



**COMPARTMENTAL ANALYSIS  
OF DRUG DISTRIBUTION**

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Clinical Center

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**DRUG DISTRIBUTION**

**The post-absorptive transfer of drug from  
one location in the body to another.**

- **Compartmental Models**  
(ordinary differential equations)
- **Distributed Models**  
(partial differential equations)

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**Pharmacokinetic Models Using  
Ordinary Differential Equations\***

MODEL	NUMBER OF COMPARTMENTS	MATHEMATICAL CHARACTERISTICS
NONCOMPARTMENTAL	0	CURVE FITTING TO DATA
COMPARTMENTAL	1 - 3	MODEL PARAMETERS FIT TO DATA
"PHYSIOLOGICAL"	4 - 20	MODEL PARAMETERS FIXED <i>A PRIORI</i>

\* From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

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## Mathematical vs. Physical Models\*

### MATHEMATICAL MODEL:

Functions or differential equations are employed without regard to the physical characteristics of the system.

### PHYSICAL MODEL:

Implies certain mechanisms or entities that have physiological, biochemical or physical significance.

\* Berman M: The formulation and testing of models. Ann NY Acad Sci 1963;108:182-94

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## Goals of Drug Distribution Lecture

- **Significance** of Drug Distribution Volumes
- **Physiological Basis** of Multi-Compartment Pharmacokinetic Models
- **Clinical Implications** of Drug Distribution Kinetics

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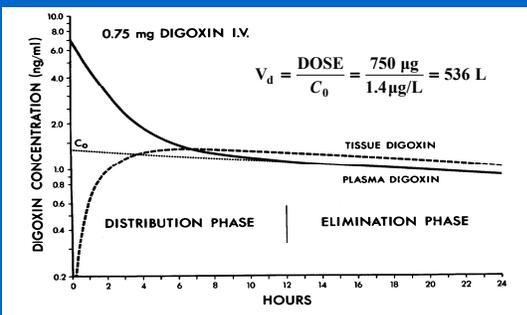
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## DIGOXIN DISTRIBUTION VOLUME



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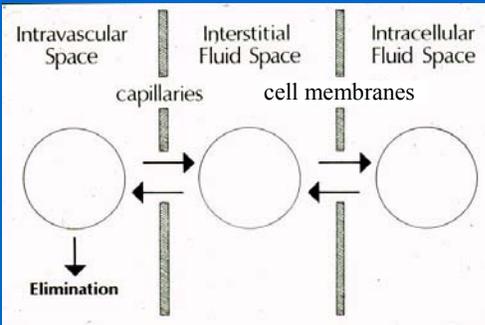
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## Body Fluid Spaces

### Catenary 3-Compartment Model



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## Volume of Distribution and Physiological Fluid Spaces

### Intravascular Space:

None

### Extracellular Fluid Space:

Inulin

Proteins and other Macromolecules

Neuromuscular Blocking Drugs ( $N^+$ )

Aminoglycoside Antibiotics (initially)

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## Volume of Distribution and Physiological Fluid Spaces

### Total Body Water

Urea

Ethyl alcohol

Antipyrine (some protein binding)

Caffeine

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## Factors Affecting Volume of Distribution Estimates

### Binding to Plasma Proteins

Thyroxine  
Theophylline

### Tissue Binding (partitioning)

Lipophilic Compounds  
Digoxin (Na<sup>+</sup> - K<sup>+</sup> ATPase)

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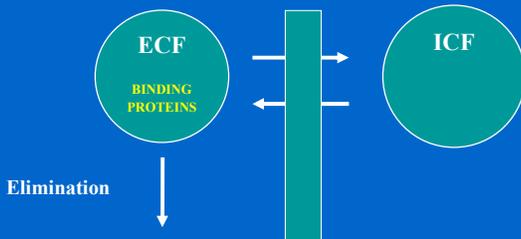
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## Effect of Plasma Protein Binding on Drug Distribution

Cell Membranes



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## Effect of Plasma Protein Binding on Apparent Volume of Distribution\*

$$V_d = ECF + f_u(TBW - ECF)$$

$f_u$  is the "free fraction", the fraction of drug in plasma that is not bound to plasma proteins.

\* Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

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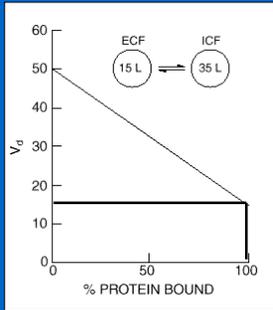
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### Impact of Protein Binding on Thyroxine Distribution Volume\*

$$f_u = 0.03\%$$

$$V_d = V_{ECF}$$



\* From Larsen PR, Atkinson AJ Jr, et al. J Clin Invest 1970;49:1266-79.

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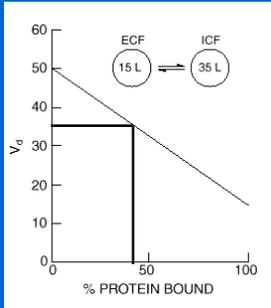
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### Impact of Protein Binding on Theophylline Distribution Volume\*

$$f_u = 60\%$$

$$V_d = V_{ECF} + f_u V_{ICF}$$



\* From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

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### Basis for Increased Theophylline Volume of Distribution in Pregnancy\*

	$f_u$ (%)	FLUID SPACE ESTIMATES (L)		TOTAL $V_d$ (L)	
		ECF	TBW	EST.	MEAS.
<b>PREGNANT</b>					
24-26 WEEKS	88.9	13	34	32	30
36-38 WEEKS	87.0	21	40	38	37
<b>POSTPARTUM</b>					
6-8 WEEKS	77.4	12	33	28	28
>6 MONTHS	71.9	12	33	27	31

\* From Frederiksen MC, et al. Clin Pharmacol Ther 1986;40:321-8.

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**Effect of Plasma Protein and Tissue Binding on the Volume of Distribution of Most Drugs\***

$$V_d = ECF + \Phi f_u (TBW - ECF)$$

$\Phi$  is the ratio of tissue/plasma drug concentration.

\* Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

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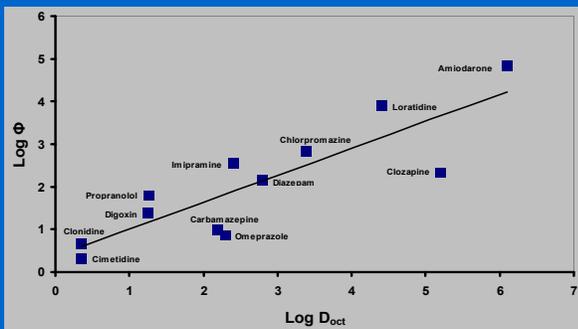
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**LIPID SOLUBILITY(D<sub>oct</sub>) and  $\Phi$**




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**Apparent Volume of Distribution for Digoxin**

$$V_d = ECF + \Phi f_u (TBW - ECF)$$

ECF= 11.2L, TBW= 45.5L,  $f_u = 0.75$ ,  $\Phi = 20.4$   
 $V_d = 11.2 + (20.4)(0.75)(34.3)$   
 $V_d = 536$  L

$\Phi$  includes binding to Na<sup>+</sup>-K<sup>+</sup> ATPase.

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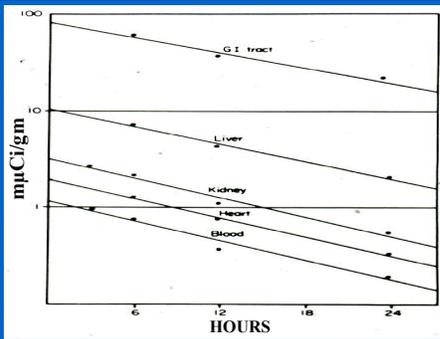
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## Tissue vs. Plasma Digoxin Levels




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## GOALS OF DRUG DISTRIBUTION LECTURE

- Significance of drug distribution volumes
- Physiologic basis of multi-compartment pharmacokinetic models
- Clinical implications of drug distribution kinetics

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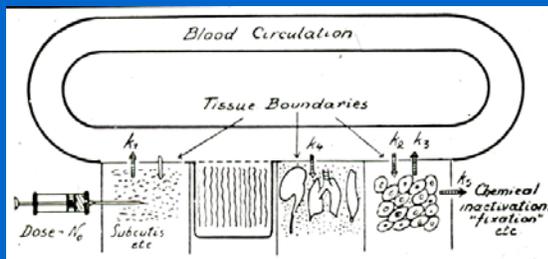
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## First Multicompartmental Analysis of Drug Distribution\*



\* From Teorell T. Arch Intern Pharmacodyn 1937;57:205-25.

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## Analysis of Experimental Data

How many compartments?

*Number of exponential phases in plasma level vs. time curve determines the number of compartments.*

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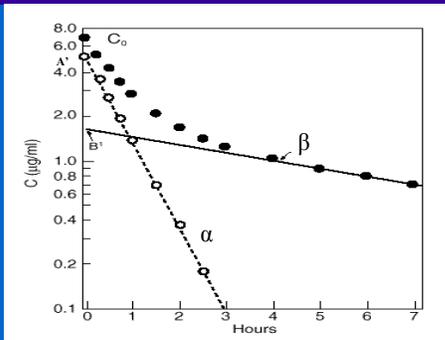
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## TECHNIQUE OF CURVE PEELING



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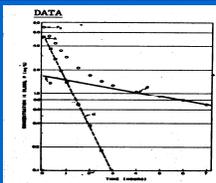
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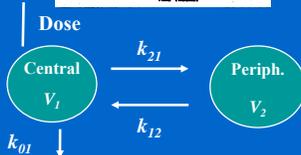
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## COMPARTMENTAL ANALYSIS



Data Equation:

$$C = A' e^{-\alpha t} + B' e^{-\beta t}$$



Model Equation:

$$dX_1/dt = -(k_{01} + k_{21})X_1 + k_{12}X_2$$

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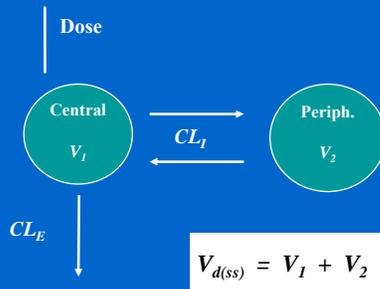
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## TWO-COMPARTMENT MODEL




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## 3 DISTRIBUTION VOLUMES

$$V_{d \text{ (extrap.)}} = \text{DOSE} / C_0$$

$$V_{d \text{ (area)}} = \frac{t_{1/2} \cdot CL_E}{0.693}$$

$$V_{d \text{ (ss)}} = V_1 + V_2 + \dots + V_n$$

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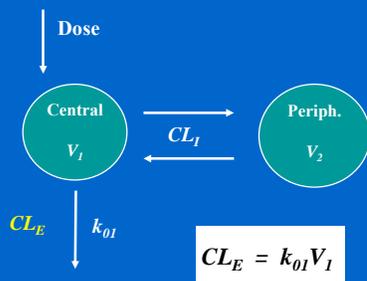
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## TWO-COMPARTMENT MODEL




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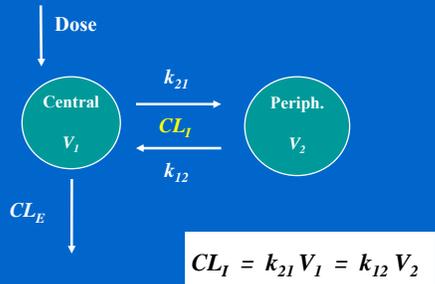
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## TWO-COMPARTMENT MODEL



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## INTERCOMPARTMENTAL CLEARANCE\*

**Volume-Independent Parameter  
Characterizing the Rate of Drug Transfer  
Between Compartments of a Kinetic  
Model**

\* From Saperstein et al. Am J Physiol 1955;181:330-6.

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## Is Central Compartment Intravascular Space?

- Usually **not** identified as such **unless** drug is given **rapidly IV**.
- NEED TO CONSIDER:
  - If distribution is **limited to ECF**, compare the central compartment volume with **plasma** volume.
  - If distribution volume **exceeds ECF** compare central compartment with **blood** volume.\*

\*(account for RBC/Plasma partition if [plasma] measured)

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### Analysis of Procainamide and NAPA Central Compartment Volumes\*

DRUG	V <sub>c</sub> (L)	RBC/P	INTRAVASCULAR SPACE (L)	
			PREDICTED	OBSERVED
PA	6.7	1.52	5.6	5.5
NAPA	7.5	1.62	5.6	6.0

\* From Stec GP, Atkinson AJ Jr. J Pharmacokinet Biopharm 1981;9:167-80.

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### If Central Compartment Volume is Based on Plasma Concentration Measurements

$$V_{C(\text{corr.})} = V_{C(\text{meas.})} / [(1 - \text{Hct}) + \text{Hct}(\text{RBC/P})]$$

RBC/P = red cell/plasma partition ratio

Hct = hematocrit

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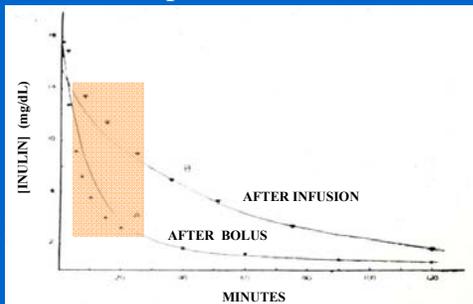
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### Analysis of Inulin Kinetics with a 2-Compartment Model\*



\* Gaudino M. Proc Soc Exper Biol Med 1949;70:672-4.

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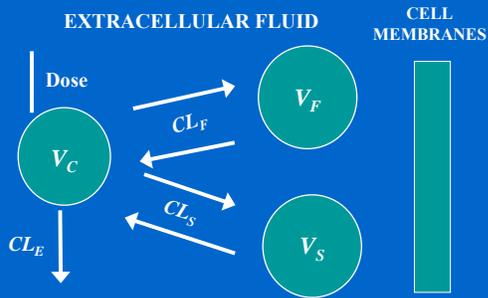
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### 3-Compartment Model of Inulin Kinetics




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### Basis for Kinetic Heterogeneity of Interstitial Fluid Space

EFFECTIVE PORE SIZE	CAPILLARY STRUCTURE	PRIMARY LOCATION
LARGE	FENESTRATED	SPLANCHNIC BED
SMALL	CONTINUOUS	SOMATIC TISSUES

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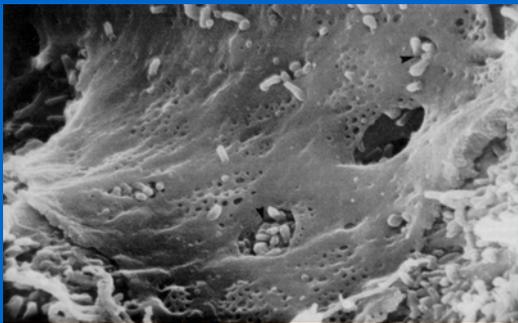
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### ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS




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**INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY**




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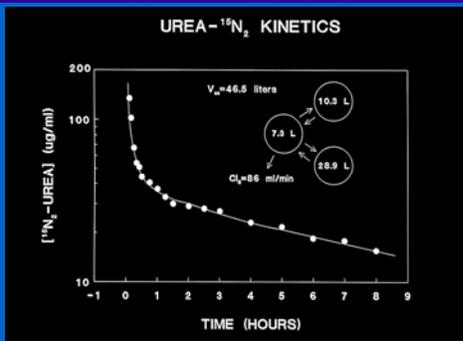
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**UREA-<sup>15</sup>N<sub>2</sub> KINETICS IN A NORMAL SUBJECT**




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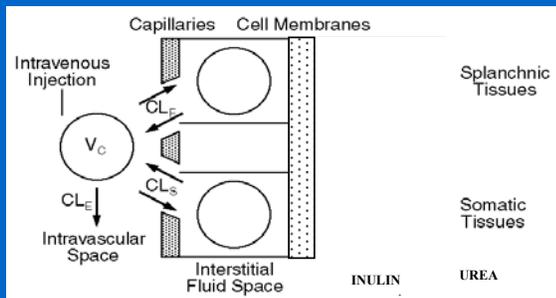
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**Multicompartment Model of Inulin and Urea Kinetics\***



\* From Atkinson AJ Jr, et al. Trends Pharmacol Sci 1991;12:96-101.

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## ROLE OF *TRANSCAPILLARY EXCHANGE*

The **central** compartment for both **urea** and **inulin** is the **intravascular** space.

Therefore, **transcapillary exchange** is the **rate-limiting** step in the distribution of urea and inulin to the **peripheral** compartments of the mammillary **3-compartment model**.

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## RENKIN EQUATION\*

$$Cl = Q(1 - e^{-P/Q})$$

Q = capillary blood flow

P = capillary permeability coefficient-surface area product (sometimes denoted P•S).

\* From Renkin EM. Am J Physiol 1953;183:125-36.

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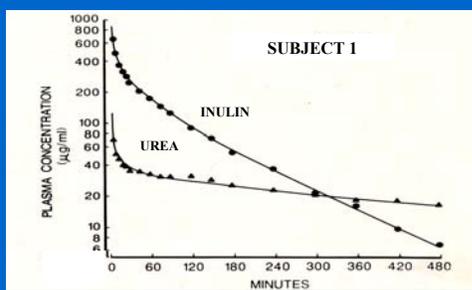
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## SIMULTANEOUS ANALYSIS OF INULIN AND UREA-<sup>15</sup>N<sub>2</sub> KINETICS



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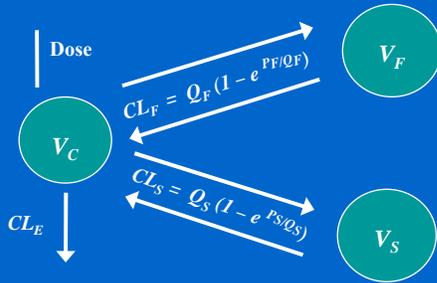
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### 3-COMPARTMENT MODEL




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### For Each Peripheral Compartment

3 UNKNOWNNS:

$$Q, P_U, P_I$$

3 EQUATIONS:

$$P_U = Q \ln \left[ \frac{Q}{Q - Cl_U} \right]$$

$$P_I = Q \ln \left[ \frac{Q}{Q - Cl_I} \right]$$

$$P_U/P_I = D_U/D_I$$

U = urea; I = inulin

D = free water diffusion coefficient

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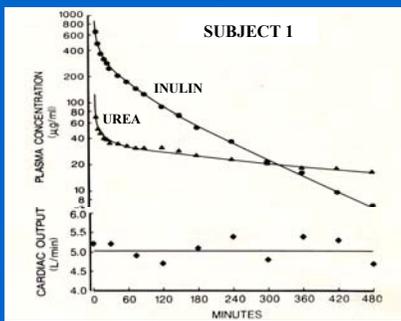
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### SIMULTANEOUS ANALYSIS OF INULIN AND UREA-<sup>15</sup>N<sub>2</sub> KINETICS



How does  $Q_F + Q_S$  compare with C.O.?

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### CARDIAC OUTPUT AND COMPARTMENTAL BLOOD FLOWS\*

	$Q_F$	$Q_S$	$Q_F + Q_S$	
	L/min	L/min	L/min	% CO
MEAN†	3.87	1.52	5.39	99

† MEAN OF 5 SUBJECTS

\* From Odeh YK, et al. Clin Pharmacol Ther 1993;53:419-25.

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### TRANSCAPILLARY EXCHANGE Mechanisms

TRANSFER OF SMALL MOLECULES (M.W. < 6,000 Da):

- **Transfer proportional to D**
  - Polar, uncharged (urea, inulin)
- **Transfer rate < predicted from D**
  - Highly charged (quaternary compounds)
  - Interact with pores (procainamide)
- **Transfer rate > predicted from D**
  - Lipid soluble compounds (anesthetic gases)
  - Facilitated diffusion (theophylline)

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### Urea and Theophylline Diffusion Coefficients\*

	MOLECULAR WEIGHT (DALTONS)	CORRECTED STOKES-EINSTEIN RADIUS (Å)	$D_m$ @ 37° C (x 10 <sup>-5</sup> cm <sup>2</sup> /sec)
UREA	60	2.2	1.836
THEOPHYLLINE	180	3.4	1.098

\* From Belknap SM, et al. J Pharmacol Exp Ther 1987;243:963-9.

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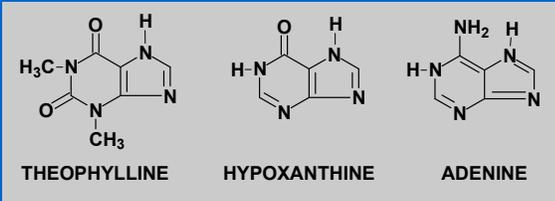
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**PRESUMED CARRIER-MEDIATED  
TRANSCAPILLARY EXCHANGE**



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**GOALS OF DRUG DISTRIBUTION  
LECTURE**

- Significance of drug distribution volumes
- Physiologic basis of multi-compartment pharmacokinetic models
- **Clinical implications of drug distribution kinetics**

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**SIGNIFICANCE OF DRUG DISTRIBUTION RATE**

1. **Affects toxicity of IV injected drugs**  
Theophylline, lidocaine
2. **Delays onset of drug action**  
Insulin, digoxin
3. **Terminates action after IV bolus dose**  
Thiopental, lidocaine

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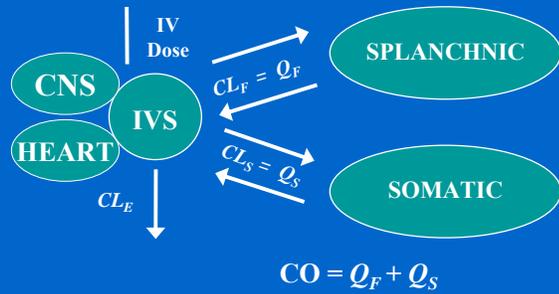
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**PK Model of THEOPHYLLINE Distribution**




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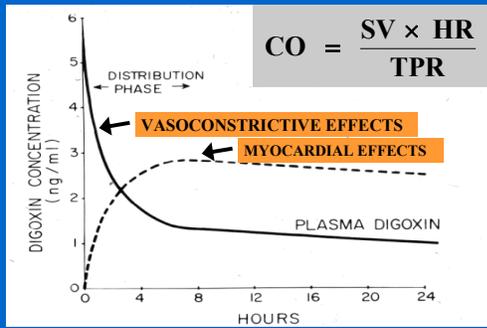
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**DIGOXIN is NOT the First Drug Given to Patients with Acute Pulmonary Edema**




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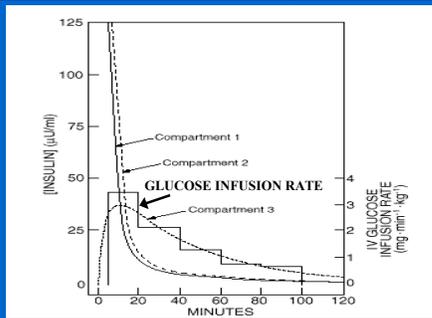
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**PK-PD Study of INSULIN Enhancement of Skeletal Muscle Glucose Uptake\***



\* From Sherwin RS, et al. J Clin Invest 1974;53:1481-92.

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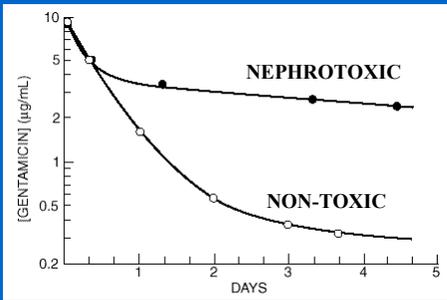
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**GENTAMICIN ELIMINATION**  
Nephrotoxic vs. Non-Toxic Patient\*



\* From Coburn WA, et al. J Pharmacokinet Biopharm 1978;6:179-86.

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**CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION**

- “Flip-Flop” Kinetics
- Effective Half-Life
- Pseudo Dose Dependency

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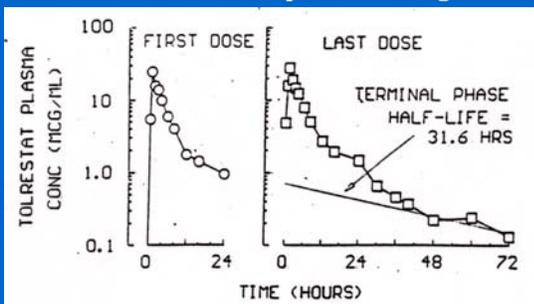
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**TOLRESTAT**  
Cumulation with Repeated Dosing\*



\*From Boxenbaum H, Battle M: J Clin Pharmacol 1995;35:763-6.

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## CUMULATION FACTOR

$$CF = \frac{1}{(1 - e^{-k\tau})}$$

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## TOLRESTAT CUMULATION

Predicted C.F. from  $T_{1/2} = 31.6$  hr: 4.32

Observed C.F.: 1.29

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## EFFECTIVE HALF-LIFE\*

$$k_{\text{eff}} = \frac{1}{\tau} \ln \left( \frac{CF_{\text{obs}}}{CF_{\text{obs}} - 1} \right)$$

$$t_{1/2\text{eff}} = \frac{\ln 2}{k_{\text{eff}}}$$

\* From Boxenbaum H, Battle M. J Clin Pharmacol 1995;35:763-66.

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### EFFECTIVE HALF-LIFE OF TOLRESTAT\*

Since  $\tau = 12$  hr and Observed CF = 1.29:

$$k_{\text{eff}} = \frac{1}{12} \ln\left(\frac{1.29}{1.29-1}\right) = 0.124 \text{ hr}^{-1}$$

$$t_{1/2\text{eff}} = \frac{\ln 2}{0.124} = 5.6 \text{ hr}$$

\* From Boxenbaum H, Battle M. J Clin Pharmacol 1995;35:763-66.

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### CONSEQUENCES OF VERY SLOW DRUG DISTRIBUTION

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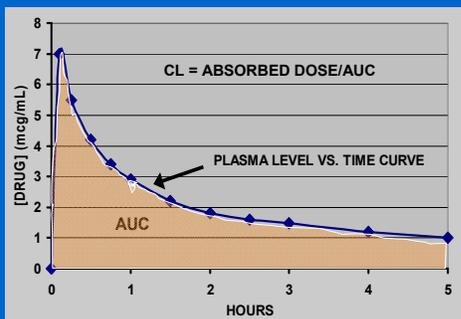
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### AREA UNDER THE CURVE Measure of Dose Proportionality



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### HYPOTHETICAL Phase I Trial Results

	DOSE 1	DOSE 2	INCREASE
DOSE (mg)	25	100	4 x ↑
AUC (µg·hr/mL)	1.32	17.91	13.6 x ↑

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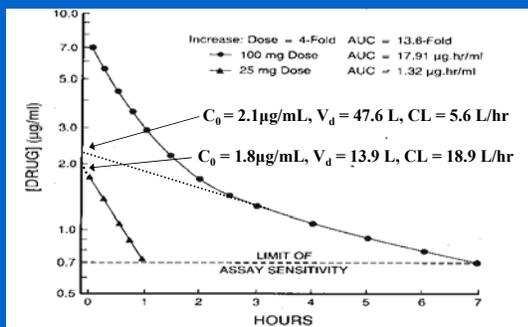
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### Dependency of PK Estimates on Identified Terminal Phase




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### DISTRIBUTION VOLUME Representative Macromolecules

MACROMOLECULE	MW (kDa)	$V_1$ (mL/kg)	$V_{d(ss)}$ (mL/kg)
INULIN	5.2	55	164
FACTOR IX (FIX)	57	136	271
INTERLEUKIN-2 (IL-2)	15.5	60	112
INTERLEUKIN-12 (IL-12)	53	52	59
GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF)	20	44	60
RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (RT-PA)	65	59	106

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CLOTting FACTOR  
PHARMACOKINETICS\*

- “The  $V_{d(ss)}$ ..... always **exceeds** the actual **plasma volume**, implying that **no drug**, not even large molecular complexes as F-VIII, is **entirely confined to the plasma space.**”
- “A too **short blood sampling** protocol gives **flawed results** not only for terminal  $T_{1/2}$  but also for the model independent parameters.”

\* Berntorp E, Björkman S. Haemophilia 2003;9:353-9.

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