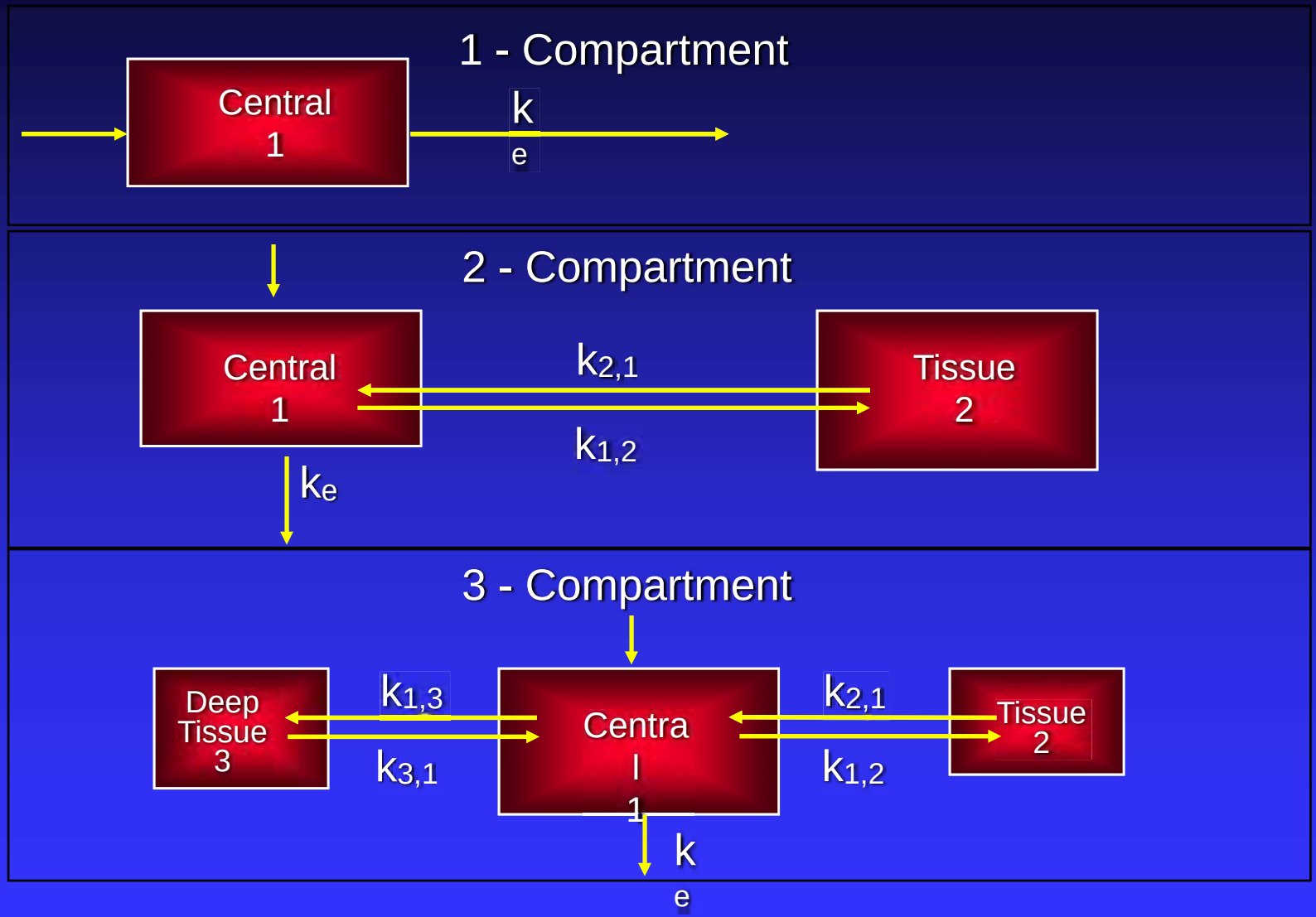
An Introduction to Pharmacokinetics

OBJECTIVES

- Provide definitions
- Examine exponential processes and therapeutic windows
- Describe the absorption process and factors that affect it
- Examine factors affecting drug distribution
- Describe volume of distribution
- Examine routes of elimination
- Describe factors affecting renal and biliary elimination
- Describe some ‘minor’ routes of elimination
- Describe clearance and half-life

Mammillary Compartmental Models



Definitions

Pharmacodynamics:

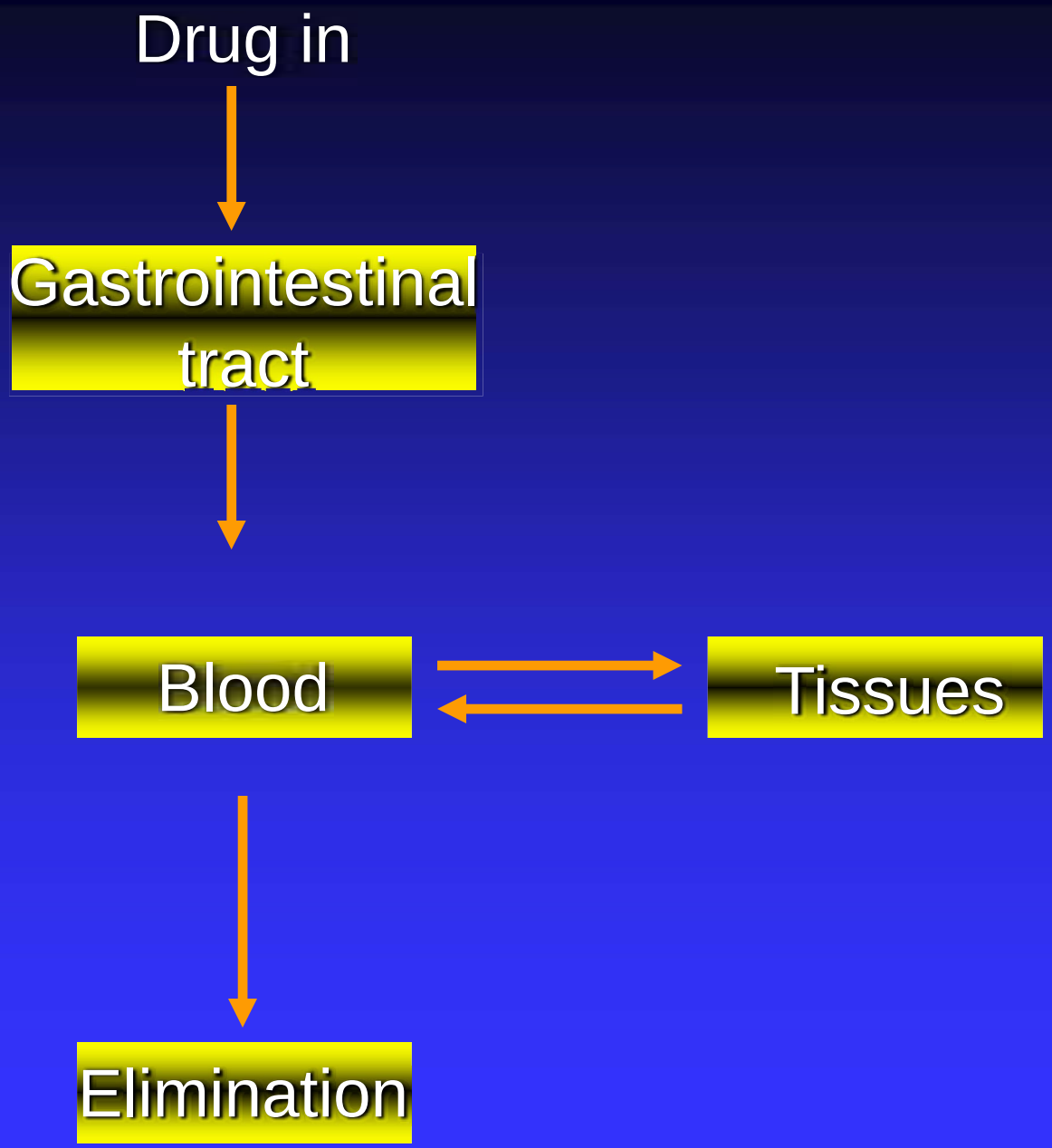
- Study of the pharmacological response to a drug
- i.e. what the drug does to the body

Pharmacokinetics:

- Study of the the movement of drugs within the body (Encompasses absorption, distribution & elimination)
- i.e. what the body does to the drug

Remember

For pharmacokinetic analysis the drug measurements need to be specific


Drug in
Gastrointestinal tract
Blood
Tissues
Elimination

Definitions

Absorption:

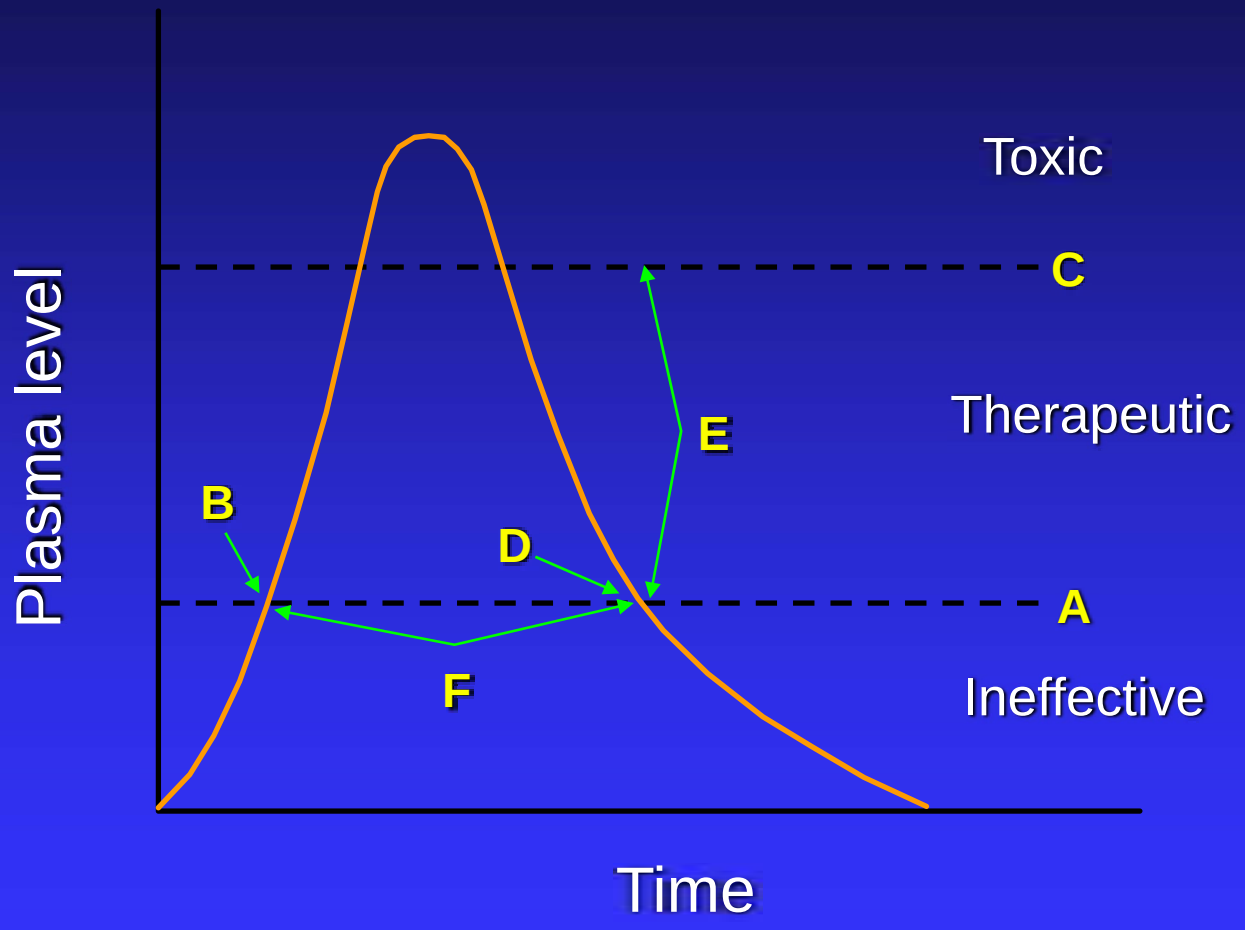
- Process by which a drug moves from the site of administration into the site of measurement

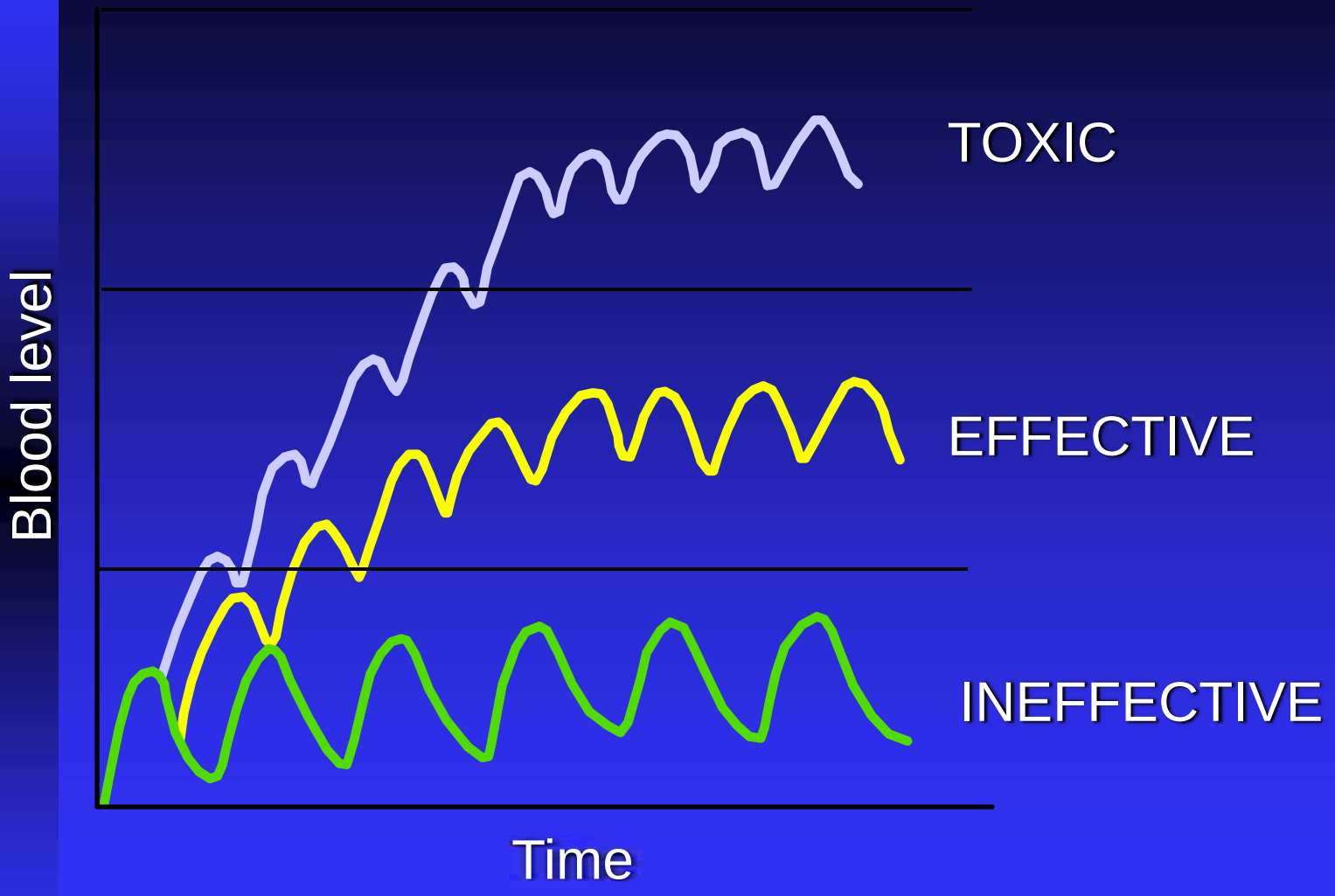
Distribution:

- Reversible transfer of a drug to and from the site of measurment
  - blood
  - plasma

Elimination:

- Irreversible transfer of a drug from the site of measurement
- Includes
  - Metabolic loss
  - Renal excretion
  - Biliary excretion (?) lungs
  - Sweat, milk, etc.


Plasma level
Toxic
C
Therapeutic
E
B
D
A
F
Ineffective
Time


TOXIC
EFFECTIVE
INEFFECTIVE
Blood level
Time

Absorption

The process by which a drug moves from the site of administration to the site of measurement

Some sites of Administration

Buccal cavity
Gastro- intestinal tract } Oral
Eyes
Skin
Nose
Lungs
Muscle
Rectum
Vagina

In virtually all cases a drug must be in aqueous solution before it can be absorbed

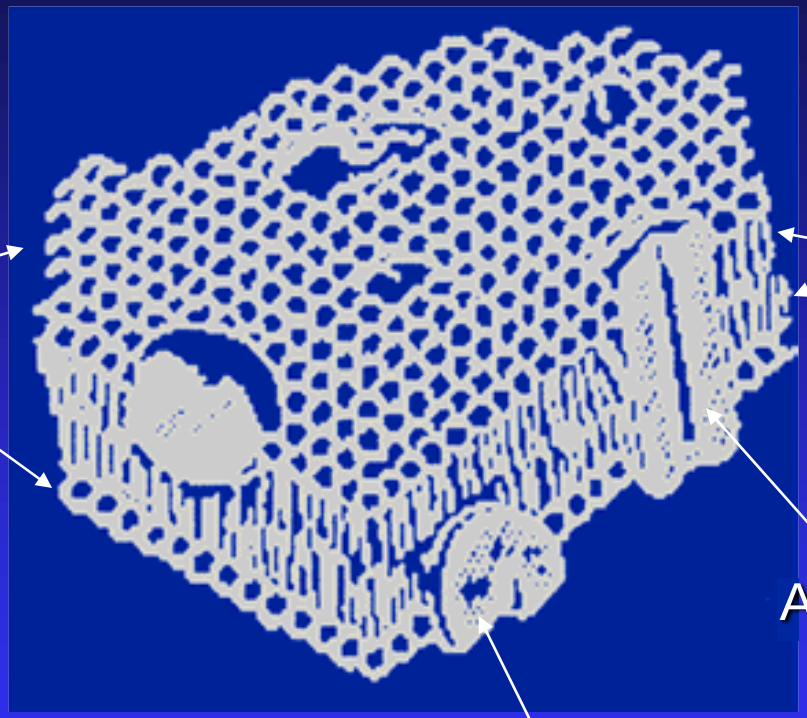
Drug Transport

1) Passive Diffusion
2) Facilitative Diffusion
3) Active Transport

Passive Diffusion

- Moves from an area of high concentration to an area of low concentration
- Non - specific
- No competition
- No saturation
- No energy requirements
- Function also of surface area of absorption layer, diffusion coefficient ($\propto \sqrt{}$mol wt) and partition coefficient (lipophilicity and thickness of membrane)

A diagram of a cell membrane



Drugs with ionisable groups can exist in ionised and unionised forms

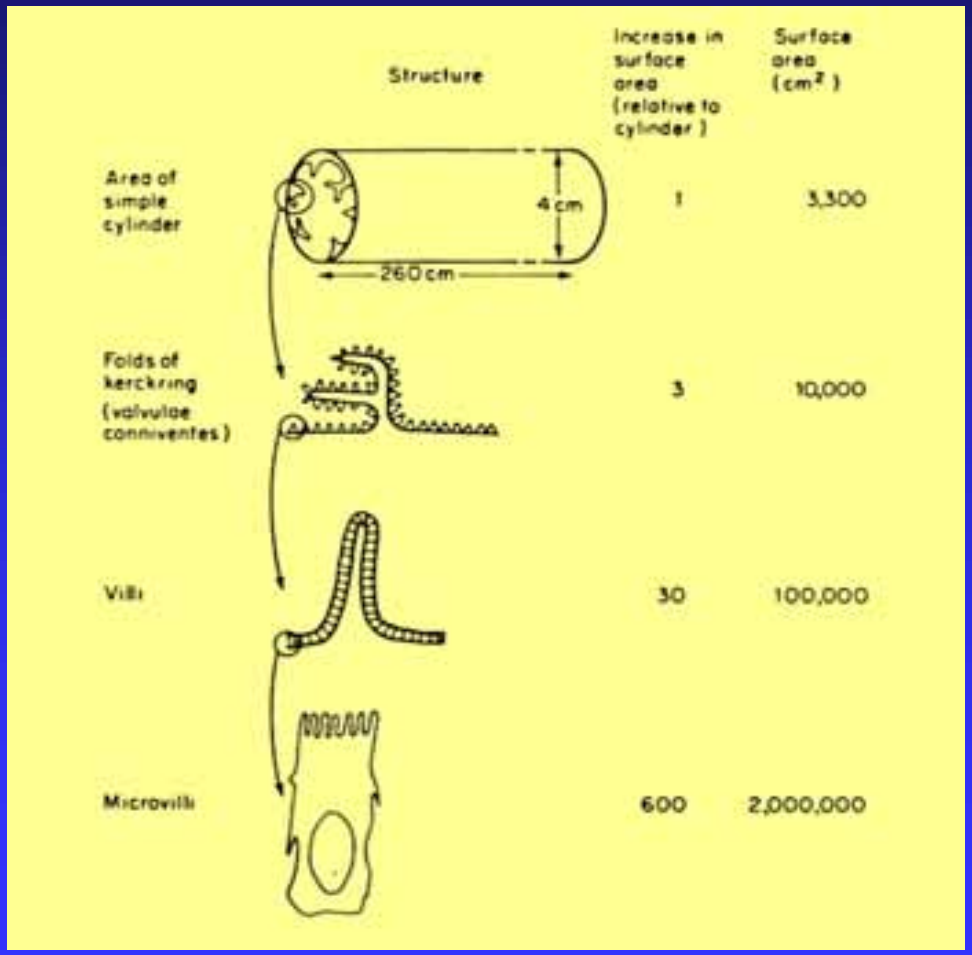
	unionised		ionised
For Acids	$[HA] + [H_2O]$	$\rightleftharpoons$	$[H_3O^+] + [A^-]$
For Bases	$[B] + [H_2O]$	$\rightleftharpoons$	$[OH^-] + [BH^+]$

PH – PARTITION HYPOTHESIS

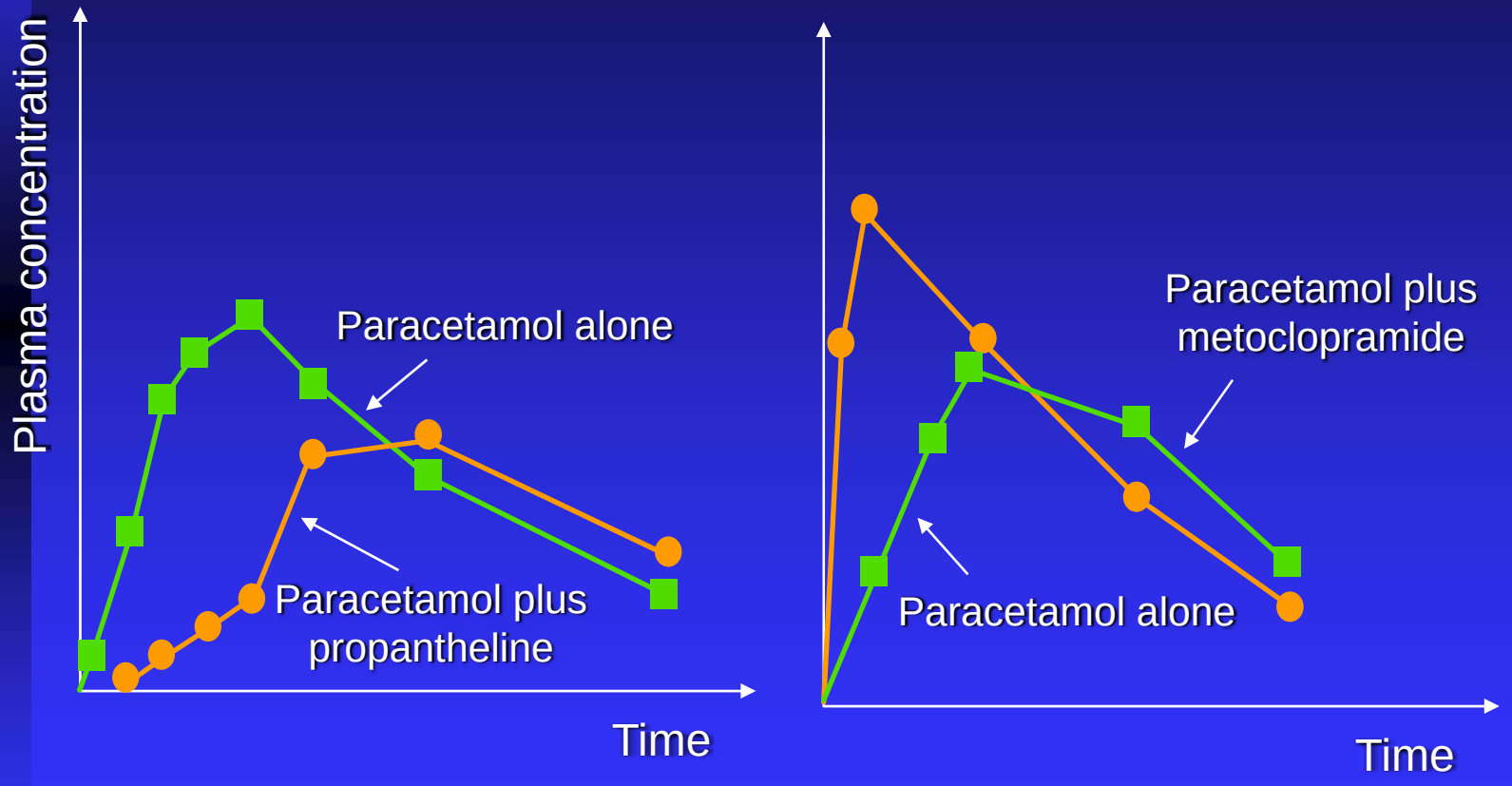
	pH Fluid	Volume of (litre/day)
Mouth	6.2 – 7.4	3 – 5
Stomach	1 – 3	6
Duodenum	5.5 – 7	
Jejunum	6.5 – 7	10
Ileum	6 – 8	

Is an acidic drug best absorbed from the stomach?

OPTIMIZATION OF SURFACE AREA IN THE SMALL INTESTINE



Effect of drugs which decrease or increase gastric emptying on the absorption of paracetamol



- **Bioavailablity**
  - The rate and extent that intact drug (or active constituent if pro-drug) reaches the systemic circulation
- *Absolute Bioavailability*
  - When the total quantity of drug reaching the systemic circulation is measured- usually performed by reference to an intravenous dose when all the dose is administered into the systemic circulation
- *Relative Bioavailability*
  - When the bioavailabity of the test formulation is compared to that of another formulation which is NOT administered directly into the systemic circulation

CALCULATION OF BIOAVAILABILITY FOR PLASMA

Absolute Bioavailablity (F) =

$$\frac{AUC_{P.O.}}{AUC_{I.V.}} \times \frac{DOSE_{I.V.}}{DOSE_{P.O.}} \times 100\%$$

Relative Bioavailability =

$$\frac{AUC_{P.O.(TEST)}}{AUC_{P.O.(STAND)}} \times \frac{DOSE_{P.O.(STAND)}}{DOSE_{P.O.(TEST)}} \times 100\%$$

CALCULATION OF BIOAVAILABILITY FROM URINE

Absolute Bioavailablity =

$$\frac{U_{P.O.}}{U_{I.V.}} \times \frac{DOSE_{I.V.}}{DOSE_{P.O.}} \times 100\%$$

Relative Bioavailability =

$$\frac{U_{P.O.(TEST)}}{U_{P.O.(STAND)}} \times \frac{DOSE_{P.O.(STAND)}}{DOSE_{P.O.(TEST)}} \times 100\%$$

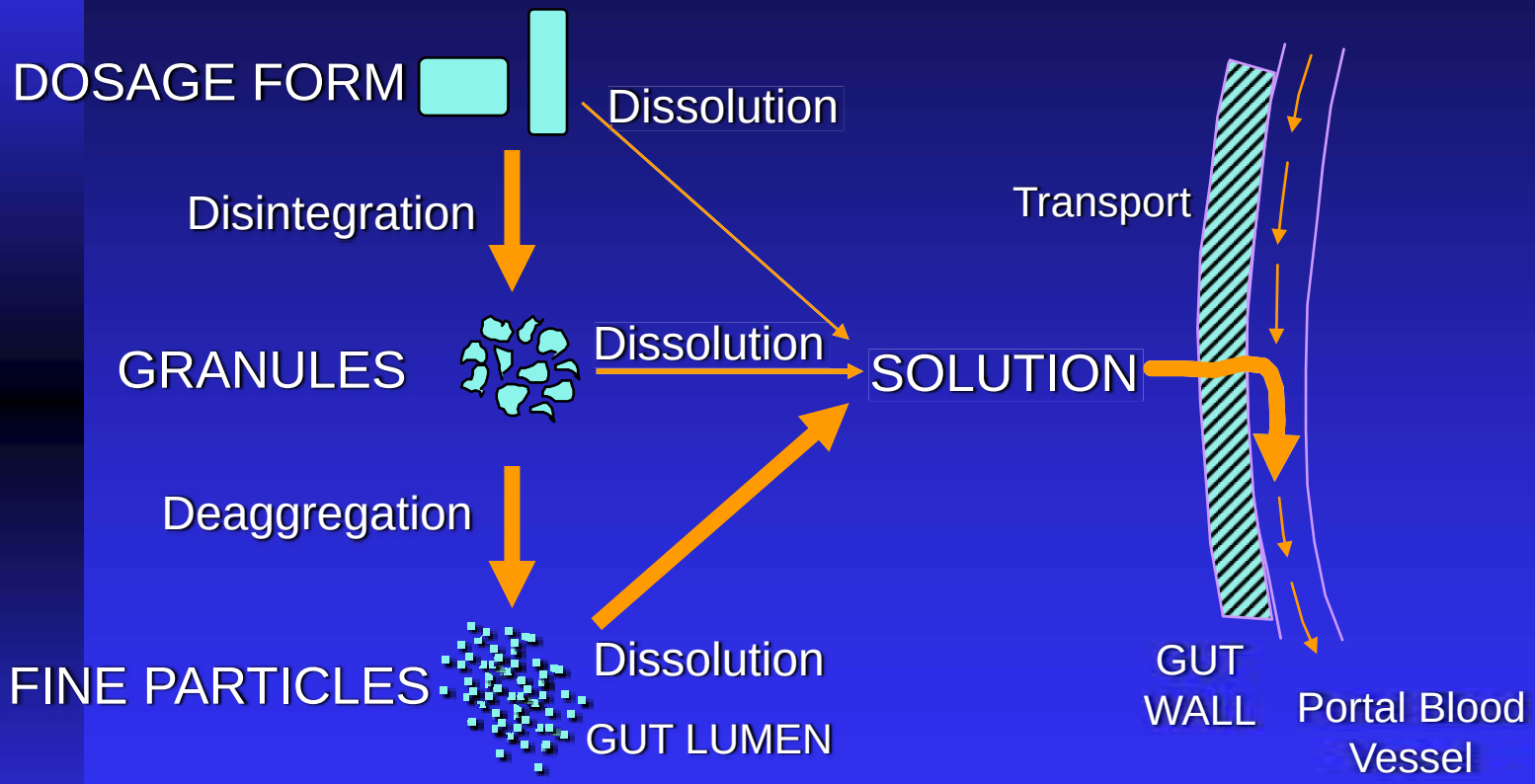
Reasons for incomplete bioavailability:

1. Instablity – Benzylpenecillin
2. Complexation – Tetracyclines and Ca^{++}
3. Gastrointestinal Transit – Insufficient time at absorptive surface
4. Microfloral metabolism
5. Gut wall metabolism
6. First pass hepatic metabolism

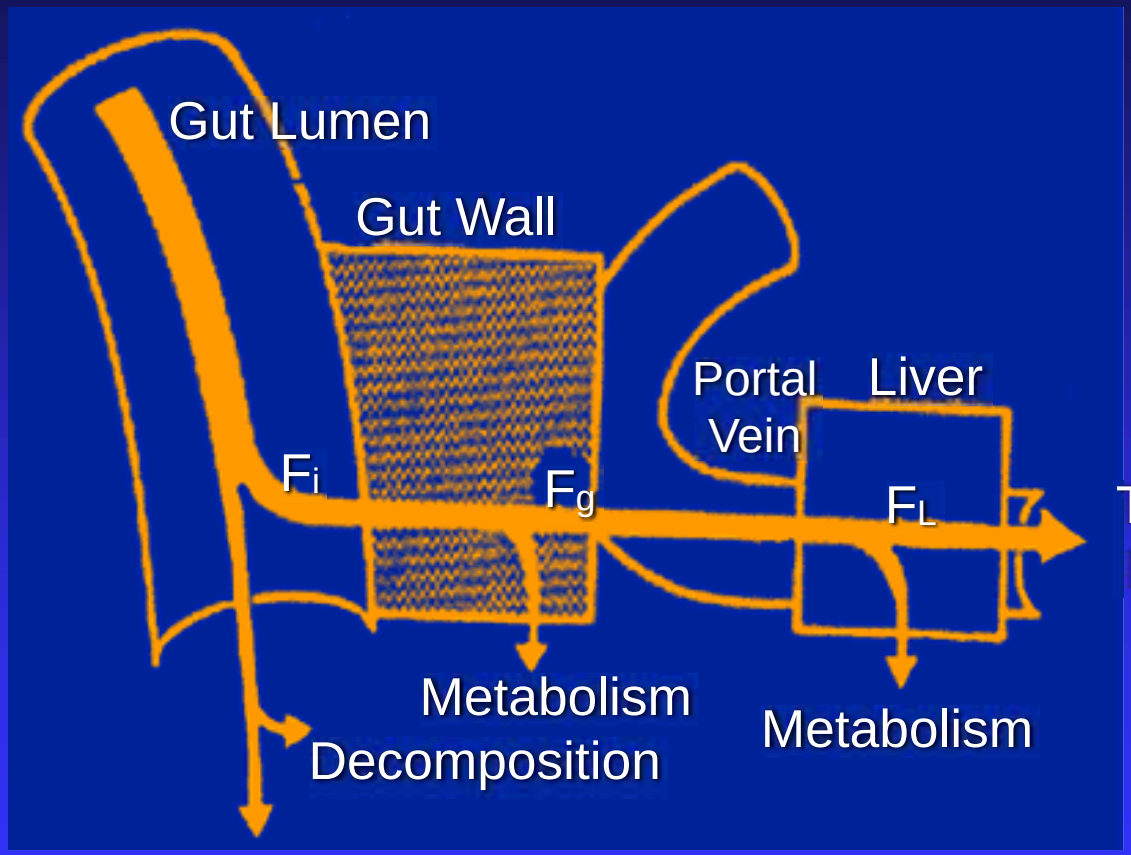
} First pass

7. Biopharmaceutical factors

Rate limiting factors in drug absorption

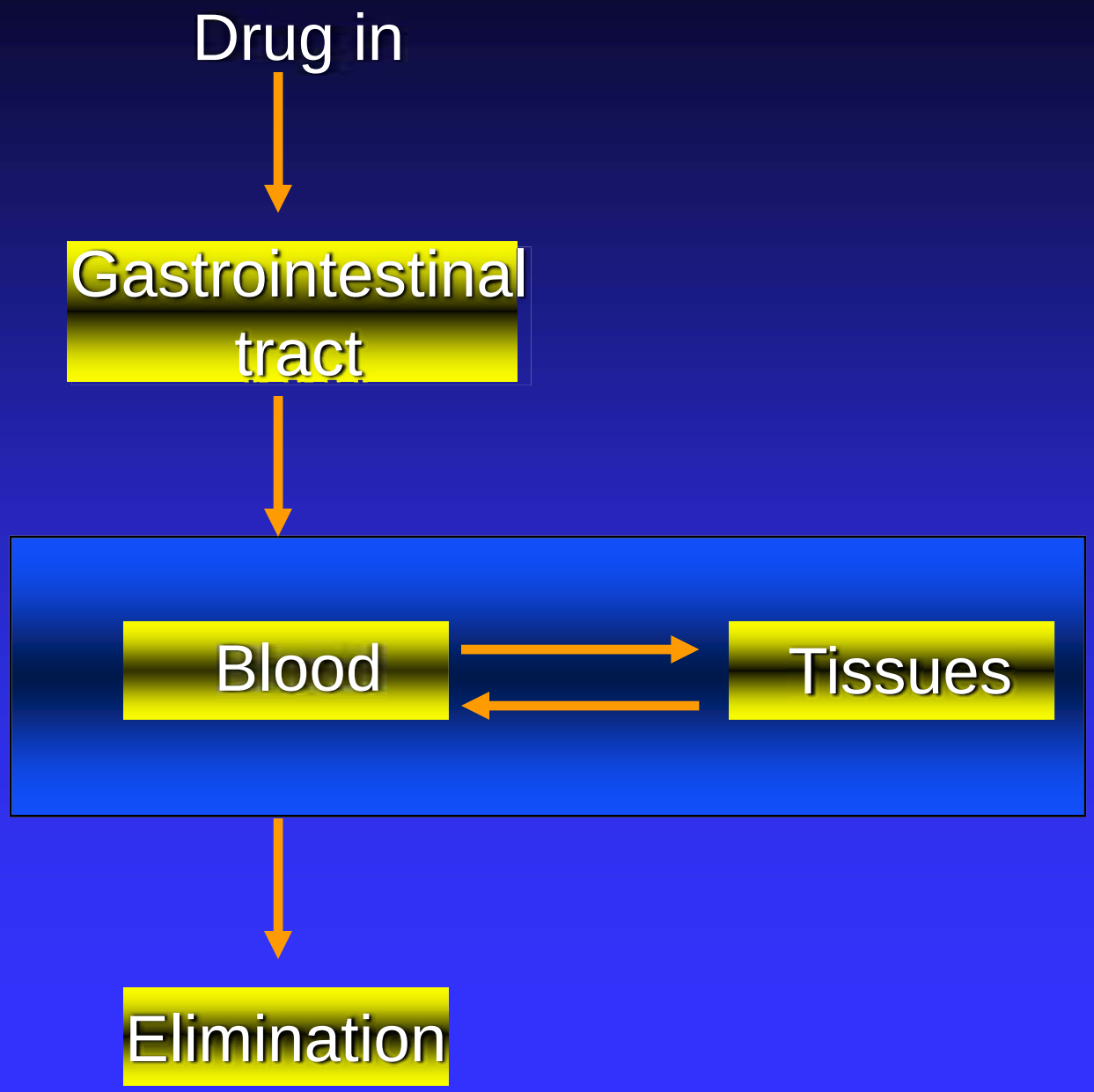


Areas of drug loss during absorption

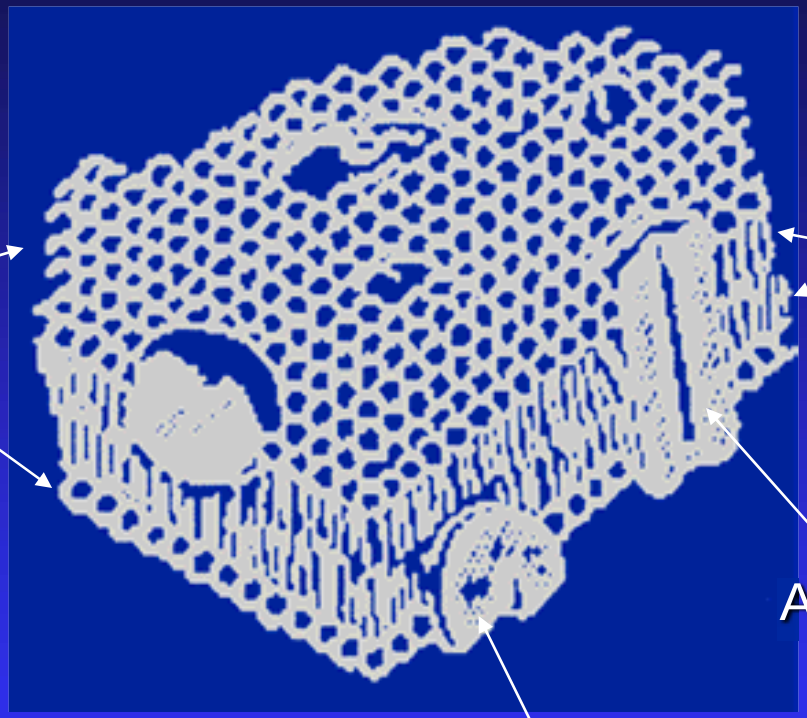


$$F = F_{INTESTINE} \times F_{GUT\ WALL} \times F_{LIVER}$$

DISTRIBUTION



A diagram of a cell membrane



DRUG PARTITION ACROSS A MEMBRANE CALCULATED FROM PH DIFFERENCES

For Acids

$$R = \frac{\text{Conc on side 1}}{\text{Conc on side 2}} = \frac{1 + 10^{pH1 - pKa}}{1 + 10^{pH2 - pKa}}$$

For Bases

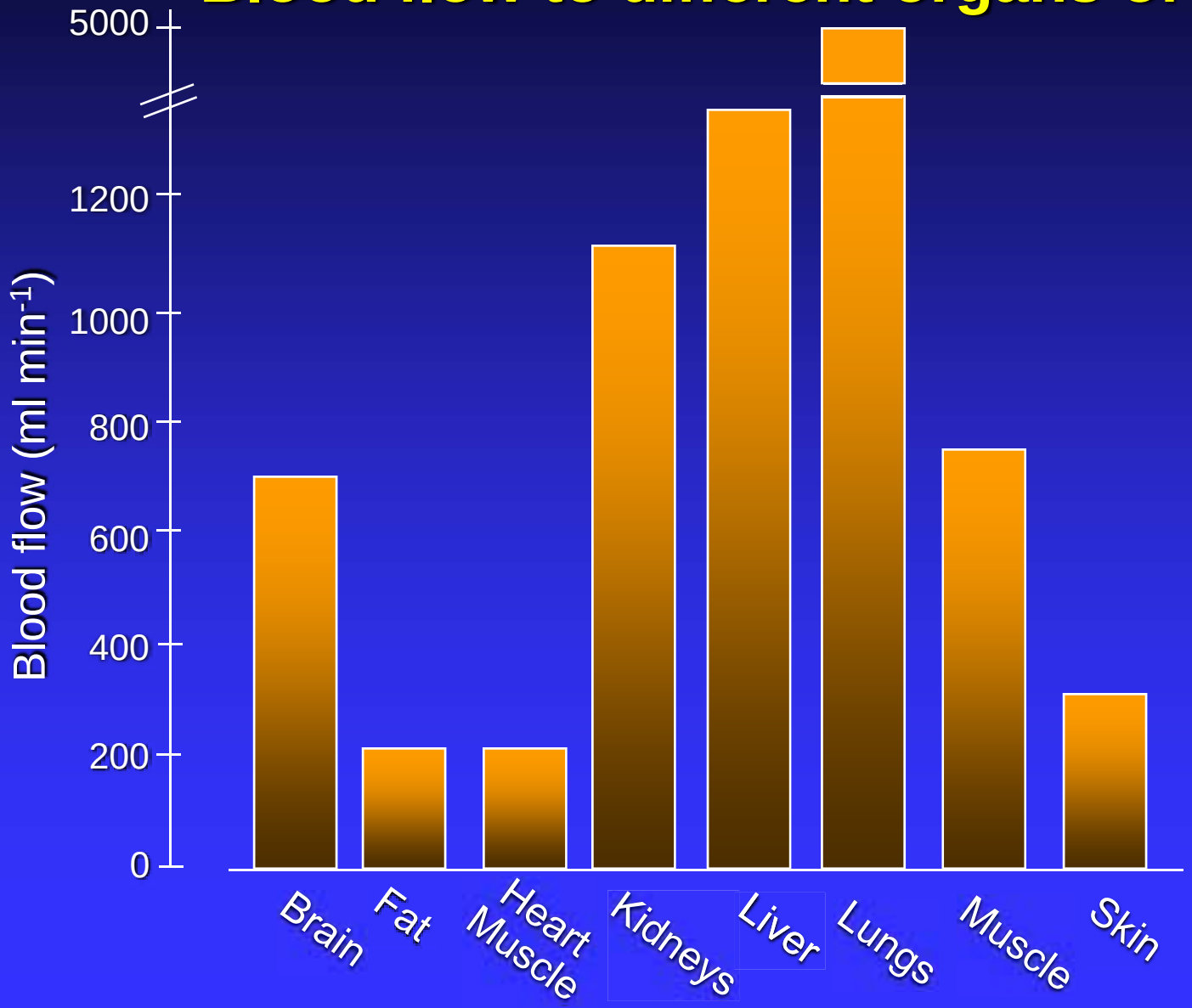
$$R = \frac{\text{Conc on side 1}}{\text{Conc on side 2}} = \frac{1 + 10^{pKa - pH1}}{1 + 10^{pKa - pH2}}$$

RMI Pharmacokinetics

Does physiological pH vary enough at different sites to influence drug distribution?

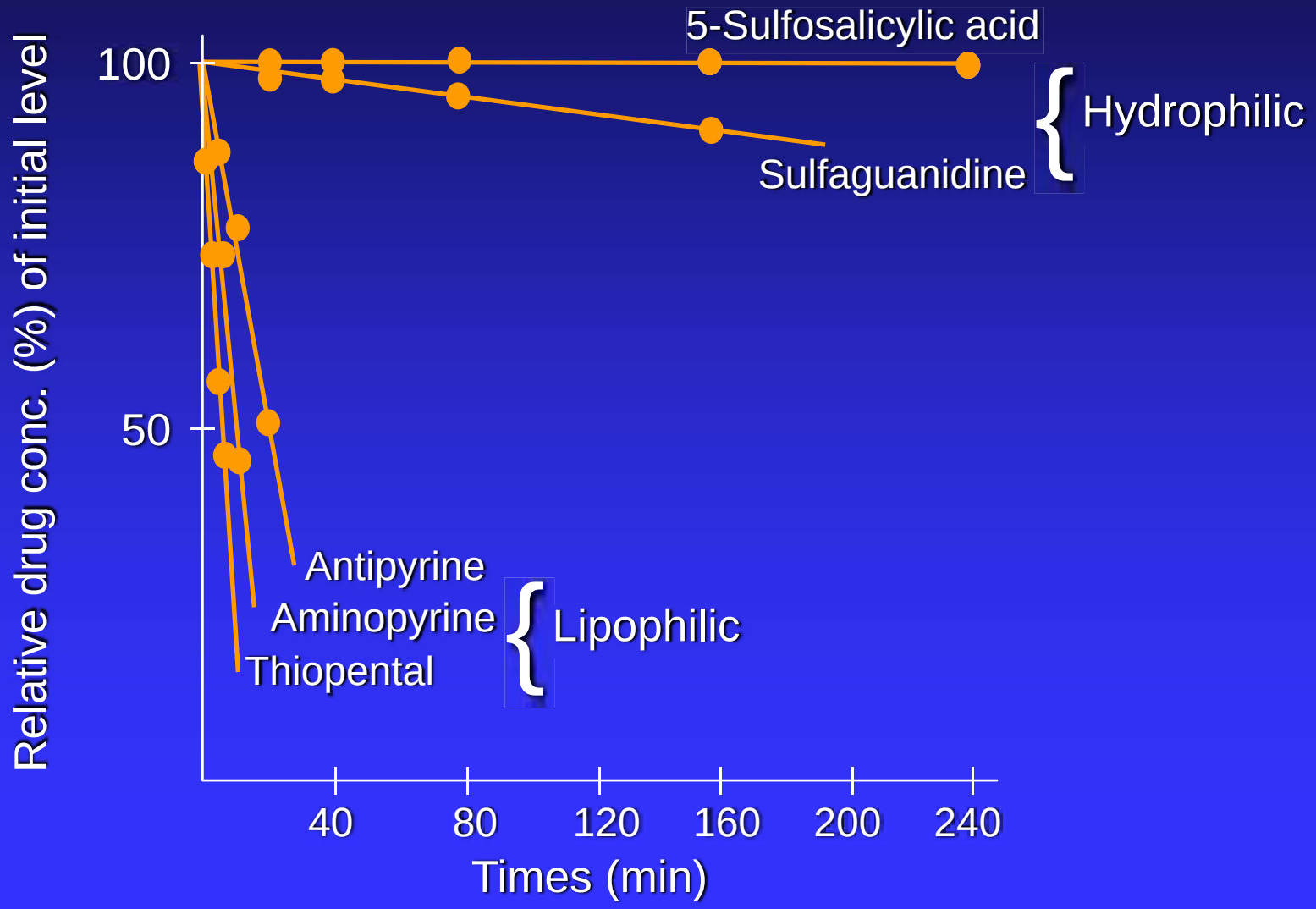
Perfusion rate limitation

Blood flow to different organs of man



Diffusion rate limitation

Relative efflux of different drugs from cerebrospinal fluid



Only unbound drug is available for distribution

Therefore

the ratio of binding to plasma and tissue protein is an important determinant in drug distribution

Types of protein to which compounds bind

Protein	Compound
Albumin	Acidic
α_1-acid glycoproteins	Basic
Globulins	Endogenous

Methods for the determination of plasma protein binding

Method	Rating
Equilibrium dialisis	Generally good
Ultracentrifugation	Generally good
Ultrafiltration	Reasonable
Gel filtration	Poor

Determination of drug distribution-

- Whole body autoradiography
  1. Dose radioactive compound to animals
  2. Kill animal at required time after dosing
  3. Immediately freeze carcass in hexane/solid CO_2
  4. Cut thin sections of animal (e.g. with cryomicrotome)
  5. Expose sections to X-ray film
- Quantitative tissue distribution studies
  1. Dose radioactive compound animals
  2. Kill animals at required time after dosing
  3. Dissect out all tissues of interest
  4. Count radioactivity in each tissue by liquid scintillation counting

Volume of distribution

The term that relates the amount of drug within the body at any one time to its concentration (normally the concentration is measured)

Type of volume term	Notation	Comment
Initial distribution volume	V_i	Measure of volume of the space that the drug equilibrates with instantaneously
Volume of distribution based on area	V	Volume of space that drug equilibrate with once distribution is complete
Steady-state vol. of distribution	V_{ss}	Volume of distribution at steady-state

$$V_i \text{ (litre)} = \frac{\text{Dose (mg)}}{C_o \text{ (mg/litre)}}$$

Initial distribution volume

$$V = \frac{\text{Dose}}{AUC_{\lambda z}}$$

Were λ_Z is the terminal exponential constant

FOR BOLUS IV

$$V_{ss} = \text{Dose} \bullet \frac{(AUMC)}{(AUC)^2}$$

$$= \text{Dose} \bullet \frac{\sum_{i=1}^{n} C_i / (\lambda_i)^2}{\left(\sum_{i=1}^{n} C_i / \lambda_i \right)^2}$$

$$V_D = V_P + V_T \frac{f_u}{f_{uT}}$$

Where

V_D = Volume of distribution

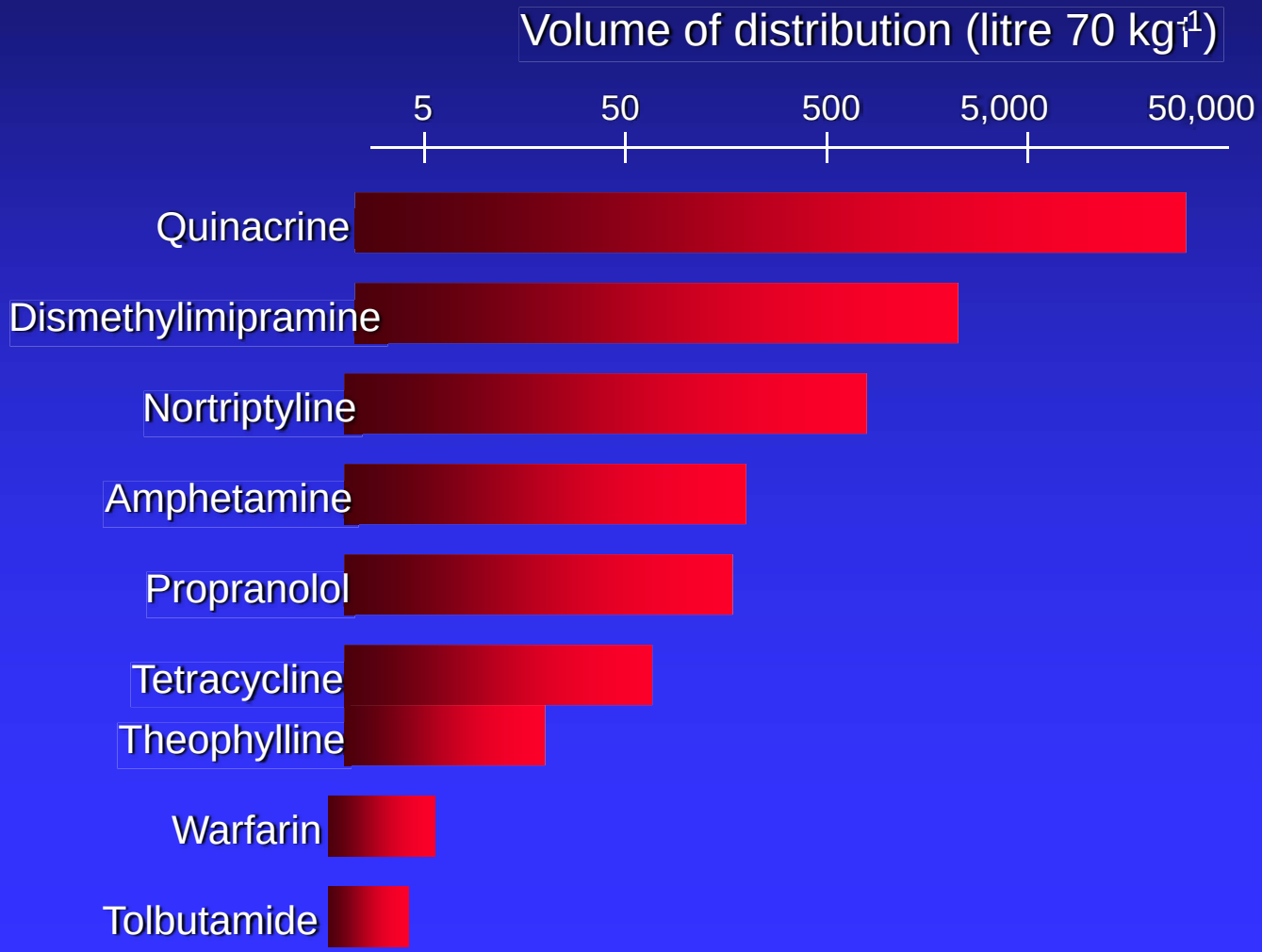
V_P = Physical volume of plasma (3 litres for man)

V_T = Physical volume of tissue

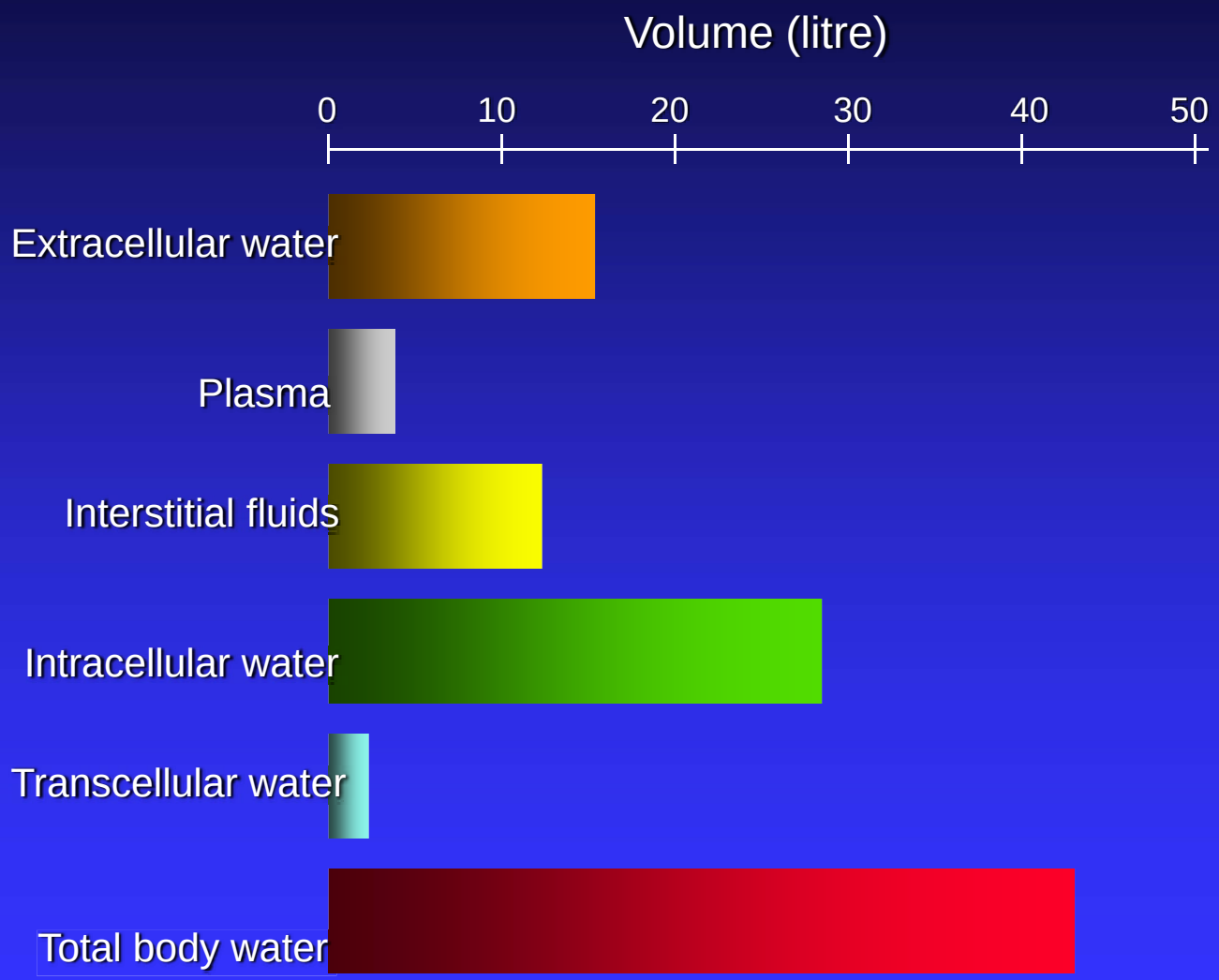
f_u = Fraction of unbound drug in plasma

f_{uT} = Fraction of unbound drug in tissue

The variation of volume of distribution, plotted on logarithmic scale, between different drugs in man



Volume of body fluids in man



Elimination

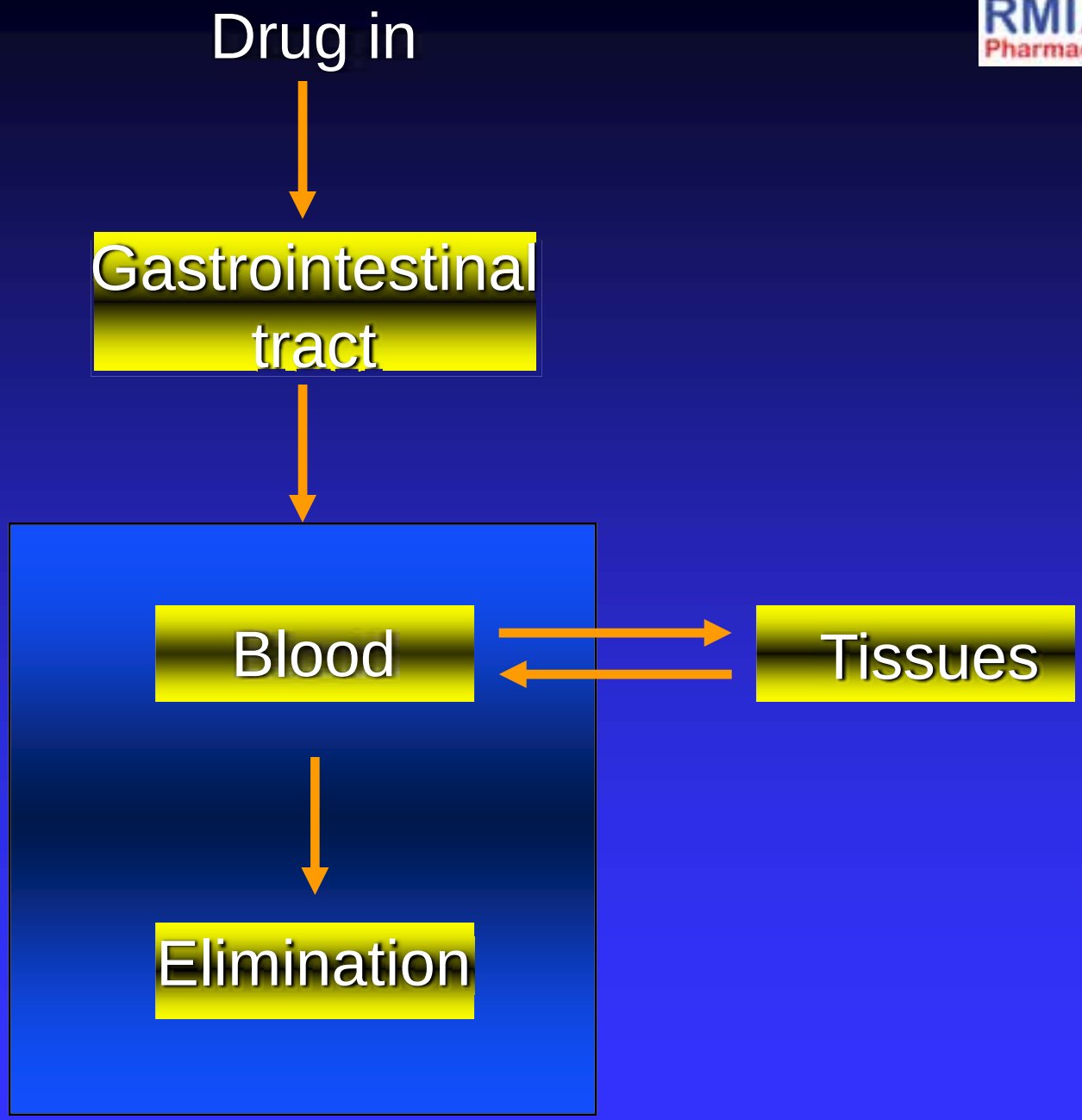
The irreversible transfer of a drug from the site of measurement.

It includes:

- Metabolism
- Renal excretion
- Biliary excretion
- Lungs
- Sweat
- Milk
- etc.

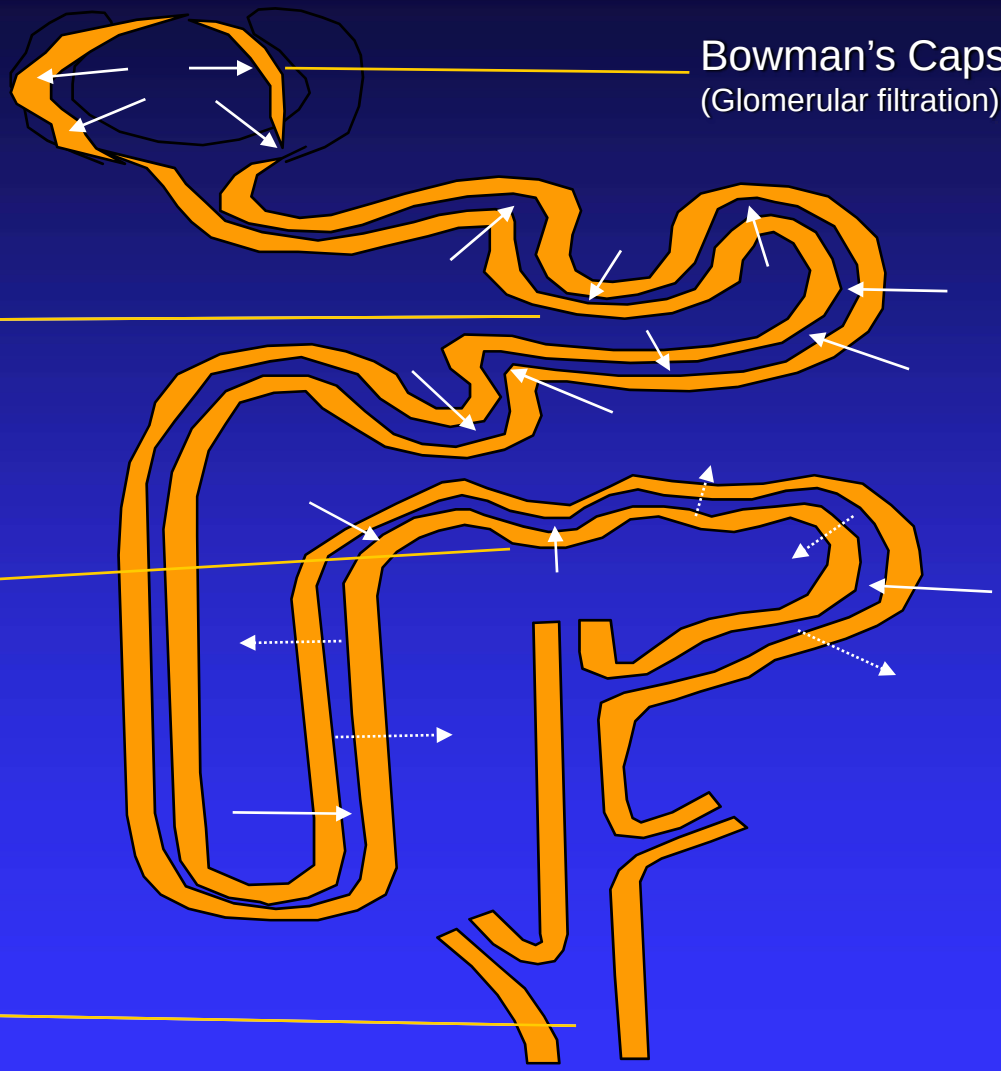
Remember

For pharmacokinetic analysis the drug measurements need to be specific

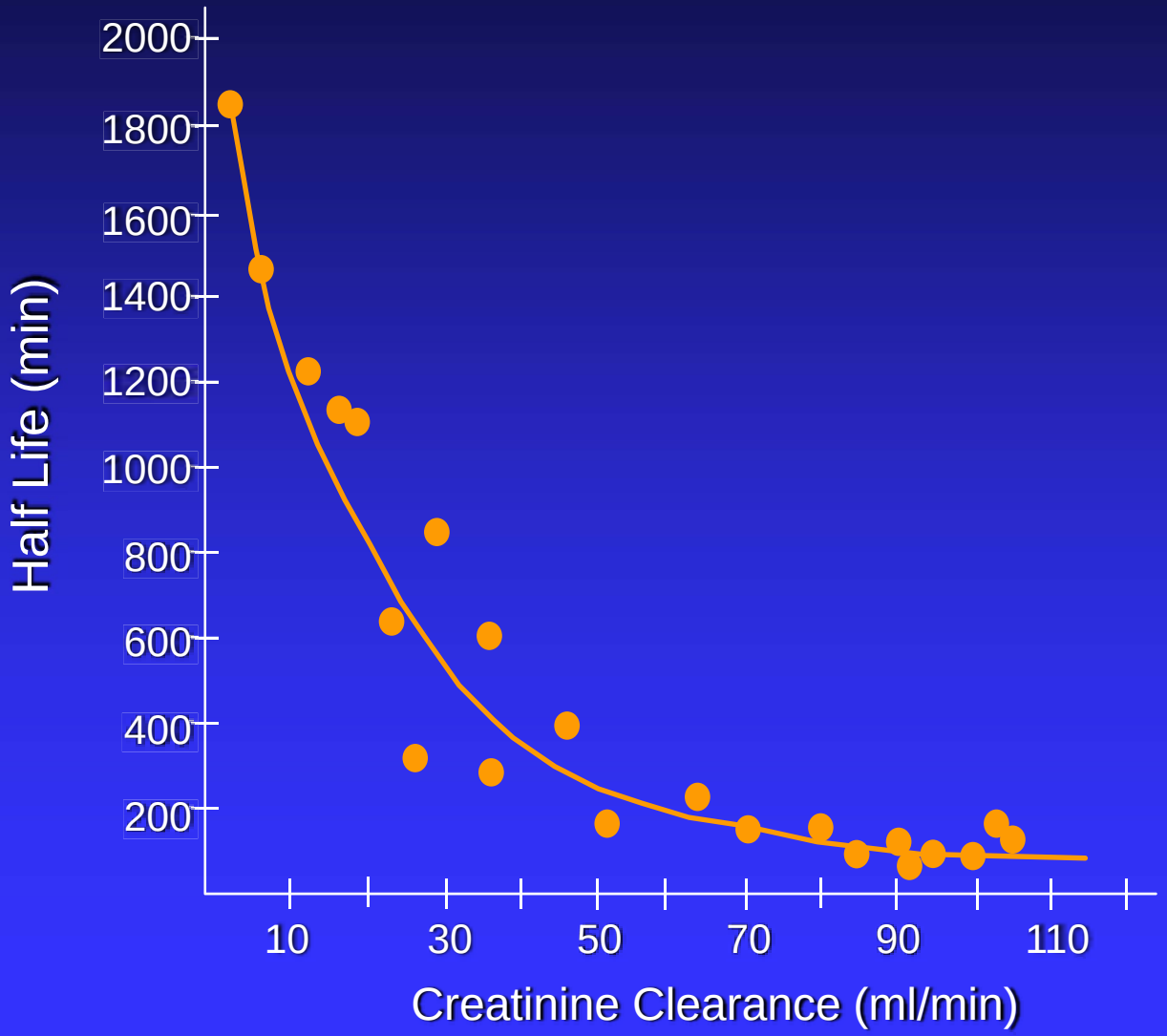

Drug in
Gastrointestinal tract
Blood
Tissues
Elimination

Renal excretion

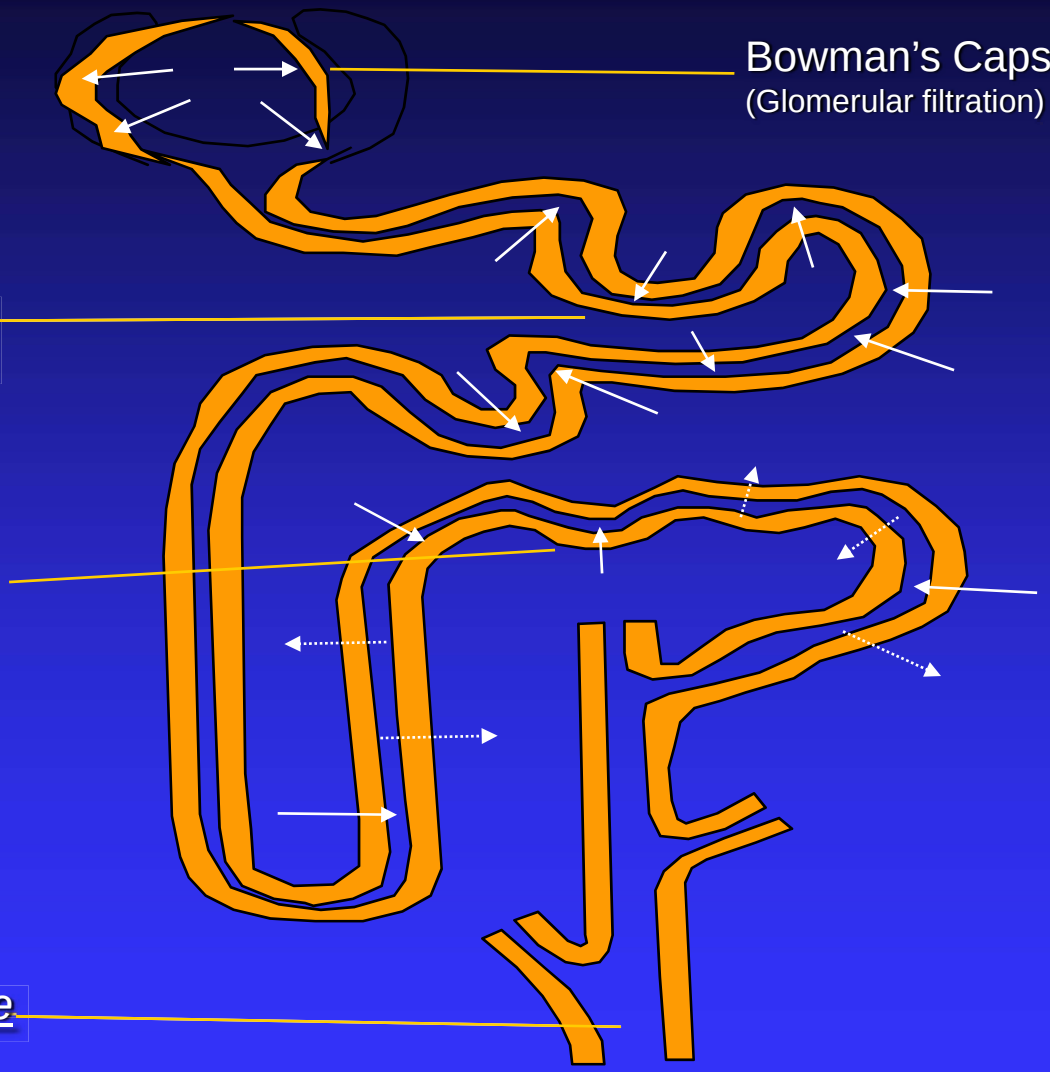
Stylized drawing of a kidney nephron



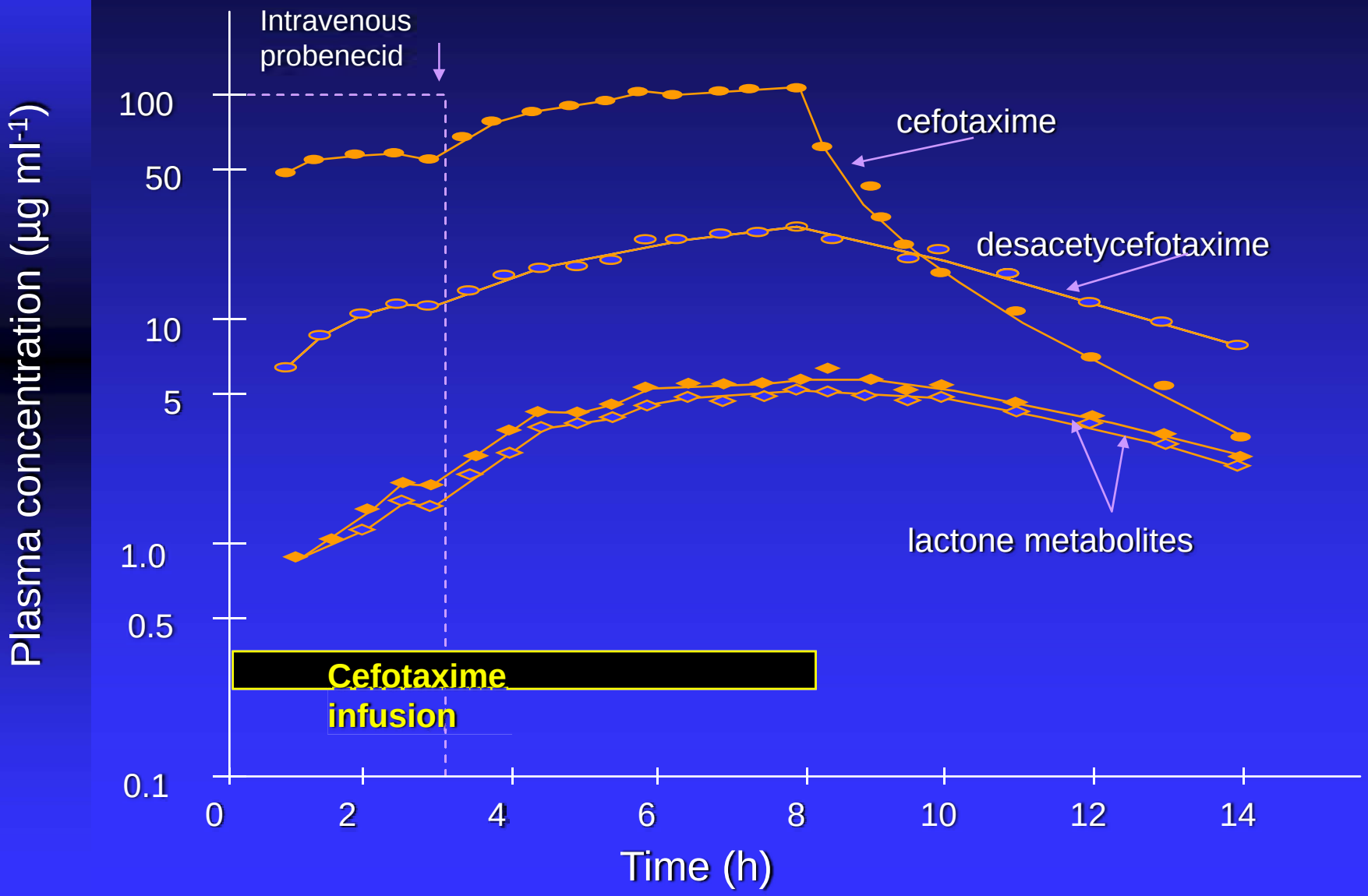
The effect of renal failure on the half-life of netilmicin in man



Stylized drawing of a kidney nephron



The effect of probenecid on the steady-state levels of cefotaxime and its metabolites



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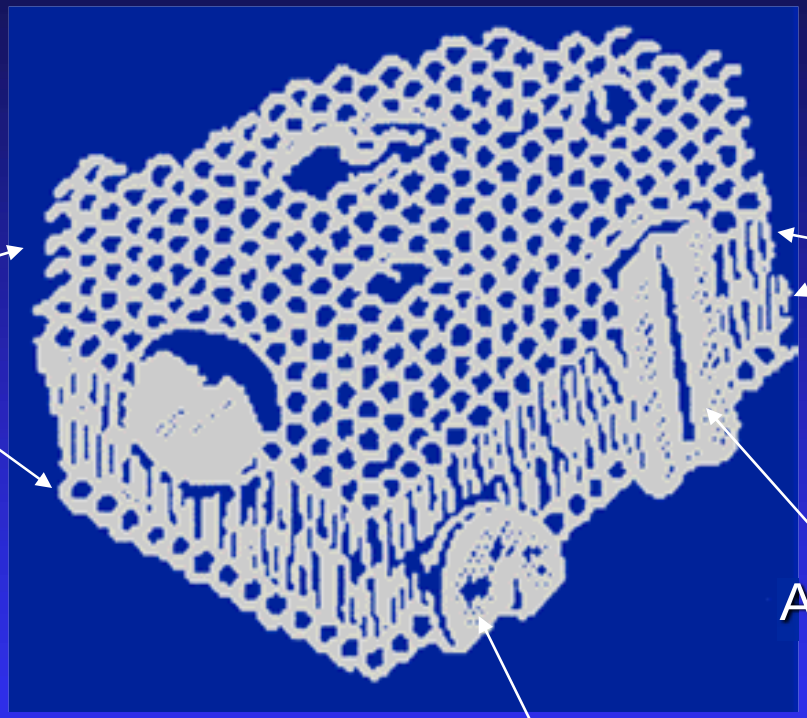

Drugs with ionisable groups can exist in ionised and unionised forms

	unionised		ionised
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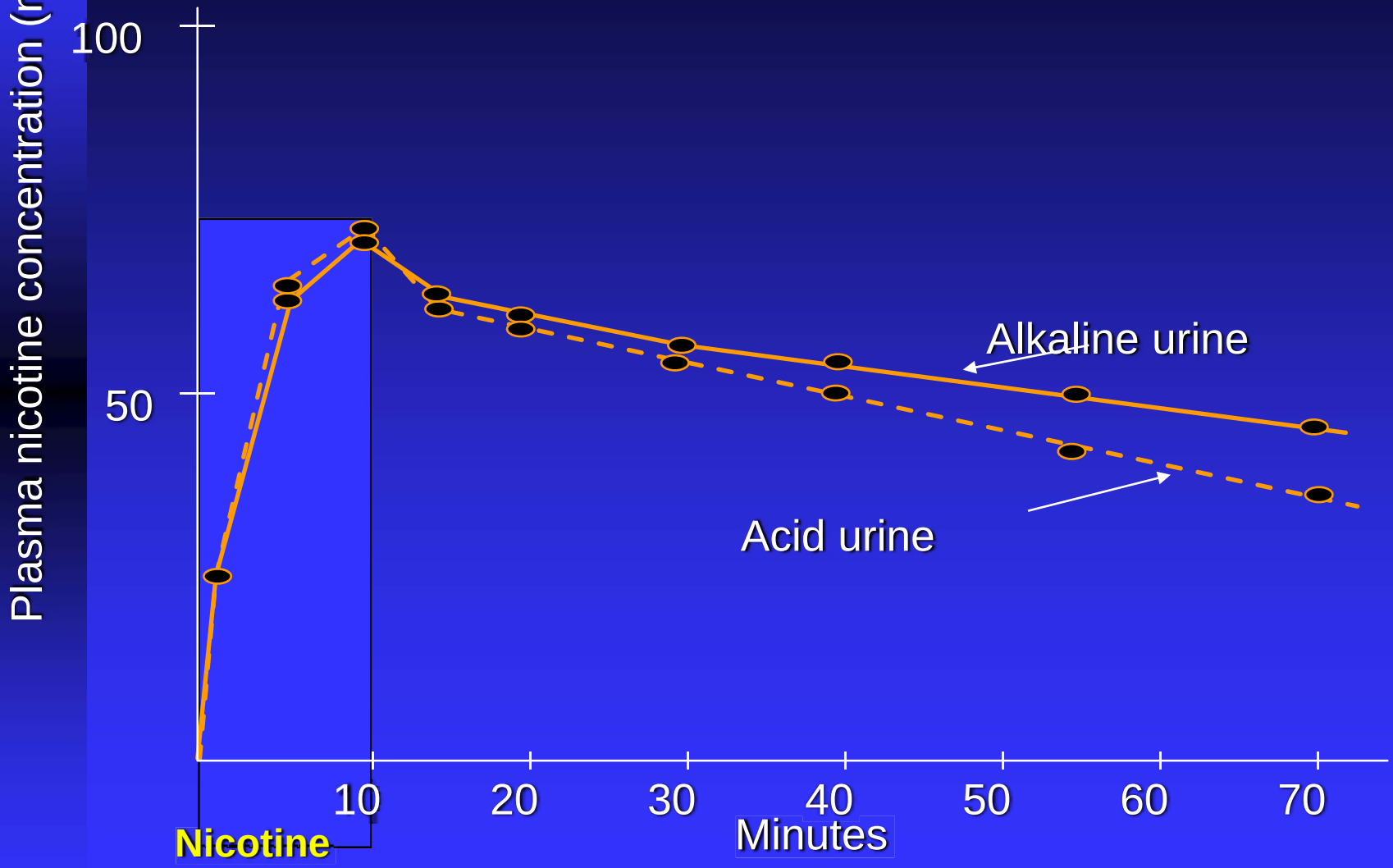
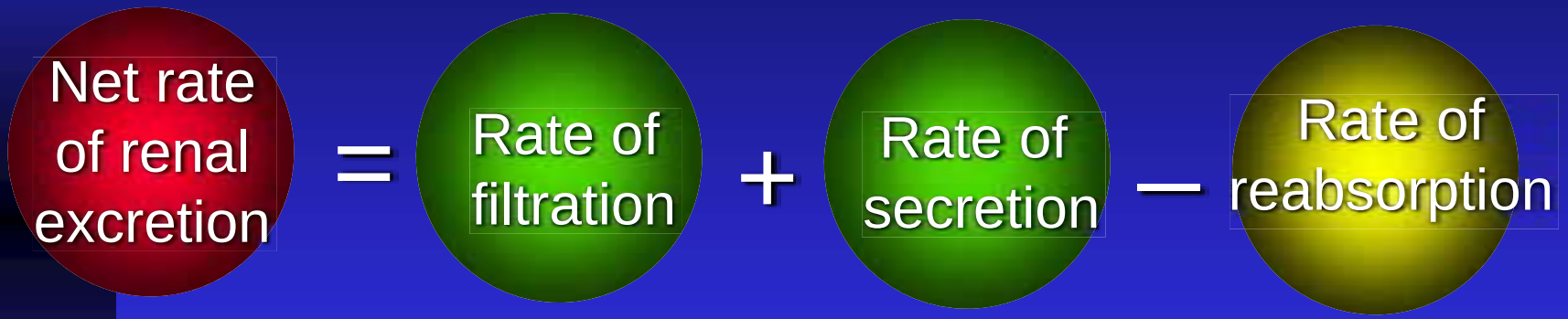
Plasma levels of intravenous nicotine to subjects with alkaline or acid urine



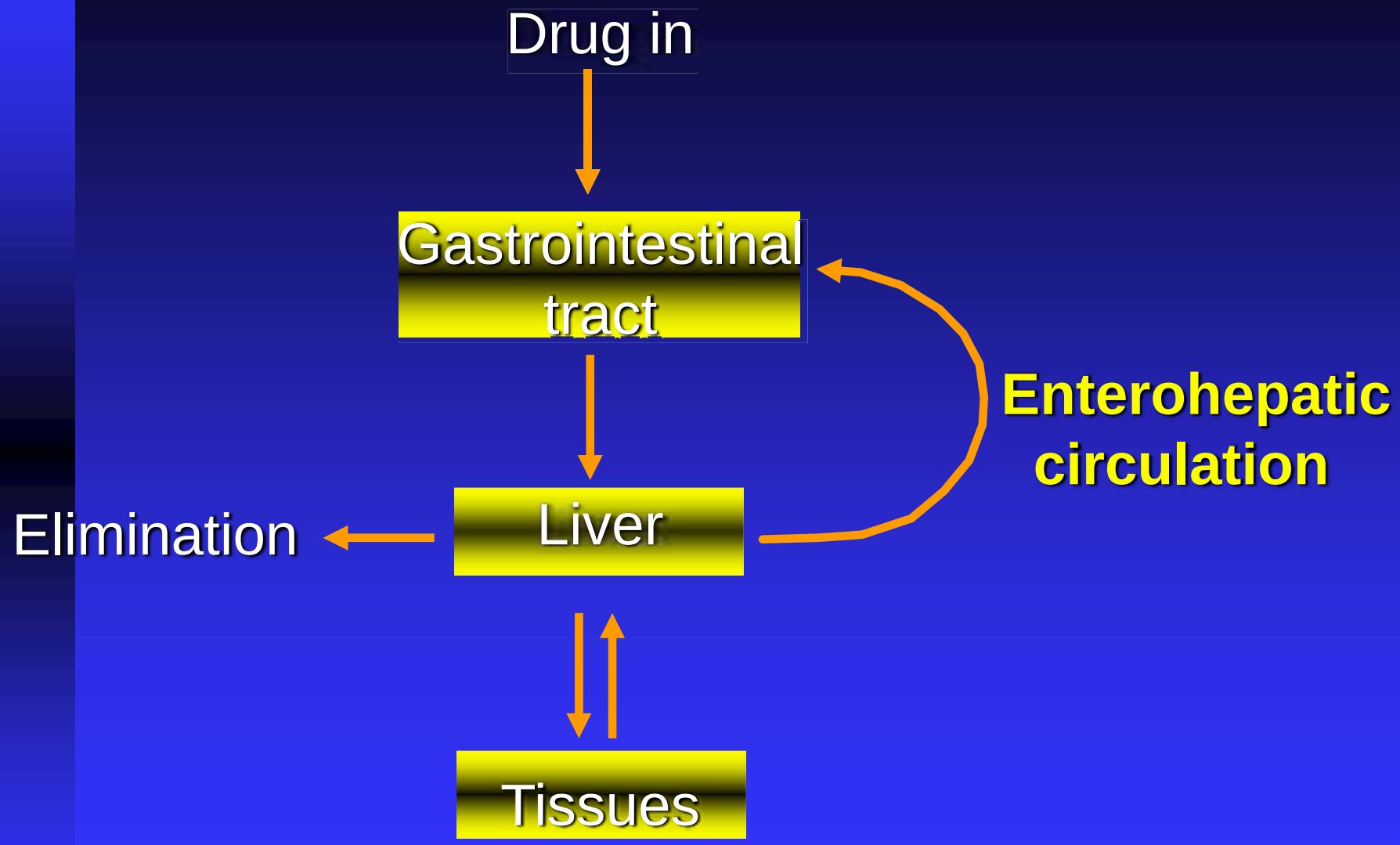

Net rate of renal excretion
=
Rate of filtration
+
Rate of secretion
–
Rate of reabsorption

Biliary excertion

- Factors affecting biliary excretion of drugs
  - Polarity
  - Structural consideration
  - Molecular weight

Approximate molecular weight thresholds for biliary excretion

Species	Molecular Weight
Rat	325
Dog	325
Guinea pig	400
Rabbit	475
Monkey	500
Man	500


Drug in
Gastrointestinal tract
Liver
Elimination
Tissues
Enterohepatic circulation

If biliary excretion occurs with subsequent enterohepatic circulation, has the drug been eliminated?

Elimination

The irreversible transfer of a drug from the site of measurement

Distribution

The reversible transfer of a drug to and from the site of measurement

Routes of elimination

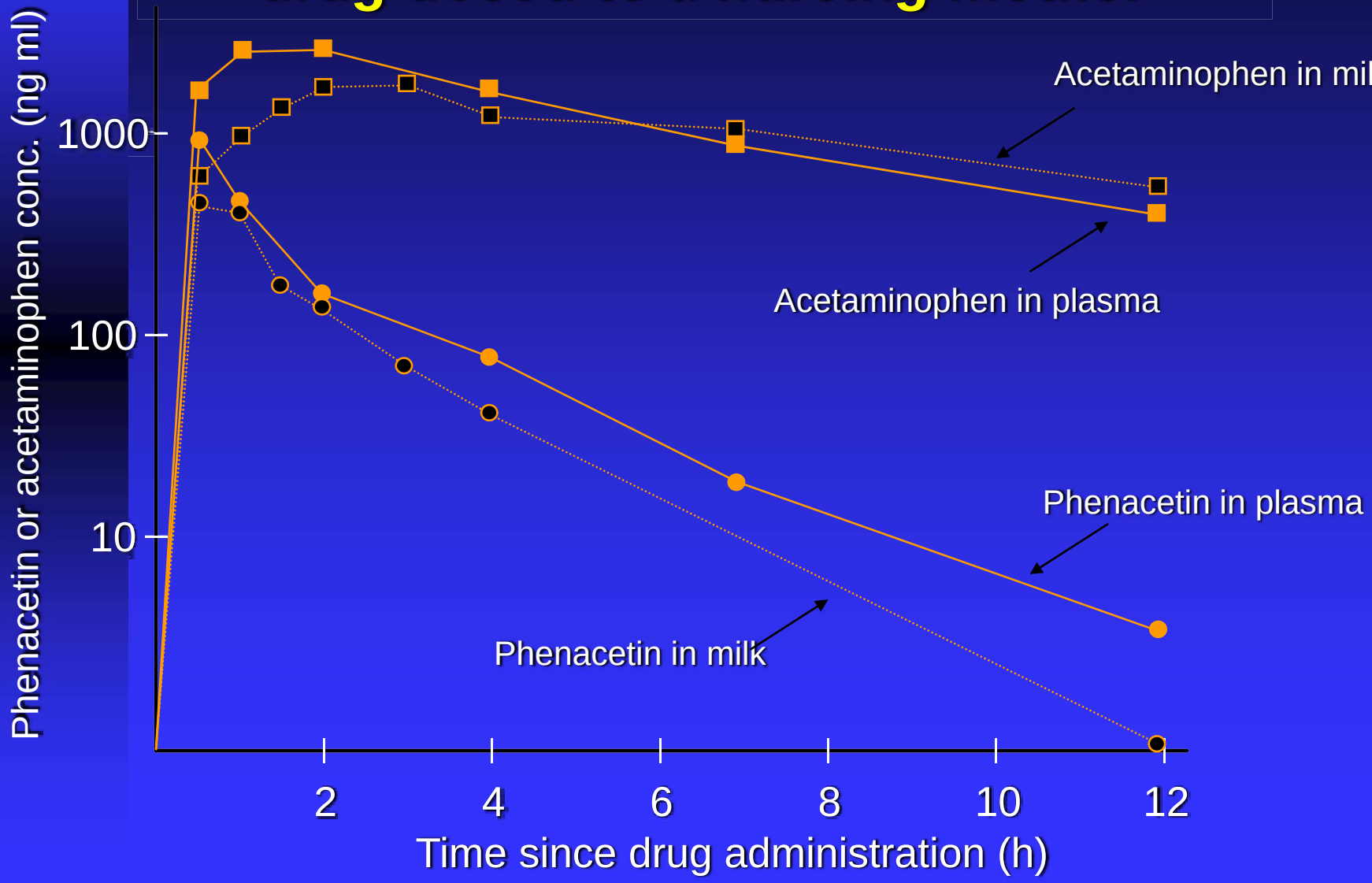
- Metabolism
- Renal excretion
- Biliary excretion

} Major

- Lungs
- Sweat
- Mammary secretion (Milk)

} Minor

Plasma and milk profile of two analgesic drug dosed to a nursing mother



Pharmacokinetic parameters of elimination

- Clearance
- Renal Clearance
- Extraction Ratio
- Half-life

❖ Clearance

Clearance is the volume of blood, plasma or serum completely cleared of total or unbound drug per unit time.

Is relates the rate of elimination to the drug concentration

Renal Clearance

Renal clearance is the volume of blood, plasma or serum completely cleared of total or unbound drug per unit time by kidneys.

Calculation of clearance

$$Cl = \frac{F \bullet Dose}{AUC_{\infty}}$$

$$Cl_R = \frac{U_{t_1 - t_2}}{AUC_{t_1 - t_2}}$$

Cl : Clearance
F : Bioavailability
AUC_{∞} : Area under curve to infinite time
U : Amount excreted in urine

Bioavailability calculation based on clearance (Cl) concept

For a drug $F_{iv} \times Cl = F_{po} \times Cl$

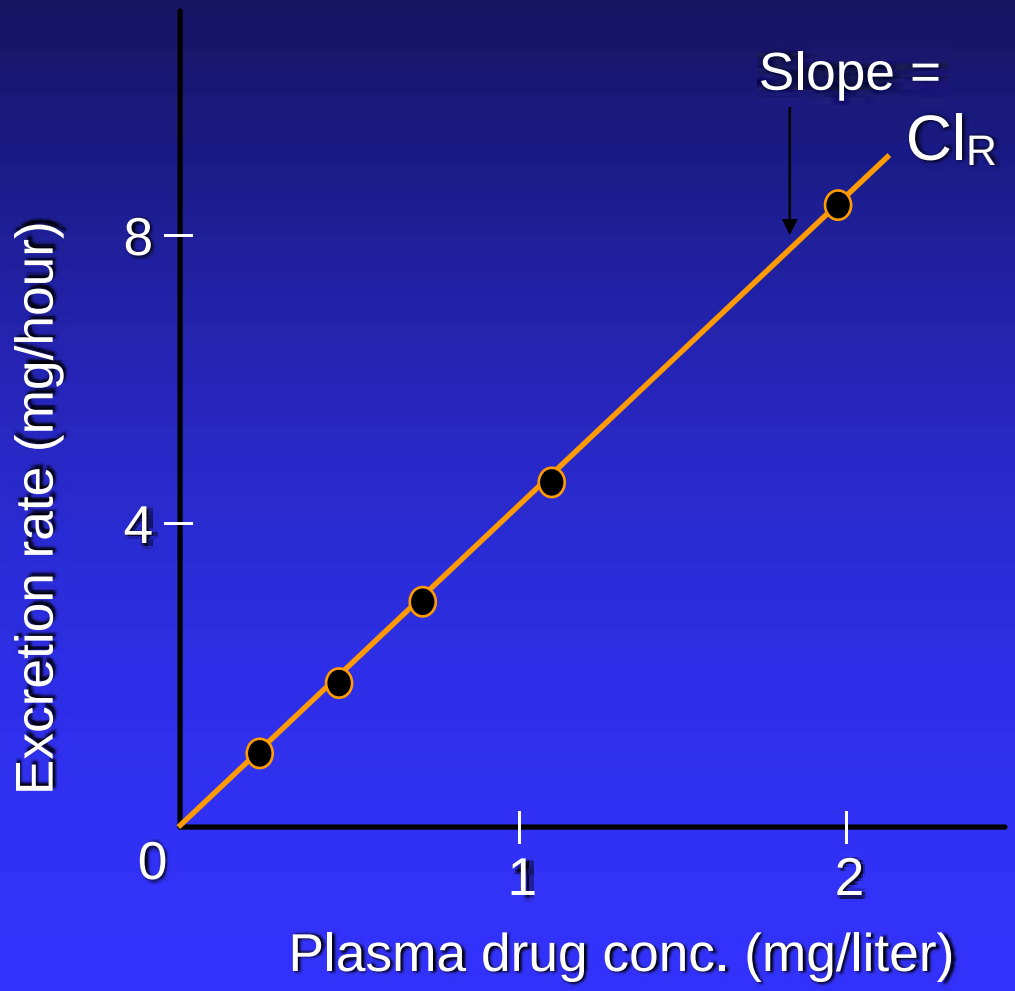
but $F_{iv} = 1$

$$Cl = \frac{Dose}{AUC}$$

Substituting $$\frac{Dose_{iv}}{AUC_{iv}} = F_{po} \cdot \frac{Dose_{po}}{AUC_{po}}$$

Rearrange $$F_{po} = \frac{AUC_{po}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{po}}$$

Determination of renal clearance by plotting excretion rate against Mid-point plasma level



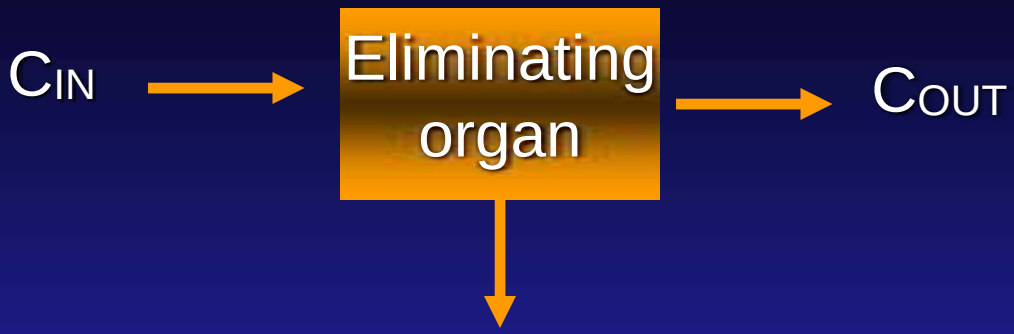
RMI Pharmacokinetics

Total Clearance = Metabolic Clearance + Biliary Clearance + Renal Clearance .....

If all of the radioactivity from a radiolabelled dose appears in urine can it be said the drug is renally cleared?

NO!

Extraction of drug by an eliminating organ



$$\text{Extraction ratio (ER)} = \frac{C_{IN} - C_{OUT}}{C_{IN}}$$

$$Cl = Q \bullet ER$$

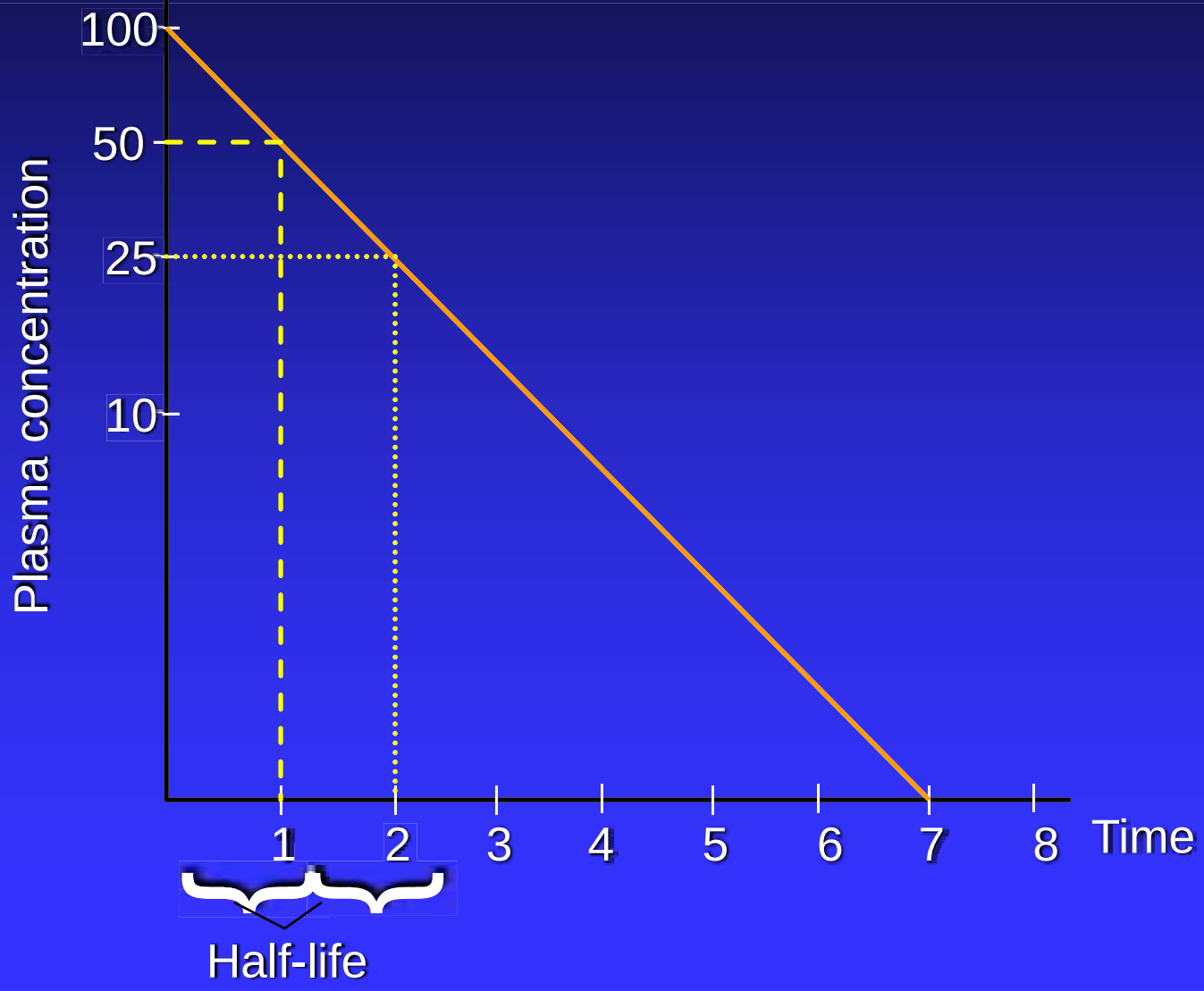
$$CL_B = Q \cdot ER$$

If ER 1

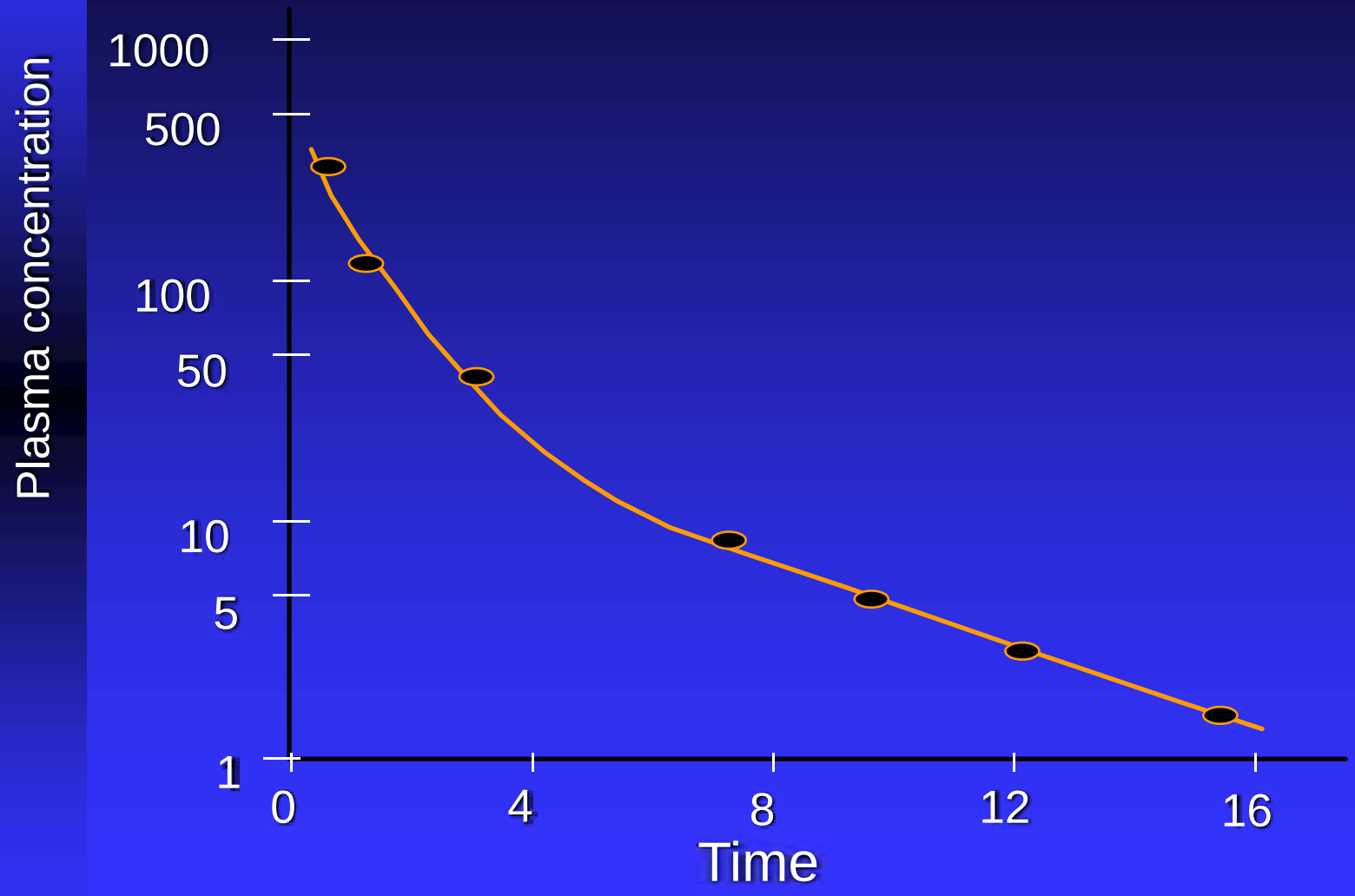
Then $CL_B = Q$.

Cl = Clearance
ER = Extraction Rate
Q = Blood Flow
CL_B = Blood Clearance
C_{IN} = Concentration of drug entering organ
C_{OUT} = Concentration of drug leaving organ

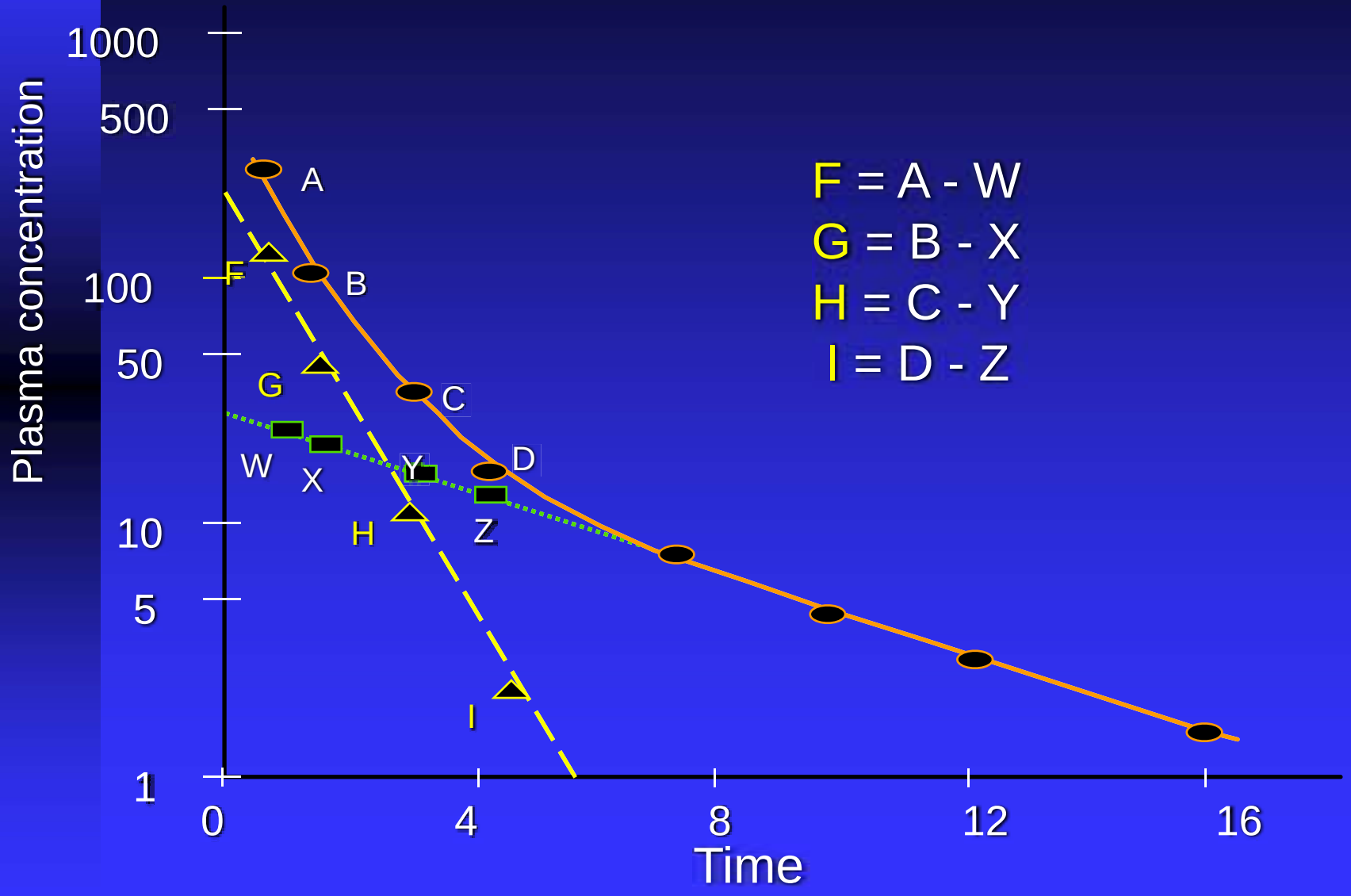
A semilogarithmic plot of plasma levels of drug *vs* time showing determination of half-life



A typical multiexponential drug-plasma curve



Calculation for the method of residuals



$$t_{1/2} = \frac{0.693 \cdot V_D}{Cl}$$

Summary

- Pharmacokinetic terms defined
  - absorption / distribution / elimination
- The exponential process and therapeutic window described with emphasis on dosage regimen design
- Absorption described
- Factors affecting distribution described
  - pH / blood flow / polarity / binding to macromolecules
- Volume of distribution
  - Vi / V / Vss
- Routes of elimination including minor ones
- Factors affecting elimination
  - renal / biliary
- Parameters of elimination
  - clearance / half-life