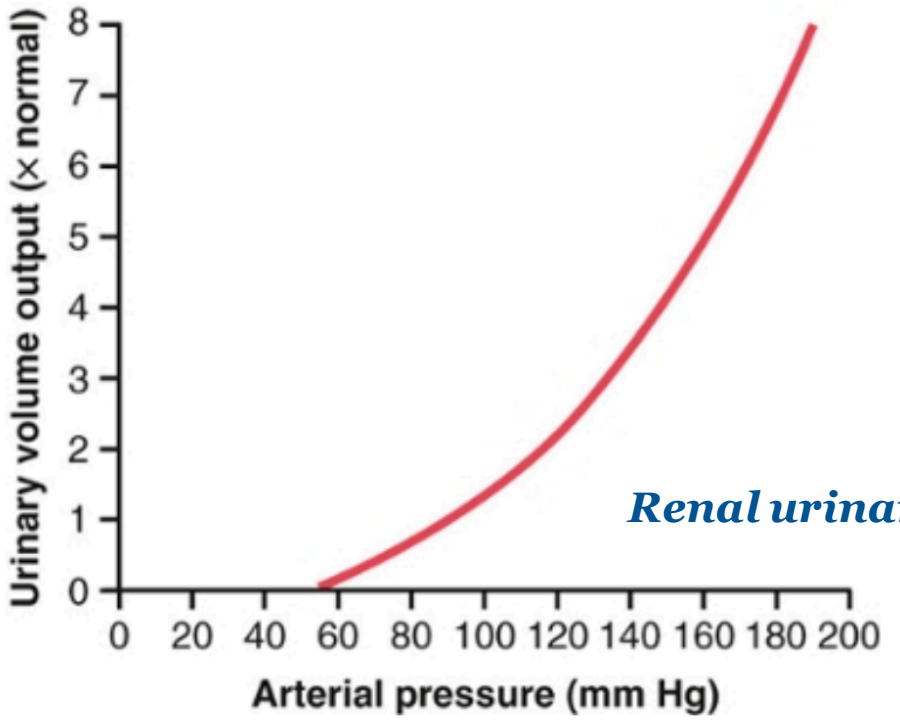
Counterregulatory Response



Eunatremia: ***Aldosterone Escape***

1. *Pressure natriuresis (↑Intraglomerular mm Hg)*
2. ADH (maintains normal osms)
3. ANP (released in response to atrial stretch)

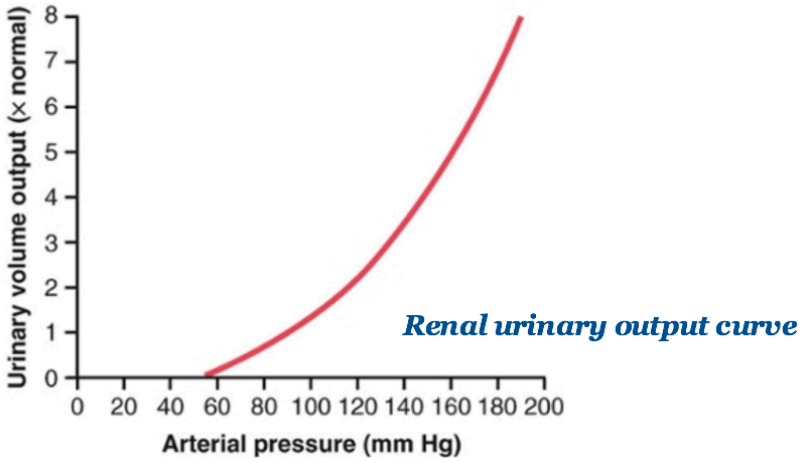
An increase in arterial pressure of *only a few mm Hg* can *double the renal output* of both salt (*pressure natriuresis*) and water (*pressure diuresis*)



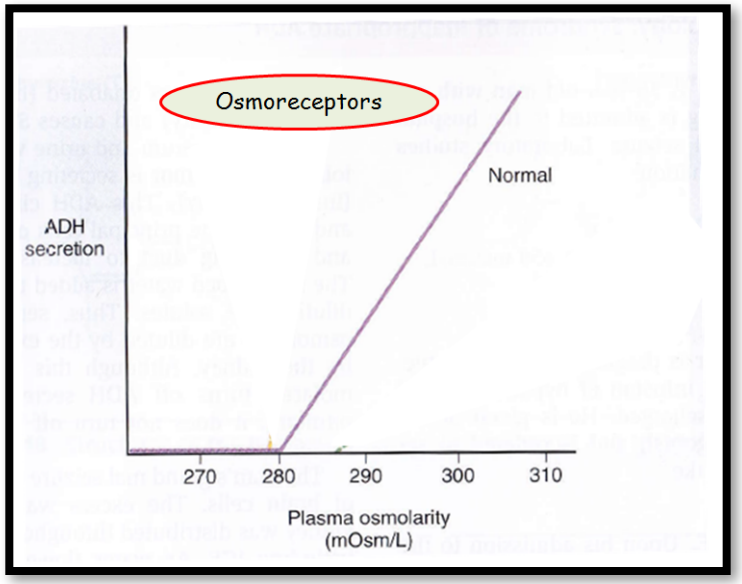
Renal urinary output curve

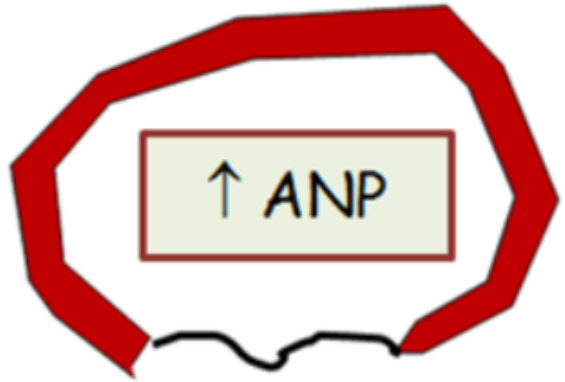
Eunatremia: ***Aldosterone Escape***

1. Pressure natriuresis (↑ Intraglomerular mm Hg)
2. ADH (maintains normal osms)
3. ANP (released in response to atrial stretch)



Renal urinary output curve





<u>Hyperaldosteronism</u>: HTN, low K, high HCO_3
No mention of hypernatremia

Patient presents with muscle cramps. BP: 200/100.
Labs: low renin and normal creatinine
What is the expected electrolyte pattern?

Posm

Na	K	HCO3
high	low	high
high	normal	normal
low	high	low
low	normal	low
normal	low	high
normal	normal	normal

Hyperaldosteronism: HTN, low K, high HCO3
No mention of hypernatremia

Patient presents with muscle cramps. BP: 200/100.
Labs: low renin and normal creatinine
What is the expected electrolyte pattern?

Posm

Na	K	HCO3
high	low	high
high	normal	normal
low	high	low
low	normal	low
normal	low	high
normal	normal	normal

Hyperaldosteronism: HTN, low K, high HCO3
No mention of hypernatremia

Patient presents with muscle cramps. BP: 200/100.
Labs: low renin and normal creatinine
What is the expected electrolyte pattern?

Posm

Na	K	HCO3
high	low	high
high	normal	normal
low	high	low
low	normal	low
normal	low	high
normal	normal	normal

Eunatremia:
Aldosterone Escape

Hyperaldosteronism: HTN, low K, high HCO3
No mention of hypernatremia

Eunatremia: ***Aldosterone Escape***

Patient with cramps and weakness (*low K+*).
No headache, sweats or palpitations (*exclude pheo*)
BP: 200/120
Labs: **Na 145** (*mild increase*); Glucose normal (*exlude Cushings*)
Which of the following diagnoses are most likely?

1. Tumor of adrenal glomerulosa
2. Tumor of adrenal fasciculata
3. Tumor of adrenal medulla
4. Tumor of pituitary
5. Graves Disease

Eunatremia: ***Aldosterone Escape***

Patient with cramps and weakness (*low K+*).
No headache, sweats or palpitations (*exclude pheo*)
BP: 200/120
Labs: Na 145 (*mild increase*); Glucose normal (*exlude Cushings*)
Which of the following diagnoses are most likely?

1. **Tumor of adrenal glomerulosa** (*adenoma*)
2. Tumor of adrenal fasciculata (*normal glucose*)
3. Tumor of adrenal medulla
4. Tumor of pituitary
5. Graves Disease

Primary Hyperaldosteronism:
Adrenal Adenoma (Conn's Syndrome)

- Physiology
  - The basics ➛ *clinical manifestations*
    1. Increases Na^+ (and Cl^-) absorption in principal cell (collecting duct): HTN
    2. K^+ wasting (maintain electrochemical gradient): Hypokalemia
    3. Stimulates H+-ATPase pump with H+ wasting: Metabolic alkalosis
  - Regulatory Systems ➛ *aldosterone escape*
- *Diagnostics*
- Therapeutics
- Loose Assocations

Primary Hyperaldosteronism: Diagnostics

- Lab Tests
  - Serum aldosterone level PLUS plasma renin level (*suppression*)
    - Hyperaldosteronism is defined by a ratio of > 20:1 [PLUS an elevated aldosterone level (>15 ng/dL)]

Primary Hyperaldosteronism: Diagnostics

- Lab Tests
  - *Serum aldosterone level PLUS plasma renin level (suppression)*
    - *Hyperaldosteronism is defined by a ratio of > 20:1 [PLUS an elevated aldosterone level (>15 ng/dL)]*
  - 24 hr urine collection of aldosterone
    - Salt or saline load (*i.e. the patient needs to be volume replete*)
  - Adrenal vein sampling *(if surgical mgmt)*
    - Differentiates between *adenoma* and *hyperplasia* (and confirms glandular hyperfunction)

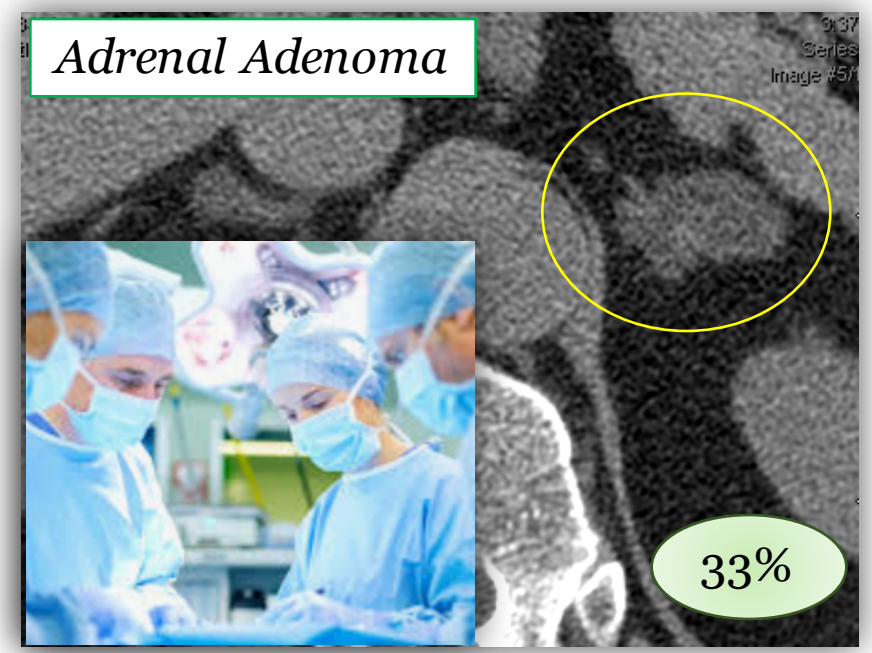
Primary Hyperaldosteronism: Diagnostics

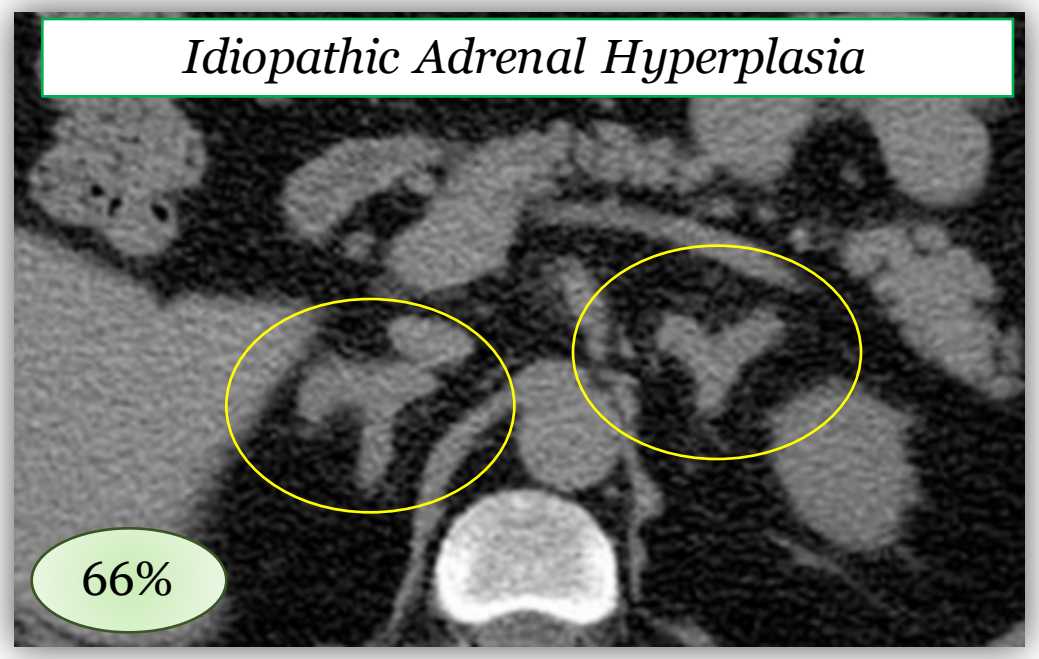
- Lab Tests
  - *Serum aldosterone level PLUS plasma renin level (suppression)*
    - *Hyperaldosteronism is defined by a ratio of > 20:1 [PLUS an elevated aldosterone level (>15 ng/dL)]*
  - *24 hr urine collection of aldosterone*
    - *Salt or saline load (i.e. the patient needs to be volume replete)*
  - *Adrenal vein sampling (if surgical mgmt)*
    - *Differentiates between adenoma and hyperplasia (and confirms glandular hyperfunction)*

- Imaging
  - CT/MRI: adenoma, bilateral nodular glands (IHA)

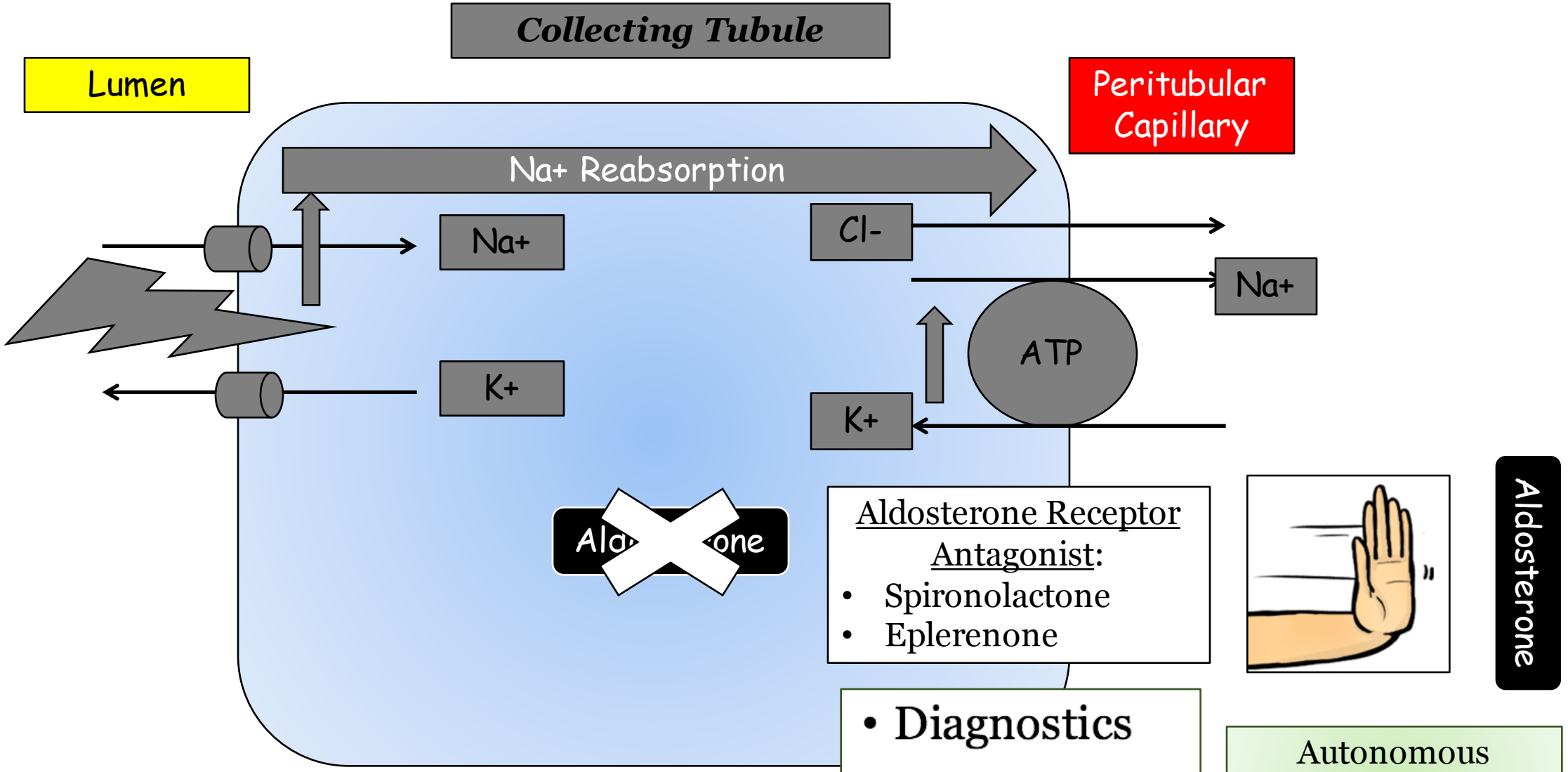
Primary Hyperaldosteronism: Diagnostics

- Imaging
  - CT/MRI: adenoma, bilateral nodular (thickened) glands





Medical Management

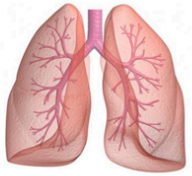

Collecting Tubule
Lumen
Peritubular Capillary
Na+ Reabsorption
Na+
Cl-
Na+
ATP
K+
K+
Aldosterone Receptor Antagonist:
• Spironolactone
• Eplerenone
Aldosterone
• Diagnostics
• Therapeutics
Autonomous Secretion (≠ ACE/ARB)

Primary Hyperaldosteronism:
Adrenal Adenoma (Conn's Syndrome)

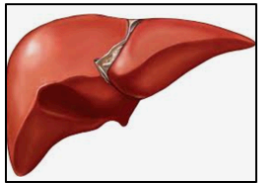
- Physiology
  - The essentials ➛ *clinical manifestations*
    1. Increases Na^+ (and Cl^-) absorption in principal cell (collecting duct): HTN
    2. K^+ wasting (maintain electrochemical gradient): Hypokalemia
    3. Stimulates H+-ATPase pump with H+ wasting: Metabolic alkalosis
  - Regulatory Systems ➛ *aldosterone escape*
- Diagnostics: Labs/Imaging
  - Aldo:Renin ratio (20:1)
- Therapeutics: Aldosterone Receptor Antagonist
- *Loose Assocations*

Aldosterone-related Trivia

- *Hyperkalemia: stimulates aldosterone synthase*
- Hypercortisolism
- Adrenal failure



Renin → Angiotensinogen → Angiotensin I → (*ACE*) → Angiotensin II

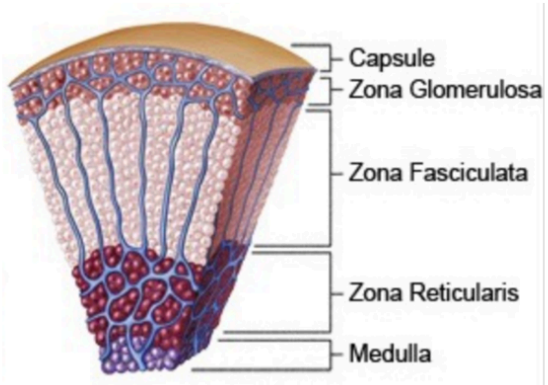


Angiotensin II → Na-HCO_3 PCT

Angiotensin II → ADH release

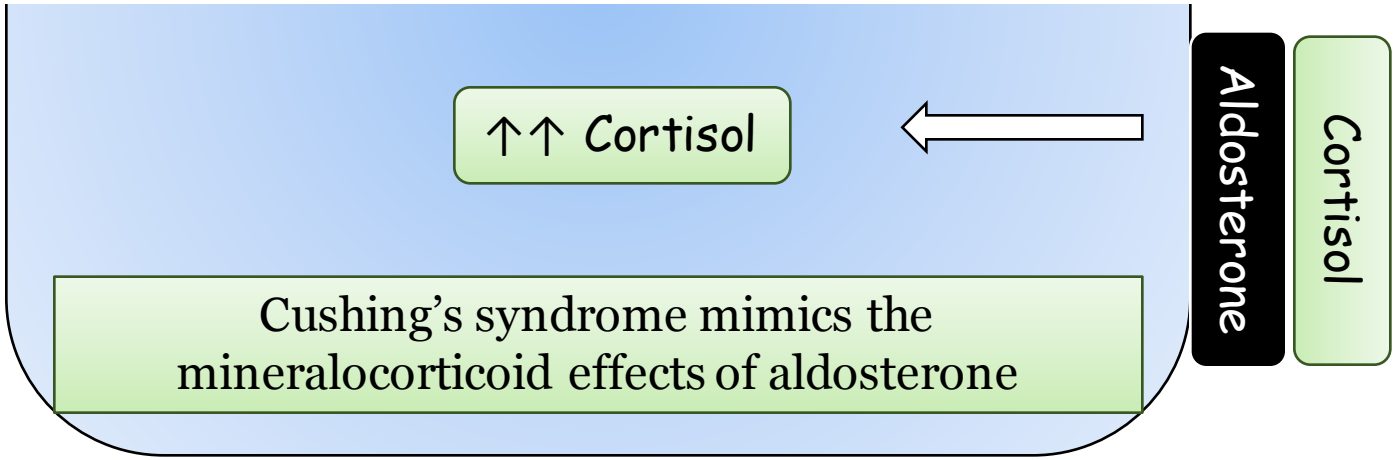
Angiotensin II → Corticosterone → Aldosterone

↑ K^+ → *Aldosterone Synthase* → Aldosterone



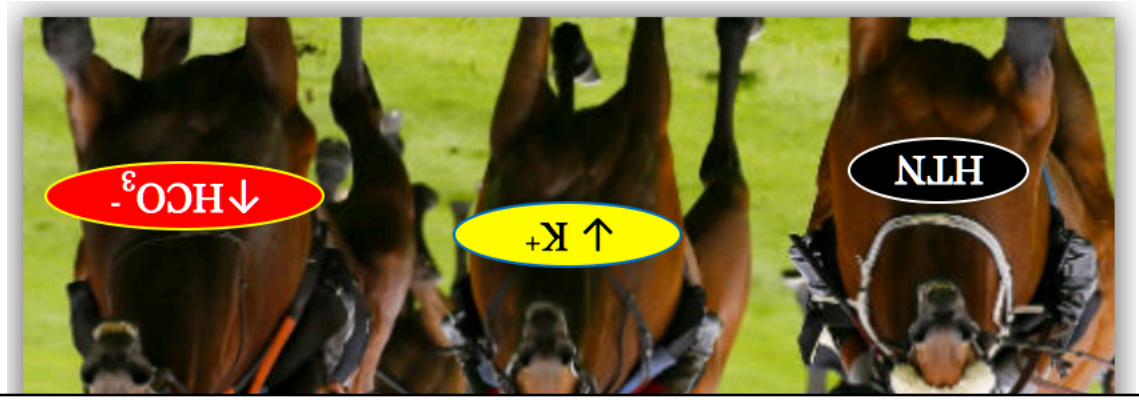
Aldosterone-related Trivia

- Hyperkalemia
- *Hypercortisolism: mineralocorticoid properties*
  - *HTN*
  - *HypoK+*
  - *Metabolic alkalosis*
  - *Normal Na^+/Posm*



Cortisol at *physiologic* concentrations is metabolized by 11-β hydroxysteroid dehydrogenase

Adrenal Failure: the Superfecta



Aldosterone-related Trivia

- Hyperkalemia
- Hypercortisolism
- *Adrenal failure: it has opposite effects (obviously)*

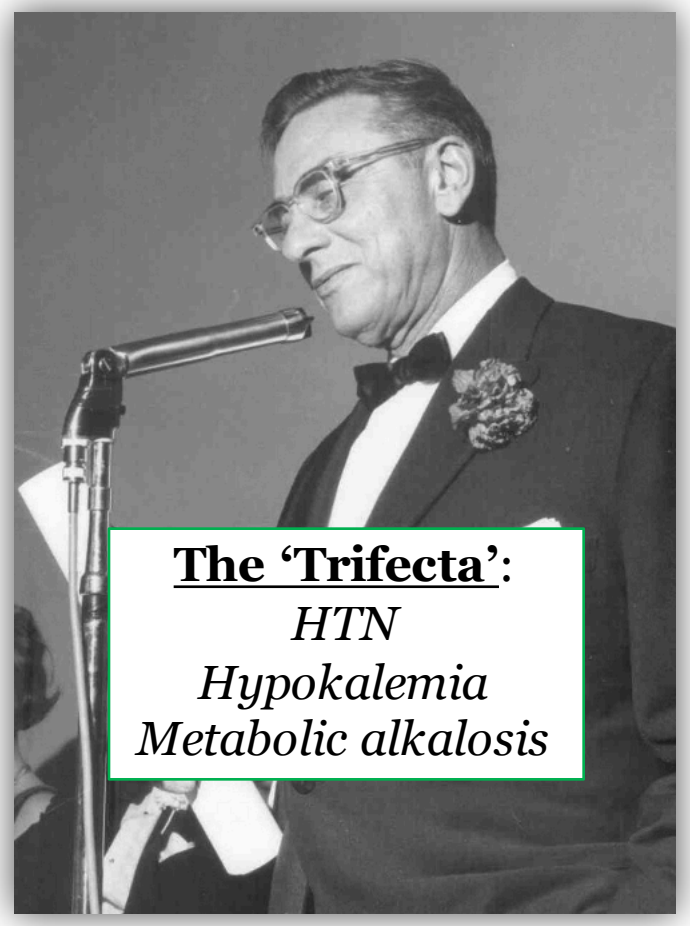
Implication of Hypoaldo:
Hypotension
Hyperkalemia
Metabolic acidosis (NAG)
HypoNa (Na^+ wasting/ADH)

Implication of Hyperaldo:
HTN 2° volume expansion
Hypokalemia
Metabolic alkalosis

Primary Hyperaldosteronism:
Adrenal Adenoma (Conn's Syndrome)

- Physiology
  - The basics ➛ *clinical manifestations*
  - Regulatory Systems ➛ *aldosterone escape*
- Diagnostics
  - Functional
  - Anatomic
- Therapeutics
  - Aldosterone antagonists
- Loose Associations
  - Hyperkalemia
  - Hypercortisolism
  - Adrenal failure

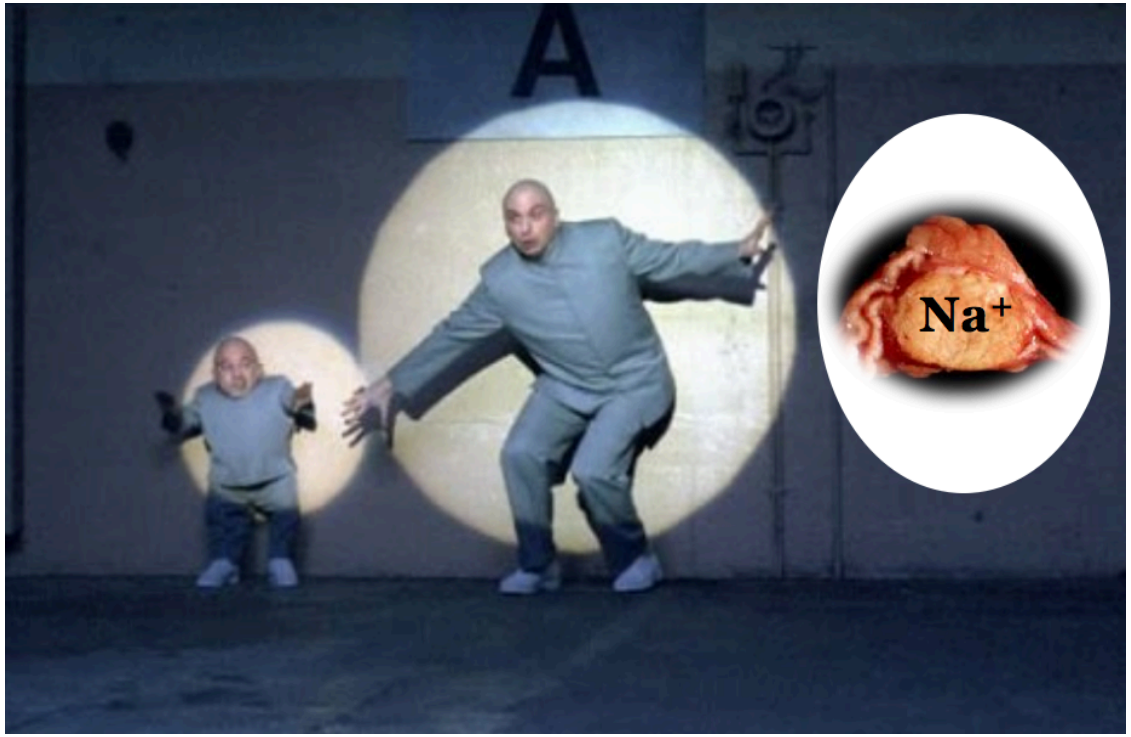
NBME



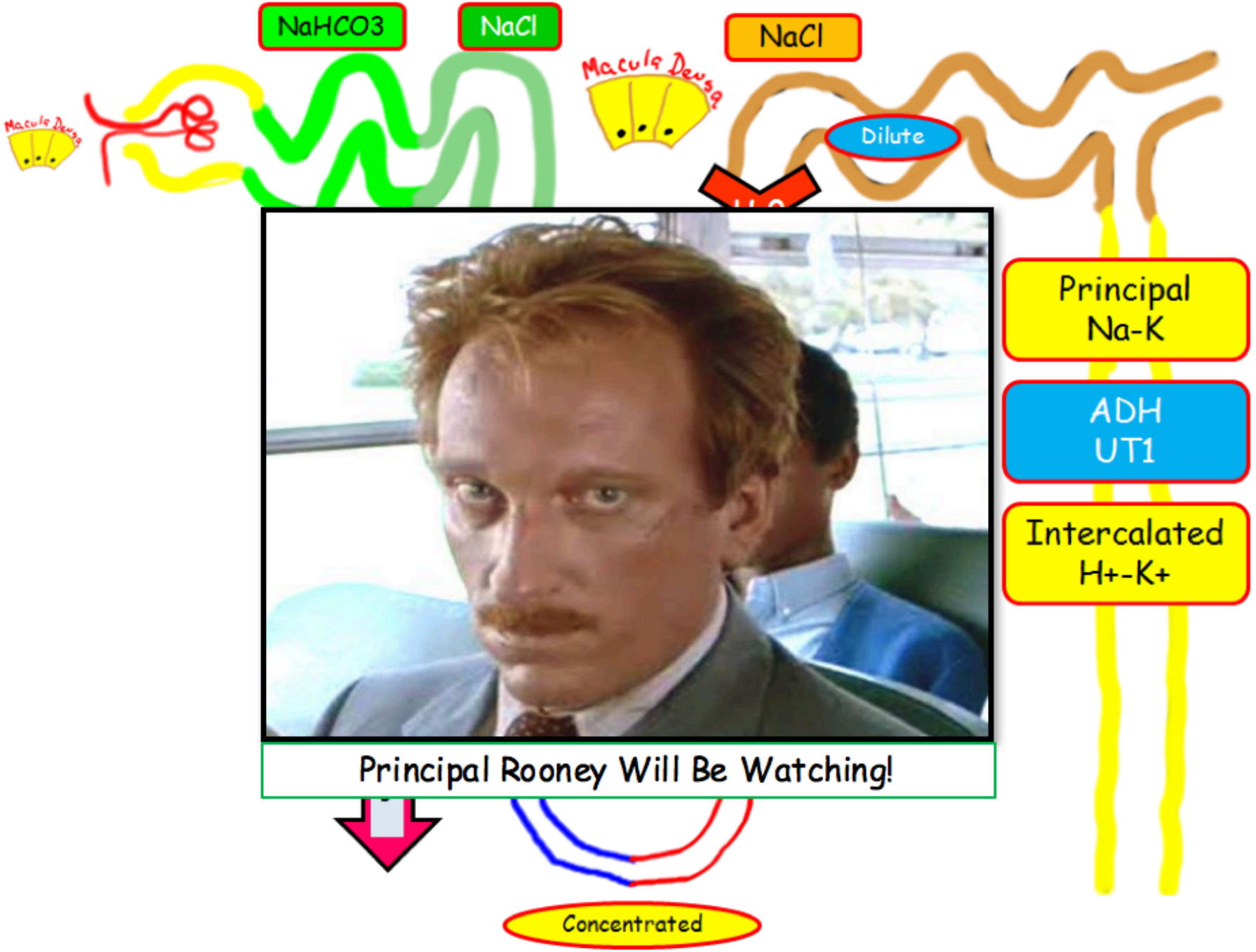
The 'Trifecta':
HTN
Hypokalemia
Metabolic alkalosis

Jerome W. Conn, MD

Hyperaldosteronism for the USMLE Step One Exam



Howard J. Sachs, MD
Associate Professor of Medicine
University of Massachusetts Medical School
www.12DaysinMarch.com; Season III
E-mail: Howard@12daysinmarch.com


NaHCO3
NaCl
NaCl
Macula Densa
Macula Densa
Dilute
Principal Rooney Will Be Watching!
Principal
Na-K
ADH
UT1
Intercalated
H+-K+
Concentrated