Sodium Disorders

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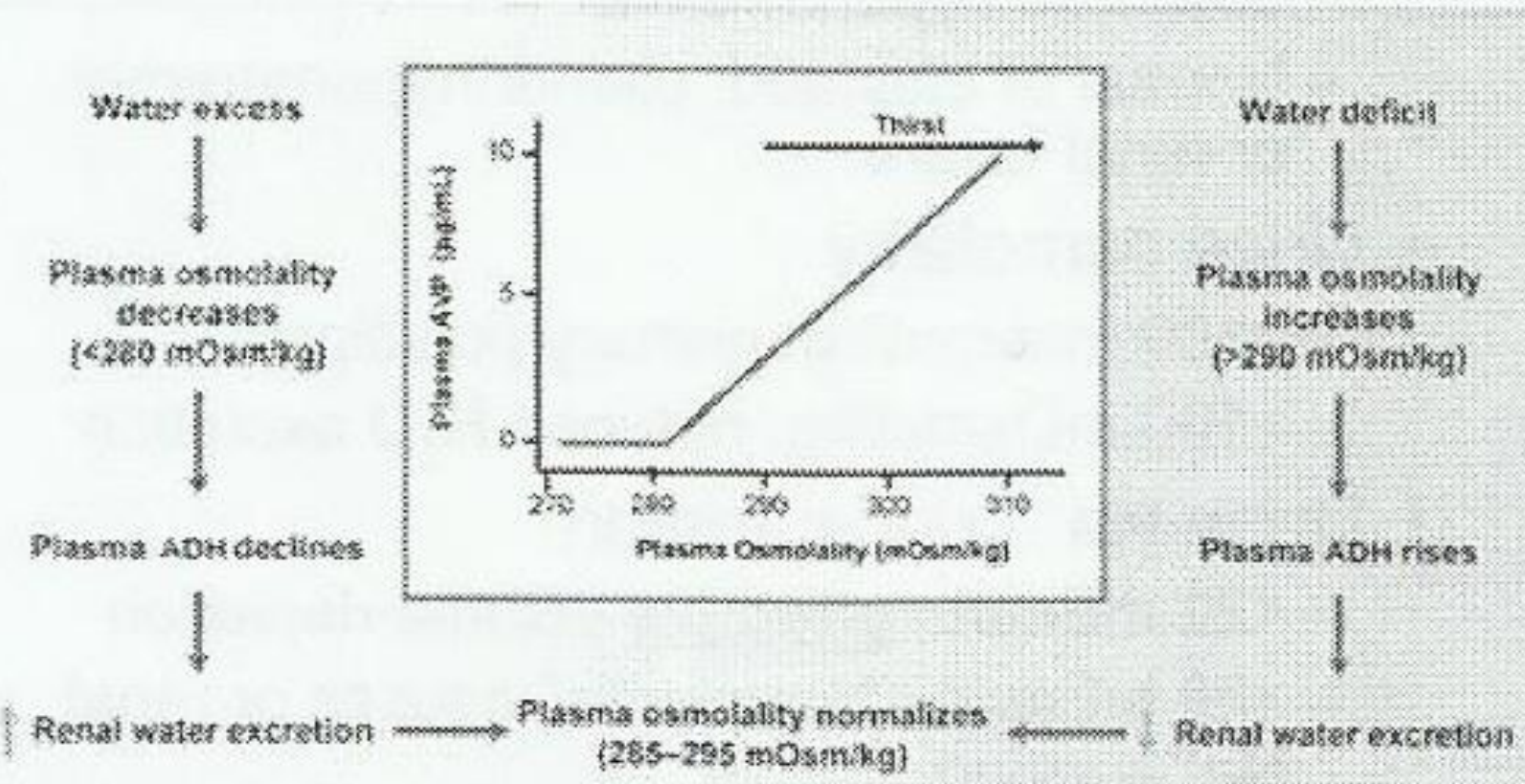
athens-NEPHROLOGY

OVERVIEW

- **Hyponatremia**
  - Pathophysiology
  - Diagnostic approach
  - Clinical sequelae
    - Acute hyponatremia
    - Chronic hyponatremia
  - Management
- **Hypernatremia/polyuria**
  - DD_x and diagnostic approach
  - Management

Vasopressin (ADH) Regulates Water Homeostasis and Osmolality



Osmoregulation versus Extracellular Volume Regulation

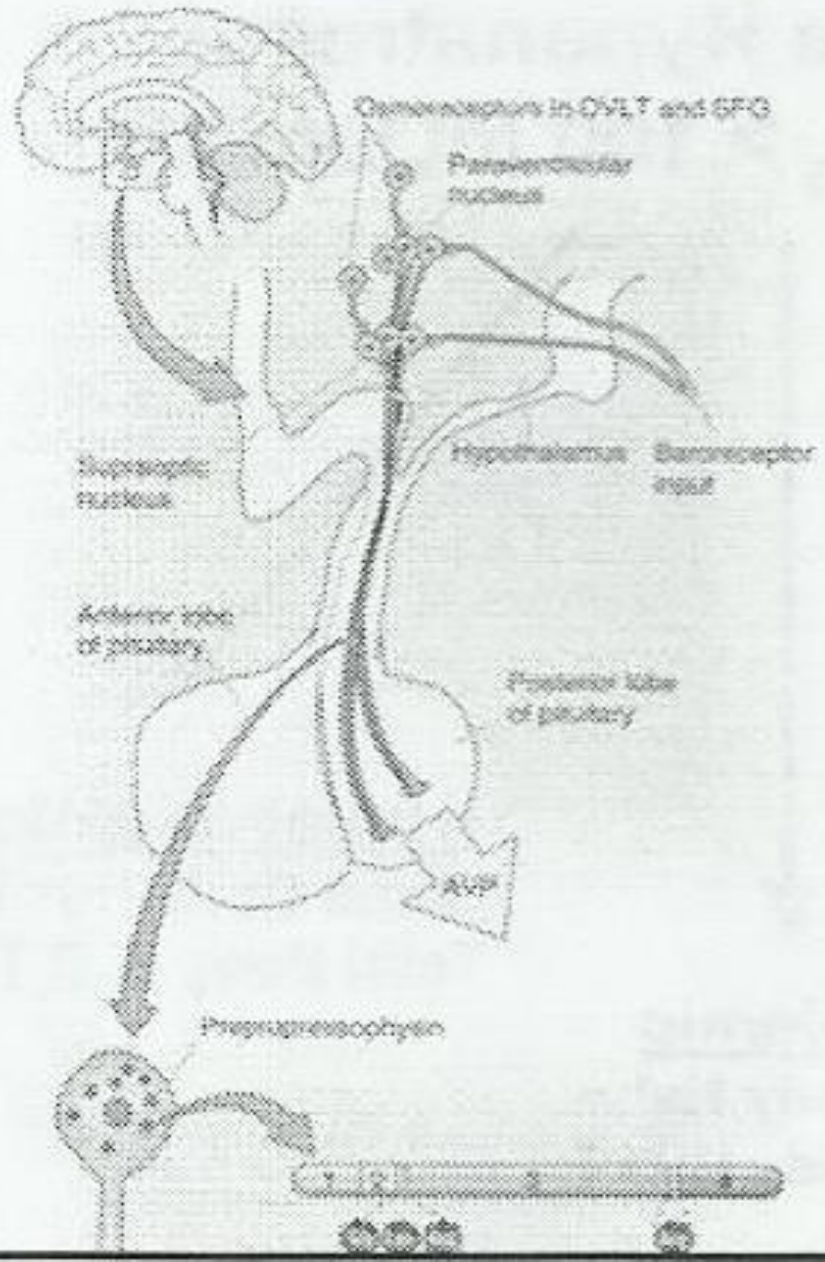
	Osmoregulation	*Volume regulation*
What is being sensed	Plasma osmolality	"Effective" circulating volume
Sensors	Hypothalamic osmoreceptors	Carotid sinus Afferent arteriole Atria
Effectors	ADH/Vasopressin Thirst	Sympathetic nervous system Renin-angiotensin-aldosterone system ANP/BNP **VASOPRESSIN**
What is affected	Urine osmolality Water intake	Urinary sodium excretion

Black and Rose, *Manual of Clinical Problems in Nephrology*, 1988

Vasopressin Receptor Subtypes

Receptor subtype	*Tissue/cell type*	*Activation effects*
V_{1A}	Vascular smooth muscle	Constriction
	Platelets	Platelet aggregation
	Hepatocytes	Glycogenolysis
	Baroreceptors	Baroreflex – bp control
	Cardiomyocytes	Hypertrophic response
V_{1B}	Anterior Pituitary	ACTH and β-endorphin release
V_2	Renal Principal cells	Water and Na-Cl absorption
	Thick Ascending Limb cells	

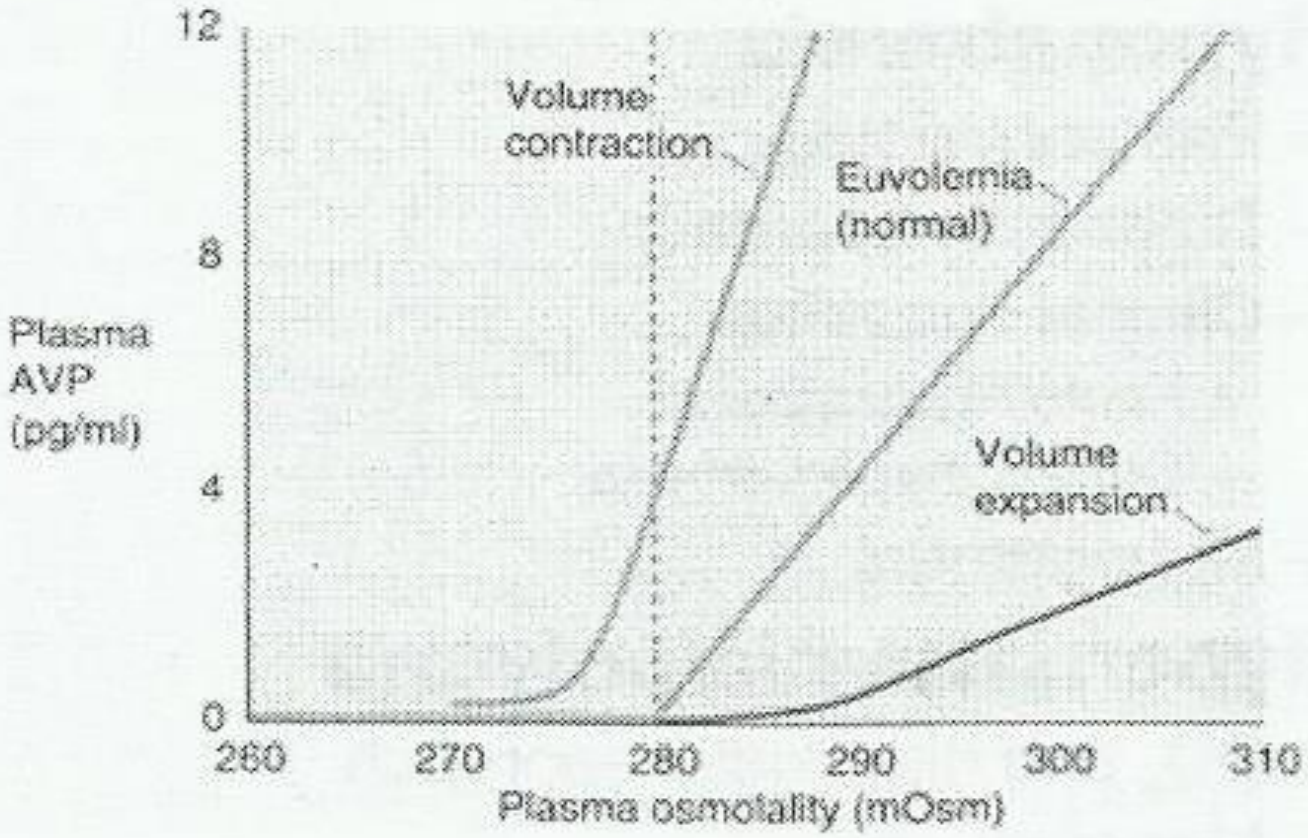
Hypothalamic Control of Vasopressin Secretion



OVLT – organum vasculosum of the lamina terminalis (periventricular, 3rd ventricle)
SFO – subfornical organ

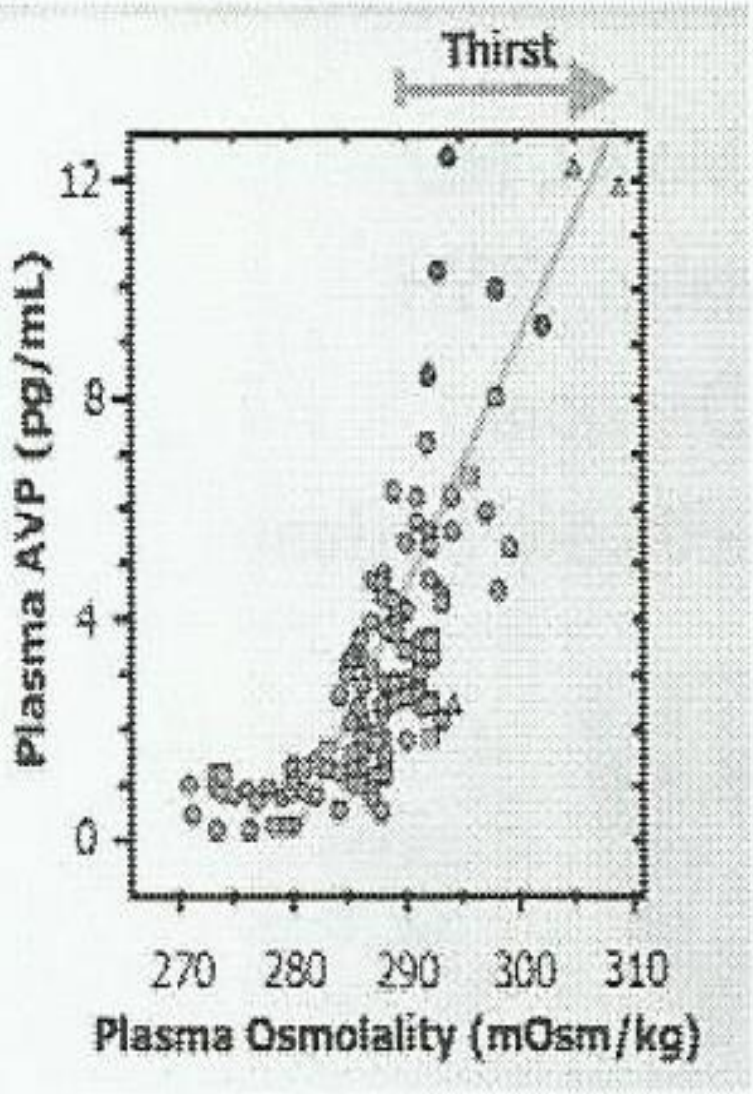
Boron and Boulpaep, *Medical Physiology*, 2004

Volume Status and Vasopressin Release



Boron and Boulpaep, *Medical Physiology*, 2004

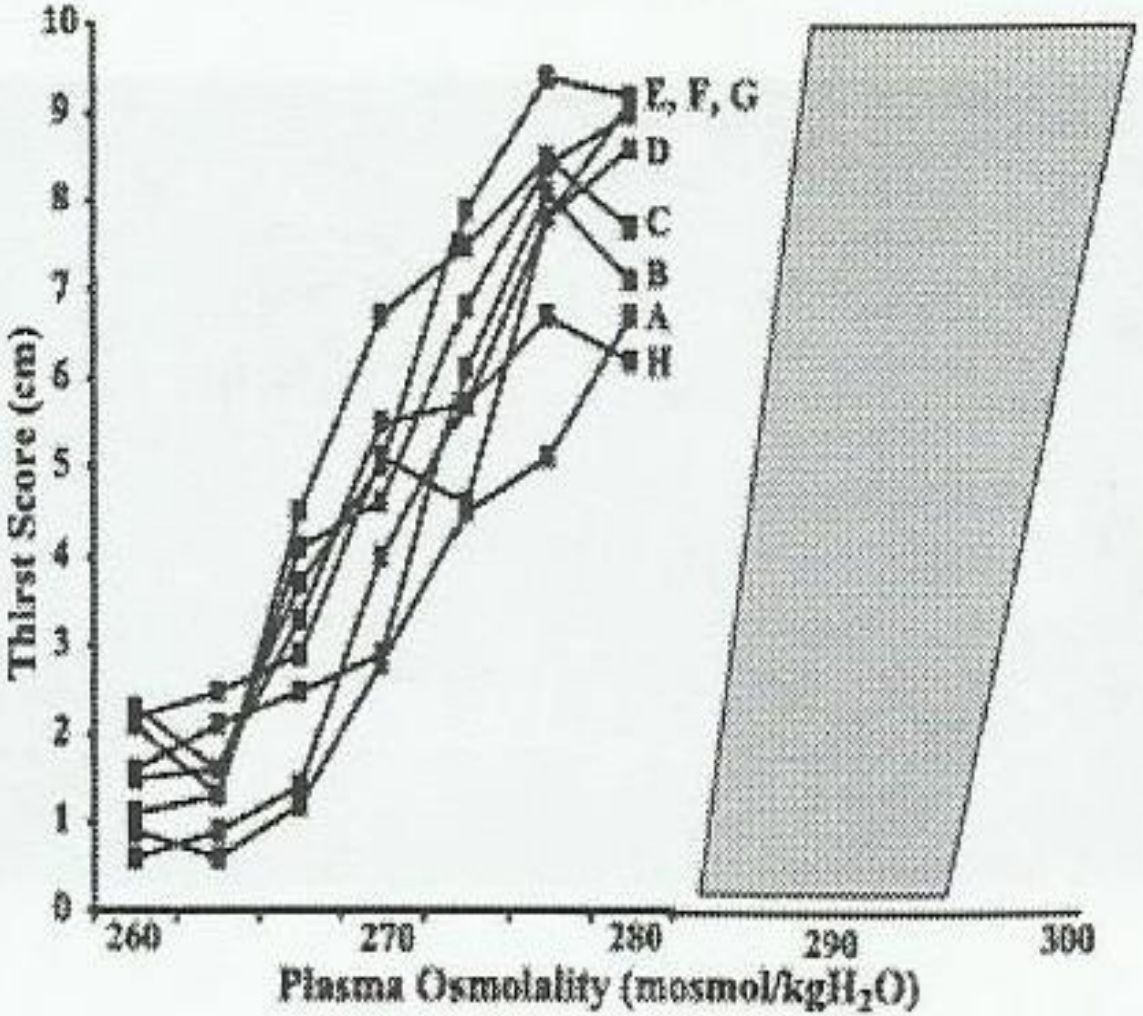
What About Thirst??



Thirst typically stimulated over same range of Osm as ADH/vasopressin

Typically need intake of H_2O to generate hyponatremia

Leftward Shift of the Thirst Response in SIADH, i.e. Thirst Also Abnormal



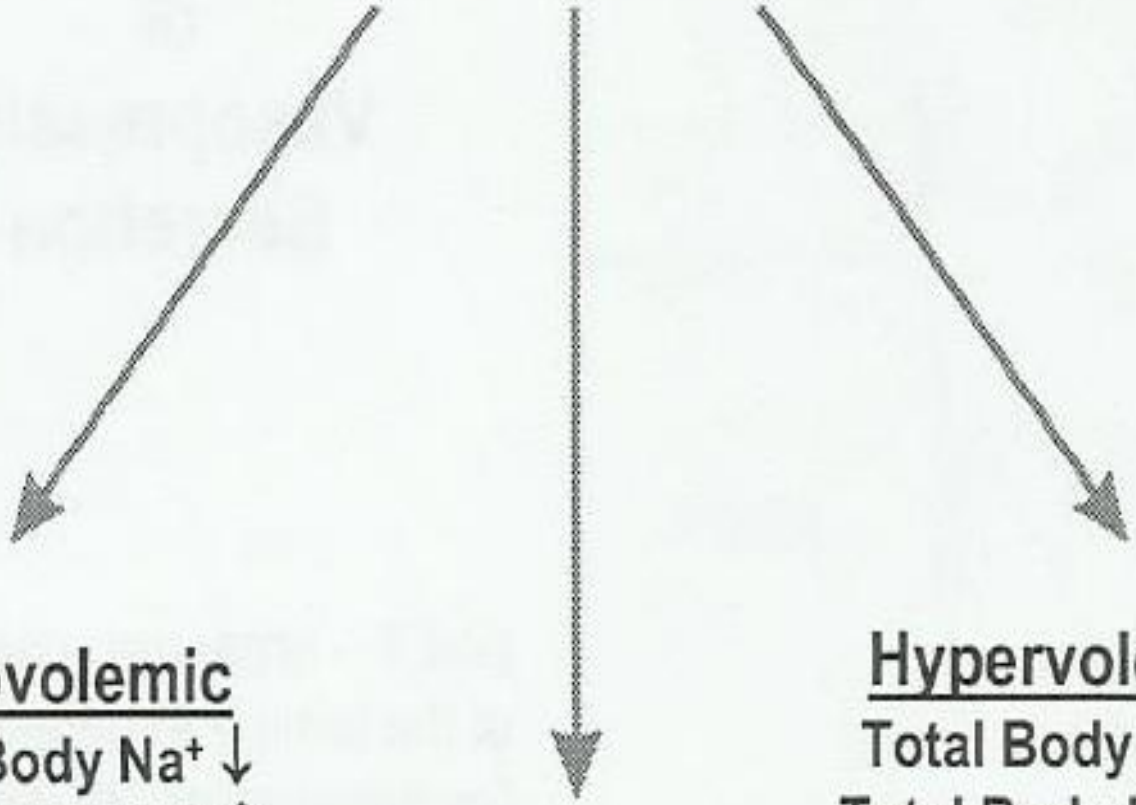
A-H: SIADH pts
Grey: Controls

Smith et al, *AJP Endocrinol*, 2004

Initial Lab Evaluation of Hyponatremia

- Plasma osmolality
  - Low: true hyponatremia
  - Normal or elevated: pseudohyponatremia or renal failure
- Urine osmolality
  - <100 mosmol/kg: primary polydipsia
  - >100 mOsmol/kg: reduced H_2O excretion
- Urine Na^+ concentration
  - <20 mEqu/L: **effective** volume depletion
  - >20 mEqul/L: "euvolemic" causes or renal Na^+ wasting

Approach to the Hyponatremic Patient with U_{osm} > 100 mOsm/kg

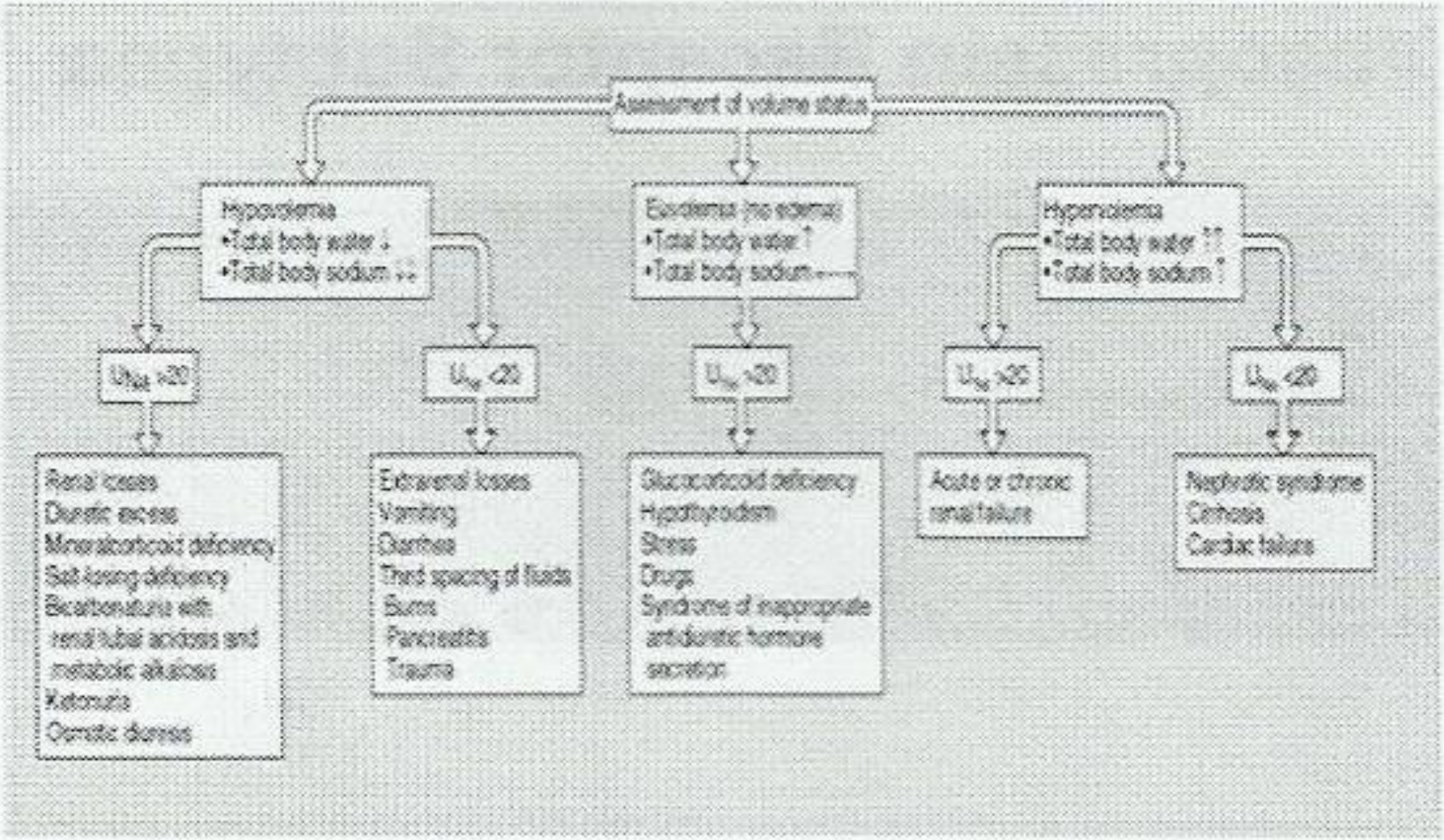


Hypovolemic
Total Body Na^+ ↓
Total Body H_2O ↑

Euvolemic
Total Body Na^+ ~
Total Body H_2O ↑

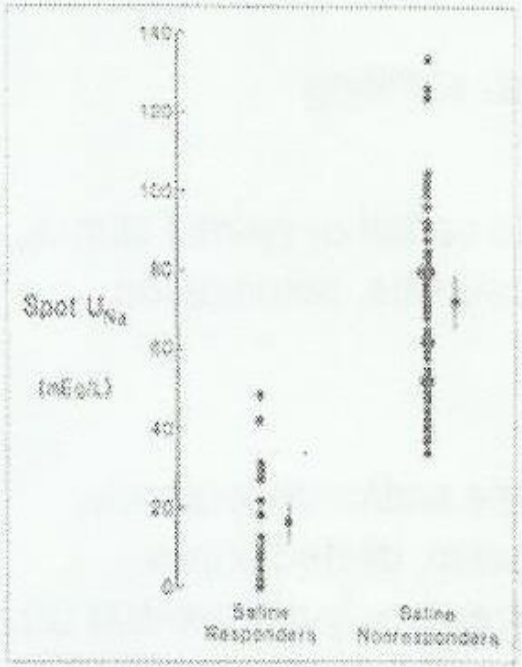
Hypervolemic
Total Body Na^+ ↑
Total Body H_2O ↑↑

Diagnostic Algorithm



Kumar and Berl, Atlas of Diseases of the Kidney, 1999

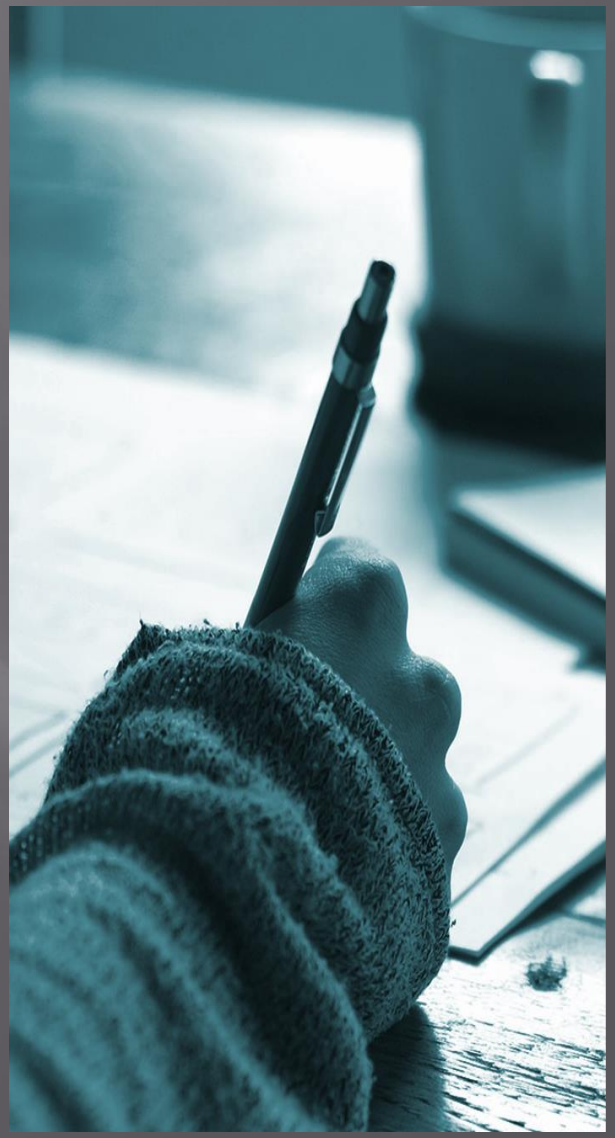
Spot Urinary Na^+ and the D_x of Hypovolemic Hyponatremia

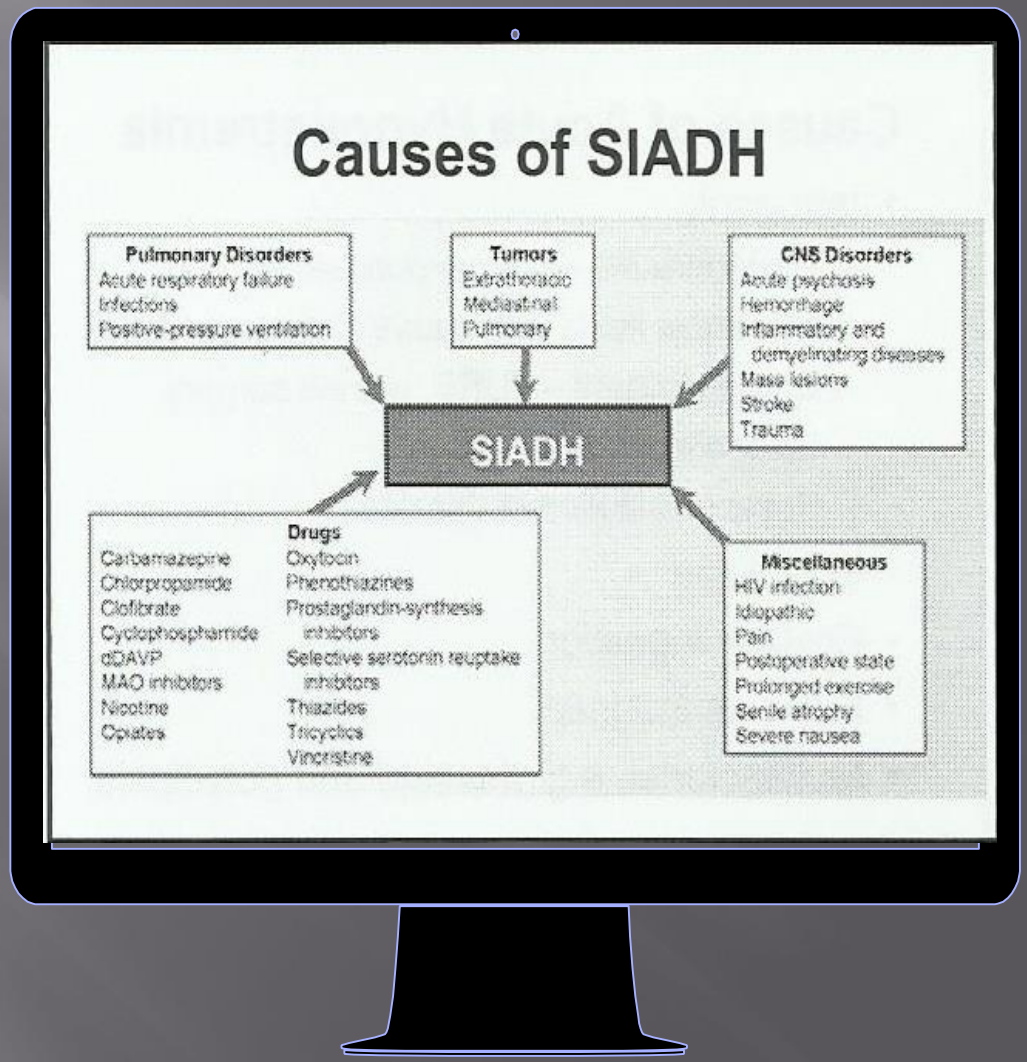


Urine Na^+ in "non-edematous" patients with hyponatremia, who do or do not respond to saline infusion with ↑ serum Na^+ .

Na^+-avid patients have ↑ vasopressin due to hypovolemia → suppressed by normal saline infusion.

Am J Med 83: 905-908, 1987




Causes of SIADH
Pulmonary Disorders
Acute respiratory failure
Infections
Positive-pressure ventilation
Tumors
Extrathoracic
Mediastinal
Pulmonary
CNS Disorders
Acute psychosis
Hemorrhage
Inflammatory and demyelinating diseases
Mass lesions
Stroke
Trauma
SIADH
Drugs
Carbamazepine
Chlorpropamide
Clofibrate
Cyclophosphamide
dDAVP
MAO inhibitors
Nicotine
Opiates
Oxytocin
Phenothiazines
Prostaglandin-synthesis inhibitors
Selective serotonin reuptake inhibitors
Thiazides
Tricyclics
Vincristine
Miscellaneous
HIV infection
Idiopathic
Pain
Postoperative state
Prolonged exercise
Senile atrophy
Severe nausea

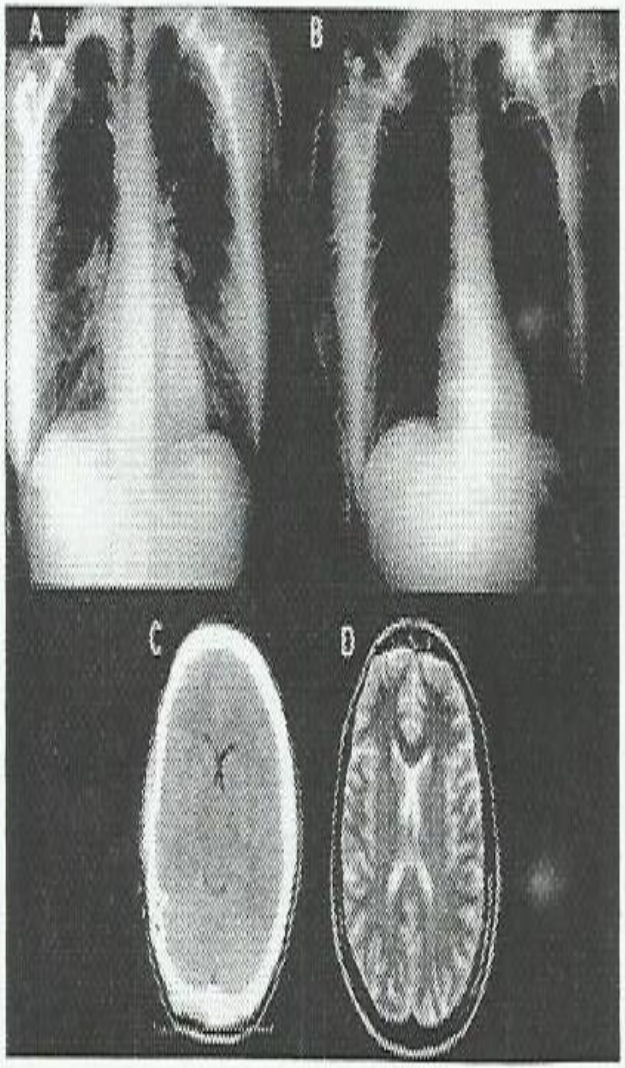
Causes of Acute Hyponatremia

- Iatrogenic
  - Postoperative – premenopausal women
  - Hypotonic fluids with cause of ↑ vasopressin
  - Glycine irrigant – TURP, uterine surgery
  - Colonoscopy preparation
  - Recent institution of thiazides
- Polydipsia
- Ecstasy ingestion
- Exercise induced
- Multifactorial, e.g. thiazide and polydipsia

Symptoms/Signs of Acute Hyponatremic Encephalopathy

- **Early**: headache, nausea, vomiting
- **Advanced**: ↓ response to verbal or painful stimuli, inappropriate behavior, asterixis, obtundation, incontinence
- **Far advanced**: decorticate and/or decerebrate posturing, hyper/hypotension, dilated pupils, **seizures**, **respiratory arrest**, polyuria (central DI), hyperglycemia

Cerebral Edema and Non-Cardiogenic Pulmonary Edema in Acute Hyponatremia

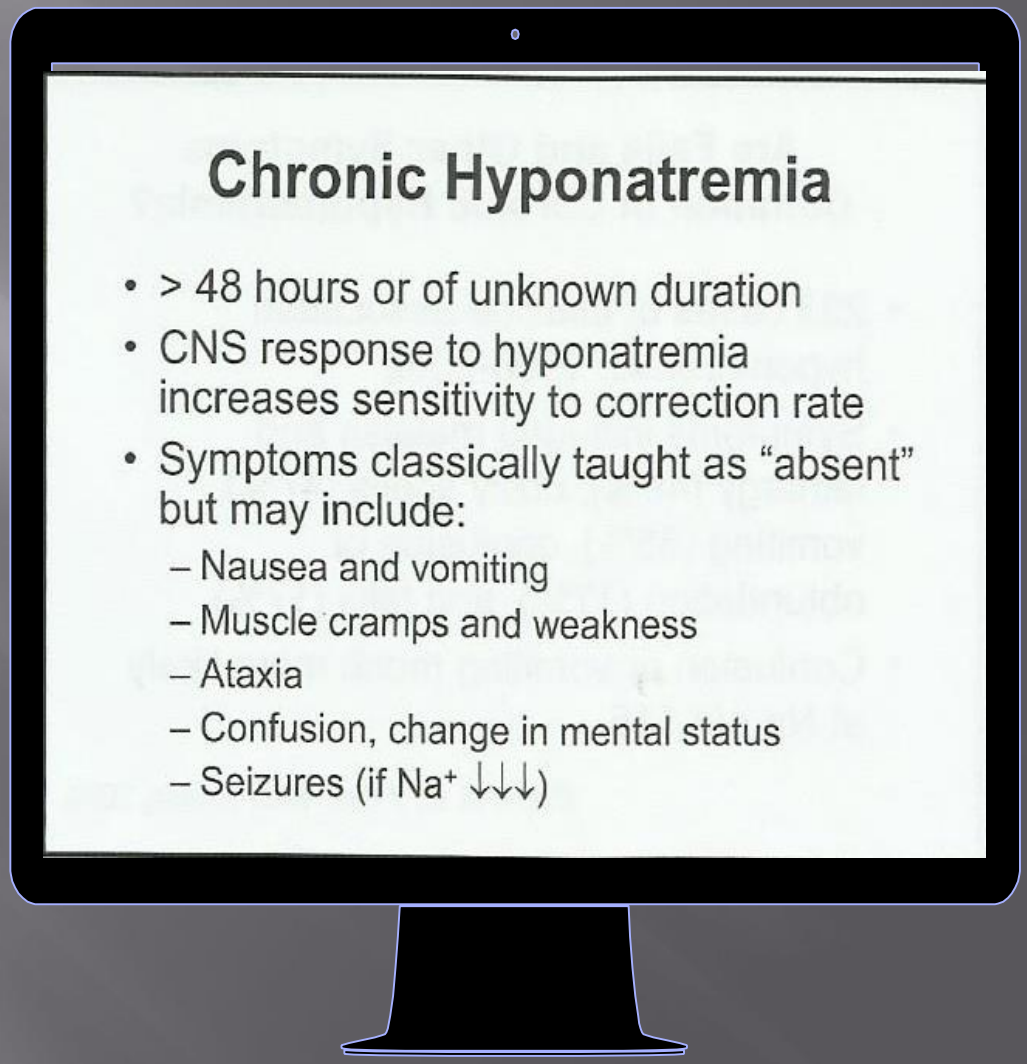


A&C – @ ER
B&D – after 24 hrs

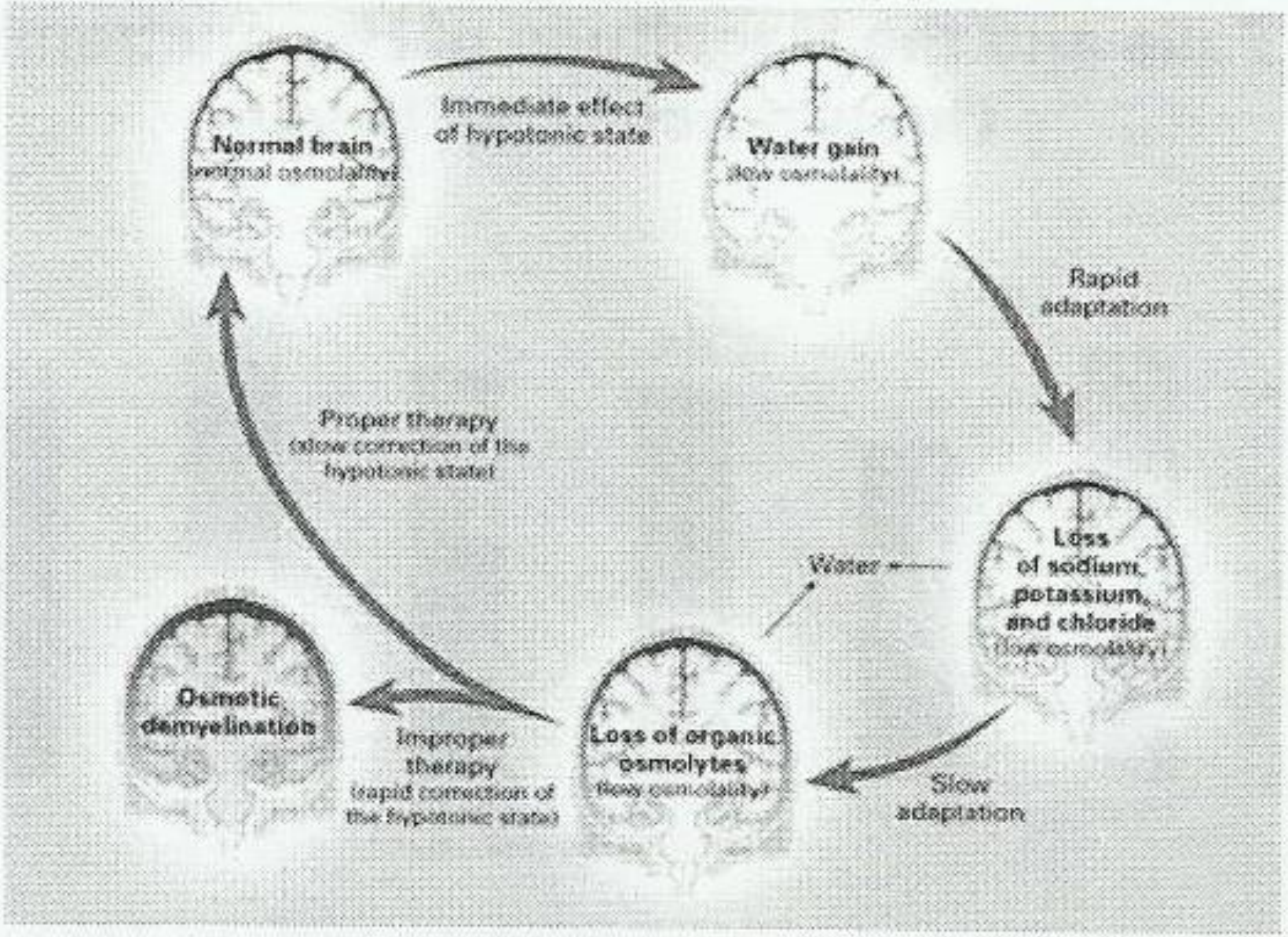
44 yo female
marathon runner

Ayus et al,
Ann Int Med, 2000

CT head MRI


Chronic Hyponatremia
• > 48 hours or of unknown duration
• CNS response to hyponatremia increases sensitivity to correction rate
• Symptoms classically taught as "absent" but may include:
– Nausea and vomiting
– Muscle cramps and weakness
– Ataxia
– Confusion, change in mental status
– Seizures (if Na^+ ↓↓↓)

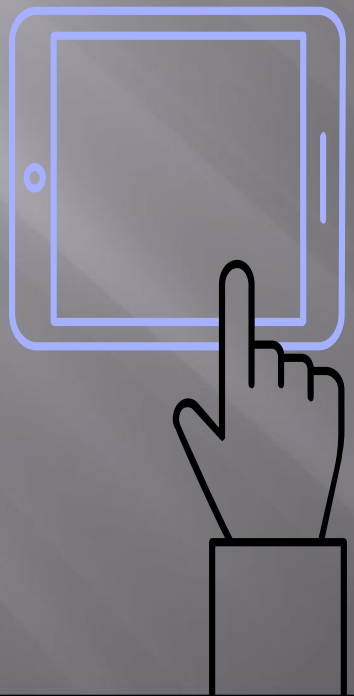
The CNS Response to Hyponatremia



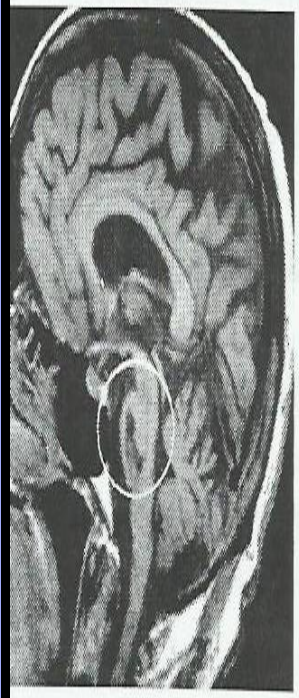
Adrogue and Madias, *NEJM*, 2000

Risk Factors for Osmotic Demyelination

- Rate of correction (although CPM/ODS can occur at accepted rates…..)
- Hypokalemia
- Alcoholism
- Malnutrition, e.g. with anorexia/bulimia
- Liver failure, liver transplantation
  - Similar changes in cerebral osmolytes in liver failure

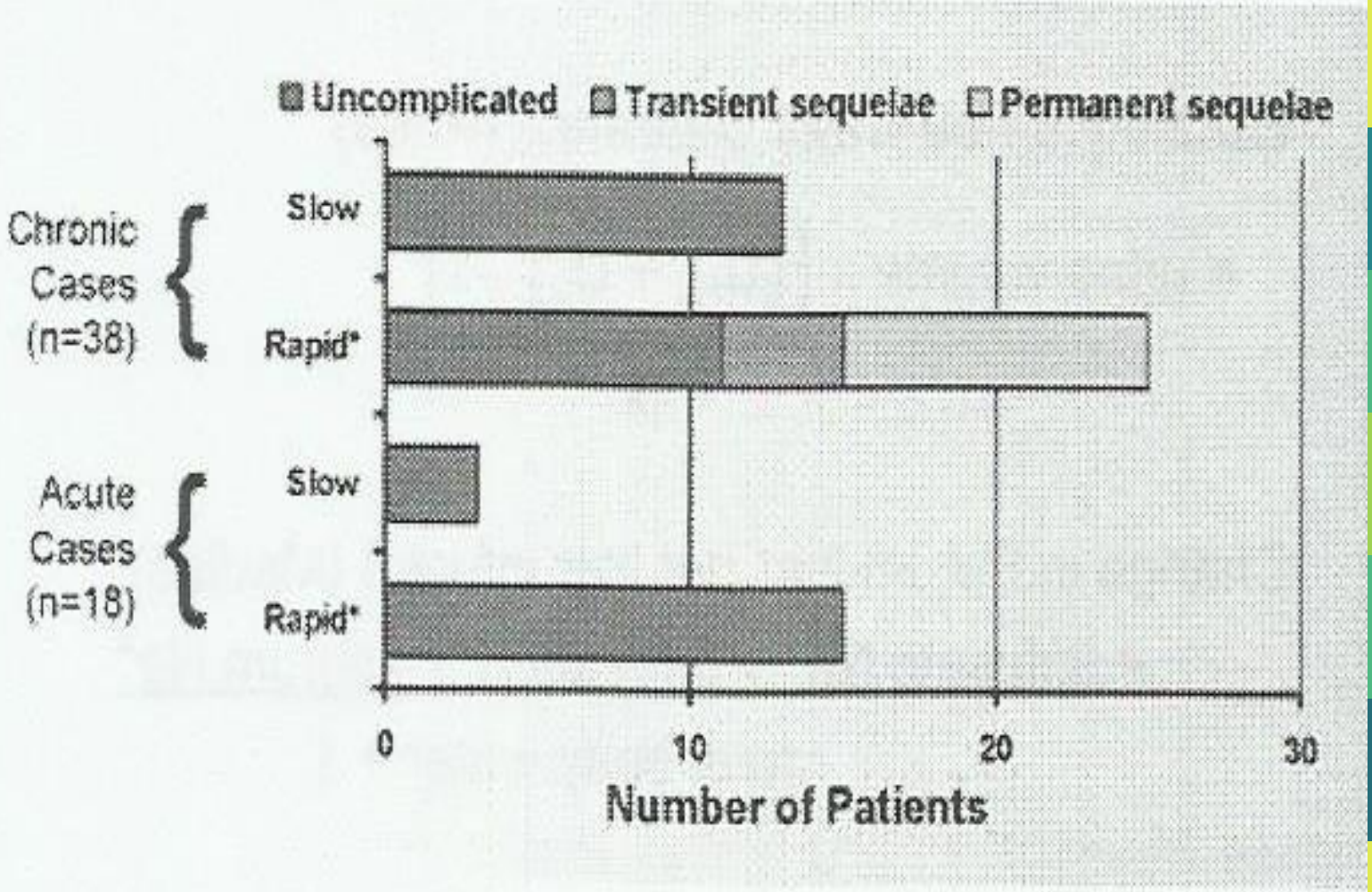


Central Pontine Myelinolysis (CPM) From Osmotic Demyelination Syndrome (ODS)



- Flaccid quadriparesis, Δ corticospinal tract
- Dysphagia, from corticobulbar tract
- Locked-in syndrome
- Symptoms from extra-pontine path are variable, depending on region involved

Rate of Correction from $[Na^+] \leq 105$ mEqu/L and Neurological Outcome



Sterns et al, *JASN*, 1994

Is Chronic Hyponatremia Really That Asymptomatic?

- Case-control series of 122 consecutive asymptomatic hyponatremia patients.
- Na ranged from 115-135
- Prevalence of falls was 21.3% versus 5.4 % in case controls ($p < 0.001$).
- Fall was often reason for admission.
- Subtle gait and attention defects in a separate cohort of hypoNa patients.

Renneboog, et al, *Am J Med*, 2006

Are Falls and Other Symptoms Common in Chronic Hyponatremia?

- 223 cases of thiazide-associated hyponatremia, 1996-2002
- Symptoms included malaise and lethargy (49%), dizzy spells (47%), vomiting (35%), confusion or obtundation (17%), and falls (17%).
- Confusion or vomiting much more likely at Na </= 115.

Chow et al, *J Nat'l Med Assoc*, 2004

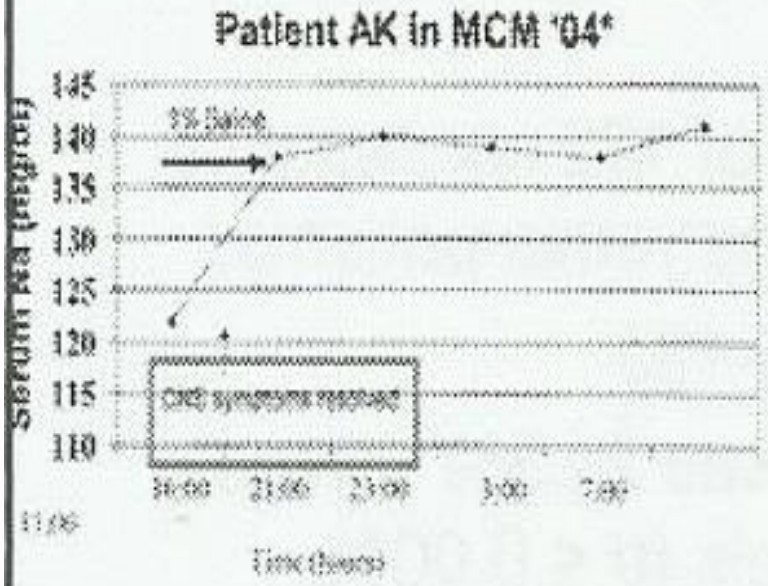
Treatment of Hyponatremia

- Management of acute, symptomatic hyponatremia
- Management of chronic hyponatremia
  - Fluid restriction
  - Lasix and salt tabs - ↓ countercurrent mechanism
  - Democlocycline - ↓ V_2R response
  - Vasopressin antagonists

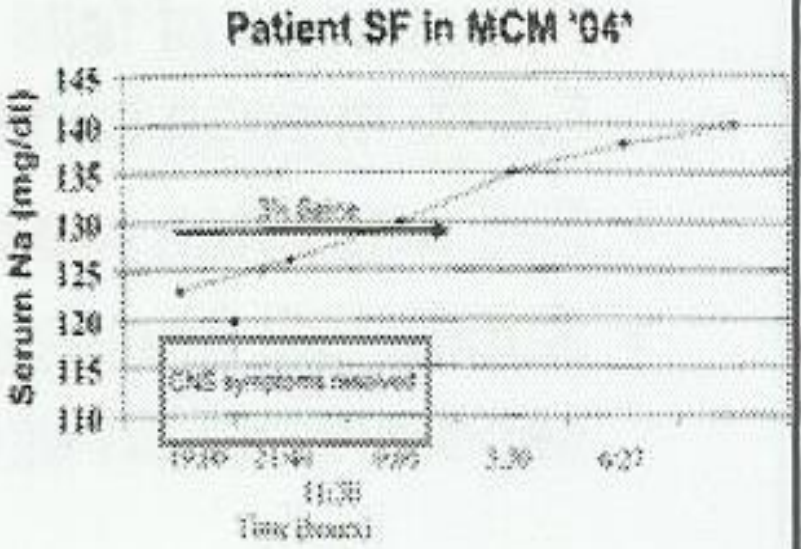
We Hopefully Agree.....

- Treatment of acute, symptomatic hyponatremia can be life-saving
- Management should include:
  - hypertonic saline
  - ABG, CXR, and CNS imaging (if available)
  - supplemental O_2 prn
  - loop diuretic (R_x of pulmonary edema and ↓ countercurrent mechanism)

Response to Hypertonic Saline in Acute Exercise-Associated Hyponatremia



Marine Corps Marathon



Siegel et al, Am J Med, 2007

Quantitative Formulas

Electrolyte-free water clearance (Rose)

$$= \text{urine volume} \times \frac{\left[\left(U_{Na} + U_{K}\right) - 1\right]}{P_{Na}}$$

Change in Serum Na^+ per liter infused (Madias)

$$= \frac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{serum } Na^+}{\text{total body water} + 1}$$

*****MAJOR CAVEAT*****

No matter how "precise" a given formula for estimating ΔNa^+ after treatment, it cannot predict changes in the underlying physiology

$\rightarrow \uparrow\uparrow$ risk of over-shooting R_x goal

What If You "Over-Correct": Treatment of Osmotic Demyelination

- DDAVP and D5W to re-induce hyponatremia – animal and human data
- Myo-inositol supplementation during correction – animal data
- Dexamethasone to restore blood brain barrier function – animal data

Vasopressin Antagonists

Drug	*Antagonism*	*Route*	*Dose*
Conivaptan	V1A/V2	IV	20-40 mg/day
Tolvaptan	V2	PO	15-60 mg/day
Lixivaptan	V2	PO	100-200 mg/day
Satavaptan	V2	PO	12.5-50 mg/day

Conivaptan

- The only FDA-approved antagonist, for euvolemic hyponatremia (2005) and for hyponatremia associated with CHF (2007)
- Not approved for cirrhosis, acute hyponatremia, or for primary R_x of CHF
- Only IV available
- IV infusion site reactions in ~50%, "overcorrection" in ~10%
- Inhibits CYP3A4 – drug interactions with ketoconazole, etc.

Hypernatremia

Increase the Numerator

$$\text{Serum } [Na^+] \propto \frac{Na^+_E + K^+_E}{\text{Total Body Water}}$$

Decrease the Denominator

Water Intake Disorders

- Insufficient water intake – very common
- High sodium intake without adequate water - rare
- Thirst/Osmoreceptor (CNS) lesions

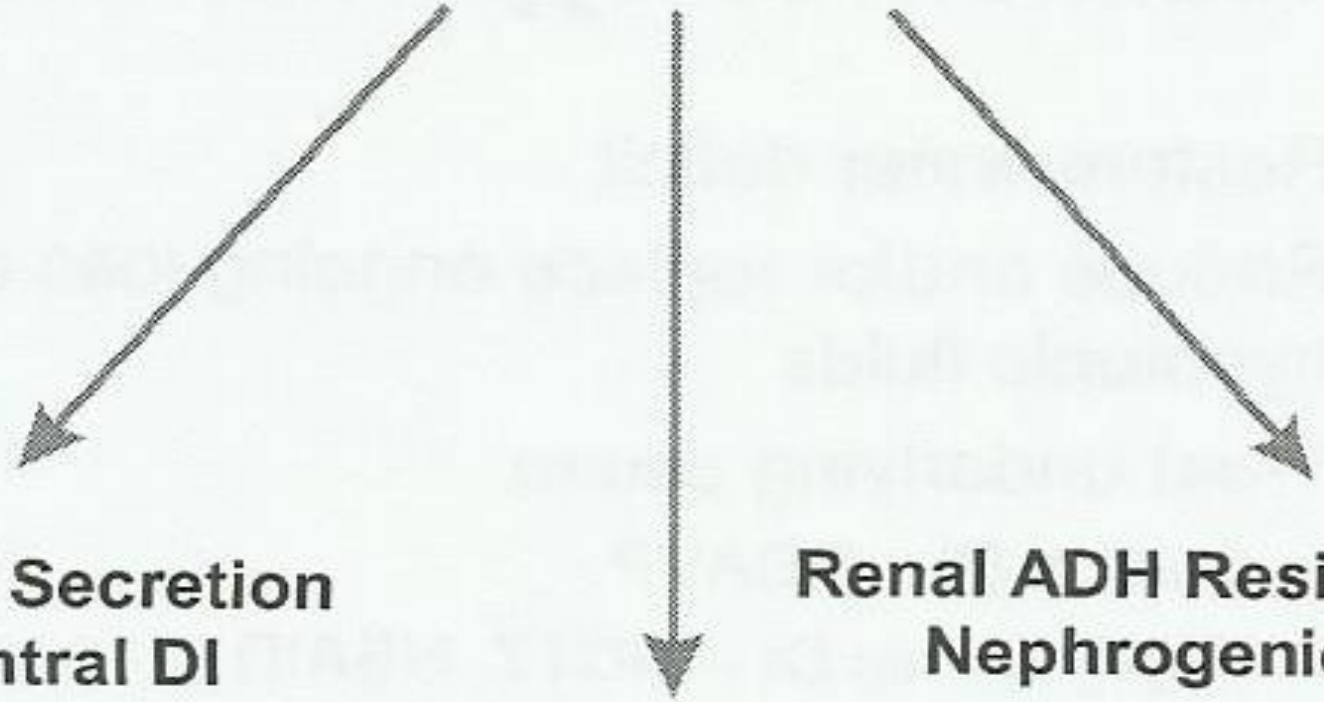
Thirst / Osmoreceptor Defects

- Infiltrating CNS tumor
- Granulomatous disease, e.g. sarcoidosis
- Ischemia
- Primary hyperaldosteronism
- **↑ Age**

Inappropriately High Water Losses

- Insensible losses (sweat, breath)
- Gastrointestinal (vomiting, diarrhea)
  - Gastric losses usually hypotonic
  - Diarrhea isotonic
    - Secretory – $[Na^+] + [K^+] = 140$
    - Osmotic – $[Na^+] + [K^+] < 100$, i.e. free water loss
- Kidney

Renal Water Loss: Diabetes Insipidus



↓ ADH Secretion
Central DI

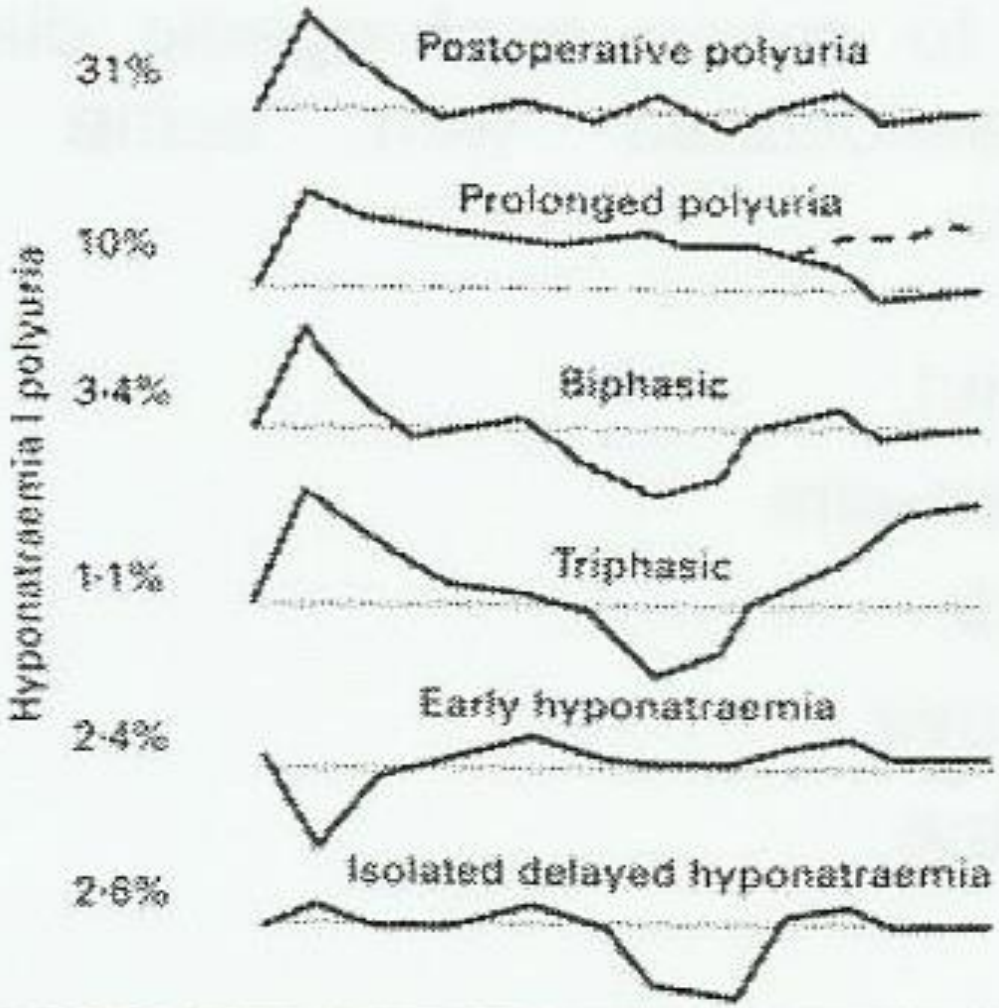
Renal ADH Resistance:
Nephrogenic DI

↑Degradation of ADH:
Gestational DI

Causes of Central DI

- Pituitary surgery
- Head trauma
- Tumors
- CVA or hypoxic encephalopathy
- Infections
- Idiopathic - ? autoimmune
- Granulomatous disease – sarcoid, histiocytosis X
- Hereditary – AD mutations in preprovasopressin/neurophysin, Wolfram syndrome

Patterns of Polyuria / Hyponatremia After Pituitary Surgery



Hensen et al,
Clin. Endo., 1999

Polyuria (Urine Output > 3L/d)

Osmolar excretion rate (UO x U_{Osm})

> 1000 mOsm/d	< 1000 mOsm/d

Serum Na^+

> 140 mEq/L	< 140 mEq/L

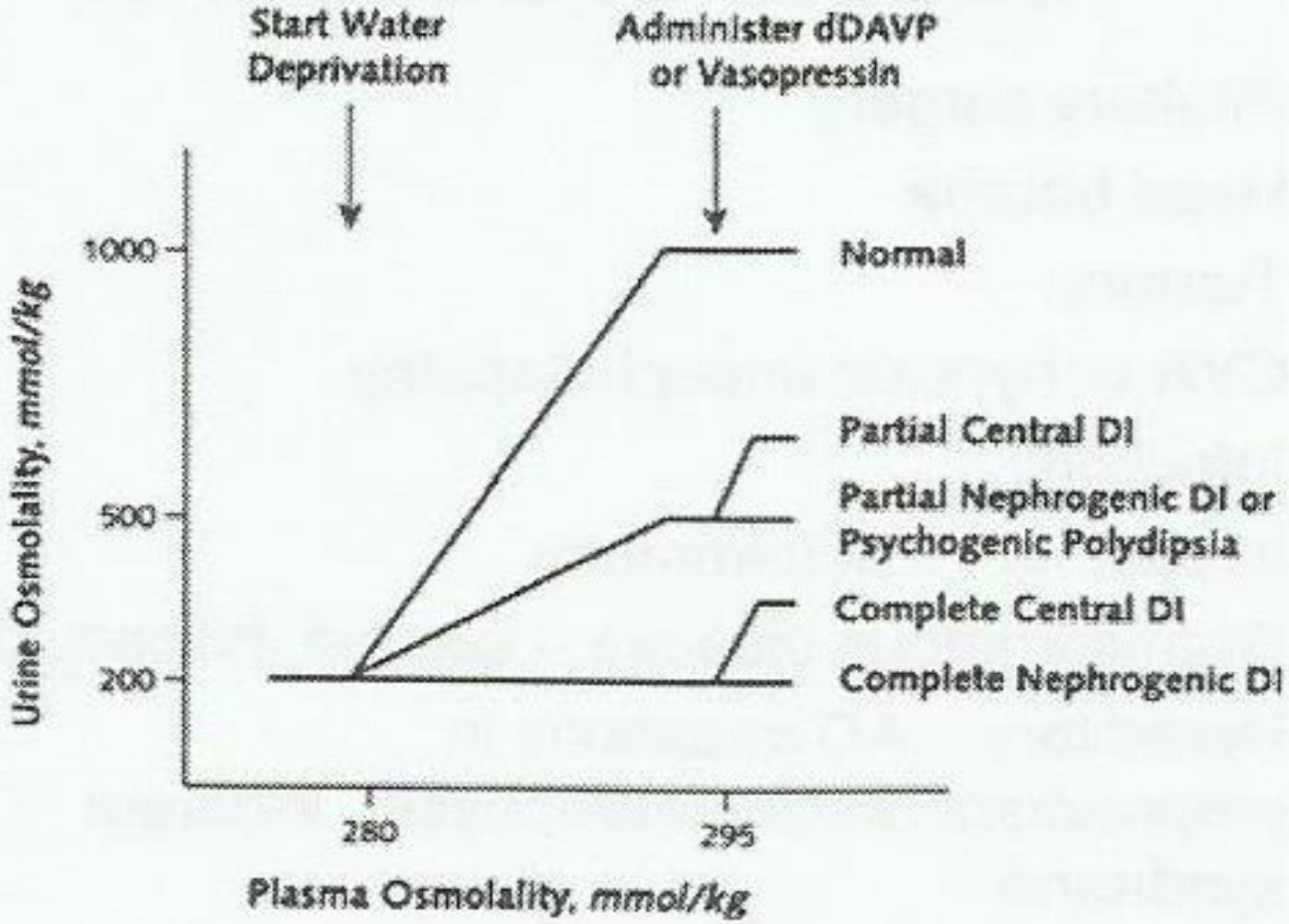
Causes of Nephrogenic DI

- Genetic
  - X-linked – V_2 vasopressin receptor
  - Autosomal recessive/dominant – aquaporin-2
  - Autosomal recessive – aquaporin-1 (proximal tubule and thin limb)
- Drug-induced, e.g. lithium, cisplatin
- Hypokalemia
- Hypercalcemia
- Infiltrating lesions, e.g. sarcoidosis, amyloidosis
- Cellular defect, e.g. after acute tubular necrosis

Gestational DI

- 1 in 300,000 pregnancies
- Increased expression/release/activity of vasopressinase, produced by placenta
- May occur in context of pre-eclampsia
- DDAVP ~ resistant to vasopressinase, hence effective

Water Deprivation Testing



Sands and Bichet, Ann. Int. Med., 2006

Treatment of Hypernatremia

- Restore water deficit
- Reduce and/or replace ongoing loss of hypotonic fluids
- Treat underlying cause
  - Central DI – DDAVP
  - Nephrogenic DI – HCTZ, NSAID
  - Gestational DI - DDAVP

Quantitative Formulas

Free water deficit = 0.6 x weight* x (1-140/Na^+)

*premorbid weight

Replace over 48 hours

Electrolyte-free ~~water clearance~~

$$= \text{urine volume} \times \left[\frac{(U_{Na} + U_K) - 1}{P_{Na}}\right]$$

Replace daily losses

Causes of Nephrogenic DI

- Genetic
  - X-linked – V_2 vasopressin receptor
  - Autosomal recessive/dominant – aquaporin-2
  - Autosomal recessive – aquaporin-1 (proximal tubule and thin limb)
- Drug-induced, e.g. lithium, cisplatin, foscarnet
- Hypokalemia
- Hypercalcemia
- Infiltrating lesions, e.g. sarcoidosis, amyloidosis
- Cellular defect, e.g. after acute tubular necrosis

Disorders of serum sodium

David B. Mount, M.D.

Objective: To review the differential diagnosis and management of sodium disorders.

Most if not all nephrologists are very comfortable with the diagnosis and management of hyponatremia and hypernatremia. However, the last two years have seen several important developments in this area. First and foremost is the FDA approval of the intravenous form of the vasopressin antagonist conivaptan, for the management of euvolemic hyponatremia and hyponatremia associated with CHF[1]; large randomized trials of the ***oral*** vasopressin antagonist tolvaptan have also been published[2]. Recent reports have highlighted the subtle but important clinical sequelae of "chronic" hyponatremia[3], suggesting a future decrease in the threshold for utilizing these agents to correct hyponatremia.

The pathophysiology of osmotic demeyelination remains something of an enigma; however, dysfunction of the blood-brain barrier is emerging as an important factor[4]. There are several new quantitative approaches for the initial therapy of hyponatremia with hypertonic saline[5]. Notably, however, these formulas tend to underestimate therapeutic changes in serum Na^+, due to the evolving physiology in individual patients[6]. For those patients who "overcorrect", a "re-induction" of hyponatremia or a reduction in the rate of correction can be accomplished with DDAVP and IV free water; this approach appears to be safe, with no evident risk of seizure or the emergence/re-emergence of other serious sequelae of hyponatremia[7].

Finally, nephrogenic SIADH[8], caused by activating mutations in the V2 vasopressin receptor, has emerged as an intriguing case of hyponatremia, explaining at last some of the cases of SIADH with suppressed vasopressin[9]; this disorder is reviewed in the basic physiology talk that precedes this lecture.