Fluid and electrolyte abnormalities

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- Disclosures:

Editor, Kidney Self Assessment Program

American Society of Nephrology

- Hyponatremia*
- Hypernatremia
- Hyperkalemia
- Hypokalemia
- Metabolic acidosis
- Hypomagnesemia

Case 1

A 73 year old gentleman presents for evaluation

He has a history of hyponatremia, hypertension and a seizure disorder

Medications: carbamazapine, hydrochlorothiazide, olmesartan, amlodipine

On physical examination:

Blood pressure was 157/86 mmHg and his heart rate was 67 beats/min, BMI 29 kg/m^2

Exam was normal with trace edema

- Review of old laboratory studies shows a serum sodium of 127 mEq/L in 2014
- Notes from cardiologist indicate that HCTZ restarted this fall for HTN, stopped when serum sodium measured at 128 mEq/L but restarted a month later at 12.5 mg because of hypertension.

Laboratory data today:

- Serum Sodium 129 mEq/L (136-145 mEq/L)
- Potassium 4.4 mEq/L
- Bicarbonate 28 mEq/L
- BUN 20 mg/dL
- Creatinine 0.8 mg/dL
- Glucose 108 mg/dL

How should we evaluate this patient, manage the hyponatremia and treat his hypertension?

Additional data:

- Serum osmolality 272 mOsm/kg (275-295)
- Urine (normals vary with intake-

  AND WHAT THE KIDNEY SHOULD DO!)

  – osmolality 600 mOsm/kg

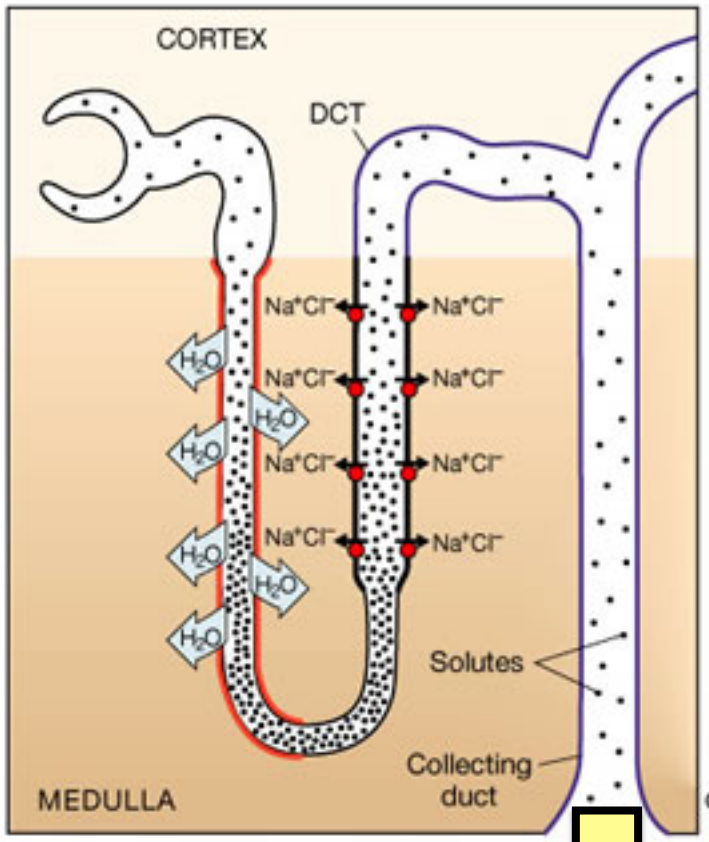
  – Na 52 mEq/L

Approach to HyPOnatremia

The following review is an approach to hyponatremia in patients with normal renal function. With acute kidney injury or with advanced CKD, patients may not be able to maximally dilute urine to handle water load.

Recall:

ADH IS NOT PRESENT

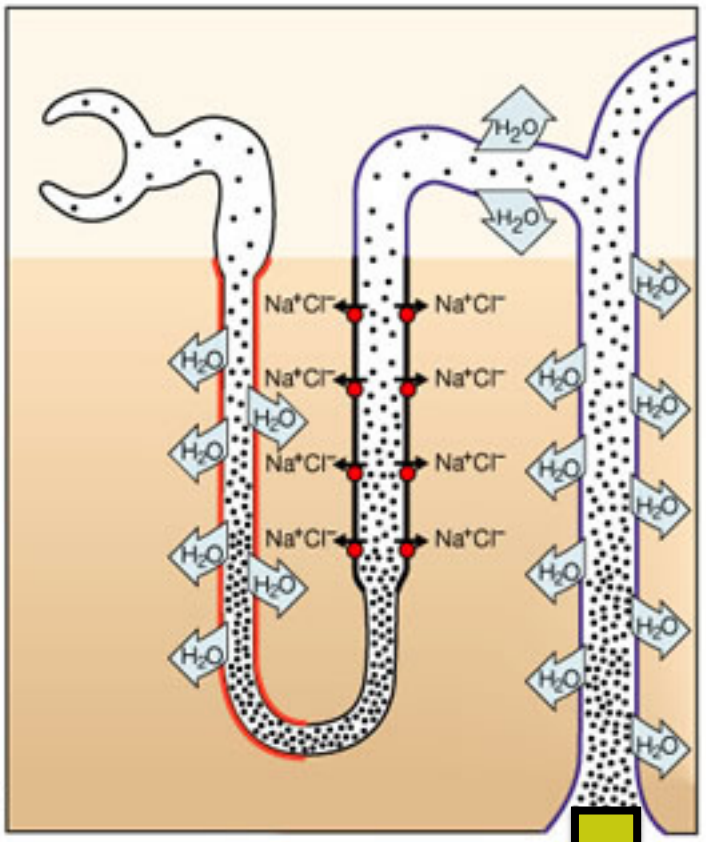


Very dilute

Very concentrated

Large volume of dilute urine

ADH IS PRESENT



Small volume of concentrated urine

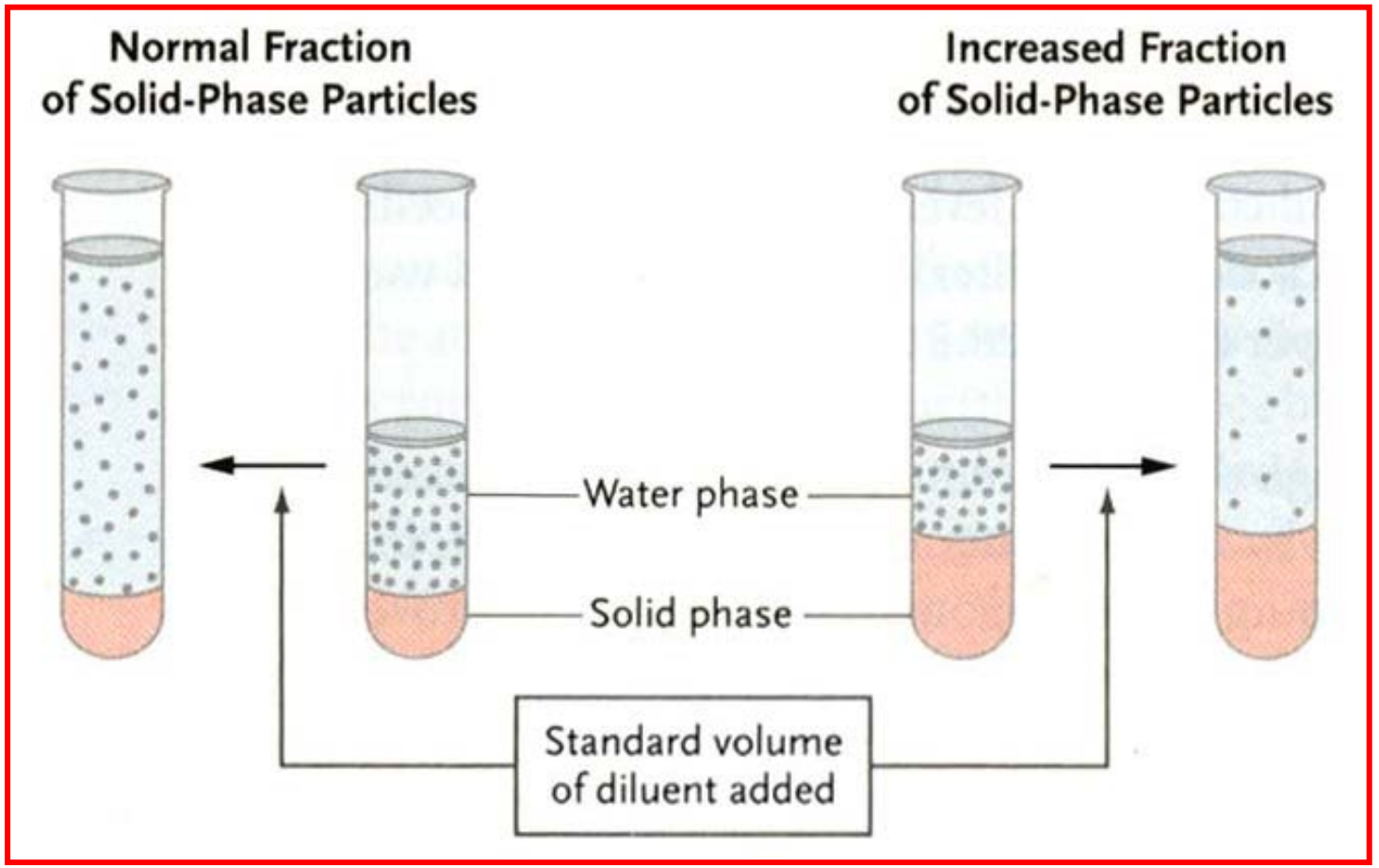
1. Step 1. Confirm the diagnosis -is it Pseudohyponatremia?

- lab error-- [Na+] is normal in plasma water but reported falsely low because of correction factor made by the lab
- Confirm by measuring plasma Osm
- Occurs with elevated lipids or plasma proteins

This is not a pipe

by Magritte

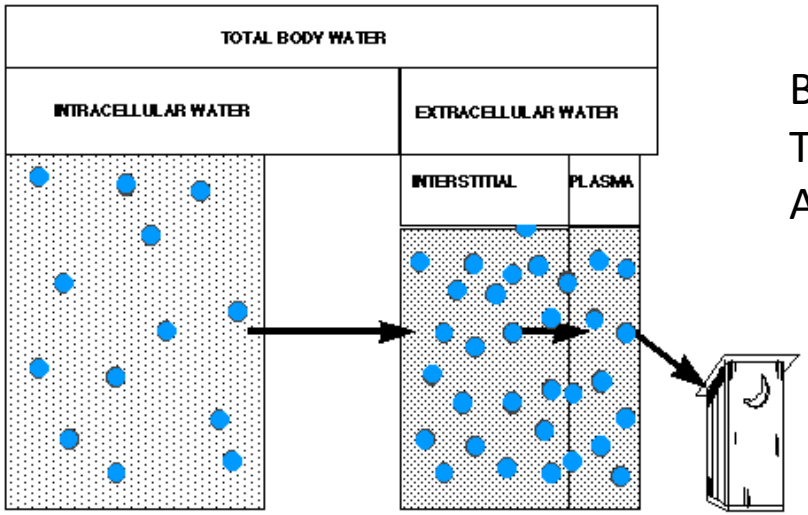
Pseudohyponatremia



Turchin A, Seifter JL, Seely EW. Clinical Problem Solving: Mind the Gap. New Engl J Med 349;15:1465-9 (aturchin@partners.org)

Step 1. Confirm the diagnosis -is it Hyperosmolar hyPOnatremia?

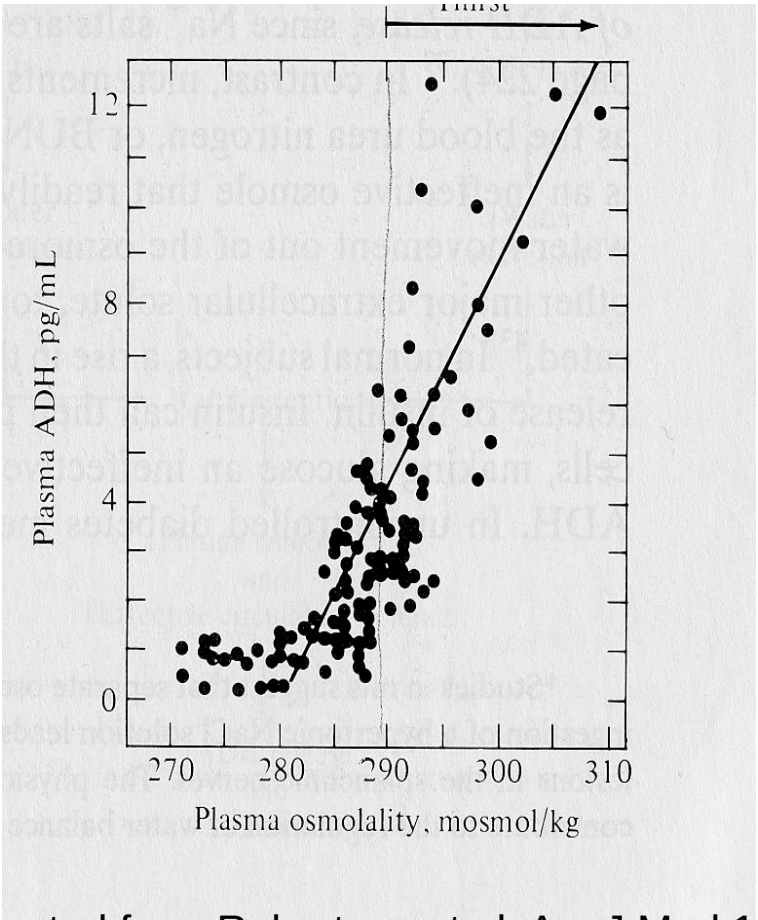
- The serum sodium is low but
  the serum osmolality is high!
- **Hyperglycemia**- Serum sodium falls 1.6 mEq/L for every 100 mg/dL rise in serum glucose over 100 mg/dL as water moves out of cells, drawn by the osmotic force of the high extracellular glucose
- Also occurs with mannitol and glycine



Blue dots represent glucose molecules
The stippled black dots represent water
Arrows reflect the movement of water

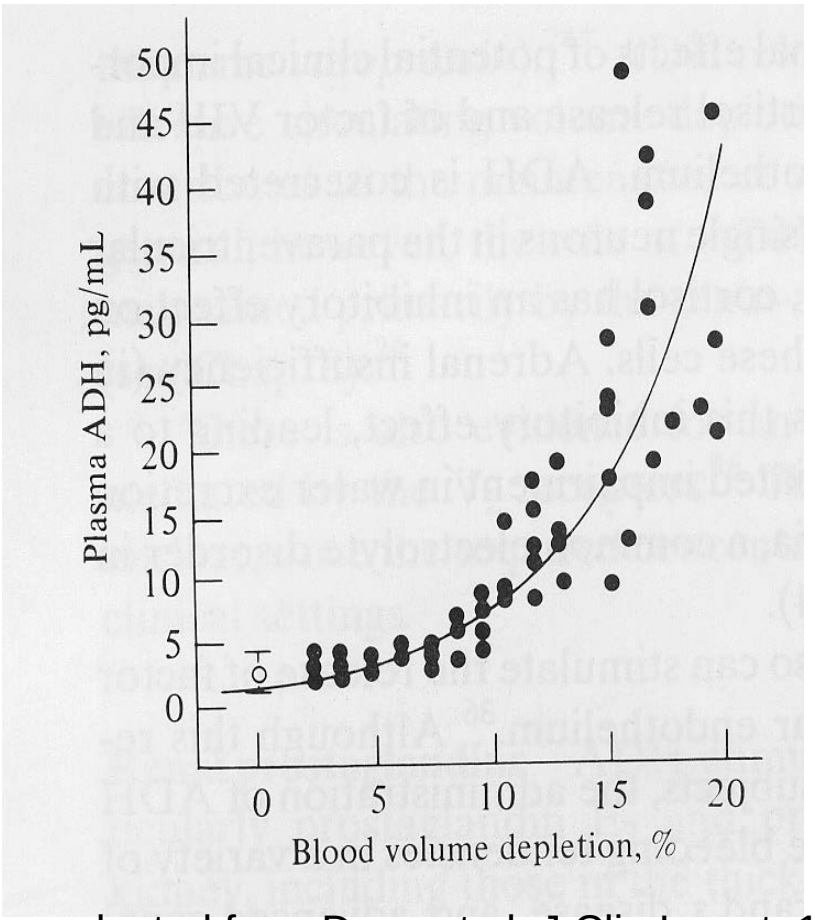
Step 2: is there an appropriate reason for ADH to be "on?"

hyperosmolality



adapted from Robertson et al, Am J Med 1982

Volume depletion



adapted from Dunn et al. J Clin Invest, 1973

Step 2: is there an appropriate reason for ADH to be "on?"

Hyponatremia

Determine volume status

Volume depleted

Euvolemic

Hypervolemic

Volume depleted
+ intake of dilute fluids

ECV depletion
i.e. CHF,cirrhosis, nephrosis
+intake of dilute fluids

STEP 3. If euvolemic, is ADH "on?"

No, urine is dilute

Uosm <100

Yes! ADH is on and it's NOT appropriate

Uosm >>100

Causes of SIADH (very abbreviated list)

	Most common example
ENDOCRINE	Severe Hypothyroidism (mech not fully understood) Adrenal insufficiency (cortisol neg feedback on CRH)
DRUGS 	SSRI, MAO I, Tricyclics, Ecstasy
PULMONARY 	Pneumonia, Abscess, TB
CNS 	Meningitis, abscess, subdural hematoma, CVA
CANCER 	Small Cell CA, Bronchogenic, colon, pancreas, ovary, prostate,
GENERAL	PAIN, STRESS RESPONSE-Caution--Perioperative Period,

Step 4. How to treat?

- Consider chronicity
- Consider symptoms
- No more than 12 mEq/24 hours (0.5 mEq/hour) or perhaps MUCH slower (**current guidelines just 6-8 mEq/24 hours**)
- Consider etiology!

Treatment of Acute symptomatic Euvolemic Hyponatremia

- initial rate of correction- may be up to 1-2meq/L/hr if necessary but NOTE-still small total for 24 hours--newer recommendations are 6-8 mEq/24 hour total

(rapid correction may lead to osmotic demyelination)

- 3% saline if severely altered mental status– esp with SIADH if Uosm is fixed and very high (>400 mosm/L)
- Loop diuretics if evidence of volume overload
- Normal saline if volume depleted
  - CAUTION #1 Correction may occur quickly once volume replete and stimulus to ADH release suppressed
  - CAUTION #2 if NOT volume depleted, saline may worsen
- Closely follow [Na^+] during correction
- No role for Vaptans in acute hyponatremia

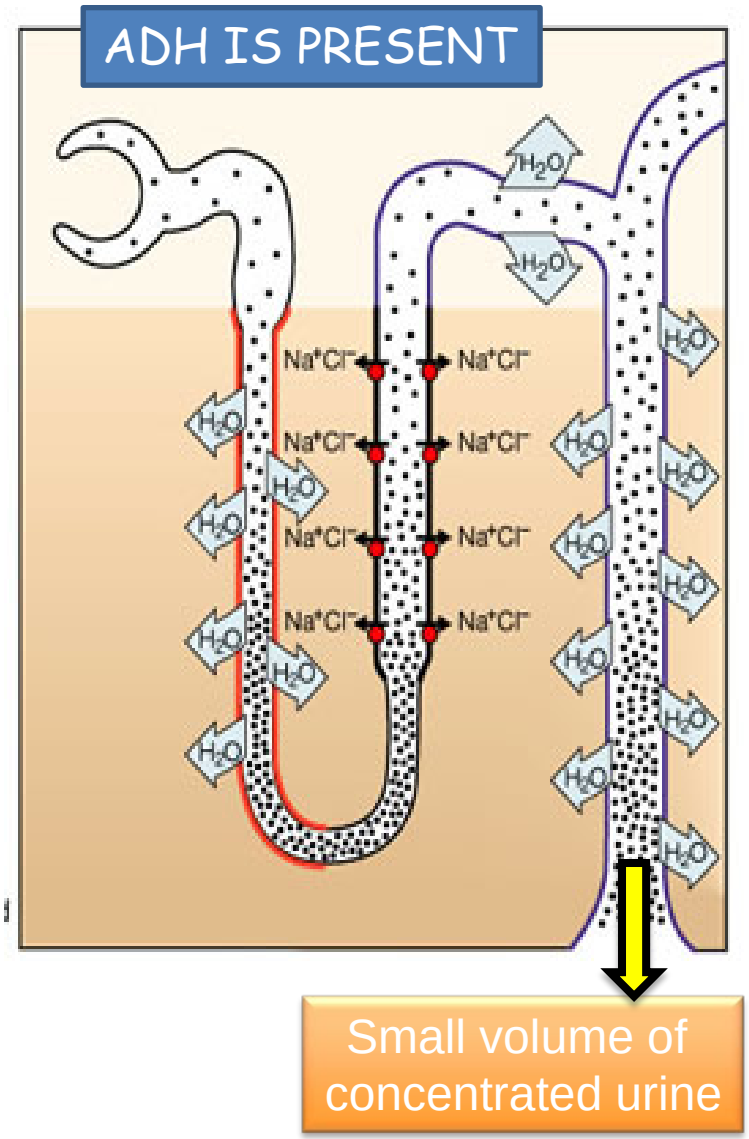
Strategies in the treatment for hyponatremia in setting of SIADH

- **Fluid intake (oral and IV)**
  - Limit fluid intake
- **Increase solute intake**
  - Salt tabs (though these make patients thirsty)
  - High protein diet
- **Medications**

Limit kidneys' ability to make concentrated urine

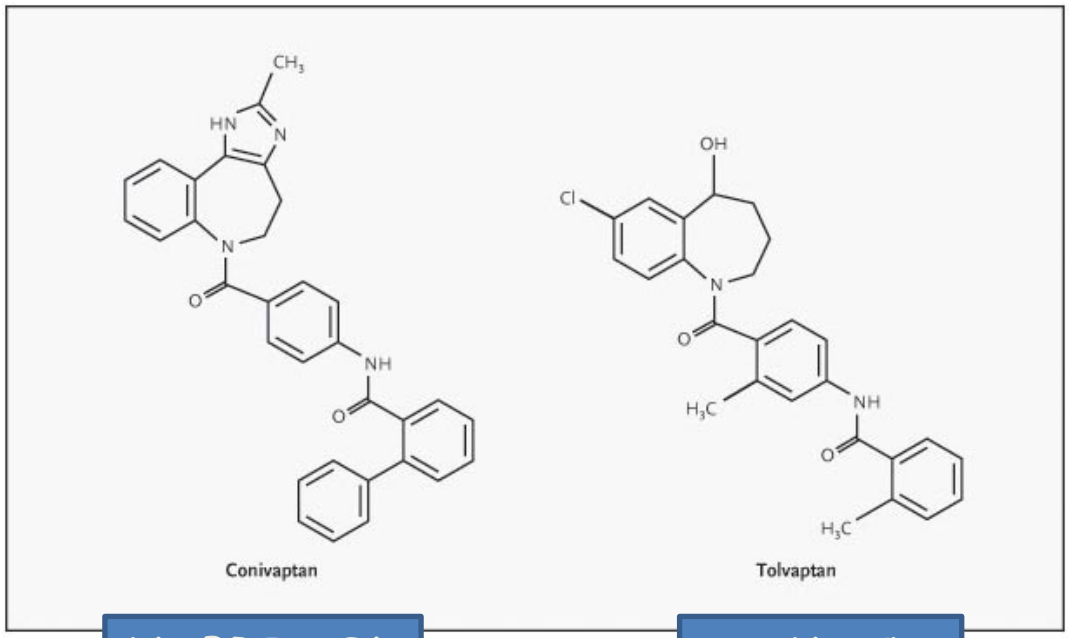
→ loop diuretics limit gradient

→V2 receptor blocker block ADH effect



Oral Vasopressin-Receptor Antagonists

- FDA approved for hyponatremia in setting of euvolemia (SIADH) and volume overload (CHF and cirrhosis) with serum Na <125
- response variable so start in hospital setting and $$$
- do not prescribe if hypodipsia or difficulty accessing water!

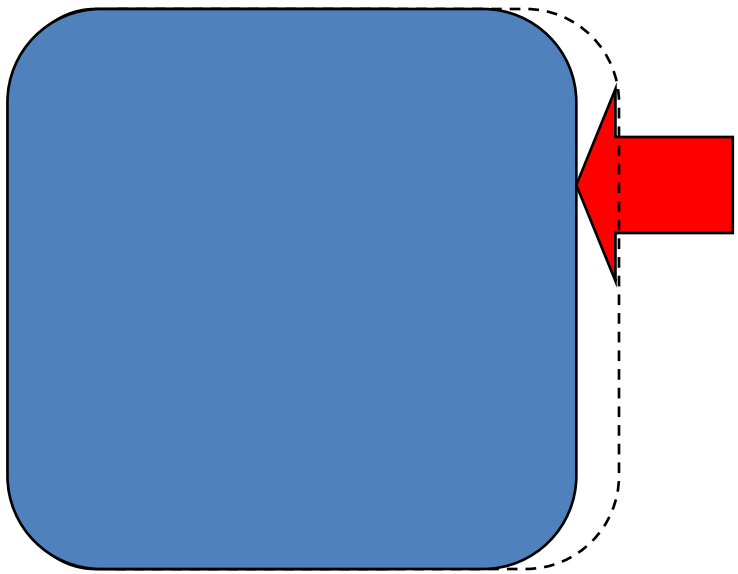


VAPRISOL
Conivaptan
IV

SAMSCA
Tolvaptan
oral

The NEW ENGLAND JOURNAL of MEDICINE

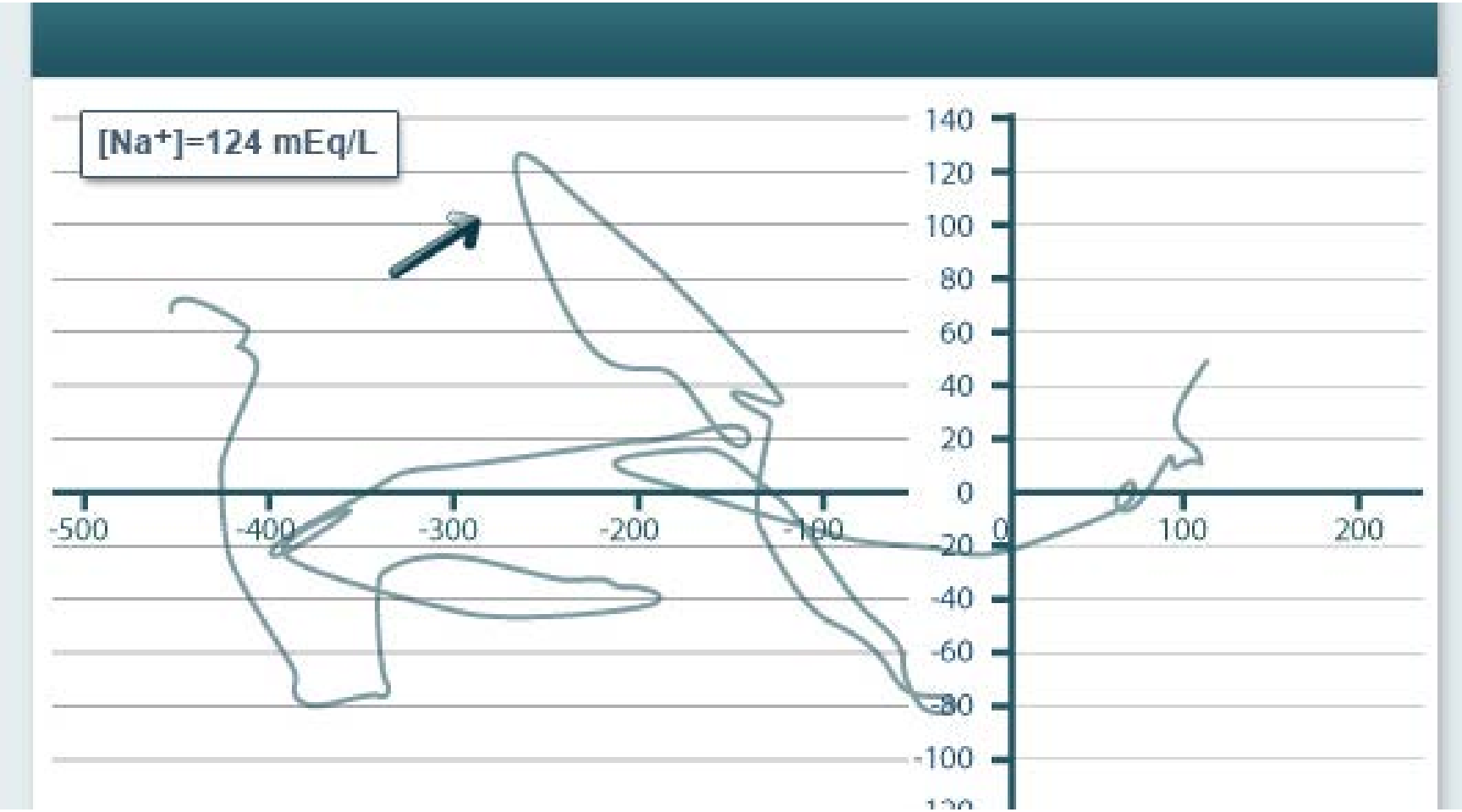
Why the concern over hyponatremia?



Symptoms are primarily neurologic:

nausea→ headache→lethargy→seizures→coma→death

Chronic hyponatremia?



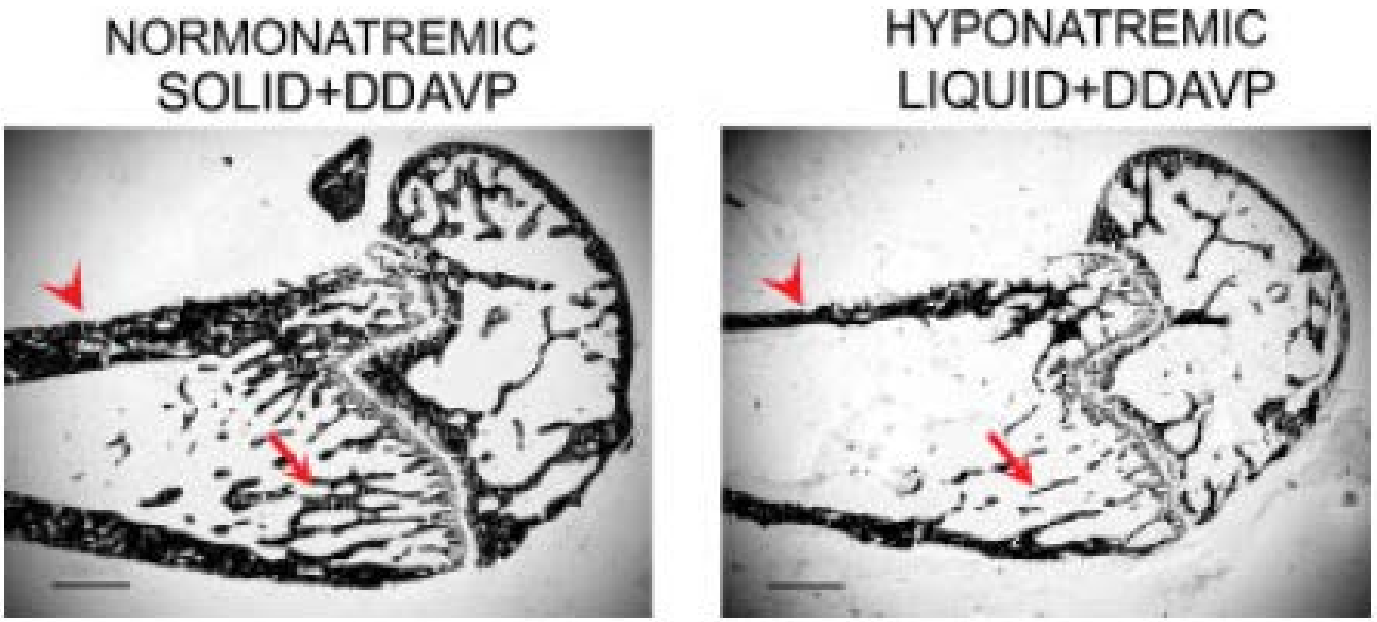
Am J Med. 2006;119:71.e1-71.e8.

Chronic hyponatremia causes osteoporosis in Rats

All rats were given dDAVP to control urine output for 3 months
The hyponatremic group received a liquid diet.

Serum sodium 141 mEq/L

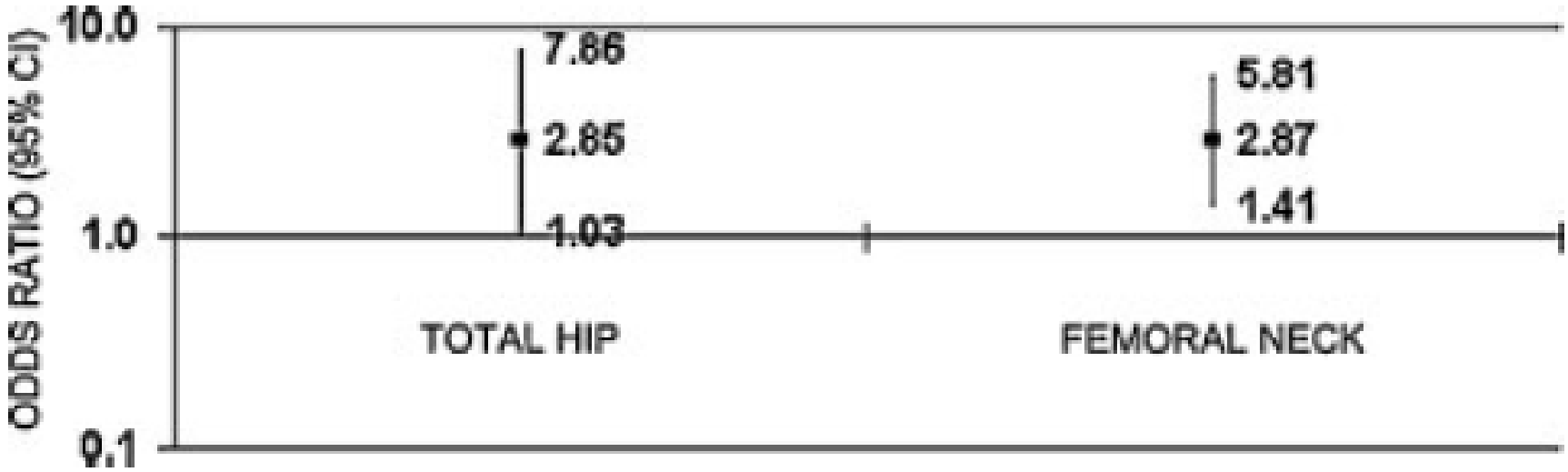
Serum sodium 110 mEq/L



Both cortical and trabecular bone are thinned

Verbalis et al. 2010 J Clin Bone Res

Odds of osteoporosis in hyponatremic individuals (serum Na 133 mEq/L) vs. normal in NHANESIII data

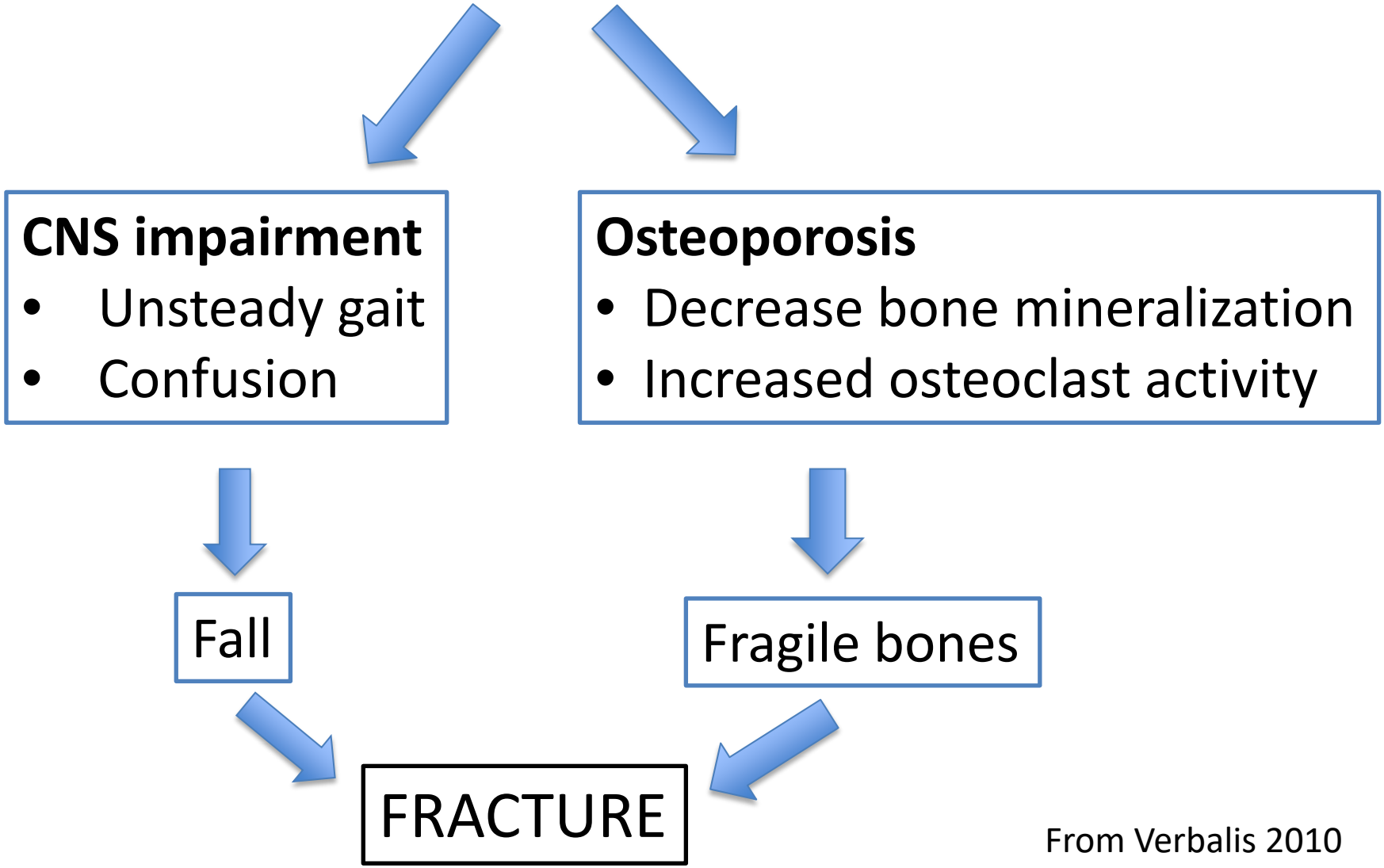


P =0.043

P=0.003

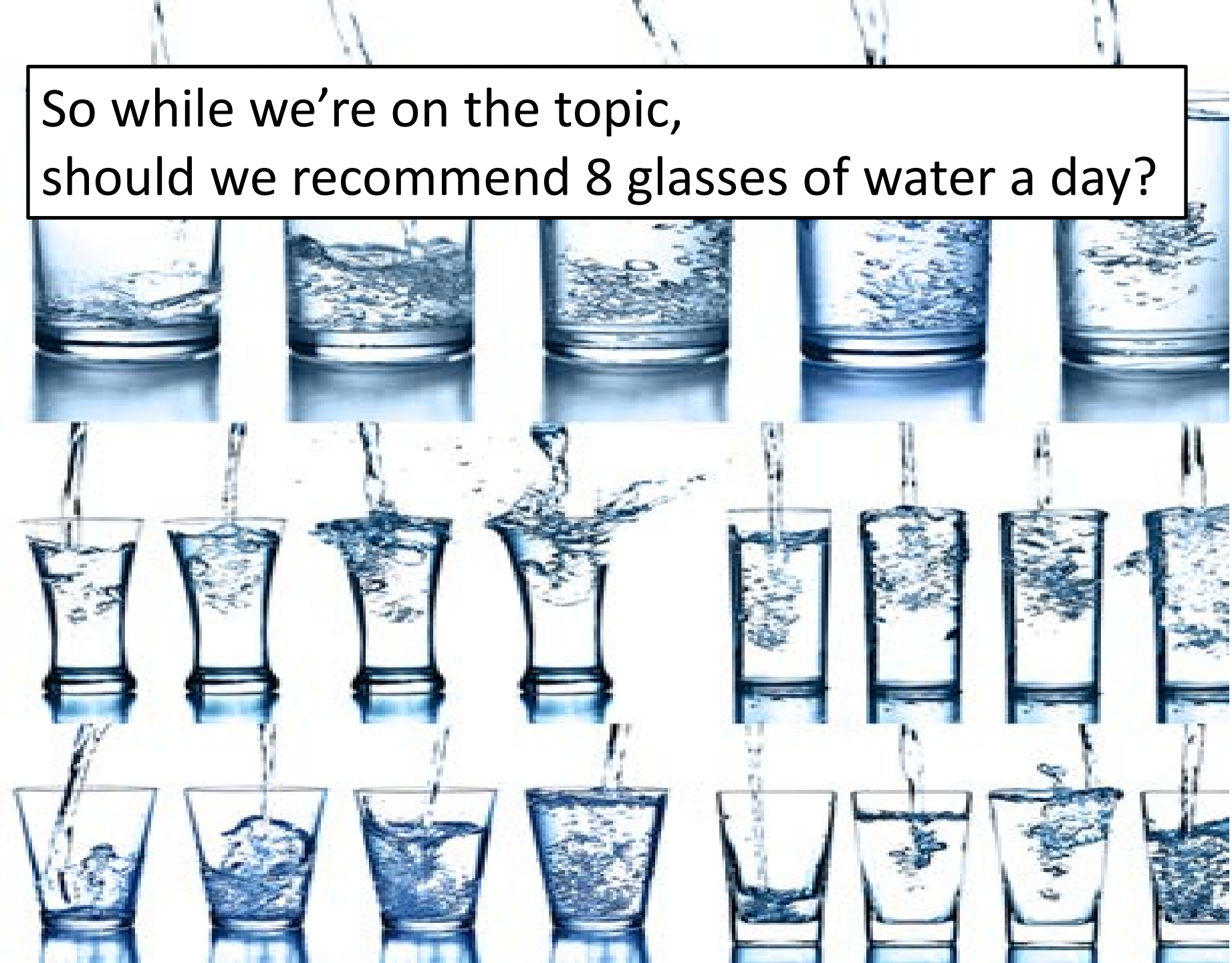
Verbalis et al. 2010 J Clin Bone Res

Chronic hyponatremia (Na <135 mEq/L)



From Verbalis 2010

So while we're on the topic,
should we recommend 8 glasses of water a day?

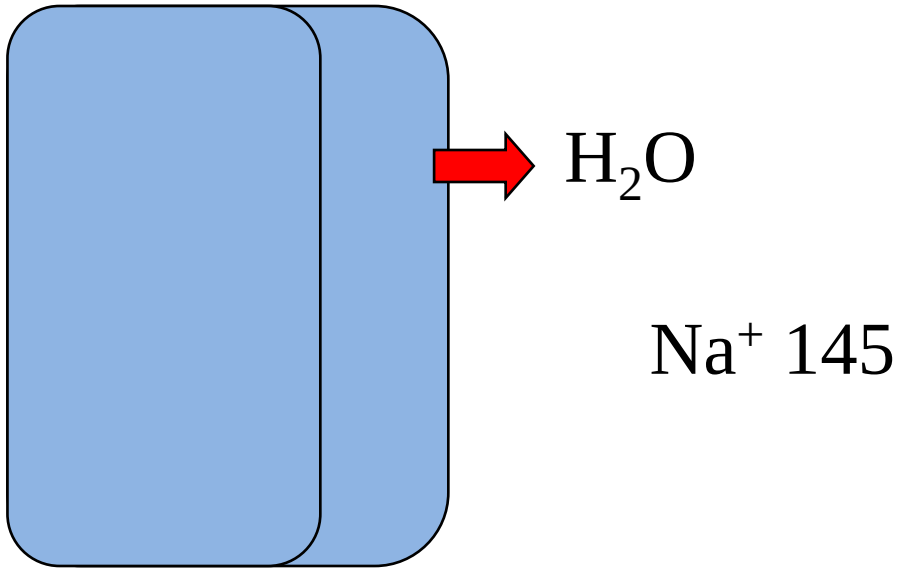


Case 2

An 82 year old man is referred for concern that he may have diabetes insipidus. He told his primary care physician that he needs to urinate every 1-2 hours. He is up most of the night urinating. He reports that he is thirsty.

Recent laboratory studies show a serum sodium of 146 mEq/L.

Hypernatremia



Symptoms are primarily neurologic:
lethargy→ weakness→irritability→seizures→coma→death

Hypernatremia

- Sodium gain

or

- Water loss*

Extrarenal loss

Renal losses

n.b. salt intake nearly always leads to thirst and then patients have normal serum sodium
(if patient cannot excrete NaCl and water load, may develop edema and HTN)

* MUCH MORE COMMON

polyuria

- Defined as >3 liters/day
- May reflect a water diuresis or a solute diure
- May be appropriate or inappropriate
- Usual intake is ≈ 600 mOsm/day
- Urine volume X Uosm ≈ total urine solute
  - If total solute is much higher, this is a solute diuresis (ie. Glycosuria in diabetes mellitus or sodium and chloride loss after excess IVF
  - If urine is dilute, this is a water diuresis.

Hypernatremia is relatively uncommon-typically multifactorial some risk factors:

- >80 years
- Dementia
- Infection (increased insensible losses)
- Hypodypsia
- Limited access to fluids
- Decreased ability to maximally concentrate the urine

Another patient with polyuria (case 3)

- A 19 year old boy is brought in for evaluation by his father. He has completed his first year of college but 2nd semester, depression and anxiety limited his performance and he opted to come home.

Case 3

Serum sodium 134 mEq/L
Potassium 3.8 mEq/L
Bicarbonate 23 mEq/L
BUN 16 mg/dL
Creatinine 0.9 mg/dL

How should we evaluate this patient?

Case 4

- A 64 year old woman presents for routine care. She has had hypertension for more than 10 years and after trial of several agents, she has done well on lisinopril 20 mg daily.
- Her blood pressure is 134/82 mmHg and her heart rate is 84 beats per minute. Her BMI is 29 kg/m^2

Case 4

Serum sodium 143 mEq/L
Potassium 5.4 mEq/L (normal 3.4-5.2mEq/L)
Bicarbonate 27 mEq/L
BUN 26 mg/dL
Creatinine 0.9 mg/dL
(estimated GFR = 58.81 mL/min/1.73m^2)

Hyperkalemia

- Pseudohyperkalemia
- Cellular redistribution
- Too much K^+ intake

  ****there must also be impaired renal excretion!**
- Too little renal excretion

Potassium content of foods

39.1 mg=1mmol or 1mEq

- Banana's 1 mEq/inch
- OJ has 12 mEq/cup
- Nu salt™

  530 mg/serving (1/6 tsp) =13 mEq
- Tomato sauce 811 mg/1cup= 20mEq
- 1 cup of raisins = 28 mEq
- baked potato = 22 mEq

Excellent resource: www.kidney.org

Factors that can block renin angiotensin aldosterone axis

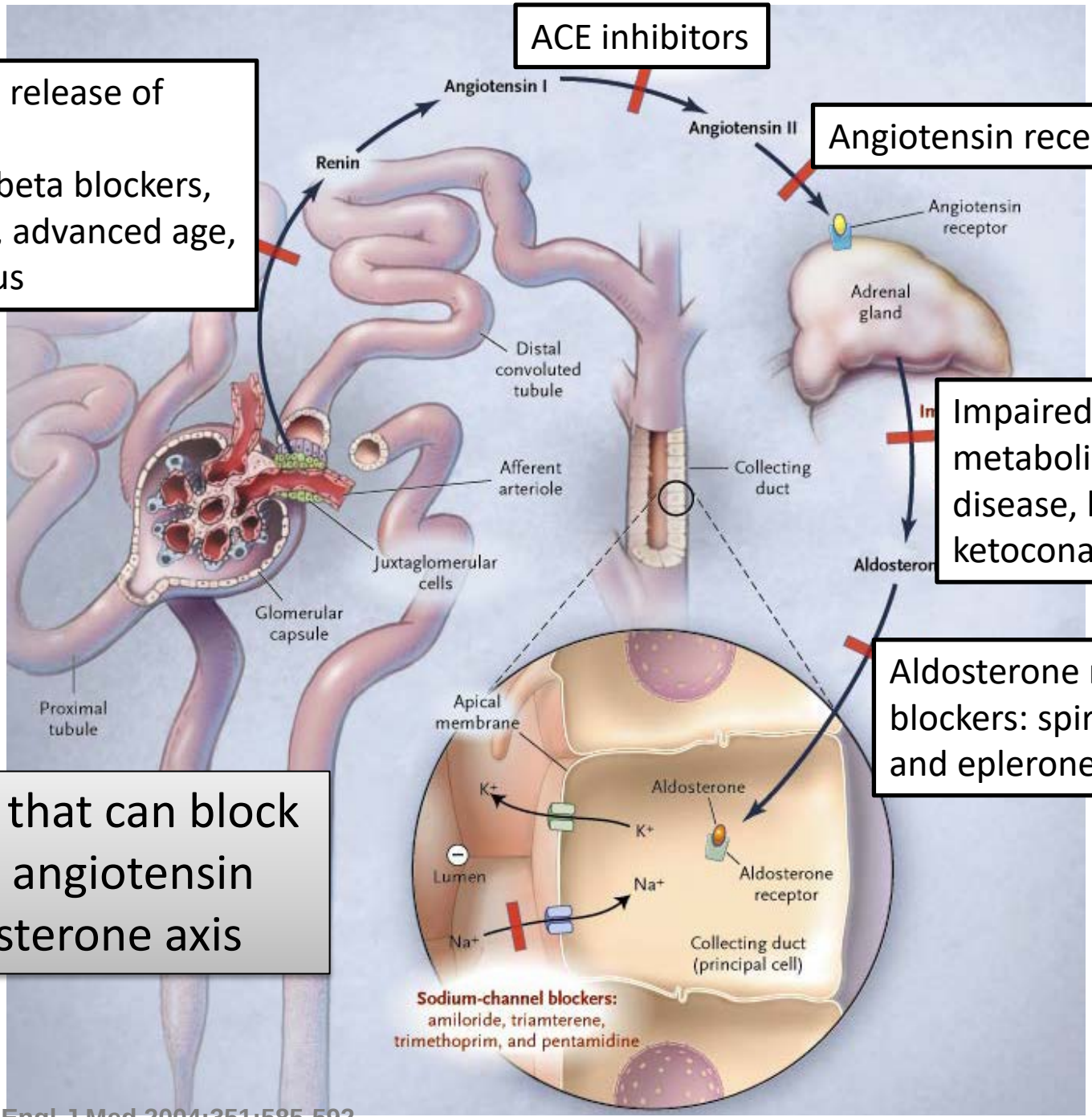
ACE inhibitors

Angiotensin receptor blockers

Impaired release of renin:
NSAIDS, beta blockers, diabetes, advanced age, tacrolimus

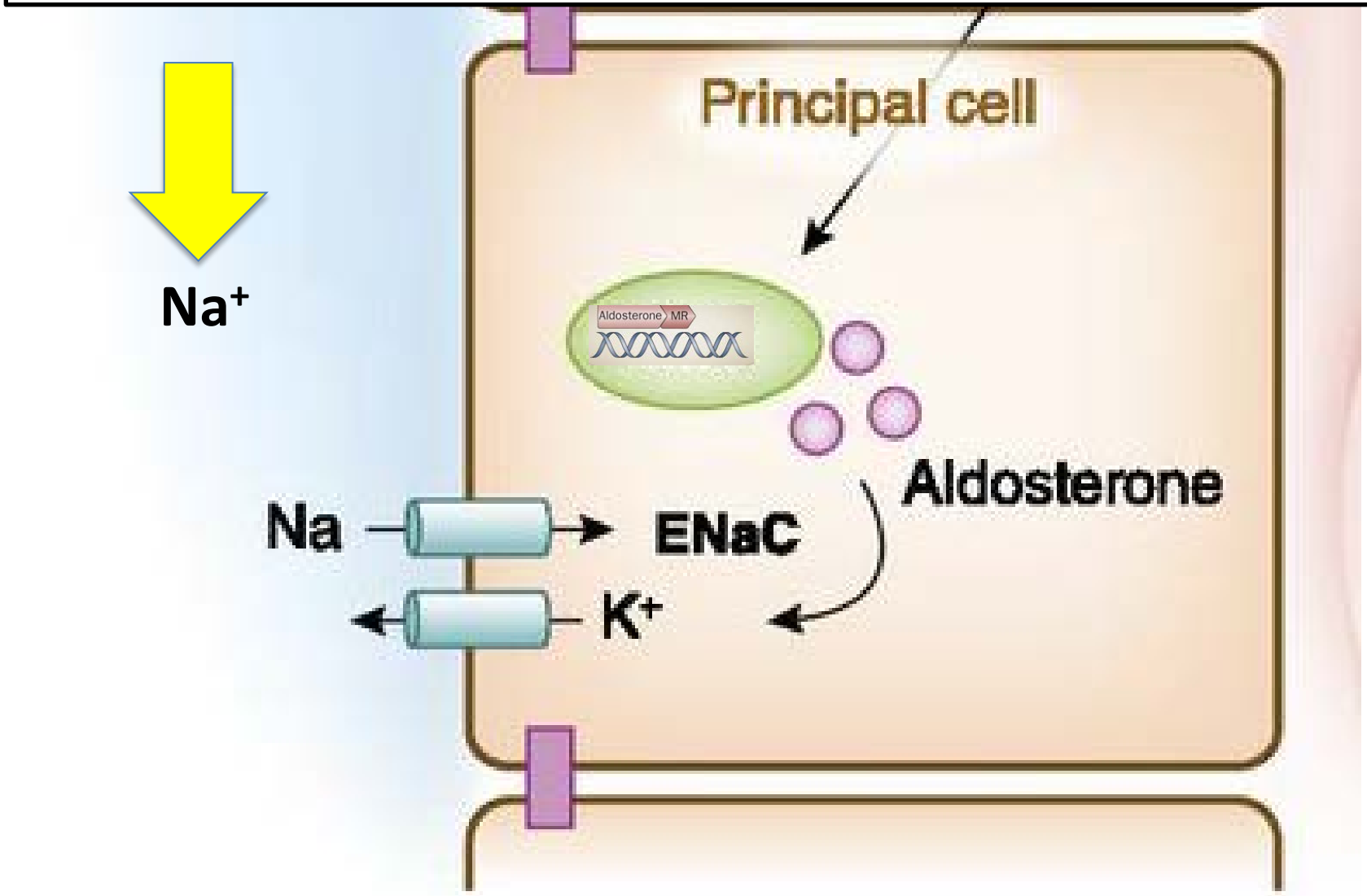
Impaired aldosterone metabolism: adrenal disease, heparin, ketoconazole

Aldosterone receptor blockers: spironolactone and eplerone



Palmer, B. F. N Engl J Med 2004;351:585-592

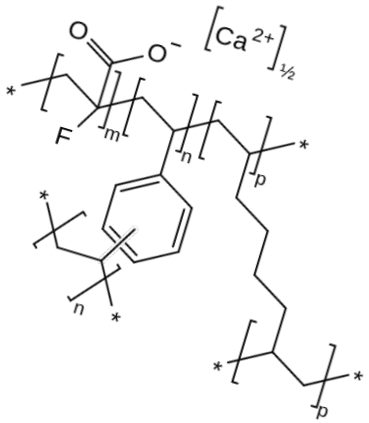
Excretion of potassium is achieved by “distal delivery of sodium” and aldosterone



Ankita Roy et al. CJASN 2015;10:305-324

Treatment for Hyperkalemia

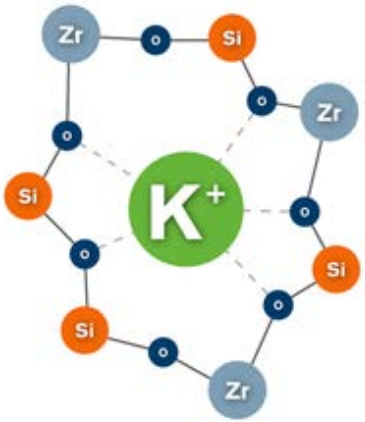
1. Ensure adequate fluid intake
2. Low potassium diet
3. Medication changes
4. K^+ wasting Diuretics
5. resins-polystyrene and newer agents



Veltessa- FDA approved for CHRONIC not acute HYPERKALEMIA

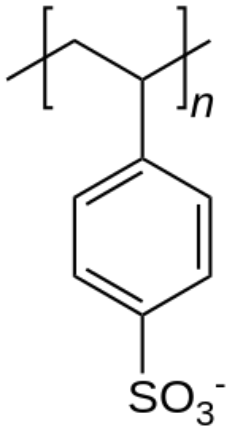
hypomagnesemia and constipation

Exchanges calcium for K+ in gut



Zs9 traps K^+
but not Mg^{++} or Ca^{++}

STILL NOT FDA approved



Polystyrene sulfonate

Efficacy never rigorously studied

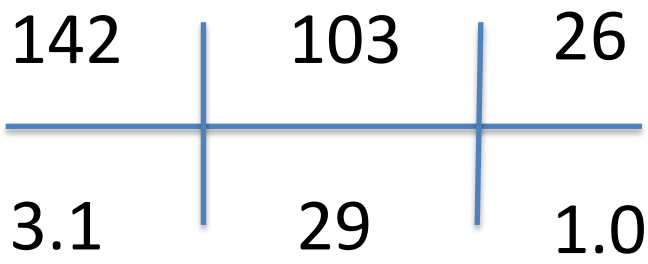
Warning! Colonic necrosis FDA now requiring manufacture to study drug interactions

Case 5

A 51 year old man is seen for hypertension. He follows a low sodium diet

Medications: Lisinopril 40 mg daily, Potassium chloride 20 mEq daily, spironolactone 25 mg daily. Metoprolol 100 mg daily.

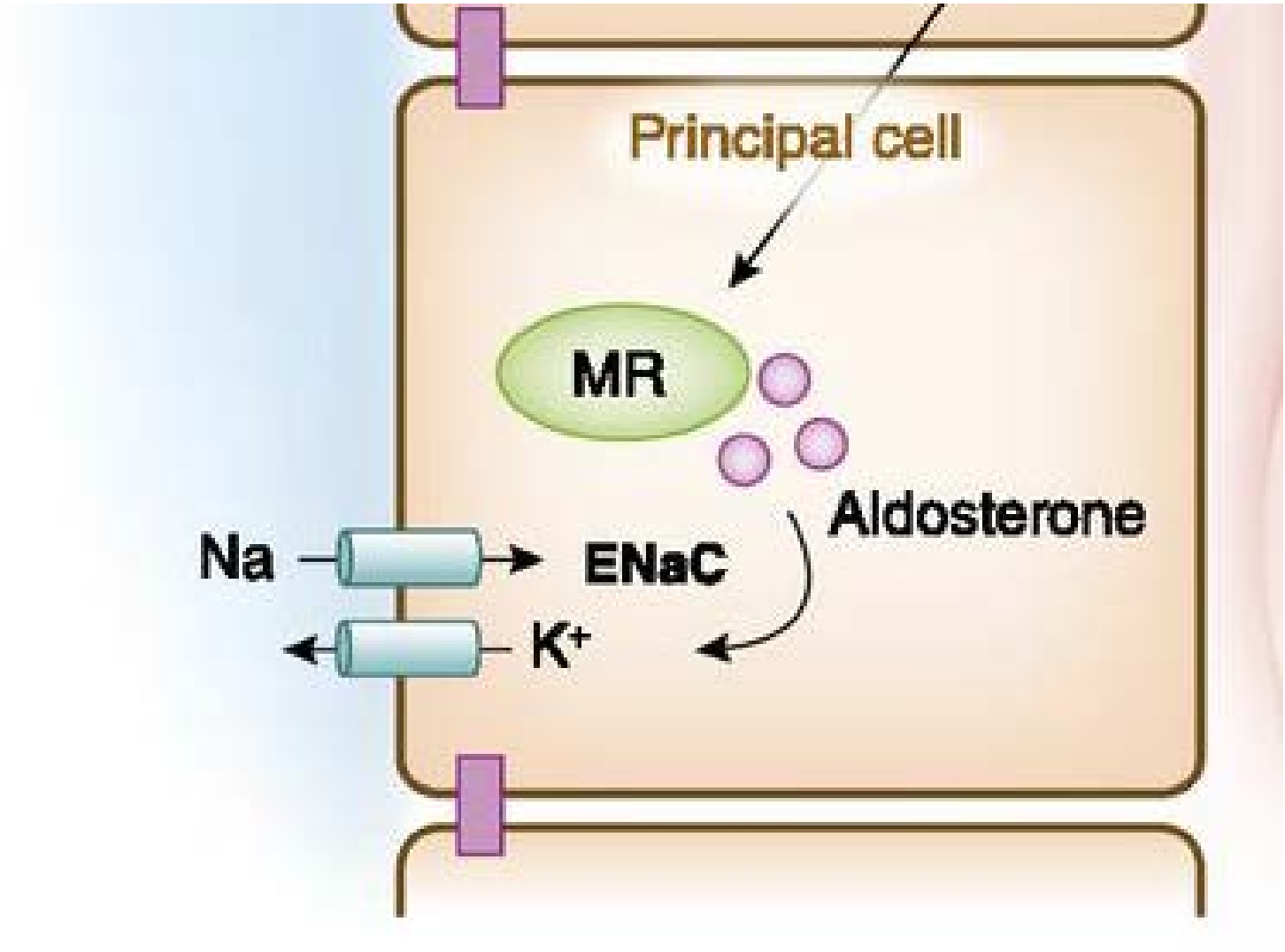
Recent laboratory data shows the following:



Hypokalemia

- Inadequate intake or K^+ free IV fluids
- Redistribution of potassium into cells
  (↑extracellular pH, insulin,
  ß adrenergic stimulation)
- Increased losses
  - sweat
  - gastrointestinal
  - renal

The presence of HYPERtension and HYPOkalemia suggests an issue with the principal cell



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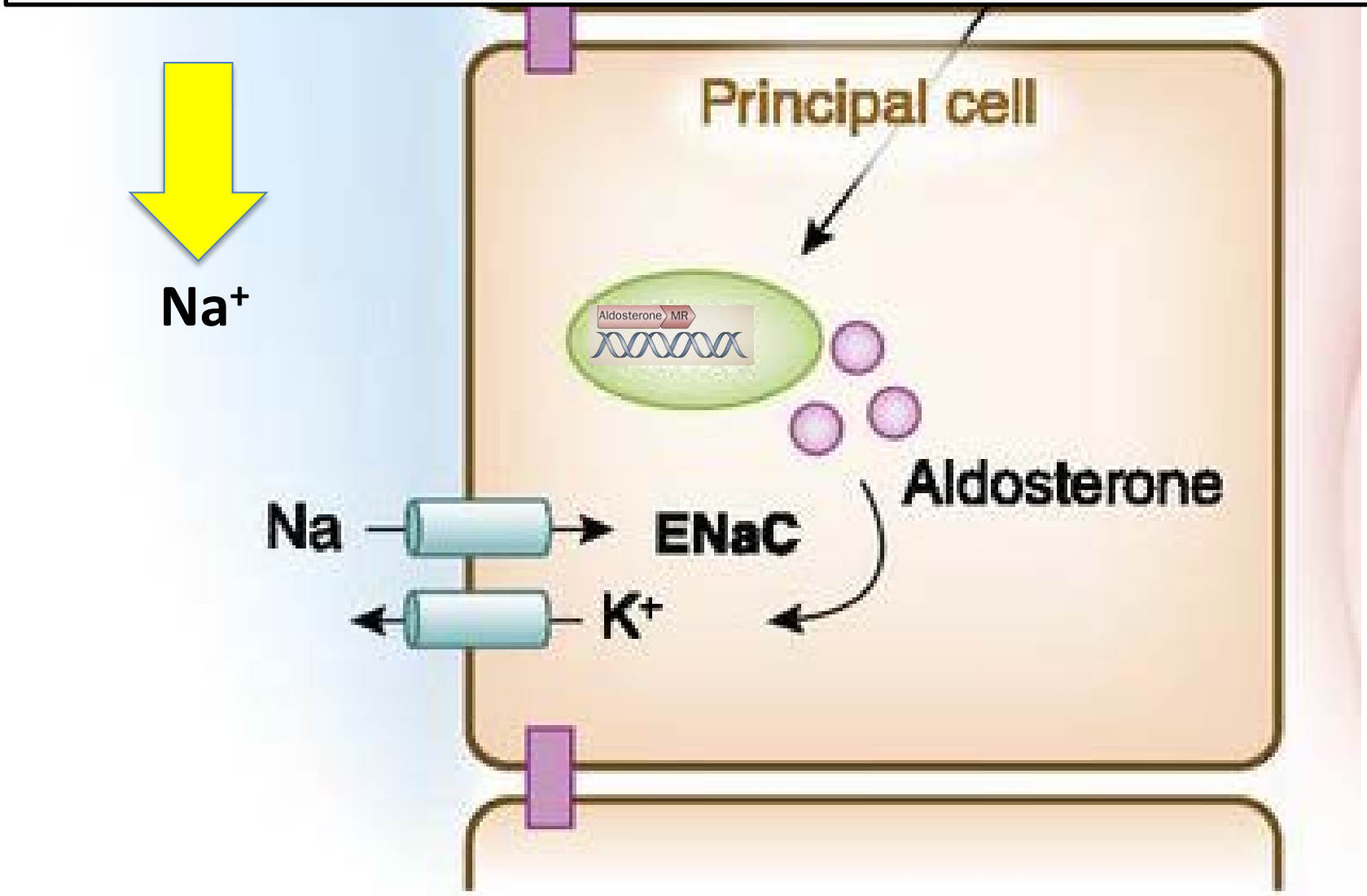
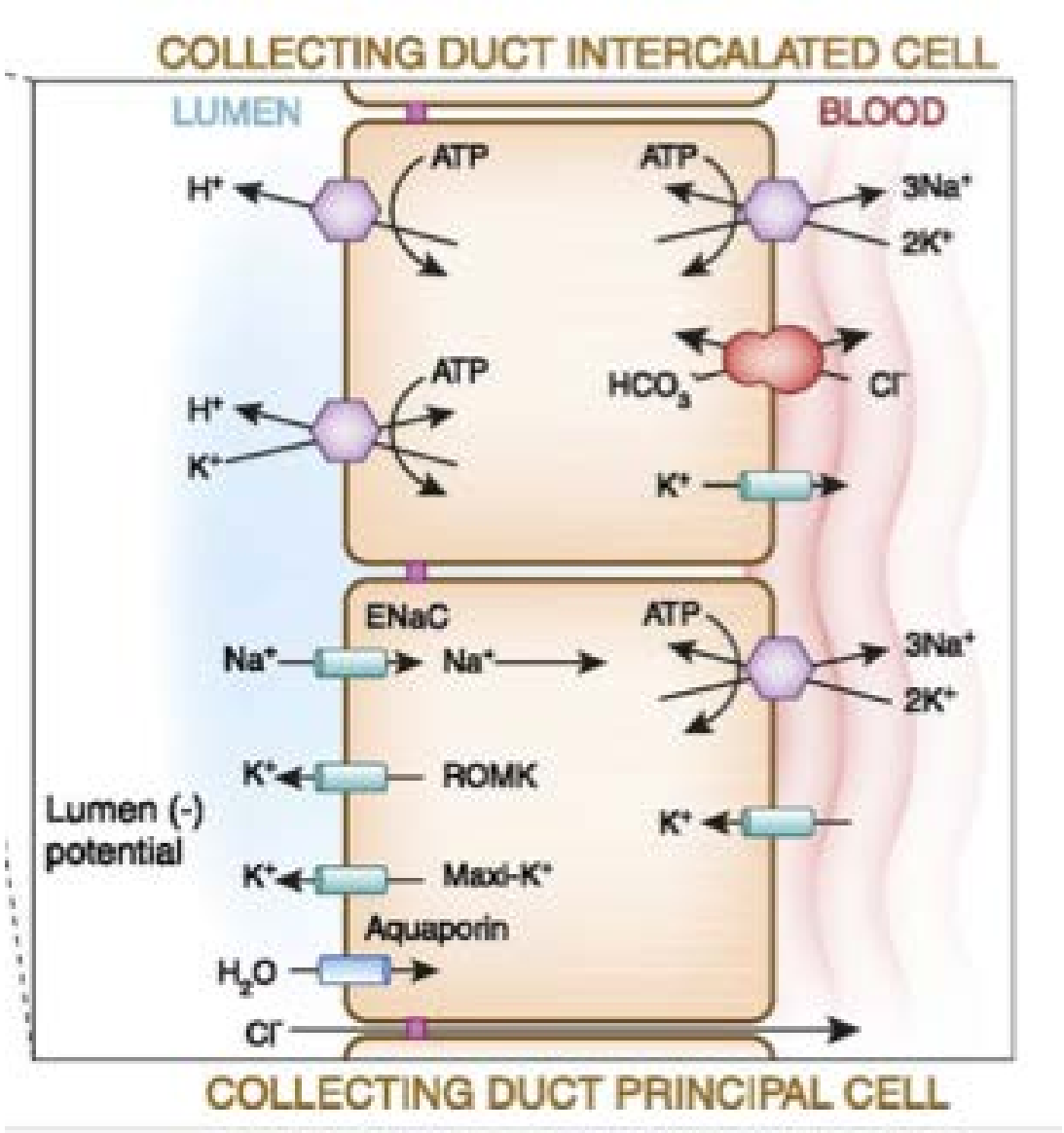
Excretion of potassium is achieved by “distal delivery of sodium” and aldosterone



Ankita Roy et al. CJASN 2015;10:305-324

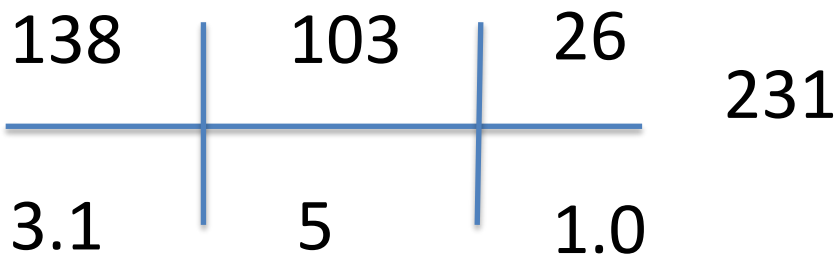
When Principal cells are active, H^+ is secreted
by neighboring Intercalated cell, this can result in a metabolic alkalosis



Case 6

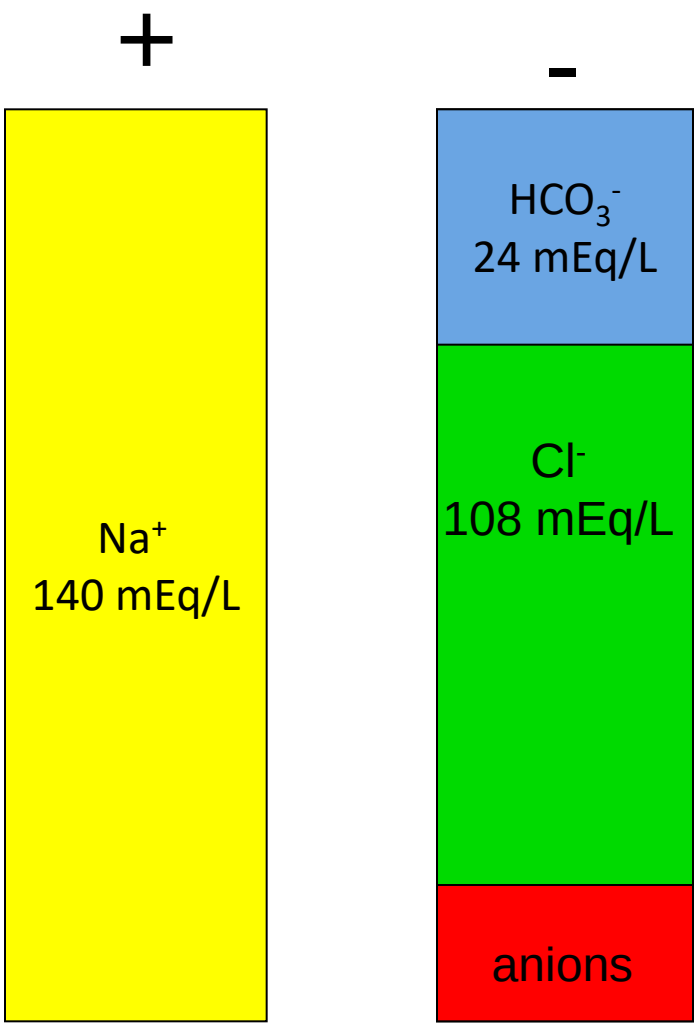
- 35 year old woman with T2 DM and history of gestational DM presents with 3 days of crampy abdominal pain, nausea and nonbloody diarrhea
- Meds: canagliflozin 300 mg daily, metformin 2000 mg qHS, insulin glargine 25 U and liraglutide 1.8 mg daily

Recent laboratory data shows the following:



Adapted from Ohri P Endocrine Society 2016 meeting SUN-752

Anion gap = $Na^+ - (Cl^- + HCO3^-)$

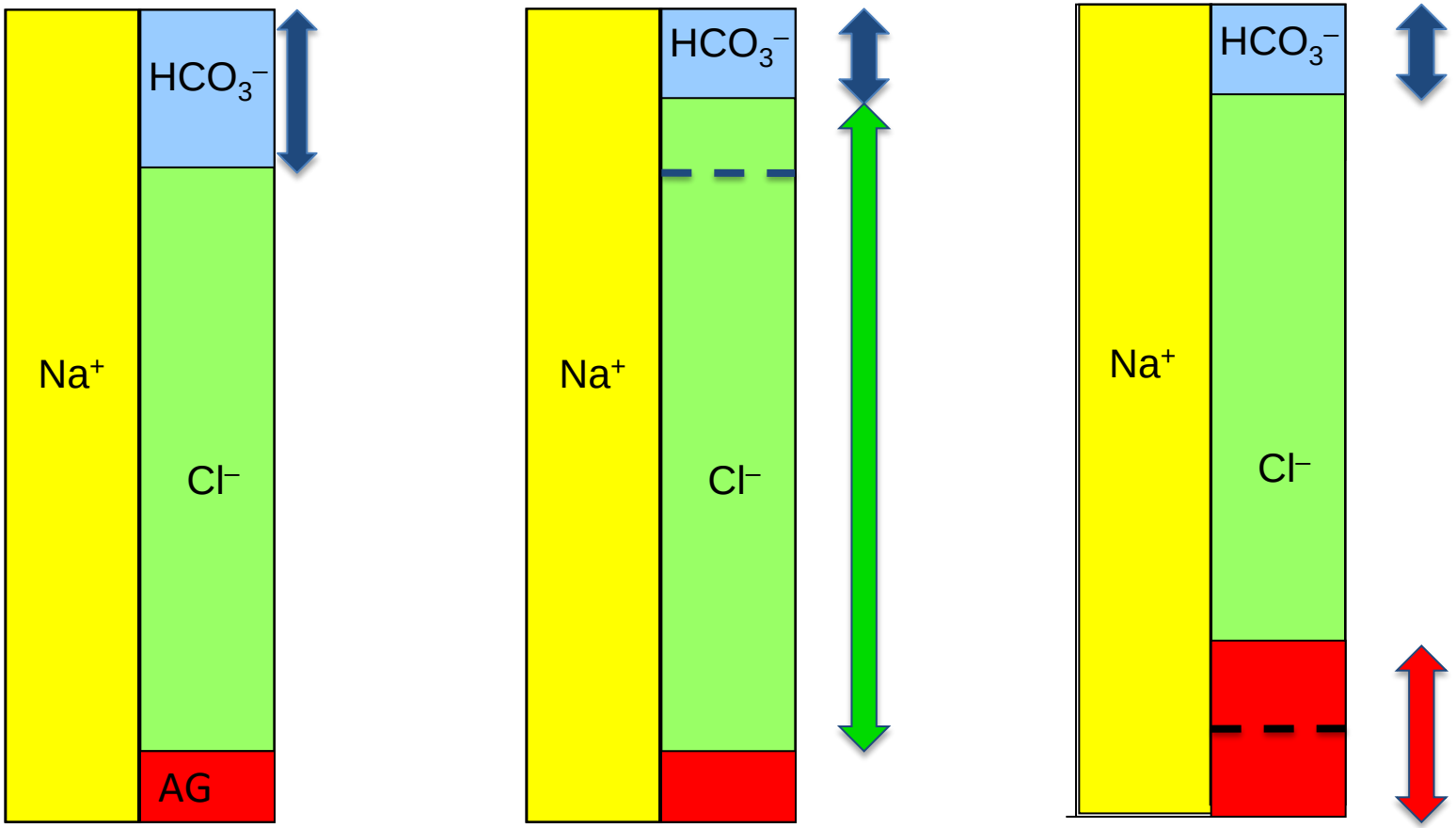


Anion gap = $Na^+ - (Cl^- + HCO3^-)$
Anion gap = 140 – (108 + 24)
= 8

These "unmeasured anions" (normally ≈ 10 mEq/L) are generally accounted for by:

- Negatively charged proteins (primarily albumin)
- sulphate
- phosphate
- organic anions

Classify by anion gap



Normal

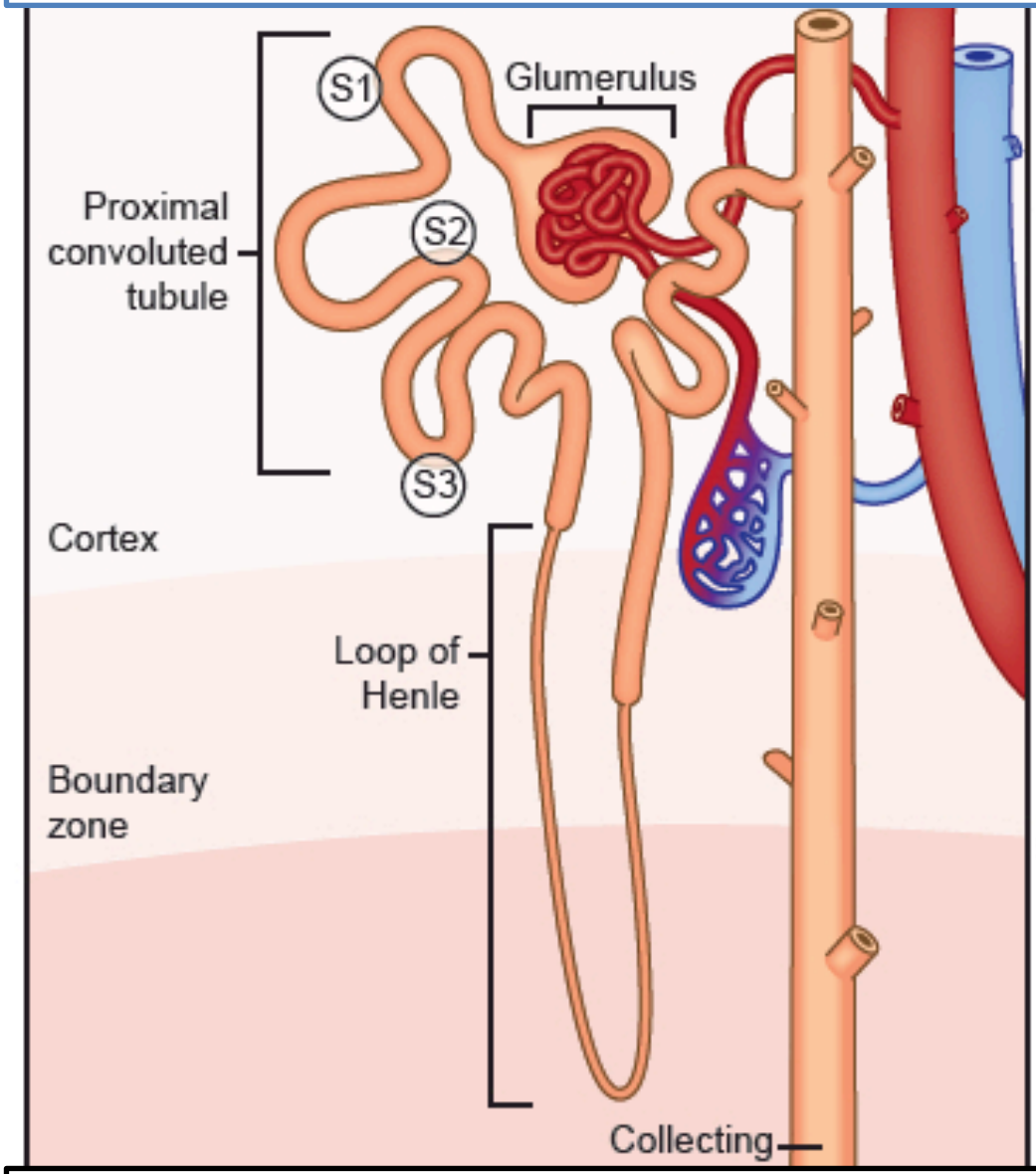
Non gap (or normal gap or “hyperchloremic”) Metabolic Acidosis

Anion Gap Metabolic Acidosis

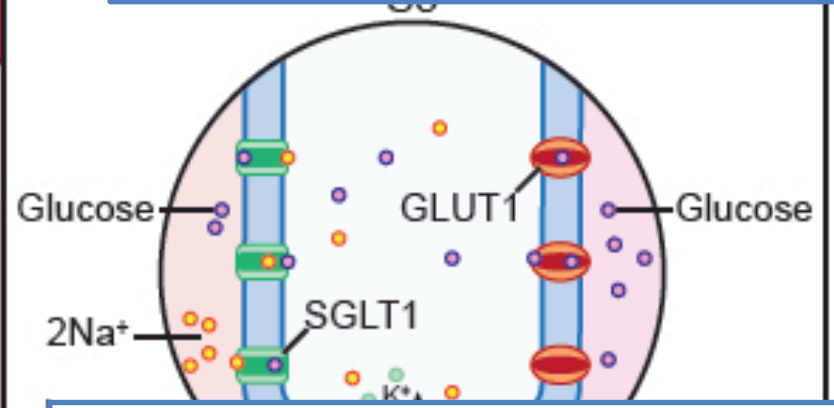
Anion Gap acidosis→

1. Ketoacidosis (starvation or diabetic)
2. Lactic Acidosis
3. Ingestions of toxins
   - Methanol (windshield wiper fluid)
   - Ethylene glycol (antifreeze)
   - Salicylates (aspirin)
4. Severely reduced renal function

Filtered glucose is absorbed in the proximal tubules with 2 types of sodium glucose transporters (SGLT). Novel Rx for DM: SGLT2 inhibitors



Low affinity high capacity transporter
Early in proximal tubule

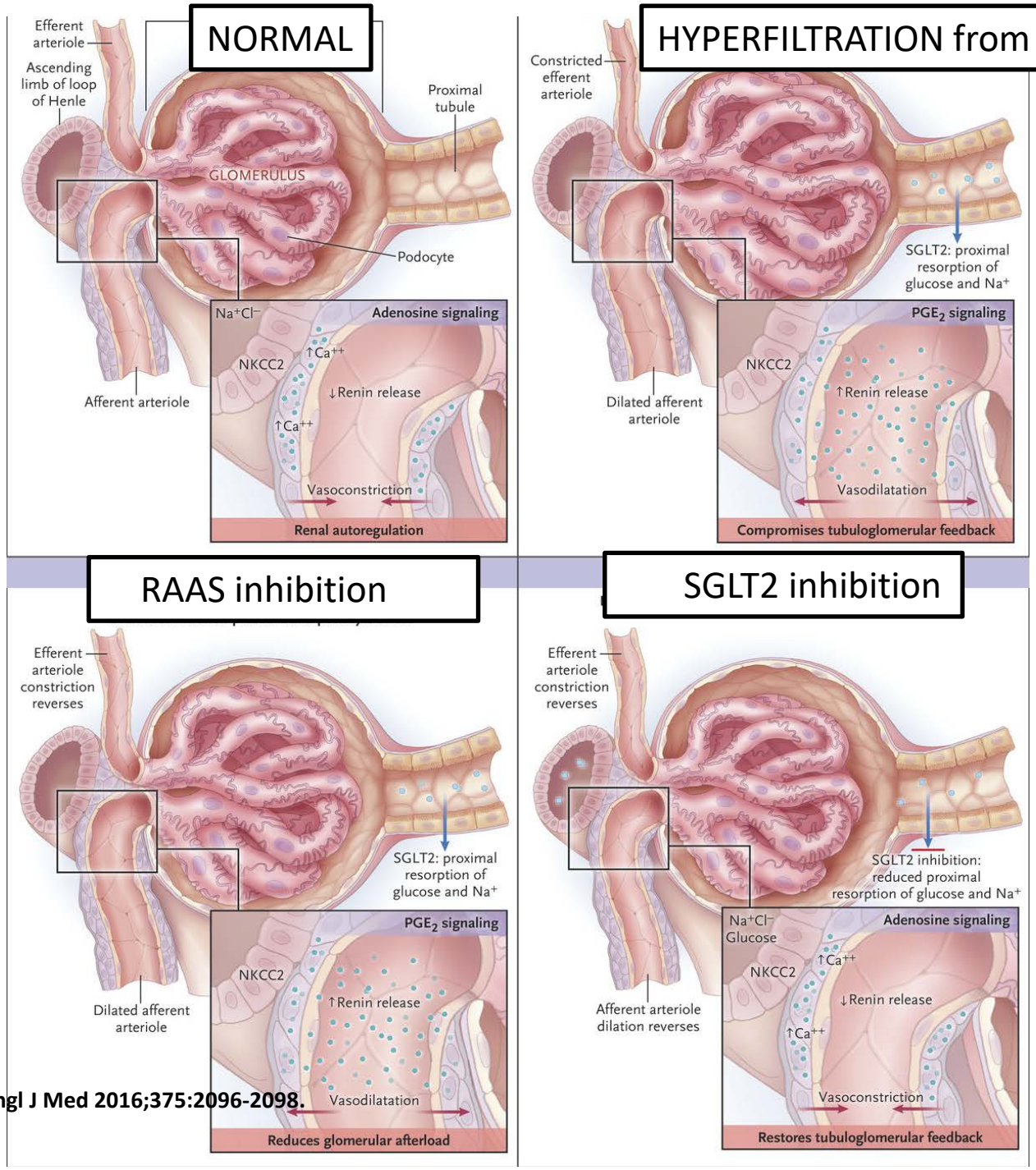


High affinity low capacity transporters
Late in the proximal tubule

http://mutagenetix.utsouthwestern.edu/phenotypic/phenotypic_rec.cfm?pk=598

SGLT2 inhibitors

- FDA approved for treatment of type 2 DM only
- 3 available and more in development
- Reduce A1c by 0.5 to 0.7%
- Also leads to a small decrease in blood pressure (perhaps secondary to sodium and water losses associated) and 2-3 kg weight loss
- Adverse effects: UTI, AKI, hypotension, bone fracture, diabetic ketoacidosis



Proximal Na^+ and glucose reabsorption

- Decreased delivery to macula densa and ↑renin
- ↑glomerular P
- Podocyte stress

Less efferent arteriole constriction

Theoretically reverses changes detailed above

Anders H et al. N Engl J Med 2016;375:2096-2098.

Case 7

- A 58 year old man is seen for follow-up. He has a history of dyspepsia and hypertension. He has been taking omeprazole for a long time and notes that it is the only thing that really works.
- Medications: omeprazole bid, chlorthalidone 25 mg daily

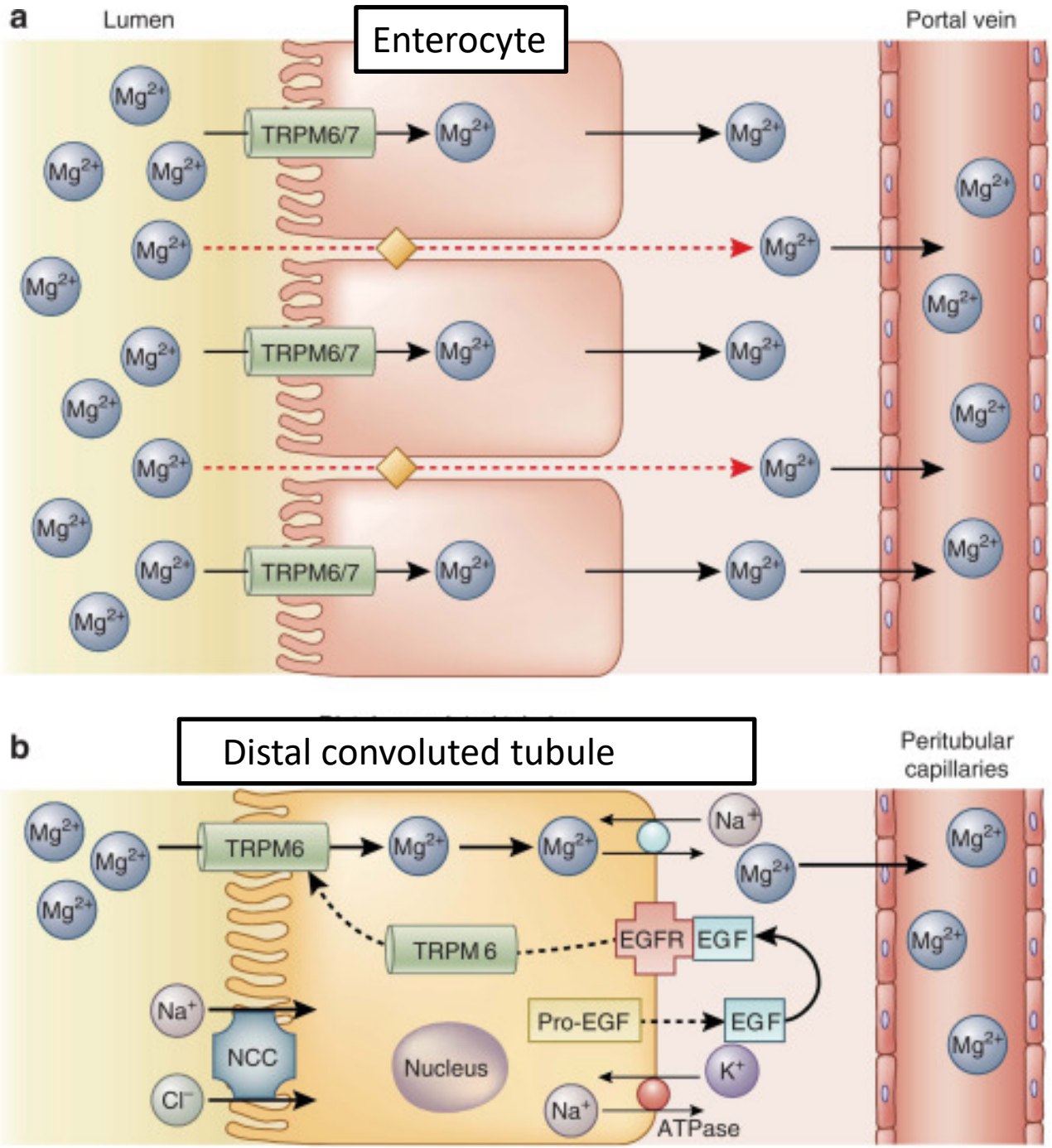
Case 7 continued

Serum sodium 141 mEq/L
Potassium 3.3 mEq/L
Bicarbonate 29 mEq/L
BUN 26 mg/dL
Creatinine 0.9 mg/dL

Magnesium 1.2 (1.6-2.6 mEq/L)

Hypomagnesemia

- Decreased intake (starvation, alcoholism)
- Renal losses
  - ✧Thiazides
  - ✧Glycosuria
  - ✧Often associated with hypokalemia and hypocalcemia
- GI losses
  - ✧Vomiting, NG suction
  - ✧Chronic PPI ingestion



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Treatment for hypomagnesemia

- Discontinue medications that contribute
- Oral replacement*
  - Diet rich in green vegetables like spinach
  - Sustained release formulations of magnesium chloride or magnesium lactate 6-8 tabs daily in divided doses
  - Magnesium oxide 800-1600 mg daily in divided doses (commonly causes diarrhea)
- Treat concomitant hypokalemia and hypocalcemia

*use less with renal impairment

Also Beware-

Original Investigation

Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

Benjamin Lazarus, MBBS; Yuan Chen, MS; Francis P. Wilson, MD, MS; Yingying Sang, MS; Alex R. Chang, MD, MS; Josef Coresh, MD, PhD; Morgan E. Grams, MD, PhD

IMPORTANCE Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide and have been linked to acute interstitial nephritis. Less is known about the association between PPI use and chronic kidney disease (CKD).

OBJECTIVE To quantify the association between PPI use and incident CKD in a population-based cohort.

10,482 participants in the Atherosclerosis Risk in Communities Study followed for 13 years-PPI users had a higher risk of CKD compared to nonusers (1.45 Hazard Ratio)