

COMPARTMENTAL ANALYSIS OF DRUG DISTRIBUTION

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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)

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 A <i>PRIORI</i>

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

Mathematical vs. Physical Models*

MATHEMATICAL MODEL:

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

PHYSICAL MODEL:

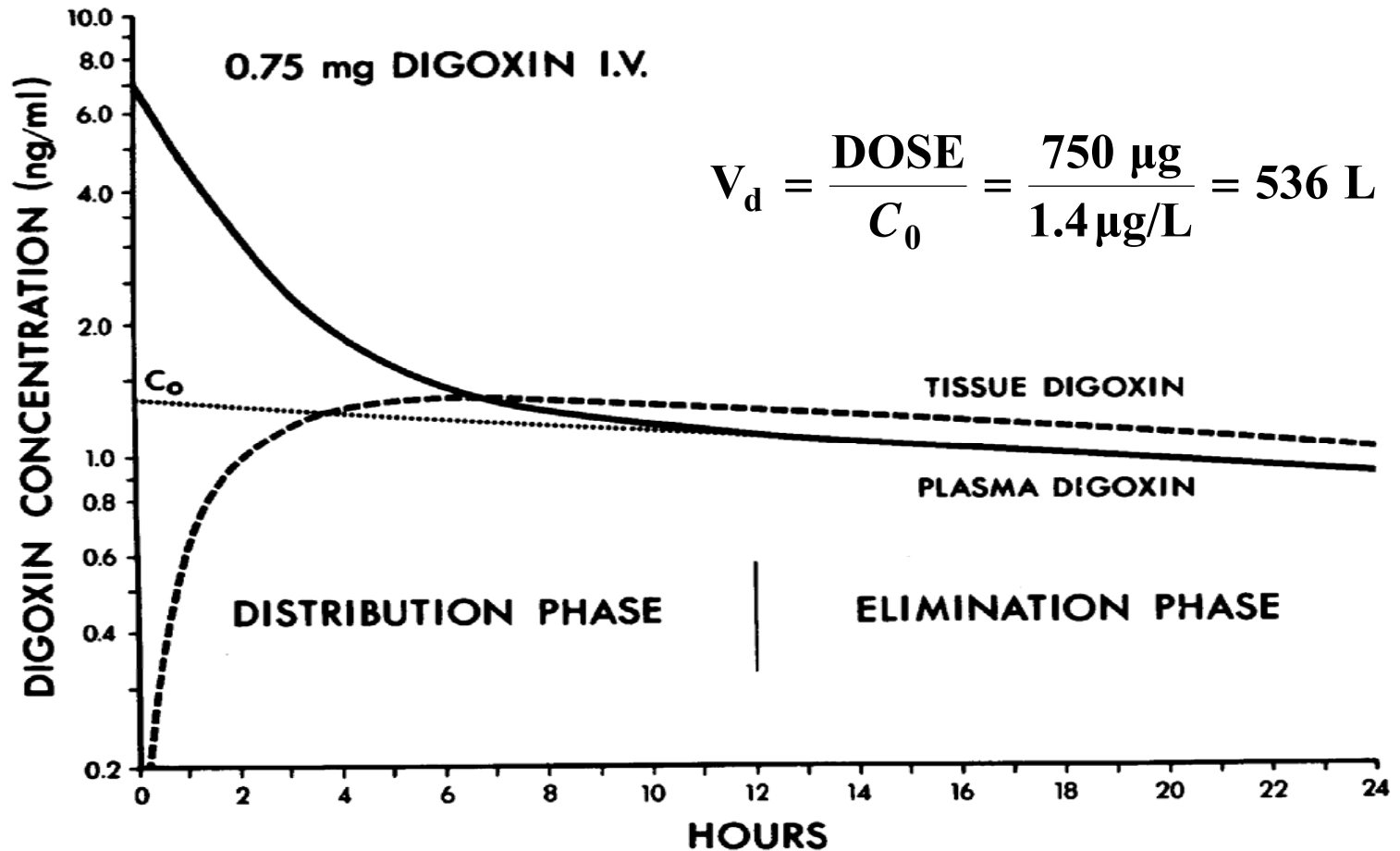
Implies certain mechanisms or entities that have physiological, biochemical or physical significance.

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

Goals of Drug Distribution Lecture

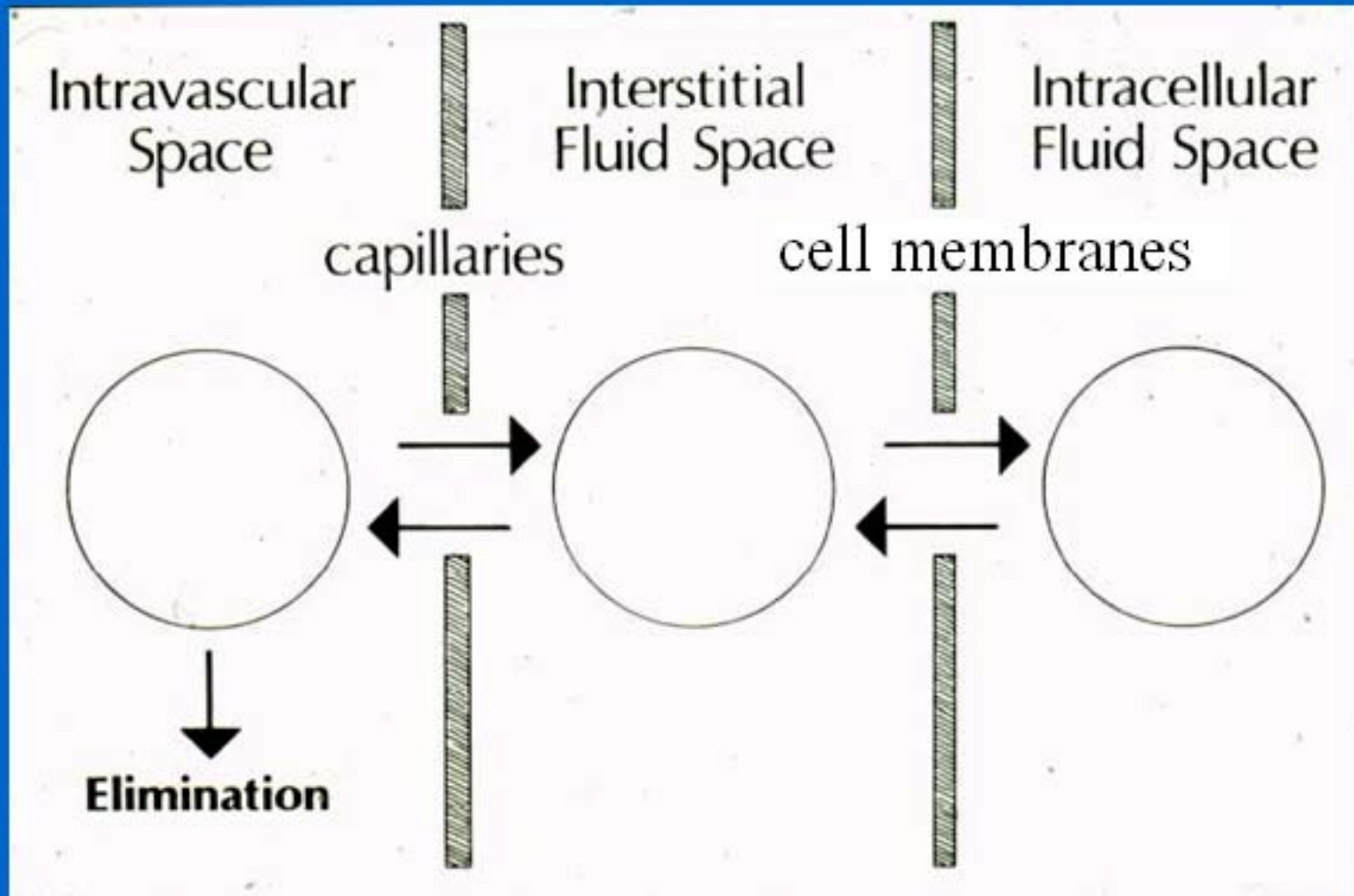
- * **Significance** of Drug Distribution Volumes
- * **Physiological Basis** of Multi-Compartment
 - Pharmacokinetic Models
- * **Clinical Implications** of Drug Distribution
 - Kinetics

DIGOXIN DISTRIBUTION VOLUME



Body Fluid Spaces

Catenary 3-Compartment Model



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)

Volume of Distribution and Physiological Fluid Spaces

Total Body Water

Urea

Ethyl alcohol

Antipyrine (some protein binding)

Caffeine

Factors Affecting Volume of Distribution Estimates

Binding to Plasma Proteins

Thyroxine

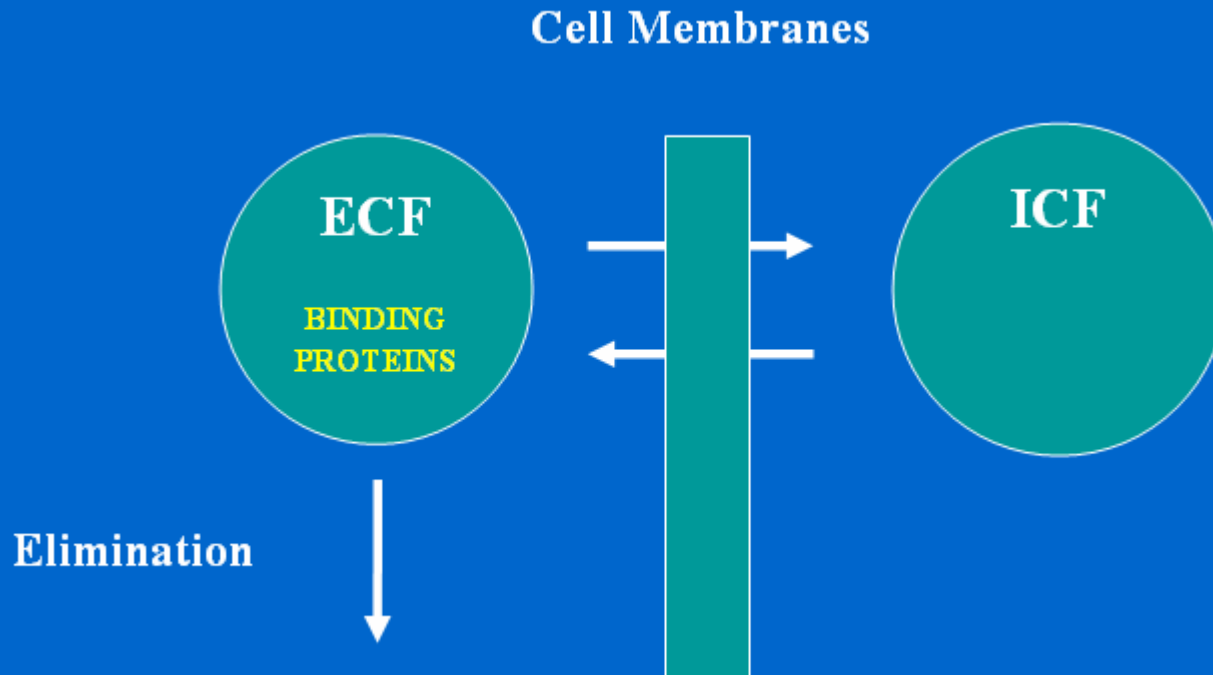
Theophylline

Tissue Binding (partitioning)

Lipophilic Compounds

Digoxin (Na^+ - K^+ ATPase)

Effect of Plasma Protein Binding on Drug Distribution



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

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

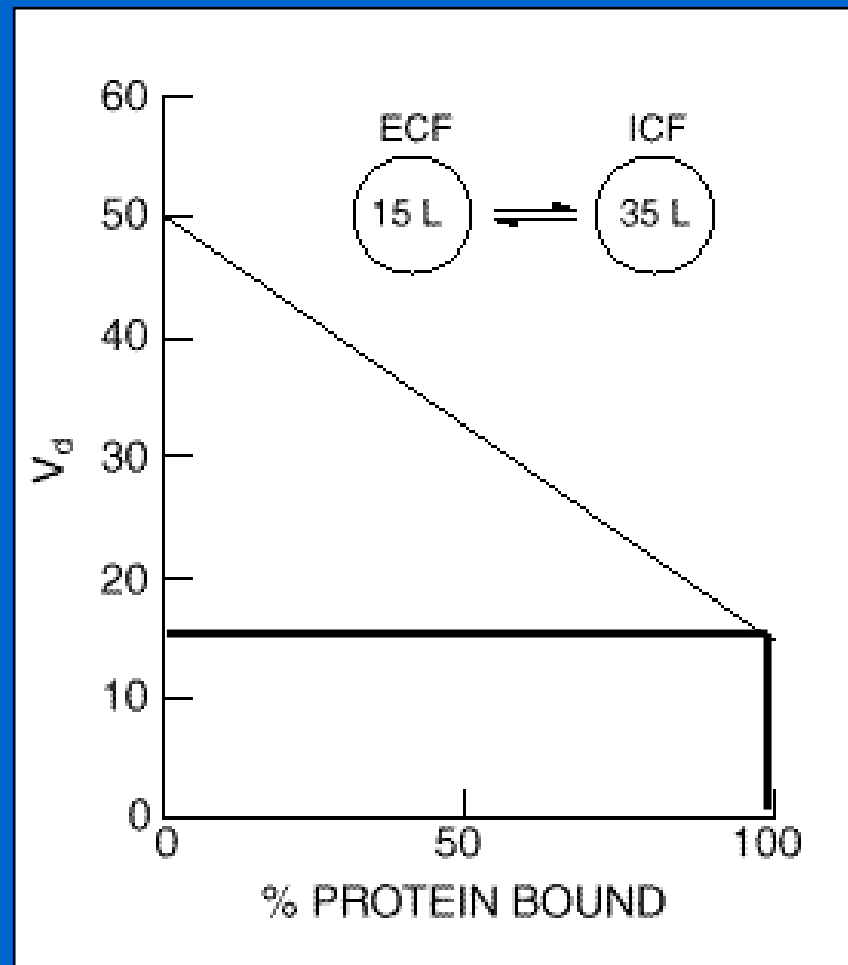
f_u is the “free fraction”, the fraction of drug in plasma that is not bound to plasma proteins.

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

Impact of Protein Binding on Thyroxine Distribution Volume*

$$f_u = 0.03\%$$

$$V_d = V_{\text{ECF}}$$

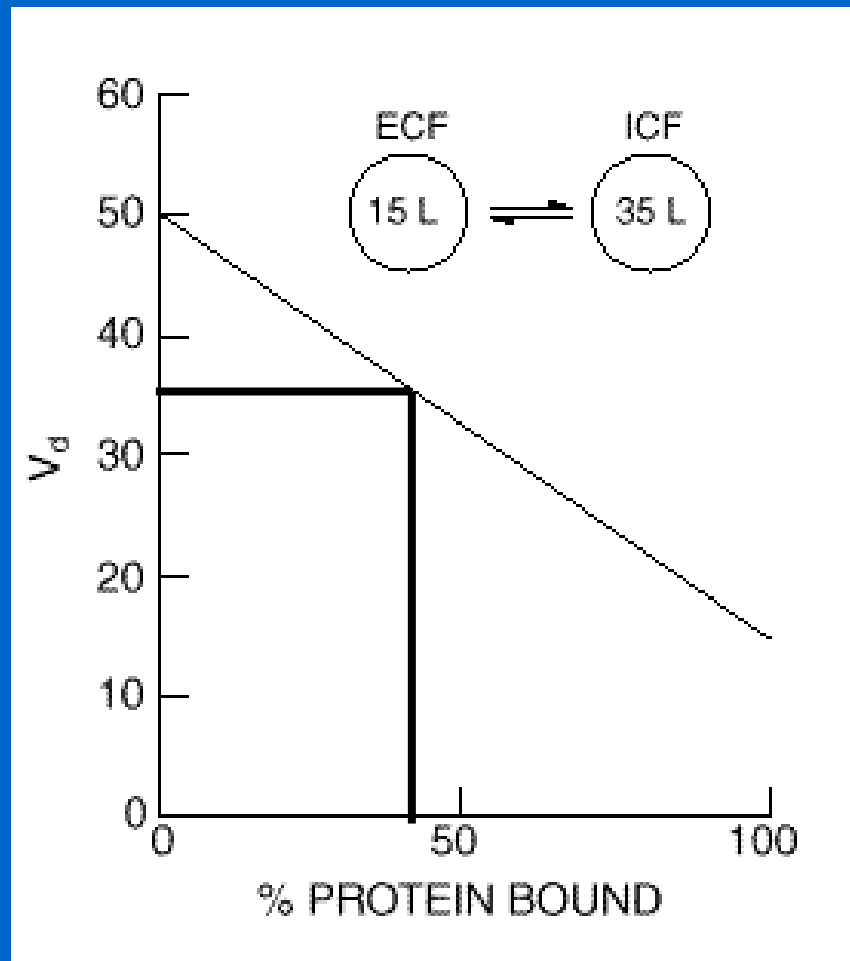


* From Larsen PR, Atkinson AJ Jr, et al. J Clin Invest 1970;49:1266-79.

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.

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

	f_u (%)	FLUID SPACE ESTIMATES (L)		TOTAL V_d (L)	
		ECF	TBW	EST.	MEAS.
PREGNANT					
24-26 WEEKS	88.9	13	34	32	30
36-38 WEEKS	87.0	21	40	38	37
POSTPARTUM					
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.

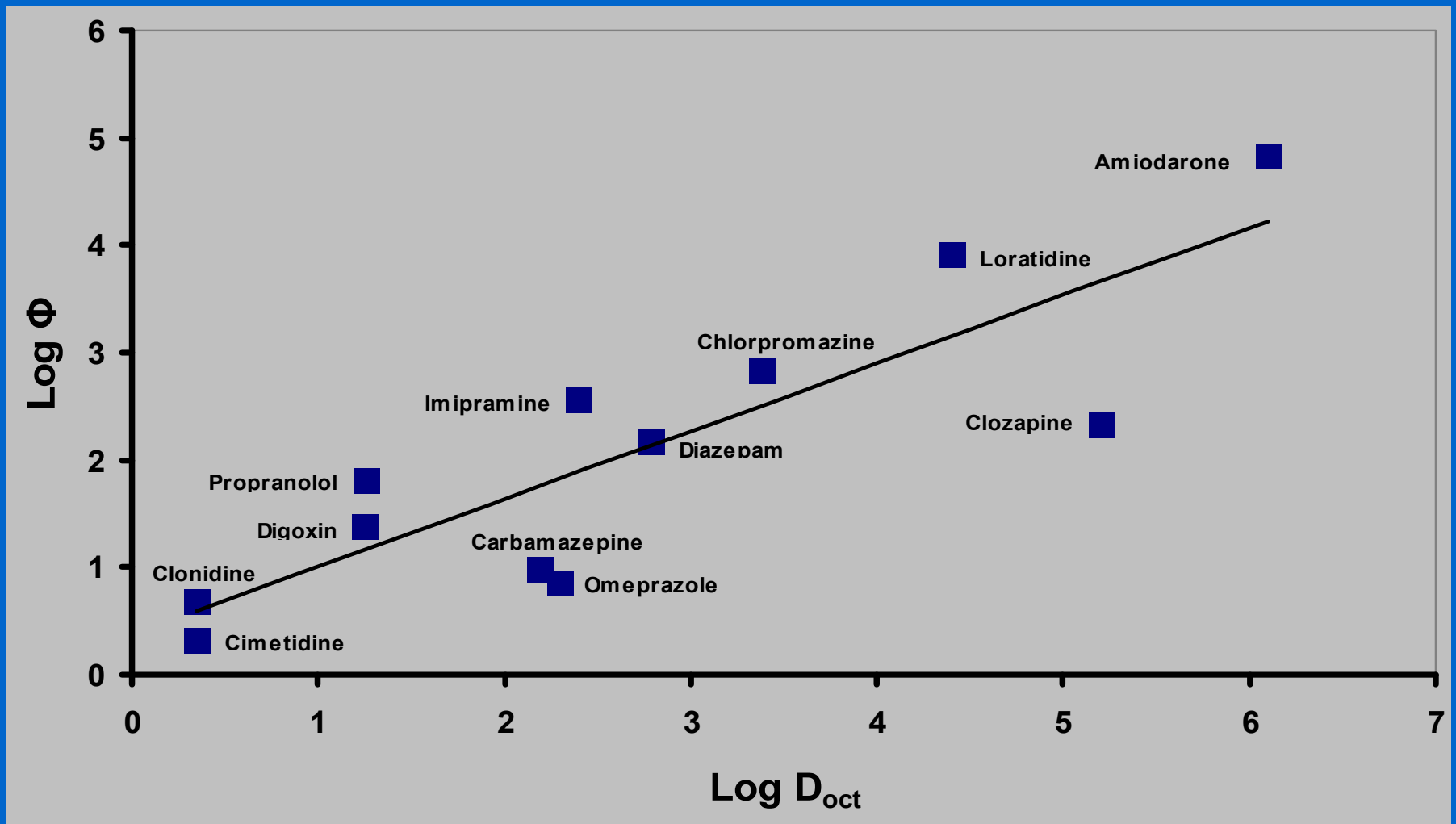
Effect of Plasma Protein and **Tissue Binding** on the Volume of Distribution of Most Drugs*

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

Φ is the ratio of tissue/plasma drug concentration.

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

LIPID SOLUBILITY (D_{oct}) and Φ



Apparent Volume of Distribution for **Digoxin**

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

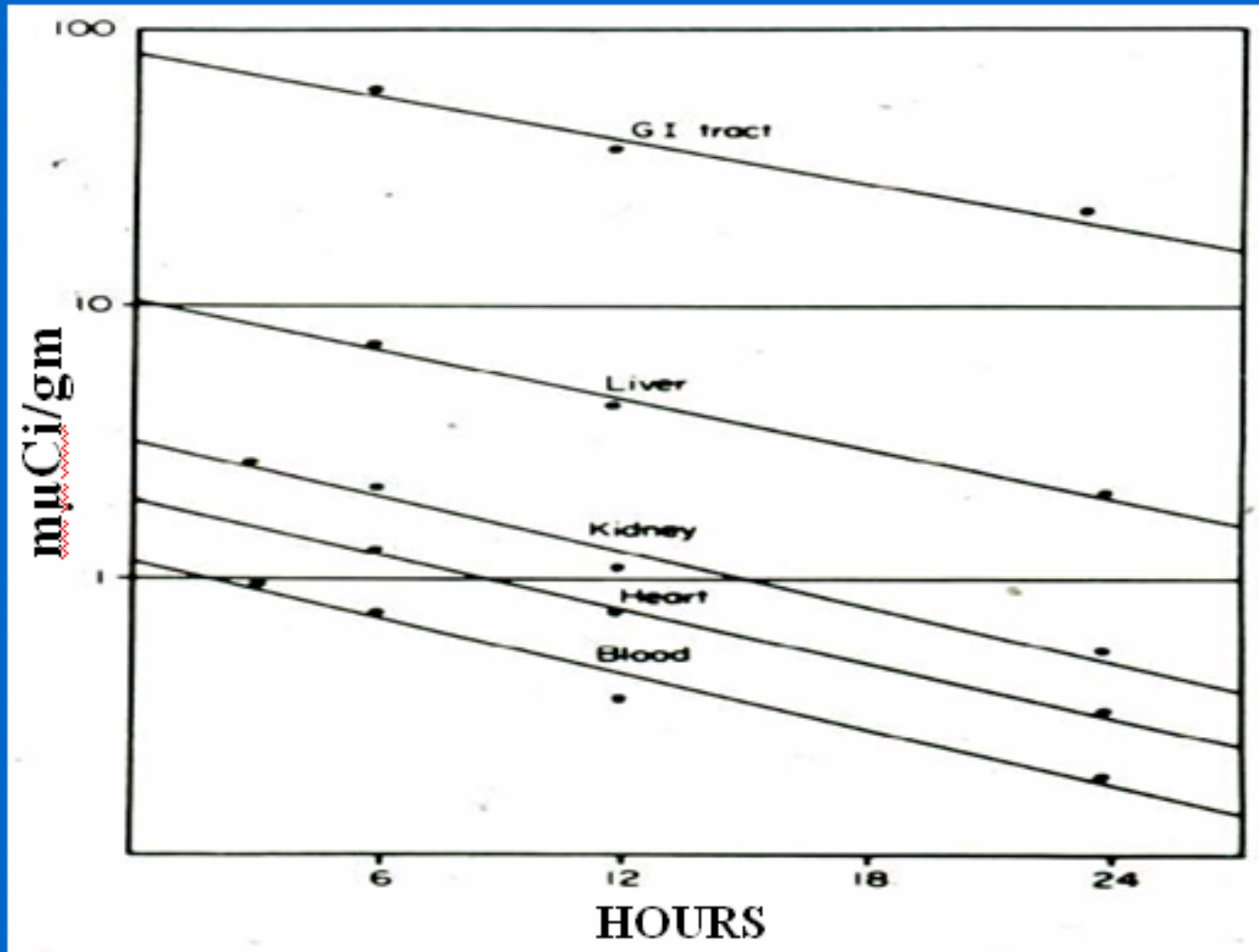
$$ECF = 11.2 \text{ L}, TBW = 45.5 \text{ L}, f_u = 0.75, \Phi = 20.4$$

$$V_d = 11.2 + (20.4)(0.75)(34.3) \text{ L}$$

$$V_d = 536 \text{ L}$$

Φ includes binding to $\text{Na}^+\text{-K}^+$ ATPase.

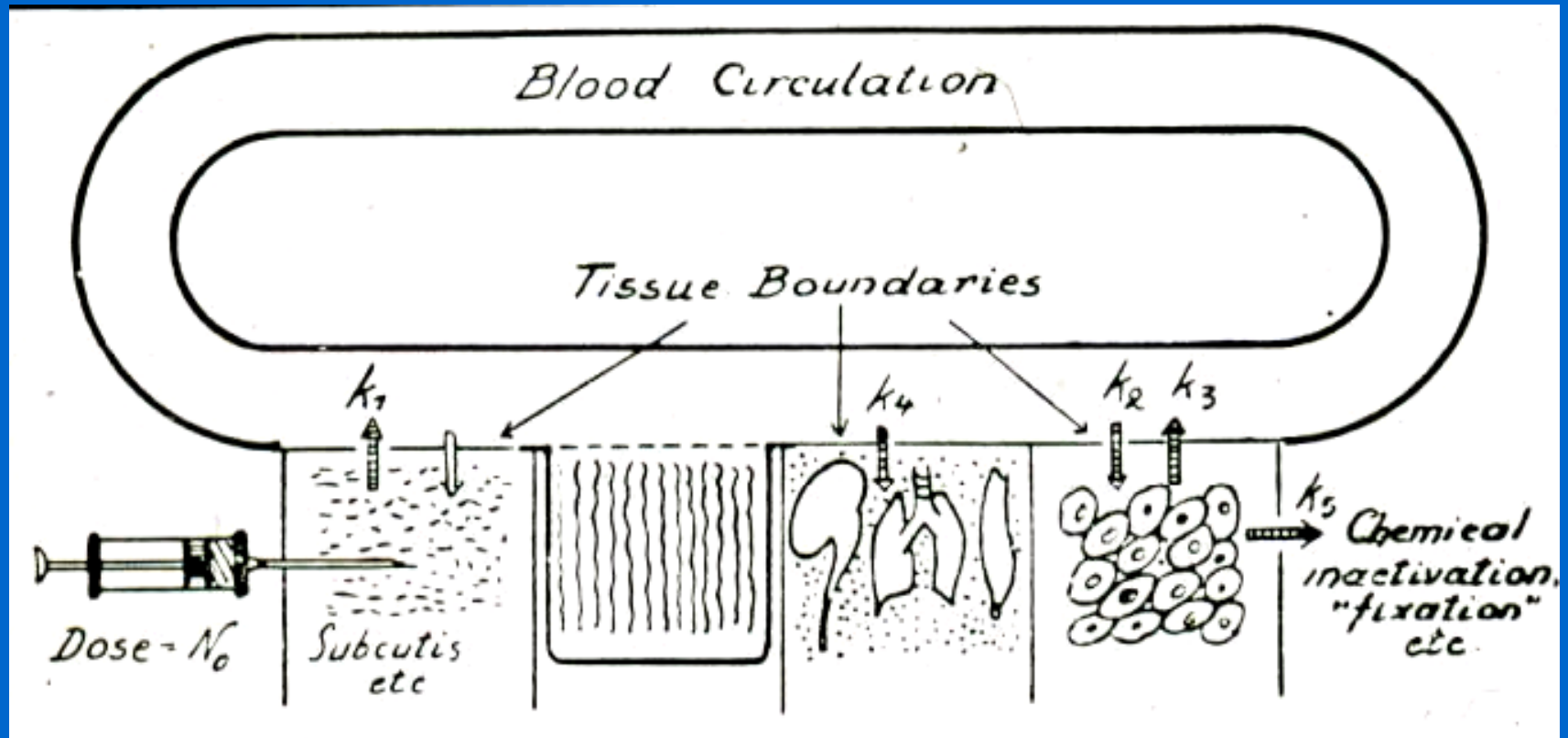
Tissue vs. Plasma **Digoxin** Levels



GOALS OF DRUG DISTRIBUTION LECTURE

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

First Multicompartmental Analysis of Drug Distribution*



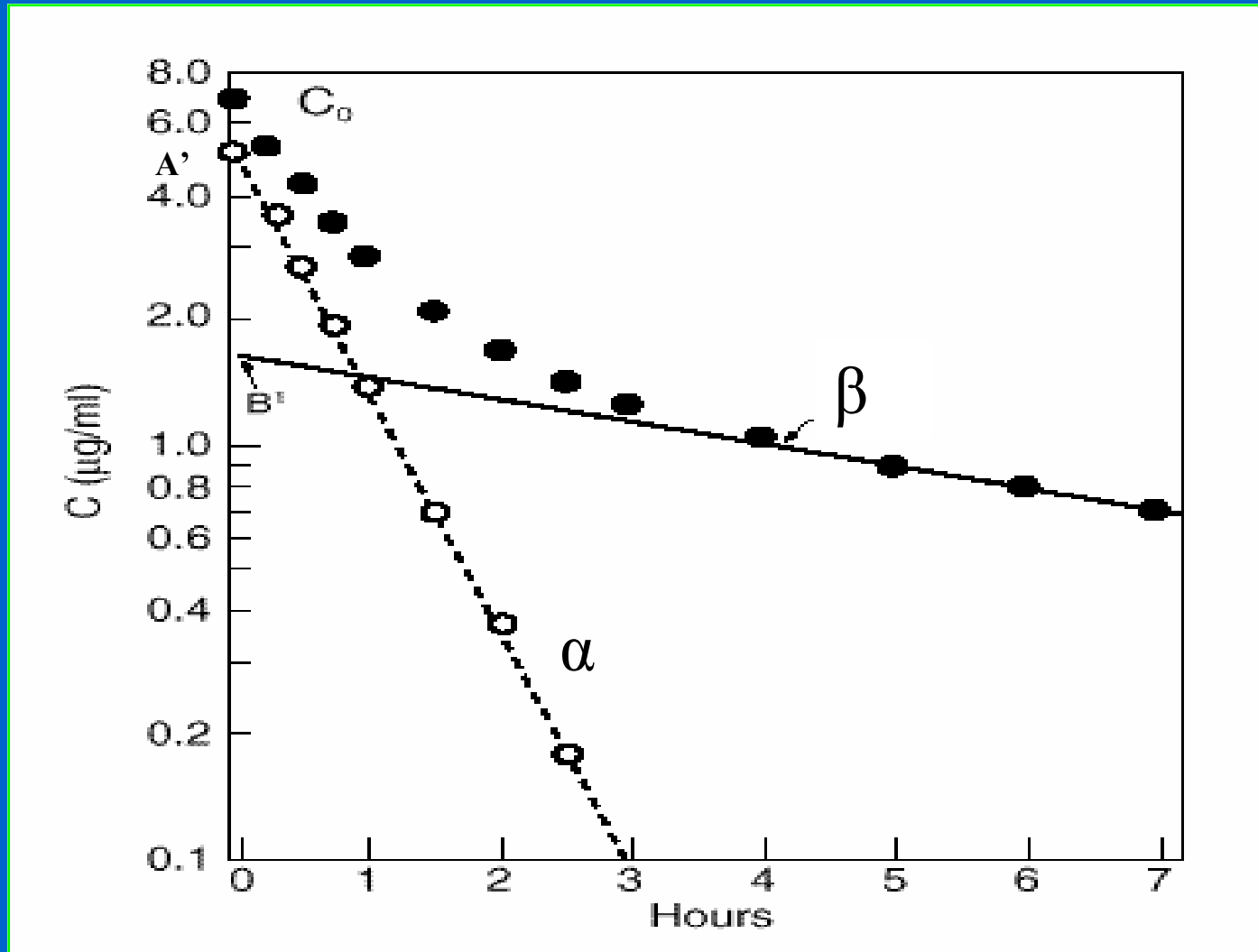
* From Teorell T. Arch Intern Pharmacodyn 1937;57:205-25.

Analysis of Experimental Data

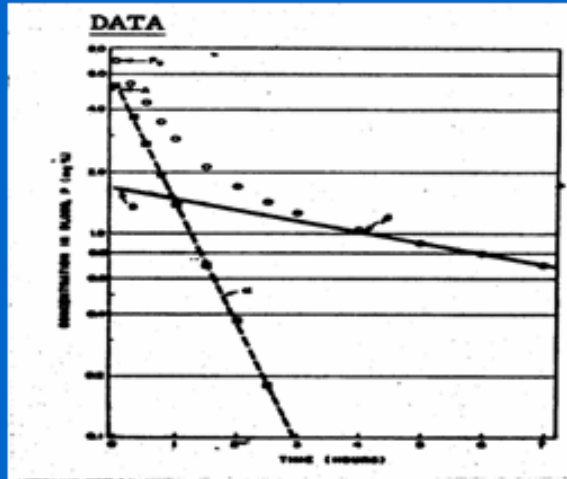
How many compartments?

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

TECHNIQUE OF *CURVE PEELING*

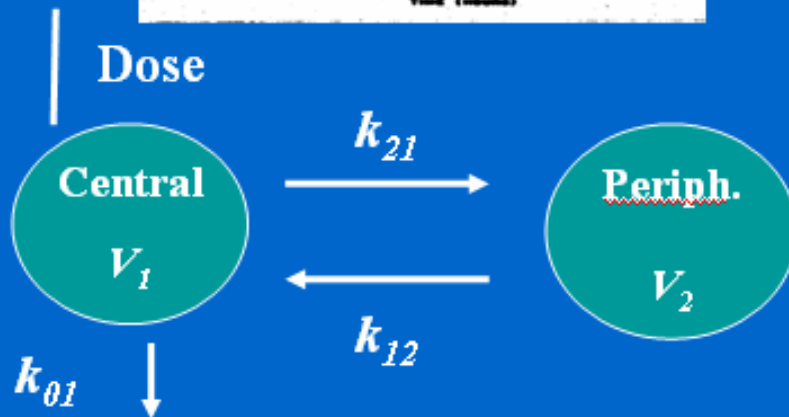


COMPARTMENTAL ANALYSIS



Data Equation:

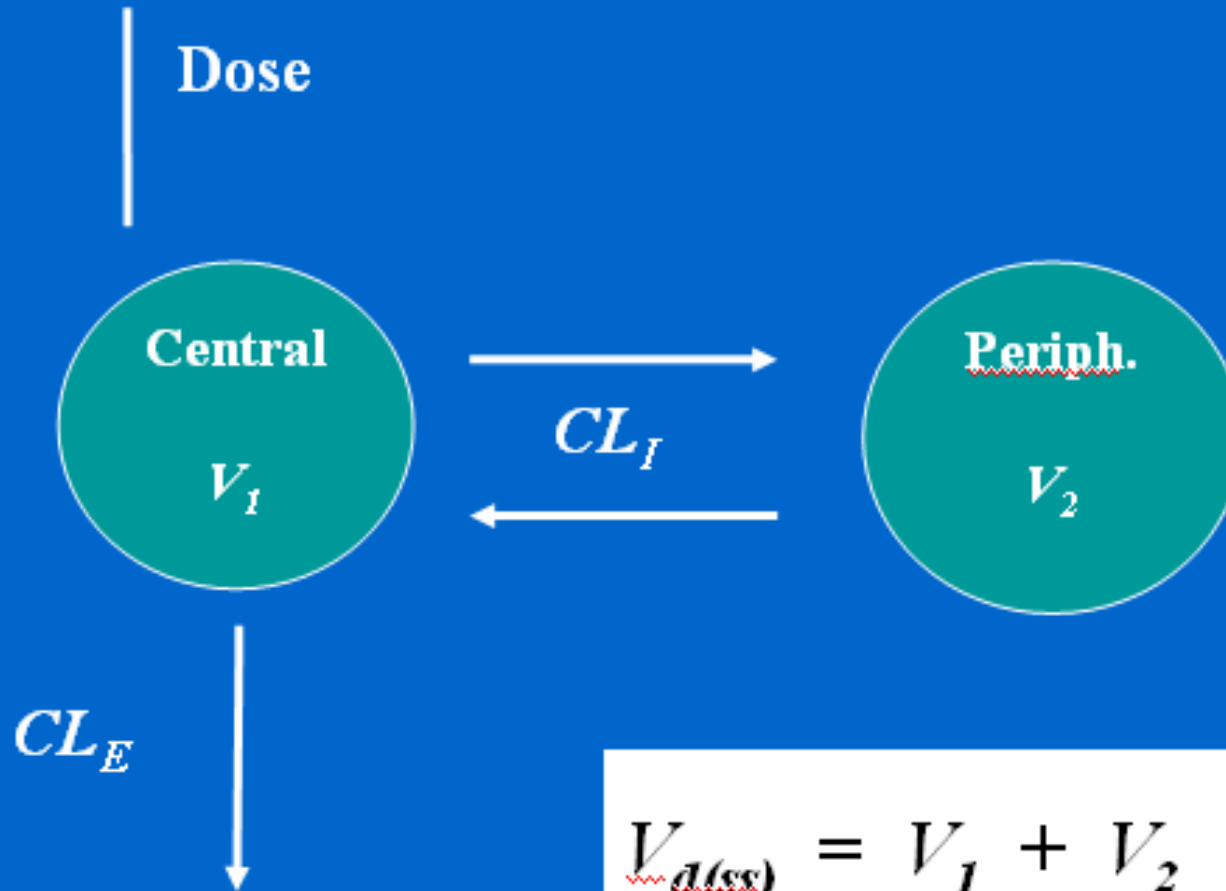
$$C = \underline{A'}e^{-\alpha t} + \underline{B'}e^{-\beta t}$$



Model Equation:

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

TWO-COMPARTMENT MODEL



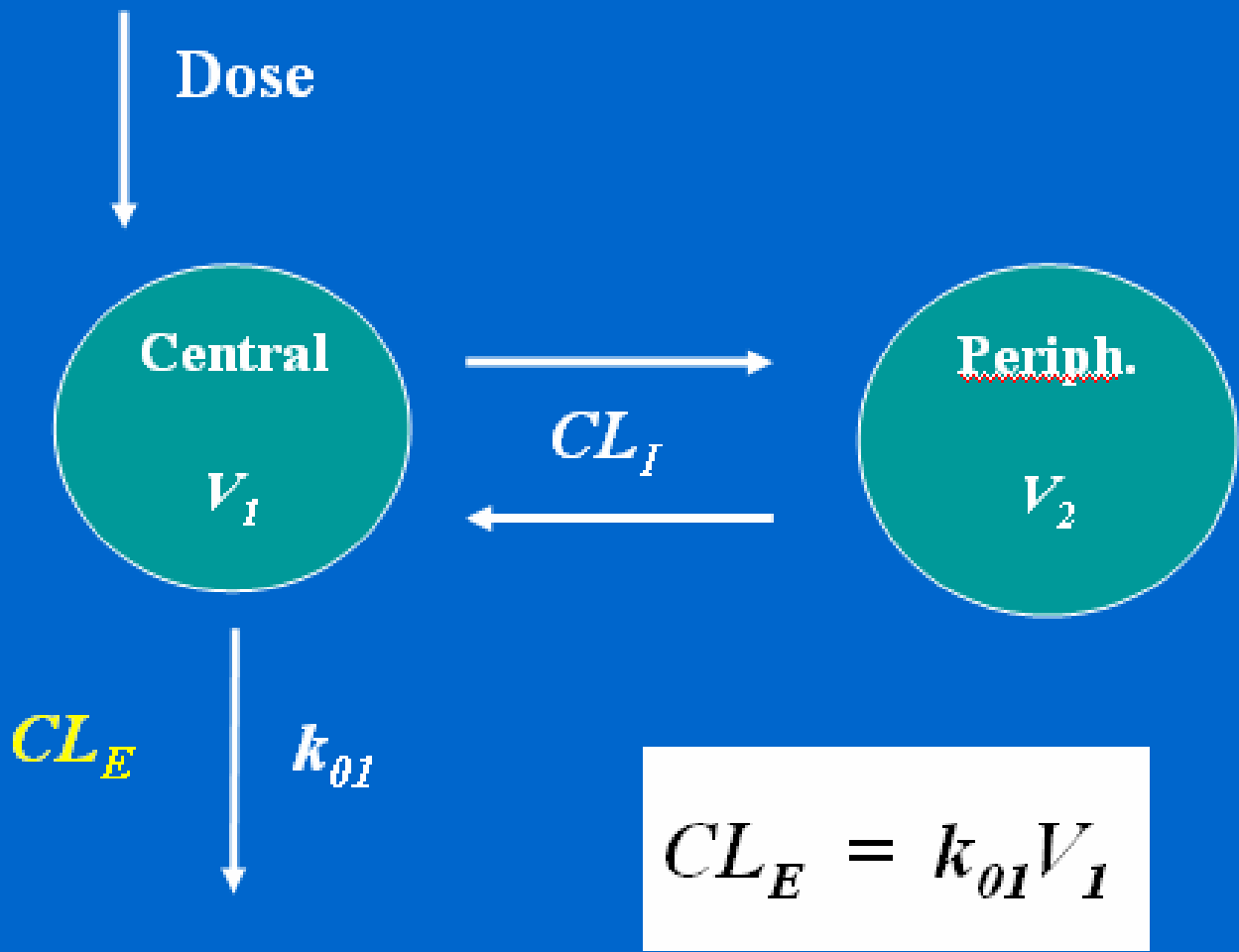
3 DISTRIBUTION VOLUMES

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

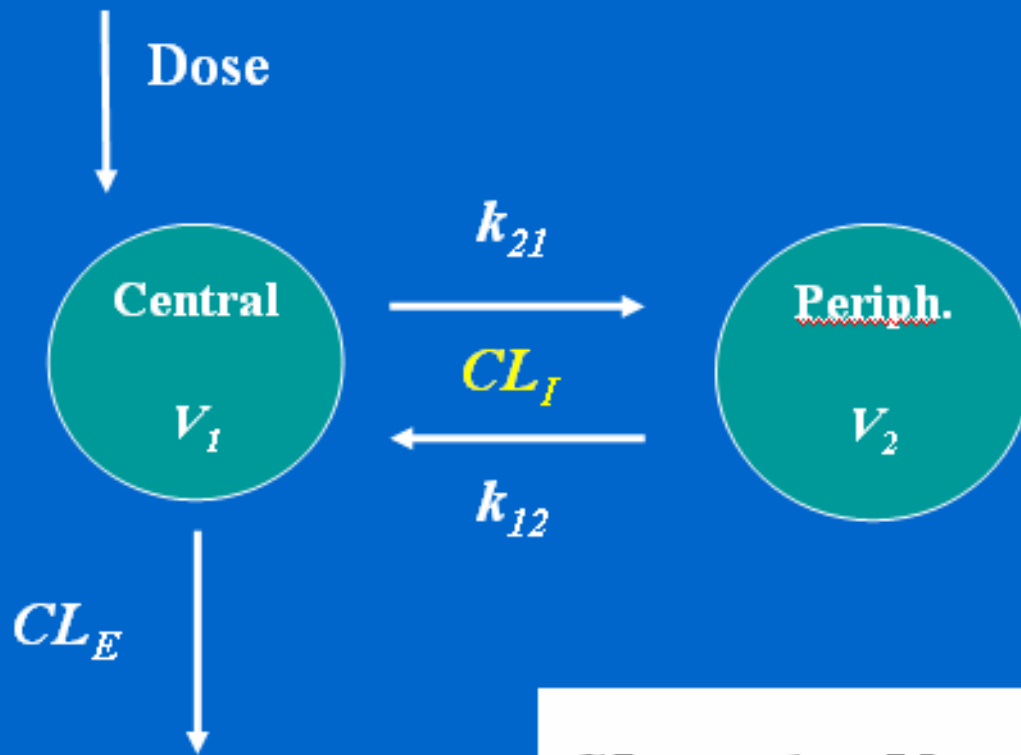
$$V_{d \text{ (area)}} = \frac{t_{1/2} \cdot \text{CL}_E}{0.693}$$

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

TWO-COMPARTMENT MODEL



TWO-COMPARTMENT MODEL



$$CL_I = k_{21} V_1 = k_{12} V_2$$

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.

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)

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

DRUG	V_c (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.

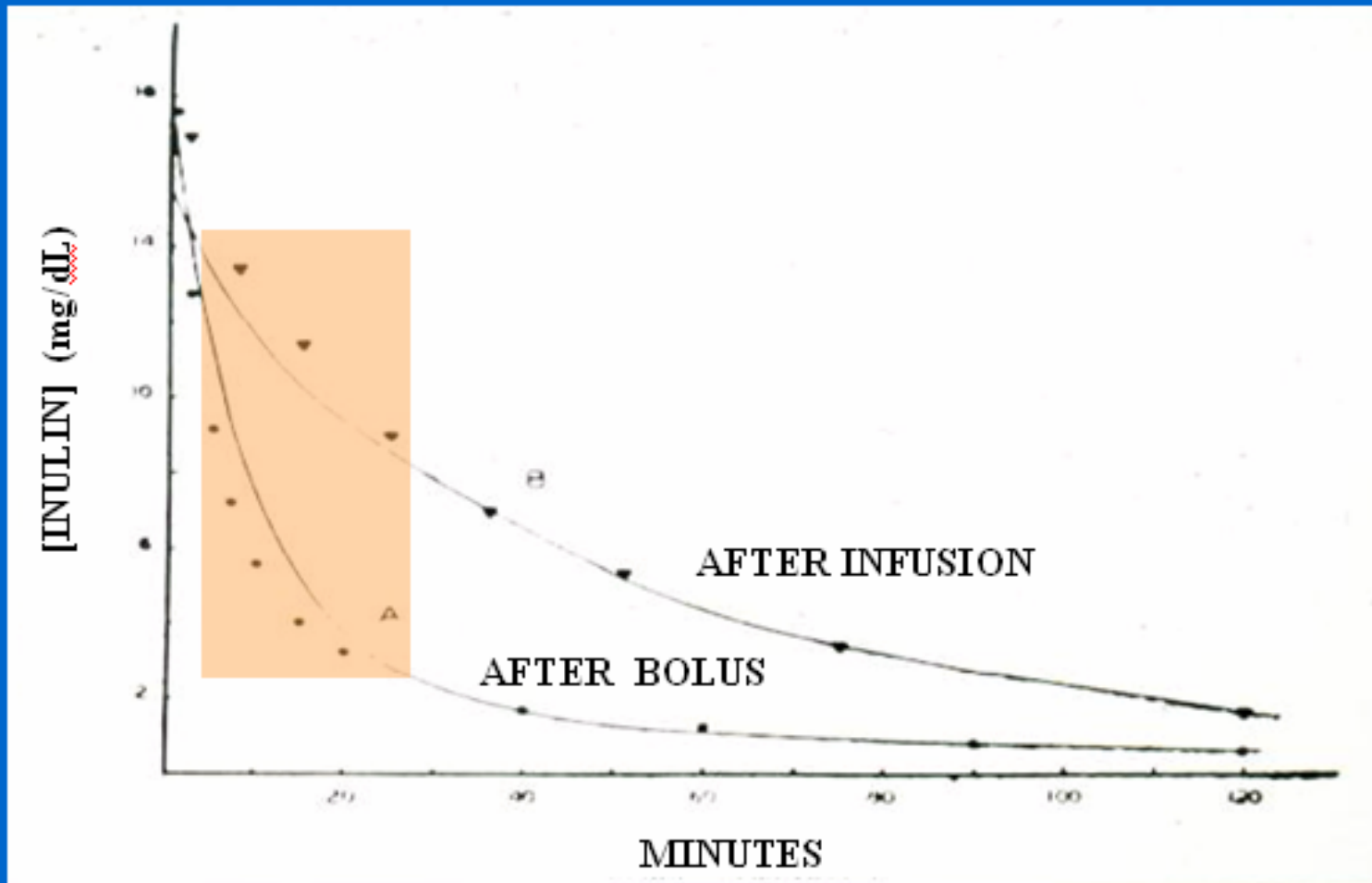
If Central Compartment Volume is Based on Plasma Concentration Measurements

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

RBC/P = red cell/plasma partition ratio

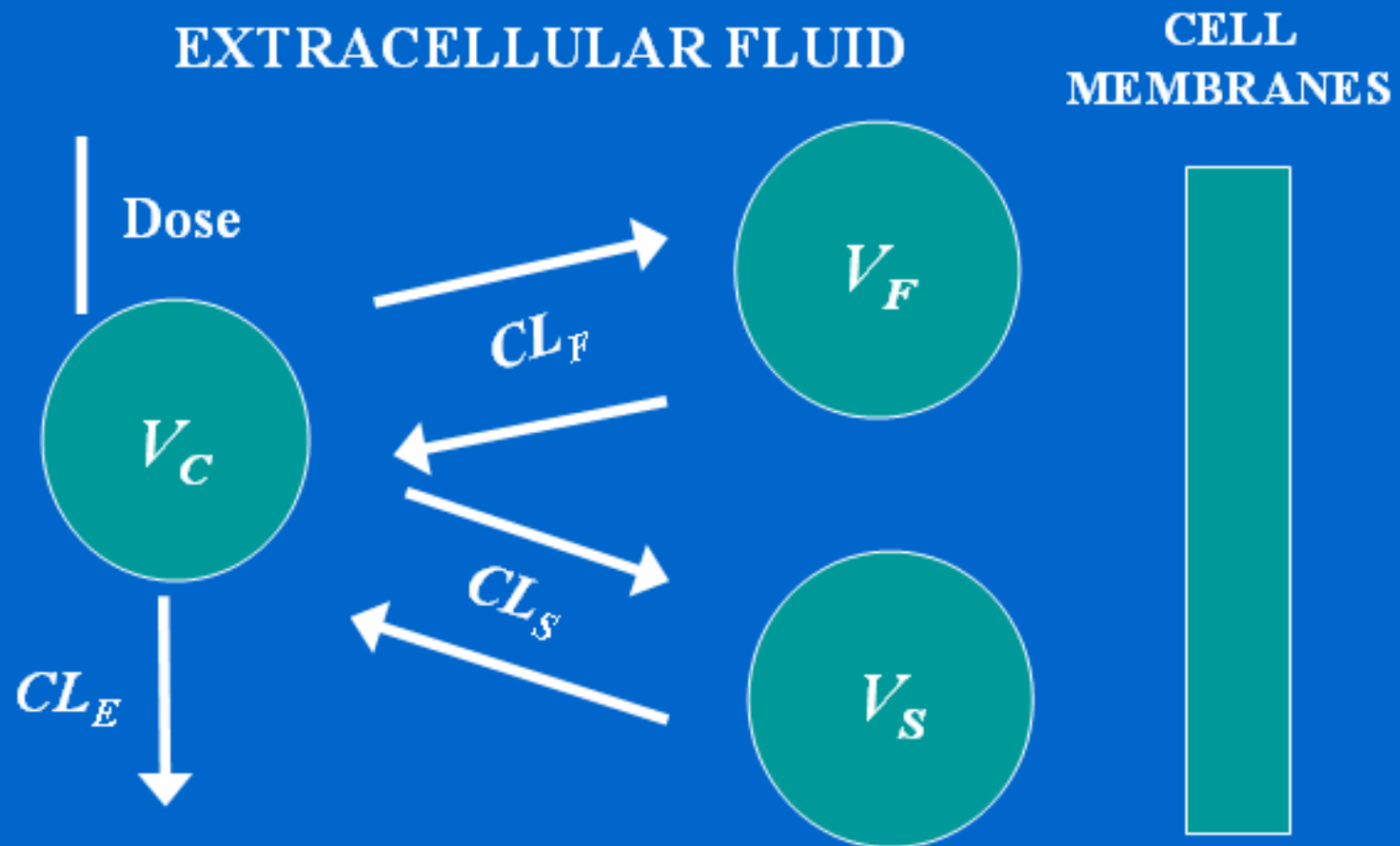
Hct = hematocrit

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



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

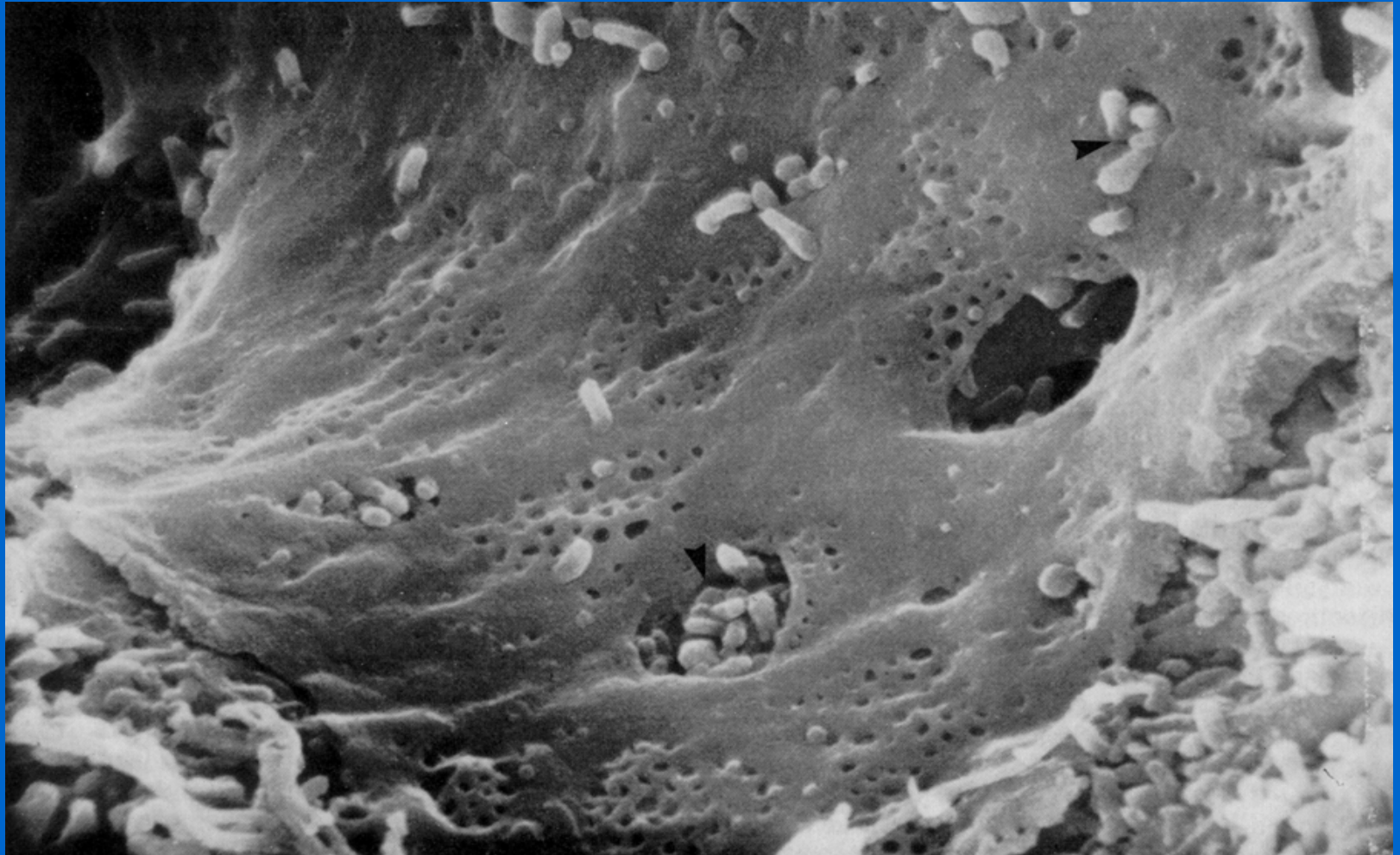
3-Compartment Model of **Inulin** Kinetics



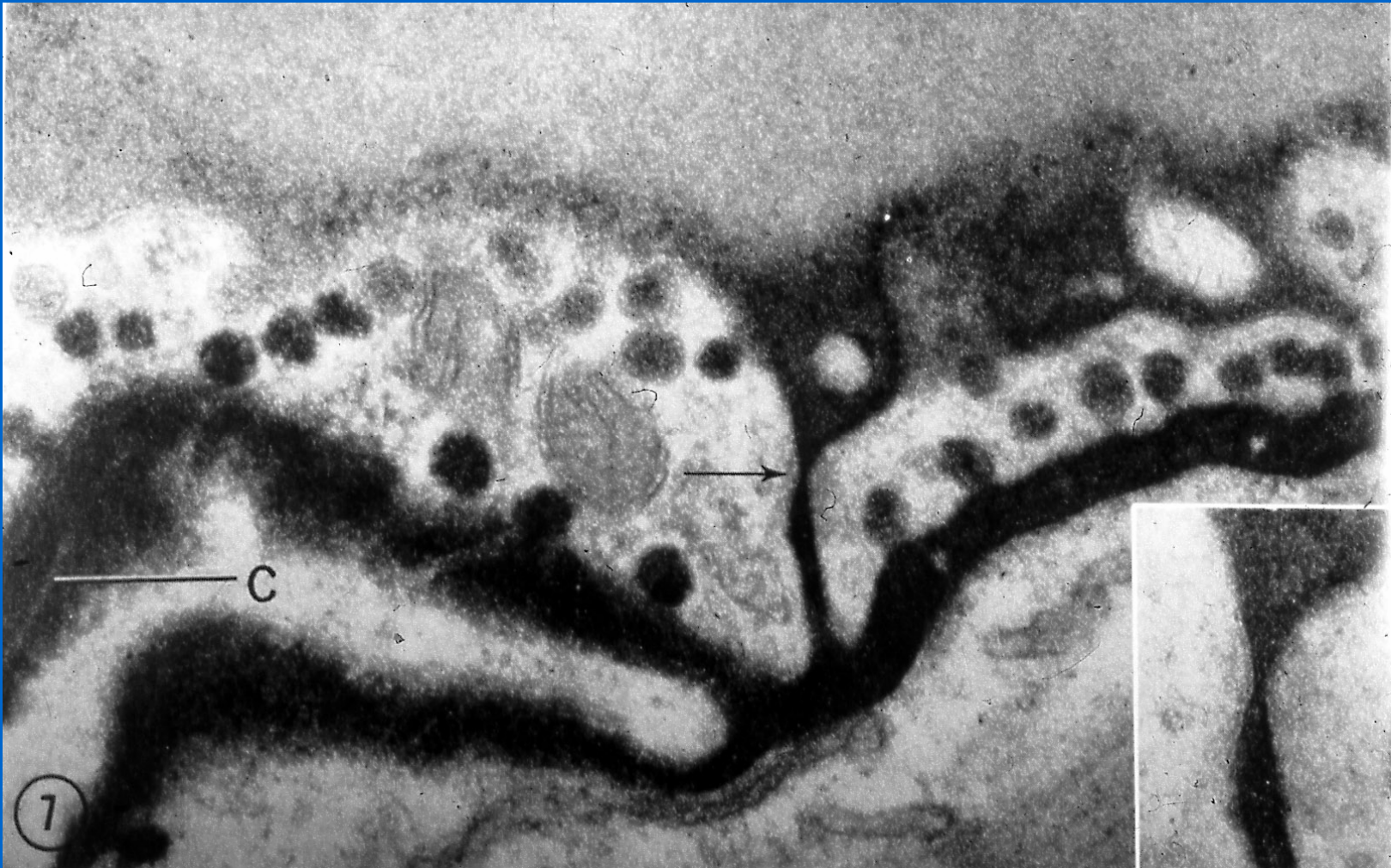
Basis for **Kinetic Heterogeneity** of Interstitial Fluid Space

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

ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS

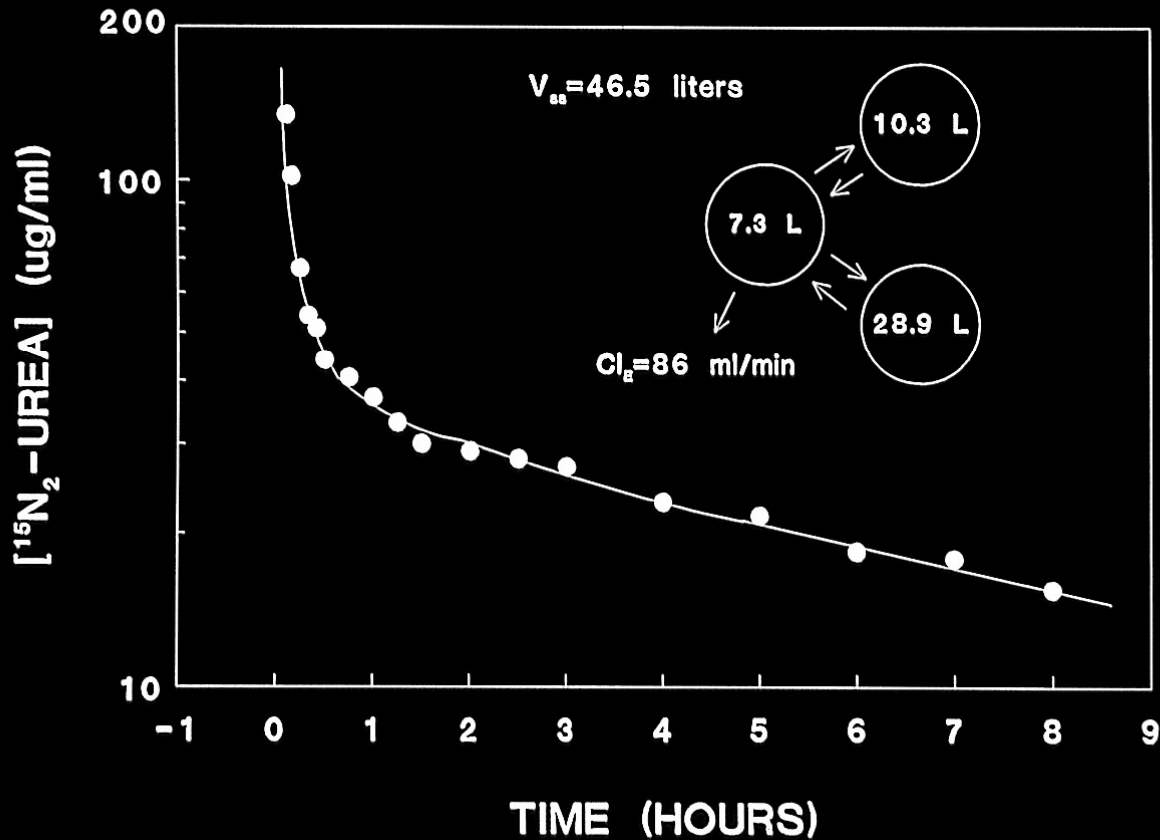


INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

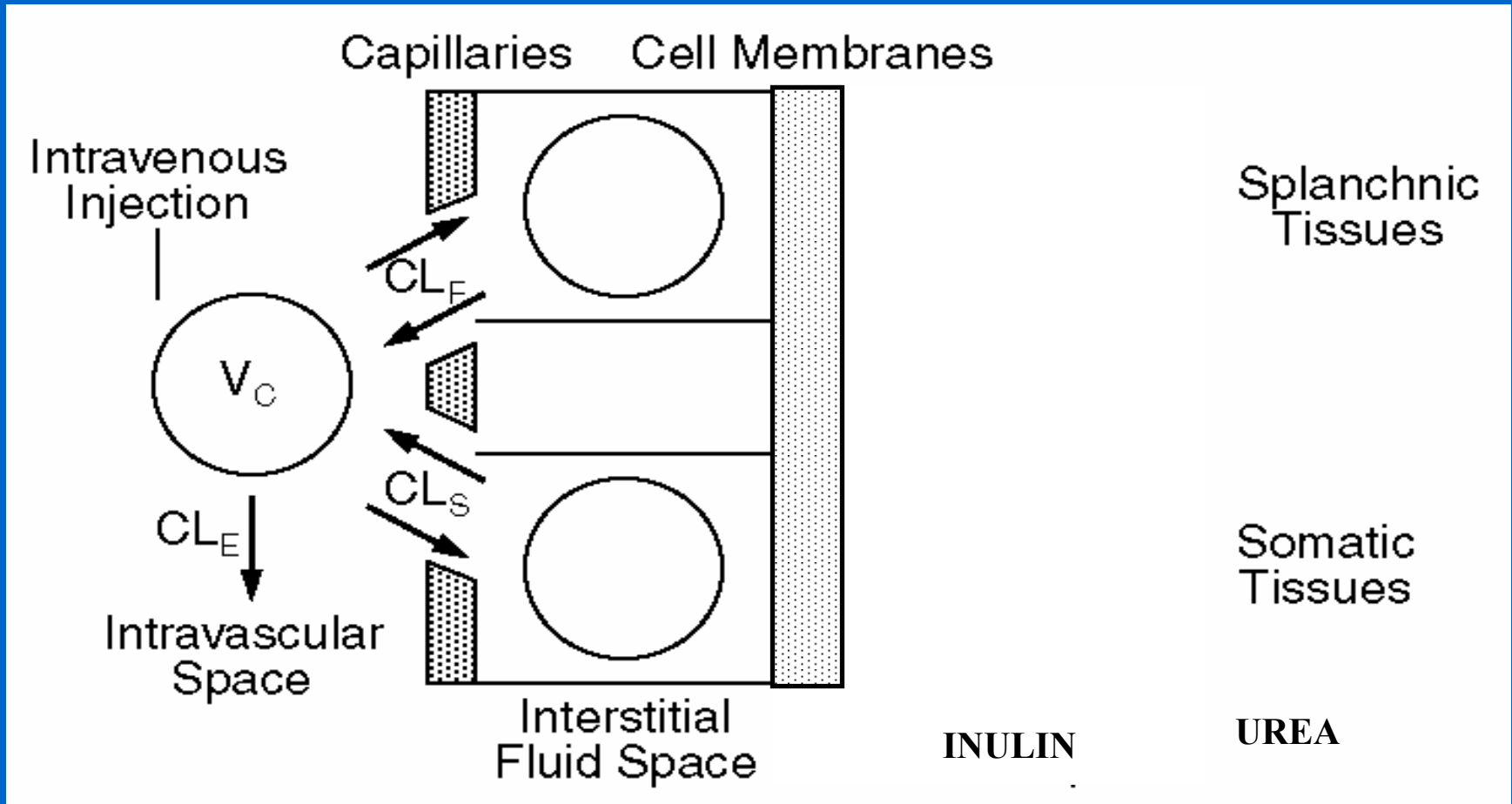


UREA-¹⁵N₂ KINETICS IN A NORMAL SUBJECT

UREA - ¹⁵N₂ KINETICS



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



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

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**.

RENKIN EQUATION*

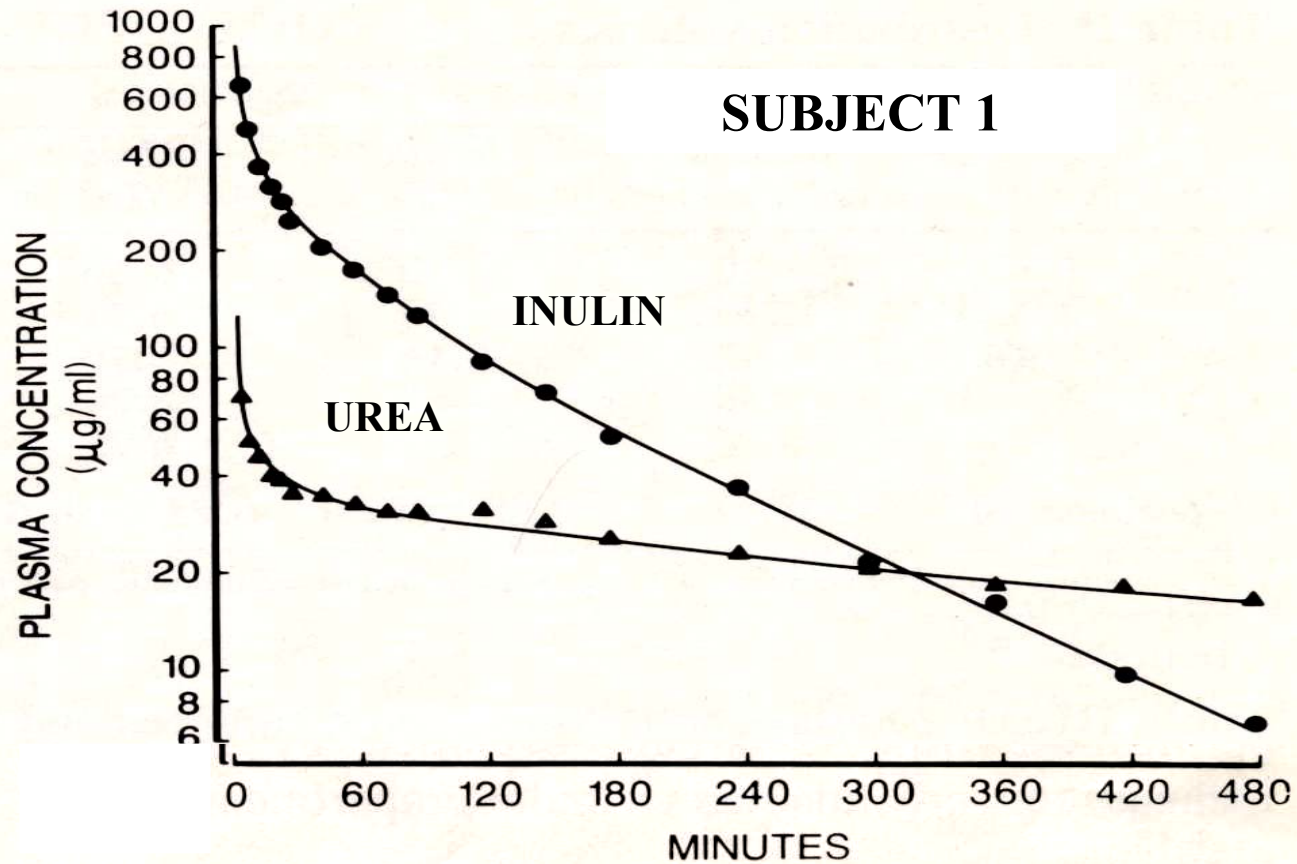
$$Cl = Q (1 - e^{-P/Q})$$

Q = capillary blood flow

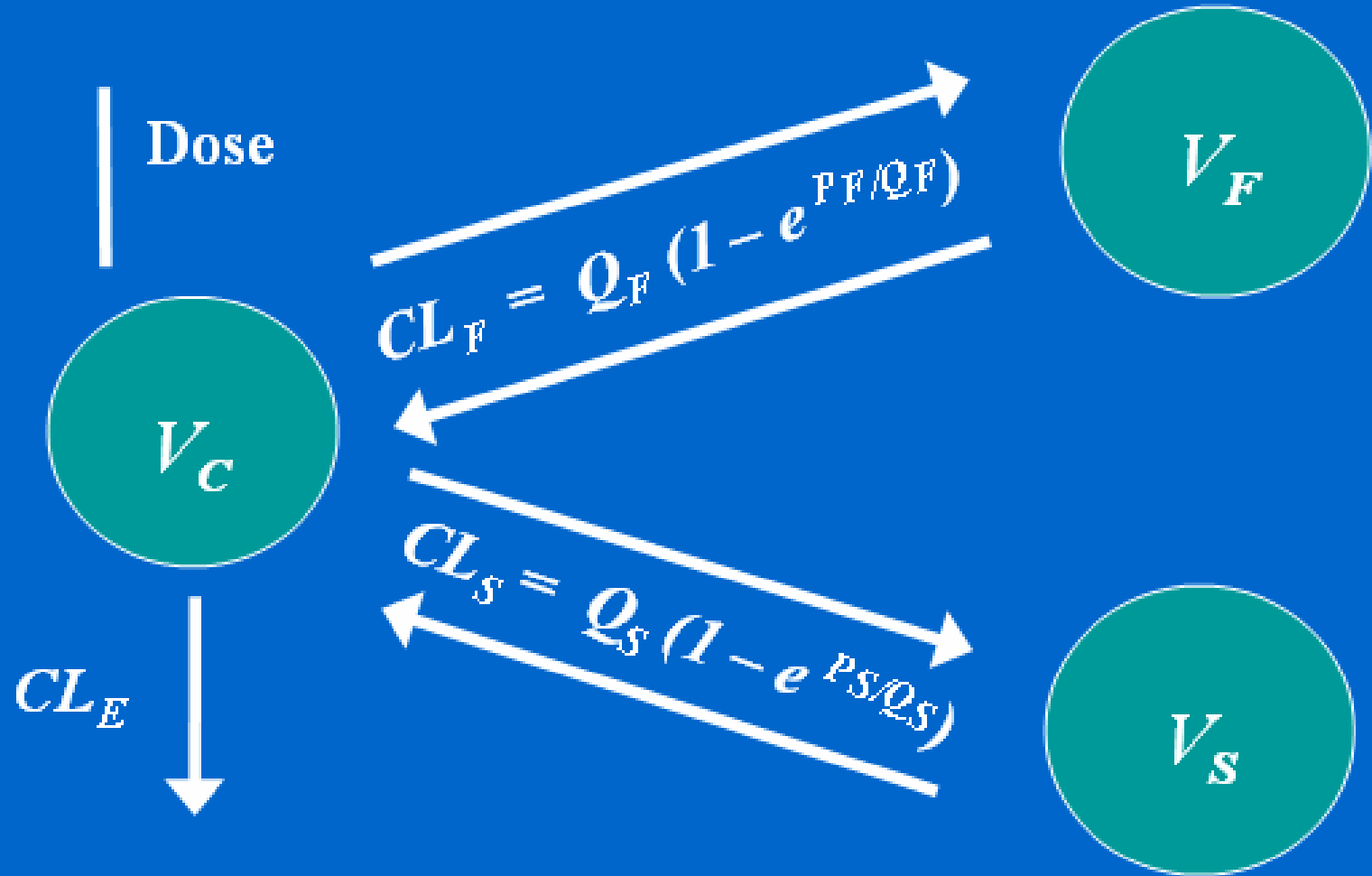
P = capillary permeability coefficient-surface area product (sometimes denoted P•S).

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

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-¹⁵N₂ KINETICS



3-COMPARTMENT MODEL



For Each Peripheral Compartment

3 UNKNOWNNS:

$$Q, P_U, P_I$$

3 EQUATIONS:

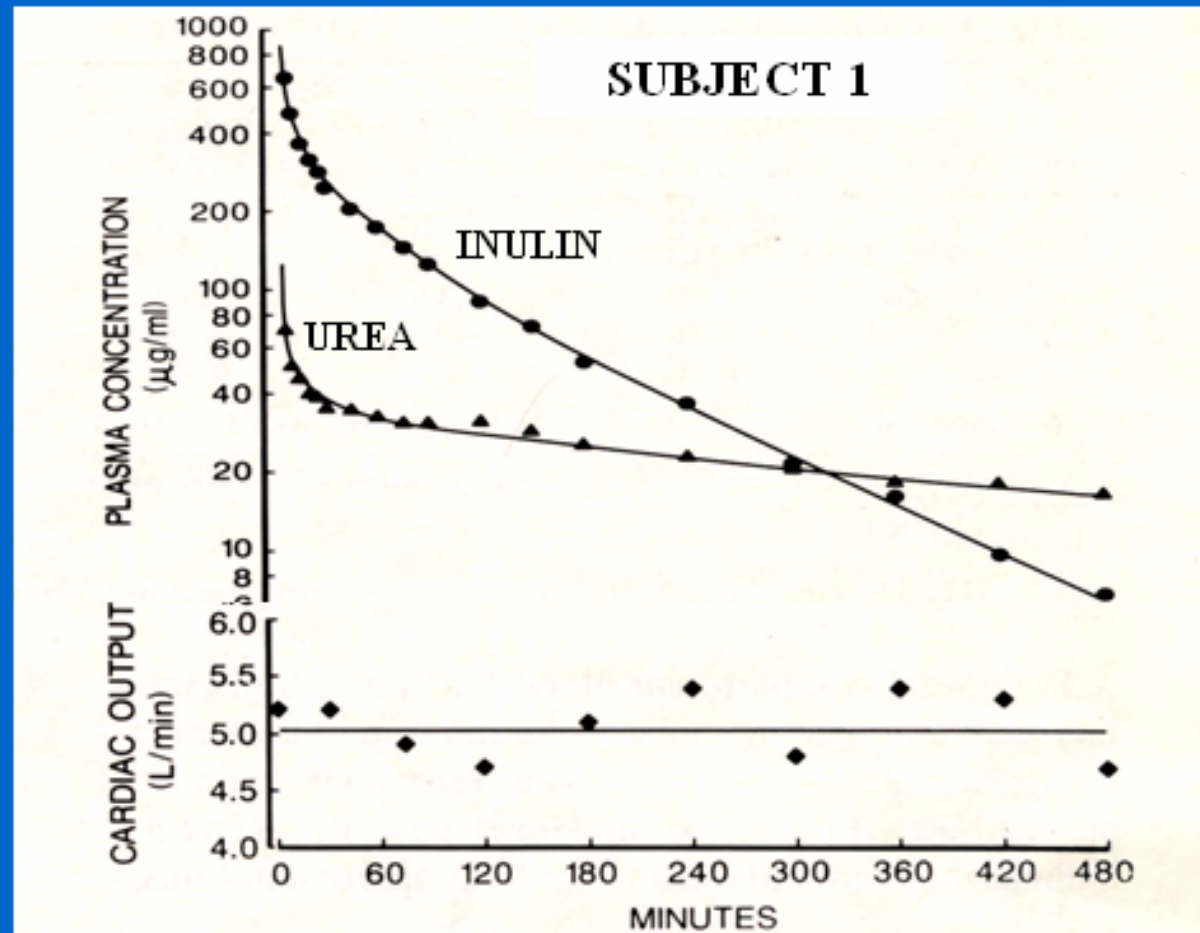
$$P_U = Q \ln \left[\frac{Q}{Q - C I_U} \right]$$
$$P_I = Q \ln \left[\frac{Q}{Q - C I_I} \right]$$
$$P_U / P_I = D_U / D_I$$

U = urea; I = inulin

D = free water diffusion coefficient

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-¹⁵N₂ KINETICS

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



CARDIAC OUTPUT AND COMPARTMENTAL BLOOD FLOWS*

	Q_F L/min	Q_S L/min	$Q_F + Q_S$ 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.**

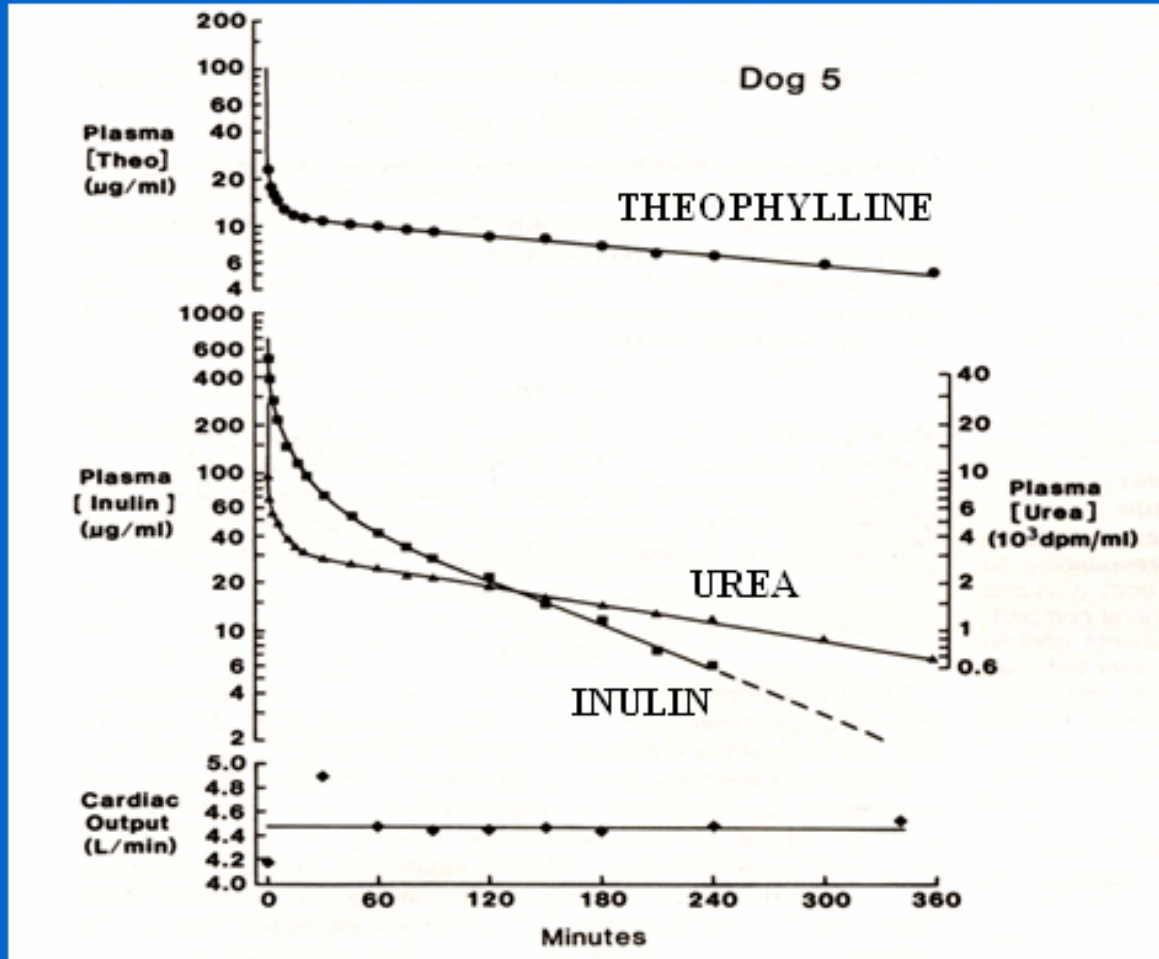
TRANSCAPILLARY EXCHANGE

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)

THEOPHYLLINE KINETICS Referenced to Inulin and Urea



THEOPHYLLINE

Intercompartmental Clearance and Compartmental Blood Flows*

	FAST COMPARTMENT L/min	SLOW COMPARTMENT L/min
I.C. CLEARANCE	4.50 ± 1.21	0.60 ± 0.14
BLOOD FLOW	4.00 ± 1.15	0.62 ± 0.21

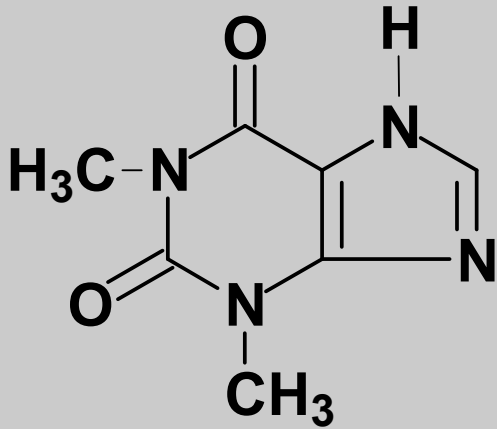
* From Belknap SM, et al. J Pharmacol Exp Ther 1987;243:963-9.

Urea and Theophylline Diffusion Coefficients*

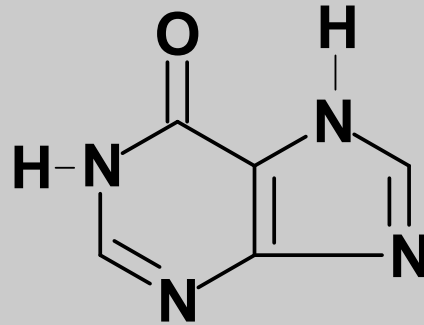
	MOLECULAR WEIGHT (DALTONS)	CORRECTED STOKES- EINSTEIN RADIUS (Å)	D_m @ 37° C (x 10⁻⁵ cm²/sec)
UREA	60	2.2	1.836
THEOPHYLLINE	180	3.4	1.098

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

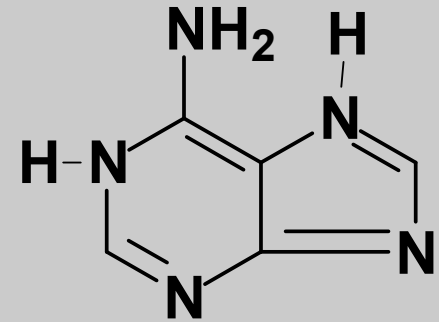
PRESUMED *CARRIER-MEDIATED* TRANSCAPILLARY EXCHANGE



THEOPHYLLINE



HYPOXANTHINE



ADENINE

GOALS OF DRUG DISTRIBUTION LECTURE

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

SIGNIFICANCE OF DRUG DISTRIBUTION RATE

1. Affects toxicity of IV injected drugs

Theophylline, lidocaine

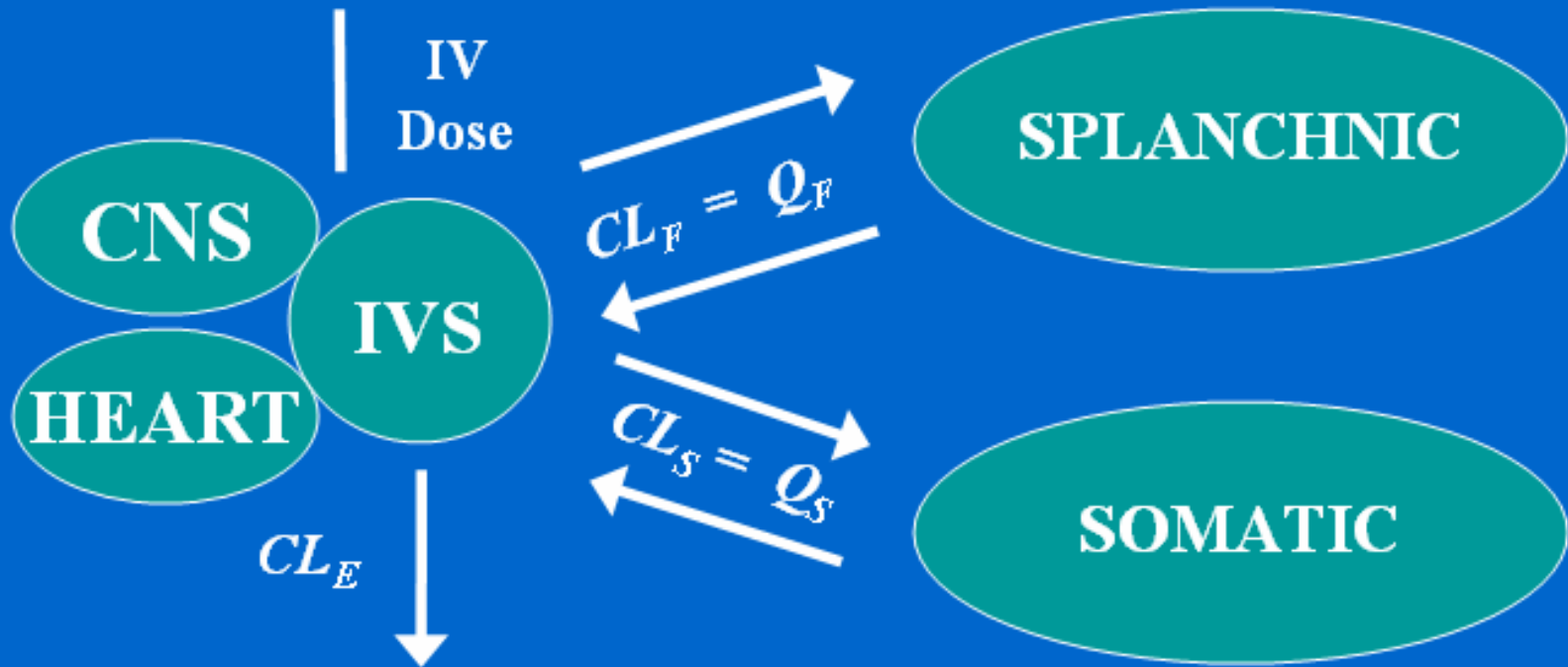
2. Delays onset of drug action

Insulin, digoxin

3. Terminates action after IV bolus dose

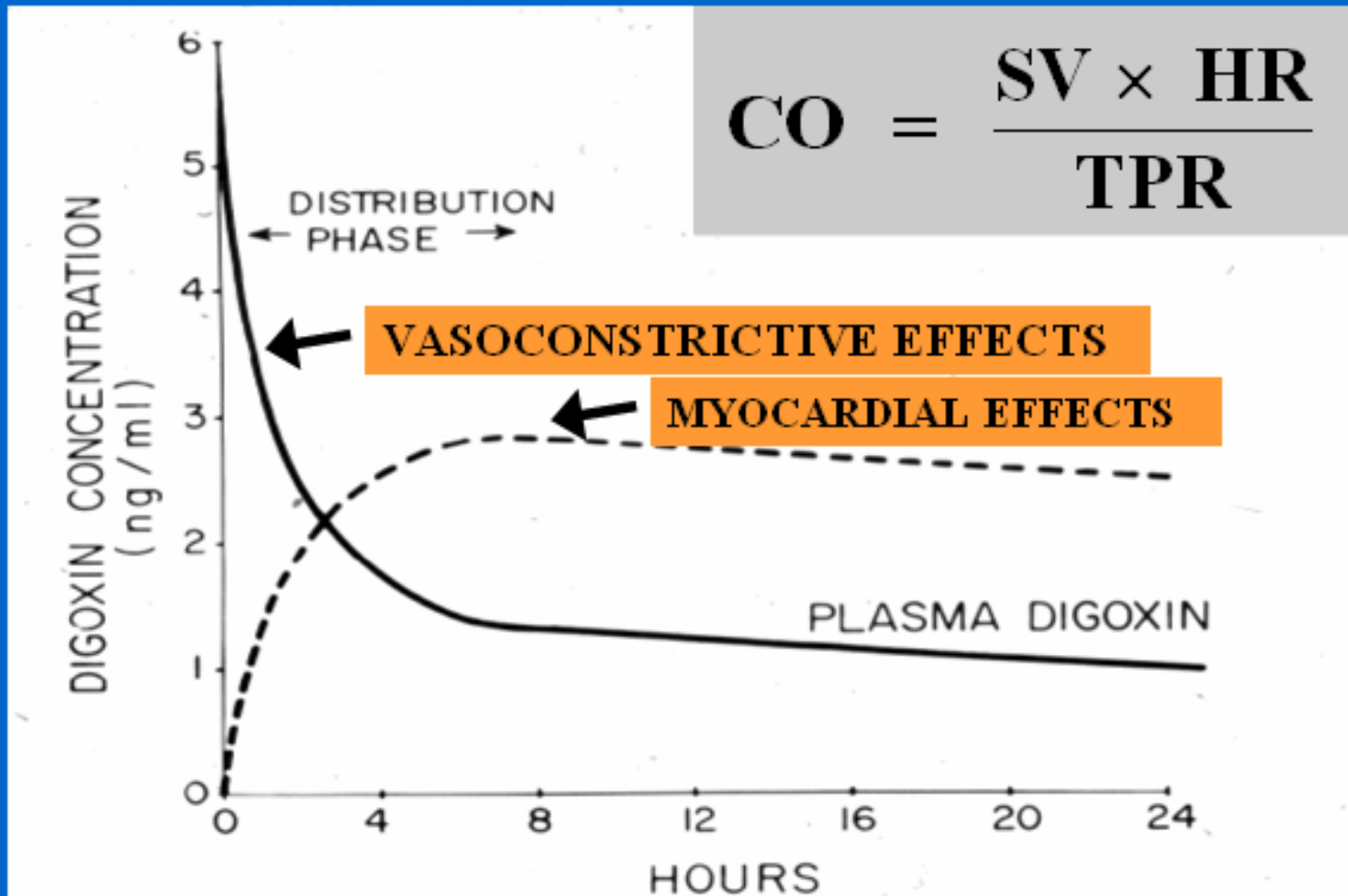
Thiopental, lidocaine

PK Model of THEOPHYLLINE Distribution

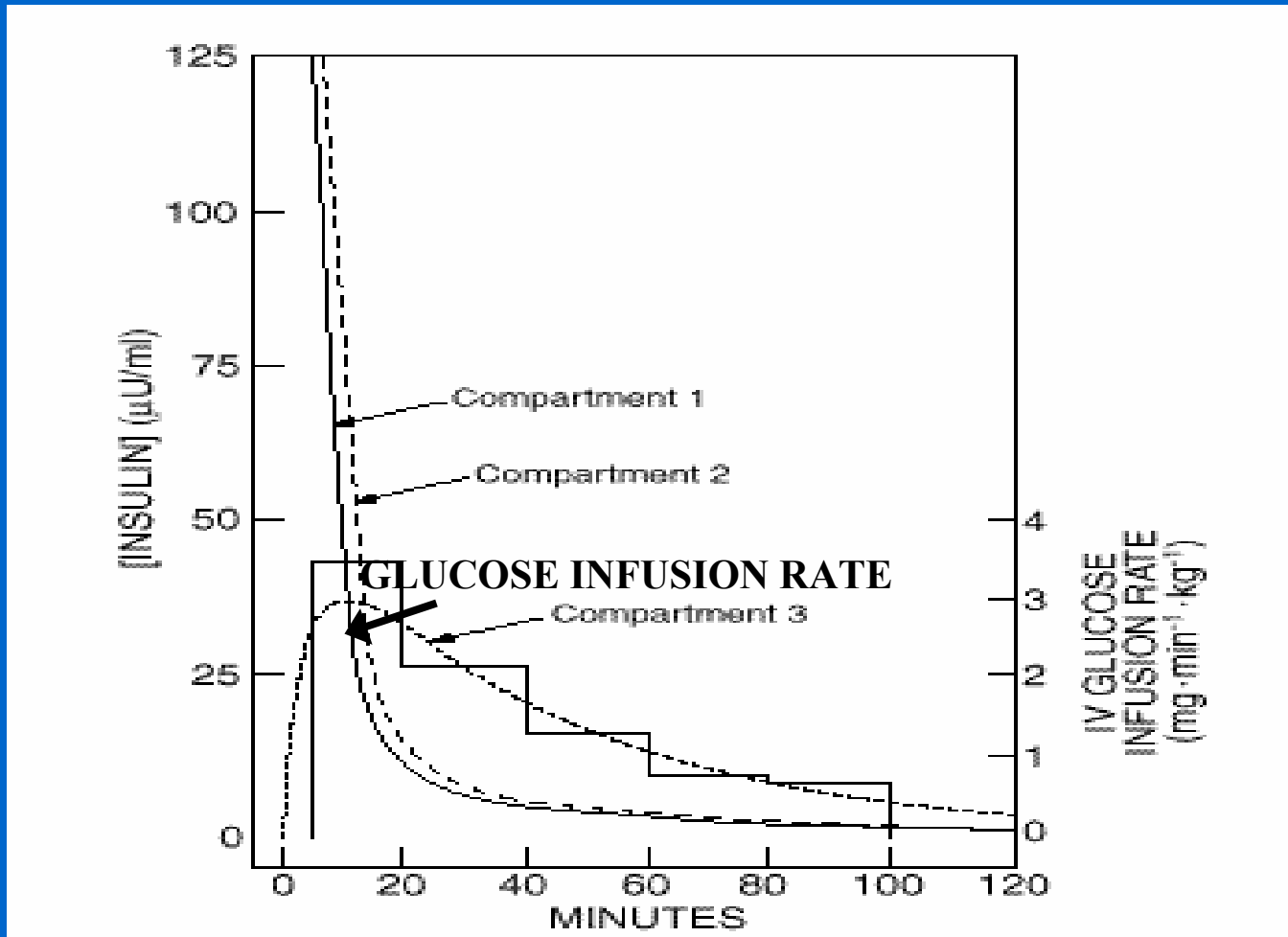


$$CO = Q_F + Q_S$$

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

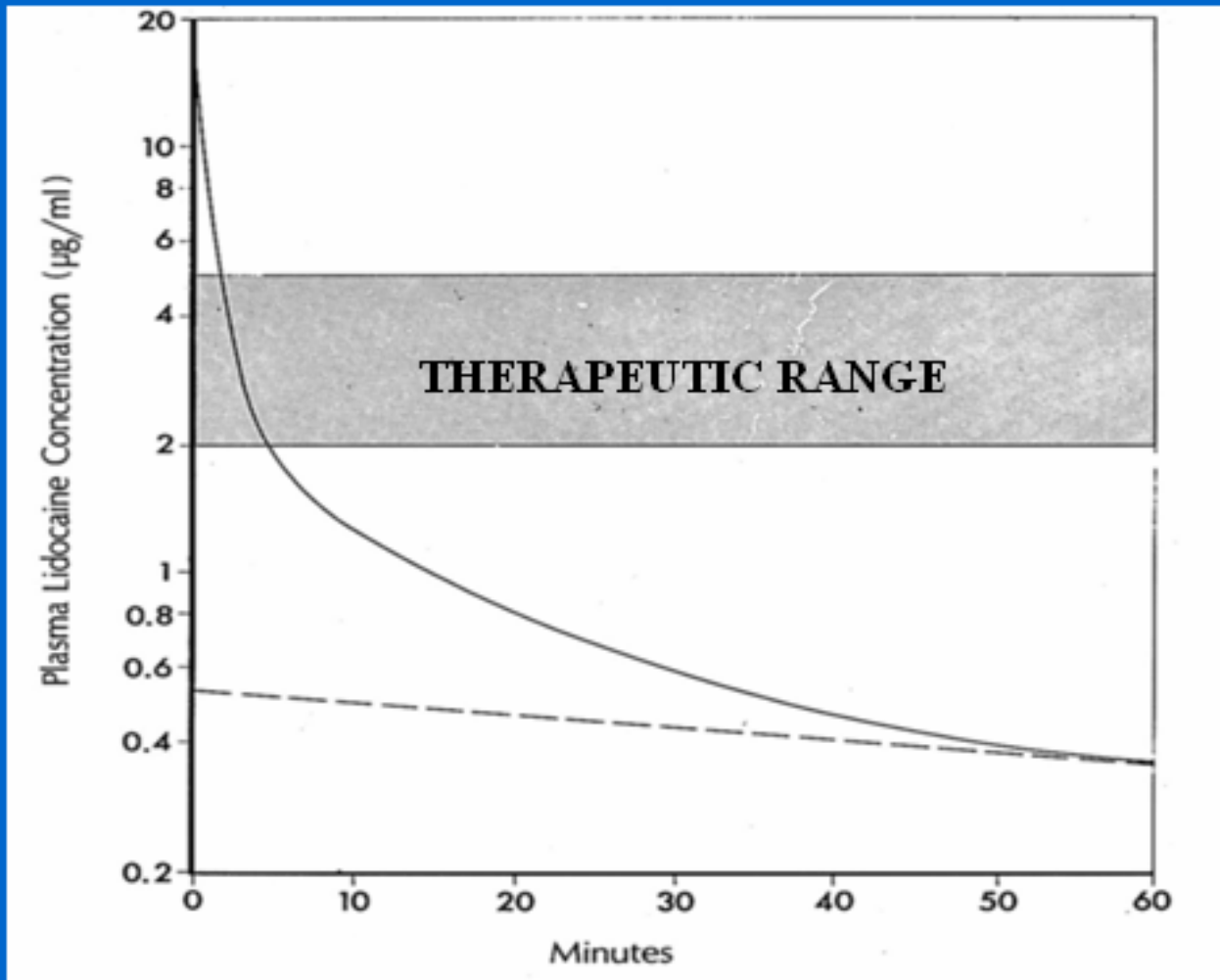


PK-PD Study of **INSULIN** Enhancement of Skeletal Muscle **Glucose Uptake***



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

DISTRIBUTION TERMINATES EFFECT BOLUS LIDOCAINE DOSE*



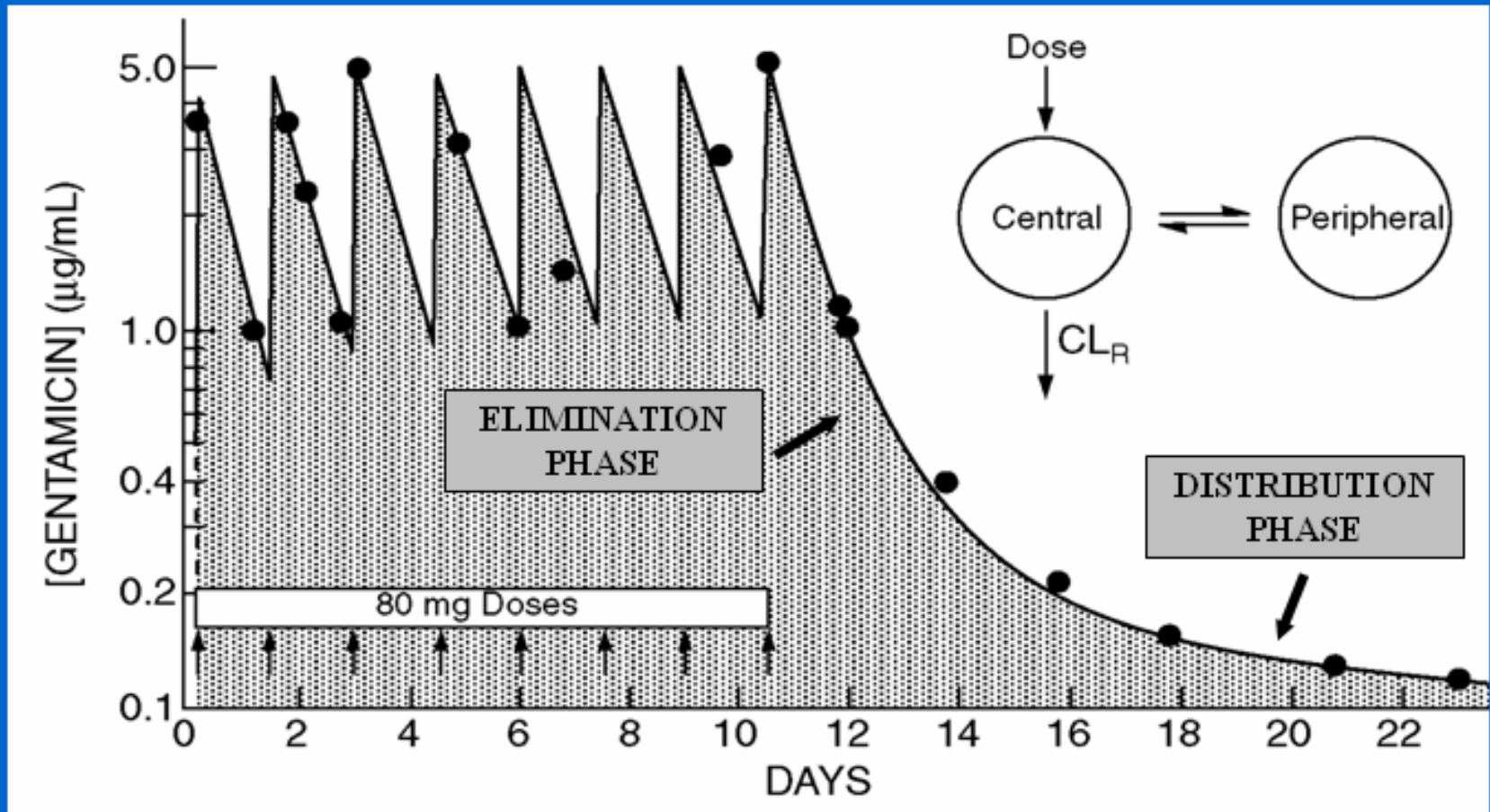
* From Atkinson AJ Jr. In: Melmon KL, ed. Drug Therapeutics: Concepts for Physicians, 1981:17-33.

CONSEQUENCES OF *VERY SLOW* DRUG DISTRIBUTION

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

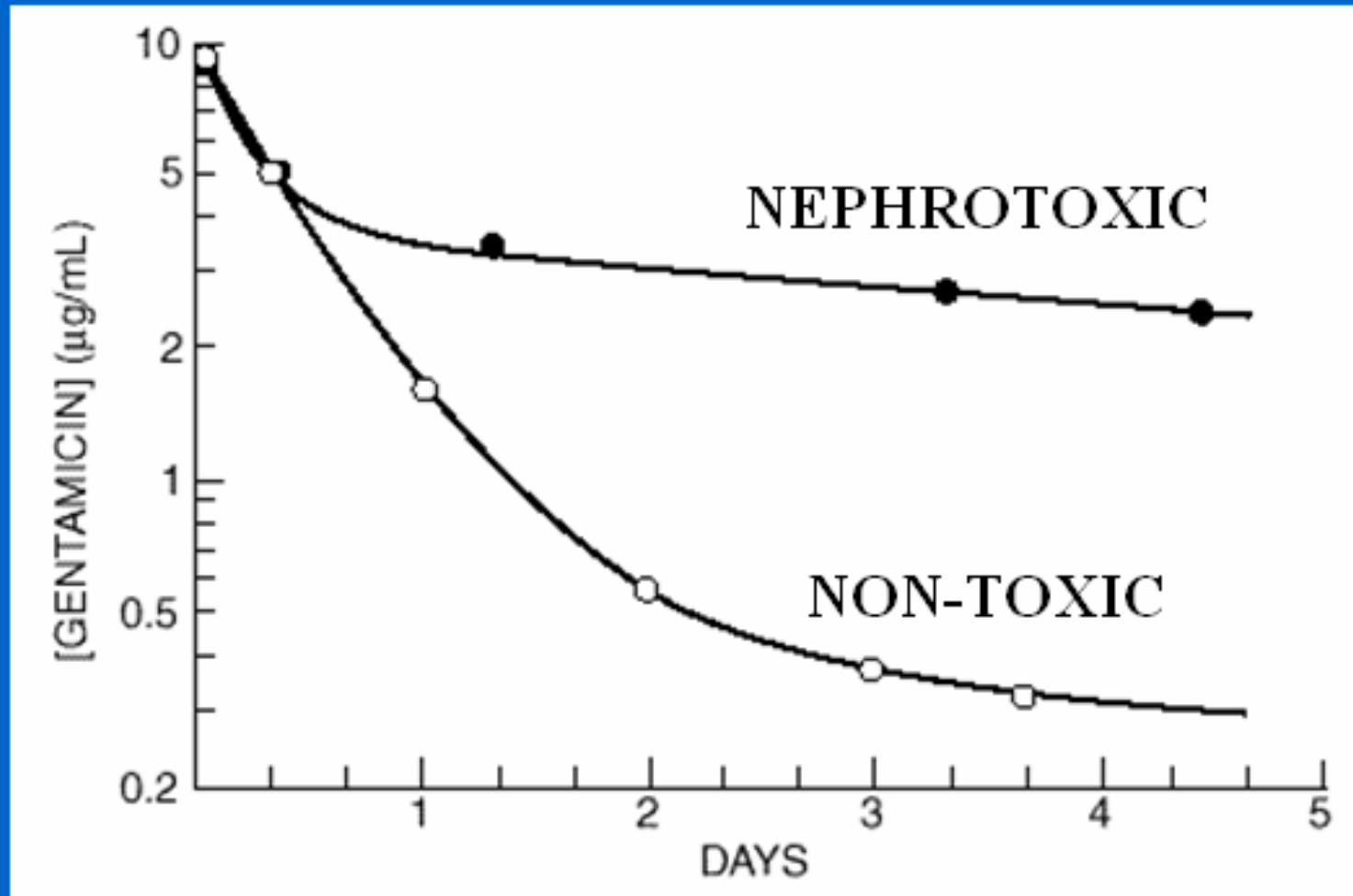
GENTAMICIN

Elimination Phase Precedes Distribution Phase*



* From Schentag JJ, et al. JAMA 1977;238:327-9.

GENTAMICIN ELIMINATION Nephrotoxic vs. Non-Toxic Patient*



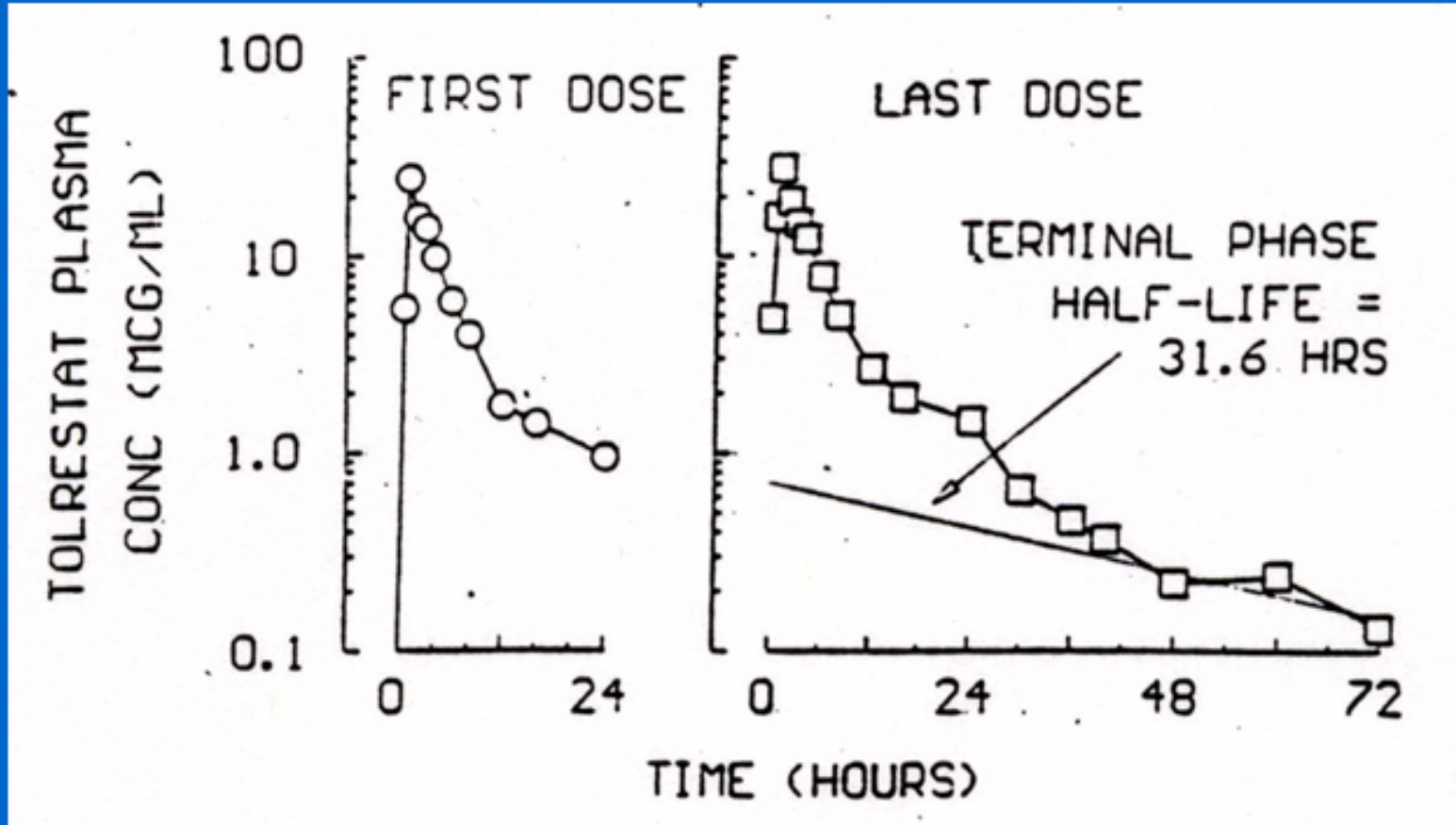
* From Coburn WA, et al. J Pharmacokinet Biopharm 1978;6:179-86.

CONSEQUENCES OF *VERY SLOW* DRUG DISTRIBUTION

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- * **Effective Half-Life**
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TOLRESTAT

Cumulation with Repeated Dosing*



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

CUMULATION FACTOR

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

TOLRESTAT CUMULATION

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

Observed C.F.: 1.29

EFFECTIVE HALF- LIFE*

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

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

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

EFFECTIVE HALF-LIFE OF TOLRESTAT*

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

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

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

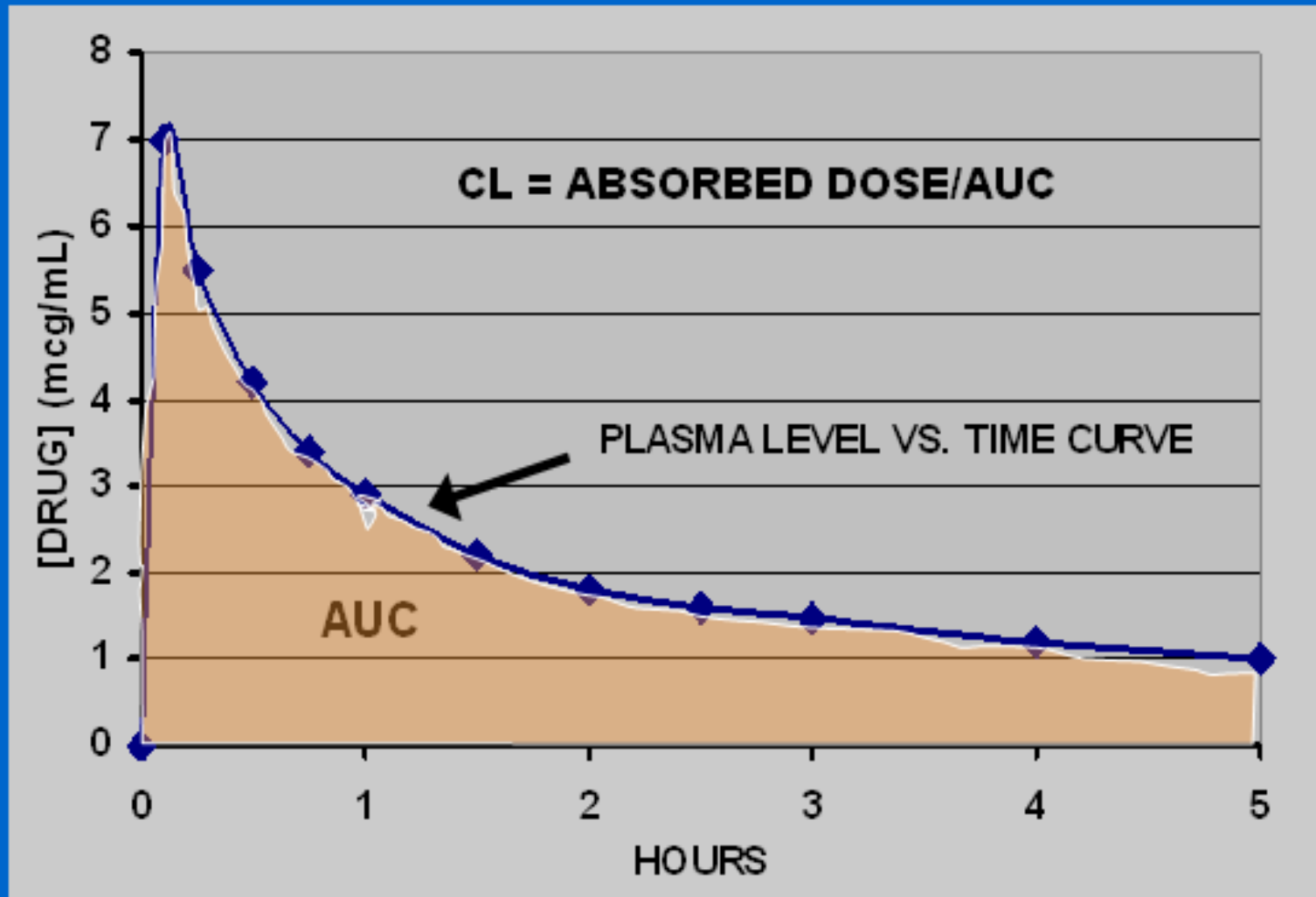
* From Boxenbaum H, Battle M. J Clin Pharmacol 1995;35:763-66.

CONSEQUENCES OF *VERY SLOW* DRUG DISTRIBUTION

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

AREA UNDER THE CURVE

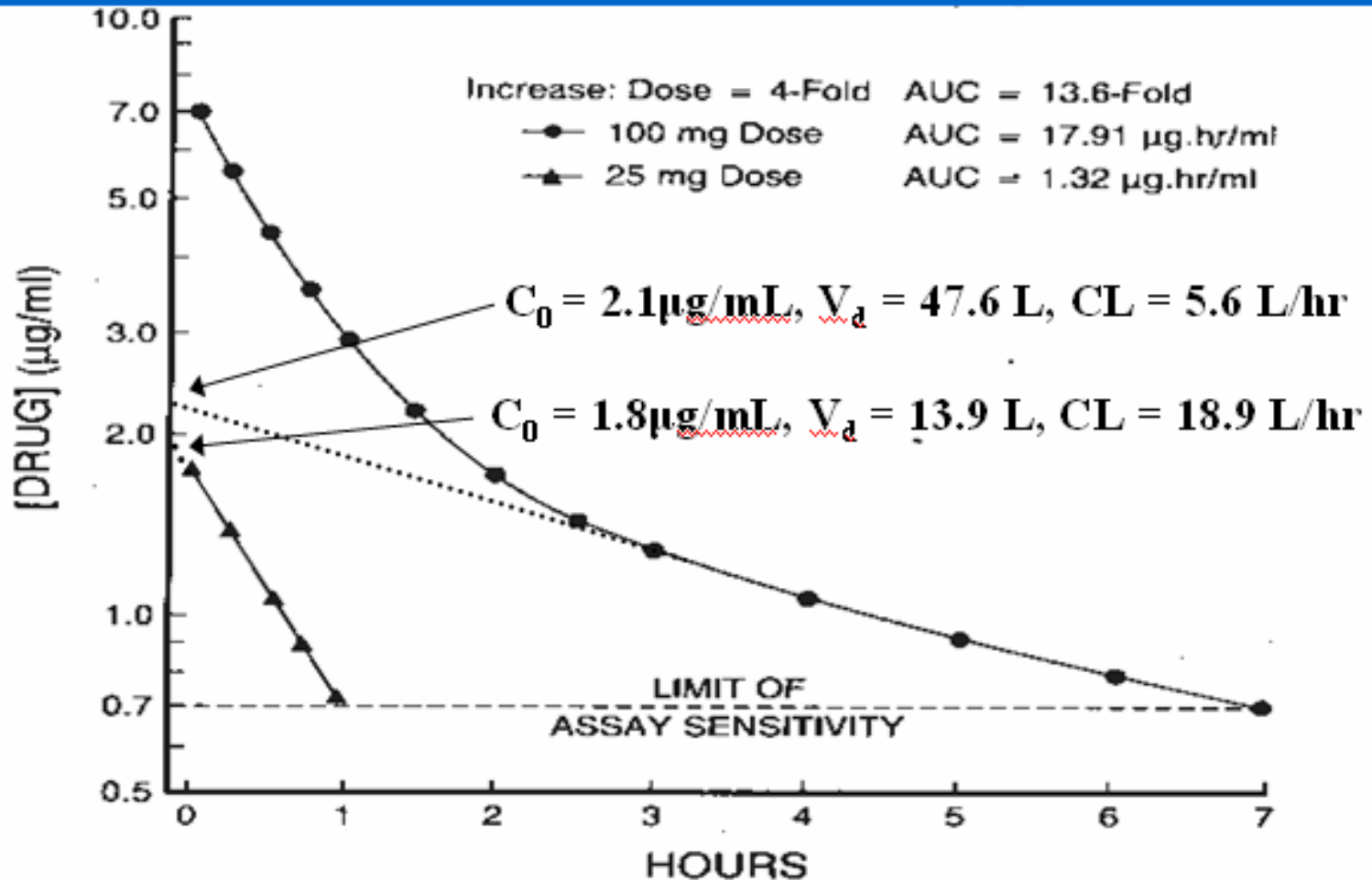
Measure of Dose Proportionality



HYPOTHETICAL Phase I Trial Results

	DOSE 1	DOSE 2	INCREASE
DOSE (mg)	25	100	4 x ↑
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	1.32	17.91	13.6 x ↑

Dependency of PK Estimates on Identified Terminal Phase



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

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.

Topics for Further Study

(See end of Chapter 3)

- * Graphical Analysis of PK Data**
- * Calculate Parameters of Compartmental Models**
- * Comparison of Three Different Distribution Volumes**