Clinical Aspects of Hyponatremia

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Trivia:
What specialty is responsible for creation of  UpToDate® ?

A. Gastroenterology
B. Internal Medicine
C. Cardiology
D. Nephrology
E. Steve Jobs

Who created UpToDate®?

- **Dr. Burton "Bud" Rose**, a brilliant **nephrologist @**Harvard

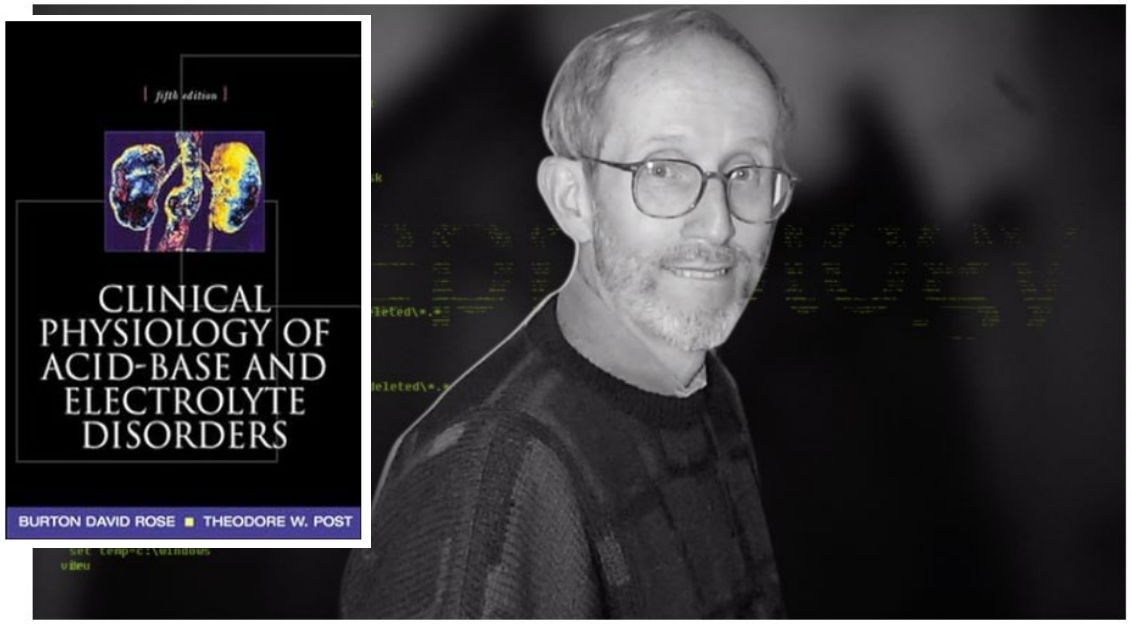
- UpToDate first focused on nephrology, then gradually opened the lens to include all of medicine.

- Rose created the **first version** of **UpToDate**, in his house in **1992**.
  - It was released on floppy disks

FIRST OPINION

Remembering UpToDate creator Burton (Bud) Rose, the 'Steve Jobs of medicine'

By Martin Pollak, Mark Zeidel, and Theodore Steinman April 25, 2020 Reprints



Burton "Bud" Rose started UpToDate in 1992

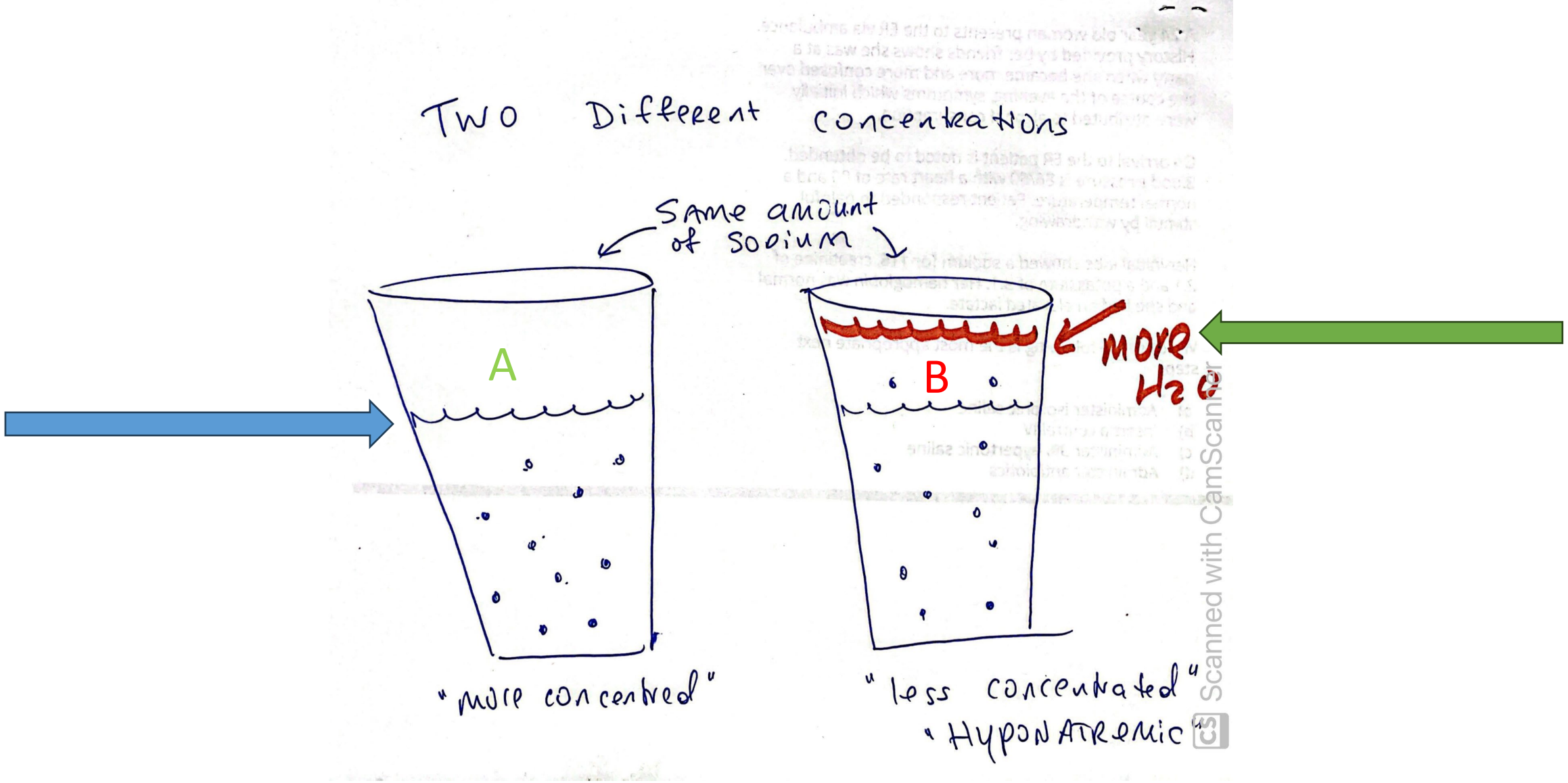
COURTESY WOLTERS KLUWER

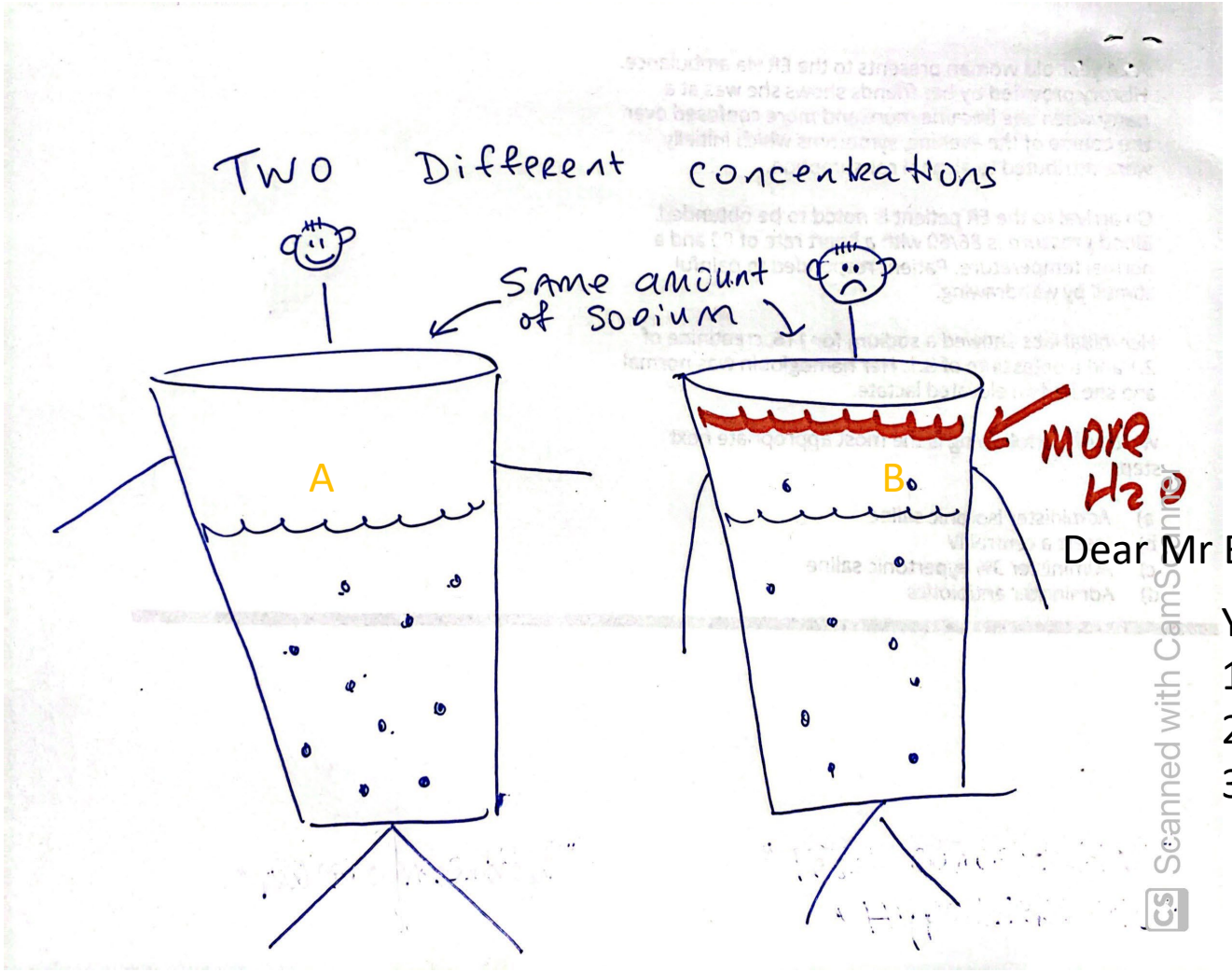
Objectives

- ❑Learn how hyponatremia is a problem of sodium concentration
- ❑Learn the steps through which ADH leads to hyponatremia
- ❑Understand the importance of osmotic gradient required for water reabsorption in the kidney
- ❑Learn that there are osmotic and nonosmotic stimuli for ADH release
- ❑Understand the adaptation process in the brain for hyponatremia
- ❑Learn about the major clinical categories of hyponatremia and common clinical scenarios within each
- ❑Understand the major treatment approaches to each of the three clinical categories
- ❑Review clinical questions/cases

- What does it mean to have hyponatremia?
  - Does it mean you have “low sodium”?
  - Does it mean you have “too much water”?
  - Is it both a problem of too much water *and* too little salt?
- Understanding what it means helps treat the problem …

Basics of sodium concentration



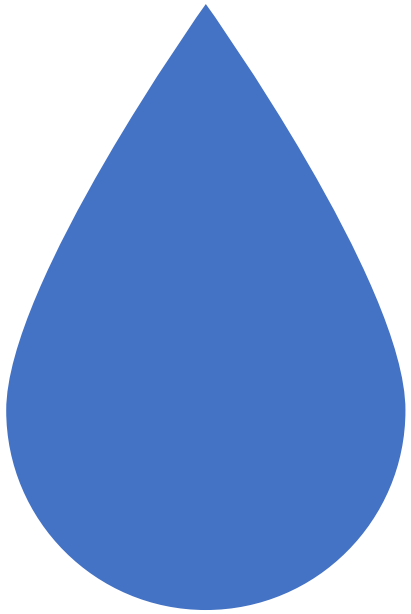


Dear Mr B- Your sodium isn't low,

You have more H2O:

1. Water intake is too large
2. Water excretion is too low
3. Combination of both

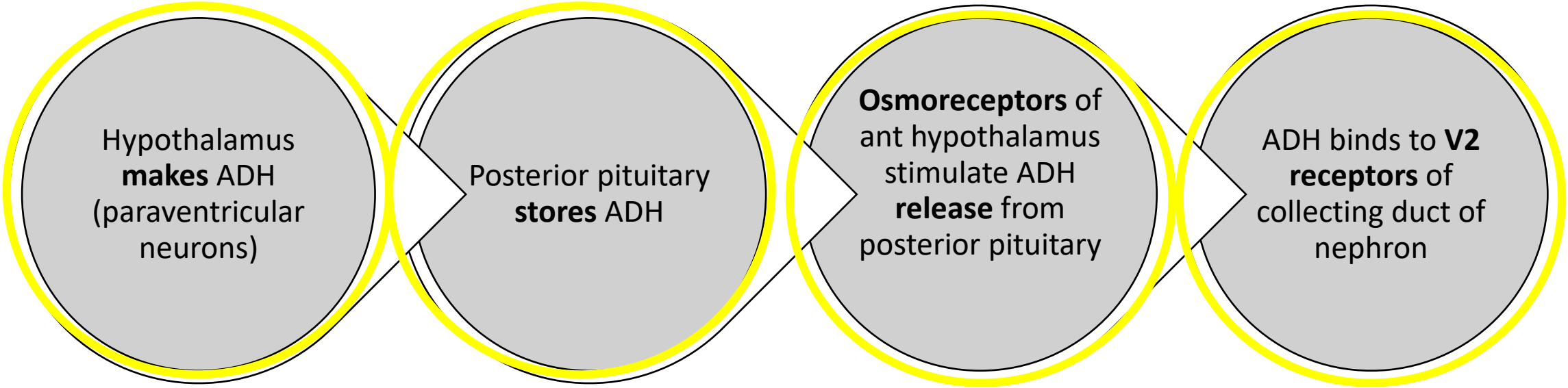
Disorders of sodium concentration reflect disorders of water imbalance



What retains water?

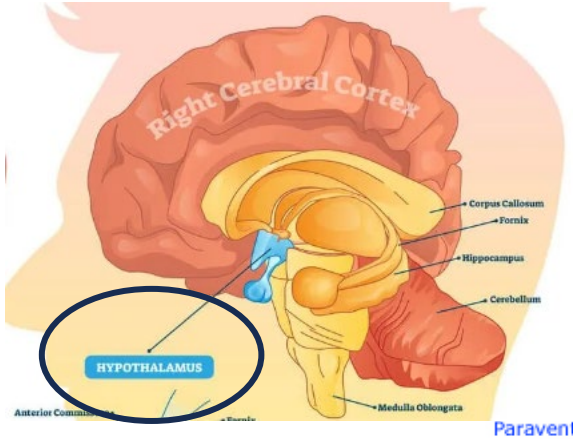
- Anti-Diuretic Hormone (ADH)

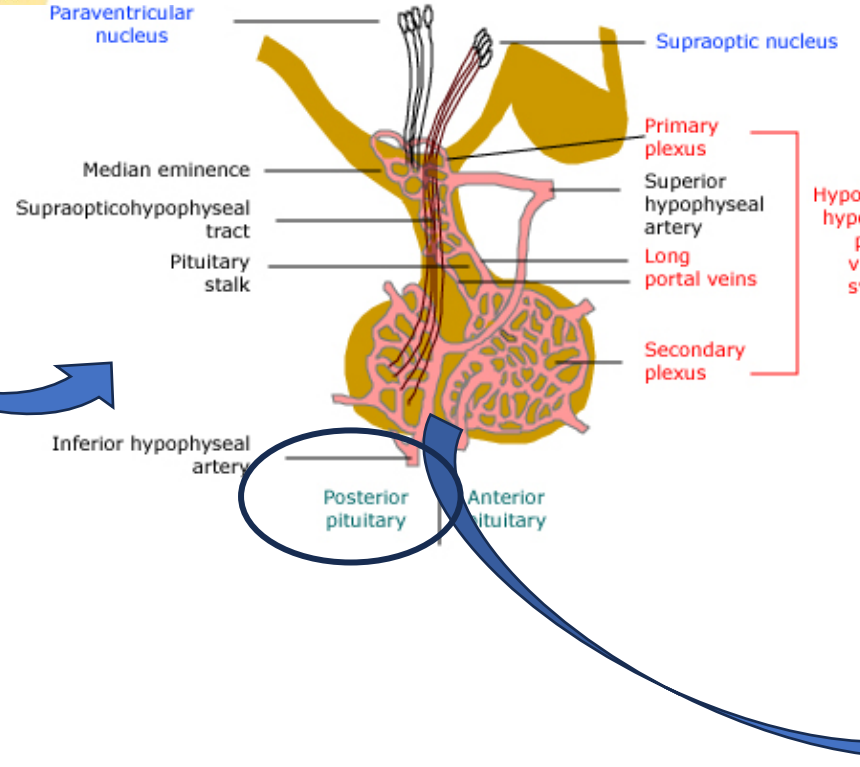
Review of steps of ADH production and release

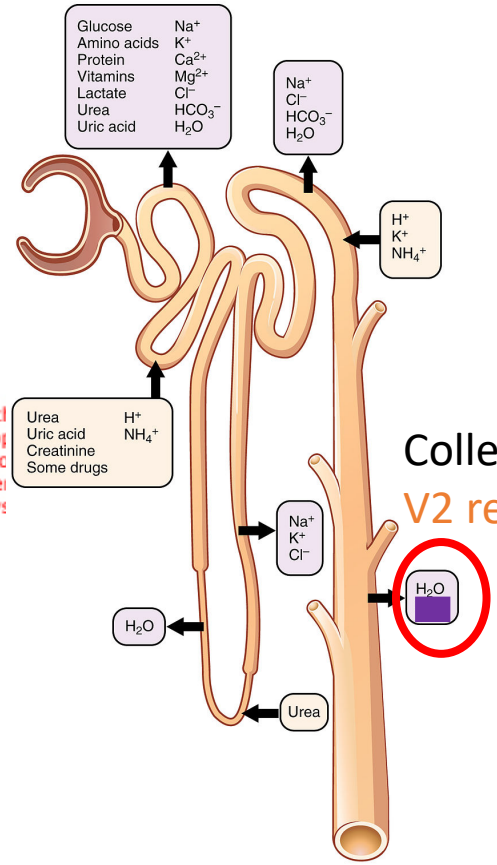


https://youtu.be/MR8BABoFTP8

Koshy et al In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-





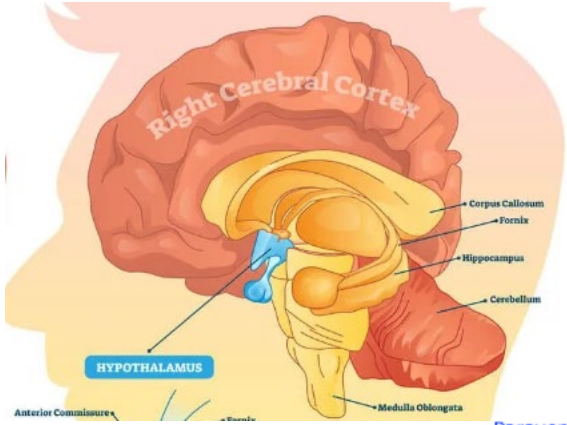


Collecting tubule

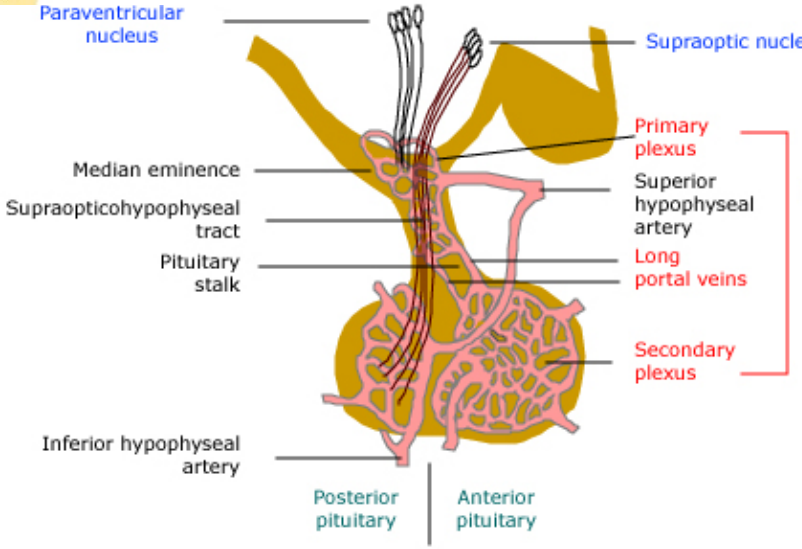
V2 receptors

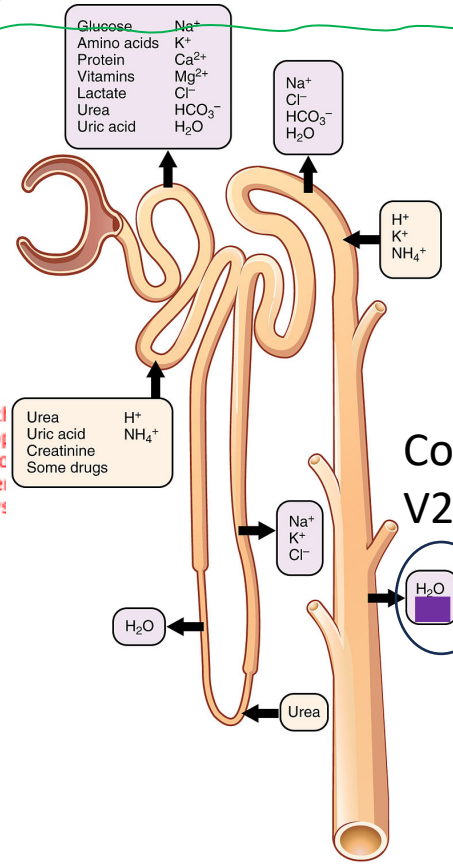
Water reabsorption via AQP channels down the **gradient**

https://commons.wikimedia.org/wiki/File:2618_Nephron_Secretion_Reabsorption.jpg#/media/File:2618_Nephron_Secretion_Reabsorption.jpg



* Because water is removed from the urine, urine is more concentrated. Thus, *in presence of ADH* urine is concentrated, urine osm >> 300 (600-1200). W/out ADH urine is dilute Urine osm < 100





Collecting tubule
V2 receptors

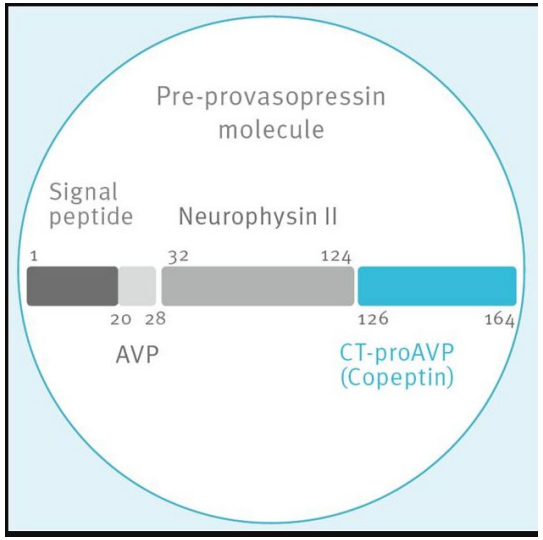
Water reabsorption via AQP channels down the gradient

Without increased interstitial gradient even in presence of ADH water cannot be adequately reabsorbed (ATN/AKI, Loop diuretic)

https://commons.wikimedia.org/wiki/File:2618_Nephron_Secretion_Reabsorption.jpg#/media/File:2618_Nephron_Secretion_Reabsorption.jpg

ADH:

- Made in hypothalamus as *pre-pro-AVP (*Arginine vasopressin):
  - Cleaved into:
    1. **Vasopressin (ADH)**
       - Cannot measure
    2. **Neurophysin II**
       - Cannot measure
    3. **Copeptin**
       - (serves as surrogate for ADH)
         - ❖Measurable (in research)



** b/c ADH Is not easily measured we rely on **urine osmolality to infer its presence**, if urine osm is > 100-200 usually that implies ADH is being produced. **Degree of** and cause for ADH production is difficult to ascertain*

ADH:

- **Released** (or release is shut off)

1) OSMOTIC ***or***

2) NON-OSMOTIC stimuli

Osmotic stimulus for ADH release

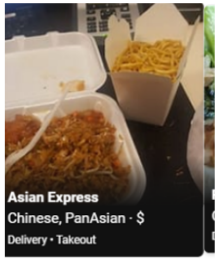
Remember: major component of plasma osmolality is sodium

Salt Loading

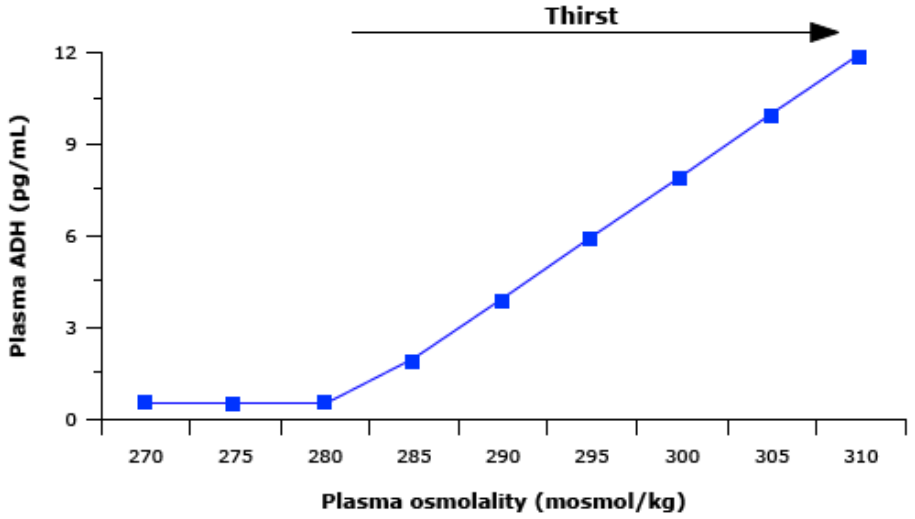
1260

Condensed soup 1600mg per can

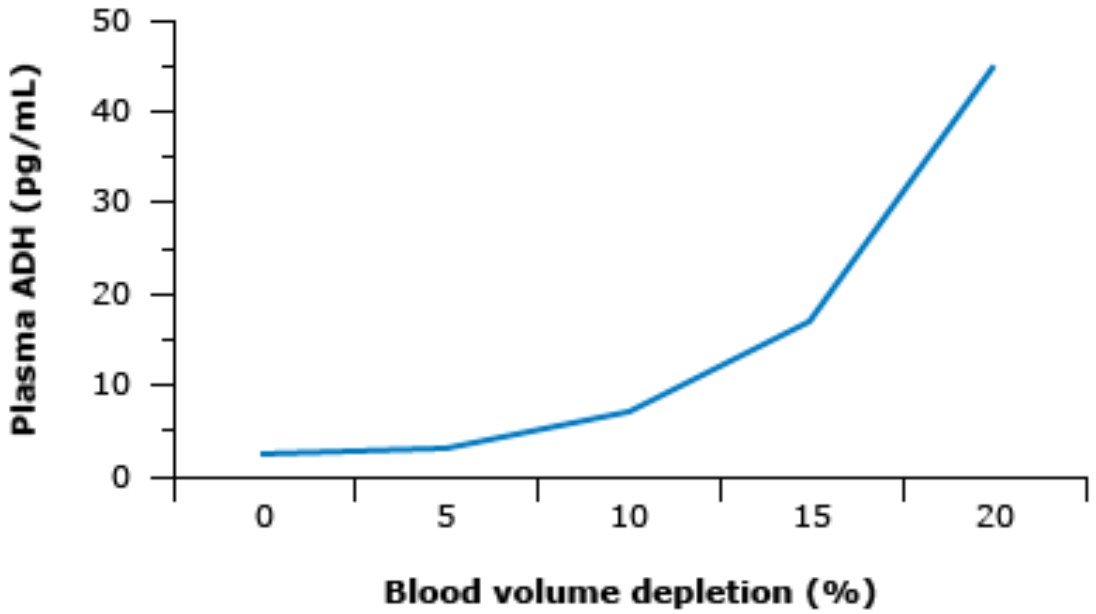
Asian take out: chow main- **980**, kang pau chicken – **800**, egg roll **390**, hot and saur soup **– 930** , soy sauce table spoon - **1,000** mg per tablespoon



total daily sodium= 6000 – 7000 or more ….



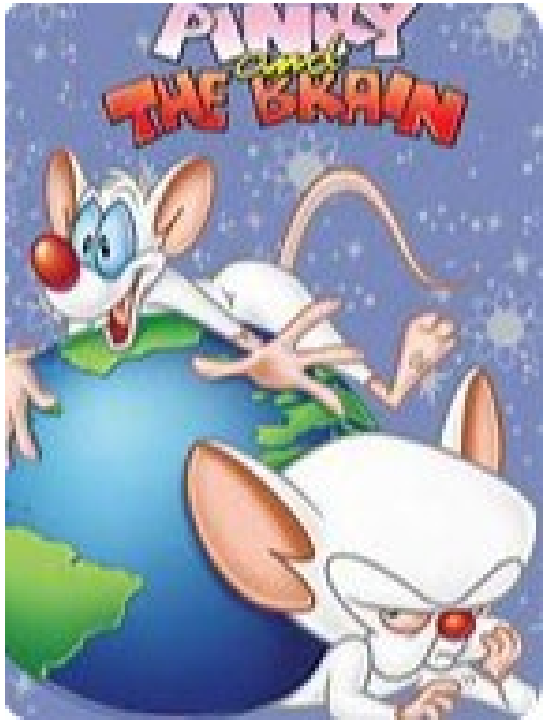
Non-osmotic stimulus for ADH release



Non-osmotic stimuli:

1. Volume depletion
2. Low effective circulating volume (CHF, HRS)
3. Nausea
4. Drugs (e. g. SSRIs)
5. Pain

- Why is hyponatremia a problem?
  - Mainly a problem for the brain



Hyponatremia: Physiology review

- Brain cell :

More particles, more concentrated

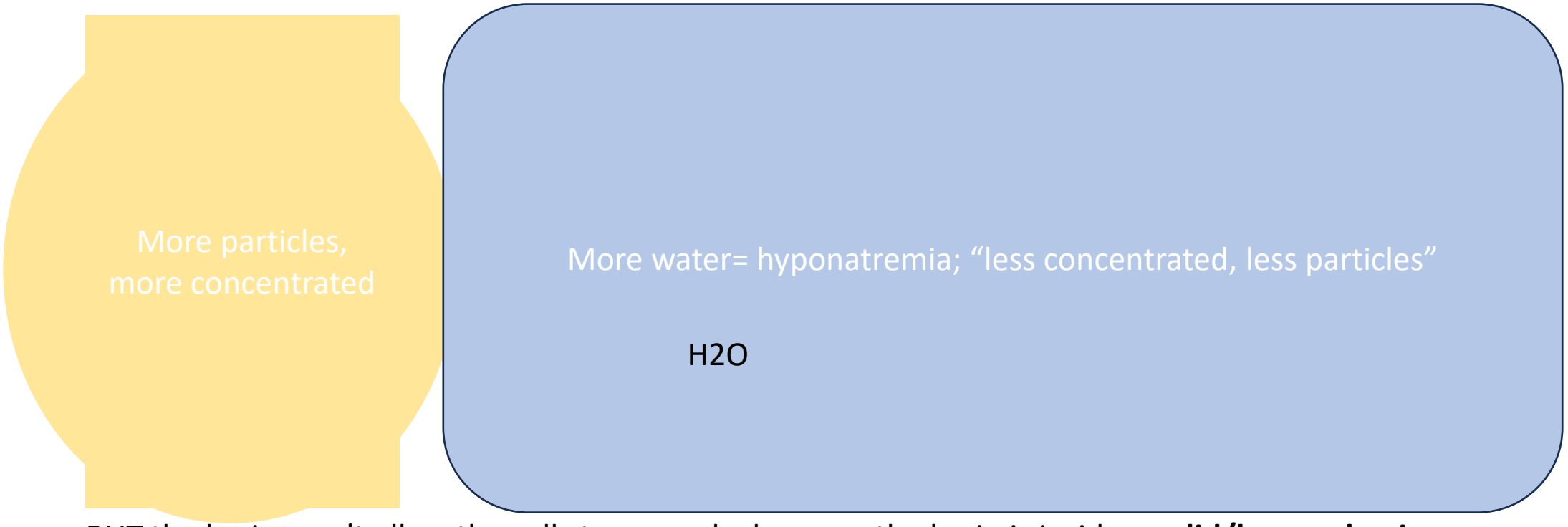
- Interstitial space:

More water= hyponatremia; “less concentrated, less particles”

H2O

Acute Hyponatremia =bad for the brain

- Brain cell :
- Interstitial space:



BUT the brain won’t allow the cells to expand – because the brain is inside a **solid/bony calvarium**, so as the brain edema ensues there is increasingly higher and higher **<u>pressure</u>** inside the brain- **seizures, AMS, herniation** 😳

Brain compensation , occurs by 48 hours

- Brain cell :
- Interstitial space:

More particles, more concentrated

Particles/osmoles

More water= hyponatremia; “less concentrated, less particles”

H2O

We don’t know what those osmoles are. Maybe **glutamine, potassium, inositol, taurine**

Summary of 1st half of objectives

- ✓Hyponatremia is a problem of sodium concentration
- ✓Steps through which ADH leads to hyponatremia
- ✓Understand the importance of osmotic gradient required for water reabsorption in the kidney
- ✓There are osmotic and nonosmotic stimuli for ADH release
- ✓Understand the adaptation process in the brain for hyponatremia

HYPONATREMIA

Determine **the volume status FIRST**

Hypovolemic

ADH release d/t low volume

Euvolemic (SIADH)

Constant ADH release without osm or volume stimulus

Hypervolemic

ADH release due to low “effective” circulating volume

HYPONATREMIA , SNA < 135 meq/L

Hypovolemic

ADH release d/t low volume

UNA < 10
UCl < 10
Urine Osm > 100

Euvolemic (SIADH)

Constant ADH release without osm or volume stimulus

UNA>20
UCl > 20
Urine Osm > 100

Hypervolemic

ADH release due to low “effective” circulating volume

UNA < 10
UCl < 10
Urine Osm > 100

- Because water is removed from the urine, urine is more concentrated and is such thru action of ADH in all three cases urine osm >> 100 (600-1200)
- LOW URINE OSM: … 1)In psychogenic polydipsia – urine osm can be low because ADH is shut off and urine is dilute; 2)tea and toast diet (not enough osmoles).

You rely on history and physical exam to determine cause of hyponatremia NOT urine studies; urine sodium is helpful in putting together the entire clinical picture together

Additional Labs/tests to get when evaluating hyponatremia

$$2(Na + K) + \frac{BUN}{2.8} + \frac{glucose}{18}$$

- Serum Osm (always) vs calculated serum osm
- Because Sodium concentration is the major component of serum osmolality
  - If serum sodium is low, then serum OSM should also be low
  - If there is a discordance it could be due to
    - Incorrect measurement , lab error , obtain **whole blood sodium**
    - It could be due to other osmoles present in the blood:
      - E.g. Alcohols
- TSH, random cortisol, uric acid
- Echo, liver US, abdominal imaging, chest XRAY
- Strict urine output record

HYPONATREMIA

Determine the volume status FIRST

Hypovolemic

Low BP
Tachy
Orthostatic

ADH release d/t low volume

History
1. Vomiting
2. Diarrhea

UNA < 10
UCl < 10
Urine Osm > 100

Treatment:
1. Isotonic saline

Euvolemic (SIADH)

Constant ADH release without osm or volume stimulus

Hypervolemic

ADH release due to low “effective” circulating volume

A 61-year-old woman is hospitalized for a 5-day history of nausea and vomiting and decreased oral intake and a 2-day history of postural lightheadedness. Her creatinine level is 7 mg/dL (creatinine level 1 month ago was 1 mg/dL). She has a history of hypertension and type 2 diabetes mellitus. Medications are aspirin, glipizide, enalapril, and chlorthalidone.

On physical examination, heart rate is 98/min and blood pressure is 85/60 mm Hg. Skin turgor is decreased. Cardiac and pulmonary examinations are normal. There is no peripheral edema. On neurologic examination, she is alert and oriented and there are no focal neurologic signs.

Laboratory studies:
Blood urea nitrogen 85 mg/dL
Creatinine 8 mg/dL
Sodium 120 meq/L
Potassium 3.7 meq/L
Chloride 86 meq/L
Bicarbonate 26 meq/L
Urinalysis Several hyaline casts/hpf
Urine sodium 4 meq/L (low is < 20 usually)

A 61-year-old woman is hospitalized for a 5-day history of **nausea and vomiting and decreased oral intake** and a 2-day history of **postural lightheadedness**. Medications are aspirin, glipizide, enalapril, and chlorthalidone.

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Creatinine 3 mg/dL
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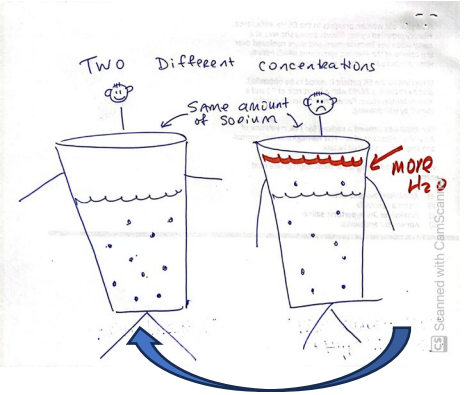
Chloride 86 meq/L
Bicarbonate 26 meq/L
Urinalysis Several **hyaline casts**/hpf
Urine sodium 4 meq/L (low is < 20 usually) * low urine sodium is telling that kidney are working hard to reabsorb sodium, **note FENA not asked to be calculated**

Which of the following is the next best step in this patient's management?

(A) Dialysis
(B) Fluid restriction
(C) Intravenous normal (0.9%) saline
(D) Intravenous 3% sodium chloride

- Why does hyponatremia correct with 0.9NS admin?
  A. Is it because we gave saline and hence salt to replace the losses
  B. Is it because the kidney is producing lots of dilute urine (autocorrection).

    - It is B - because we shut off nonosmotic stimulus for ADH and no longer reabsorbing the water (and bringing down the water level back to usual so sodium concentration increases back to normal).
    - Peeing out “excess” water



HYPONATREMIA

Hypovolemic

ADH release d/t low volume

Euvolemic (SIADH)

NL BP
No edema
No history of volume losses

Constant ADH release without osm or volume stimulus

1. Drugs:
    1. SSRI
    2. diuretics: thiazide (HCTZ)
2. Pain
3. Nausea
4. Cancer
5. Hypothyroid
6. Adrenal insufficiency

Hypervolemic

ADH release due to low “effective” circulating volume

A 35 year old woman is seen in the office eight days after being admitted for pyelonephritis. Her urine culture grew sensitive E.Coli and she was discharged home on trimethoprim-sulfamethoxazole and acetaminophen. She takes no other medications except for an oral contraceptive that she has been on for three years.

On physical examination, temperature is 36.6 °C (97.8 °F), heart rate is 84/min, respiration rate is 12/min, and blood pressure is 110/60 mm Hg without orthostatic changes. She appears thin and in no apparent distress, Cardiac examination is normal. The lungs are clear. There is no peripheral edema. Neurologic examination, including mental status, is normal.

Laboratory studies:

Glucose 122 mg/dL
Blood urea nitrogen 12 mg/dL
Creatinine 0.7 mg/dL
Sodium 124 mEq/L
Potassium 3.6 mcq/L
Serum osmolality: 266 mosm/kg H_2O

Urine sodium 110 meq/L
Urine osmolality 407 mosm/kg H_2O

A 35 year old woman is seen in the office **eight days** after being admitted for **pyelonephritis**. Her urine culture grew sensitive E.Coli and she was discharge home on trimethoprim-sulfamethoxazole and acetaminophen. She takes **no other medications** except for an oral contraceptive that she has been on for three years.

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Serum osmolality: 266 mosm/kg H_2O

Urine sodium 110 meq/L
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Which of the following is the most likely cause of her hyponatremia?

A) Adrenal insufficiency
B) Polydipsia
C) Oral Contraceptives
D) SIADH
E) Volume depletion

HYPONATREMIA

Hypovolemic

ADH release d/t low volume

Euvolemic (SIADH)

Constant ADH release without osm or volume stimulus

Hypervolemic

ADH release due to low “effective” circulating volume

Low normal BP
++ edema
++ history
no volume losses
Cirrhosis, jaundice

1. CHF
2. Cirrhosis
3. Nephrotic syndrome

65 yo man w/ CAD/PCI, CHF, low EF presents with shortness of breath, 10 lbs weight gain. Exam notable for 3+ b/l LE edema. He says he was taking diuretics as prescribed along with his other medications but eating take out regularly (daily). BP is low 90s/60s.

Laboratory studies:

Glucose 122 mg/dL
Blood urea nitrogen 35 mg/dL
Creatinine 1.7 mg/dL
Sodium 124 mEq/L
Potassium 3.6 mcq/L
Serum osmolality: 266 mosm/kg H_2O
Urine NA : <10 meq /L
Urine osmolality 407 mosm/kg H_2O

Which of the following is the most best treatment for the patient's hyponatremia?

A) Give IVFs b/c Cr is up
B) Hold diuretics and ACEI b/c Cr is up
C) Give IVFs b/p is low
D) Start diuretics

HYPONATREMIA **TREATMENT**

Goals: 1) turn off ADH,2)excrete the water, 3) prevent water retention

Hypovolemic

ADH release d/t low volume

Shut off ADH

Vomiting

Isotonic saline

Euvolemic (SIADH)

ADH release for reason other than volume or osmolality

Drugs: SSRI, HCTZ

1. Stop meds, treat pain, treat nausea, treat hypothyroid – to shut off ADH
2. Fluid restriction

Prevent H2O retention

3. Other:
   - ❑ Loop diuretic
   - ❑ Salt tabs
   - ❑ Urea
   - ❑ Tolvaptan

Excrete water

Hypervolemic

ADH release due to low "effective" circulating volume

1. CHF, cirrhosis

Fluid restriction
Loop diuretic +

Prevent H2O retention & excrete water

To shut off ADH treat underlying condition management- inotropes, chf afterload reduction therapies, liver transplant, heart transplant , etc

What is a fluid a restriction?

- Fluid (all fluids) restriction </=800ml *(4 glasses of water/liquids) in 24 hours*
  - *Compare to:*
    - *2000 ml is 8 -10 glasses of water/liquids – unless liquid tastes like salt it's made of water, so restriction is in **all** liquids.*

❖*Fluid restrictions is most important treatment for SIADH is fluid restriction*

*In patients with a highly concentrated urine (eg, 500 mosmol/kg or higher), fluid restriction alone may be insufficient to correct hyponatremia.

Additional SIADH Treatment Strategies

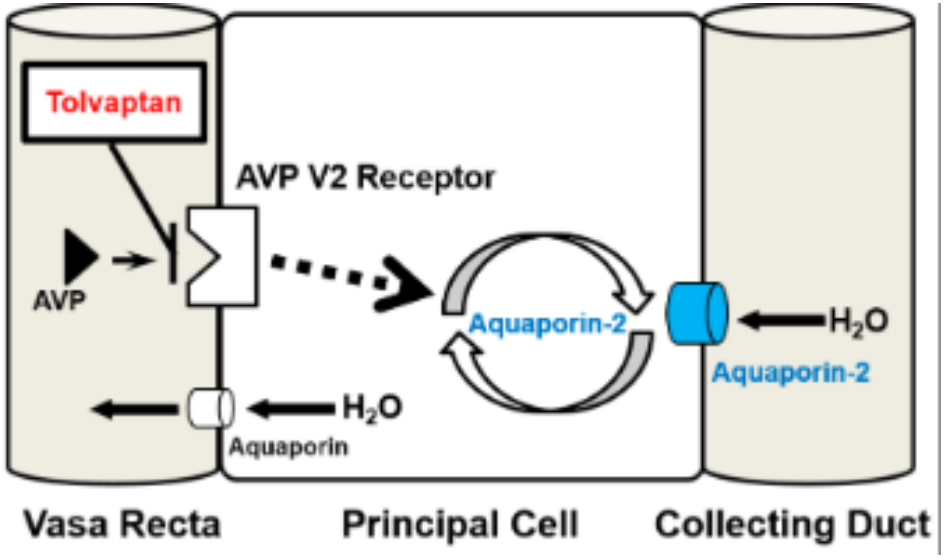
- **Loop diuretics (as opposed to thiazides)**
  - E.g. Furosemide can **treat** hyponatremia of SIADH
    - Abolishes the interstitial osmotic gradient →
    - Impairs H2O reabsorption
      "protects" patients from developing hyponatremia despite increased ADH
    - Voiding out extra water from the body so the systemic serum sodium concentration increases

Additional SIADH Treatment Strategies

- **Salt tablets : NaCL** dose ~
  - Remember how much:
    - equivalent to American diet of salt intake or
    - that of 1L 0.9NS isotonic saline
    - or 3gm TID or 9 gm a day of NACL
  - Oral salt tablets should *not be given to edematous patients or hypervolemic (think CHF, Cirrhosis, pulm edema, etc)*
  - Mechanism:
    - osmotic diuresis -> peeing out more water required to lose the osmoles
  - May need to admin along with loop diuretic

Additional SIADH Treatment Strategies

- **<u>V2 receptor blocker</u>**
  - e.g. Tolvaptan
  - prevents ADH from binding to its target in the collecting tubule thus blocking water reabsorption, similar to loop diuretic removing excess water
  - tolvaptan should not be used in any patient for longer than 30 days and should not be given to patients with **liver disease (including cirrhosis)**



Additional SIADH Treatment Strategies

- **Urea :** creates osmotic diuresis, poor taste, patients don't stay compliant easily with this

UreaAide Urea Powder for Low Sodium Unflavored 30 Servings Oral Urea Powder for Hyponatremia-Single Ingredient 100% Medical Grade Urea with 15 gram Dose Scoop Mixes with Flavored Drinks by KidneyAide

Visit the KidneyAide Store

3.9 ★★★★☆ 12 ratings | Search this page

$53.99 ($3.37 / Ounce)

Apply now and get a $10 Amazon Gift Card upon approval of the Amazon Store Card, or see if you pre-qualify with no impact to your credit bureau score.

Brand	KidneyAide
Item Form	Powder
Unit Count	16.0 Ounce
Flavor	Unflavored
Number of Items	1

About this item

Roll over image to zoom in

A 60-year-old male presents to the clinic to review labs. He has a history of hypertension, diabetes, and lung cancer for which he is undergoing treatment. He voices no complaints at this time. He underwent a colonoscopy two years ago that did not identify any lesions or polyps. He is up to date with his eye exams. He says his appetite has been great and denies any weight loss. He also denies vomiting or diarrhea. His only medications are metformin and lisinopril.

His blood pressure is 124/82mmHg Standing and 120/80mmHg sitting. His physical exam does not reveal any jugular venous distention (JVD) or lower extremity edema.

Labs show:
HgbA1c 6.4%
CBC normal
LDL 58mg/dL
CMP is normal except for a sodium level of 123mg/dL
Serum osmolarity 250mOsm/L

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His blood pressure is **124/82mm**Hg Standing and **120/80mmHg sitting**. His physical exam does **not reveal any jugular venous distention (JVD) nor lower extremity edema.**

Labs show:
HgbA1c 6.4%
CBC normal
LDL 58mg/dL
CMP is normal except for a sodium level **of 123mg/dL**
Serum osmolarity **250mOsm/L**

Which of the following is the best solution for his hyponatremia at this time?

A. Furosemide

B. 3% normal saline

C. 0.9% normal saline

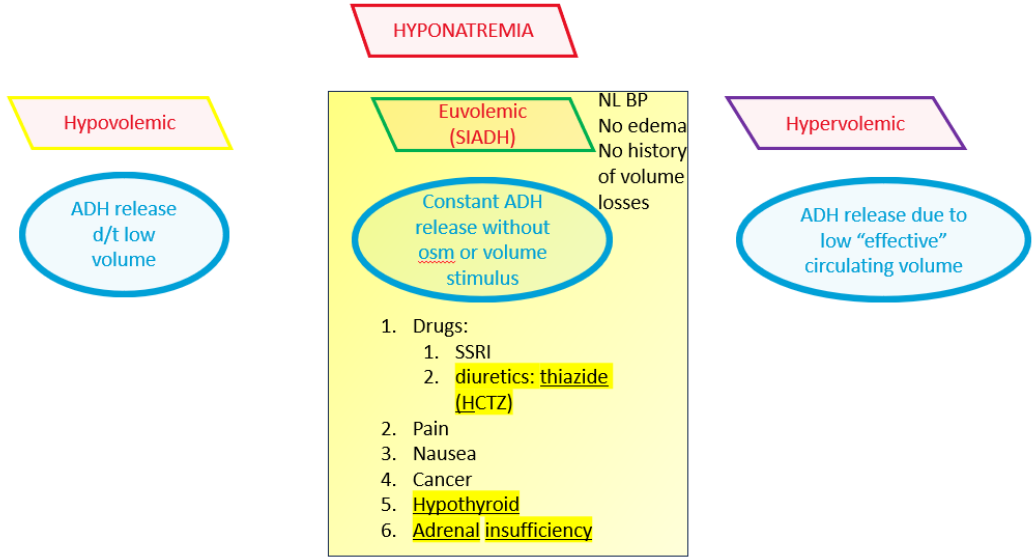
D. Fluid restriction

E. 5% dextrose in water (D5W solution)

How much fluid restriction? 800ml of all liquids

Unusual causes of hyponatremia

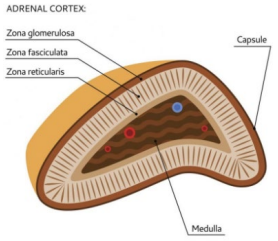
- Focus on (in the middle section , SIADH category) :
  1. Adrenal insufficiency
  2. Hypothyroid
  3. Thiazides



Adrenal Insufficiency Hyponatremia

Primary Adrenal Insufficiency

- deficiencies are at the level of **adrenal gland**
- Not seen w/ secondary (at level of brain/pituitary)
- Deficiency of aldosterone **AND** cortisol
- **primary adrenal** insufficiency: **BOTH** aldosterone and cortisol are low, low aldosterone is what leads to **hyperkalemia** (*clue to cause of hyponatremia)



THE ADRENAL GLAND

Major causes:

1. TB
2. autoimmune adrenalitis (Addison's disease)
3. meningococcal septicemia
4. acute adrenal hemorrhage
5. surgical resection

RARE

- 144 per million

Mechanism for Hyponatremia in AI

- Multifactorial
  1. Hypovolemia (low cardiac output, low volume)
  2. Main reason is related to *increase in ADH* production*:*
     (b/c cortisol normally provides negative feedback on ADH)

- Normal: ↑ cortisol causes (-) feedback on ↓ CRH and ↓ ACTH

in AI: Inhibitory effect that is removed in adrenal insufficiency-> ↓ cortisol ->

↑ hypothalamic secretion of corticotropin-releasing hormone (CRH)- *

↑ in CRH causes a nonosmotic stimulus for ↑ ADH release

▪**primary adrenal** insufficiency: **BOTH** aldosterone and cortisol are low, low aldosterone is what leads to **hyperkalemia** (*clue to cause of hyponatremia)

Treatment for Adrenal Insufficiency

- ✓Cortisol administration (hydrocortisone)
- ✓Volume repletion (Isotonic saline)

A 22-year-old woman is evaluated in the emergency department because of severe dizziness, weakness, nausea, and vomiting of 1 week's duration. She has noted fatigue and moderate weight loss over the preceding 2 months. She has a history of hypothyroidism and takes levothyroxine, 100 mcg daily.

On physical examination, the patient is 168 cm (66 in) tall and weighs 53 kg (116 lb). Blood pressure is 90/60 mm Hg supine and 80/50 mm Hg standing, and pulse rate is 84/min supine and 96/min standing. Her skin is tanned, and there is markedly increased pigmentation of the gums and palmar creases.

Labs reveal:

Serum creatinine 1.2 mg/dL
Blood urea nitrogen 39 mg/dl.
Serum sodium 124 meq/L
Serum potassium 5.8 meq/L.
Plasma glucose 61 mg/dl.

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Serum creatinine 1.2 mg/dL
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Plasma glucose 61 mg/dl.

What is the most likely underlying cause of the hyponatremia?

(A) Acute adrenal hemorrhage

(B) Autoimmune adrenalitis (Addison's disease)

(C) Fulminant meningococcemia

(D) Pituitary apoplexy

(E) Tuberculosis

- Focus on :
  - Adrenal insufficiency
  - **Hypothyroid**
  - Thiazides

Hyponatremia of Hypothyroid (hypothyroidism is severe)

- Proposed mechanisms (multifactorial):

1. ↓ cardiac output → ↑ ADH via the carotid sinus baroreceptors
2. ↓ GFR may also be a contributing cause of hyponatremia
    - Not filtering out the water drunk
3. SIADH
    - Urinary sodium is *not* typically low in hypothyroid
        - as would be expected if a reduced cardiac output or kidney function impairment were responsible

- Focus on :
  - Adrenal insufficiency
  - Hypothyroid
  - **Thiazides**
    - Thiazides are one of **the most common** causes of hyponatremia requiring hospitalization

Thiazide induced hyponatremia

- Within the first **one to two** weeks
  - Occasionally, may occur **months or years** after initiation of thiazide therapy
    - usually during an illness that results in inappropriate ADH secretion (two hit)
- Can **recur** after rechallenge with the thiazide
- **Clinically euvolemic (SIADH) or even volume expanded**

Thiazide induced hyponatremia

Risk factors:

- Older women with low body weight are most susceptible
- low dietary solute intake

Frenkel Thiazide-induced hyponatraemia is associated with increased water intake and impaired urea-mediated water excretion at low plasma antidiuretic hormone and urine aquaporin-2. J Hypertens. 2015 Mar;33(3):627-33.

Thiazide Hyponatremia: Mechanisms (complicated!)

- An underlying tendency to *increased water intake (aka polydipsia),* 2543 versus 1828 mL/day

- *Volume depletion* stimulates the release of ADH

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Thiazide Hyponatremia: Mechanisms (complicated!)

- Thiazides do not affect the medullary concentration gradient
- Volume depletion - > Incr ADH ->
  - Will lead to increased water reabsorption in the inner medullary collecting duct b/c the medullary gradient is present
- Increased **potassium depletion** (due to the diuretic) may enhance ADH medicated water reabsorption through stimulation of osmoreceptors (and release ADH)
- Impaired water excretion independent of ADH

César. Thiazide induces water absorption in the inner medullary collecting duct of normal and Brattleboro rats. Am J Physiol. 1999 Nov;277(5):F756-60.

Thiazide Hyponatremia: Mechanisms (complicated!)

- ~ 50 % who develop thiazide-induced hyponatremia carry a *single-nucleotide* ***polymorphism*** in the gene encoding the **prostaglandin transporter**, expressed in the renal collecting duct.
  - The variant transporter allows higher levels of luminal prostaglandin E2, which activate the luminal prostaglandin E2 receptor 4, **activating water reabsorption in the collecting duct,** despite suppression of ADH

A 73-year-old woman is brought to the emergency department after falling at home. Her family states that she has been very confused and disoriented over the past 2 days and that she began a new medication 4 days ago. She has type 2 diabetes mellitus, hypertension, and glaucoma. A bag containing the patient's medications includes glyburide, metformin, hydrochlorothiazide, acetazolamide, and enalapril.

On physical examination, temperature is 37 °C (98.6 °F), heart rate is 68/min, respiration rate is 12/min, and blood pressure is 115/65 mm Hg. She is confused and unable to
answer questions appropriately. Cardiac examination is nor
mal. The lungs are clear. There is no edema.

Laboratory studies:

Blood urea nitrogen 17 mg/dL
Creatinine 1.1 mg/dL.
Sodium 107 meq/L
Potassium 2.9 meq/L
Chloride 76 meq/L
Bicarbonate 24 meq/L

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Which of the following drugs was most likely recently started in this patient?

(A) Acetazolamide

(B) Enalapril

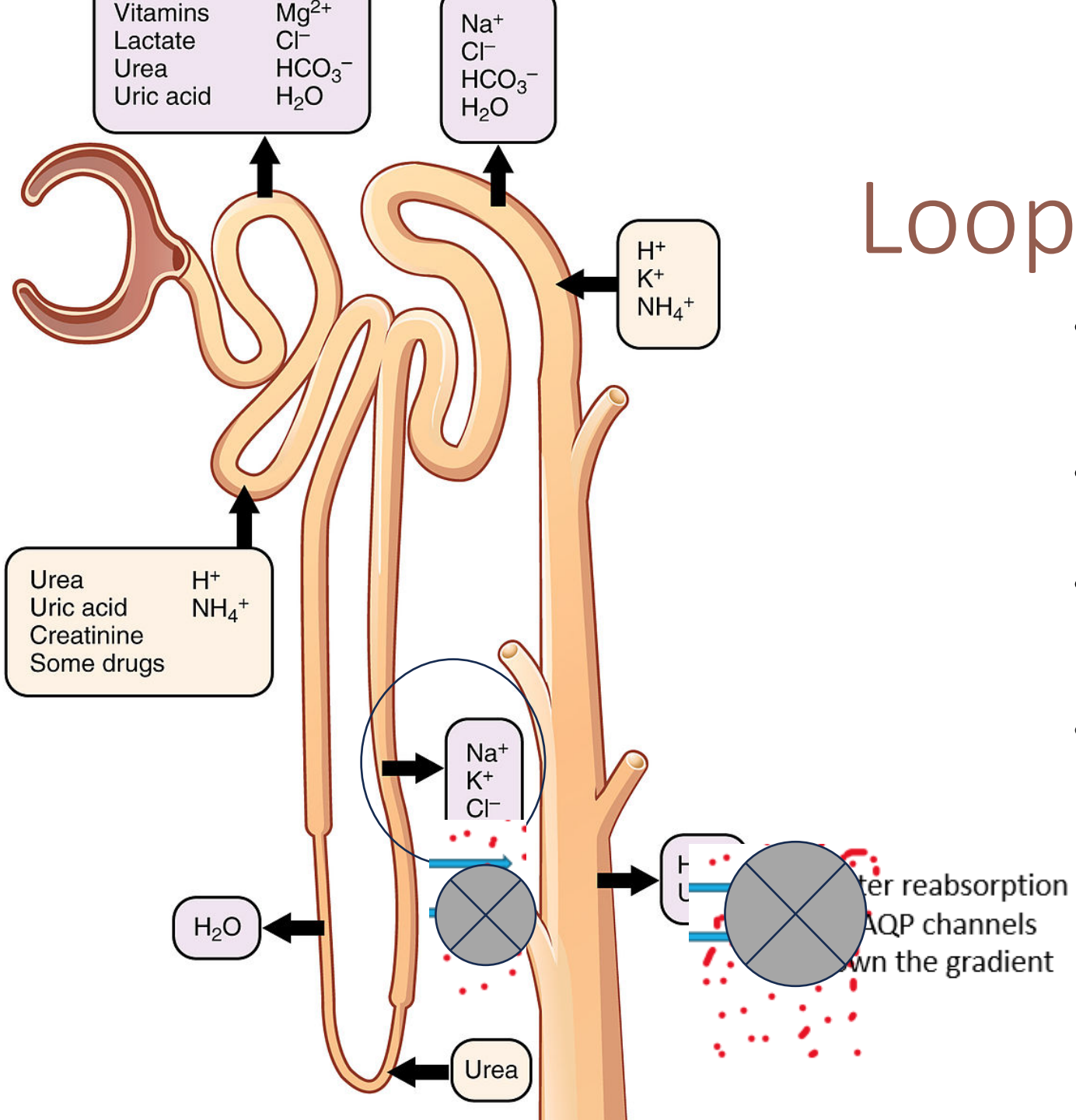
(C) Glyburide

(D) Hydrochlorothiazide

(E) Metformin

Loop diuretics

- Do loop diuretics cause hyponatremia?
  - Answer: No
  - Loop diuretics interfere with the generation of high osmotic gradient in the medullary interstitial gradient
  - This prevents water reabsorption despite presence of ADH
  - Loop diuretic protects from hyponatremia



Loop diuretics

- *no reabsorbing Na/CL/K - > no/reduced medullary osmotic gradient
- Reduced response to ADH
- … loop diuretic can fix hyponatremia or protect from hyponatremia
- Avoid thiazide diuretics in beer drinkers and patients with psychogenic polydipsia and to measure the plasma sodium concentration within a few days after therapy has begun in older adults, especially those with a low body mass

When to use 3% saline:

Symptomatic hyponatremia

- Symptoms may occur in:
  - **Acute (< 48 hrs)** hyponatremia because brain has not had time to adapt to hyponatremia
  - **Severe chronic (> 48 hrs)** hyponatremia usually when SNA < 120
    - However, most patients even with severe hyponatremia do not have symptoms
  - **Symptoms**
    - * AMS, seizures, tremors, brainstem herniation, coma, death

How to administer 3% saline?

- **In the ICU, q 2-4 hours** monitoring of SNA

- 3% saline (554 meq of NA in 1 liter, or 0.5 meq per ml)

    - 100ml bolus over 10 " to raise (about 50 meq) to raise serum sodium concentration 4 -6 meq to decrease brain edema , okx1-2 to repeat until symptoms resolve.

Without symptoms:

- * majority of hyponatremia is without symptoms
- * 3% not indicated
- * but you may need to admit to the ICU for close monitoring of SNA q 2-4 hrs

Severe Hyponatremia Treatment, presumed chronic > 48 hours

- **LIMIT** (not a goal) rate of correction of approximately 6-8 mEq/L per day
    - No matter how low the initial sodium is

A 24 year old woman presents to the ER via ambulance. History provided by her friends shows she was at a party when she became more and more confused over the course of the evening, symptoms which initially were attributed to alcohol consumption.

On arrival to the ER patient is noted to be obtunded. Blood pressure is 86/60 with a heart rate of 80 and a normal temperature. Patient responded to painful stimuli by withdrawing.

Her initial labs showed a sodium for 116, creatinine of 2.1 and a potassium of 3.1. Her hemoglobin was normal and she had an elevated lactate.

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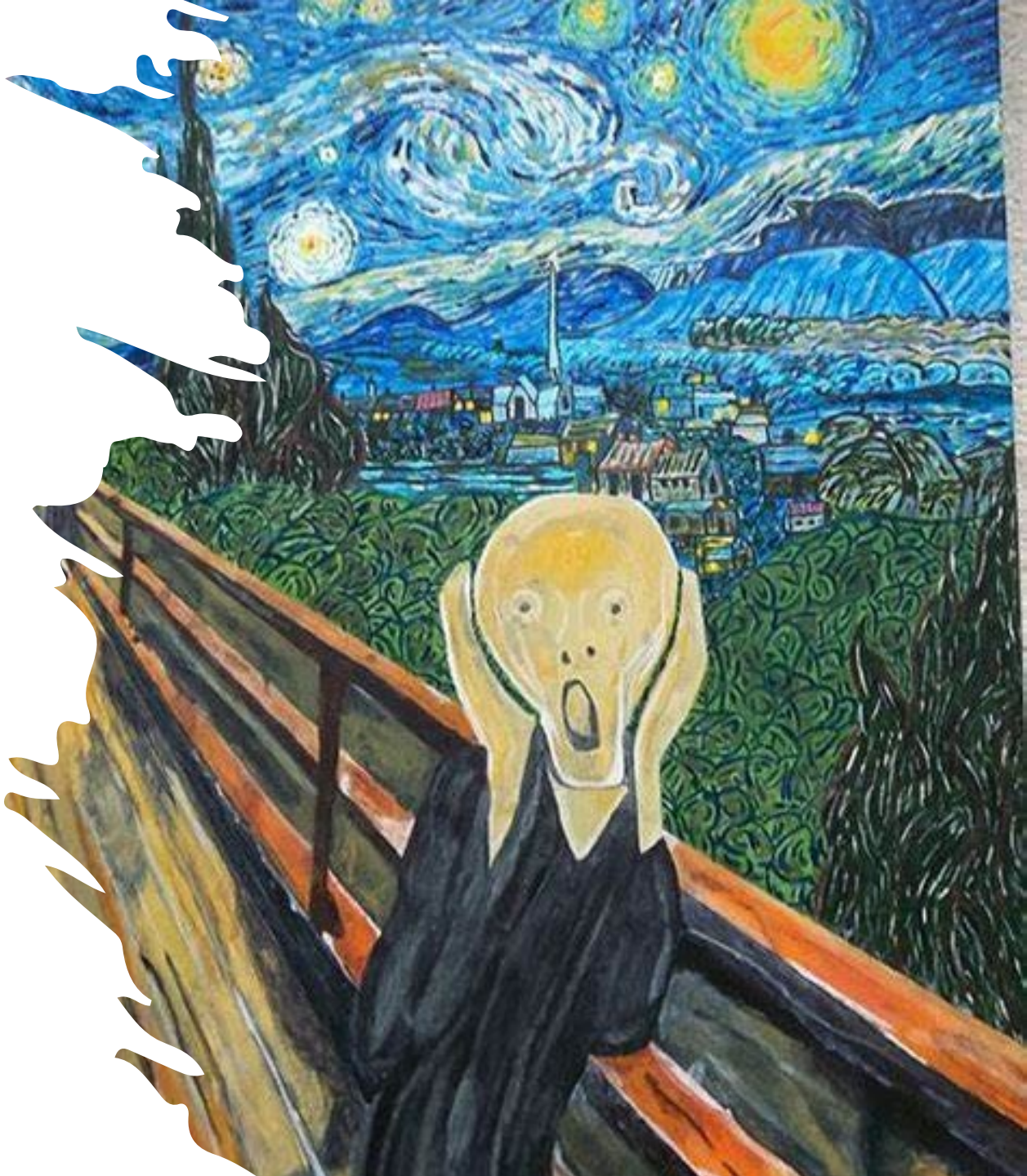
Which of the following is the most appropriate next step:

a) Administer isotonic saline
b) Insert a central IV
c) Administer 3% hypertonic saline
d) Administer antibiotics

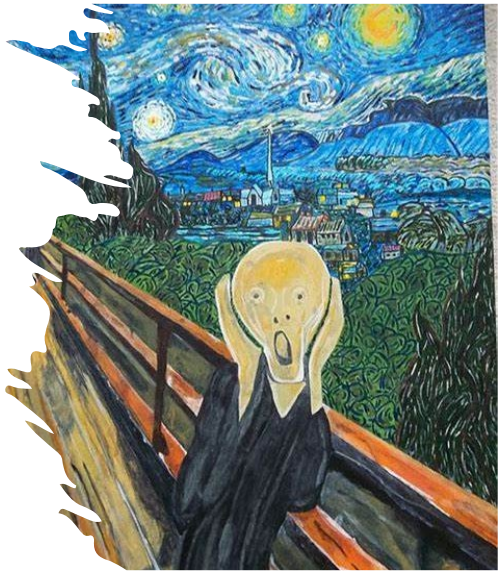
Why slow is better?

- **Osmotic Demyelination Syndrome:**
  - The majority of ODS cases occur in patients whose sodium concentrations at presentation are ≤110 mEq with correction rates > 6-8 meq /l per day (over-correction_
  - How the ODS occurs is not completely understood
  - **Risk factors:**
    - liver disease, malnourished, risk of rapid over correction after stimulus for ADH has been removed

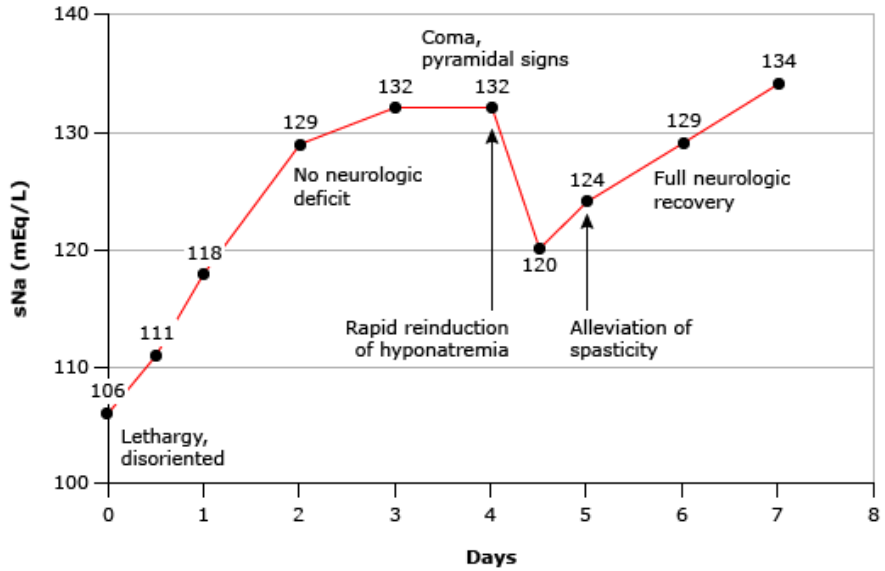


ODS Symptoms

- Dysarthria
- Dysphagia
- paraparesis
- **Quadriparesis**
- behavioral disturbances
- movement disorders
- **Seizures**
- Lethargy
- Confusion
- Disorientation
- Obtundation
- Coma
- **"locked in“**
- **Mute**
- Corticospinal signs



Delayed appearance of osmotic demyelination and relowering of the serum sodium

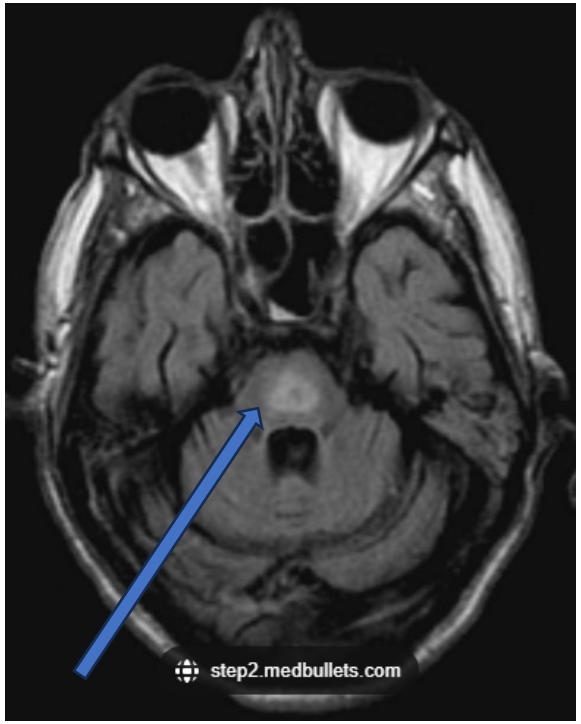


Neurologic symptoms of osmotic demyelination syndrome (ODS) typically occur 2 to 6 days after correction of the hyponatremia. In this patient, severe hyponatremia was corrected too quickly (23 mEq/L in 48 hours), and coma developed 2 days later. The serum sodium was quickly relowered and then slowly corrected. Neurologic symptoms improved, which may have been due to relowering of the serum sodium or may have represented spontaneous resolution.

sNa: serum sodium.

ODS Diagnosis: Clinical

- Imaging: brain MRI
  - Bright spot in pons



- central pontine demyelination **only**
- **both** central pontine and extrapontine demyelination
- **extrapontine** demyelination only

Other hyponatremias

Pseudohyponatremia

- Due to indirect potentiometry measurement
- Order *"whole blood sodium"* for direct potentiometry for accurate measurement of serum sodium concentration
  - Check
    - Lipids
    - total protein gap (r/o MM)

Use serum osm to confirm it is true hyponatremia

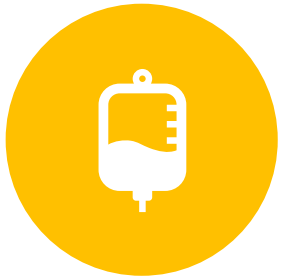
- Remember normal serum osm 285-295, and sodium is biggest contributed

- Hyperglycemia hyponatremia
  - Calculate *corrected serum sodium:*
    - Add 2 mEq/L to the serum sodium for every 100 mg/dL of serum glucose above the normal value
    - In severe hyperglycemia with blood glucose > 650 there is also a component of 'pseudohyponatremia' b/c high blood glucose concentration interferes with indirect sodium measurements by ion-selective electrodes

When hyponatremia AND urine osm is **dilute** (Osm < 100)

Massive water intake, thereby overwhelming a normal ability to excrete water

Diet deficient in protein, severely limiting urine solute osmole, ‘tea and toast’



urine osmolality **measured after** the cause of increased ADH release had already resolved ‘correction of volume status w/ saline’

Reset osmostat - we can talk about this off lecture

Review questions

1. What is the main reason for ADH release in primary adrenal insufficiency?
2. What medications can be used to bind to V2 receptor that usually binds ADH?
3. What makes ADH ? – paraventricular neurons of hypothalamus as pre-pro-AVP
4. What stores ADH ? – posterior pituitary
5. What must be present in order for water reabsorption to occur once ADH binds to its receptor and increases number of AQP channels? – osmotic gradient
6. Which diuretic is likely to cause hyponatremia, loop or distal?
7. Which diuretic can be used to treat hyponatremia, loop or distal?
8. Hyperkalemia occurs w/ primary adrenal insufficiency or secondary and why?
9. Be able to interpret urine sodium without doing FENA
10. How much “salt” or NaCL is in 1 liter 0.9NS? 9 gm
11. How much “sodium” or Na is in 1 liter 0.9NS? ~ 3.5 gm
12. **to ponder on … do esrd or anephric patients have nephrons, how do they get hyponatremic**

- Thiazide mediated hyponatremia is purely d/t development of hypovolemia? T/F
- Name some non-osmotic stimuli for ADH release
- What is the most important treatment for SIADH? Fluid restriction 800ml to 1000ml
- Why do we have to rely on physical exam and history for assessment rather than just measure ADH? -- ADH is not measurable , copeptin is but not common in clinical practice
- Which molecule serves as a surrogate for ADH? – copeptin
- What is the major determinant of plasma osmolality? Potassium, sodium, urea, glucose ?? .. Sodium ; when you have hyponatremia serum osm should be also low
- T or F, Only factor to cause in thiazide hyponatremia is volume depletion
- How does tolvaptan treat hyponatremia?
- In which case you cannot administer tolvaptan?
- T or F, it safe to administer oral salt tab to patients with peripheral, pulmonary, or both edema
- T or F , a single cause can explain why hyponatremia may develop in primary adrenal insufficiency

- If there is time

From the perspective of salt: the lay of the land

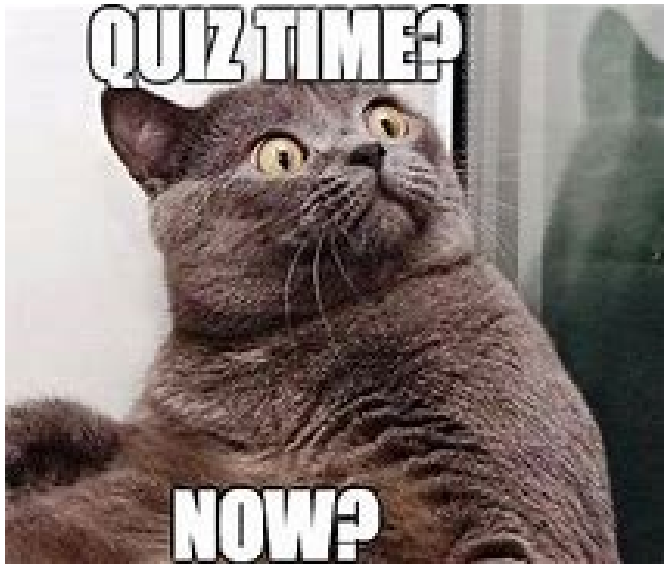
- Teaspoon of salt -> 2300mg of Na+ (NA+ vs NACL)
- 2000mg is typical total **daily** sodium restriction for patients with congestive heart failure, chronic kidney disease, hypertension, and cirrhosis

Type	Approximate amount of sodium in 1 teaspoon
Iodized table salt, fine	2,300 mg
Kosher salt, coarse	1,920 mg
Kosher salt, fine, Diamond Crystal®†	1,120 mg
Sea salt, fine	2,120 mg
Sea salt, coarse	1,560 mg
Pink (Himalayan) salt	2,200 mg
Black salt	1,150–2,200 mg
Fleur de sel	1,560–2,320 mg
Potassium salt (salt substitute)	0 mg (contains 2,760–3,180 mg potassium)

Salt and Sodium | The Nutrition Source | Harvard T.H. Chan School of Public Health

Trivia

- How much sodium is in sea water?
  - **Seawater** has a salinity of about 3.5% (35 g/L, 35 ppt, 600 mM)
  - * this is **equivalent** to **3% saline (IV)**
- How much sodium is in tablespoon soy sauce?
  - **1 tablespoon** of table salt contains ~ **1000 milligram**s of sodium.



Salt Comparisons

- Condensed soup 1600mg per

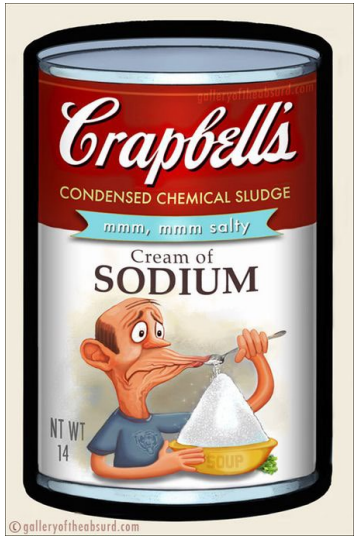
- 0.9% Saline (1L) 3500mg of Na

- 3% Saline (1L) (12,000mg)

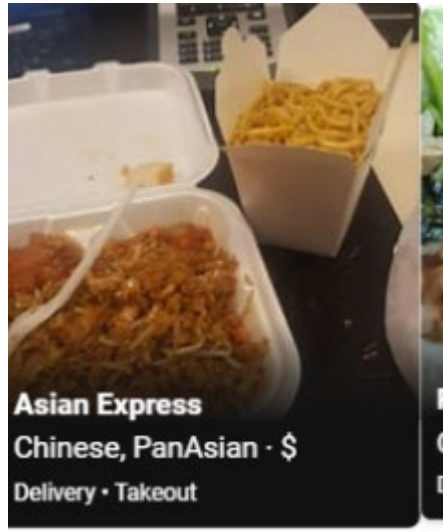
Salt Loading

1260

Condensed soup 1600mg per can



Asian take out: chow main- **980**, kang pau chicken – **800**, egg roll **390**, hot and saur soup **– 930** , soy sauce tablespoon - **1,000** mg per tablespoon



Average American total daily sodium intake = 6000 – 7000 or more ….

Should we advise someone with hyponatremia to drink Gatorade – an electrolyte rich fluid ?

How many teaspoons of sodium are in a liter of Gatorade?

Gatorade

Nutrition Facts

Serving Size 8 fl oz (240 mL)
Servings Per Container 4

Amount Per Serving	
Calories 50	
	% Daily Value*
Total Fat 0g	**0%**
Sodium 110mg	**5%**
Potassium 30mg	**1%**
Total Carbohydrate 14g	**5%**
Sugars 14g	
Protein 0g	

Not a significant source of Calories from Fat, Saturated Fat, Cholesterol, Dietary Fiber, Vitamin A, Vitamin C, Calcium, Iron.

* Percent Daily Values are based on a 2,000 calorie diet.

- One bottle 1 liter of Gatorade
  - 110mg of sodium per serving x 4 servings => 440mg per liter
  - 1/5th of teaspoon! (19meQ of NA)

Can you replace salt (rehydrate with electrolytes (AKA sodium) with Gatorade? NO

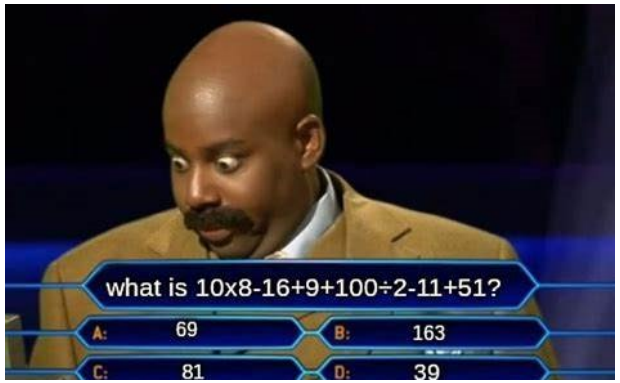
Can you replace salt (rehydrate with electrolytes (AKA sodium) with soy sauce? – YES
1.5 tablespoons and four cups of water

Thus you are adding 960ml of ‘free ‘ water (almost same as a liter of D5W) to your ECF and ICF (2/3, 1/3)

Gatorade Trivia

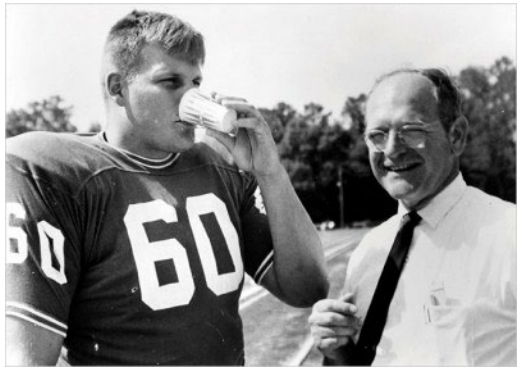
- Who is the lead inventor for Gatorade and it’s billion $$$ business?

“The test won’t even be that hard. It’s multiple choice.”



University of Florida **Nephrologist**

- Dr. J Robert Cade (1927-2007)



•Sodium 45 mEq (45x23=**1035mg**) in 1 liter

Oral Rehydration Therapy

PEDIALYTE (1 liter)

½ teaspoon of salt (same is in McD’s breakfast sandwich and less than in a can of soup)

Osmolality 250 mOsm/kg

Sodium 45 mEq (45x23=**1035mg**)

Potassium 20 mEq

Chloride 35 mEq