COMPARTMENTAL ANALYSIS OF DRUG DISTRIBUTION

Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
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Office of Clinical Research Training
and Medical Education
National Institutes of Health
Clinical Center

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 PRIORI*

* 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:

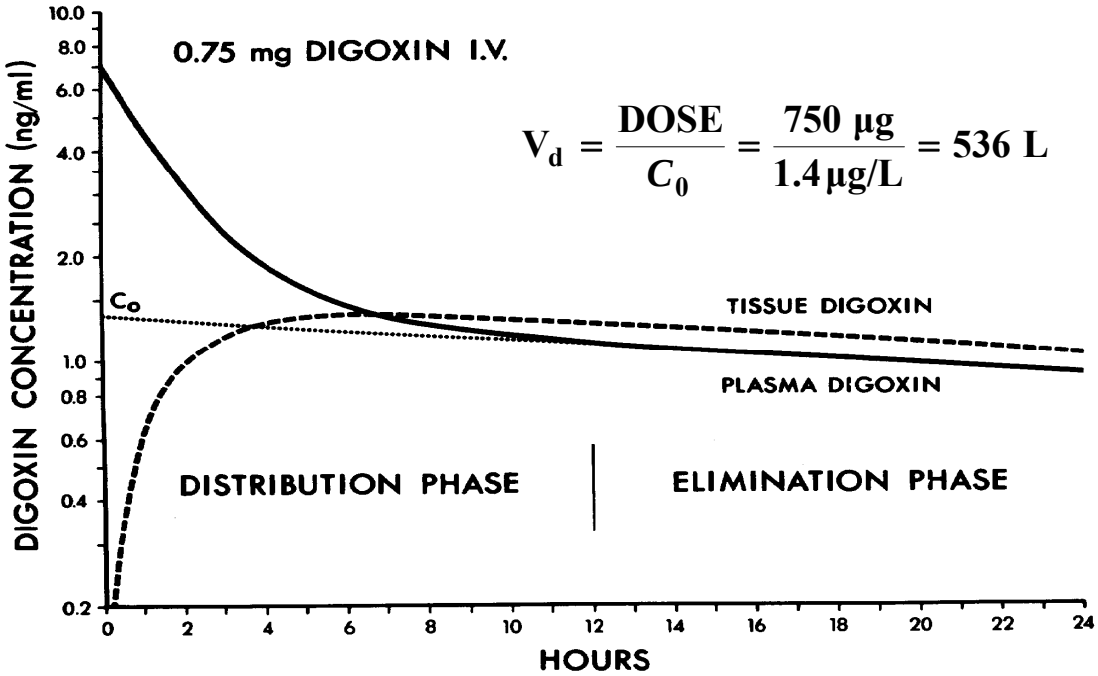
Implies certain mechanisms or entities that have physiological, biochemical or physical significance.

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

Goals of Drug Distribution Lecture

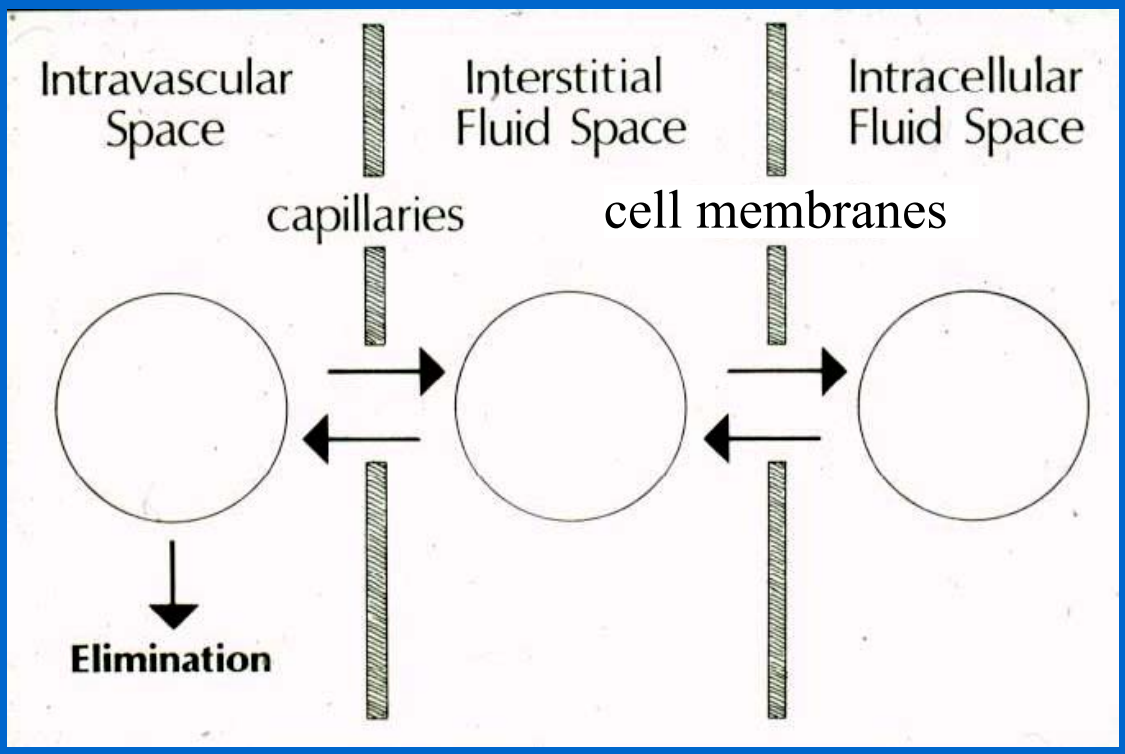
- **Significance** of Drug Distribution Volumes
- **Physiological Basis** of Multi-Compartment Pharmacokinetic Models
- **Clinical Implications** of Drug Distribution Kinetics

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

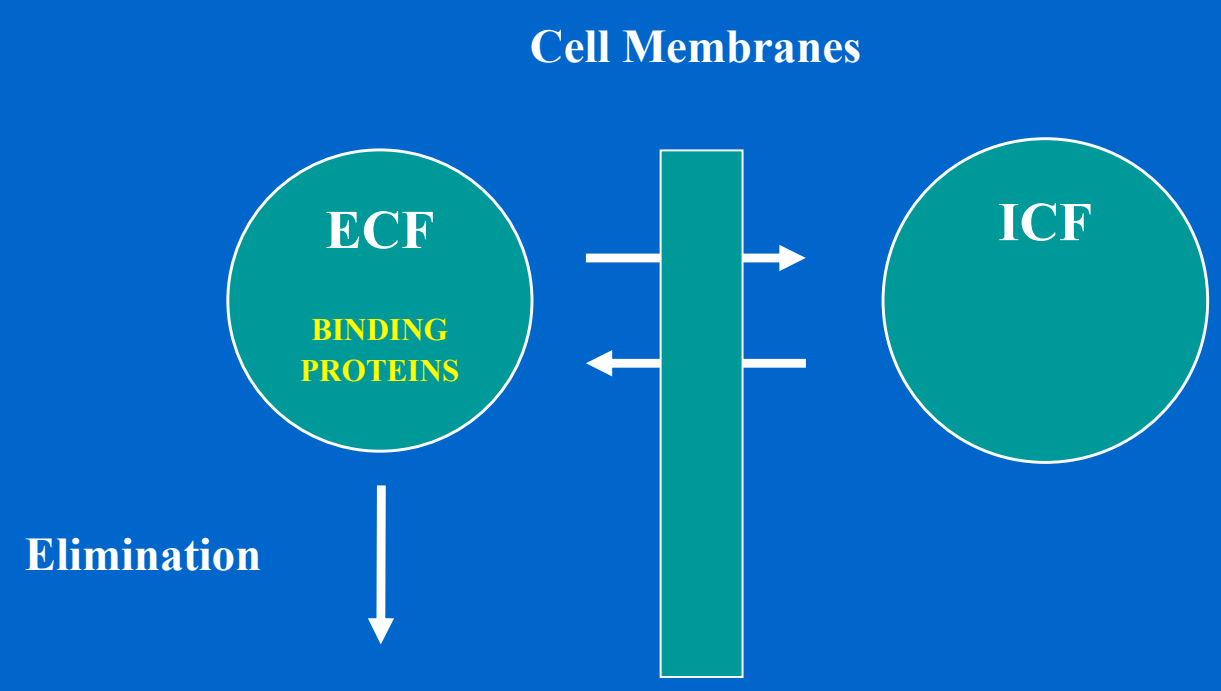
Theophylline

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*

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

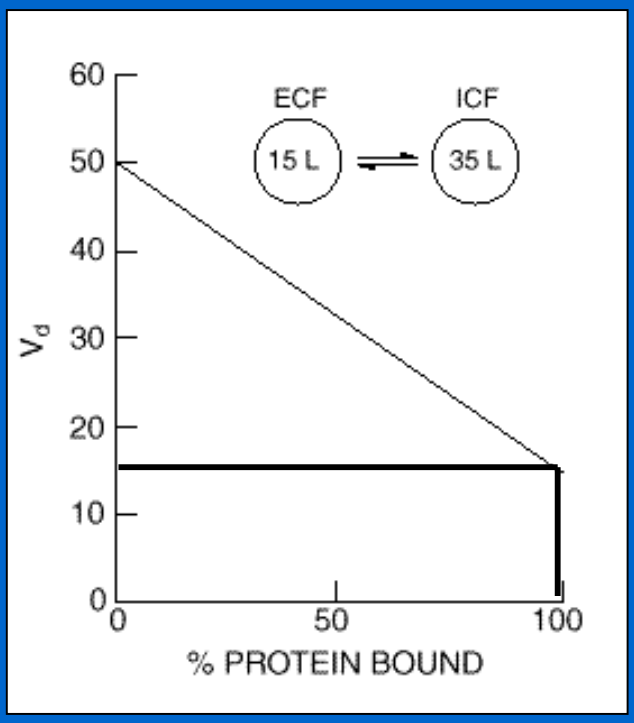
f_u is the "free fraction", the fraction of drug in plasma that is not bound to plasma proteins.

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

Impact of Protein Binding on Thyroxine Distribution Volume*

$f_u = 0.03\%$

$V_d = V_{ECF}$

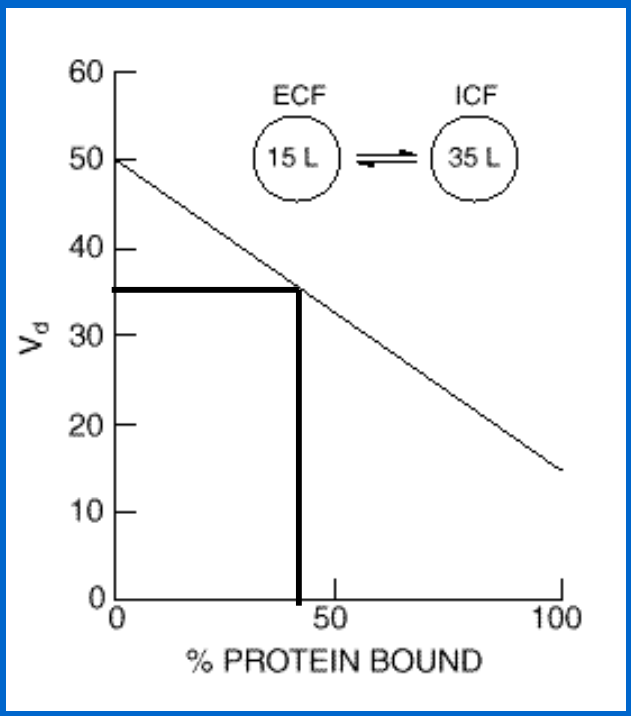


* From Larsen PR, Atkinson AJ Jr, et al. J Clin Invest 1970;49:1266-79.

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.

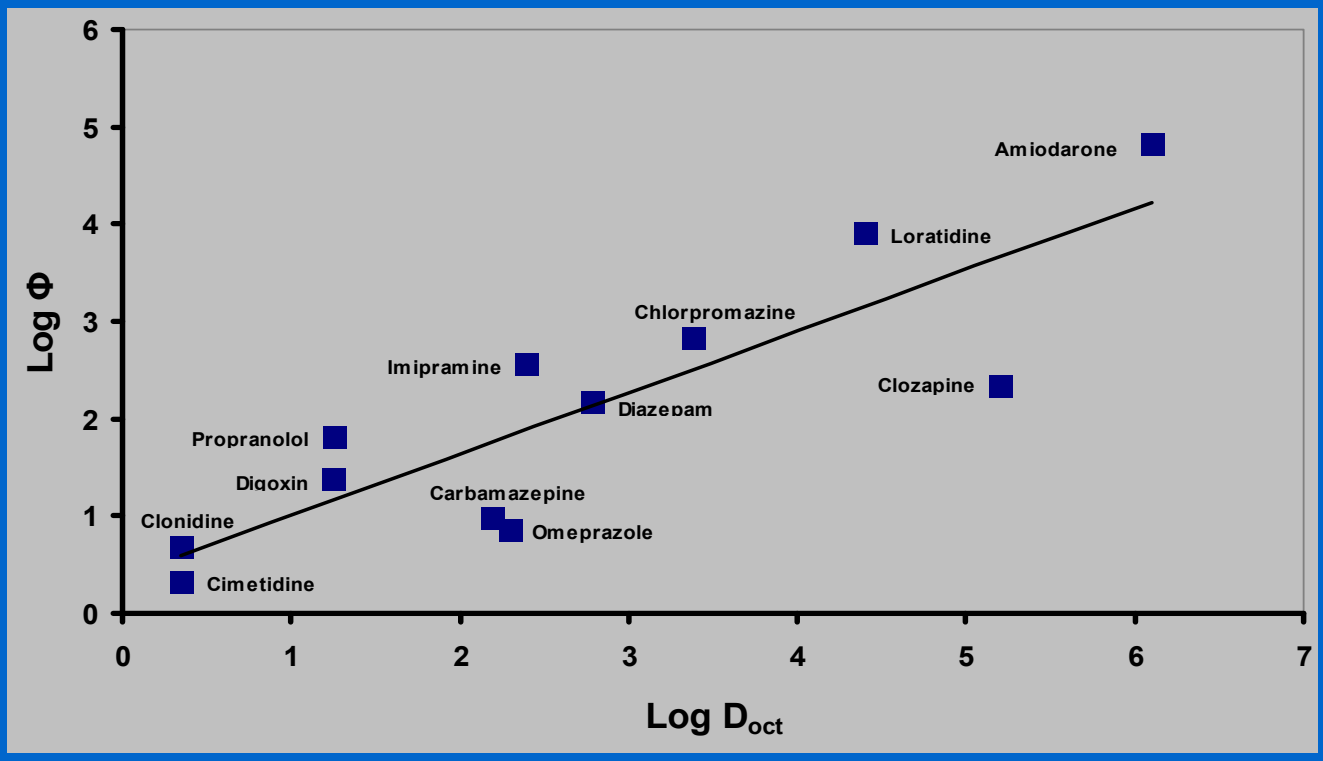
Effect of Plasma Protein and Tissue Binding on the Volume of Distribution of Most Drugs*

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

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

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

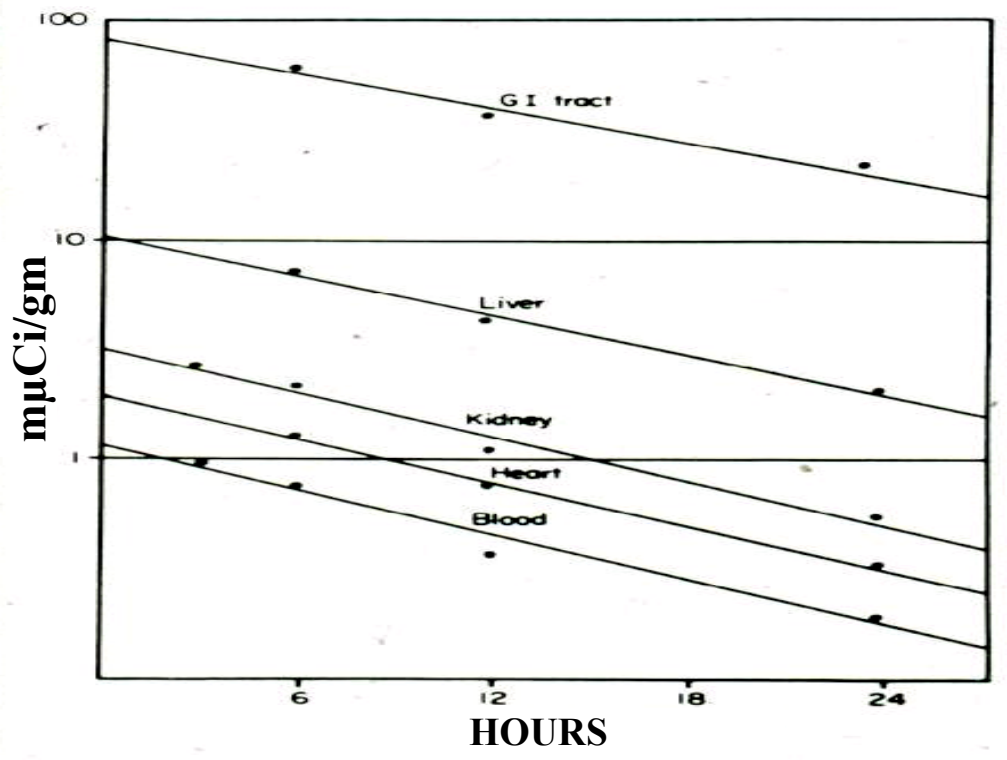
$$ECF = 11.2L,\ TBW = 45.5L,\ f_u = 0.75,\ \Phi = 20.4$$

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

$$V_d = 536\ L$$

Φ includes binding to Na^+-K^+ ATPase.

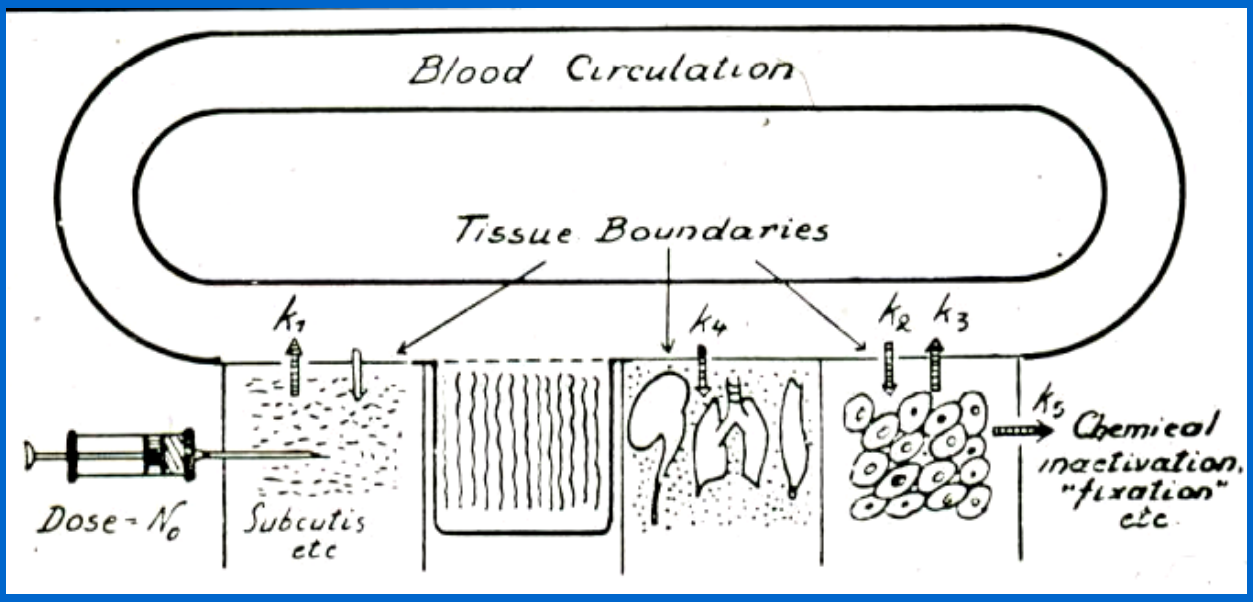
Tissue vs. Plasma Digoxin Levels



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*



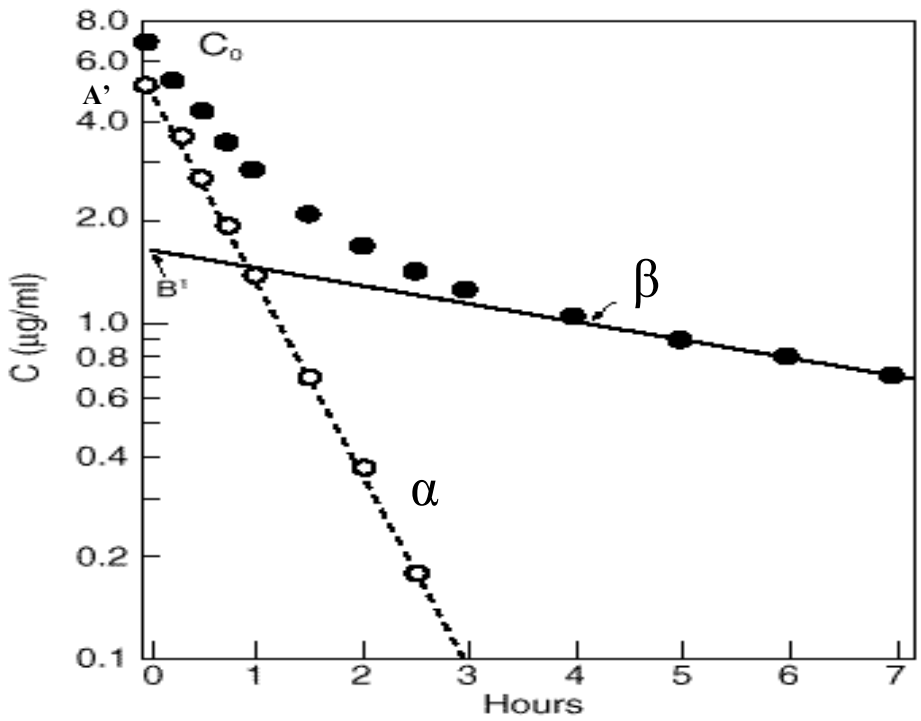
* From Teorell T. Arch Intern Pharmacodyn 1937;57:205-25.

Analysis of Experimental Data

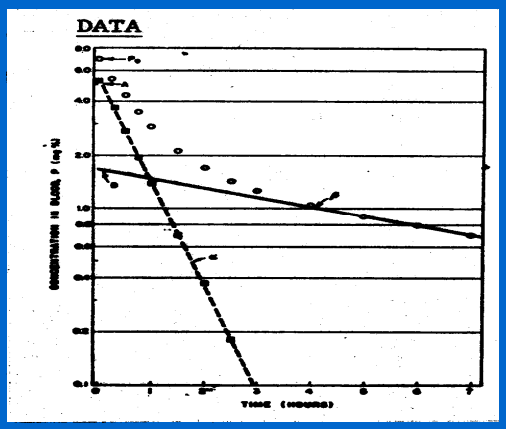
How many compartments?

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

TECHNIQUE OF *CURVE PEELING*

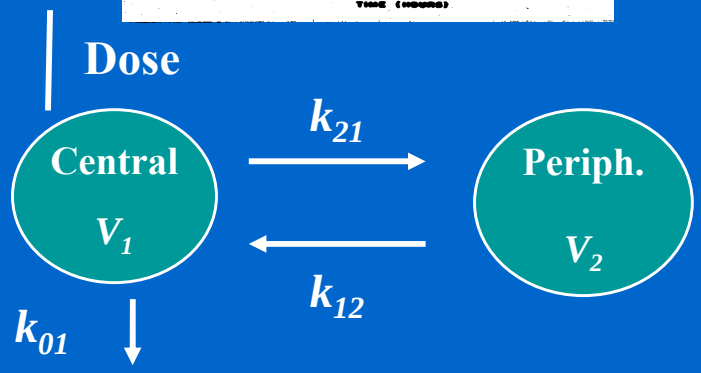


COMPARTMENTAL ANALYSIS



Data Equation:

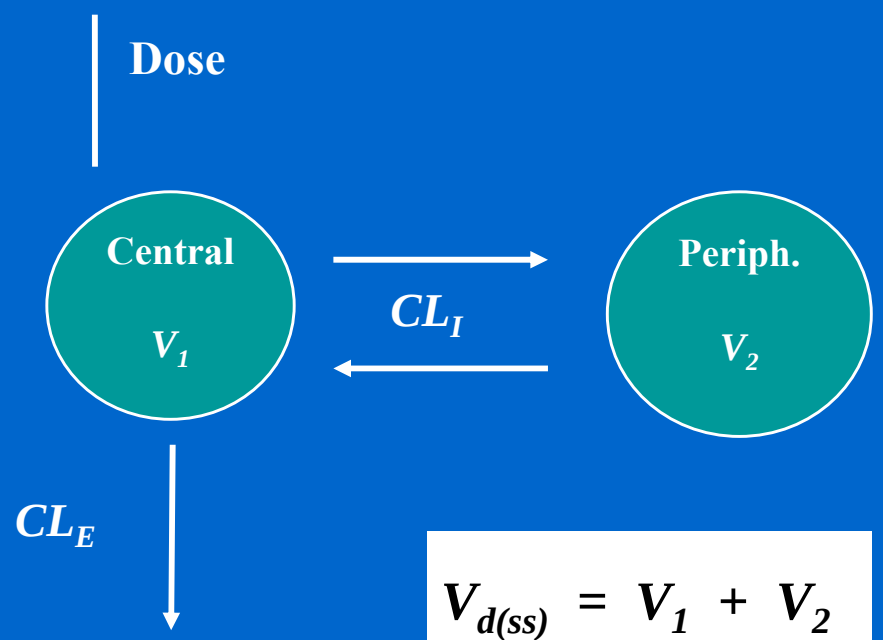
$$C = A' e^{-\alpha t} + B' e^{-\beta t}$$



Model Equation:

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

TWO-COMPARTMENT MODEL



$$V_{d(ss)} = V_1 + V_2$$

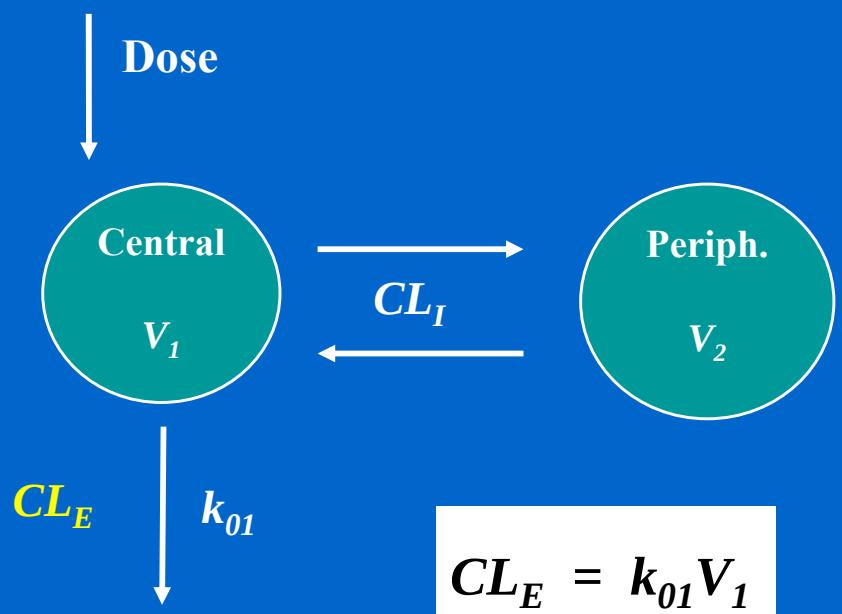
3 DISTRIBUTION VOLUMES

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

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

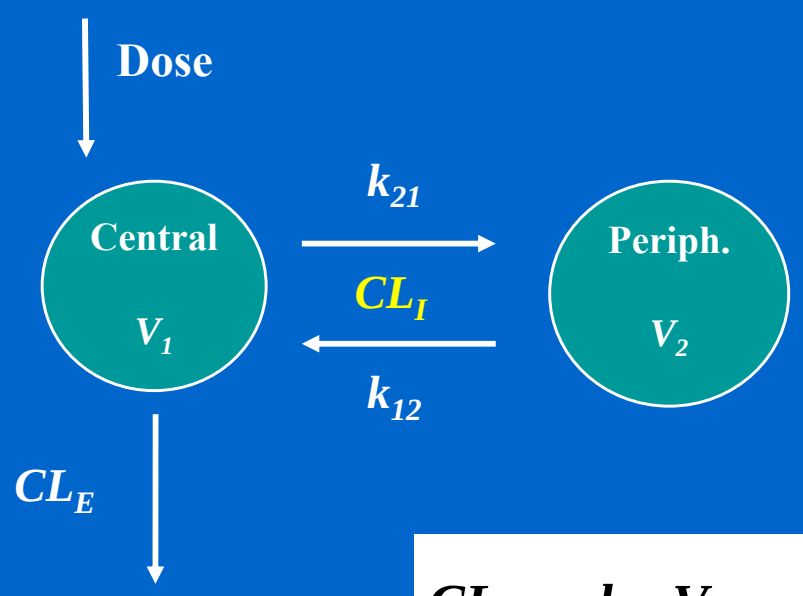
$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

TWO-COMPARTMENT MODEL



$$CL_E = k_{01}V_1$$

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.

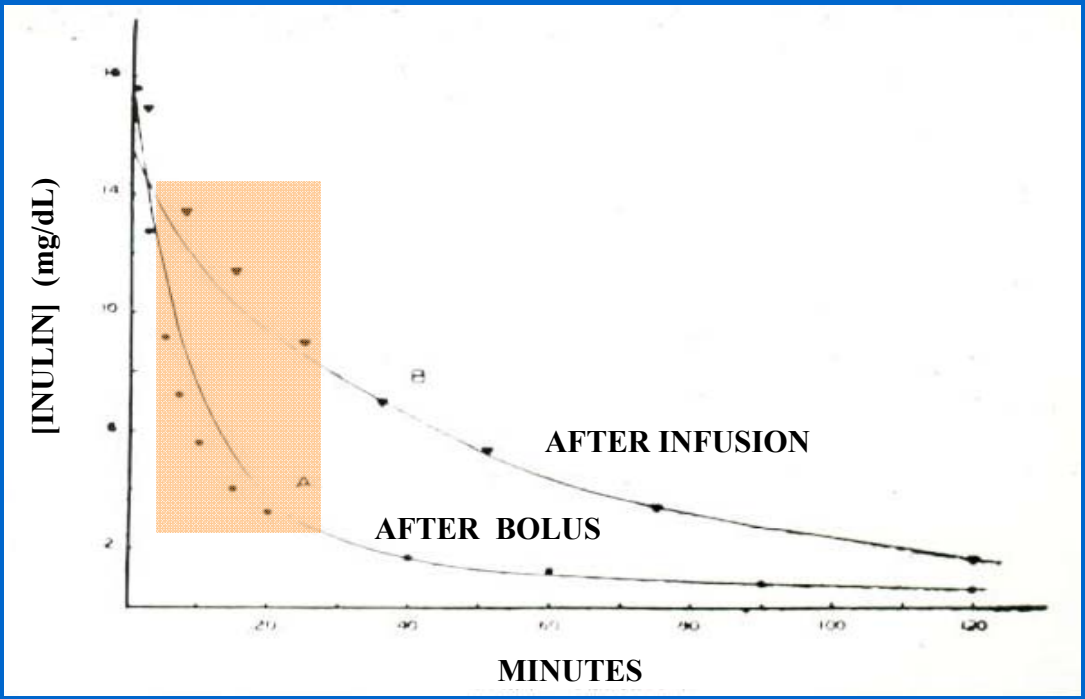
If Central Compartment Volume is Based on Plasma Concentration Measurements

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

RBC/P = red cell/plasma partition ratio

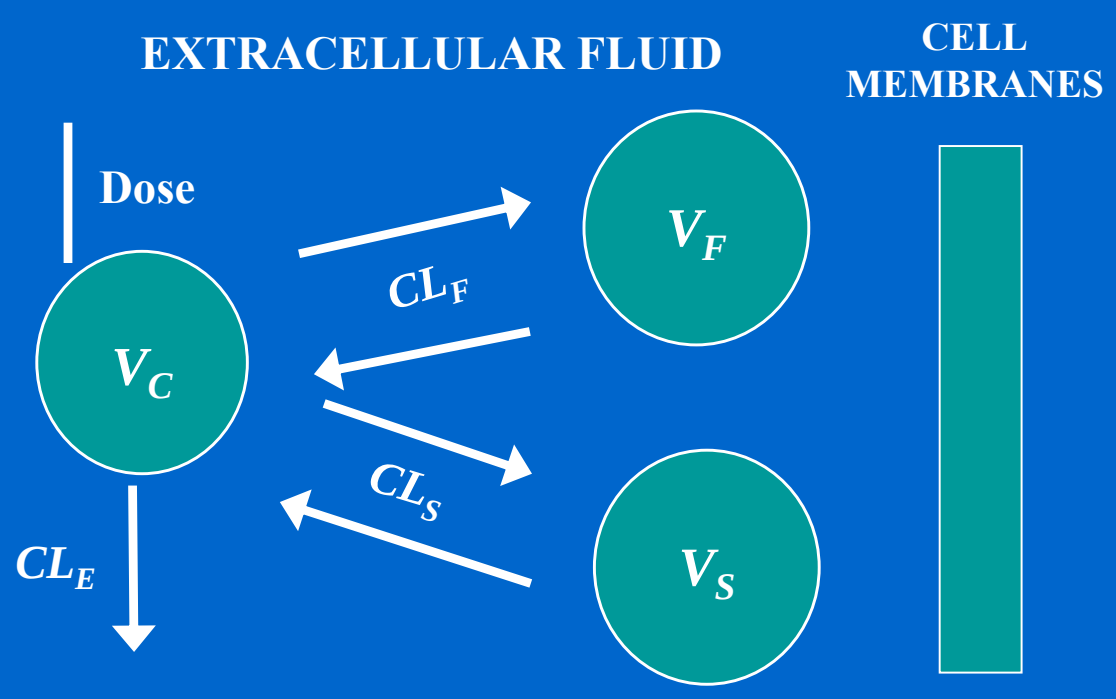
Hct = hematocrit

Analysis of Inulin Kinetics with a 2-Compartment Model*



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

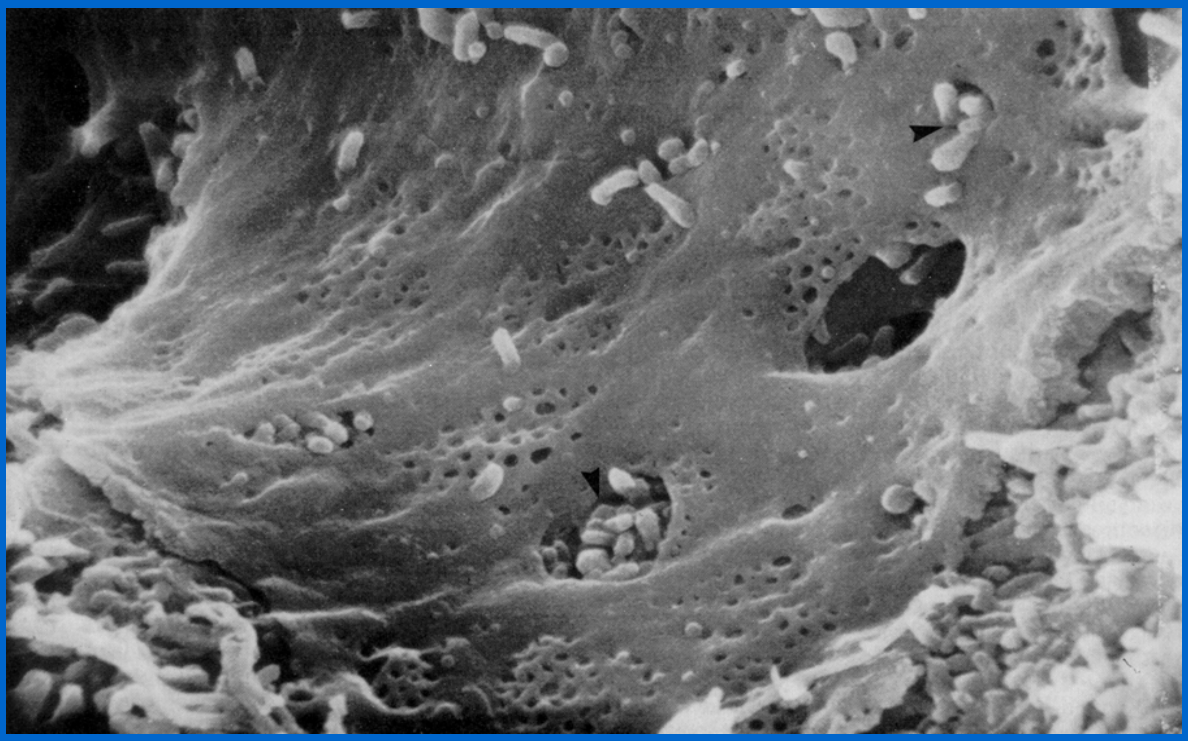
3-Compartment Model of Inulin Kinetics



Basis for Kinetic Heterogeneity of Interstitial Fluid Space

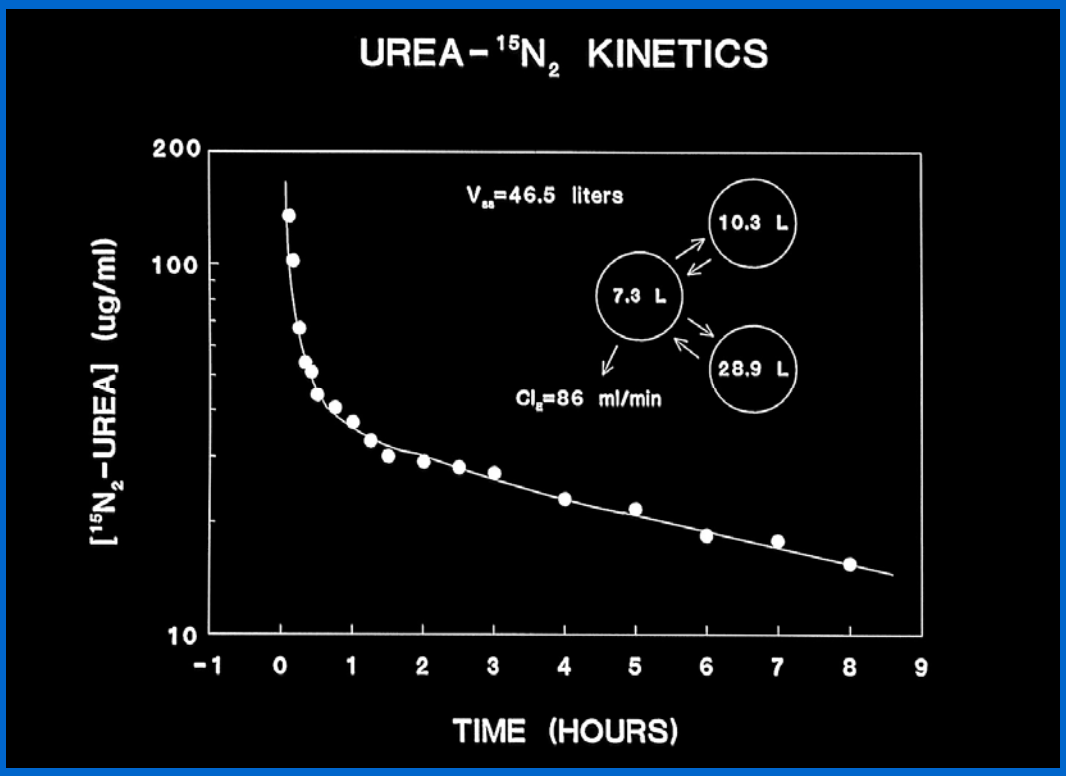
EFFECTIVE PORE SIZE	CAPILLARY STRUCTURE	PRIMARY LOCATION
LARGE	FENESTRATED	SPLANCHNIC BED
SMALL	CONTINUOUS	SOMATIC TISSUES

ENDOTHELIAL FENESTRAE IN HEPATIC SINUSOIDS

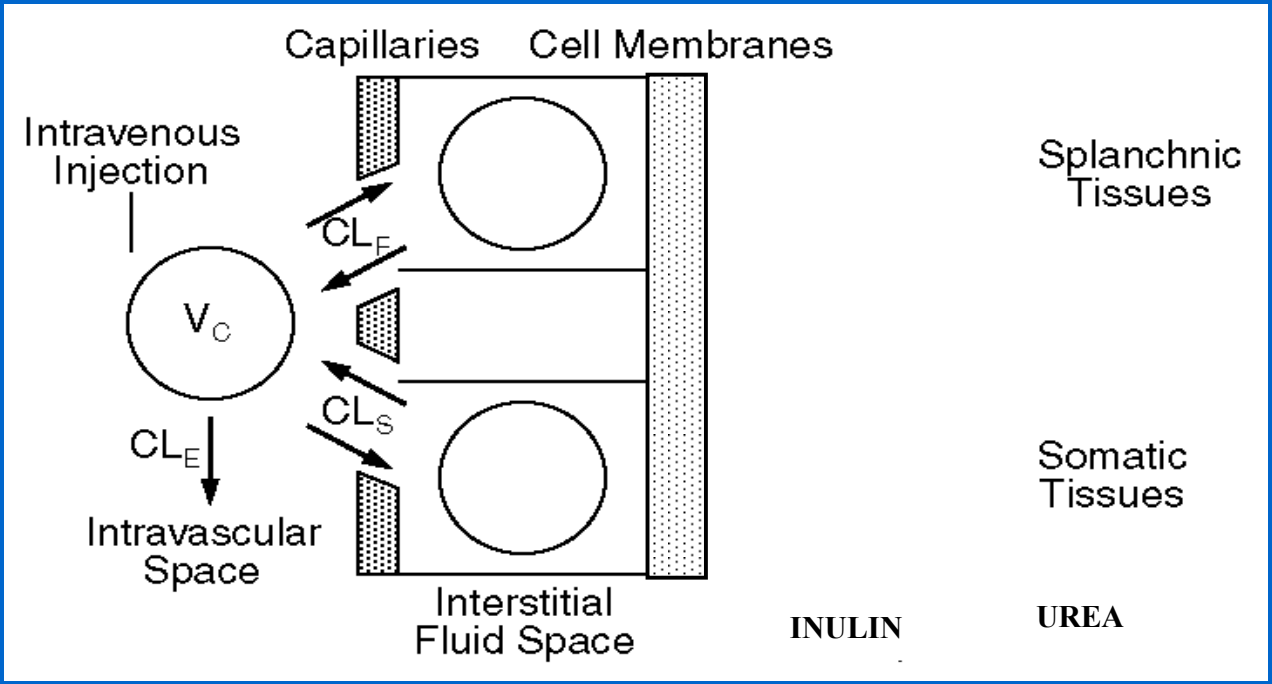


INTERENDOTHELIAL CELL JUNCTION IN CONTINUOUS CAPILLARY

UREA-$^{15}N_2$ KINETICS IN A NORMAL SUBJECT



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*

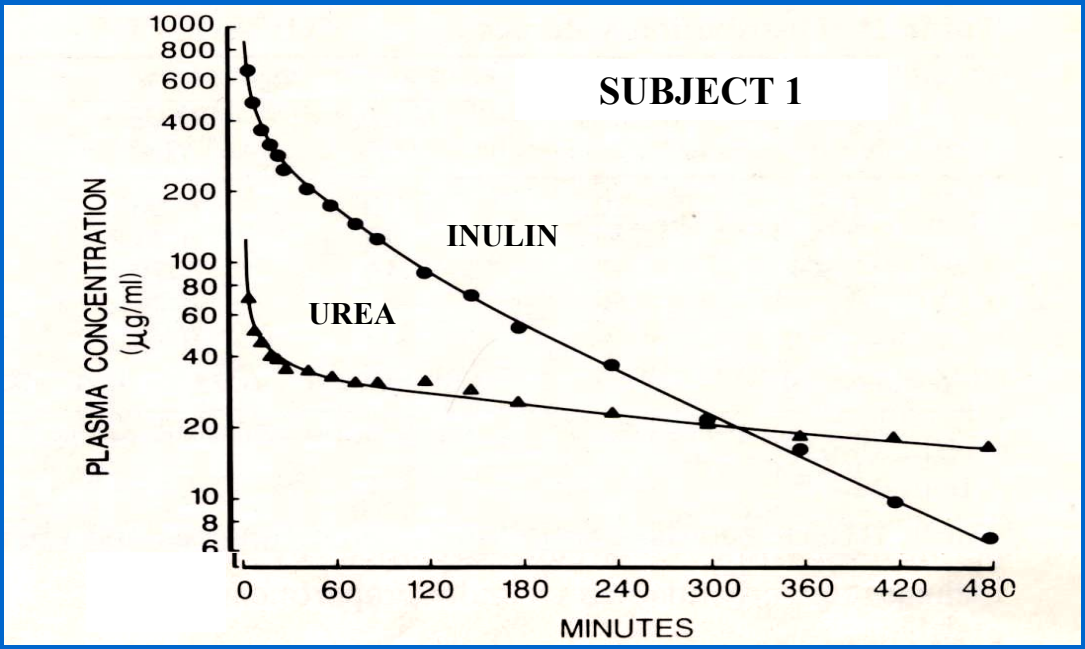
$$Cl = Q(1 - e^{-P/Q})$$

Q = capillary blood flow

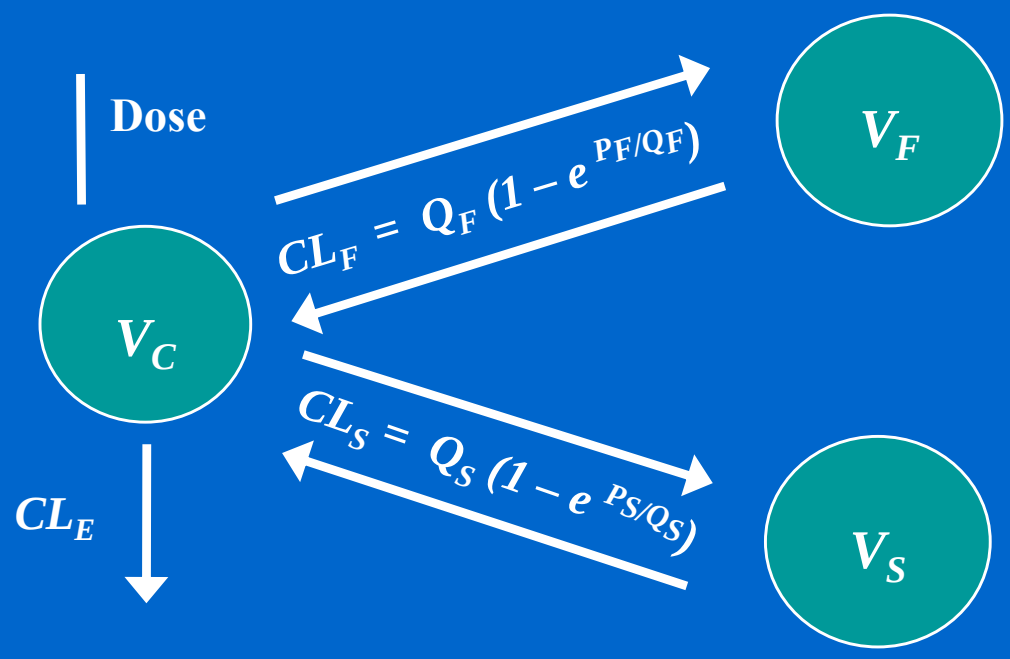
P = capillary permeability coefficient-surface area product (sometimes denoted P•S).

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

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-$^{15}N_2$ KINETICS



3-COMPARTMENT MODEL



For Each Peripheral Compartment

3 UNKNOWNS:

$$Q,\ P_U,\ P_I$$

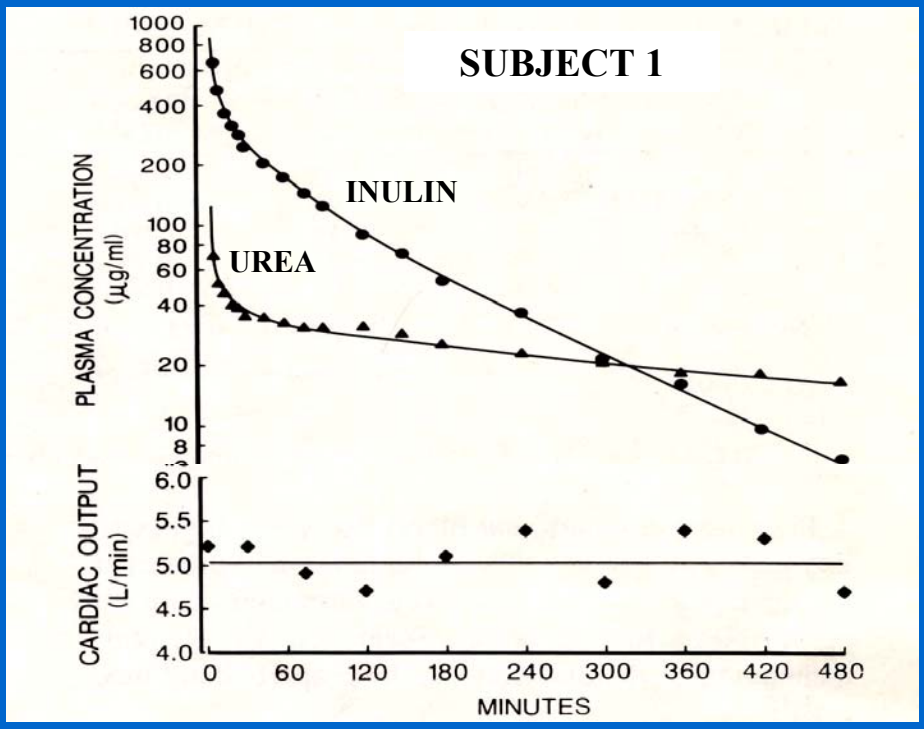
3 EQUATIONS:

$$P_U = Q \ln\left[Q/\left(Q - Cl_U\right)\right]$$
$$P_I = Q \ln\left[Q/\left(Q - Cl_I\right)\right]$$
$$P_U/P_I = D_U/D_I$$

U = urea; I = inulin

D = free water diffusion coefficient

SIMULTANEOUS ANALYSIS OF INULIN AND UREA-$^{15}N_2$ KINETICS



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

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.

TRANSCAPILLARY EXCHANGE
Mechanisms

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

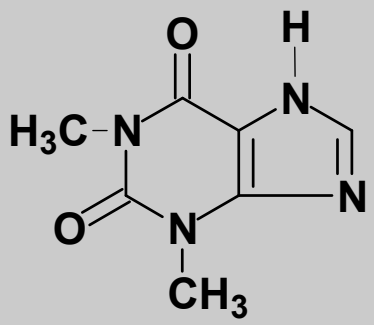
- **Transfer proportional to D**
  - Polar, uncharged (urea, inulin)
- **Transfer rate < predicted from D**
  - Highly charged (quaternary compounds)
  - Interact with pores (procainamide)
- **Transfer rate > predicted from D**
  - Lipid soluble compounds (anesthetic gases)
  - Facilitated diffusion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

Urea and Theophylline Diffusion Coefficients*

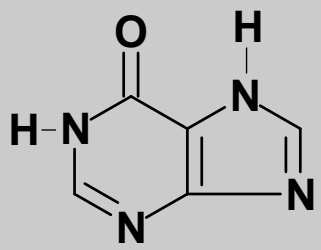
	MOLECULAR WEIGHT (DALTONS)	CORRECTED STOKES-EINSTEIN RADIUS (Å)	D_m @ 37° C (x 10^{-5} cm^2/sec)
UREA	60	2.2	1.836
THEOPHYLLINE	180	3.4	1.098

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

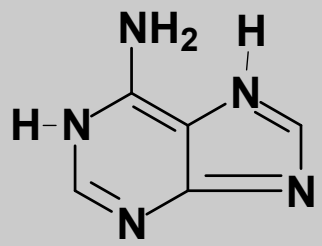
PRESUMED *CARRIER-MEDIATED* TRANSCAPILLARY EXCHANGE



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

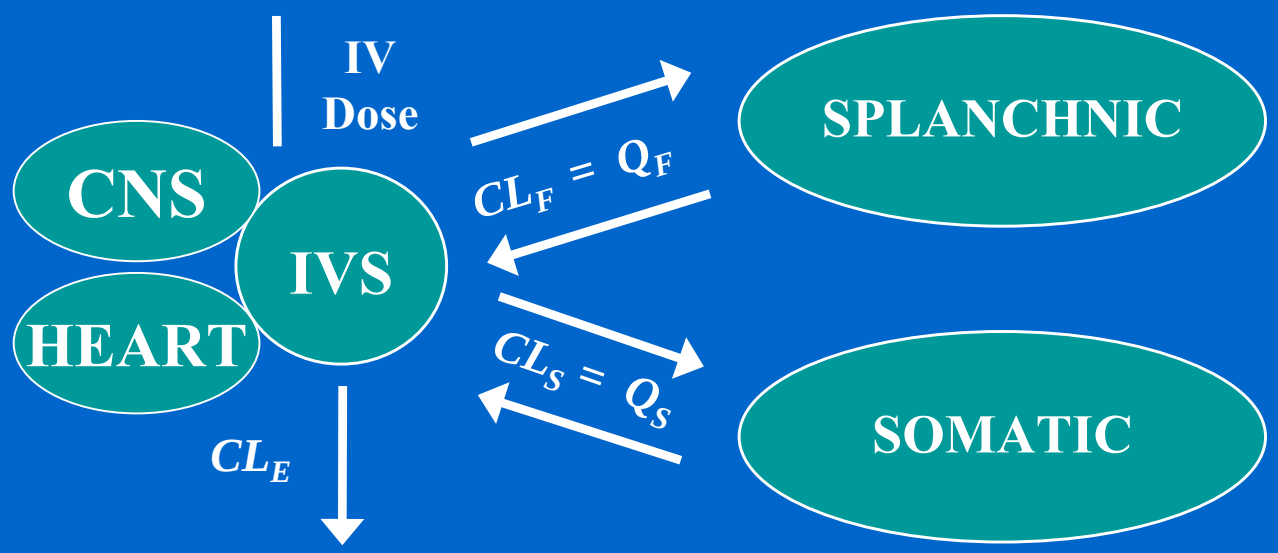
2. **Delays onset of drug action**

   Insulin, digoxin

3. **Terminates action after IV bolus dose**

   Thiopental, lidocaine

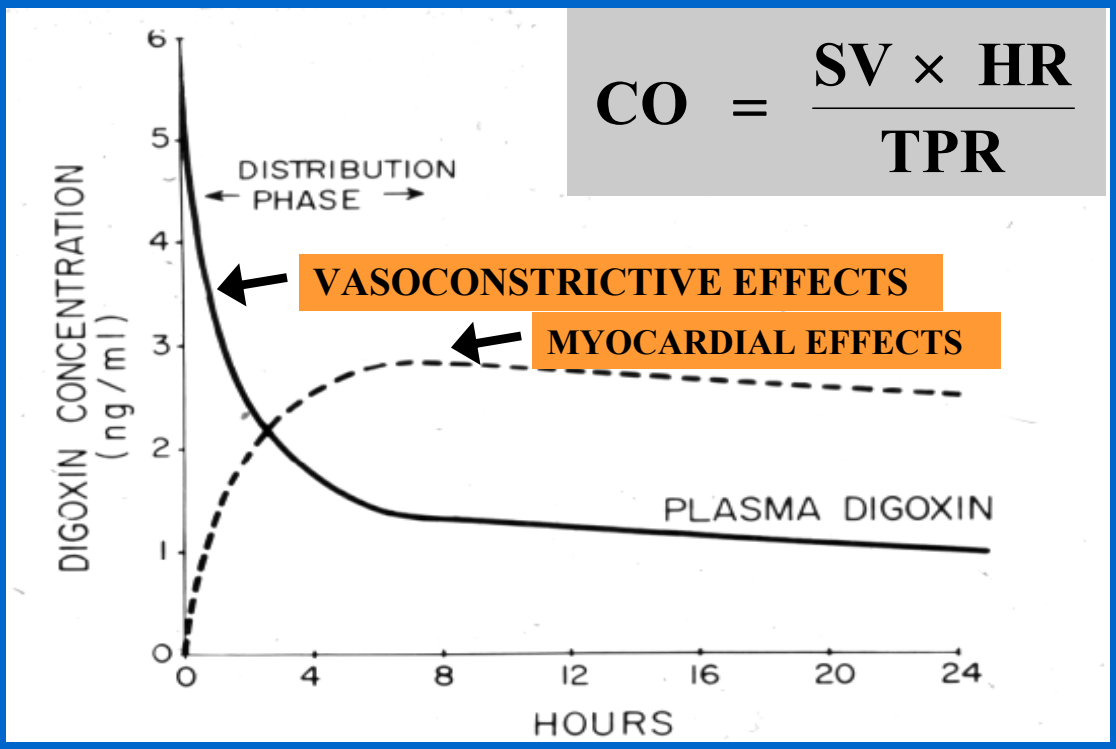
PK Model of THEOPHYLLINE Distribution



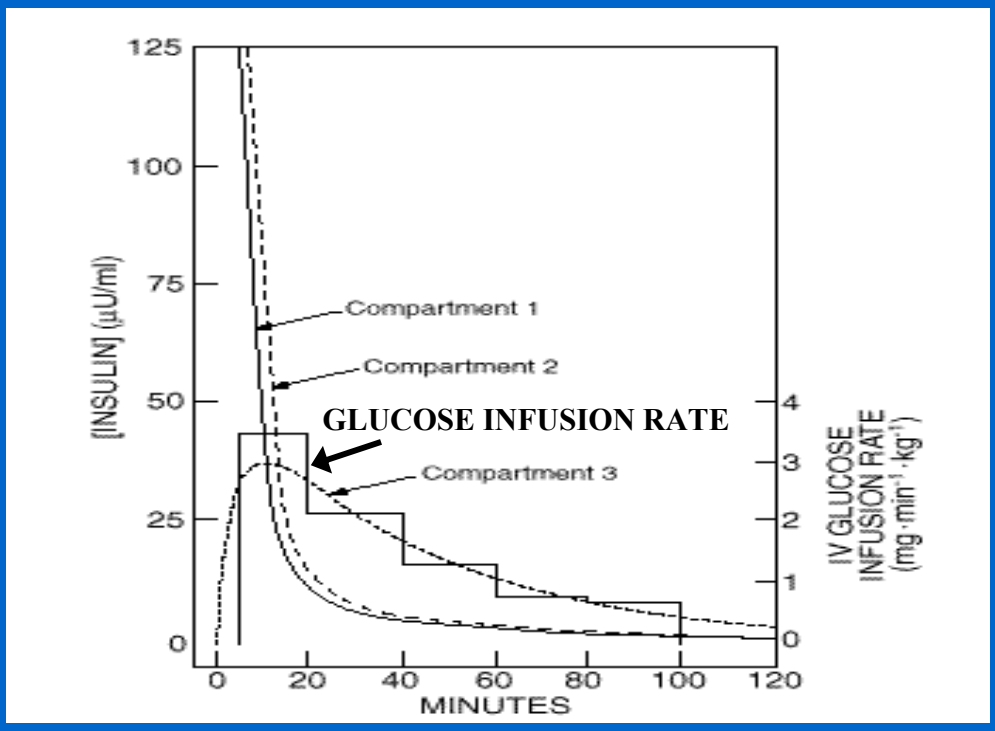
$$CO = Q_F + Q_S$$

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

$$CO = \frac{SV \times HR}{TPR}$$

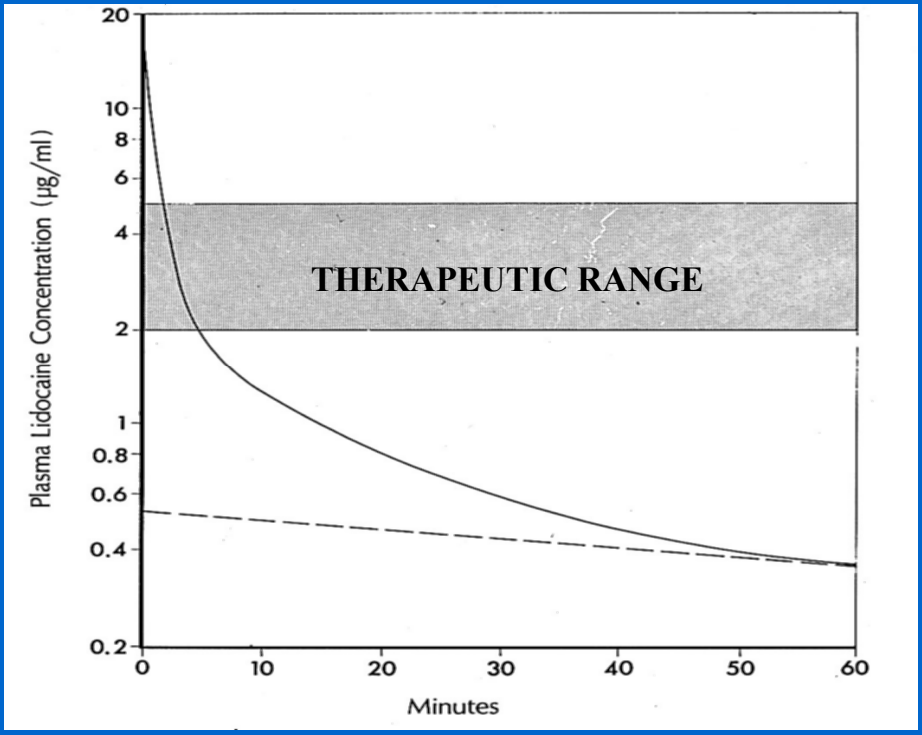


PK-PD Study of INSULIN Enhancement of Skeletal Muscle Glucose Uptake*



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

DISTRIBUTION TERMINATES EFFECT
BOLUS LIDOCAINE DOSE*

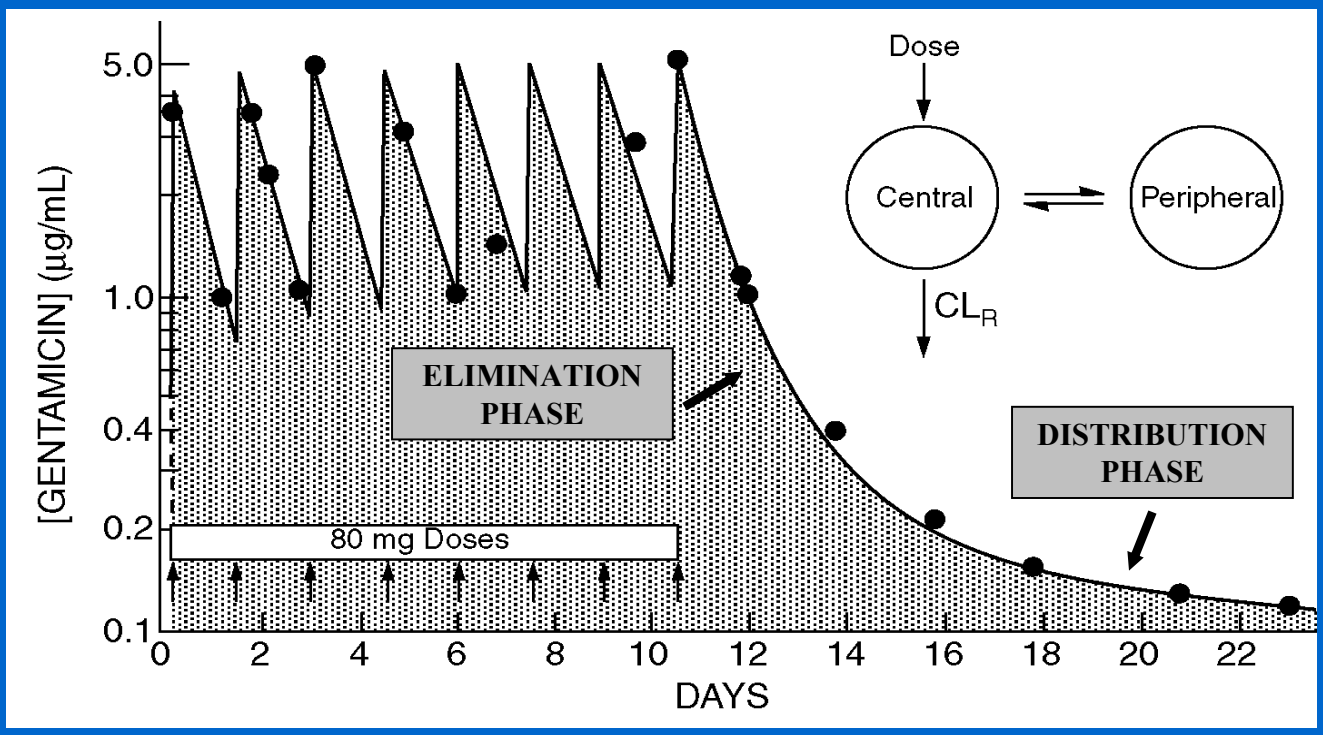


* From Atkinson AJ Jr. In: Melmon KL, ed. Drug Therapeutics: Concepts for Physicians, 1981:17-33.

CONSEQUENCES OF *VERY SLOW* DRUG DISTRIBUTION

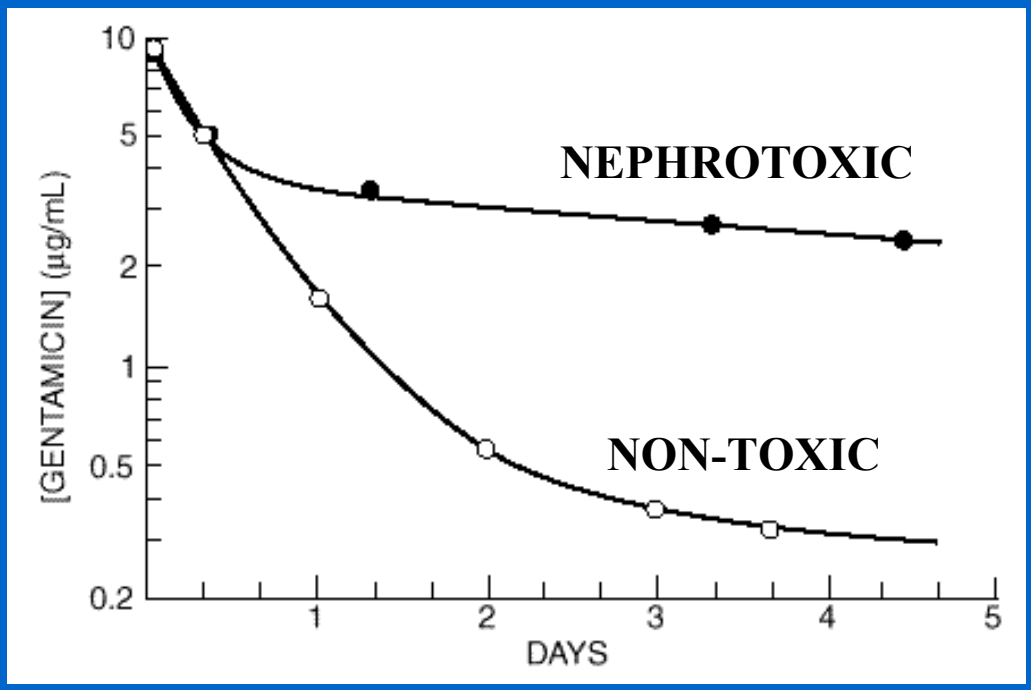
- "Flip-Flop" Kinetics
- Effective Half-Life
- Pseudo Dose Dependency

GENTAMICIN
Elimination Phase Preceeds 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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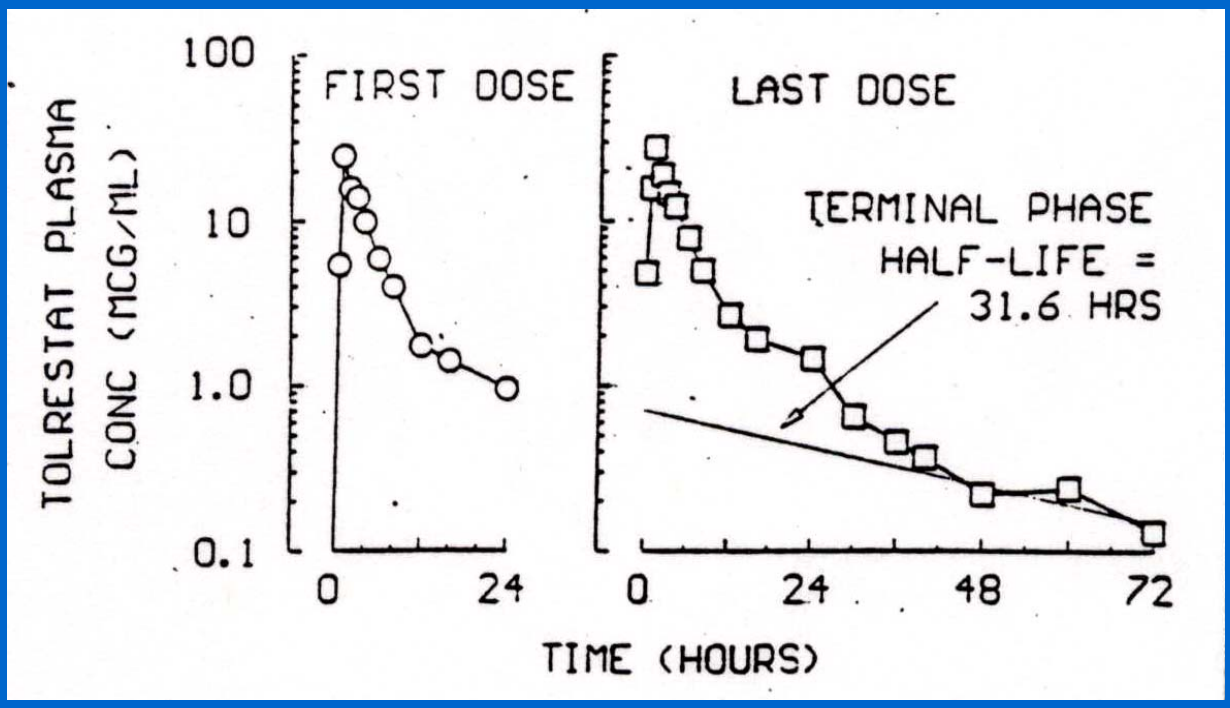
- Effective Half-Life
- Pseudo Dose Dependency

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*

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

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

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

EFFECTIVE HALF-LIFE OF TOLRESTAT*

Since τ = 12 hr and Observed CF = 1.29:

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

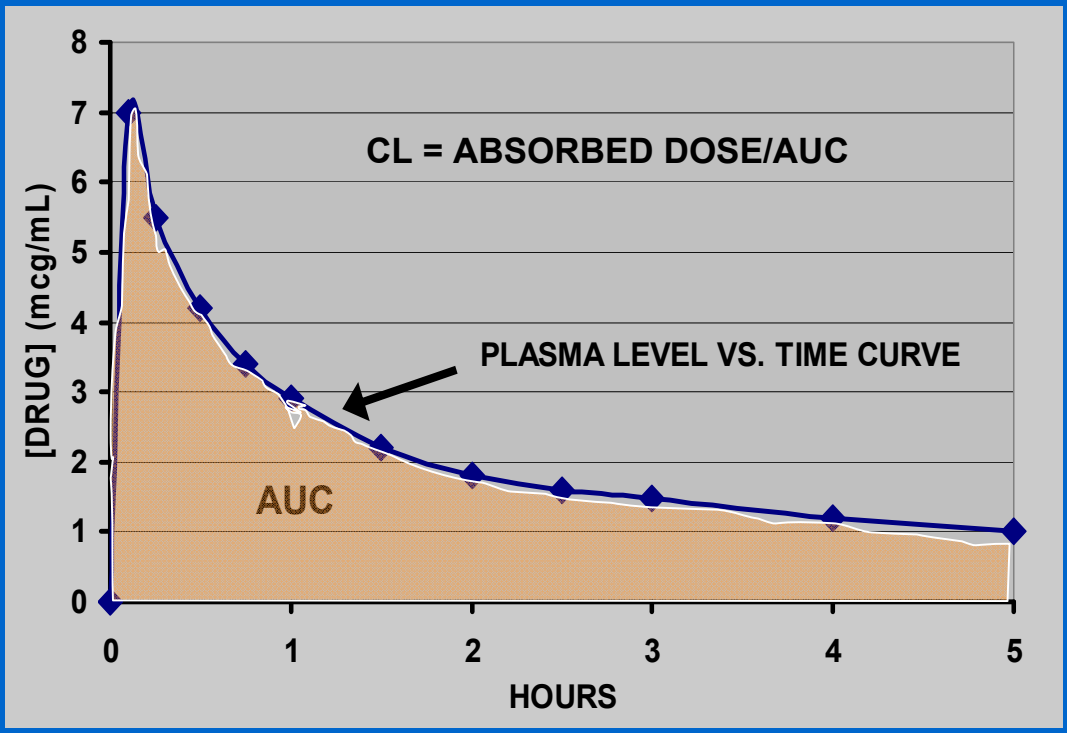
$$t_{1/2eff} = \frac{\ln 2}{0.124} = 5.6\ hr$$

* 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

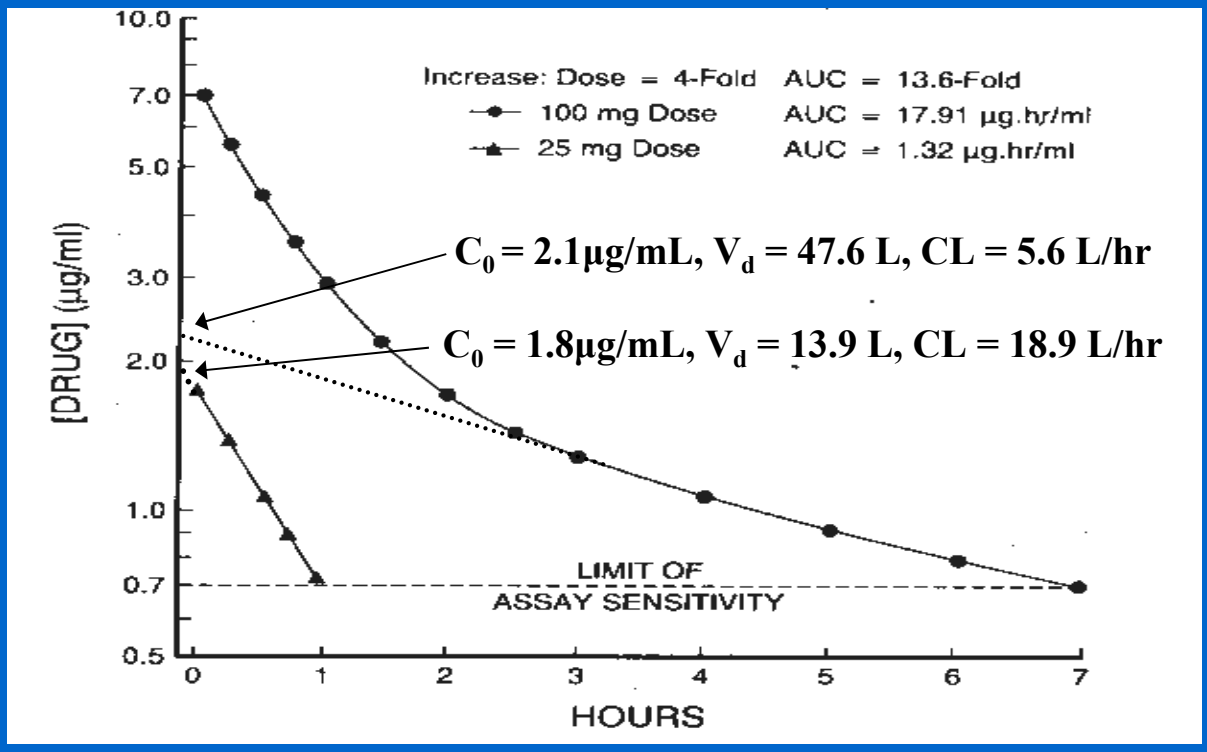
AREA UNDER THE CURVE
Measure of Dose Proportionality



HYPOTHETICAL
Phase I Trial Results

	DOSE 1	DOSE 2	INCREASE
DOSE (mg)	25	100	4 x ↑
AUC (µg·hr/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 T1/2 but also for the model independent parameters."

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