Not all Hyponatremia is a Saline Deficiency
SIADH in the Real World

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Case #1

- An 82 year old woman from an ECF, who presented to the ED for acute mental status changes. Per staff the patient was fatigued and difficult to arouse. Patient's daughter was contacted, and noted the patient had a history of hydrocephalus. History was severely limited by patient's mental status. On exam the patient's blood pressure was 153/57 with a pulse of 46. Physical exam was unremarkable per ED note except for mental status, patient was noted to be A&O x 0. Her sodium on presentation was 121. A CT of head was preformed which was unrevealing of acute process and did not mention hydrocephalus. The patient was given 1 L of NS in the ED and admitted.

Case #1

- On admission more history was elucidated. The patient noted some sore throat and was started on cephalexin per assisted living staff. She was also recently started on quetiapine. Relevant chronic medications include sertraline. On repeat exam by admitting physician the patient was noted to be A&O x 3 with a supple neck. No comment is made on oral mucosa.

Case #1

- Admitting diagnosis was: “Somnolence/forgetfulness found to have severe hyponatremia, associated with mild normocytic anemia”
- Plan:
  - “TSH pending, Vit D, serial sodium check Q4H, urine electrolytes, fluid restrict 1.5L
  - s/p 1 L NS in ER, IVF 50/hr, consider diuresis
  - Hold setraline/new quetiapine”

Case #1

- Labs, taken at admission:
  - Serum osmolality: 259, Urine osmolality: 414, Urine sodium 44
- Sodium levels: 123 3 hours later, 127 12 hours later, back to 124 next morning.
- The following morning a different physician took over the case and noted the patient to be in euvolemic hyponatremia, likely due to SIADH with suspected causes being psychiatric medications and/or URI. NS was stopped.
- Over the course of 5 days the patient's sodium slowly increased to 130 with fluid restriction and her mentation improved. She was discharged to SNF without sertraline or quatiapine.

Case #2

- A 66 year old man with history of recent traumatic subarachnoid hemorrhage, 6 days prior treated nonoperatively, presented to the ED for AMS. Associated symptoms included bowel incontinence, fever (38.1), generalized weakness. Pertinent medications include Venlafaxine. Physical exam in the ED was notable for dry lips and a non-focal neurological exam except for altered mentation. CT of head showed a new sub-acute left frontal infarct with new region of parenchymal hemorrhage and new bilateral subdural fluid collections w/ persistent subarachnoid hemorrhage. CT was discussed with neurosurgery at Harborview with the conclusion that CT findings are as expected for his injury. WBC 19.1 with 62% PMNs. Sodium was 123, 6 days prior it was 136. BUN 15 Cr 0.63

Case #2

- In the ED he was treated with IV Vancomycin and oral Vancomycin due to concern for C. Diff.
- The admitting physician noted the patient to have a moist mucosa with dry lips with normal skin turgor.
- Admitting diagnoses included:
  - Acute encephalopathy possibly secondary to intracranial hemorrhage as well as hyponatremia
  - Acute hyponatremia with plan noting that the patient was euvolemic with high suspicion for SIADH due to subarachnoid hemorrhage with a component of hypovolemic hyponatremia. Per admitting resident recommendations 100 mL of 3% was to be given, however the attending overrode this in favor of 100 mL/hr of NS.

Case #2

- Labs on admission: Serum osmolality 263, urine osmolality 867 and urine sodium was 131
- The patient's mental status worsened the next morning. Serum sodium was noted to increase to 126 on redraw and was not changed in the morning.
- The patient was given two doses of 100 mL of 3% saline. NS was stopped by nephrology. He had some improvement in his mentation by the following day. His sodium however decreased to 125 after transient increase. He was placed on a 1 L fluid restriction. His sodium increased to 128. He was discharged on hospital day 8.

Case #3

- A 63 year old man with past medical history of hilar adenopathy and splenomegaly presented to the ED after new onset generalized seizure lasting about 5 minutes that began while the patient was sleeping. The episode woke his wife who called EMS. She provides much of the history as the patient is somnolent. His BP on arrival was 185/95 with pulse of 88. Physical exam notes moist mucous membranes, tongue laceration, non-focal neurological exam. Patient was noted to be somnolent but improving. Labs revealed a sodium of 116, BUN 20, Cr 1.13. Most recent labs from 9 months ago show sodium of 140. A head CT did not show any acute intracranial process. The patient was given a 100 mL bolus of 3% saline over 30 minutes. The patient was admitted to the CCU.

Case #3

- Repeat physical exam of admitting physician again noted moist mucous membranes, supple neck and normal skin turgor.
- On admission the patient was diagnosed with “severe hyponatremia”
- Plan included: BPM Q2H, IVFs as needed, serum and urine osmolality, and consideration for nephrology consultation in the AM.
- The patient was started on NS at 75 mL/hr by admitting physician.
- Nephrology was consulted in the AM, IVF was stopped. The patient did note that he was started on chlorthalidone a few weeks prior to admission.

Case #3

- Serum osmolality 272, urine osmolality at 639, with urine sodium at 89.
- The patient sodium had increased from 116 to 128 in about 1.5 hrs, then to 130 4 hours later and was down to 127 one hour later on recheck when nephrology was involved.
- The patient was placed on a 1.5 L fluid restriction. The following day the patient’s sodium was stable at 127 and normalized to 130 on the day of discharge. The patient was discharged without chlorthalidone.

Case #4

- A 72 year old woman admitted to SVH due to progressive weakness, poor memory and worsening back pain. The patient noted several weeks of decline in memory, unsteady gait, nausea and vomiting as well as salt cravings for the last year. The patient sees a naturopath and is on multiple herbal supplements but is uncertain of what they are. In the ED the patient's BP was normal, physical exam was negative for poor skin turgor or edema. CXR showed a ? small lung nodule. Her sodium was 125 on admission. The patient was started on 100 mL/HR of NS and this continued for over 36 hours. Nephrology service was consulted on hospital day 3.

Case #4

- The patient's sodium decreased to 124. The NS was continued. The patient also received multiple doses of Toradol for pain.
- Serum osmolality was then measured and noted to be 262, urine osmolality was 418, urine sodium was 125.
- Normal saline was stopped on hospital day 3. She was placed on fluid restriction of 800 mL. On hospital day 5 her sodium returned to normal with fluid restriction.

Hyponatremia

- The most common electrolyte problem in both inpatient and outpatient setting
- Defined as serum sodium<135 mmol/L, usually<130 mmol/L
- Severe hyponatremia<120-125 mmol/L
- Hyponatremia drastically increases the risk of all cause mortality in all patient populations
- Severity of the symptoms directly proportional to rate of decease of the sodium level

Am J Med. Expert Panel on Hyponatremia 2013; 126: supplement 1-41.

Role of Sodium

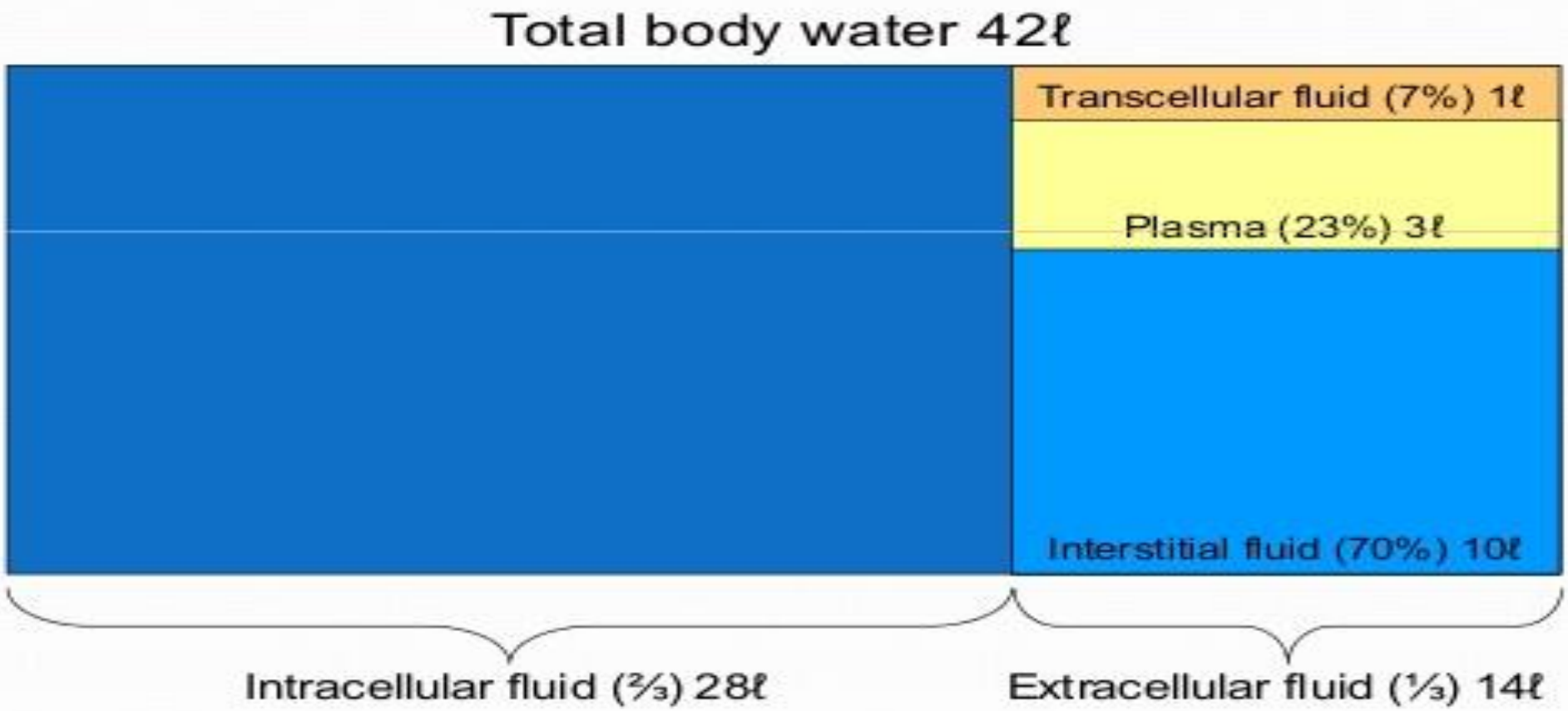
- Major extracellular cation (+)
- Major determinant of serum osmolarity
- Membrane balance for neuromuscular function
- Blood pressure and cardiovascular function
- Cellular pumps e.g. Na/K-ATPase

Sodium and Water in the Kidney

- 99% of filtered sodium is reabsorbed
- 1% excreted
- 99-99.5% of filtered water is reabsorbed
- 0.5-1% excreted
- In states of excess sodium and water-more excretion (normally)
- In dehydration-body holds onto sodium and water

Fluid compartments

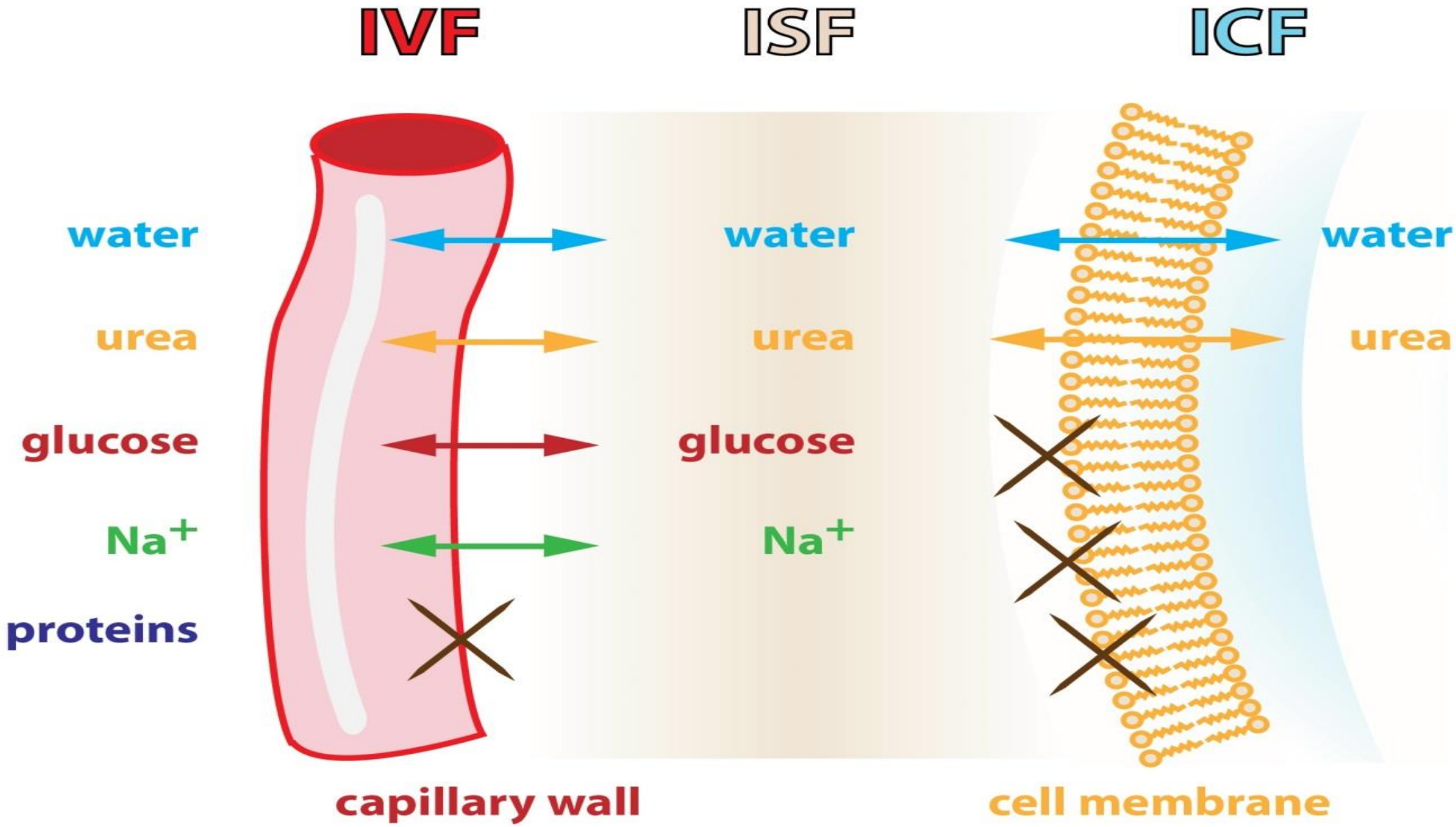
- Human body is approximately 60% water



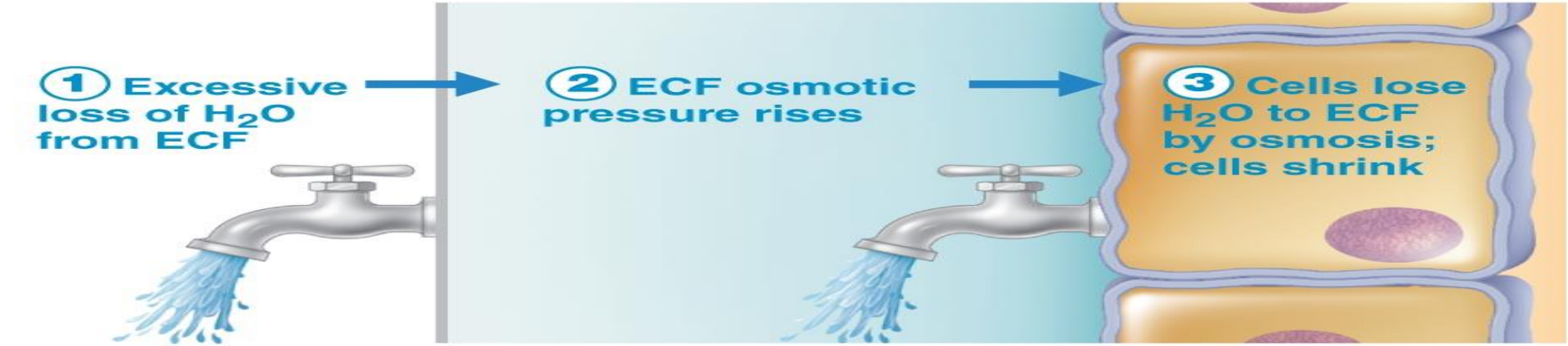
Composition of body fluids

Extracellular fluid (plasma)		
Na^+	142	mmol/ℓ
K^+	4	mmol/ℓ
Ca^{2+}	2	mmol/ℓ
Mg^{2+}	1	mmol/ℓ
Cl^-	105	mmol/ℓ
HCO_3^-	27	mmol/ℓ
Phosphates	1	mmol/ℓ
Protein	70	g/ℓ
Osmolarity	290	mosm/ℓ

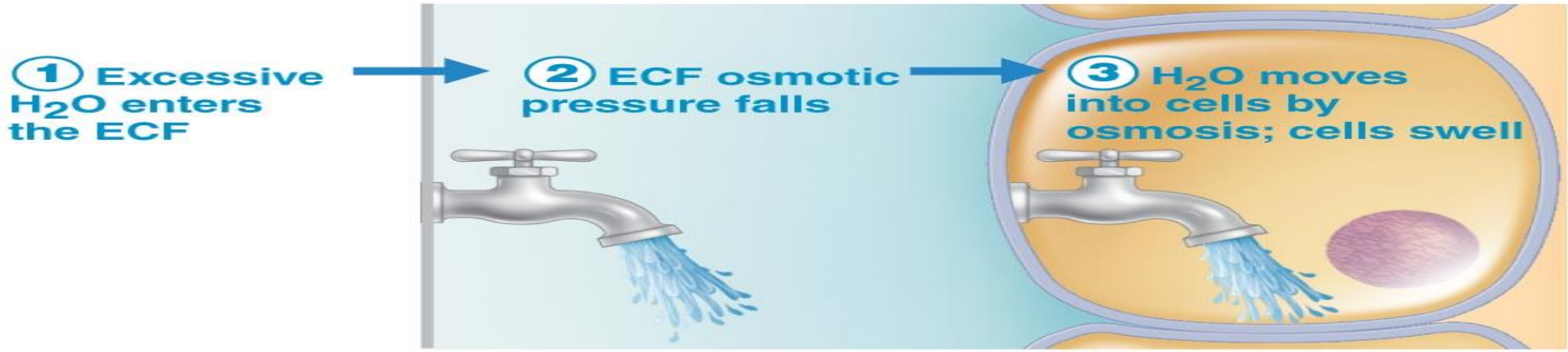
Intracellular fluid		
Na^+	10	mmol/ℓ
K^+	160	mmol/ℓ
Ca^{2+}	<0.01	mmol/ℓ
Mg^{2+}	13	mmol/ℓ
Cl^-	3	mmol/ℓ
HCO_3^-	10	mmol/ℓ
Phosphates	100	mmol/ℓ
Protein	200	g/ℓ
Osmolarity	290	mosm/ℓ


IVF
ISF
ICF
water
urea
glucose
Na+
proteins
water
urea
glucose
Na+
water
urea
capillary wall
cell membrane

Cellular Response to Water



(a) Consequences of dehydration. If more water than solutes is lost, cells shrink.



(b) Consequences of hypotonic hydration (water gain). If more water than solutes is gained, cells swell.

Substances that the body jealously protects for minute to minute functioning

Multiple built in redundant mechanisms to maintain:

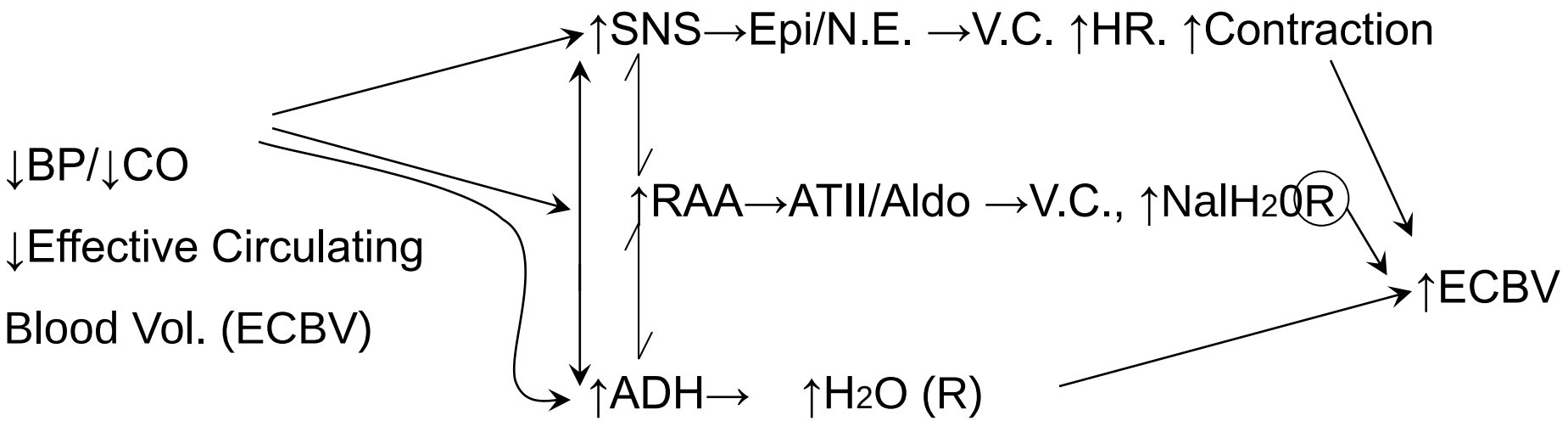
- Oxygen content
- Glucose
- Sodium/Water
- Potassium
- pH

Body's Response to Salt and Water Loss

- Increased Catecholamine secretion
- Increased Renin Angiotensin Aldosterone activity
- Increased Antidiuretic Hormone secretion (Vasopressin)

- All in an attempt to restore cardiac output/blood pressure and organ perfusion: vasoconstriction, increased cardiac output, sodium and water reabsorption.

Renal Response to Dehydration



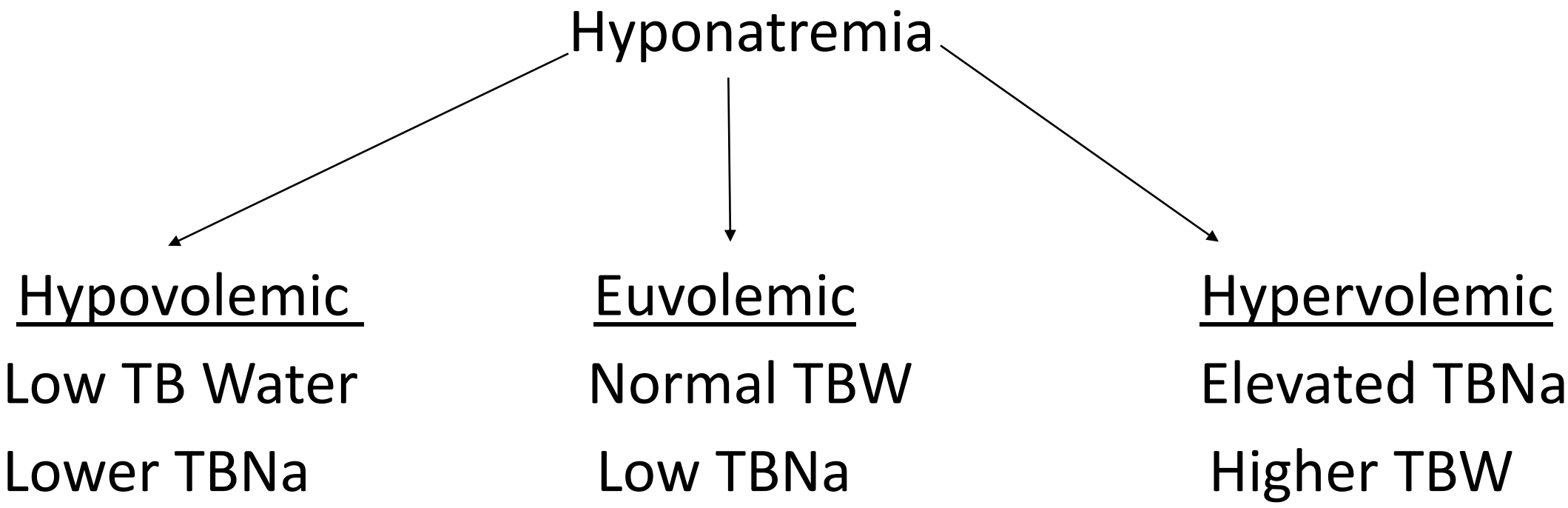
Thus Una < 20

U osm ↑ > 500

Why??

In Any disorder of Sodium and/or Water, the Most critical factor is to determine the patient's volume status.

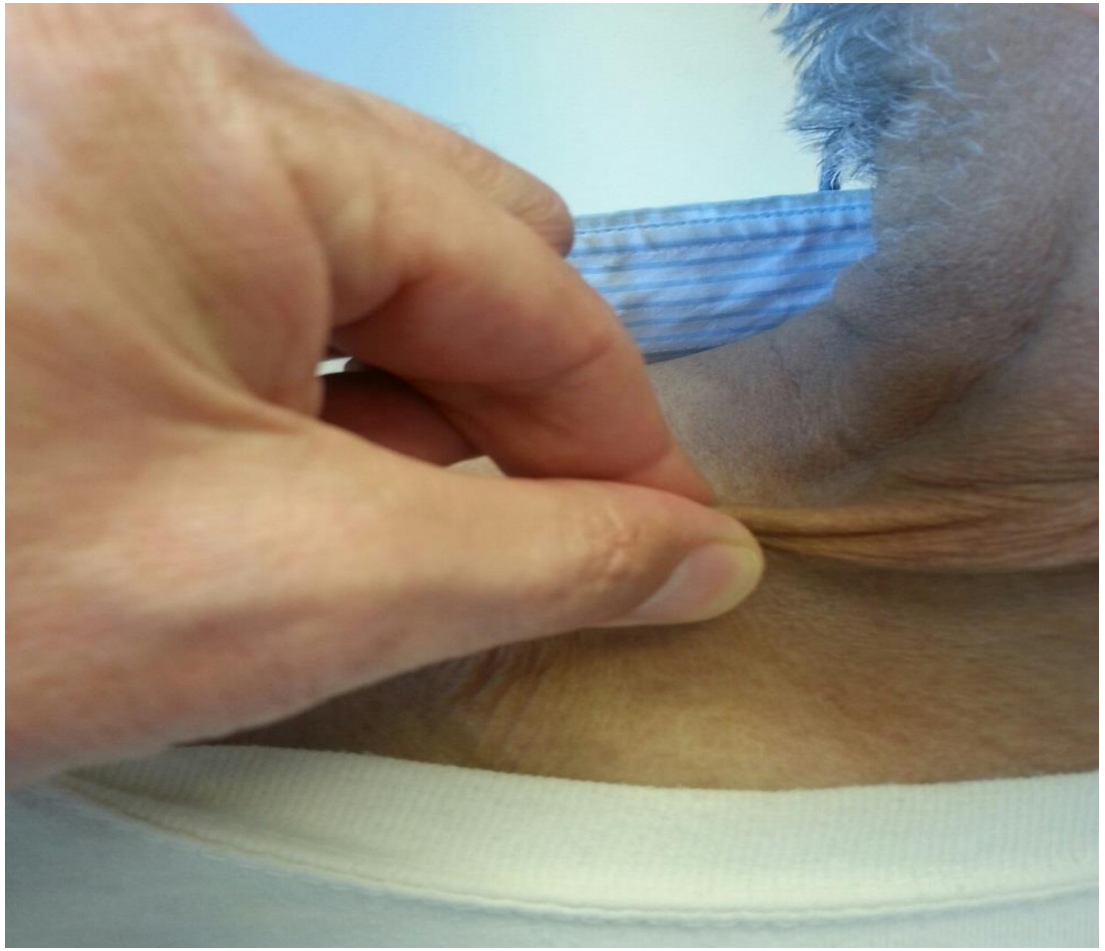
Classification of Hyponatremia



Bedside Evaluation of Volume Status

- Mental status
- Color
- Skin turgor
- Perspiration or lack of
- Axillary moisture
- Heart rate and blood pressure
- Orthostatic BP and pulse

A Poor Man’s Swan-Ganz Catheter



Volume Status Hints

Hypovolemic

- Low BP, tachycardia
- +orthostatic change
- Poor skin turgor
- Dry axilla
- Dry mucous membranes
- Urine Na<20
- Urine Osm>500

Euvolemic

- Normal BP, pulse
- -orthostatic change
- Normal skin turgor
- Moist axilla
- Moist mucous membranes
- Urine Na>30
- Urine Osm>300

Hyponatremia Does NOT Always =Saline Deficiency!

Euvolemic Hyponatremia

- Normal Total Body Water
- Low Total Body Sodium

Causes-Hypothyroidism

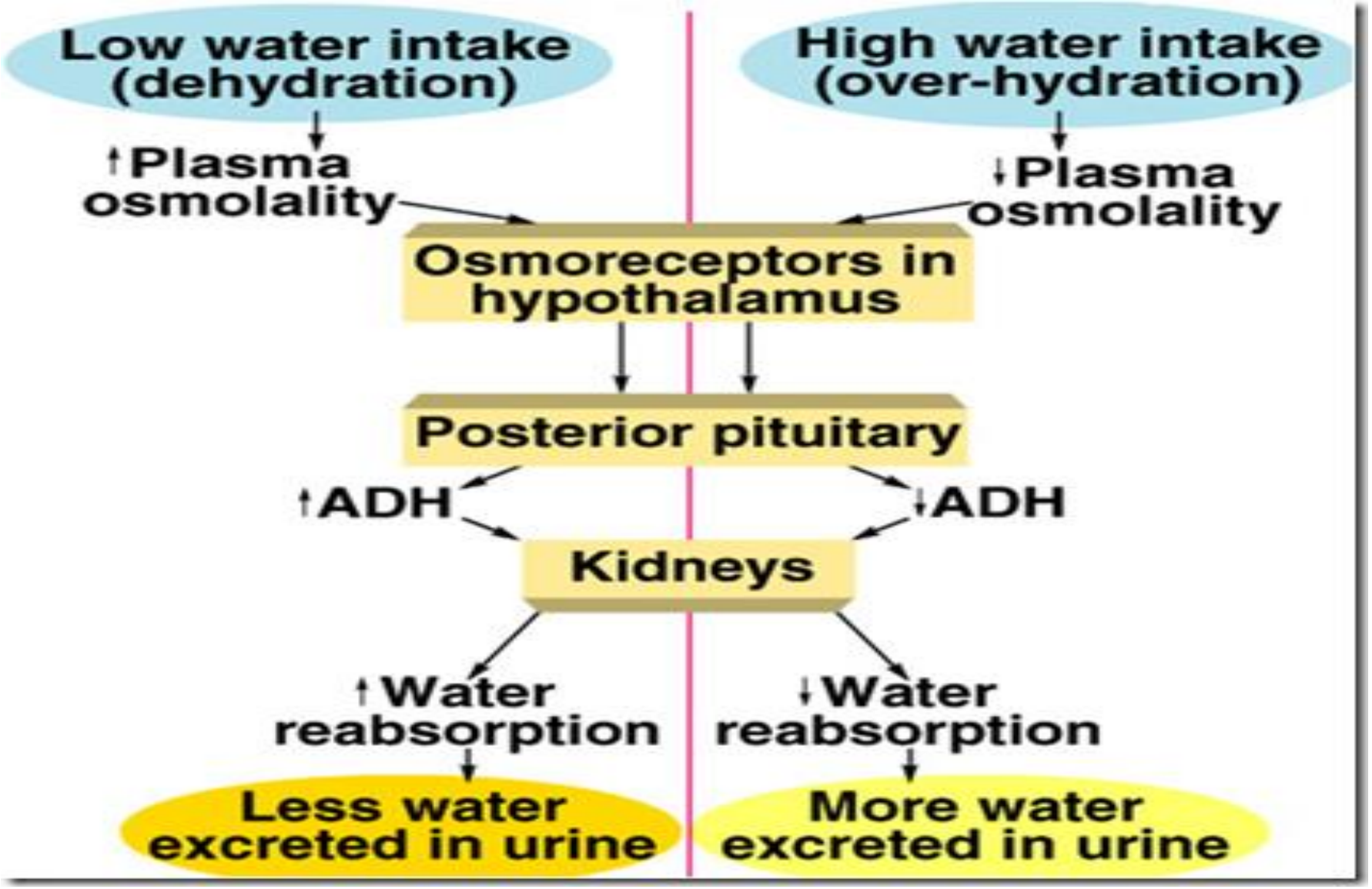
-Stress, Psychosis

-SIADH

-Exercise associated hyponatremia (EAH)

-Psychogenic Polydipsia

Antidiuretic Hormone



Antidiuretic Hormone (2)

- Regulates G-Protein V_2 receptor, which controls microtubule formation for water reabsorption in the collecting duct

Stimulation of ADH:

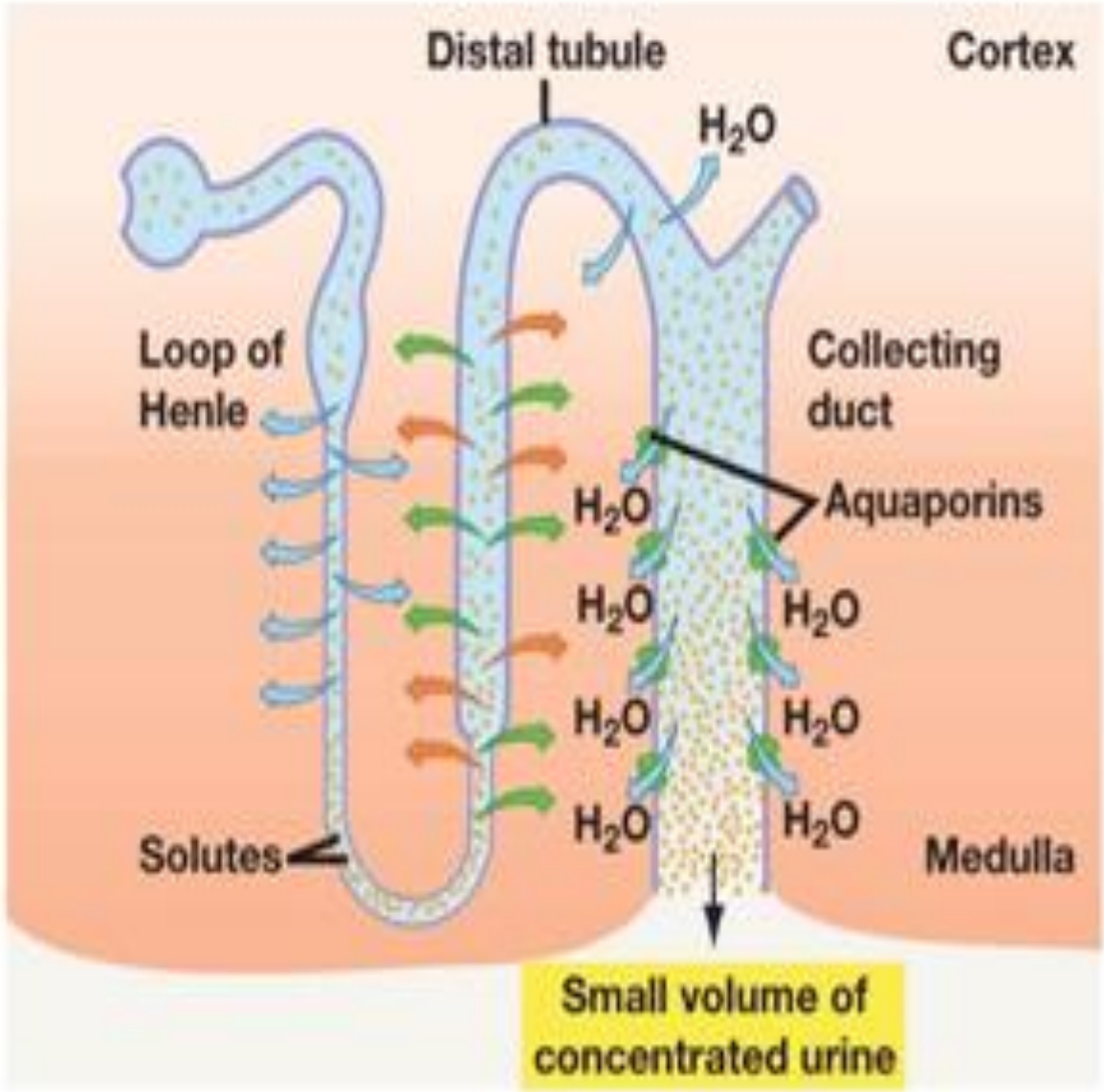
Osmotic-3% change in serum osmolarity

Non-Osmotic-Hypotension, decreased tissue perfusion, SNS and RAAS activation in turn stimulates the release of ADH

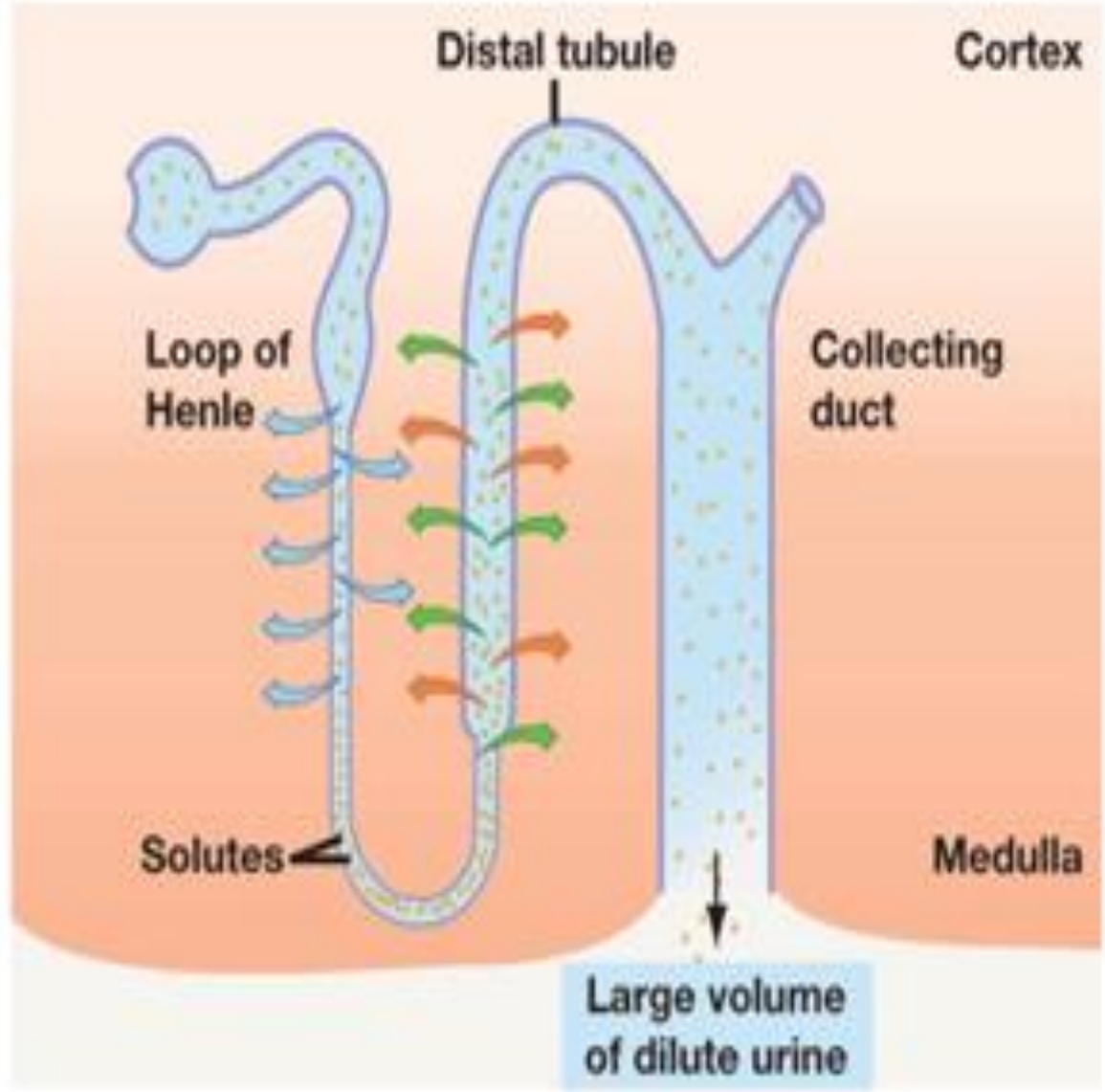
Normal ADH Feedback

- In states of volume depletion, ADH is released by the pituitary and acts on the collecting duct to reabsorb water.
- Once adequate fluid balance is restored and perfusion is back to normal, ADH is suppressed.
- If excess water is taken in, ADH is further suppressed and the urine osmolarity is 50-100 mOsm, because no water is reabsorbed in the tubule, thus dilute urine is excreted. Therefore the urine is “maximally dilute.”

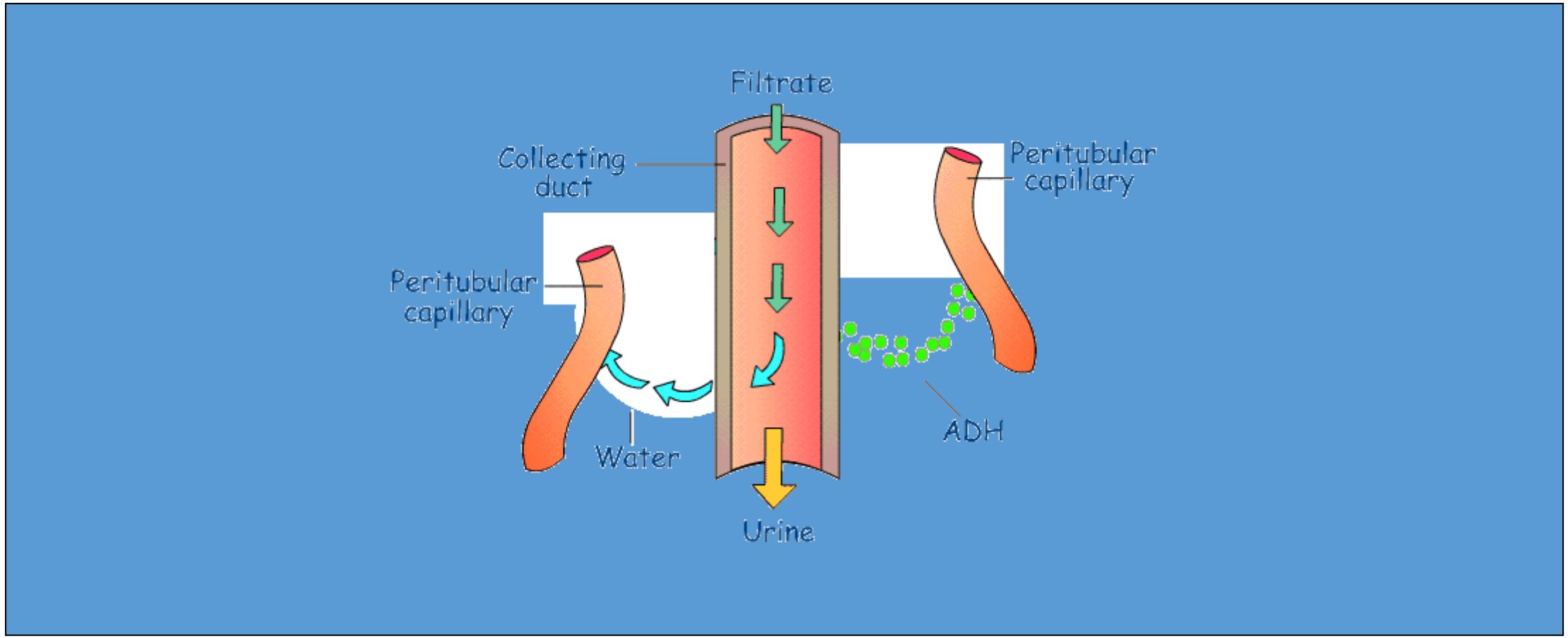
(a) **ADH present:** Collecting duct is highly permeable to water.



(b) **No ADH present:** Collecting duct is not permeable to water.



Antidiuretic Hormone



Antidiuretic Hormone Release

Appropriate ADH Release

- Volume loss: dehydration, hemorrhage
- Sepsis
- CHF (underperfusion)
- Cirrhosis (underfill/overflow)
- Nephrotic Syndrome (low oncotic pressure, opening of shunts)

Inappropriate ADH Release

- ADH is release in the face of normal fluid status, cardiac, renal and hepatic function hence **INAPPROPRIATE** for the clinical conditions

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

- Excess production of ADH without normal osmolar or non osmolar stimulation in the setting of euvolemia, leading to increased water reabsorption in the collecting duct and into the body.
- The net effect is that there is a dilutional hyponatremia in the blood and excretion of concentrated urine (due to water being reabsorbed)
- Serum sodium is low and serum osmolarity is <280 mOsm
- Urine sodium >20-30 mmol/
- Urine osmolarity >Serum osmolarity
- Euvolemia

Syndrome of Inappropriate ADH Secretion (SIADH)

Causes:

- Age
- Malignancies
- Pulmonary Problems
-EAH?
-Medications(SSRI, NSAIDs, PPIs, mood stabilizers, etc.)
-CNS problems

Common Medications in SIADH

- Thiazides>Loop diuretics
- SSRI Antidepressants
- MAO-I
- Antipsychotics: dozapine
- Anticonvulsants: carbamazepine
- Hypnotic: tamazepam
- Chemotherapeutic agents: platins, vincristine, cyclophosphamide
- NSAIDs
- COX-2 inhibitors
- Quetiapine
- Sulfonylureas
- PPIs
- DDAVP
- Ecstasy

Diagnosis of SIADH (Barter and Schwartz 1967)

- Euvolemia
- Normal cardiac, renal, hepatic and thyroid fxn, no edema
- Hyponatremia <135 mmol/L
- Hypoosmolar serum <275 mOsm/L
- Urine Na>20-30 mmol/L
- Urine osmolarity >100 mOsm/L and > serum osmolarity

Am J Med. 1967;42:790-806

Hyponatremic Encephalopathy/Seizures

- Directly related to rapidity of fall of sodium concentration
- Hyponatremia is seen in >70% of non-febrile infant seizure in <6 m.o.
- Responsible for ~10% of status epilepticus cases
- Mortality of 40%
- Improper treatment-acute osmotic demyelination syndrome (ODS)
- ODS is from over correction NOT hyponatremia
- Pons and extra-pontine structures are most susceptible

Epilepsia. 2006; 47:1990-1997.

J Clin Neurol. 2016;12:21-33

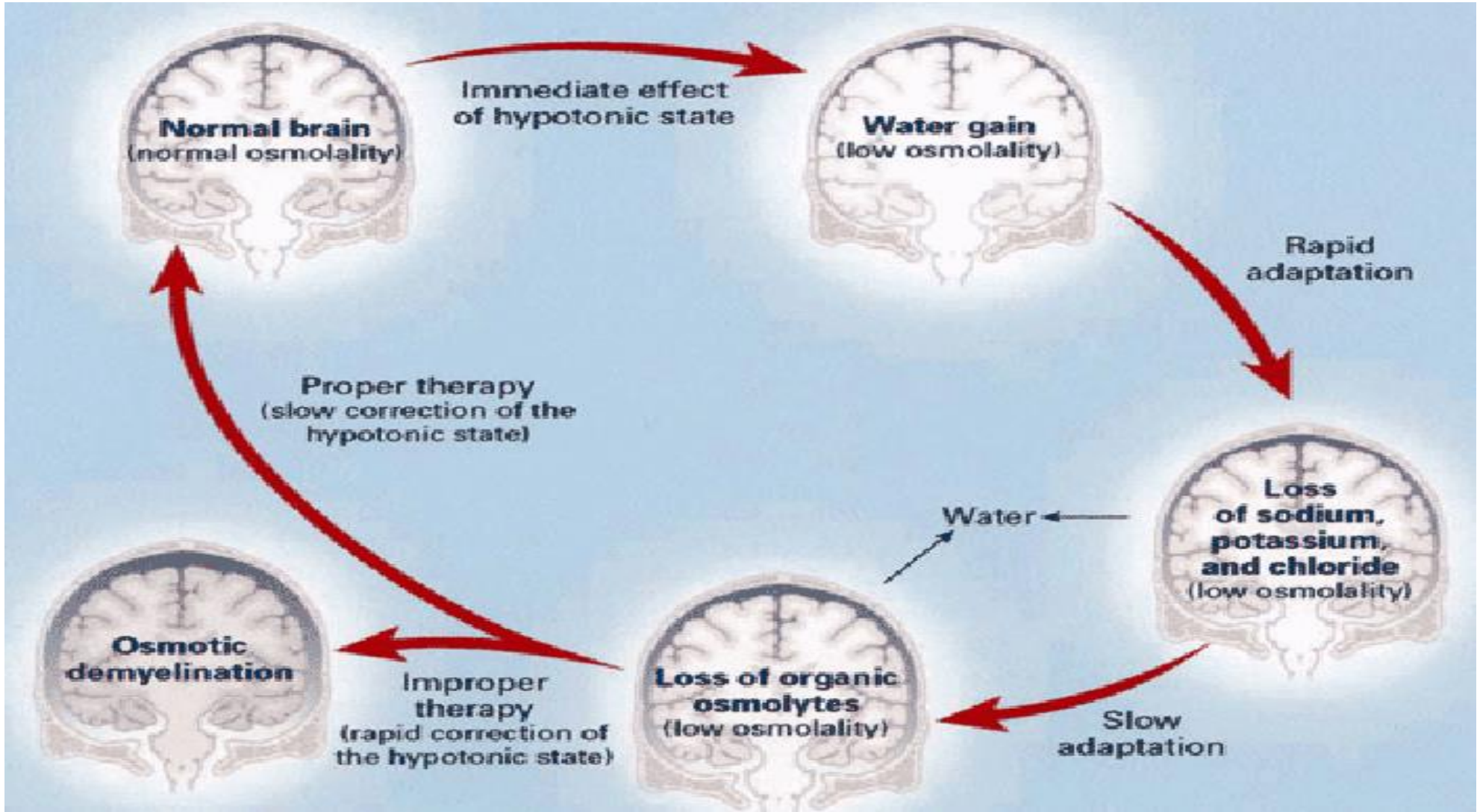
Risk Factors

- Age 20-30 and >60
- Female>>>Male, especially premenopausal (25 fold increase)
- Associated hypokalemia, hypomagnesemia
- Psychiatric history, psychogenic polydipsia
- Endurance athletes
- Prior CVA, Subarachnoid, subdural, seizure hx
- Medications, especially antipsychotics, SSRIs, Thiazides, NSAIDs, DDAVP

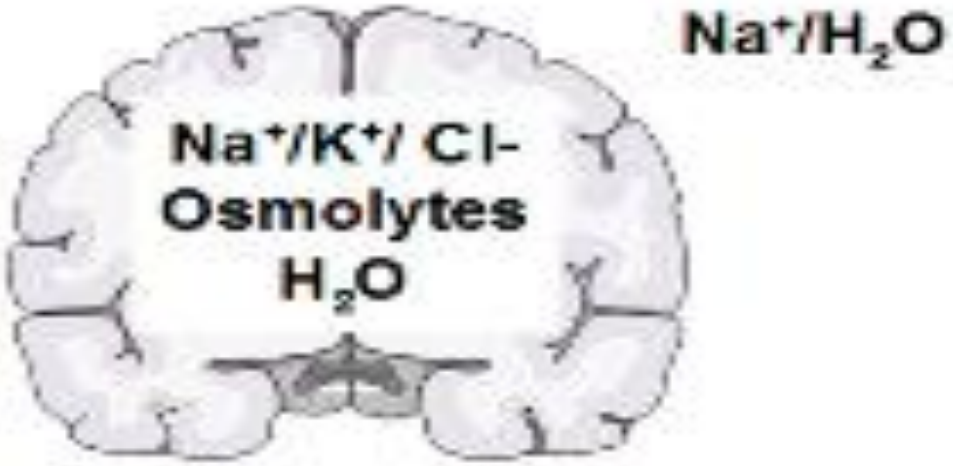
Epilepsia. 2006; 47:1990-1997.

J Clin Neurol. 2016;12:21-33

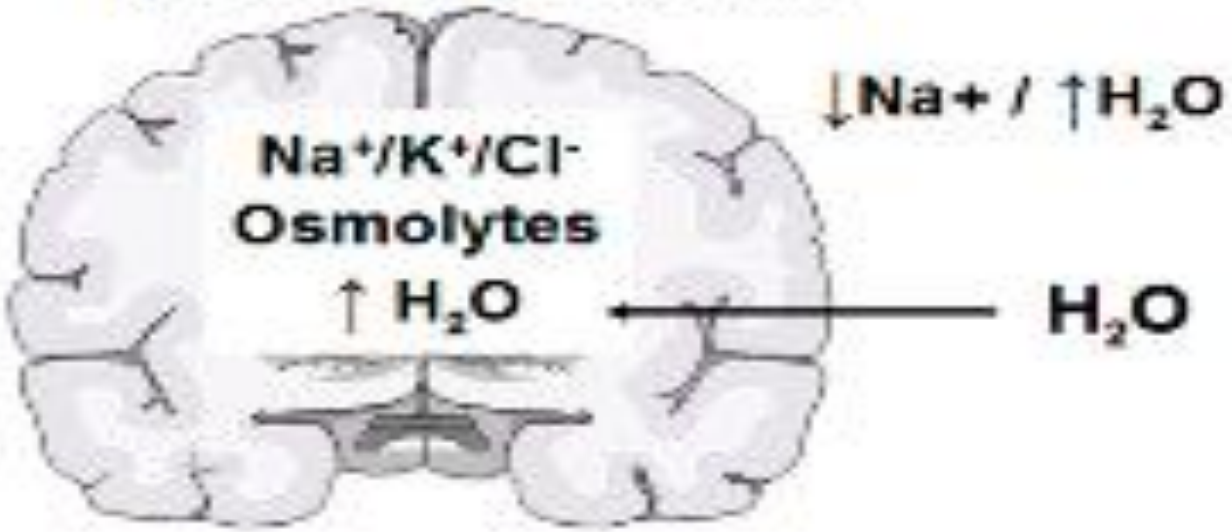
Osmolarity and the Brain(NEJM 2002)



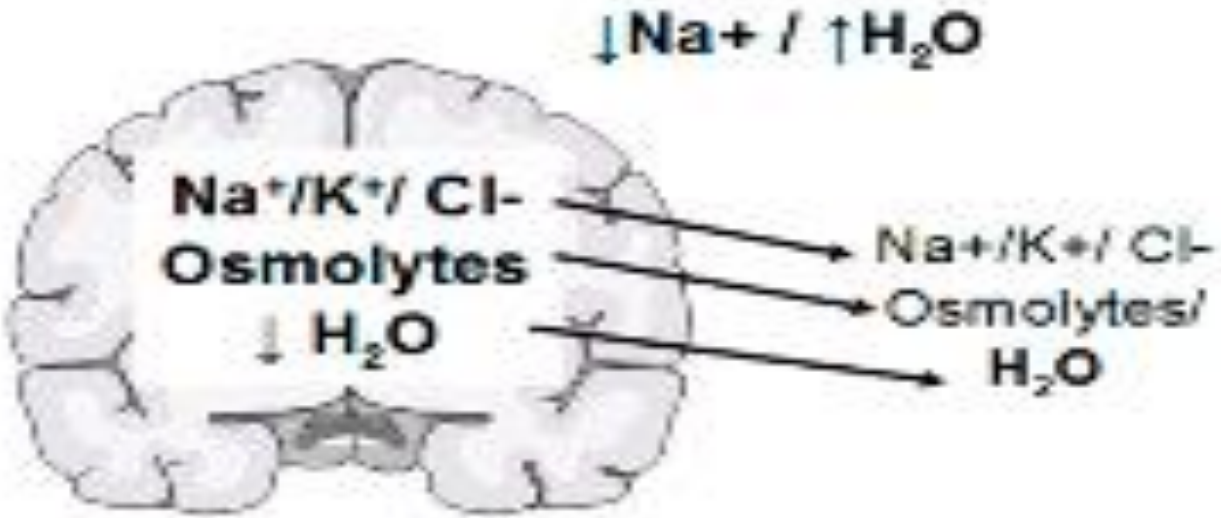
a) Normonatremia



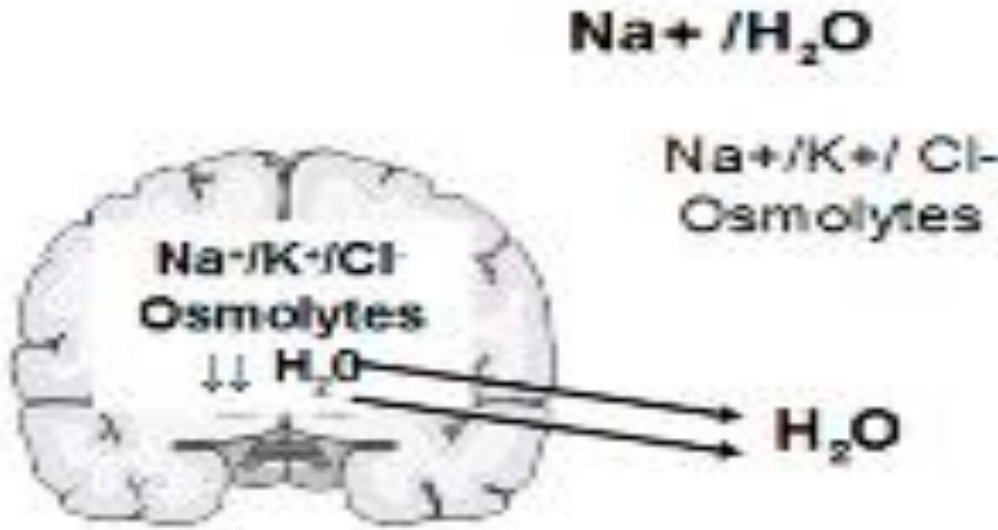
b) Acute hyponatremia



c) Chronic hyponatremia



d) Osmotic demyelination



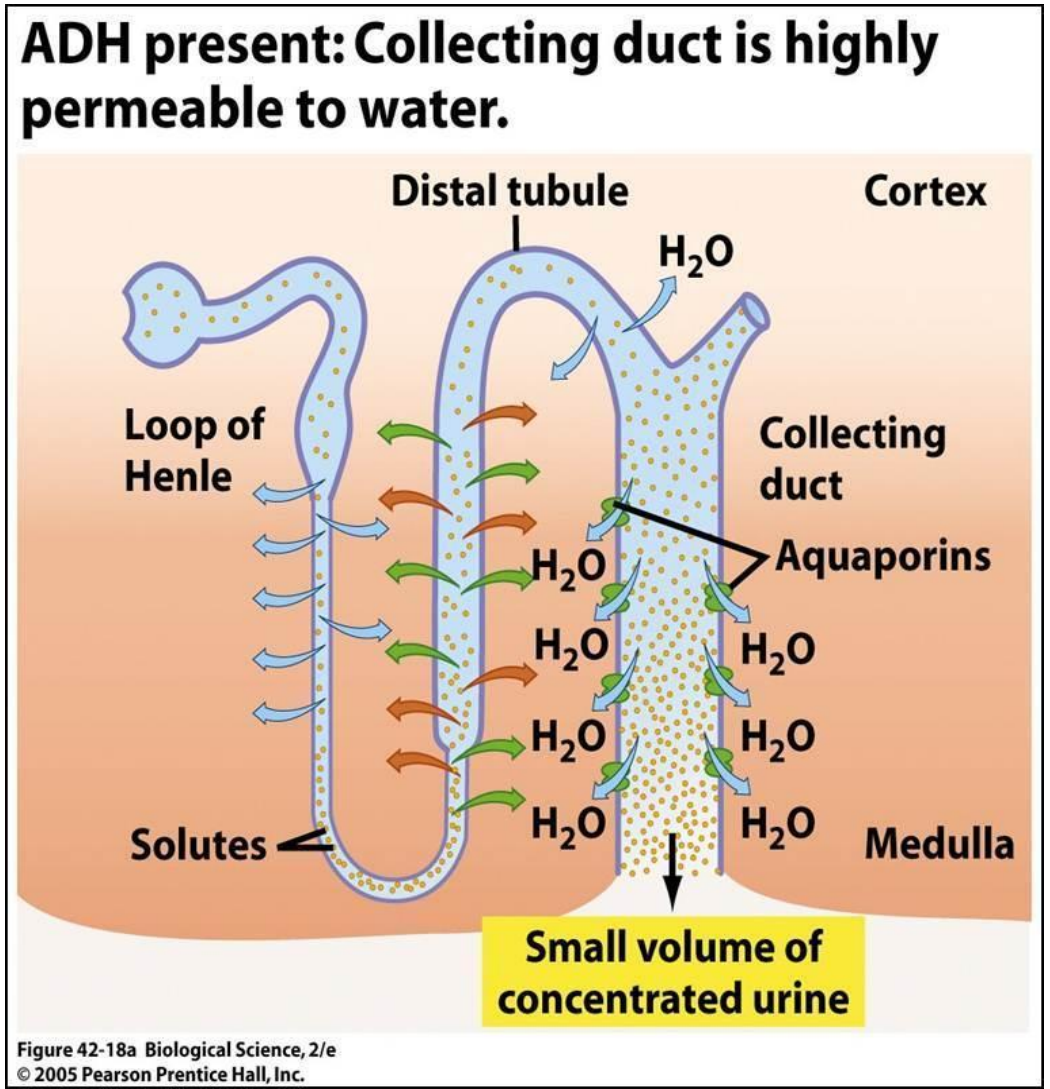
ODS at a cellular level

- It is not the hyponatremia that causes ODS but the rapid correction
- When normal saline or too much 3% saline is given is causes an acute shift of water our of the neurons and glial cells leading to demyelination

Fluid Menu

- 5% Dextrose in water, ½ (0.45%) saline or normal saline
- 1/2 (0.45%) normal saline 77 mEq/ liter sodium
- (0.9%) saline 154 mEq/ liter sodium
- 3% saline 513 mEq/ liter sodium
- Ringers lactate w/ or w/o 5% dextrose 130 mEq sodium

Effects of Normal Saline in SIADH



- Water is maximally reabsorbed, while sodium is not, which further dilutes the serum sodium/osmolarity worsening the hyponatremia.

Treatment of SIADH

- Fluid restriction 800-1000 ml/day
- Stop offending drugs
- Correct underlying causes, if possible
- Primum non nocere
- 3% saline *if* indicated
- Vaptans (V_2 and V_1 antagonists) cautiously
- Urea

Indications for 3% Saline (513 mEq/L Na)

- Seizures
- Acute mental status change
- Severe headache
- Focal neurological findings
- Myoclonic jerks or new tremors

Principles of Treatment 3% Saline

- A SMALL correction can lead to a good outcome. (2-3 mEq/l initially) Do not over correct or normalize.
- Do not correct unless evidence of hyponatremia is present or compelling clinical situation e.g. seizure, myoclonus, confusion, coma, etc.
- 100 ml of 3% saline should provide some improvement, if none it may be repeated every 10 min. for a total of 3 doses or clinical improvement
- Fluid restriction
- Nephrology consult

2nd Conference Exercise Associated Hyponatremia *Clin J Sport Med;* 2008; 18:111-121.

How Much?

- No large trials have been undertaken, but most experience has been with exercise associated hyponatremia in endurance athletes
- Goal small correction in serum sodium of 2-3 mmol/L over a few hours
- No more than 4-8 mmol/L over 24 hours
- 100 ml of 3% saline over 10 min, repeat x1-2 with ~10 min in between and wait for response. If after 1 dose there is improvement, stop.
- Added sodium with induce an osmotic diuresis

Am J Med. Expert Panel on Hyponatremia 2013; 126: supplement 1-41.

What are the underlying features in these four cases?

1. Improper evaluation of the patient's fluid status

2. Not recognizing that the patient was Euvolemic, yet all 4 patients were given NS at 100 ml/hr.

3. Not recognizing the Syndrome of Inappropriate ADH secretion (SIADH)

4. Not recognizing that in this scenario, normal saline can do more harm than good

In Conclusion

- Many cases of hyponatremia are seen in euvolemia or hypervolemia, hence no need for i.v. normal saline
- Evaluated the volume status before treating
- Part of the fluid evaluation includes the serum osmolarity, urine sodium and osmolarity
- Do no harm

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Morbidity, Mortality & Improvement Conference: May 3, 2017

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