

# Interactive Endocrine Consults

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# Disclosures

**None**

# Learning Objectives

- Review the clinical guidelines for the evaluation and treatment of primary hyperparathyroidism
- Review the clinical evaluation of hyponatremia
- Review the clinical presentation and assessment of a patient with fatigue and hyponatremia

# Case # 1

67 yo F found to have incidental hypercalcemia on routine labs prior to a screening colonoscopy

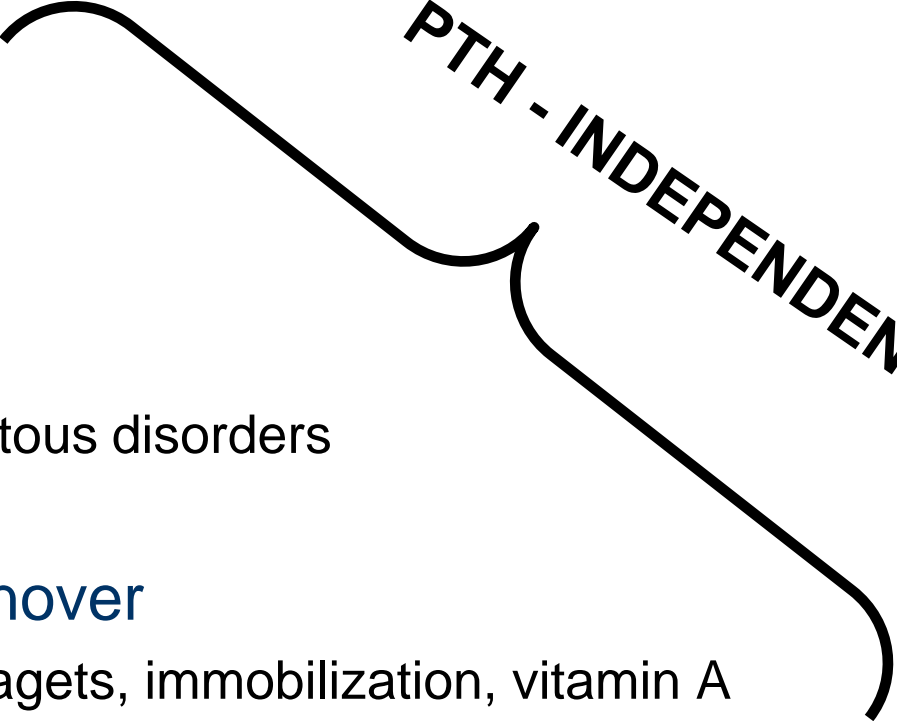
- PMH: HTN, breast cancer ~ 10 yrs ago
  - s/p lumpectomy & XRT, 5 yrs of treatment with tamoxifen
  - No fractures or kidney stones
- Meds: Lisinopril 20 mg, CaCarbonate 500 mg/d
- SH: former smoker (30 pk-yr) quit 10 yrs ago
- PE: 138/72, 88, BMI 32, unremarkable exam

138	104	13	89
4.3	25	0.9	

Ca 11.3 mg/dL (nl <10.5)

# Causes of Hypercalcemia

- #1= PTH-dependent
- #2= Malignancy
- Others
  - Milk-Alkali
    - Sarcoid, granulomatous disorders
    - Excess intake
  - Vitamin D excess
    - Sarcoid, granulomatous disorders
    - Excess intake
  - Increased bone turnover
    - Hyperthyroidism, Pagets, immobilization, vitamin A



PTH - INDEPENDENT

# Calcium Homeostasis

- PTH increases serum Ca

## Bone

– ↑ mobilization of Ca

## Kidney

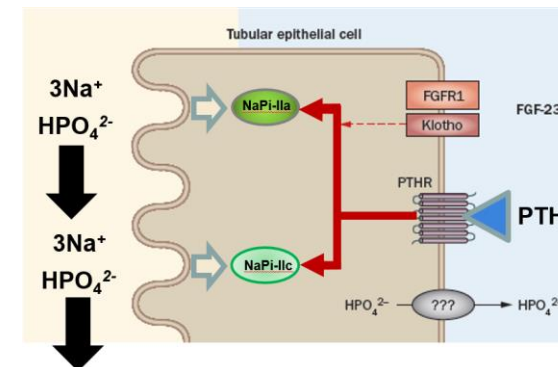
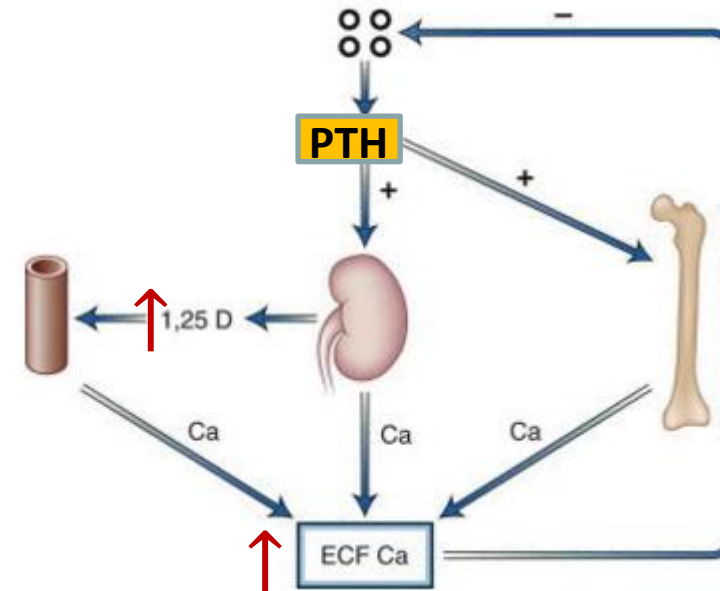
– ↑ calcium reabsorption

– ↑ 1 alpha hydroxylase

## GI

– ↑ dietary Ca absorption

- PTH decreases serum phos

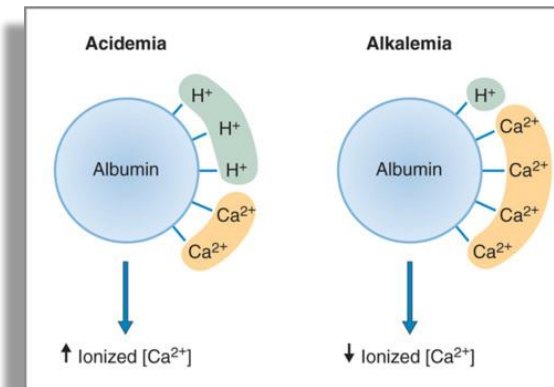


# Circulating Calcium Concentration

- Only ~50% of circulating calcium is ionized
  - 10% bound to inorganic anions (phos, etc.)
  - 40% bound to Albumin

$$[\text{Ca}]_{\text{corrected}} = [\text{Ca}]_{\text{measured}} + 0.8(4 - [\text{Alb}])$$

- Percentage bound is determined by pH
  - Acidosis- ↓ bound , ↑ free
  - Alkalosis- ↑ bound, ↓ free



# Initial Evaluation

- Calcium, albumin (+/- ionized Ca)
- Phosphate
- PTH
- 25-OH vitamin D

If PTH suppressed:

- 1,25 (OH)<sub>2</sub> vit D; PTHrP; TSH; ACE; Alk phos
- Imaging studies (skeletal survey, +/- bone scan)-CA, granulomatous dz



## Case # 1 Labs

- Repeat calcium 10.9 mg/dl (*nl* <10.5)
- Albumin 3.6 g/dl
- Phosphate 2.2 mg/dl (*nl* >2.5)
- 25-OH vitamin D 38 ng/mL (*nl* >30)
- PTH 105 pg/mL (*nl* <60)

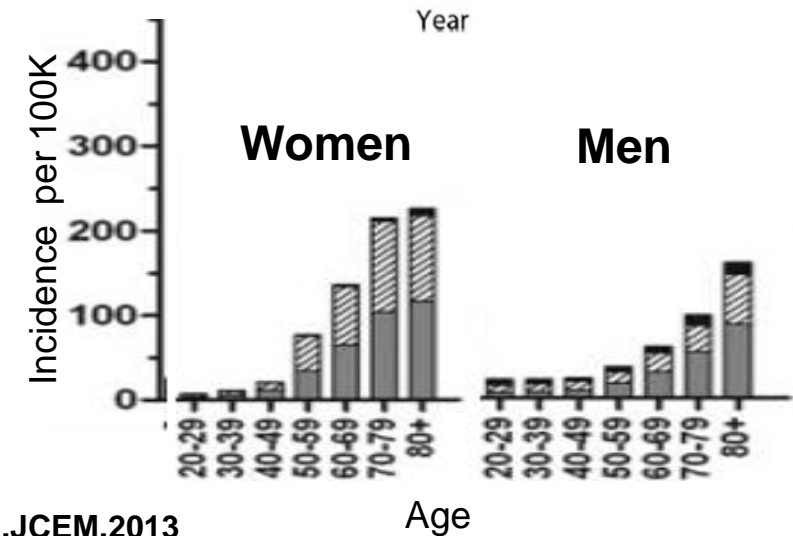
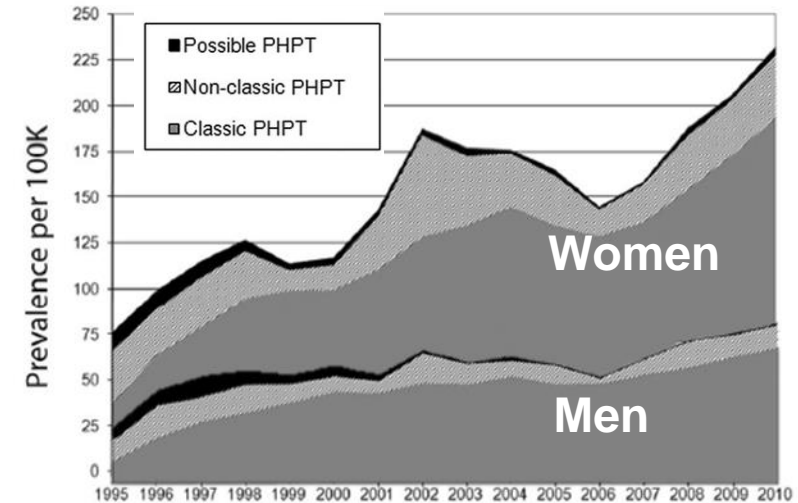
Diagnosis = 1° Hyperparathyroidism

# PTH – Dependent Hypercalcemia

- Single Adenoma (85%)
- Multigland/Hyperplasia (15%)
  - Sporadic
  - Syndromic/Familial
    - MEN 1 (*MEN1*), MEN 2A (*RET*), MEN 4 (*CDKN1B*)
    - Jaw Tumor Syndrome (*CDC73*), *CDKN*
- Rare
  - Carcinoma
  - Ectopic PTH
    - Lung, Ovarian, Thymus CA, PNET, Islet Tumor
  - FHH/AHH
    - Abnormal Ca-sensing receptor ,  $G\alpha_{q/11}$ ,  $AP2\sigma1$
  - Meds- Lithium

# Epidemiology of 1<sup>o</sup> Hyperparathyroidism

- Prevalence
  - Increased 6 fold since 1970s
  - Women > Men
    - 233 vs 85 per 100K
    - ~1/50 postmenopausal
- Incidence
  - ~100K new dx/yr
  - Increased with age
    - Age ↑ gender difference



# Additional Work-Up

67 yo F incidental hypercalcemia

- No stones, fractures
- No symptoms

138	104	13	} 89
4.3	25	0.9	

- Ca **11.3 & 10.9** mg/dl
- Albumin 3.6 g/dl
- Phos **2.2** mg/dl
- PTH **105** pg/ml
- 25OH vit D 38 ng/ml

Which of the following is **NOT** required at this time?

- A. Parathyroid scan
- B. DXA
- C. Vertebral spine imaging
- D. 24 hr urine Ca/Creat
- E. Renal U/S

# Additional Work-Up

67 yo F incidental hypercalcemia

- No stones, fractures
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Which of the following is **NOT** required at this time?

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- B. DXA
- C. Vertebral spine imaging
- D. 24 hr urine Ca/Creat
- E. Renal U/S

# Recommended Work-Up

<b>Serum</b>	<ul style="list-style-type: none"><li>• <b>25-OH Vitamin D</b> (phos, alk phos, BUN)</li></ul> <p>1,25 vitD <b><u>NOT</u></b> recommended</p>
<b>Renal</b>	<ul style="list-style-type: none"><li>• <b>Creatinine</b></li><li>• <b>24h urine for*</b><ul style="list-style-type: none"><li>• <u>Calcium</u>, Creatinine, Creatinine Clearance</li><li>• Stone risk profile</li></ul></li><li>• <b>Abdominal imaging for kidney stones*</b><ul style="list-style-type: none"><li>• U/S, X-ray, CT</li></ul></li></ul> <p>*= New since 2008 guidelines</p>
<b>Skeletal</b>	<ul style="list-style-type: none"><li>• <b>DXA (Spine, hip, &amp; distal 1/3 radius)</b></li><li>• <b>Dedicated vertebral spine assessment*</b><ul style="list-style-type: none"><li>• DXA-VFA or X-Ray</li></ul></li></ul>
<b>Optional</b>	<ul style="list-style-type: none"><li>• HRpQCT, TBS by DXA, bone turnover markers</li><li>• DNA testing if suspect genetic cause of PHPT</li></ul>

# Asymptomatic PHPT

**Surgery**

**or**

**No Surgery**

# Indications for Surgery (Any One)

## Age

- < 50 yo

## Serum

- Ca > 1.0 mg/dl above ULN

## Renal

- Crt clearance < 60 ml/min
- **Presence of kidney stones on imaging\***
- **↑ Risk of kidney stones\***
  - 24h Uca > 400 mg AND
  - ↑ Urine Oxalate/Phos/Uric acid or ↓ Urine Citrate

## Skeletal

- **Osteoporosis**
  - DXA T<-2.5 (spine, hip, & *distal 1/3 radius*)
- **Vertebral spine fractures\***
  - *DXA-VFA or spine imaging*

\*= New since 2008 guidelines

## Relative Indications

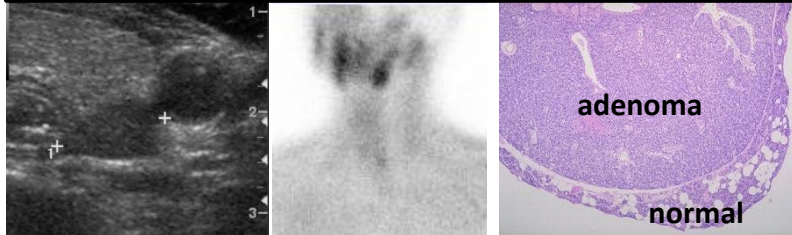
- Patient preference, poor follow-up
- Vitamin D deficiency



# Alternate Paths

## Parathyroidectomy

- Localization
  - U/S
  - Tech-Sestamibi SPECT
  - 4D CT
- Surgical Approach
  - Neck exploration
  - Minimally invasive



## Monitoring

- Serum Ca every 6-12mo
- Serum Creat every 6-12mo
- BMD (3 sites) every 1-2 yrs
- Vertebral imaging if clinical signs
  - X-Ray, VFA
- Renal stone eval if clinical signs
  - 24h Urine stone profile
  - Renal imaging

**~ 1/3 Develop an  
Indication for PTX  
within 10yr**

# Case # 1 Work-Up

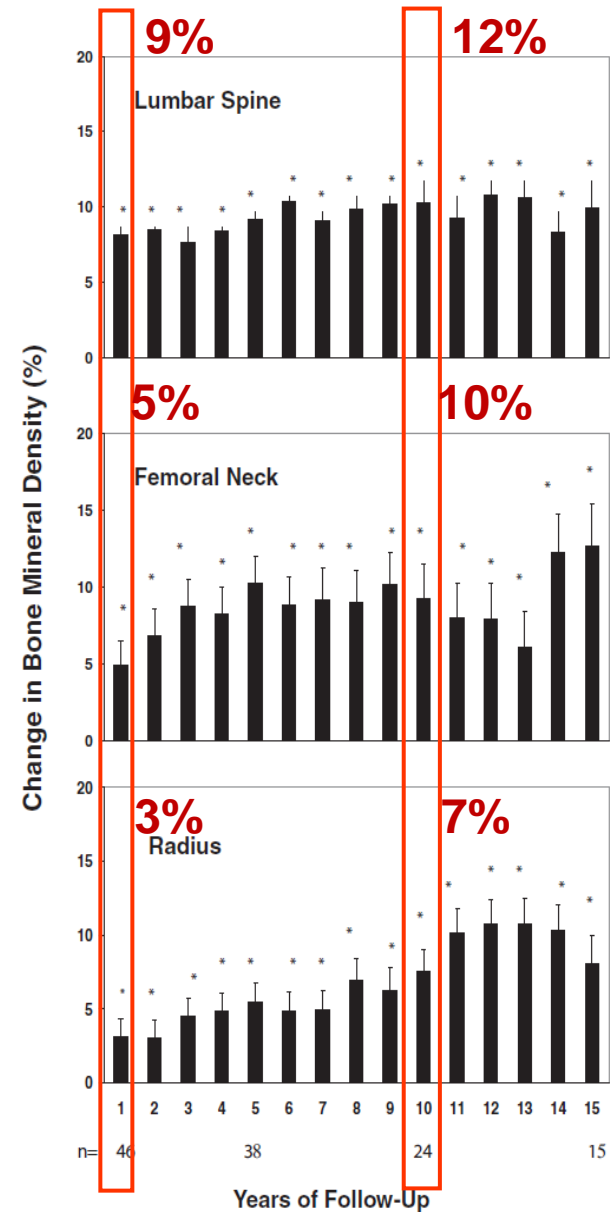
- 67 yo, no h/o fractures or kidney stones
- Labs:
  - Calcium 11.1 & 10.9 mg/dl, (PTH 105 pg/mL)
  - 25-OH vitD – 38 ng/mL (nl>32)
  - Creatinine clearance > 60 ml/min
- DEXA
  - T:- 2.0 spine, -2.4 fem neck, -2.7 hip, -2.8 wrist
  - VFA: no vertebral frx
- 24h Urine calcium – 220 mg Ca
- Abd U/S- no kidney stones

**Osteoporosis as indication for surgery**

# Improvement in BMD

Post-surgical improvement

- Spine
  - 9% after 1 yr
  - 12% after 10 yr
- Femoral Neck
  - 5% after 1 yr
  - 10% after 10 yr
- Radius
  - 3% after 1 yr
  - 7% after 10 yr

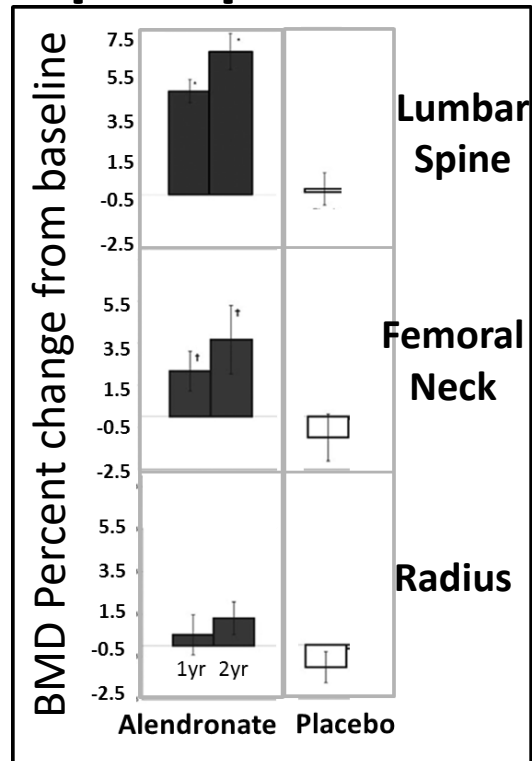


# What If...

...Patient refused surgery

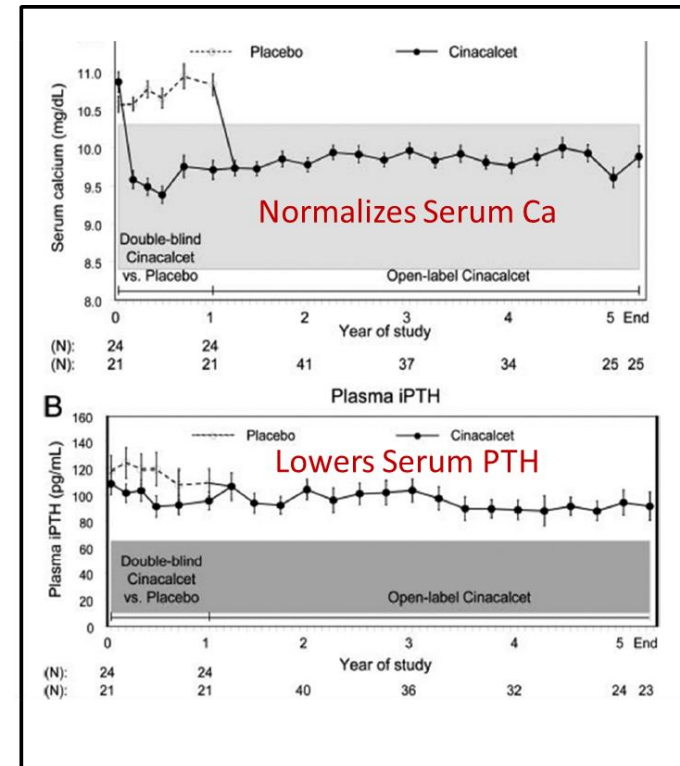
- Available medical therapy include:

## Bisphosphonates



Khan.JCEM.2004

## Cinacalcet



Peacock.JCEM.2009

# Case #2

72 yo thin F w prior tobacco use

- Depression on SSRI
- HTN on HCTZ
- Mild memory impairment
- Recent n/v, diarrhea & wt loss

Admitted with AMS and falls

<b>117</b>	71	24	113
2.9	33	1.3	

Baseline Creat ~ 0.9

- Serum Osm 258 mOsm
- Urine spec. gravity 1.021
- Urine Osm 660 mOsm/L
- TSH 3.8, am cortisol 21
- Ca 10.1, Alb 4.3, Hct 48%

## Case # 2

72 yo thin F w prior tobacco

- Depression on SSRI
- HTN on HCTZ
- Mild memory impairment
- Recent n/v, diarrhea & wt loss

Admitted with AMS and falls

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2.9	33	1.3	

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- TSH 3.8, am cortisol 21
- Ca 10.1, Alb 4.3, Hct 48%

What is the best test to determine the cause of her hyponatremia?

- A. Urine Na
- B. Renin & Aldosterone
- C. Fractional Excretion of Uric Acid (FeUA)
- D. Fractional Excretion of Urea (FeUrea)
- E. ACTH

## Case # 2

72 yo thin F w prior tobacco

- Depression on SSRI
- HTN on HCTZ
- Mild memory impairment
- Recent n/v, diarrhea & wt loss

Admitted with AMS and falls

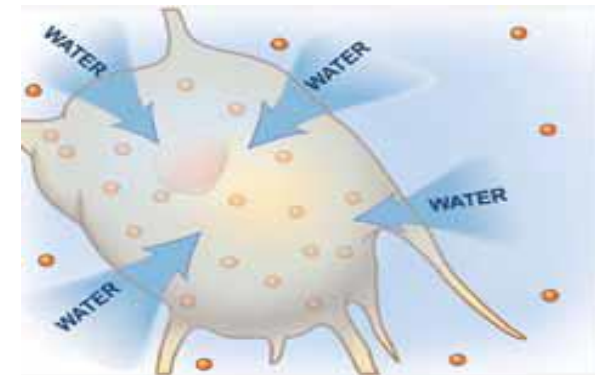
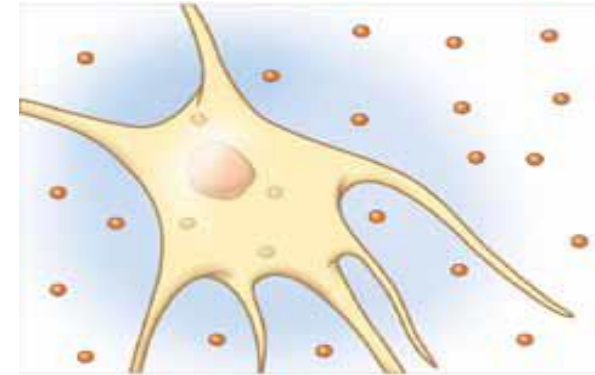
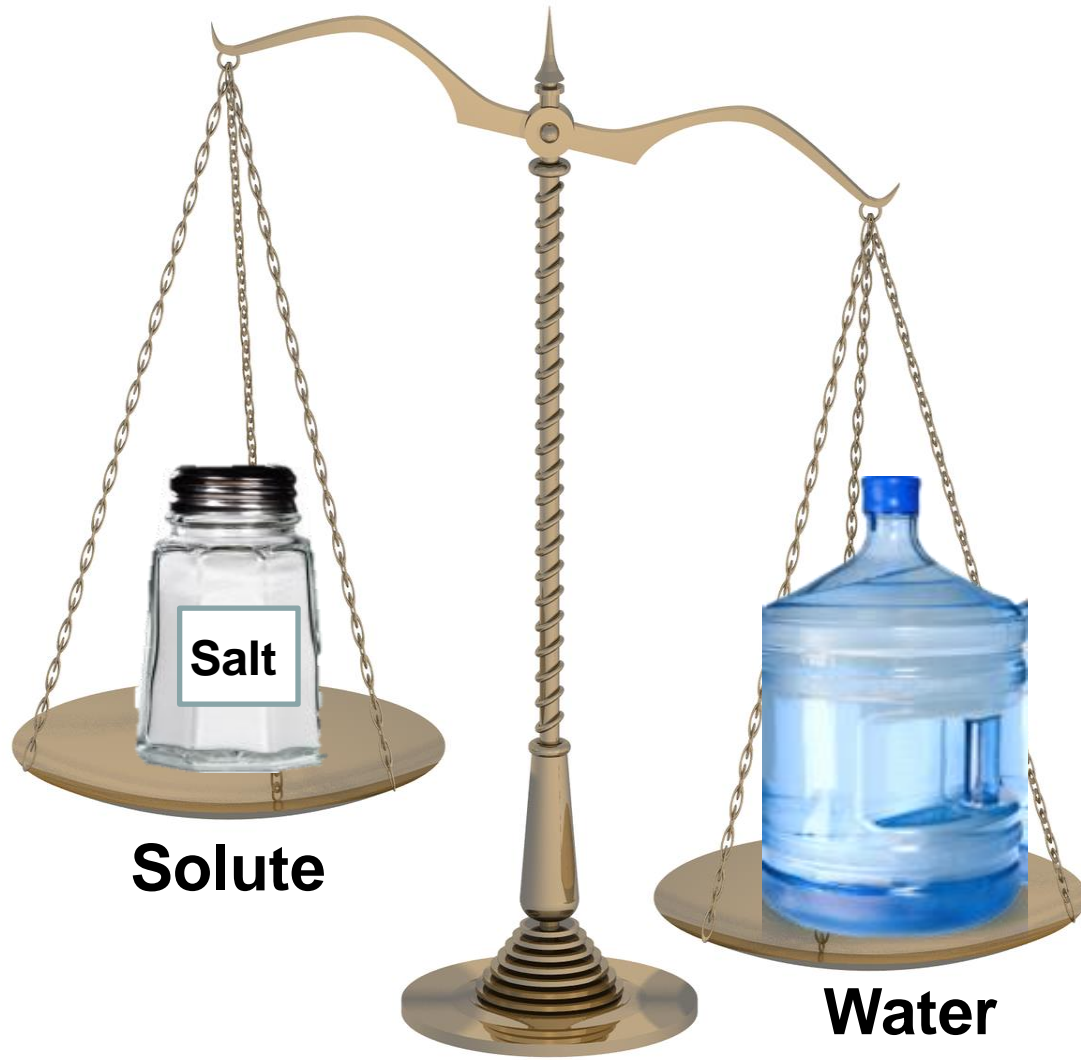
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# Hyponatremia



**"Cellular Drowning"**



# Symptoms

130-125  
mEq/L

- Nausea, decreased appetite
- Headache
- General malaise, ↓ coordination

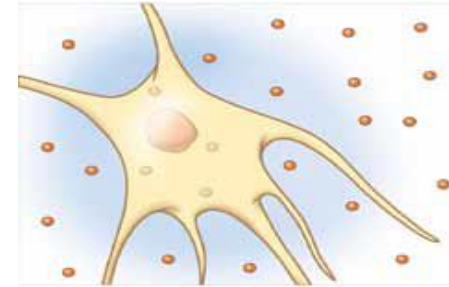
125-115  
mEq/L

- Lethargy
- Delirium
- Psychosis

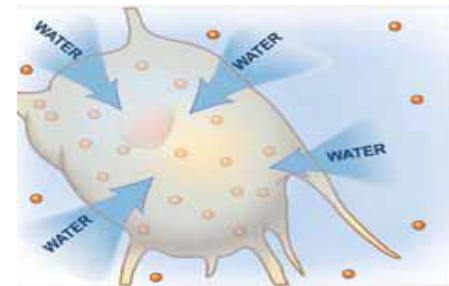
<115 mEq/L

- Seizures
- Coma, herniation
- Pulmonary edema

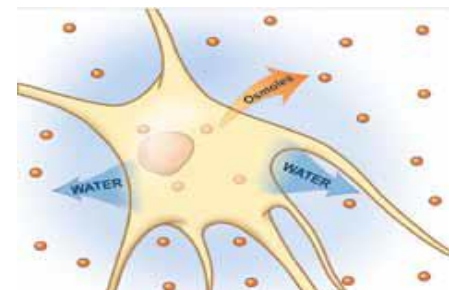
Normal State



Acute ↓Na



Adaptation

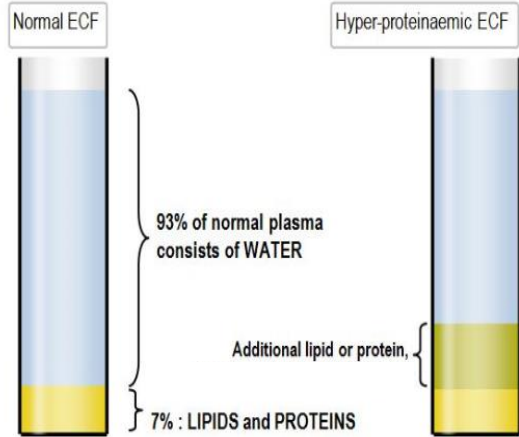


Symptom severity is more often associated with rate of decline rather than the absolute sodium level

# Hyponatremia

Rare

**Isotonic**  
(nl serum Osm)  
Pseudohyponatremia

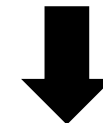
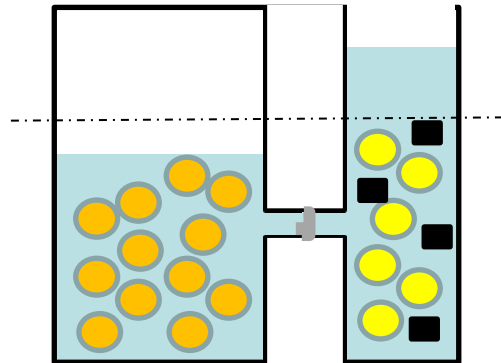
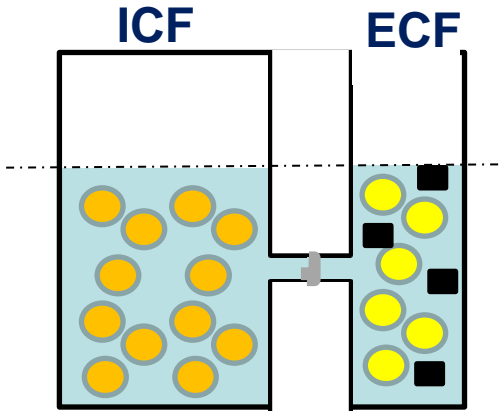


Most Common

**Hypotonic**  
(↓ Serum Osm)

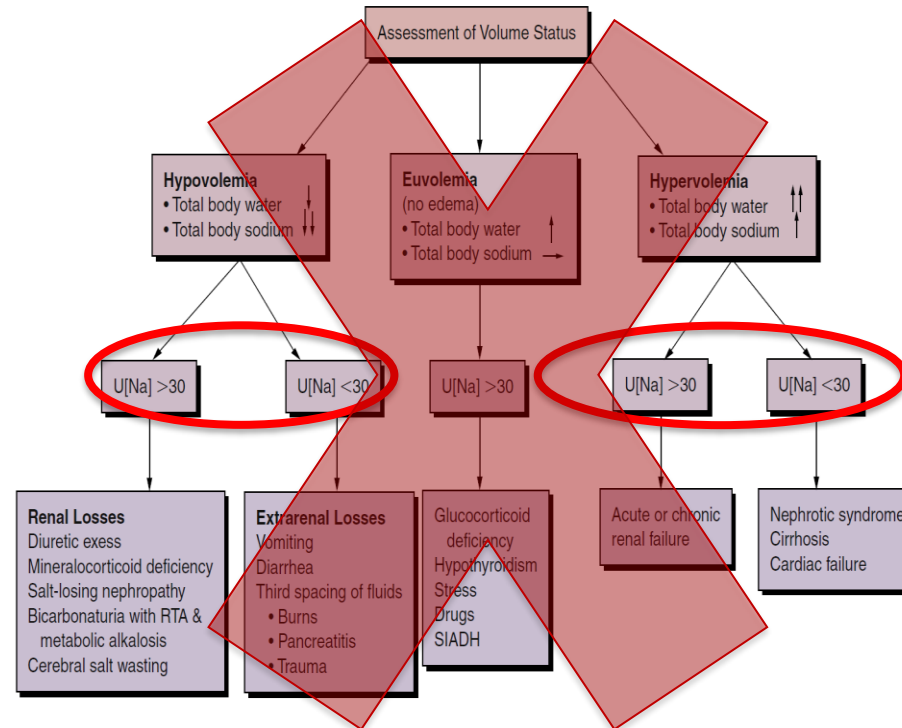
**Hypertonic**  
(↑ serum Osm)

- Glucose
- Mannitol



Is it ADH dependent?

# Hypotonic Hyponatremia



- **Volume status (TBW vs Total body Na)**
  - Hypovolemic, Euvolemic, Hypervolemic
- **Urine Na**
  - <30 vs >30 mEq/L

# Evaluation of Hyponatremia

1. Is it **Hypotonic**?
2. Is it **ADH Dependent**?
3. Is it **Appropriate**?

Confirm:

↓ Serum Osmol

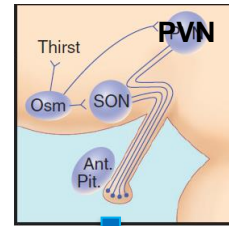
Assume:

If No ↑↑: gluc, prot, lipids

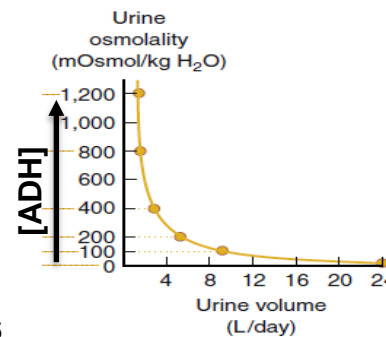
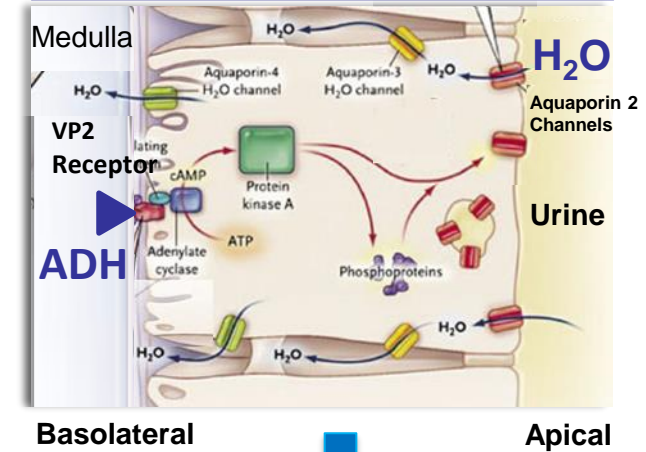
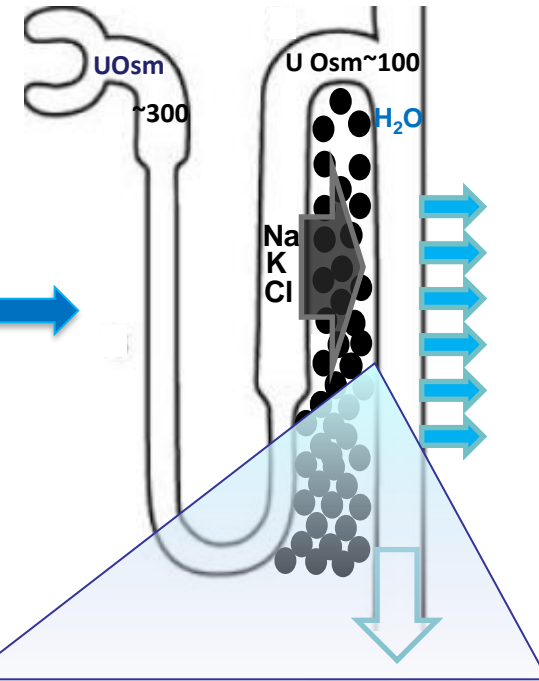
# Water Excretion

- Collecting Duct
  - Dilute urine
  - High interstitial osmolarity
- ADH (Anti-Diuretic Hormone)
  - Regulated by osmotic receptors
    - $\uparrow$  tonicity  $\rightarrow$   $\uparrow$  ADH
    - $\downarrow$  tonicity  $\rightarrow$   $\downarrow$  ADH
  - $\uparrow$  Collecting duct permeability
    - $\uparrow$  water re-absorption
    - $\uparrow$  Urine osmols,  $\downarrow$  UOP

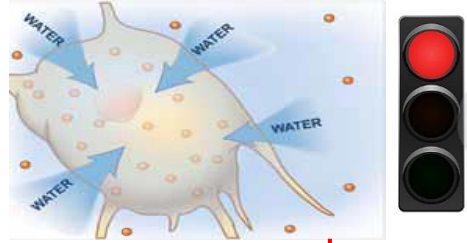
## Hypothalamus



ADH

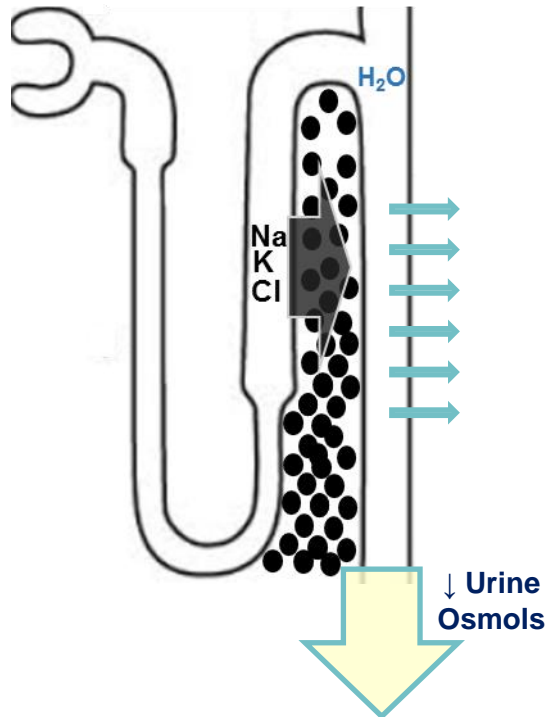


# Hypotonic

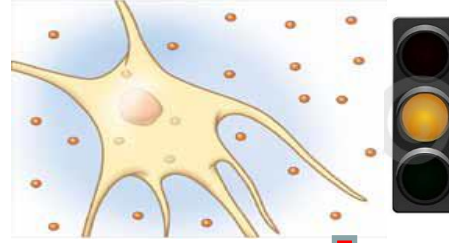


↓ Serum Osmols

↓ ADH

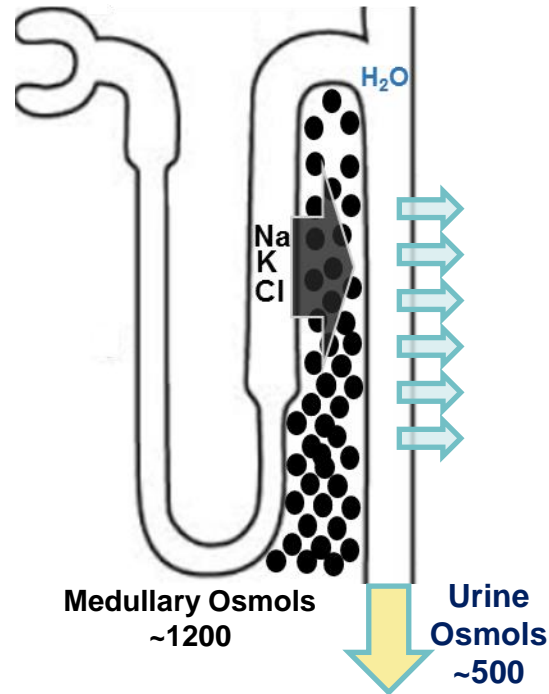


# Normal

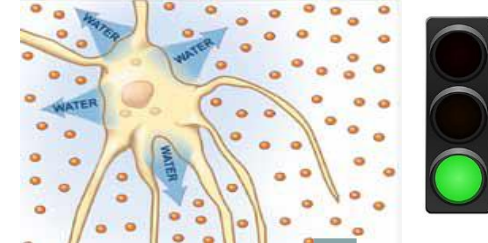


Serum Osmols  
~285

ADH

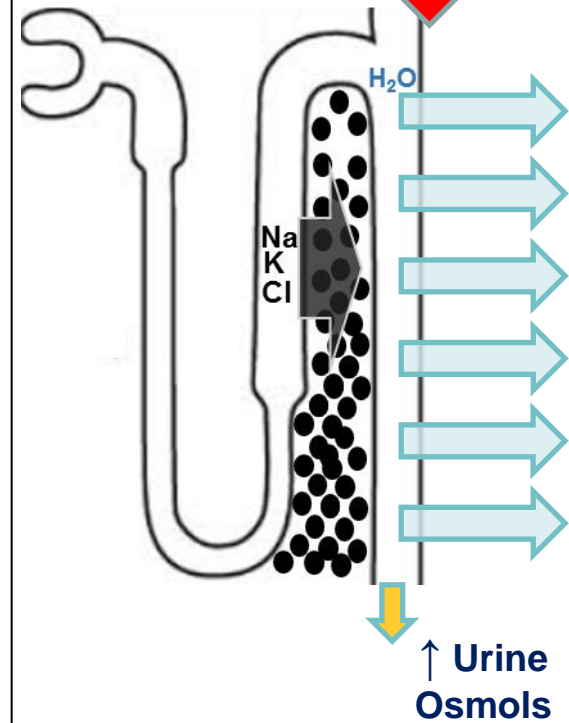


# Hypertonic

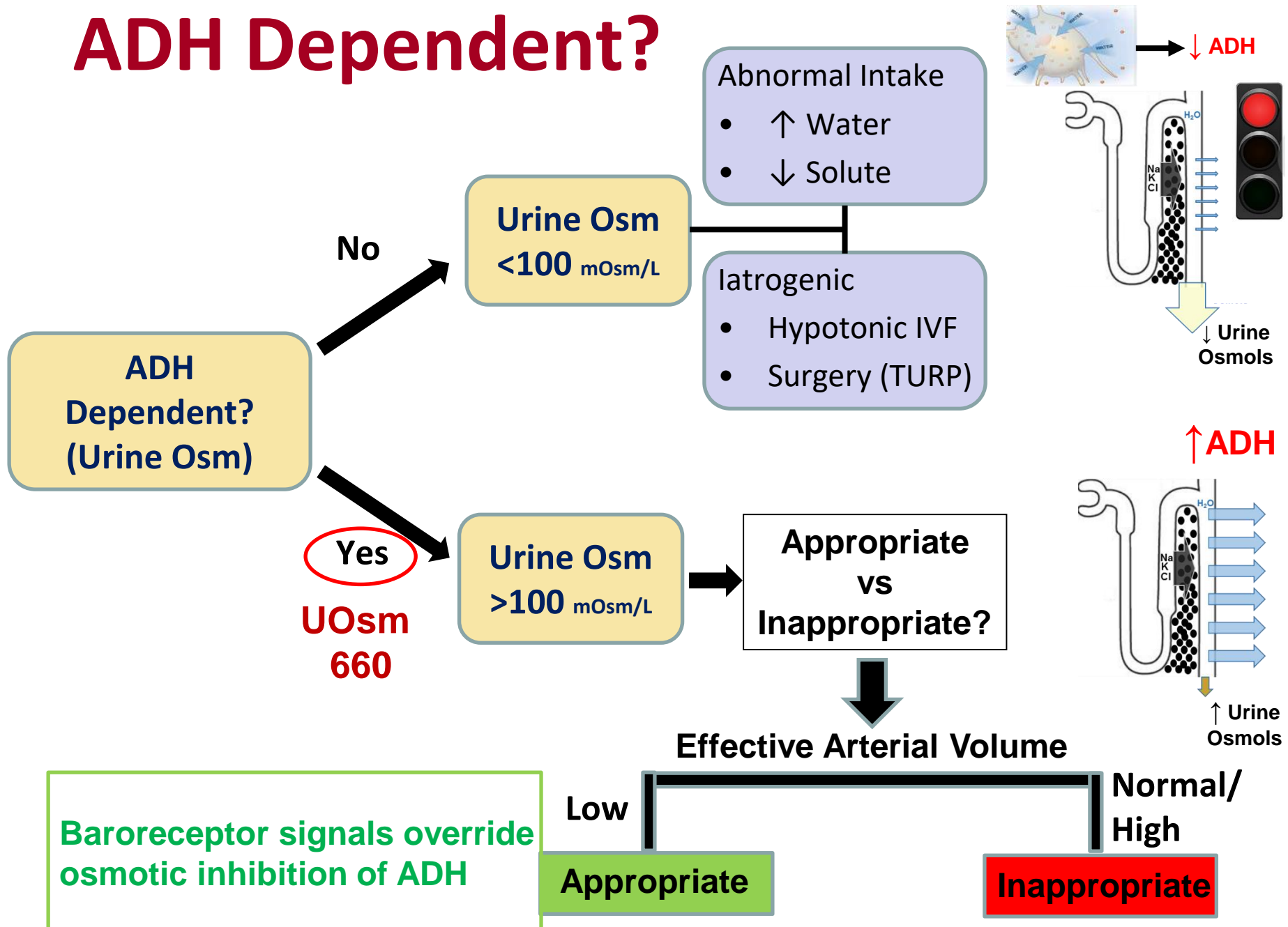


↑ Serum Osmols

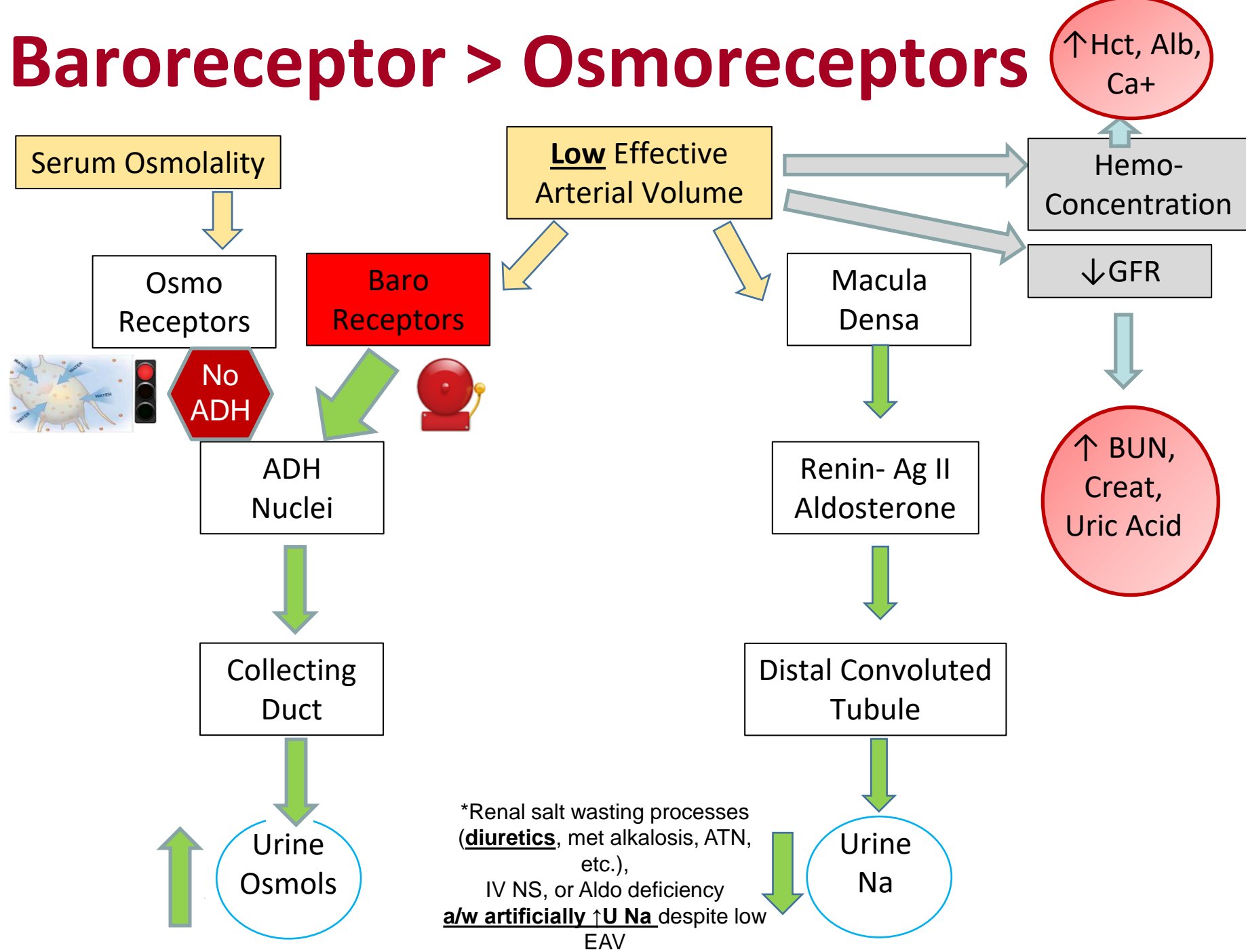
↑ ADH



# ADH Dependent?



# Baroreceptor > Osmoreceptors



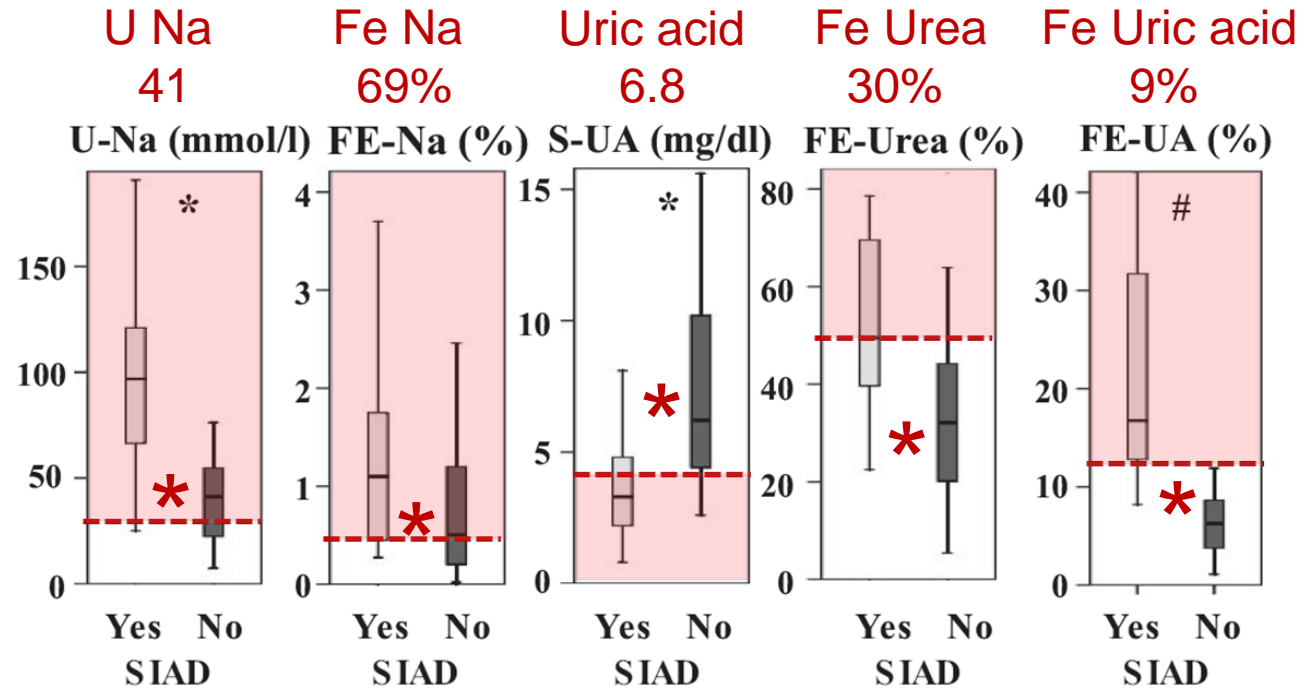


# SIADH vs Low EAV with Diuretic Use

= SIADH  
 = Low Volume

## In pts on diuretics

- Fe UA >12% had best discriminant function



SIADH	UNa >30 (mmol/L)	Fe NA >0.5 (%)	SUA < 4 (mg/dL)	Fe Urea >55 (%)	Fe UA >12 (%)
Sensitivity (%)	94	75	65	46	86
Specificity (%)	24	47	76	96	100

# Case # 2

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- Recent n/v, diarrhea & wt loss

Admitted with AMS and falls

	117	71	24	113
↑Aldo	2.9	33	1.3	

- Osm 258 mOsm/L
- UOsm 660 mOsm/L
- TSH 3.8, am cortisol 21

Hemo[ ] - Ca 10.1, Alb 4.3, Hct 48%

**DX: Low effective arterial volume**  
**Rx: Stop HCTZ, IVF NS->D5W**

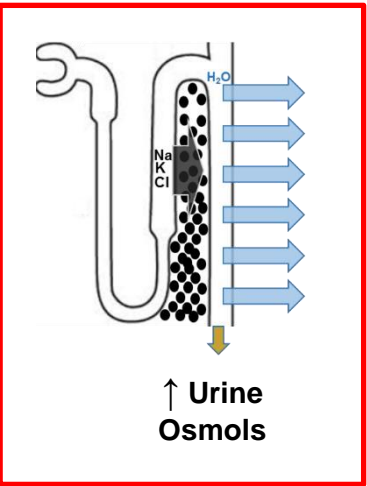
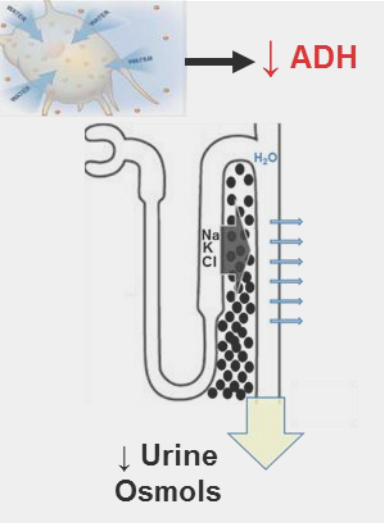
What is **the best test** to determine the cause of her hyponatremia?

- A. Urine Na
- B. Renin and Aldosterone
- C. Fe Uric Acid
- D. Fe Urea
- E. ACTH

UNa 41 mEq/L  
FeNa 69%

Uric acid 6.8 (2.3-6.6 mg/dL)  
Fe Uric acid 9%  
Fe Urea 30%

# Hypotonic Hyponatremia



**ADH Dependent? (Urine Osm)**

- No** → **Urine Osm <100 mOsm/L**
  - Abnormal Intake
    - ↑ Water
    - ↓ Solute
  - Iatrogenic
    - Hypotonic IVF
    - Surgery (TURP)
- Yes** (↑ADH) → **Urine Osm >100 mOsm/L** → **Effective Arterial Volume?**
  - UNa
  - Uric Acid, FeUA
  - BUN, Crt
  - Hemoconcentration
  - NS Response
  - Appropriate** → **↓EAV**
    - Extra-Renal Loss
      - GI losses, ↓ PO
      - Bleeding, Sweat
    - Renal Loss
      - Diuretics
      - CSW?
    - Edematous states
      - CHF, cirrhosis
      - 3<sup>rd</sup> Spacing
  - Inappropriate** → **↑EAV**
    - SIADH
      - Drugs, Tumors
      - Pulm, CNS d/o
    - Hormone deficiency
      - Adrenal Insuff
      - Hypothyroidism

## Case # 3

- 34 yo F w no PMH, triathlon coach evaluated for progressive fatigue x 3yrs
  - Significant decrease in her performance time in races
  - Lightheaded, n/v after races, longer recovery w joint pain
  - Change in diet: forced food to maintain wt, ↑↑ salt
  - “Racing the clock”: extreme fatigue in late afternoon/evening
- Meds: OCPs, no allergies
- SH: married to MD, 2 children, no tob, rare ETOH
- PE: 108/62, 88, BMI 22
  - NAD, A&O x 3, hyperpigmentation

# Case # 3

34 yo F with chronic fatigue:

131	98	9	70
5.0	22	0.8	

- Hct 41%, nl WBC & Plt
- Morning cortisol 3.5  $\mu\text{g/dL}$
- TSH 10 U/L (*nl* <5)
- FT4 1.0 ng/dL (*nl* >0.9)
- Positive anti-TPO Ab
- Urine Osm 540, UNa 34



**2011**



**2014**

# Primary Etiology

What is the most likely cause of this patient's fatigue?

- A. Excess exercise
- B. SIADH
- C. Hypothyroidism
- D. Pituitary dysfunction
- E. Primary adrenal insufficiency

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- C. Hypothyroidism
- D. Pituitary dysfunction
- E. Primary adrenal insufficiency**

# Case

34 yo F with chronic fatigue:

131	98	9	70
5.0	22	0.8	

- U Osmols 540
- TSH 10 U/L, FT4 1.0 ng/dL, +TPO
- Morning cortisol 3.5 µg/dL
- Corticotropin (250µg) stimulation test (1h)
  - Cortisol 2.7 → 8.3 µg/dL (nl > 15-18),
- ACTH 264 pg/mL (6-76 pg/mL)
- Renin 27 ng/ml/h (nl <11), aldosterone <4.0 ng/dL
  - FeUric Acid ~ 10%



**2011**



**2014**

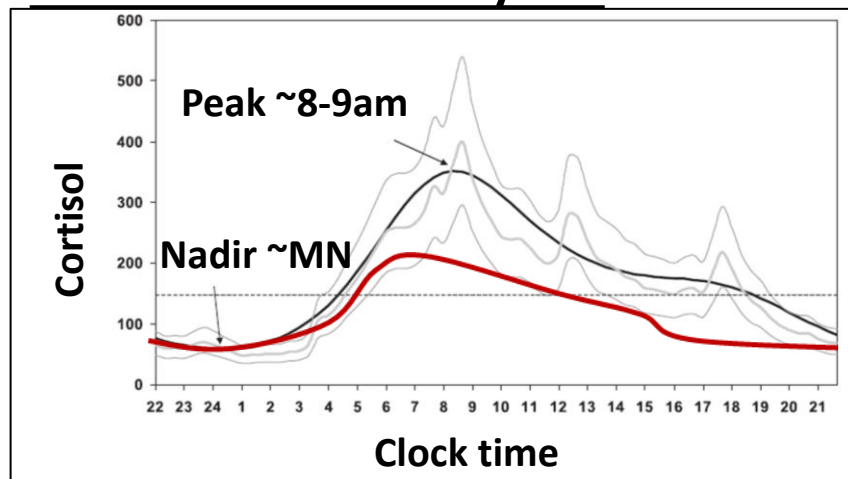


# Adrenal Insufficiency

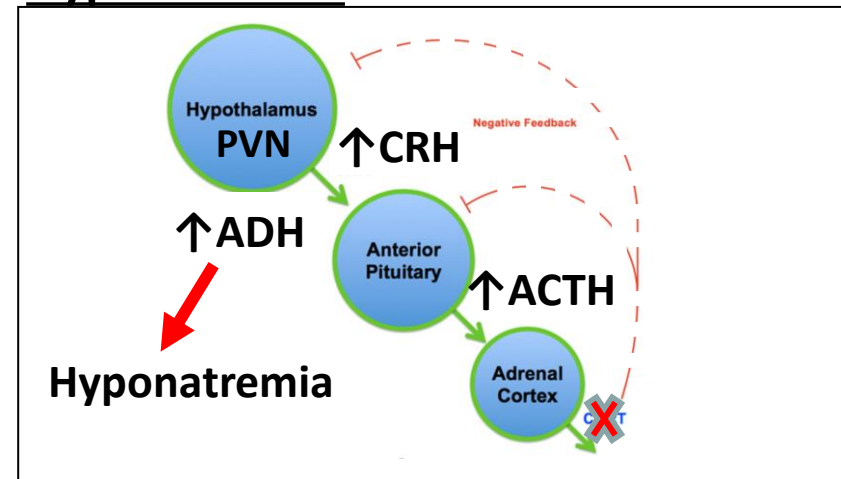
- Signs and Symptoms
  - Weakness, fatigue, anorexia
  - Weight loss, nausea/vomiting, abd pain
  - Orthostatic hypotention
  - Myalgias, arthralgias
  - Fever, eosinophilia, hyponatremia



## Cortisol Circadian Rhythm



## Hyponatremia

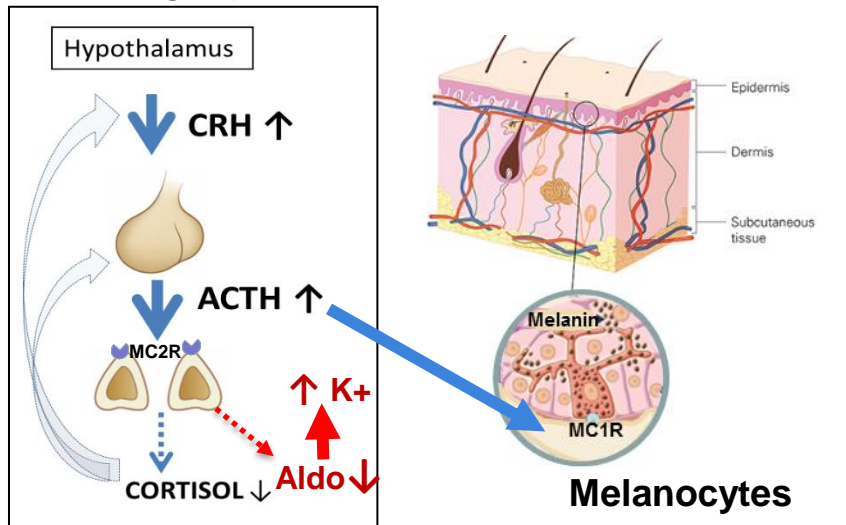


# Primary vs Central AI

## Primary AI Only

- ↑ pigmentation (↑ACTH)
- ↑K<sup>+</sup>, acidosis (↓ Aldo)
- **Autoimmune**, infx, vasc, surgery
- Other autoimmune d/o (Hashimoto's, vitiligo, T1DM, etc.)

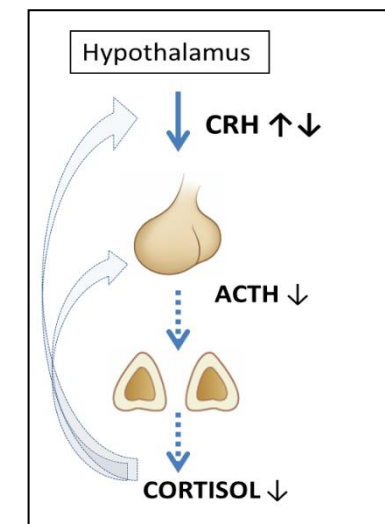
### Primary (↑ACTH)



## Central AI Only

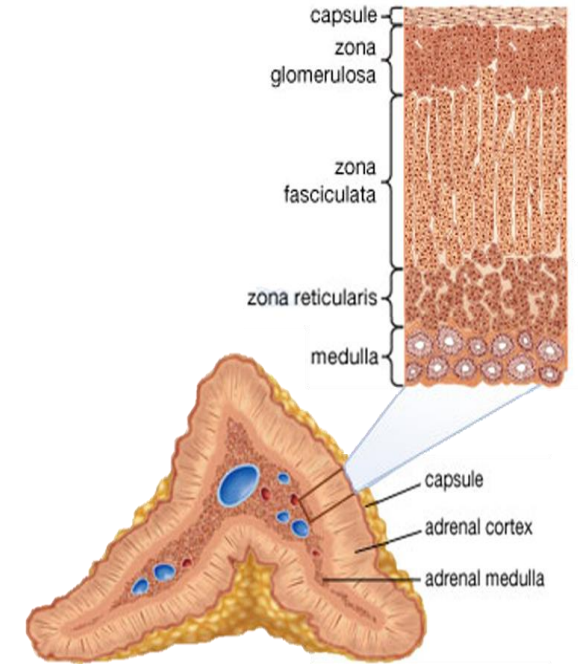
- **Glucocorticoid w/d**
- Hypothalamic/pituitary d/o
  - Pituitary dysfunction
    - Central hypothyroidism, hypogonadism, hyperprolactinemia
    - Diabetes Insipidus
  - Mass effect

### Central (↓ACTH)



# Treatment

- Glucocorticoid replacement **BEFORE** T4 replacement
  - Hydrocortisone ( $\sim 10\text{-}12\text{ mg/m}^2$ ): 15 mg am/5 mg pm
  - Prednisone:  $\sim 5\text{ mg}$
- Mineralocorticoid replacement
  - Fludrocortisone: 0.1-0.2 mg
- Sick rules
  - “3x3 Rule”-  $\uparrow$  glucocorticoid dose  $\sim 3x$  for 3 days
  - Injectable glucocorticoids in case of emergency
  - Medical alert bracelet / Emergency Medical Information Card
- Stress doses
  - Minor - 25 mg hydrocortisone (HC) on day of procedure
  - Moderate - 50 -75 mg HC on day of surgery and first post-op day
  - Major – 50 mg HC q 8-12h for 2-3 days



# Take Home Points

- Hyperparathyroidism
  - Surgery or no surgery
  - Parathyroid imaging only in preparation for surgery
- Hyponatremia
  - Is it Hypotonic? = No excess glucose, protein, lipids
  - Is it ADH dependent? = High urine osmols
  - Is it Appropriate? = Baroreceptor-mediated
- Adrenal Insufficiency
  - Primary vs Central
  - Glucocorticoids +/- mineralocorticoids

**Thank You!**

