RENAL PHYSIOLOGY

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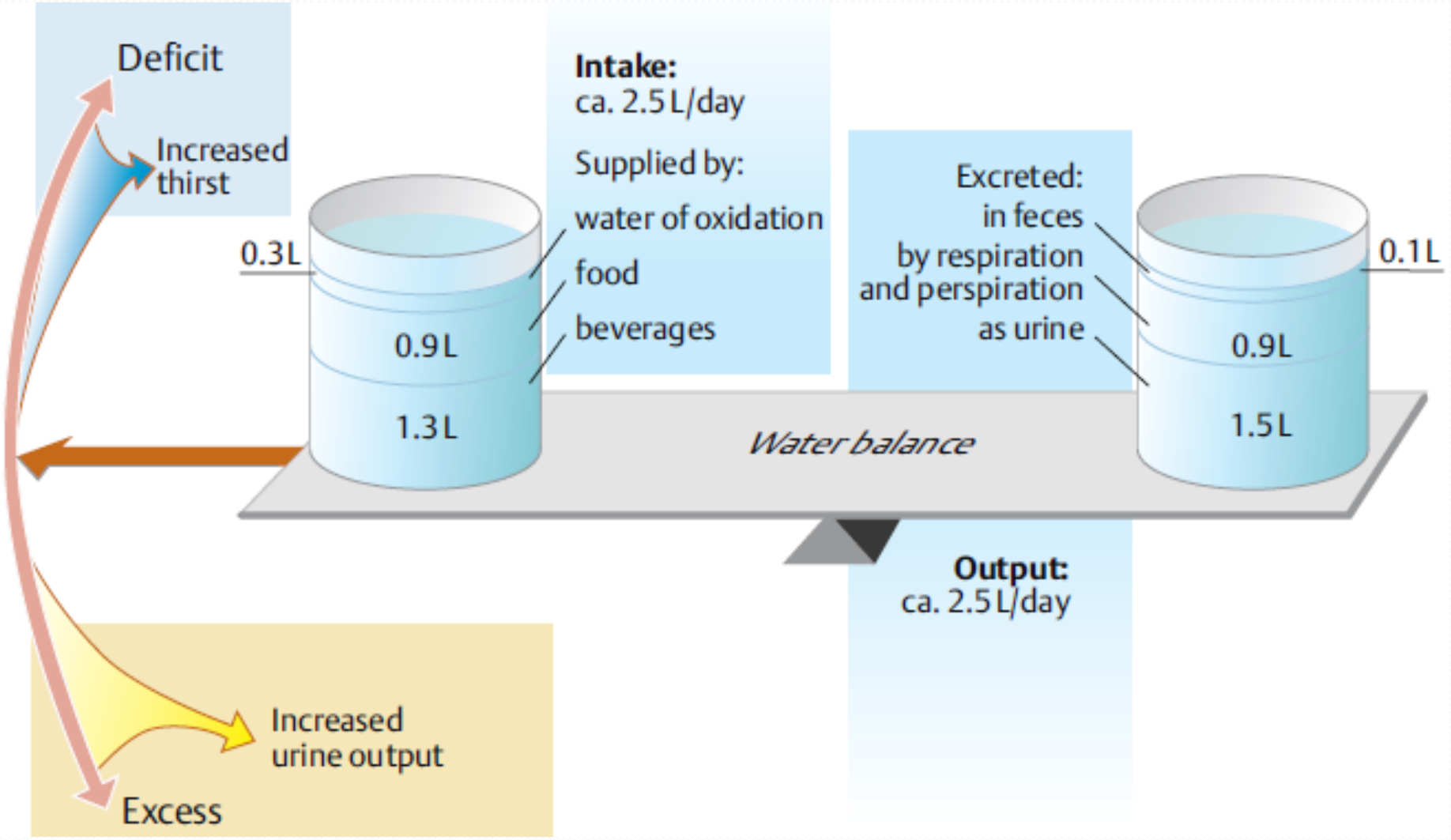
BODY FLUID COMPARTMENTS
ECF & ICF FLUIDS

- **HARMONY IN BODY FLUID CONCENTRATION IS VERY VITAL FOR HOMEOSTASIS**

- **Maintenance of nearly constant conditions in the internal environment.**

- FLUID INTAKE AND OUTPUT ARE BALANCED DURING STEADY STATE CONDITIONS

INTAKE = OUTPUT


Deficit
Increased thirst
Intake:
ca. 2.5 L/day
Supplied by:
water of oxidation
food
beverages
0.3 L
0.9 L
1.3 L
Excreted:
in feces
by respiration and perspiration
as urine
0.1 L
0.9 L
1.5 L
Water balance
Output:
ca. 2.5 L/day
Increased urine output
Excess

DAILY WATER INTAKE

- Two Sources
  1. Ingested Food & water = 2100ml/ day
  2. Synthesized in the body = 200ml/ day

  Total Intake = 2300ml/ day
- Intake is highly variable
  - Climate
  - Habits
  - Level of physical activity

DAILY LOSS OF BODY WATER

- Insensible losses from:
  - Skin (350 ml/day)
  - Respiratory Tract (350 ml/day)
  - Total = 700 ml/day

- Insensible loss of water from skin is independent of sweating.
- Minimized by cholesterol filled cornified layer of epithelium.
- Increased loss in cases of burns

- Water loss through respiratory tract is utilized in humidification of inspired air
- Air is humidified to a vapor pressure of 47mmHg
- Vapor pressure of atmosphere reaches ommHg during winter

FLUID LOSS IN SWEAT

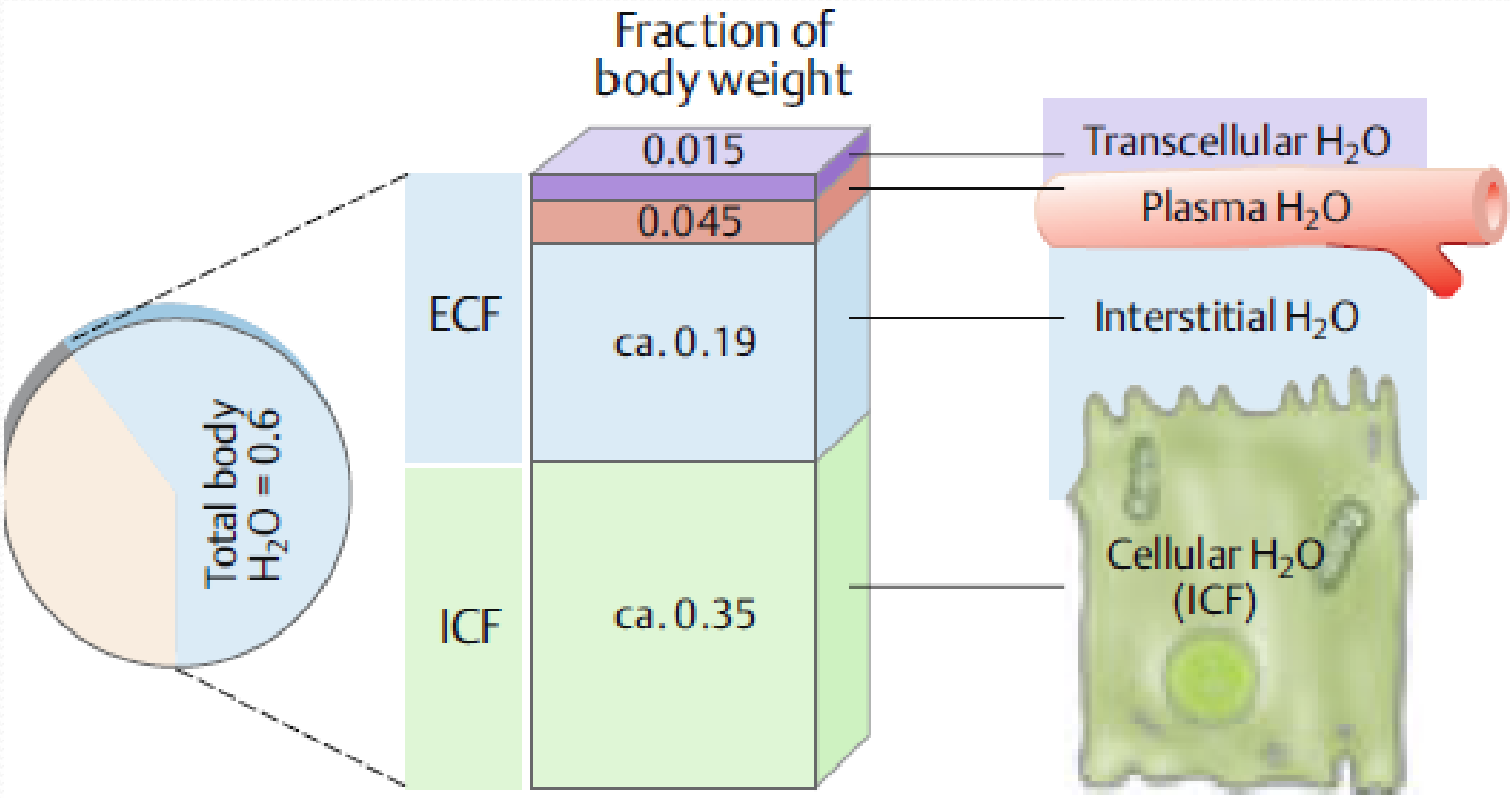
- Normal fluid loss in sweat is 100ml/day
- Increased up to liters in:
  - Exercise
  - Hot Weather

FLUID LOSS IN FECES

- Normal = 100ml/day
- Increased up to liters in patients of severe diarrhea

FLUD LOSS BY KIDNEYS

- Most important in regulation of water and electrolyte balance
- Is highly variable.
- Urine volume is variable ---0.5L/day to 20L/day.
- Salt intake highly variable ---Na intake 20mEq/day to 500mEq/day.


Fraction of body weight
0.015
0.045
ca. 0.19
ca. 0.35
ECF
ICF
Total body $H_2O = 0.6$
Transcellular H_2O
Plasma H_2O
Interstitial H_2O
Cellular H_2O (ICF)

Daily Intake and Output of Water (ml/day)

	Normal	Prolonged, Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible—skin	350	350
Insensible—lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

Body Fluid Compartments

Two main compartments:

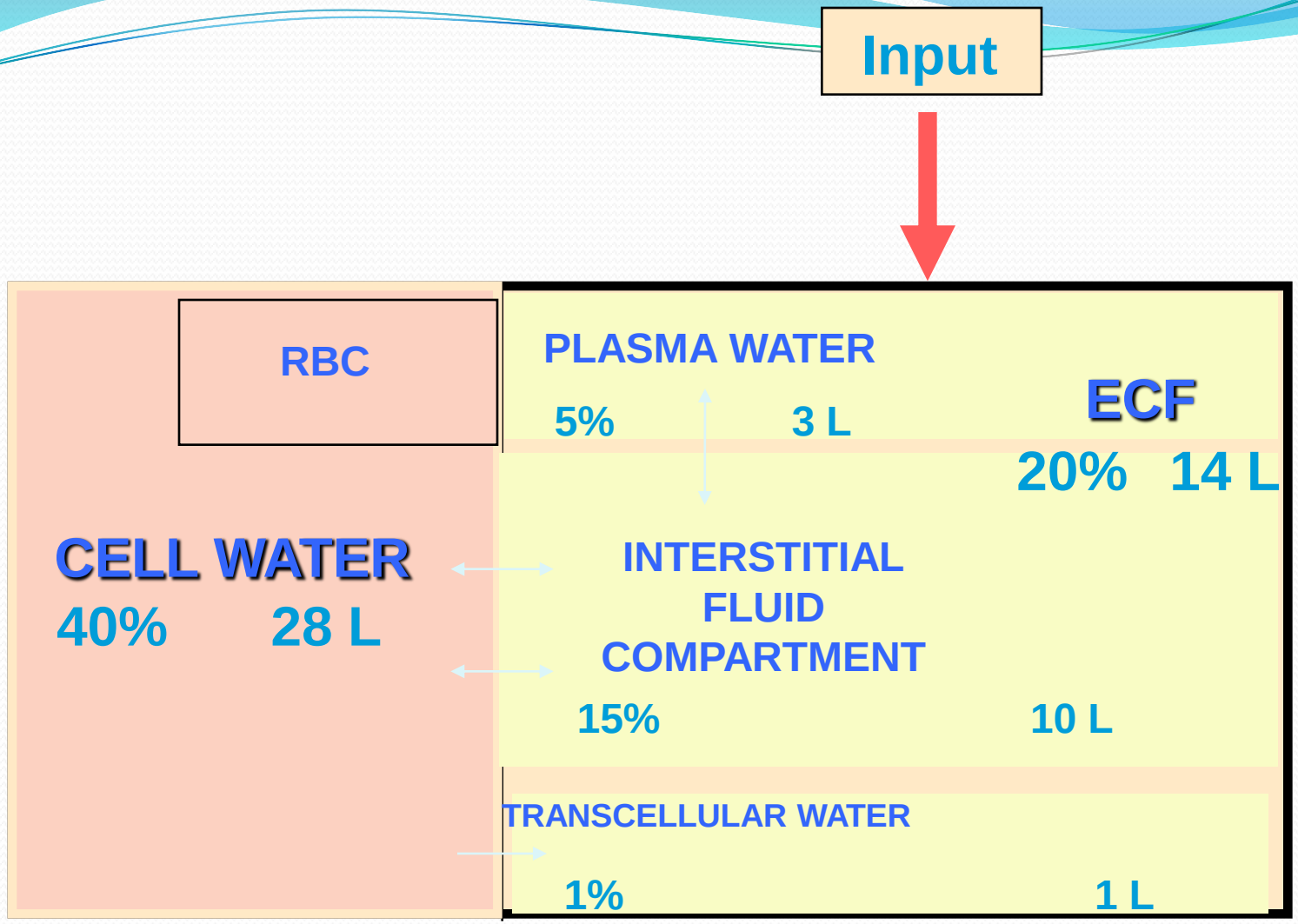
- Extracellular compartment
- Intracellular compartment
- Transcellular fluid (1-2 liters)
  - Synovial fluid
  - Peritoneal fluid
  - Pericardial fluid
  - CSF
  - aqueous humor
  - Specialized type of ECF (1.5% of B.Wt.)
- In a 70kg adult TBW is 60% of B.Wt. i.e. 42liters
  - Percentage changes with age, gender, degree of obesity

Intracellular Fluid Compartment

- 2/3 of body water (40% body weight) is present in the 75 trillion cells.
- Fluid in each cell is a mixture of several constituents but concentration of these is almost same in all cells.

Extracellular Fluid Compartment

- 1/3 of body water (20% body weight)
- 14 liters in a 70kg adult
- Two compartments
  - 1/4th the blood plasma (water=4.5% body weight)
  - 3/4th interstitial fluid and lymph (water=15% body weight)
- Plasma
  - Non-cellular part of blood
  - Continuous exchange of fluids b/w plasma and interstitial fluid
  - Same composition as interstitial fluid except proteins


Input
RBC
PLASMA WATER
5%
3 L
ECF
20%
14 L
CELL WATER
40%
28 L
INTERSTITIAL
FLUID
COMPARTMENT
15%
10 L
TRANSCELLULAR WATER
1%
1 L

Blood Volume

- Blood is a part of ECF as well as ICF
- 7% of B.Wt.
- 5 liters
- 60% of blood --- plasma
- 40% of blood --- RBC
- These %ages vary with age, gender, weight.

Hematocrit (Packed Cell Volume)

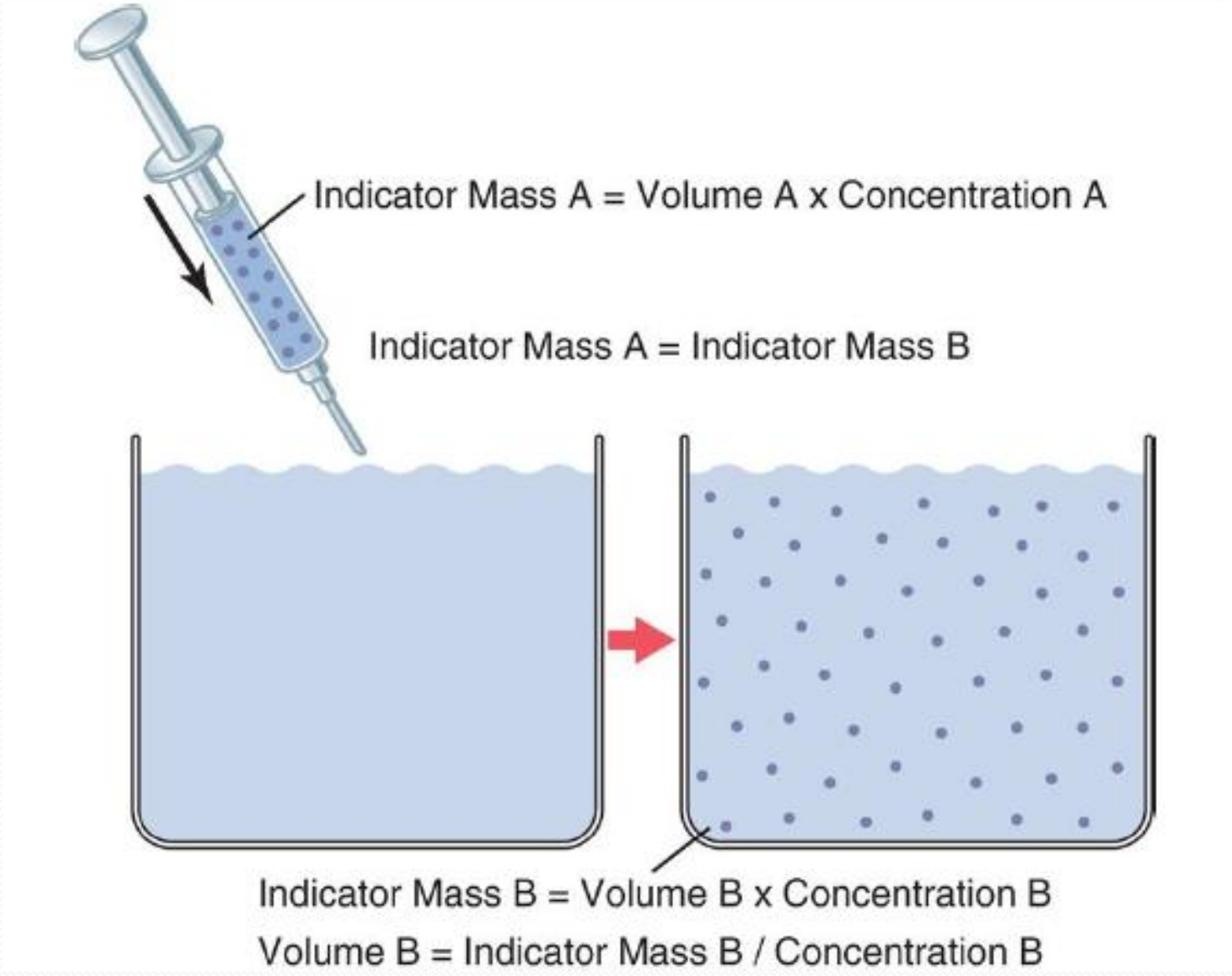
- Fraction of blood composed of RBCs
- Determined by centrifugation of blood
- Actual PCV is 3-4% less than actual
  - Normal Values
    - Males 0.40
    - Females 0.36
      - Decrease in ----- anemias
      - Increased in ----- polycythemias

Measurements of fluids in different body compartments

- **Indicator-Dilution Method**
  - **Principle**

    An indicator is placed in the compartment & allowed to disperse evenly and then analyzed extent of dilution.

  - **Can be used to measure volume of all body compartments as long as:**
    - **Indicator disperses evenly throughout the compartment**
    - **Indicator disperses only in that compartment**
    - **Indicator is not metabolized or excreted**


Indicator Mass A = Volume A x Concentration A
Indicator Mass A = Indicator Mass B
Indicator Mass B = Volume B x Concentration B
Volume B = Indicator Mass B / Concentration B

DETERMINATION OF VOLUMES OF SPECIFIC COMPARTMENTS OF BODY

- Measurement of Total Body Water
  - Radioactive water
    - Tritium or
    - Heavy water
  - Antipyrine
    - Highly lipid soluble

MEASUREMENT OF ECF

- Can be measured by injecting a substance that does not permeate the cell membrane
  - Radioactive sodium
  - Radioactive chloride
  - Radioactive iothalamate
  - Thiosulfate ion
  - Inulin

CALCULATION OF ICF

- No method of direct measurement
- Can be calculated

$$ICF = TBW - ECF$$

MEASUREMENT OF PLASMA VOLUME

- Can be measured by substance that does not permeate the capillary membrane & remains in vascular system
  - Radioactive Albumin
  - Evans blue dye (Binds to Plasma proteins)

Calculation of Interstitial Fluid

Interstitial fluid volume = ECF volume – Plasma volume

MEASUREMENT OF BLOOD VOLUME

- Radioactive labelled RBCs
- Can also be calaculated

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

Table 25-3. Measurement of Body Fluid Volumes

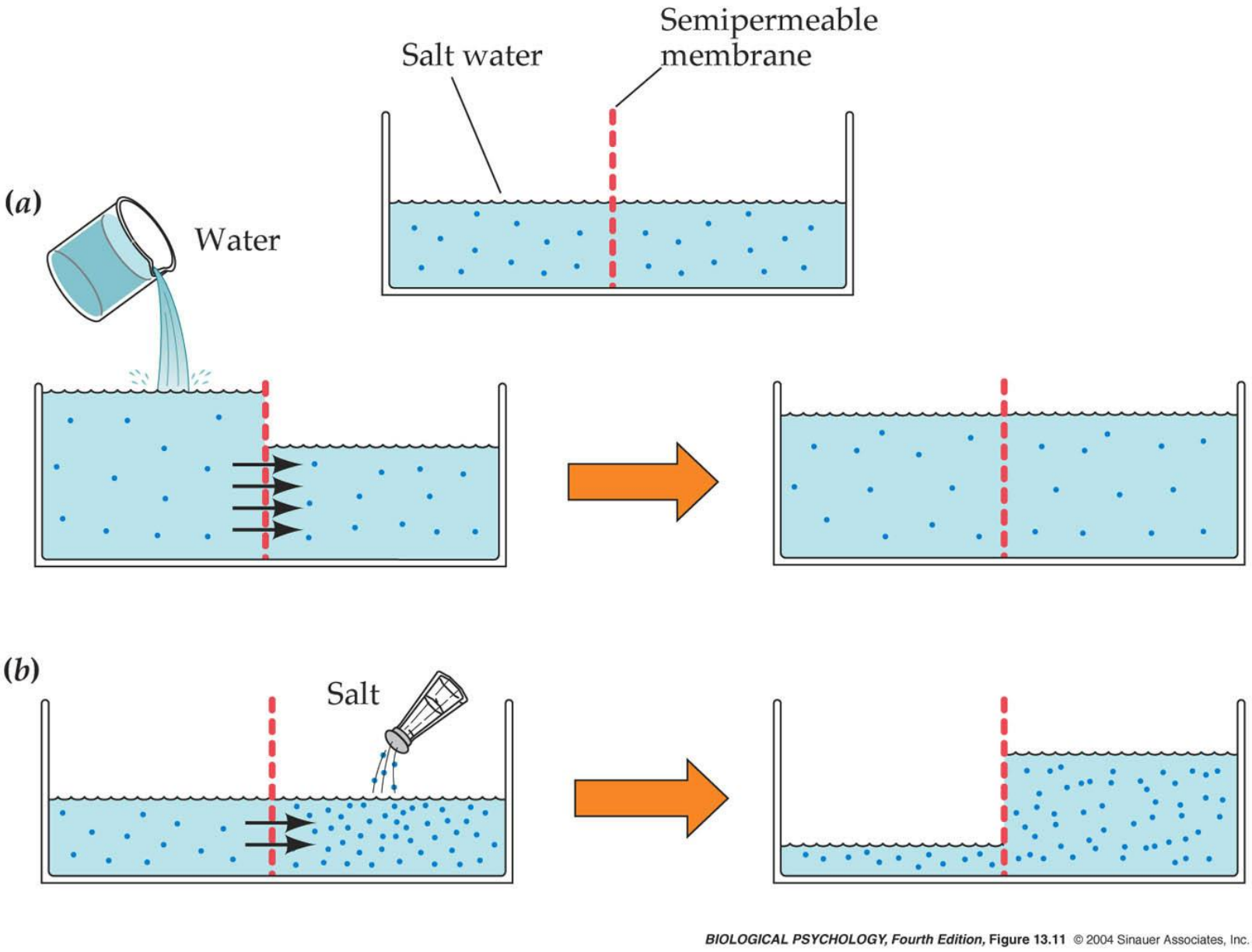
Volume	Indicators
Total body water	$^{3}H_2O$, $^{2}H_2O$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water - Extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = Plasma volume/(1 - Hematocrit)
Interstitial fluid	(Calculated as extracellular fluid volume - Plasma volume)

- Maintenance of adequate fluids in ECF & ICF ------ Important Clinical problem
- **Hydrostatic** forces & **Colloid osmotic** forces across capillary membrane responsible for this equilibrium within ECF
- **Osmotic effect of solutes** responsible for equilibrium b/w ICF & ECF
- Important role of Cell membrane

Osmosis

Net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration.

OSMOSIS



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CELL MEMBRANE

- Semipermeable membrane
- Highly water soluble
- Almost impermeable to solutes
- Addition or removal of solutes from one side results in osmosis
- Rate of diffusion of water molecules is called **Rate of Osmosis**

MOLES & OSMOLES

- Total no. of osmotically active particles in a solution is measured in **Osmoles**
- 1 osm = 1 mole (**If substance does not dissociate**)
- A solution containing 1 mole of glucose in a liter has a conc. of 1 osm/liter
- 1 mole of NaCl = 2 osm/liter
- 1 mole of Na_2SO_4 = 3 osm/liter
- 1 milliosmole (mOsm) = 1/1000 Osm

OSMOLALITY & OSMOLARITY

- No. of osmoles per kg of water—OSMOLALITY
- No. of osmoles per liter of water is OSMOLARITY
- In dil. solutions like body fluids both are same

OSMOTIC PRESSURE

- The amount of pressure required to oppose the movement of water molecules, and to stop osmosis --- Osmotic Pressure
- It is the indirect measurement of solutes & water.
- Higher the osmotic pressure, lower the water content.

OSMOTIC PRESSURE & OSMOLARITY

- Osmotic pressure directly proportional to no. of osmotically active particles
- Independent of molecular wt
- Albumin & Glucose exert same osmotic pressure
- NaCl has double osmotic effect

- Each mOsm/Liter of a solute exerts an osmotic pressure of 19.3 mmHg
- Calculating the osmolarity & osmotic pressure of a solution
- 1 liter 0.9% NaCl solution
- 308 mosm/liter
- Osmotic pressure of 5944 mm Hg
- Correction factor(Osmotic Coefficient) 0.93
- Corrected osmolarity = 286mosm/liter

- Osmolarity of body fluids
- Na & Cl --- maintain osmolarity of ECF (80%)
- K --- maintains osmolarity of ICF
- Plasma osmolarity slightly higher than Interstitial fluid
- Corrected osmolarity --- 282 mosm/liter

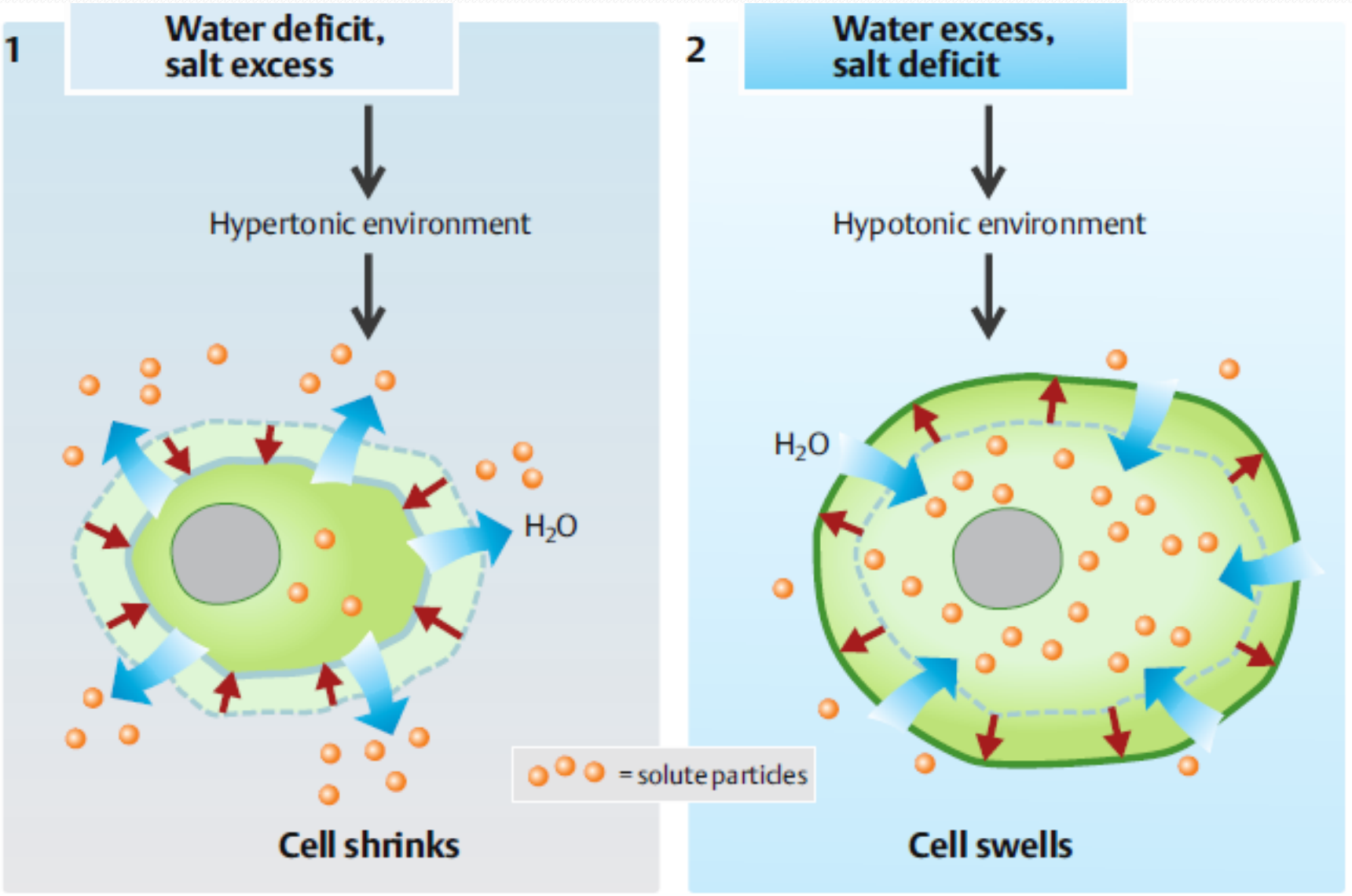
COMPARISON OF ECF & ICF

Osmolar Substances in Extracellular and Intracellular Fluids

	Plasma (mOsm/L H_2O)	Interstitial (mOsm/L H_2O)	Intracellular (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{++}	1.3	1.2	0
Mg^+	0.8	0.7	20
Cl^-	108	108	4
HCO_3^-	24	28.3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^-	0.5	0.5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate			5
Hexose monophosphate			3.7
Glucose	5.6	5.6	
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	301.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg)	5443	5423	5423

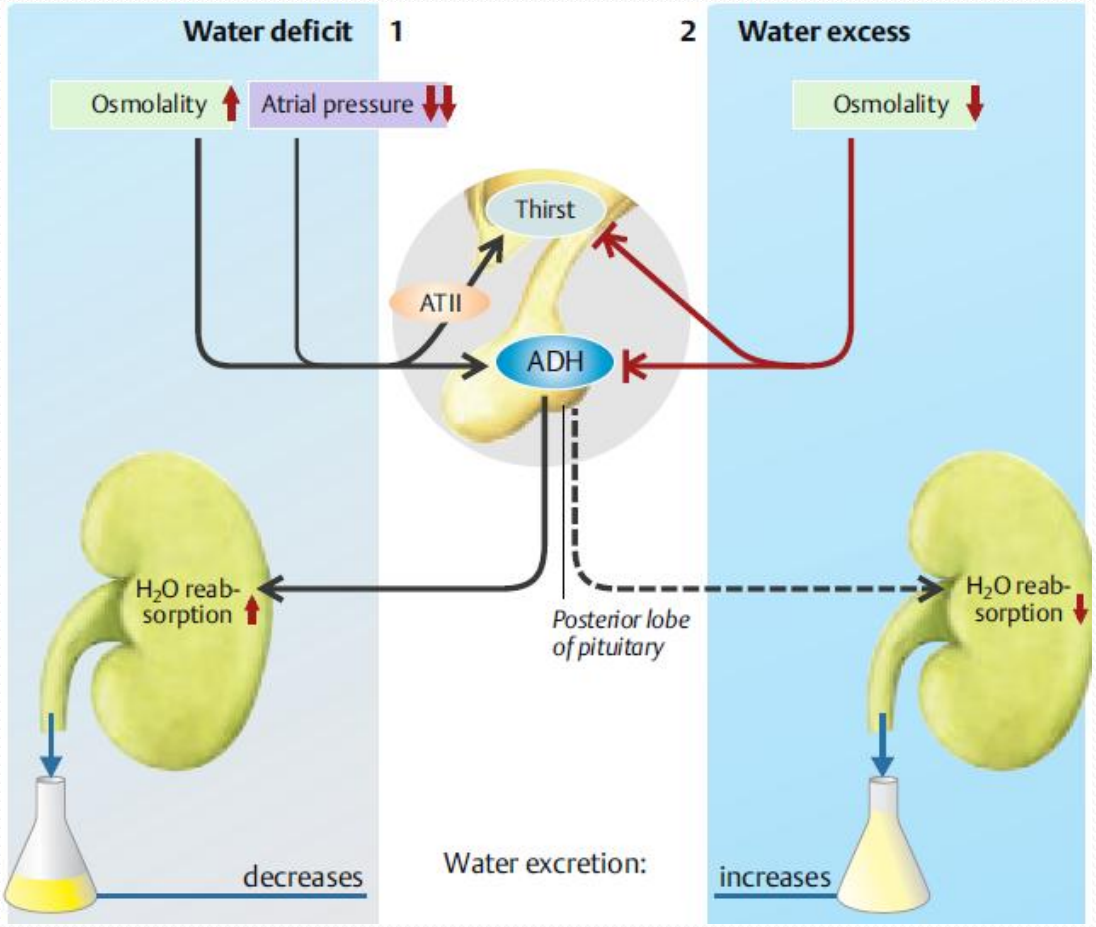
MAINTAINANCE OF OSMOTIC EQUILIBRIUM B/W ECF & ICF

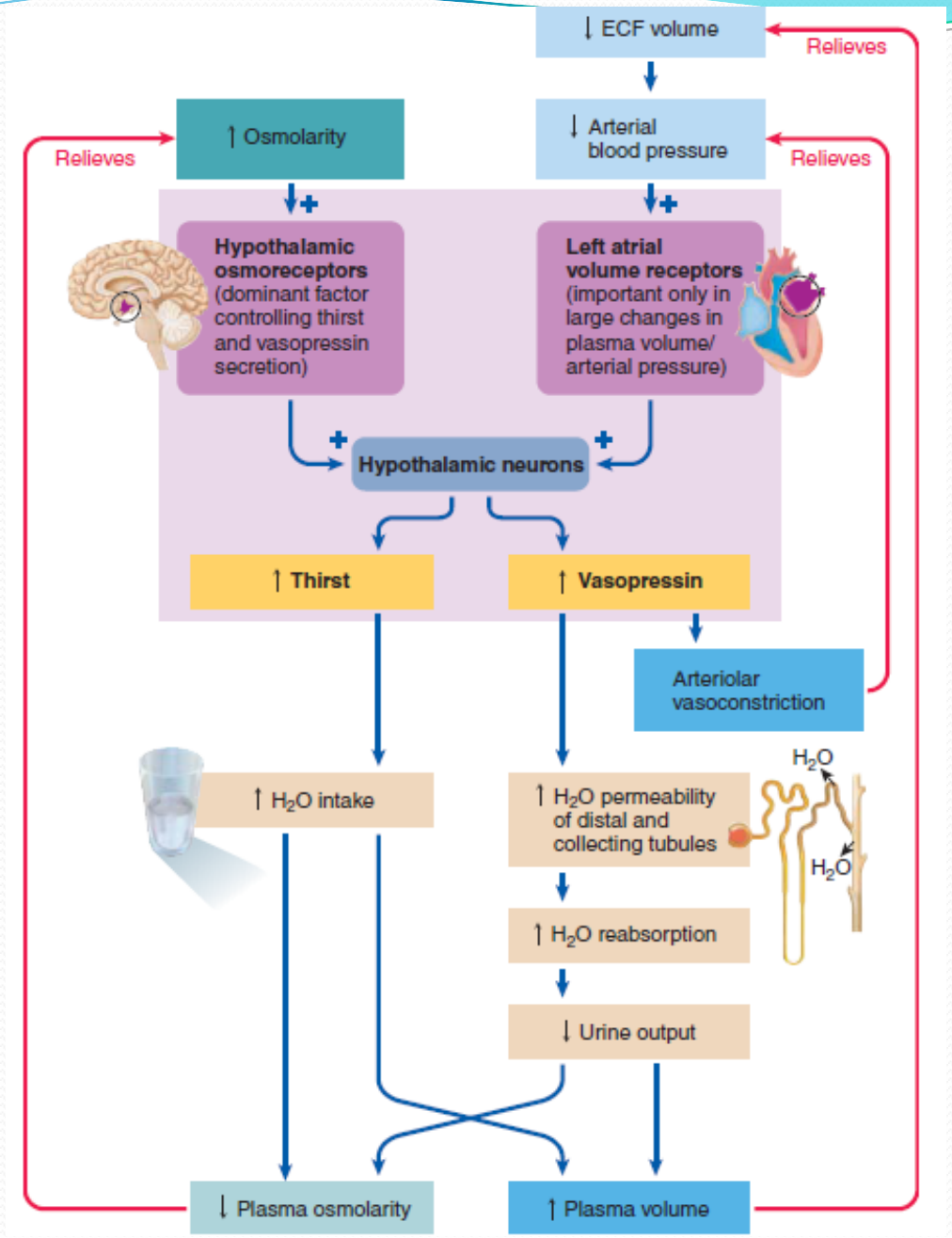
- Minute changes in solute conc. lead to large increase or decrease in osmotic pressure
- Hypertonic
- Isotonic
- Hypotonic
- 0.9% NaCl solution
- 5% Glucose solution

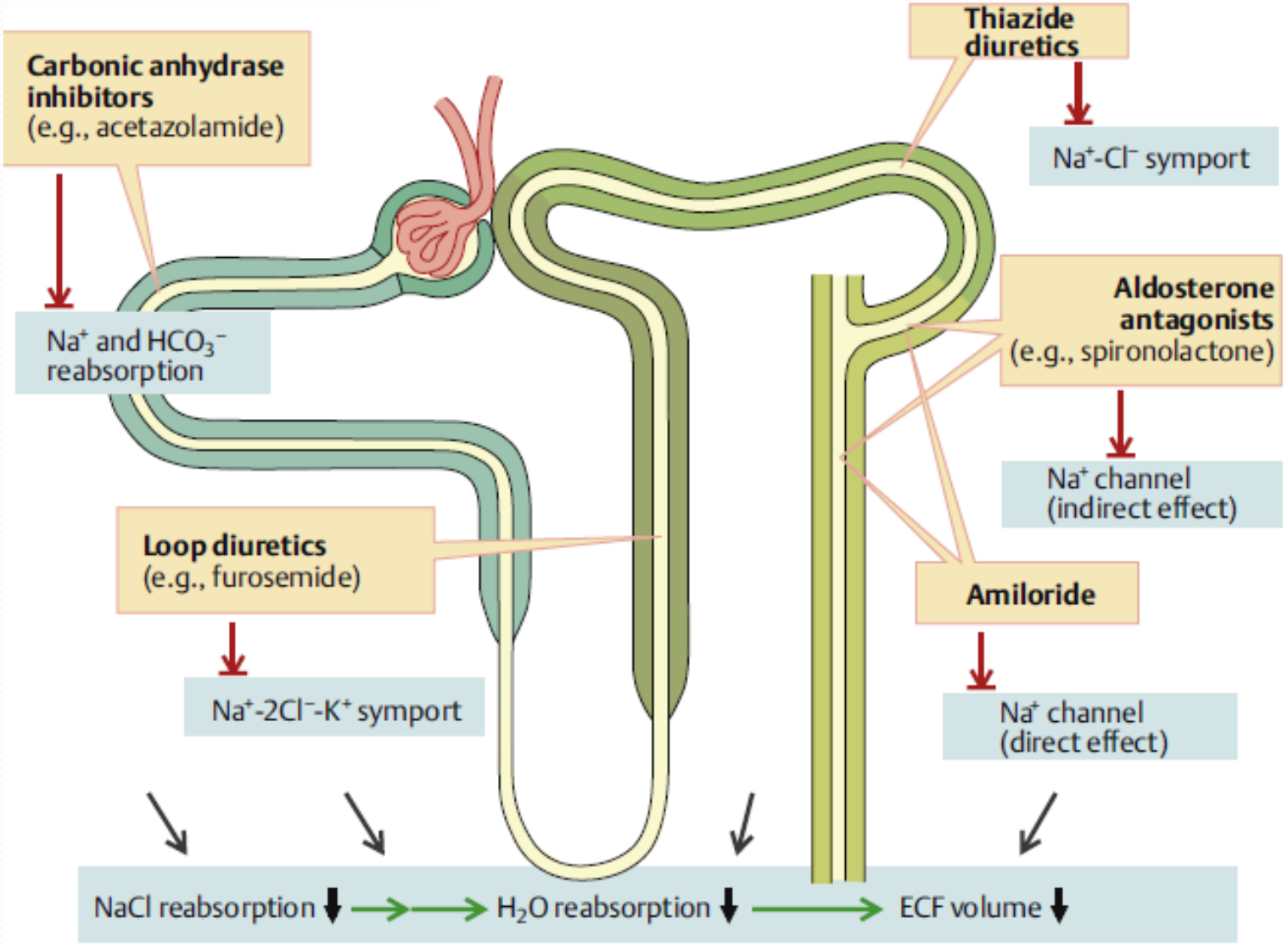

1
Water deficit, salt excess
Hypertonic environment
H_2O
Cell shrinks
2
Water excess, salt deficit
Hypotonic environment
H_2O
= solute particles
Cell swells

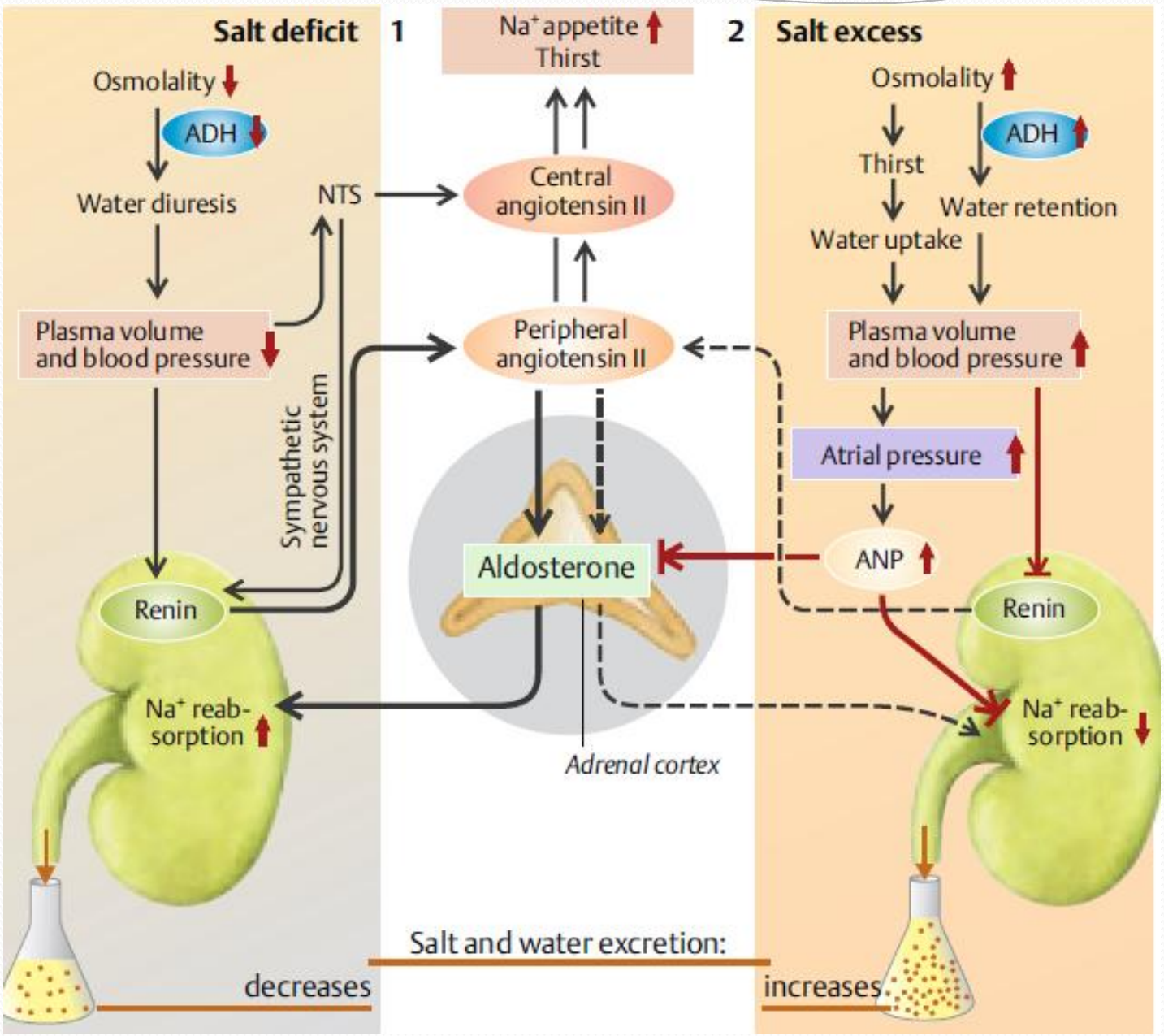
- Isosmotic
- Hyposmotic
- Hyperosmotic
- Permeating and non-permeating solutes
- NaCl
- Urea
- Osmotic equilibrium is maintained within minutes

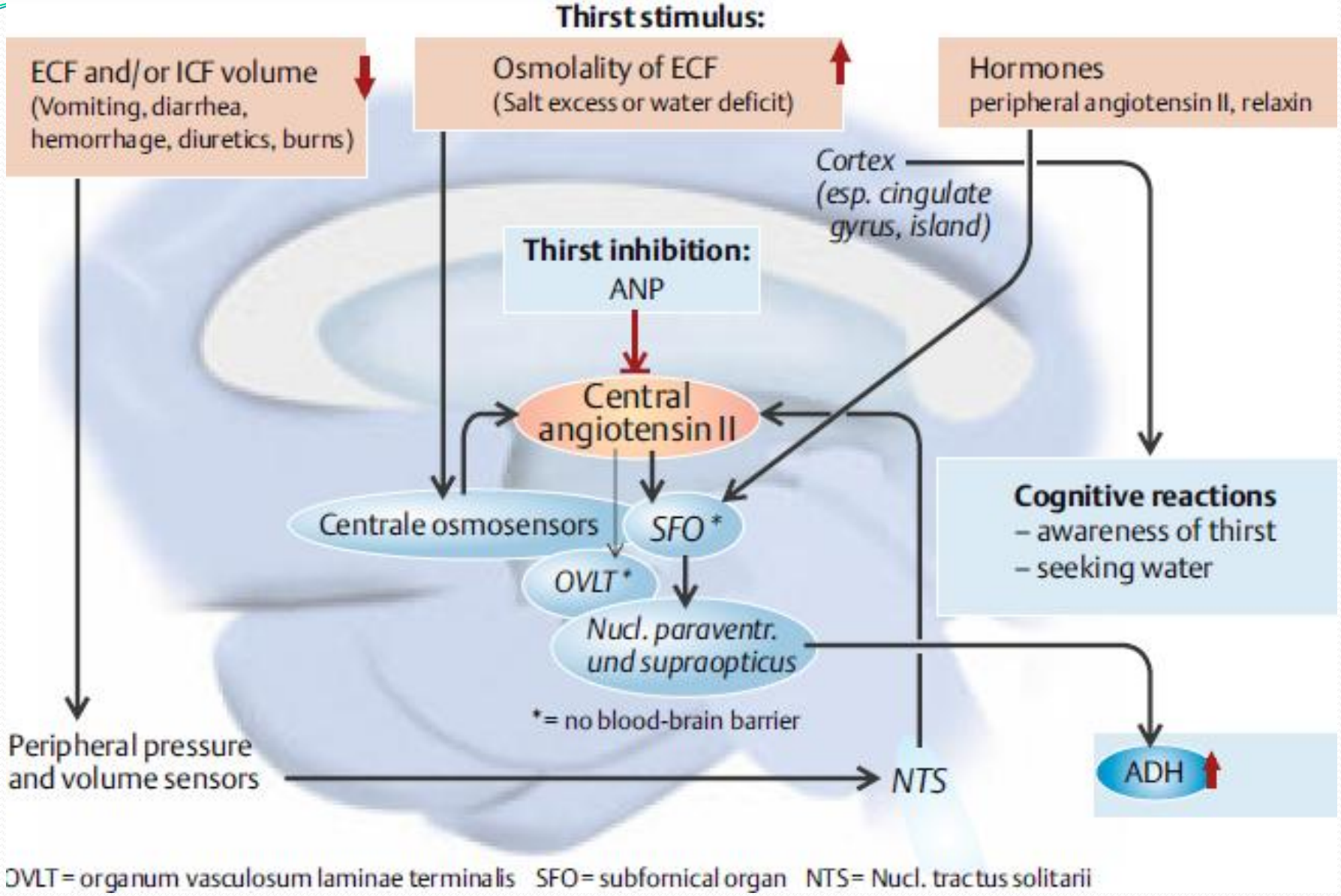
Regulation of water and salt balance




↓ ECF volume
Relieves
↑ Osmolarity
↓ Arterial blood pressure
Relieves
Relieves
Hypothalamic osmoreceptors (dominant factor controlling thirst and vasopressin secretion)
Left atrial volume receptors (important only in large changes in plasma volume/ arterial pressure)
Hypothalamic neurons
↑ Thirst
↑ Vasopressin
Arteriolar vasoconstriction
↑ H_2O intake
↑ H_2O permeability of distal and collecting tubules
H_2O
H_2O
↑ H_2O reabsorption
↓ Urine output
↓ Plasma osmolarity
↑ Plasma volume


Carbonic anhydrase inhibitors
(e.g., acetazolamide)
Na+ and HCO3− reabsorption
Loop diuretics
(e.g., furosemide)
Na+-2Cl−-K+ symport
Thiazide diuretics
Na+-Cl− symport
Aldosterone antagonists
(e.g., spironolactone)
Na+ channel
(indirect effect)
Amiloride
Na+ channel
(direct effect)
NaCl reabsorption
H2O reabsorption
ECF volume


Salt deficit
1
Na+ appetite
Thirst
2
Salt excess
Osmolality
ADH
Water diuresis
NTS
Central angiotensin II
Osmolality
ADH
Thirst
Water retention
Water uptake
Plasma volume and blood pressure
Peripheral angiotensin II
Plasma volume and blood pressure
Sympathetic nervous system
Atrial pressure
Aldosterone
ANP
Renin
Renin
Na+ reab-sorption
Na+ reab-sorption
Adrenal cortex
Salt and water excretion:
decreases
increases


Thirst stimulus:
ECF and/or ICF volume
(Vomiting, diarrhea, hemorrhage, diuretics, burns)
Osmolality of ECF
(Salt excess or water deficit)
Hormones
peripheral angiotensin II, relaxin
Cortex
(esp. cingulate gyrus, island)
Thirst inhibition:
ANP
Central angiotensin II
Centrale osmosensors
SFO *
OVLT *
Nucl. paraventr. und supraopticus
*= no blood-brain barrier
Cognitive reactions
– awareness of thirst
– seeking water
Peripheral pressure and volume sensors
NTS
ADH
OVLT = organum vasculosum laminae terminalis SFO = subfornical organ NTS = Nucl. tractus solitarii

VOLUME & OSMOLARITY OF ECF & ICF IN ABNORMAL STATES

- WATER INGESTION
- DEHYDRATION
- I/V INFUSION
- GIT LOSSES
- PROFUSE SWEATING
  - WATER MOVES RAPIDLY ACROSS THE MEMB.
  - CELL MEMB. IMPERMEABLE TO SOLUTES

Effect of addition of 2 Liters of 3% NaCl to ECF

Step 1. Initial Conditions

	Volume (Liters)	Concentration (mOsm/L)	Total (mOsm)
Extracellular fluid	14	280	3,920
Intracellular fluid	28	280	7,840
Total body fluid	42	280	11,760

SOLUTIONS USED FOR NUTRITIVE PURPOSES

- .

- Glucose
- Amino acids
- Homogenized fat solution

CLINICAL ABNORMALITIES OF FLUID VOLUME REGULATION

- **Hyponatremia**
- **Hypernatremia**

Hyponatremia Defined

- Definition: Serum Na+ <135 meq/L
  - Generally associated with decreased osmolality to <275
  - Most common electrolyte abnormality in the US
  - Occurs in 3% of hospitalized patients

- Caused by retention of water
  - Usually a drop in osmolality will suppress ADH to allow excretion of the excess water via dilute urine
  - Most forms of hyponatremia are associated with elevated ADH (whether appropriate or inappropriate), which concentrates urine

Signs & Symptoms

- More profound when the decrease in sodium is **very large** or occurs **rapidly** (i.e. over hours)
- Generally asymptomatic if Na+ level >125
- Symptoms include:
  - Headache
  - Nausea, vomiting
  - Muscle cramps
  - Disorientation, depressed reflexes, lethargy, restlessness
  - Seizure, coma, permanent brain damage, respiratory arrest, brainstem herniation & death
    - Serious complications are more commonly seen in primary polydipsia, after surgery, and in menstruating women

Causes of hyponatremia

Decreased total body water	GI losses (diarrhea, emesis), diuretics, Addisons Disease
Increased total body water	CHF, acute renal failure, SIADH, water intoxication (dilute formula feeding), Bronchogenic CA
Normal total body water	Hyperglycemia
Pseudohyponatremia	Severe hyperlipidemia or hypoproteinemia

- Hyperglycemia leads to hyperosmolarity with translocation of fluids from intracellular to extracellular space

- Pseudohyponatremia: displacement of plasma water resulting in falsely low serum by laboratory measurement

Clinical manifestations of hyponatremia

- Neurologic symptoms related to edema caused by hypo-osmolarity
  - Children at higher risk due to higher brain-to-skull ratio
- Symptoms include headache, nausea, emesis, weakness, disorientation
- Severity worsens as edema increases leading to signs of cerebral herniation
  - Respiratory changes, posturing, pupillary changes, seizure

Fluid management goals

- Hyponatremia with neurologic symptoms is a **medical emergency**

Clinical picture	Fluid	Rate
Seizure	3% hypertonic saline	raise serum sodium by 4-8 mEq/L/hour until seizure activity stops
No seizure activity but not at neurologic baseline	3% hypertonic saline	raise serum sodium by 1mEq/L/hour until: -patient at baseline -plasma sodium increases by 20-25mEq/L OR -serum sodium increases to 125-130mEq/L
Asymptomatic	0.9% normal saline	raise sodium no faster than 0.5 mEq/L/hour

Hypernatremia

- Defined as serum sodium >/= 145mEq/L

- Causes:

Excess sodium intake	Concentrated formula, salt ingestion (seawater, accidental), hypertonic IV fluids, sodium bicarbonate, blood products
Increased free water losses	1) Renal: diabetes insipidus, tubular disorder 2) GI: diarrhea, vomiting, colostomy/ileostomy output, malabsorption 3) Insensible: fever, tachypnea, burns
Decreased free water intake	Ineffective breastfeeding, poor access to water, blunted thirst mechanisms, fluid restriction

Clinical Manifestations and Evaluation of Hypernatremia

- Early neurologic signs include agitation and irritability→can progress to seizure and coma
- Neurologic exam can reveal increased tone, brisk reflexes and rigidity
- Lab evaluation can include:
  - Serum osmolarity
  - Serum glucose
  - Urine osmolarity and specific gravity

Neurologic Sequelae

- In acute phase:
  - Intracellular fluid moves to extracellular space-volume loss in brain → separation from meninges
- If hypernatremia has existed for >2-3 days:
  - Neurons protect themselves by making osmolytes to maintain gradient
  - With rapid correction, neurons can swell leading to cerebral edema
- Mortality estimated at 10-16% despite correct rate of rehydration

What is this ????

EDEMA

- Abnormal accumulation of fluid in the body tissues
  - Intracellular Edema
  - Extracellular Edema

Intracellular Edema

- Three main causes
  - Hyponatremia
  - Depression of Metabolic systems
  - Lack of adequate nutrients
    - Lack or decrease in tissue blood supply
    - Inflammatory conditions lead to edema

Extracellular Edema

- Two general causes
  - Abnormal leakage of fluid from plasma into interstitial spaces across the capillaries
  - Failure of lymphatics to return fluid back to plasma (**Lymphedema**)
- Increased capillary fluid filtration is the most common cause

Organ specific:

- Brain: Cerebral edema
- Lung: Intra-alveolar=pulmonary edema, intra-pleural=pleural effusion
- Peritoneum=ascites
- Severe generalized edema=anasarca

Factors increasing Capillary filtration

- Increased capillary filtration coefficient.
- Increased capillary hydrostatic pressure.
- Decreased plasma colloid osmotic pressure

Lymphatic Blockage

- Failure of lymphatics to return plasma proteins back to plasma.
- Causes
  - Infections of lymph nodes. e.g., **Filaria Nematode**
  - Cancers
  - Surgical removal of lymph nodes. e.g., Radical Mastectomy

SUMMARY OF CAUSES OF EXTRACELLULAR EDEMA

I. Increased capillary pressure

A. Excessive kidney retention of salt and water

1. Acute or chronic kidney failure
2. Mineralocorticoid excess

B. High venous pressure and venous constriction

1. Heart failure
2. Venous obstruction
3. Failure of venous pumps
    (a) Paralysis of muscles
    (b) Immobilization of parts of the body
    (c) Failure of venous valves

C. Decreased arteriolar resistance

1. Excessive body heat
2. Insufficiency of sympathetic nervous system
3. Vasodilator drugs

II. Decreased plasma proteins

A. Loss of proteins in urine (nephrotic syndrome)

B. Loss of protein from denuded skin areas

1. Burns
2. Wounds

C. Failure to produce proteins

1. Liver disease (e.g., cirrhosis)
2. Serious protein or caloric malnutrition

III. Increased capillary permeability

A. Immune reactions that cause release of histamine and other immune products

B. Toxins

C. Bacterial infections

D. Vitamin deficiency, especially vitamin C

E. Prolonged ischemia

F. Burns

IV. BLOCKAGE OF LYMPH RETURN

A. Cancer

B. Infections (e.g., filaria nematodes)

C. Surgery

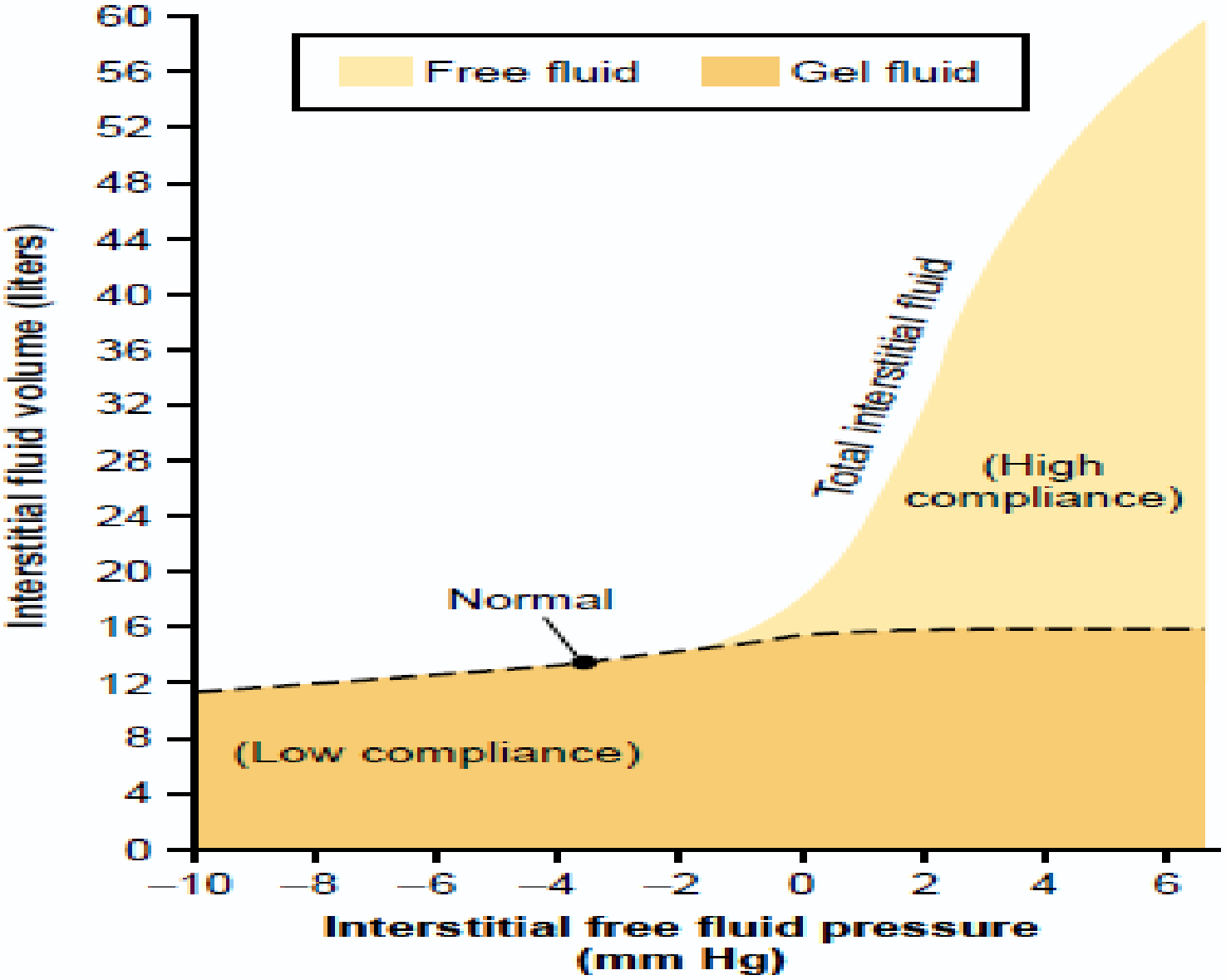
D. Congenital absence or abnormality of lymphatic vessels

Safety Factors Preventing Edema

- Low compliance of interstitium when I.F. pressure is in negative range
- 10-50 fold increase in lymph flow
- Wash down of interstitial fluid protein concentration

Low Compliance of Interstitium

- Normal I.F. pressure = -3mmHg
- Slight suction pressure
- Low compliance when pressure is in negative range


Free fluid
Gel fluid
Interstitial fluid volume (liters)
60
56
52
48
44
40
36
32
28
24
20
16
12
8
4
0
Total interstitial fluid
(High compliance)
Normal
(Low compliance)
−10
−8
−6
−4
−2
0
2
4
6
Interstitial free fluid pressure (mm Hg)

Importance of Interstitial Gel

- Interstitium is in the form of gel supported by proteoglycan filaments
- Accumulation of free fluid in +ve range
- Pitting Edema
- Non-Pitting Edema

Increased Lymph Flow

- 10-50 fold increase in lymph flow
- Removal of fluids and proteins from interstitium
- 7mm Hg

Washdown of I.F. proteins

- Increased I.F. volume --- Increased I.F. pressure
- Increased lymph flow
- Increased removal of proteins
- 7mm Hg

Summary of safety factors

- Low compliance=3 mmHg
- Increased lymph flow=7 mmHg
- Washdown of Plasma Proteins=7mmHg
- Total safety factor = 17mmHg

Fluids in potential spaces

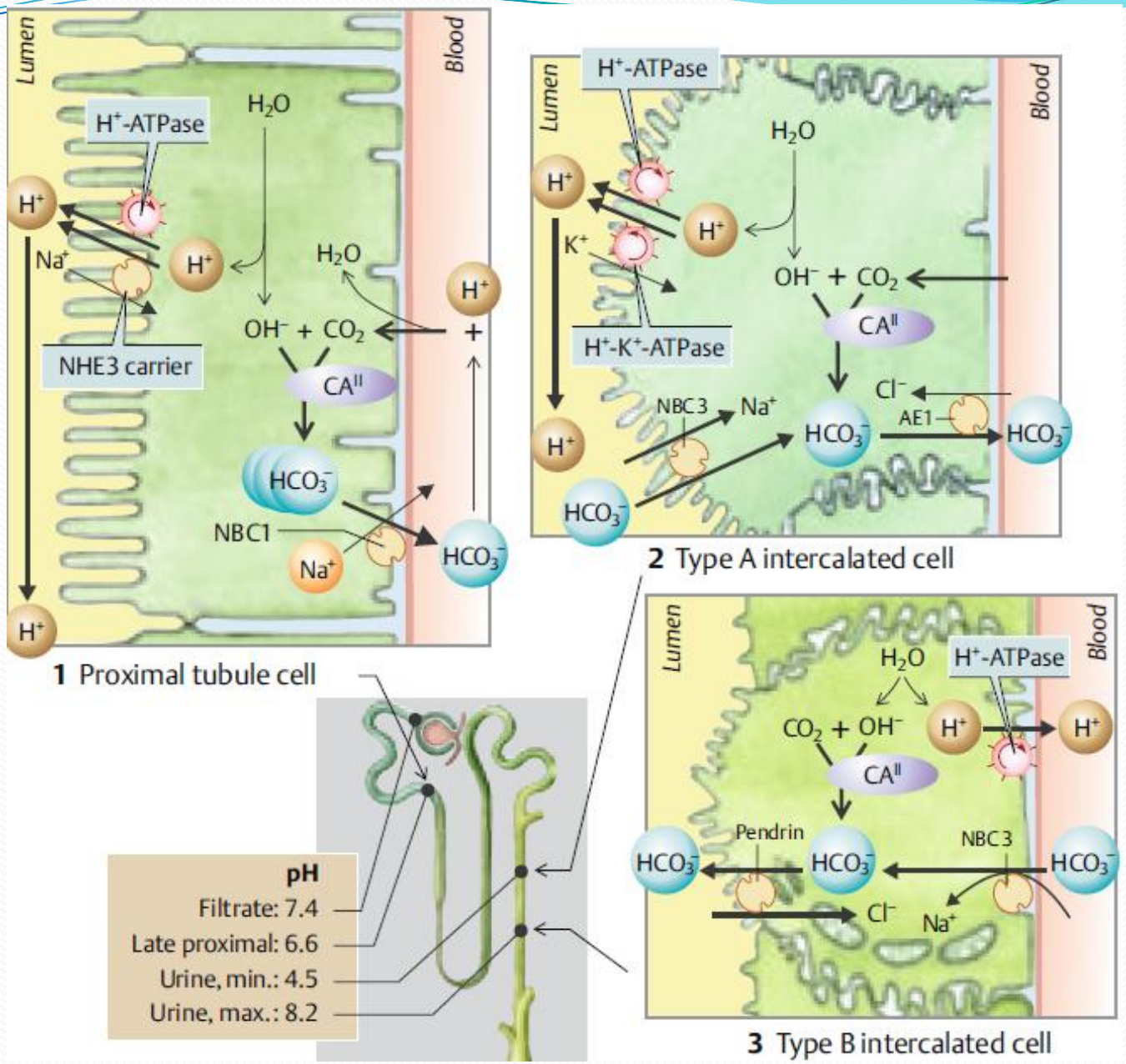
- Pleural cavity
- Pericardial cavity
- Peritoneal cavity
- Synovial cavity

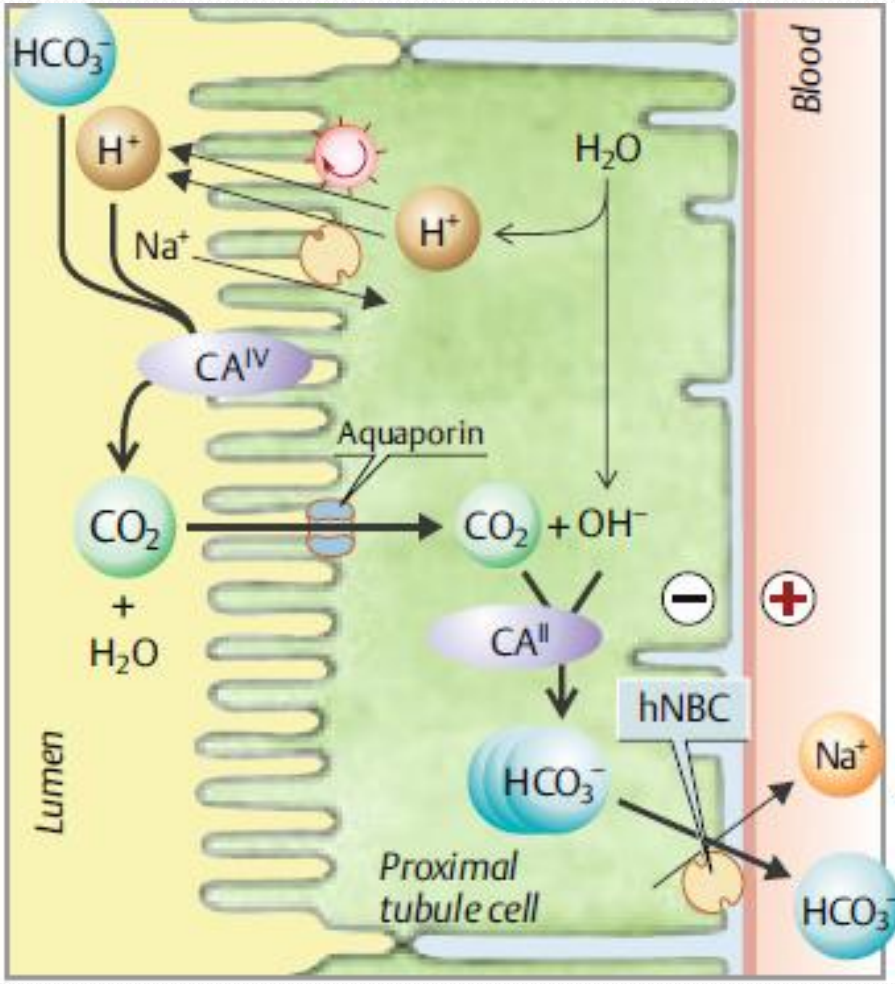
Effusion

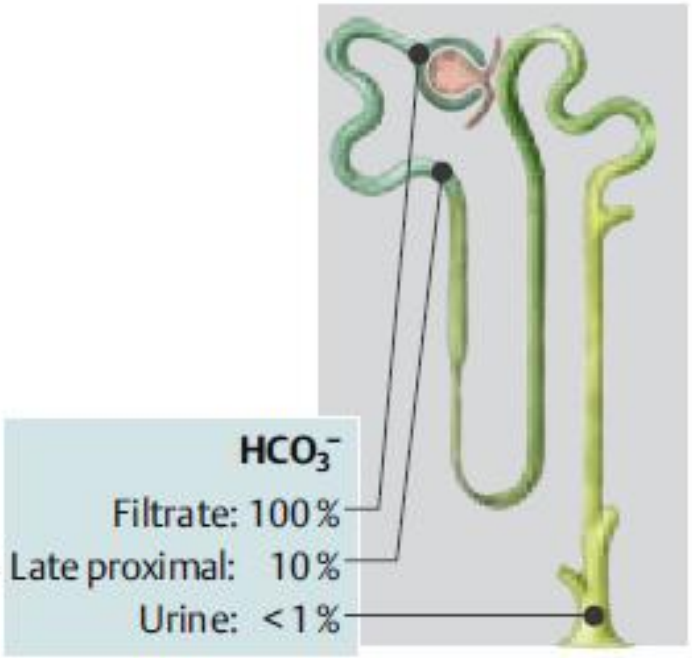
- Collection of fluid in potential spaces
- Pleural effusion, pericardial effusion
- Ascites--- collection of fluid in peritoneal cavity. (May be upto 20 liters)
- Cause of effusion--- Infection, Injury, lymphatic blockage

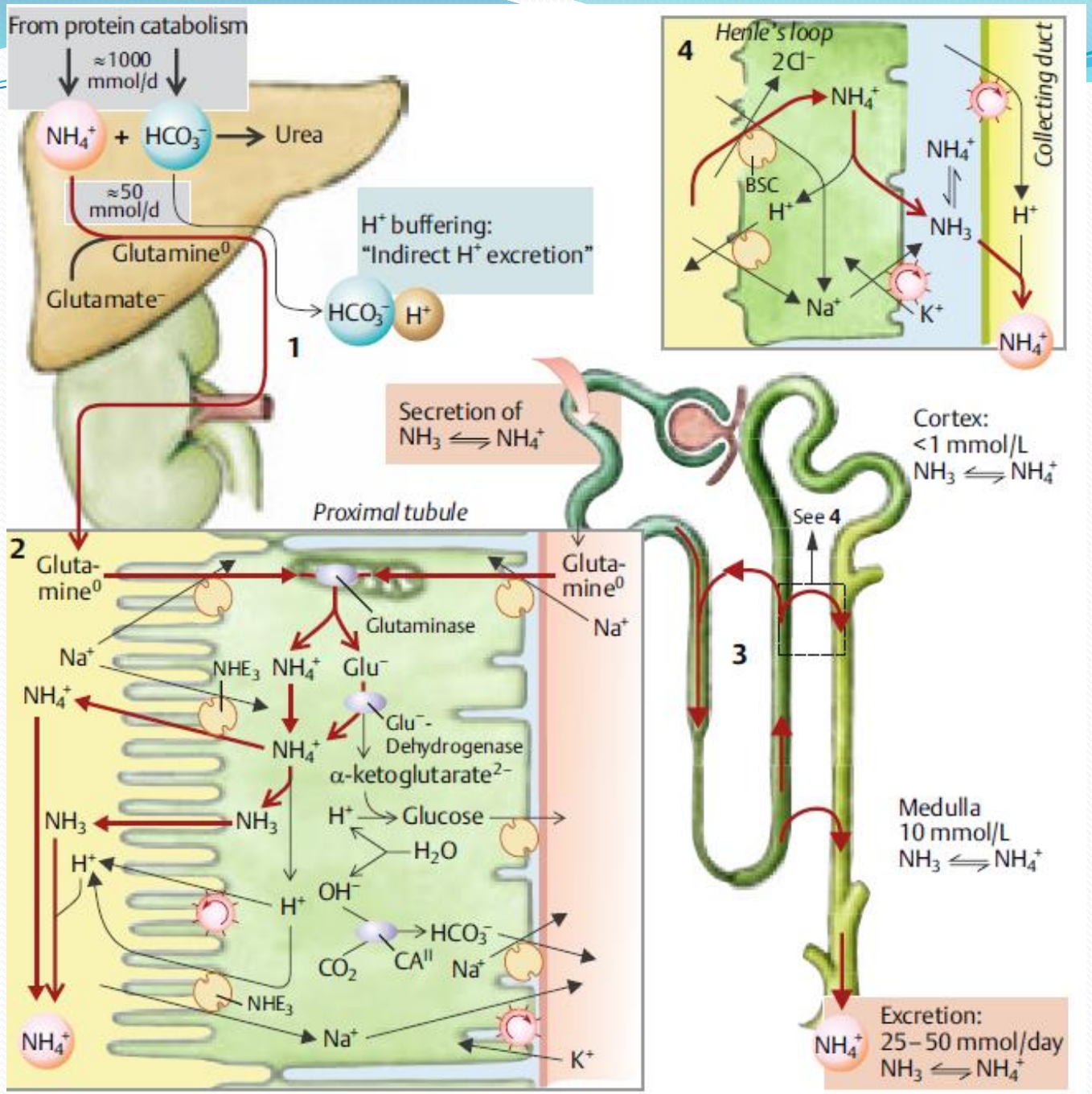
Kidney and Acid Base Balance

- Kidneys adjust their rate of hydrogen ion excretion by varying the extent of hydrogen ion secretion
- Kidneys conserve or excrete bicarbonate ions depending on the plasma hydrogen ion concentration
- Kidneys secrete ammonia during acidosis to buffer secreted hydrogen ions
- The phosphate buffer system is an important urinary buffer


Lumen
Blood
H+-ATPase
H2O
H+
Na+
NHE3 carrier
OH− + CO2
CAII
HCO3−
NBC1
1 Proximal tubule cell
H+-K+-ATPase
K+
NBC3
AE1
Cl−
2 Type A intercalated cell
Pendrin
pH
Filtrate: 7.4
Late proximal: 6.6
Urine, min.: 4.5
Urine, max.: 8.2
3 Type B intercalated cell


HCO_3^-
H^+
H_2O
Blood
H^+
Na^+
CA^{IV}
Aquaporin
CO_2
$CO_2 + OH^-$
+
H_2O
CA^{II}
hNBC
Na^+
HCO_3^-
Lumen
Proximal tubule cell
HCO_3^-


HCO_3^-
Filtrate: 100 %
Late proximal: 10 %
Urine: < 1 %


From protein catabolism
≈1000 mmol/d
NH_4^+ + HCO_3^- → Urea
≈50 mmol/d
Glutamine⁰
Glutamate⁻
H^+ buffering:
"Indirect H^+ excretion"
HCO_3^- H^+
1
Secretion of
$NH_3 \rightleftharpoons NH_4^+$
Proximal tubule
2
Gluta-mine⁰
Glutaminase
Na⁺
NHE_3
NH_4^+
Glu^-
Glu^--Dehydrogenase
α-ketoglutarate²⁻
NH_3
H^+
Glucose
H_2O
OH^-
HCO_3^-
CO_2
CA^{II}
K^+
4
Henle's loop
$2Cl^-$
BSC
Collecting duct
3
See 4
Cortex:
<1 mmol/L
$NH_3 \rightleftharpoons NH_4^+$
Medulla
10 mmol/L
$NH_3 \rightleftharpoons NH_4^+$
Excretion:
25–50 mmol/day
$NH_3 \rightleftharpoons NH_4^+$