Integrative Sciences: Biological Systems A
Fall 2011

Body Fluids Compartments, Renal Clearance and Renal Excretion of Drugs

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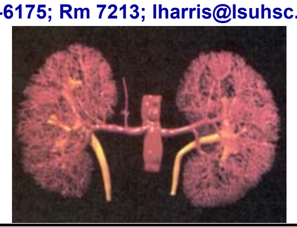
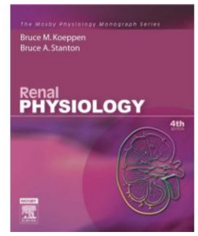
Lisa M. Harrison-Bernard, Ph.D.
Department of Physiology; Associate Professor
568-6175; Rm 7213; lharris@lsuhsc.edu



Recommended Textbook



Body Fluid Compartments
Chapters 1 & 3 in Koeppen & Stanton Renal Physiology

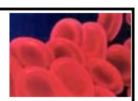
a) Terminology
b) Body Fluid Compartments

Terminology

Molarity – number of moles of solute / Liter of solution

- Molar (M) = moles/L
- millimolar (mM) = mmol/L

Terminology



Tonicity – of solution related to effect on cell volume – ability of solute to cross cell membrane

- Isotonic solution: *no change* in cell volume
- Hypotonic solution: causes cell to *swell*
- Hypertonic solution: causes cell to *shrink*

Terminology

Osmole – amount of substance that dissociates in solution to form **1 mole of osmotically active** particles

- **1** mole glucose = **1** osmole of solute
- **1** mole NaCl = **2** osmoles of solute

Terminology

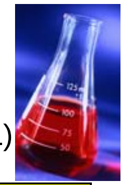
Osmolality - osmoles/kg H_2O

- dependent on number molecules in solution, not size, nature, charge
- body fluid shifts between compartments
- Normal value - **290** mOsmoles/kg solution

Terminology

Osmolarity - concentration of osmotically active particles in solution –

- osmoles/Liter (Osm/L)
- mosmoles/Liter (mOsm/L)



Dilute solutions:
osmolality ~ osmolarity

Terminology

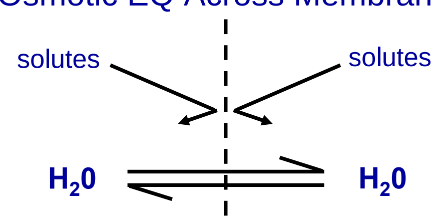
Isosmotic - same osmolarity as plasma

- hypoosmotic - below
- hyperosmotic - above

Role of Kidneys

Maintain the **volume** and **composition** of body fluids constant despite wide variation in daily intake of water & solute.

Osmotic EQ Across Membrane



Water diffuses across *semipermeable* cell membranes through water channels, **AQUAPORINS**. Net movement of water to achieve osmotic EQ.

Osmotic Driven Water Flow

INITIAL CONDITIONS			
	A	B	Total
Volume (L)	3	3	6
Conc (mOsm)	400	200	---
Total Solute (mosmoles)	1,200	600	1,800

Total Solute (mosmoles) = Conc (mosmoles/L) X Volume (L)
Conc (mOsm) = 1,800 mosmoles / 6 L
= 300 mOsm

Osmotic Driven Water Flow

INITIAL CONDITIONS			
	A	B	Total
Volume (L)	3	3	6
Conc (mOsm)	400	200	---
Total Solute (mosmoles)	1,200	600	1,800

EQ CONDITIONS			
	A	B	Total
Final Volume (L)	4	2	6
Conc (mOsm)	300	300	---
Amount Solute (mosmoles)	1,200	600	1,800

Solute Composition of Body Fluid Compartments Appendix B

Solute	Units	Normal Plasma Range	PLASMA Conc	Cell
Na^+	mmol/L	135 - 147	*** 145**	10-15
K^+	mmol/L	3.5 - 5.0	**4.4**	*150
Ca^{+2} (ionized)	mmol/L	1.14 - 1.3	**1.2**	100nM
H^+	pH	7.35 - 7.45	**7.4**	~7.2

Solute Composition of Body Fluid Compartments Appendix B

Solute	Units	Normal Plasma Range	PLASMA Conc	Cell
Cl^-	mmol/L	95 – 105	*** 102**	20
HCO_3^-	mmol/L	22 – 28	*** 24**	15
Protein	g/dl	6 - 7.8	**7**	*30
Glucose	mg/dl	70 – 110	**100**	---
Osmolality	mOsm/kg H_2O	285 - 295	**290**	290

Major Cations and Anions

	Cation	Anion
Extracellular	**Na^+**	**Cl^-, HCO_3^-**
Intracellular	**K^+**	Organic Phosphates, Proteins

Water in Body

Water - most abundant substance in body

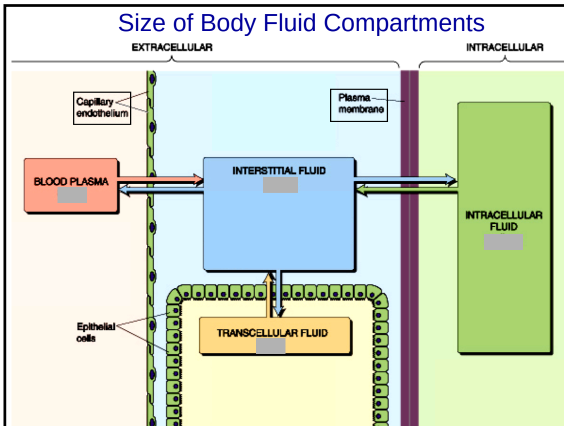
Solvent for all dissolved constituents

Intracellular volume – volume of fluid in all cells

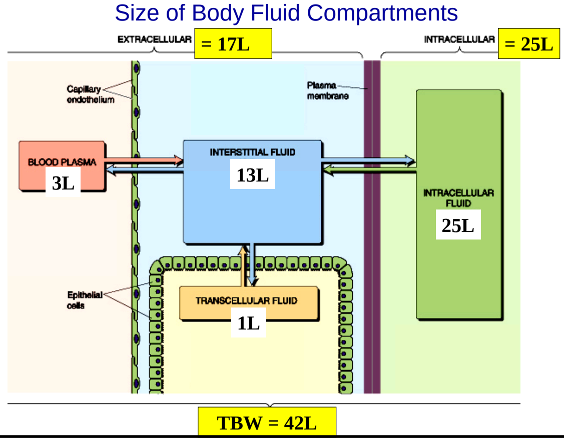
Extracellular volume – fluid throughout compartment

- interstitial space, vascular compartment

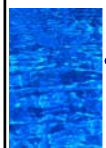
Size of Body Fluid Compartments



Size of Body Fluid Compartments



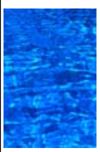
Approximate Water Distribution 70Kg Adult Human



- Total Body Water (**TBW**)
  - ~ 60% Body Weight **(BW)** = ~ **42L**
- Intracellular Fluid (**ICF**)
  - ~ 40% BW = ~ **25L**
- Extracellular Fluid (**ECF**)
  - ~ 20% BW = ~ **17L**

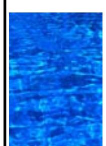
" 20, 40, 60 " rule of thumb

Approximate Water Distribution 70Kg Adult Human



- TBW
  - 60% BW = ~ **42L**
- Intracellular Fluid (ICF)
  - 60% TBW = ~ **25L**
- Extracellular Fluid (ECF)
  - 40% TBW = ~ **17L**

ECF = **17L**



- Interstitial Fluid (**ISF**)
  - 75% ECF = **13L**
- Plasma Volume (**PV**)
  - 20% ECF = **3L**
- Blood Volume (**BV**)
  - PV/(1-Hct) = **5.5L**
- Transcellular Fluid (synovial & cerebrospinal fluid)
  - 5% ECF = **1L**

Calculating Changes in Body Fluid Volumes

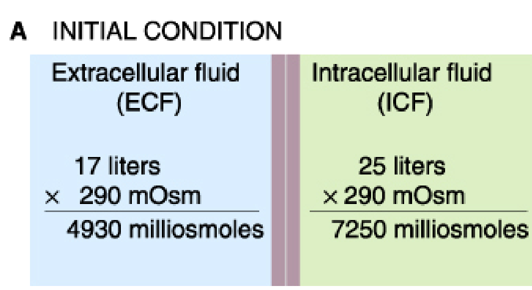
Osmoles (milliosmoles) = Osmolarity (milliosmoles/L) X Body Water (L)

Total Body
12,180 milliosmoles = 290 mosmoles/L X 42 L

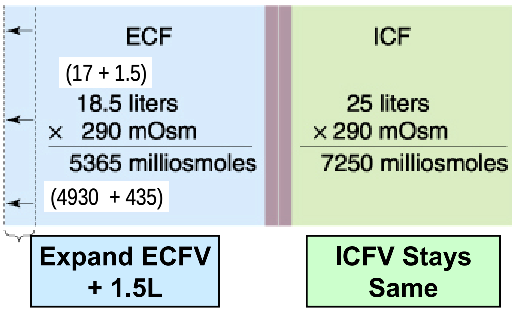
ICF
7,250 milliosmoles = 290 mosmoles/L X 25 L

ECF
4,930 milliosmoles = 290 mosmoles/L X 17 L

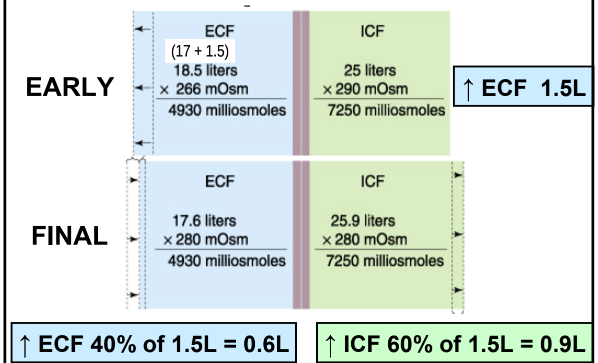
Body Fluid Compartments



INFUSE 1.5L Isotonic Saline (145 mM NaCl)



Infuse 1.5 L Pure Water (Isotonic Glucose)



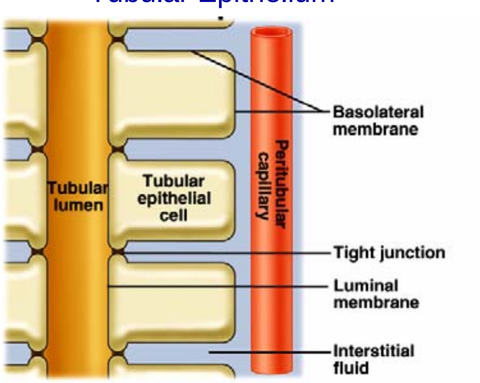
Summary I

1. Determine body fluid volumes based on body weight
2. Predict changes in fluid volume and osmolality caused by salt and fluid loss and gains

Renal Clearance

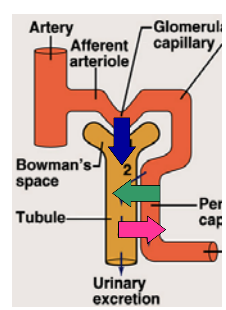
1. Concept of Clearance
2. Clearance of Inulin, Creatinine = Estimates of Glomerular Filtration Rate (GFR)
3. PAH, estimate of Renal Plasma Flow (RPF)

Tubular Epithelium



Renal Processes

- **Filtration**
  Glomerular capillary lumen ⇒ Bowman's space (bulk flow)
- **Tubular Reabsorption**
  Tubular lumen ⇒ peritubular capillary plasma
- **Tubular Secretion**
  Peritubular plasma (capillary lumen) ⇒ interstitial space ⇒ tubular cell ⇒ tubular lumen
  (tubular cell interior to tubular lumen)



Renal Plasma Clearance

- Renal CLEARANCE of any substance

volume of plasma from which a substance is completely removed (cleared) by kidneys per unit time

Units = Volume plasma per time

ml/min

- QUANTITATIVE evaluation of how kidney handles a specific substance

Clearance X =

$$\frac{\textbf{Mass X excreted / time}}{\textbf{Plasma [X]}}$$

$$Cl_X \cdot P_X = U_X \cdot \dot{V}$$

$$\boxed{Cl_X = \frac{U_X \cdot \dot{V}}{P_X}}$$

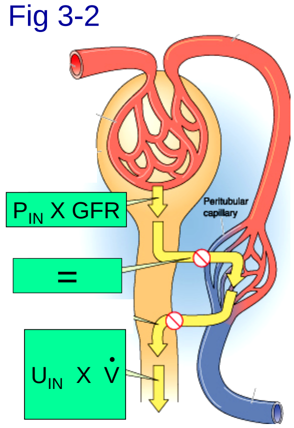
Substance	CLEARANCE (ml/min)
Glucose	0
Na^+	0.9
K^+	12
Inulin	***125***
Creatinine	***140***
PAH	***560***

Inulin

Cl_{IN} = GFR

Inulin ~ Fig 3-2

- MW 5,000 Da
- Freely filterable
- NOT reabsorbed
- NOT secreted
- NOT metabolized, synthesized, stored
- Does not alter GFR
- Nontoxic
- Infusion required
- P_{IN}, U_{IN} - analytic method



Inulin
Measurement of GFR

Amount Filtered = Amount Excreted

$$GFR \cdot P_{IN} = U_{IN} \cdot \dot{V}$$

$$\boxed{GFR = \frac{U_{IN} \cdot \dot{V}}{P_{IN}} = Cl_{IN}}$$

Creatinine
Cl_{Cr} ~ GFR

Creatinine

Rate of Production = Rate of Excretion

1 g/day = 1 g/day

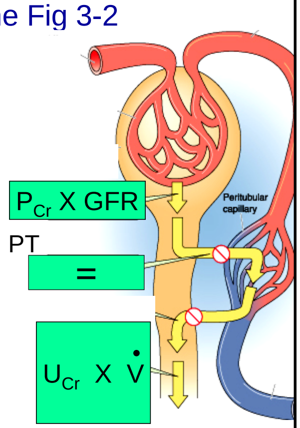
Index of GFR

$$GFR(Clearance_{Cr}) = \frac{U_{Cr} \bullet \dot{V}}{P_{Cr}}$$

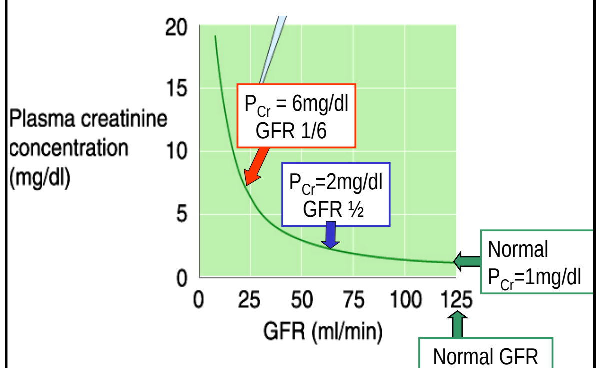
Cl_{Cr} is inversely related to P_{Cr}

Creatinine Fig 3-2

- Metabolism of creatine phosphate in muscle
- Produced continuously
- Freely filtered
- NOT reabsorbed
- Small amount secreted PT
- NO infusion required
- Stable P[Cr]
- P[Cr] & U[Cr] – colorimetric method



$Plasma_{Cr}$ Inversely Related to GFR Fig 3-3



Plasma Creatinine Concentrations

P_{Cr} = 0.8 – 1.2 mg/dl (1.0 mg/dl)

normal range for adult

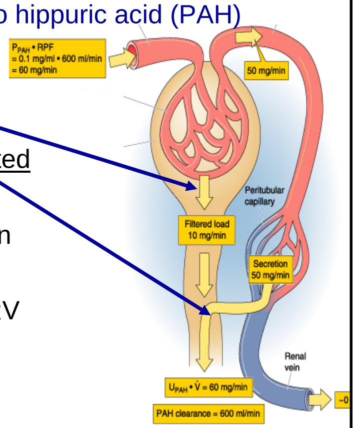
$Plasma_{Cr}$ *inversely* related to GFR

GFR ml/min	P_{Cr} mg/dl
120	1
60	2
30	4
15	8

PAH
Para-amino hippuric acid
Cl_{PAH} ~ RPF

Para-amino hippuric acid (PAH)

- Organic anion
- Freely filtered
- Vigorously secreted PT
- ≥ 90% removed in single circuit
- ~ 10% remains RV
- NOT produced
- Infusion required



Para-amino hippuric acid (PAH)

PAH Clearance ~ Renal Plasma Flow

$$RPF \cdot P_{PAH} = U_{PAH} \cdot \dot{V}$$

Rearrange

$$Cl_{PAH} = RPF = \frac{U_{PAH} \cdot \dot{V}}{P_{PAH}}$$

- **Filtered Load of Substance A**

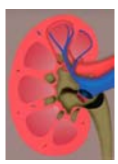
GFR **x** Plasma [A]

$$GFR \cdot P_A$$

- **Excretion Rate**

Urine [A] **x** Urine flow

$$U_A \cdot \dot{V}$$



Clearance

- Cl_X **<** GFR *net* reabsorption X
- Cl_X **>** GFR *net* secretion X
- C_X **<** C_{IN} reabsorbed, i.e. *glucose*
- C_X **>** C_{IN} secreted, i.e. *PAH*
- Protein bound drug is not filtered
- filtered load **>** rate of excretion = reabsorption X

Summary II

1. *Clearance* of certain substances – index of renal function
2. Plasma *creatinine* - tool for diagnosing and following renal function

Problem Set Posted on Schedule

1. Body Fluid Problems
2. Renal Clearance

Time for Questions