After completing the preparation materials, students should be able to:

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Links

Scholar Rx Bricks: (Required)

General Principles

Pharmacokinetics and Pharmacodynamics > Pharmacokinetics: Drug Concentration and Dosing
https://exchange.scholarrx.com/brick/drug-concentration-and-dosing

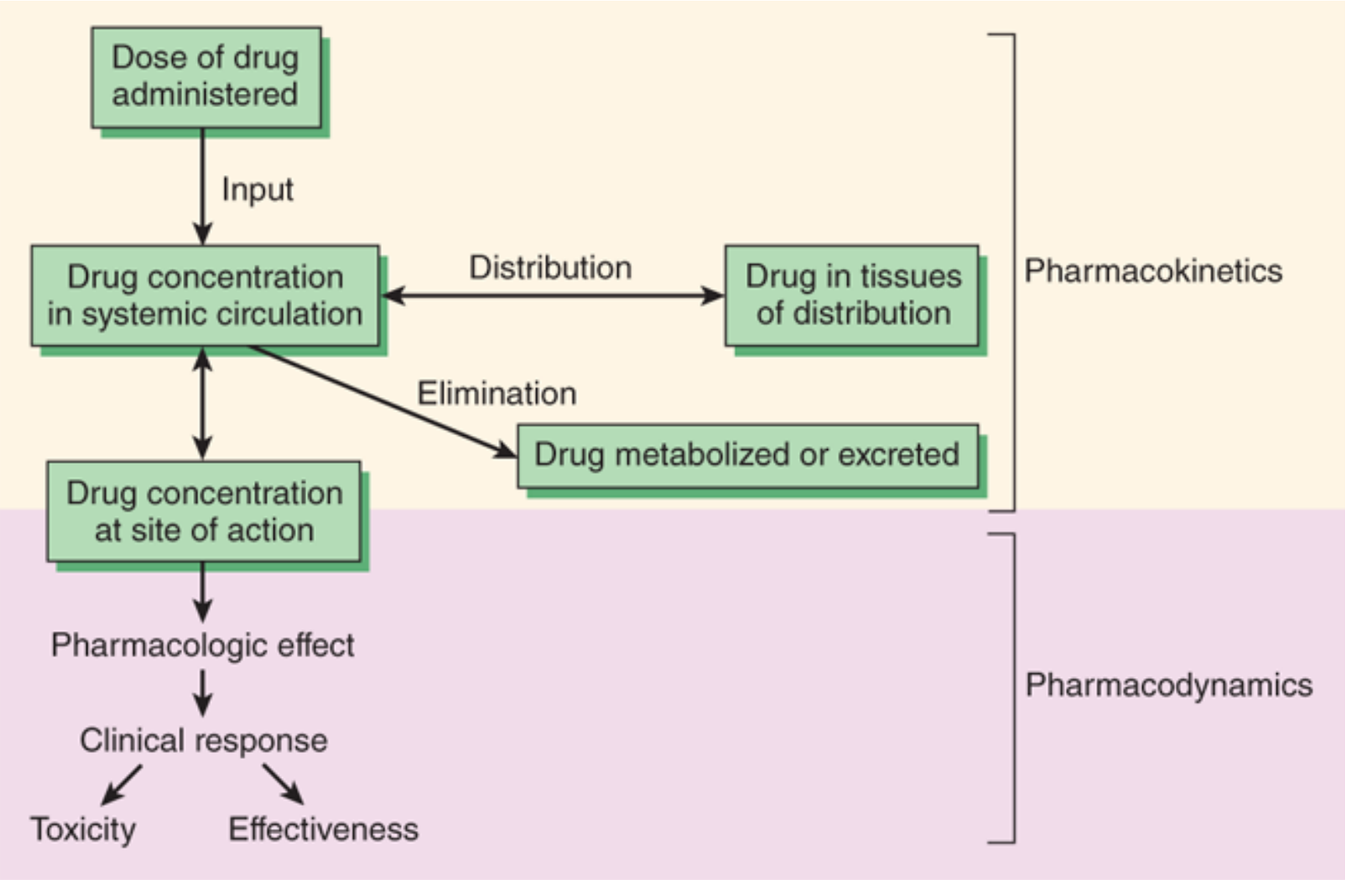
Enzymes as Drug Targets https://exchange.scholarrx.com/brick/enzymes-as-drug-targets

Katzung & Vanderah's Basic & Clinical Pharmacology, 16e, 2024; Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281747069

THE REVIEW BOOKS HAVE PRACTICE QUESTIONS

Katzung & Trevor's Pharmacology: Examination and Board Review, 14e, 2024
Chapter 3: Pharmacokinetics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285589076

LWW Health Library Premium Basic Sciences; Lippincott Illustrated Reviews: Pharmacology, 8e, 2023: Chapter 1: Pharmacokinetics
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253324942&bookid=3222



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition
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A rational approach to achieving ***a desired beneficial effect with minimal adverse effects*** combines the principles of pharmacokinetics and pharmacodynamics to clarify the dose-effect relationship.

The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are input, distribution, and elimination.

Citation: Chapter 3 Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021, Figure 3-1. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250594300 Accessed: August 17, 2021
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Key points: What you need to know and understand Terms

Clearance (CL) CL = elimination rate / C_p Thus, Elimination rate = CL x C_p C_p: plasma concentration	The volume of blood from which the drug is removed per unit of time: it is the proportionality factor that relates the rate of elimination to drug concentration. Units: volume/time (mL/min or L/h)
Bioavailability (F)	The fraction of the administered dose of drug that reaches the systemic circulation Intravenous (IV) administration: F = 1 (100%)
Apparent Volume of distribution (V_d) V_d = Dose / C_p	The proportionality factor that relates the amount of drug in the body to the concentration of drug in the blood or plasma Units: Liters or Liters/kg body weight
Elimination half-life (t½) t½ = (0.693 x V_d) / CL Units: time	The time required for the amount of drug in the body or blood to fall by 50%. For drugs eliminated by first-order kinetics, this number is a constant regardless of the concentration.

What you need to know and understand
Terms to know

Extraction ratio $E_H = CL_H / Q$ and $F = 1 - ER$ H: hepatic; Q: blood flow	A measure of an organ's intrinsic capacity for eliminating a given drug from the systemic circulation over a single pass through the organ (usually liver or kidney)
Area under the concentration-time curve (AUC) $F = AUC_{oral} / AUC_{IV}$ $F = AUC_{formulation\ A} / AUC_{formulation\ B}$ Units: Cp x time (mg x min)/ml	The integration of the variation in plasma drug concentration over time after a single dose or during a single dosing interval AUC reflects ***the actual (total) body exposure*** to an administered dose of a drug, irrespective of the rate of absorption.
First-order elimination A constant ***fraction*** of drug is eliminated per unit of time	Drug clearance is a constant. That is, the ratio of rate of elimination to plasma concentration is the same over a broad range of plasma concentration. t½ is constant.
Zero-order elimination A constant ***amount*** (not fraction) of drug is eliminated per unit of time	Capacity-limited elimination: the drug metabolizing enzymes eventually will become saturated as the concentration of substrate increases. The rate of elimination (t½) varies depending on drug concentration.

What you need to know and understand
Terms to know

Multidose kinetics Continuous or intermittent dosing rate	Drug accumulation: The average concentration of drug will increase until a mean steady state (plateau) is reached (first-order elimination only)
Steady state	Dynamic equilibrium (first-order elimination only): the rate of drug elimination = the rate of drug administration It takes 4 half-lives to achieve 94% of steady state.
Therapeutic window	The range of safe and effective drug doses between the minimum therapeutic and minimum toxic concentrations for the drug
Peak concentration	the maximum concentration the drug achieves for a given dose
Trough concentration	the minimum concentration of the drug immediately before the next dose is given
Minimum effective concentration	the minimum concentration required to produce a therapeutic effect

What you need to know and understand: Terms to know

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Don't forget to factor in bioavailability, F.

Loading dose $LD = \frac{C_{desired} \times V_d}{F}$	The dose of drug that promptly raises the concentration of drug in plasma to the target concentration. A loading dose may be desirable when the steady state concentration needs to be achieved rapidly, e.g. life-threatening situation or a drug with a very large V_d or long t½. ➢ Switch to maintenance dose after loading dose to reduce toxicity risk.
Maintenance dose $MD = [(C_p \times CL) / F] \times \tau$ τ: dosing interval	The dose of drug required per unit time to maintain a desired steady state plasma concentration.

Simple models to describe drug distribution and elimination (first-order elimination).
The time course of drug elimination is plotted on a graph.

One-compartment model of distribution and elimination	This model assumes that the body acts like a single, uniform compartment and that a rapid intravenous injection of a dose of drug equilibrates immediately.
Two compartment model of distribution and elimination	Initial rapid changes in plasma concentration are observed because of a distribution phase – the time required for the drug to reach equilibrium distribution between the central compartment (blood) and a second compartment (tissues and fluid) followed by a slower elimination phase.

Parameters Governing Drug Disposition

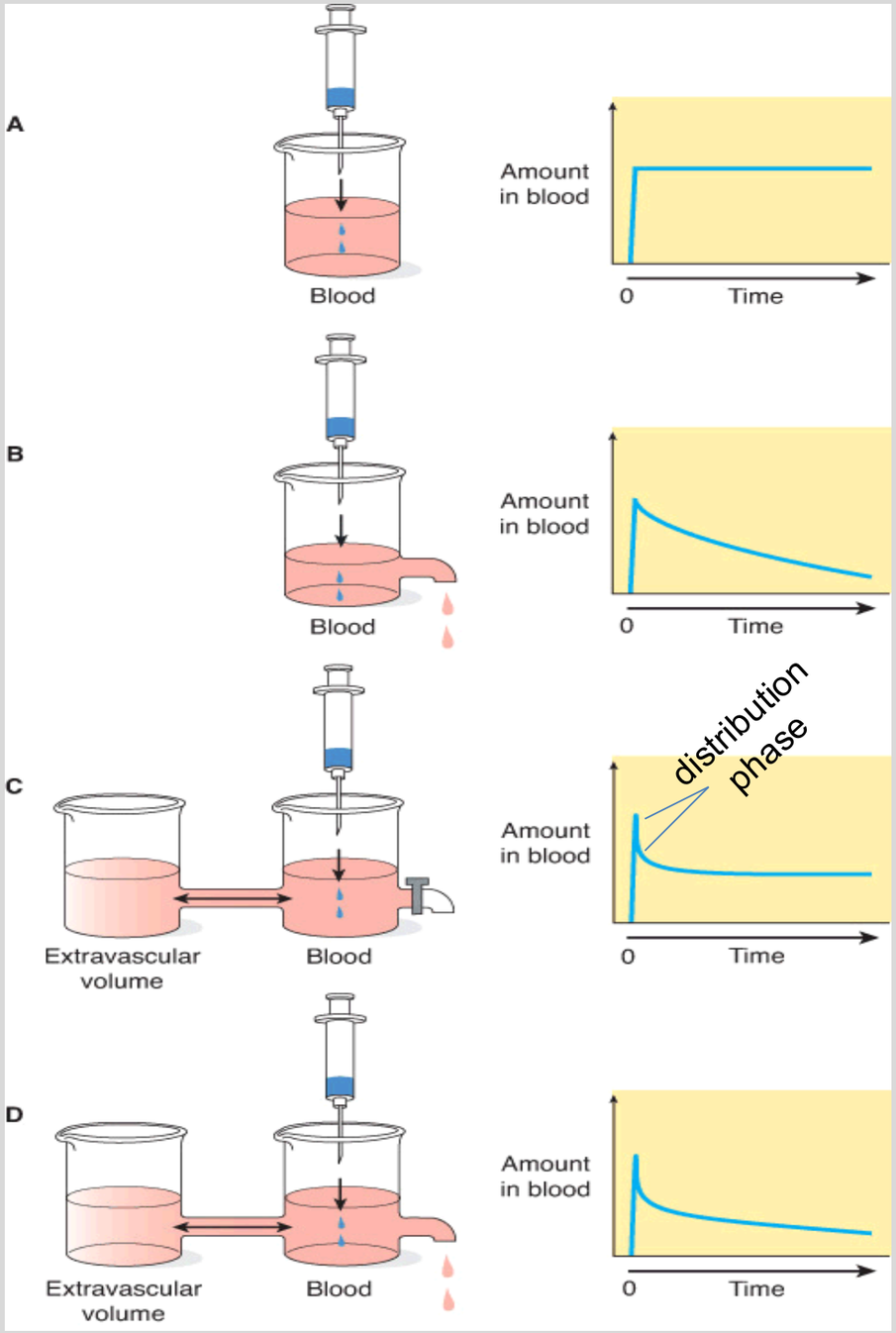
- Clearance
- Bioavailability
- Volume of distribution
- Elimination half-life

- Area under the concentration vs time curve (*AUC*)
- Steady state

dynamic equilibrium with continuous dosing

the rate of elimination = the rate of drug administration

Models of drug distribution and elimination



<u>One compartment model</u>:

no movement of drug out of the beaker ⇒ steep rise to maximum concentration followed by a plateau

route of elimination is present ⇒ a sharp rise to a maximum followed by a slow decay

<u>Two compartment model:</u>

distribution from blood to extracellular fluids and tissues (rapid equilibration)

drug in blood ⇆ drug in extravascular volume

1st compartment 2nd compartment

distribution phase followed by the slower elimination phase

Basic & Clinical Pharmacology **Figure 3-2.** Models of drug distribution and elimination.

CLEARANCE

Clearance is the proportionality factor that predicts the rate of elimination in relation to the drug concentration.

- the **rate** of drug elimination is directly proportional to drug **concentration** when clearance is constant

$$CL = \frac{\text{rate of drug elimination (mg/min)}}{\text{drug concentration in measured fluid (mg/mL/kg)}}$$

- Rearranging: Drug elimination rate = CL x C_{plasma}

At steady state

- Dosing rate_{ss} = Rate of elimination_{ss}
- Dosing rate_{ss} = CL_{ss} x C_{ss}

Extraction Ratio (*E*):

a clearance model of an organ's ***intrinsic capacity***

for eliminating a drug in a single pass through the organ at steady state

Extraction ratio compares plasma levels of free drug at steady state immediately before entering and just after exiting the organ:

$$E = \frac{(C_{in} - C_{out})}{C_{in}}$$

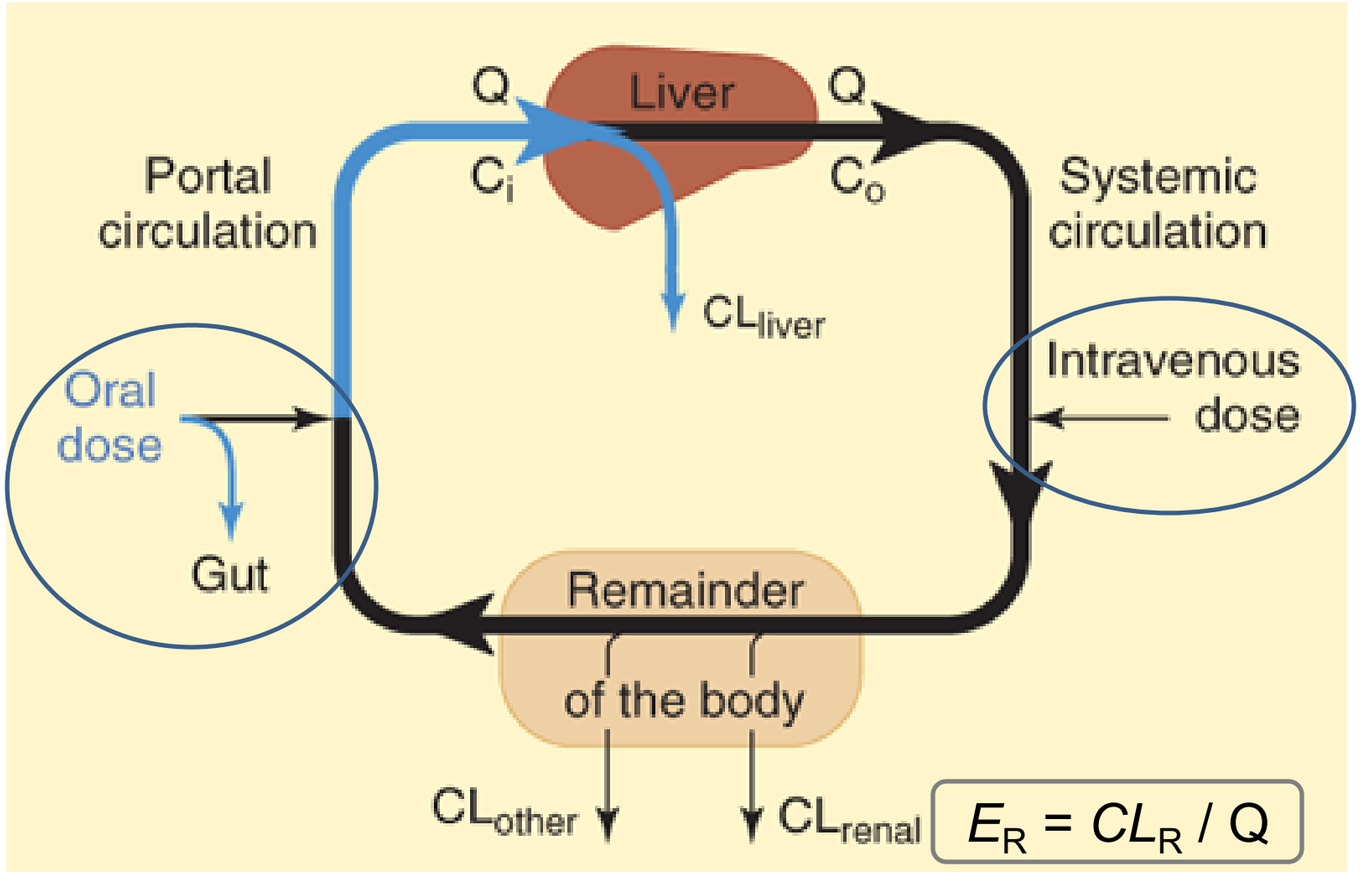
$$CL = Q \times \frac{(C_{in} - C_{out})}{C_{in}} \rightarrow CL = Q \times E$$

$$E = CL / Q$$

Drug clearance is determined by:

1. Blood flow (*Q*) through the eliminating organ
2. Free (unbound) fraction of drug in plasma
3. Intrinsic clearance – the intrinsic ability of clearance mechanisms of the organ (ie, hepatic enzymes to metabolize the particular drug or renal excretory processes)

Illustration of Hepatic and Renal Extraction (E_H and E_R) of a Drug



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Katzung & Trevor's Pharmacology: Examination & Board Review, 13e
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$E = (C_{in} – C_{out}) / C_{in}$

C: concentrations of unbound drug

Blood flow determines the rate of presentation of drug to the liver and the rate of exit from the liver.

$CL = Q \times (C_{in} – C_{out}) / C_{in}$

$E_H = CL_H / Q$

Bioavailability of oral drugs can be predicted:

$F = f \times (1 – E)$

f: fraction of dose absorbed

The principles of organ extraction and first-pass effect are illustrated. Part of the administered oral dose (blue) is lost in the gut in the feces or to metabolism, and lost to metabolism in the liver before it enters the systemic circulation: This is the first-pass effect. The extraction of drug from the circulation by the liver is equal to blood flow (Q) times the difference between entering and leaving drug concentration, ie, $Q \times (C_i – C_o)$. CL, clearance. (Modified with permission from Katzung BG: Basic & Clinical Pharmacology, 8th ed. New York, NY: McGraw Hill; 2001.)

Citation: Chapter 3 Pharmacokinetics, Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. *Katzung & Trevor's Pharmacology: Examination & Board Review, 13e;* 2021, Figure 3-5. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255304212 Accessed: August 23, 2021
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Effect of reduced hepatic blood flow on systemic drug levels

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Blood flow-dependent extraction

For drugs with high E_H (>0.7)

- **Shunting of blood past the liver will result in substantial increases in drug availability in systemic circulation.**

Hepatic clearance approximates blood flow.

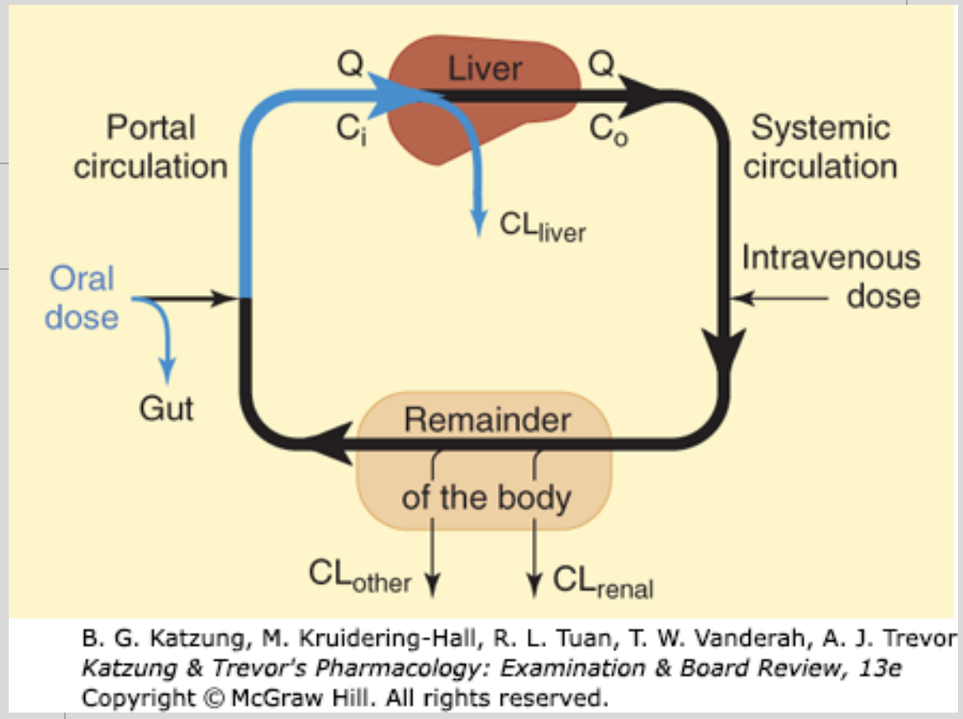
Capacity-limited extraction

For drugs with low E_H (<0.3)

- **Shunting of blood past the liver will cause little change in bioavailability.**

Clearance will be proportional to:

the unbound fraction and the drug's intrinsic clearance.



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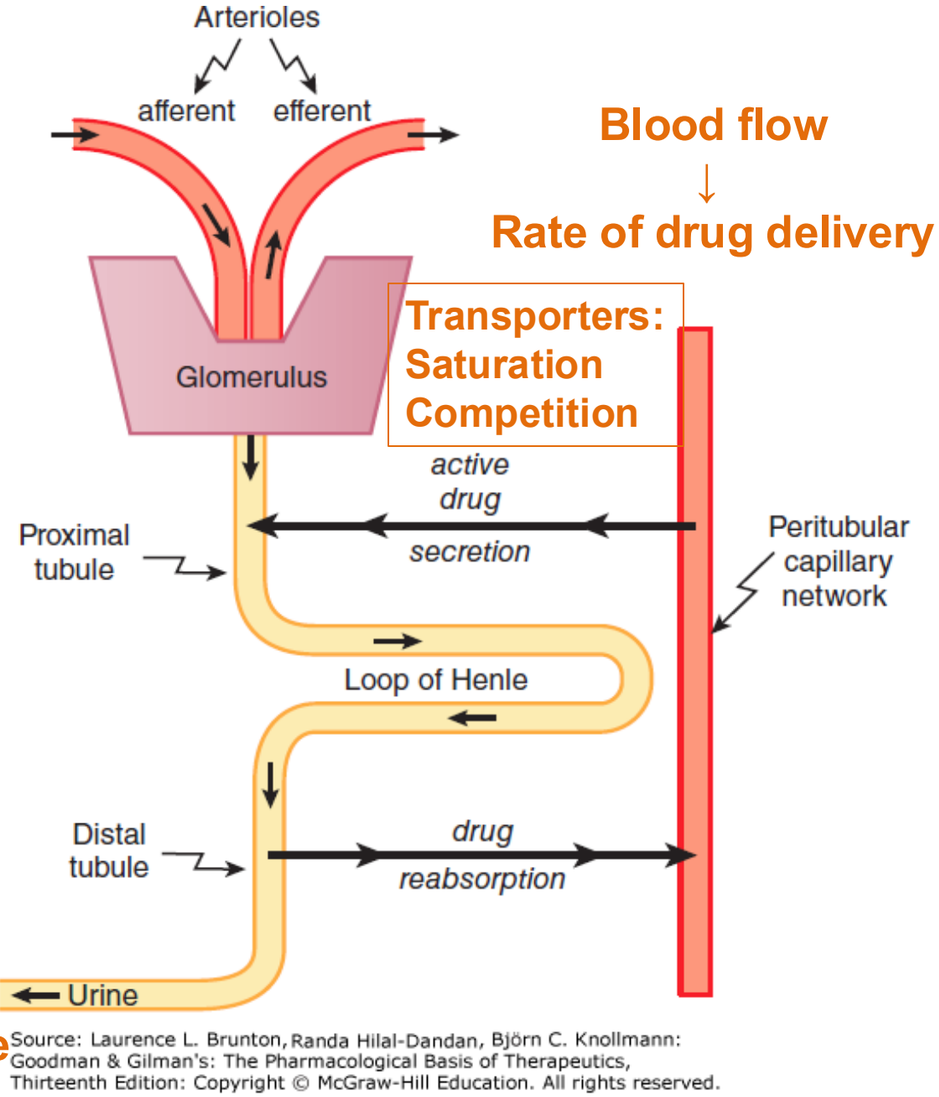
Renal Extraction:

Fraction of active drug excreted in the urine

Renal clearance is affected by:

1. Renal blood flow, protein binding, function of nephrons
2. Glomerular filtration rate
3. Secretion rate from peritubular fluid into tubular fluid
4. Reabsorption from tubular fluid back into the blood stream



E_{renal}:
Fraction of drug excreted in urine

Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Renal drug handling. Drugs may be filtered from the blood in the renal glomerulus, secreted into the proximal tubule, reabsorbed from the distal tubular fluid back into the systemic circulation, and collected in the urine. Membrane transporters (OAT, OCT, MDR1, and MRP2, among others) mediate secretion into the proximal tubule (see Figures 5–12 and 5–13 for details). Reabsorption of compounds from the distal tubular fluid (generally acidic) is pH sensitive: Ionizable drugs are subject to ion trapping, and altering urinary pH to favor ionization can enhance excretion of charged species (see Figure 2–2).

Citation: Chapter 2 Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017, Figure 2-5. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=166182905 Accessed: August 23, 2021
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Bioavailability is factored into oral dosing calculations.

Example

- Verapamil $E_H \approx 0.67$
- Expected oral bioavailability of verapamil

$F_{\text{verapamil}} = 1 - 0.67$

$= 0.33 \Rightarrow 33\%$

Note: Considerable interpatient variability; the actual oral bioavailability of verapamil varies from 20% to 35%

$$\text{dosing rate} = \frac{CL \times C_{ss}}{F}$$

Converting a patient from verapamil I.V. to oral form

- I.V. dose = 5 mg / hour
- = 120 mg / 24 hours
- oral dose = dose / $F_{\text{verapamil}}$

oral dose = 120 mg / 0.33

oral dose = 360 mg / 24 hrs
extended release capsule

AUC
area under the plasma concentration-time curve

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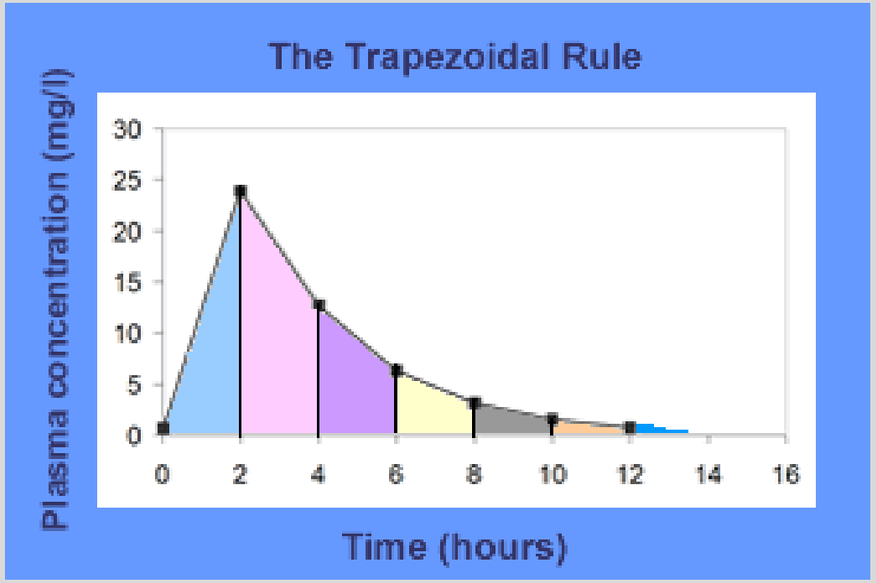
AUC assesses the extent of ***the total body exposure*** to a dose of drug

- By integrating the concentration of drug in plasma over time
- For a single dose or during a single dosing interval at steady state.



http://sepia.unil.ch/pharmacology/index.php?id=66

- Clearance may be estimated from AUC:

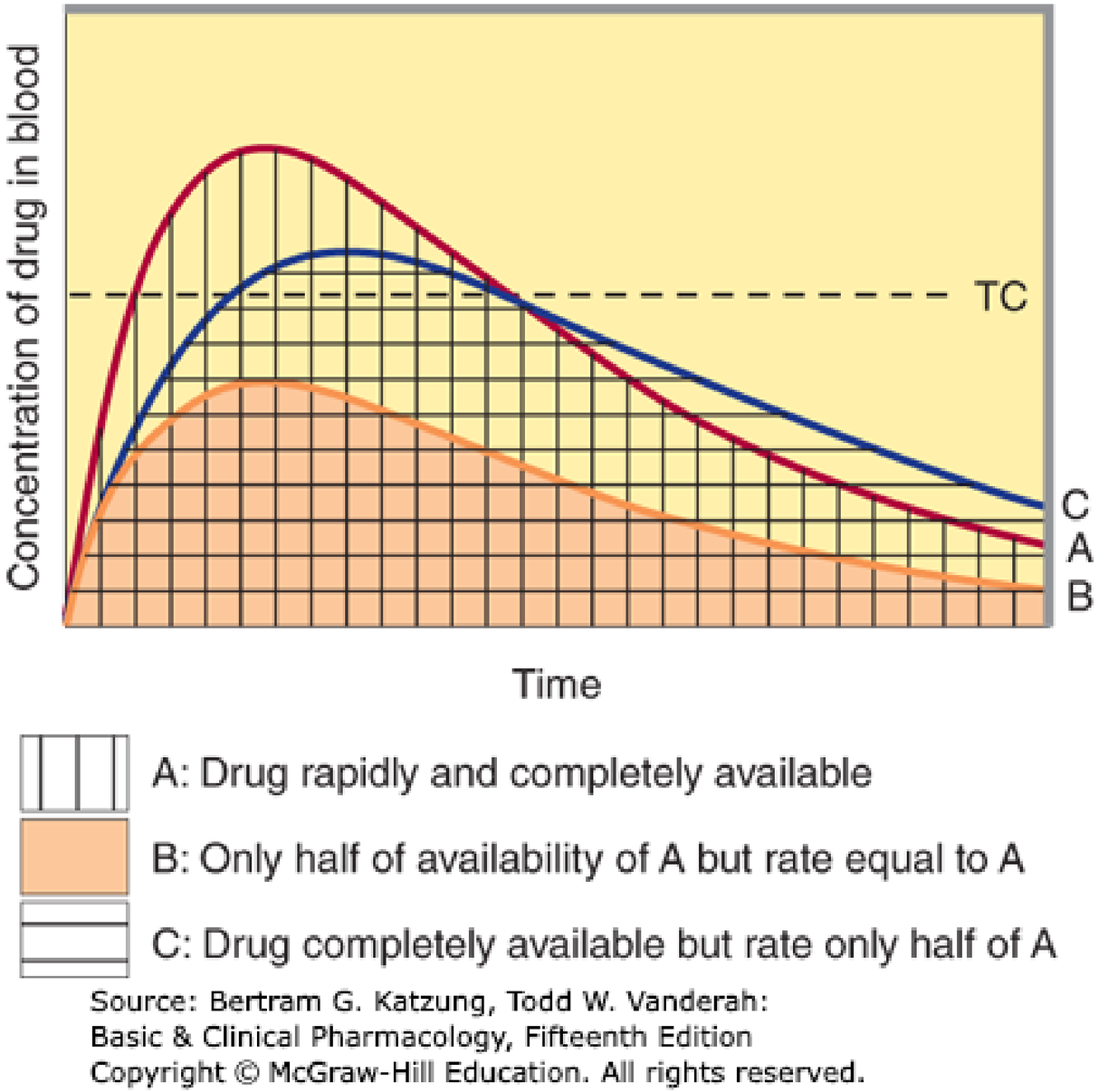
  CL = dose / C_{ss} *therefore,* CL = dose / AUC

- The bioavailability of a drug determines its concentration in plasma, which, over time, determines the actual body exposure to the drug.

The area under the blood concentration-time curve (AUC) is proportional to the dose and the extent of bioavailability for a drug if its elimination is first-order.

The blood concentration-time curves illustrate how changes in the rate of absorption and extent of bioavailability can influence both the duration of action and the effectiveness of the same total dose of a drug administered in three different formulations.

The dashed line indicates the target concentration (TC) of the drug in the blood.



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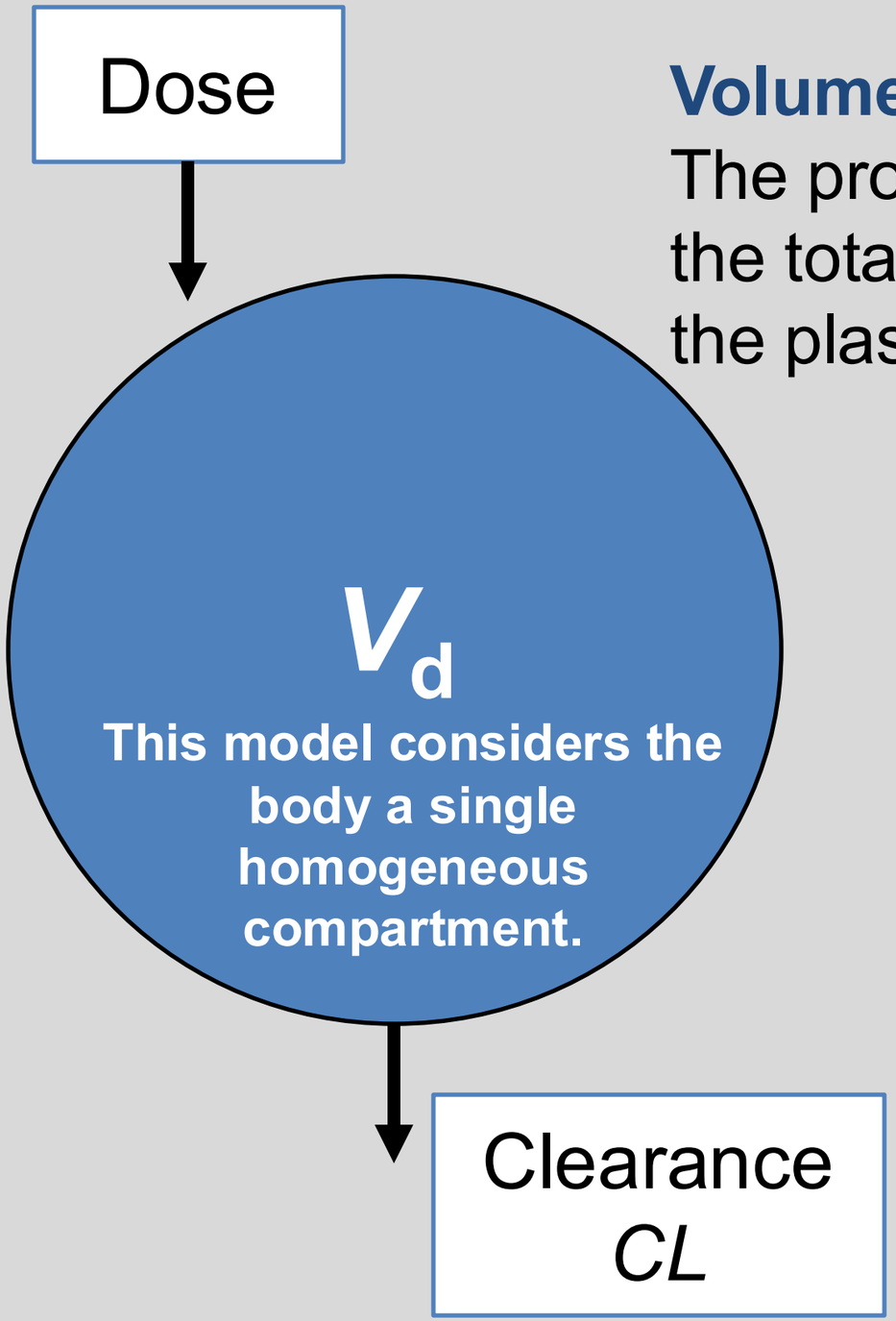


Volume of Distribution:

The proportionality constant that relates the total amount of drug in the body to the plasma concentration at a given time.

$$V_d = \frac{\text{Dose}}{C_{\text{blood or plasma}}}$$

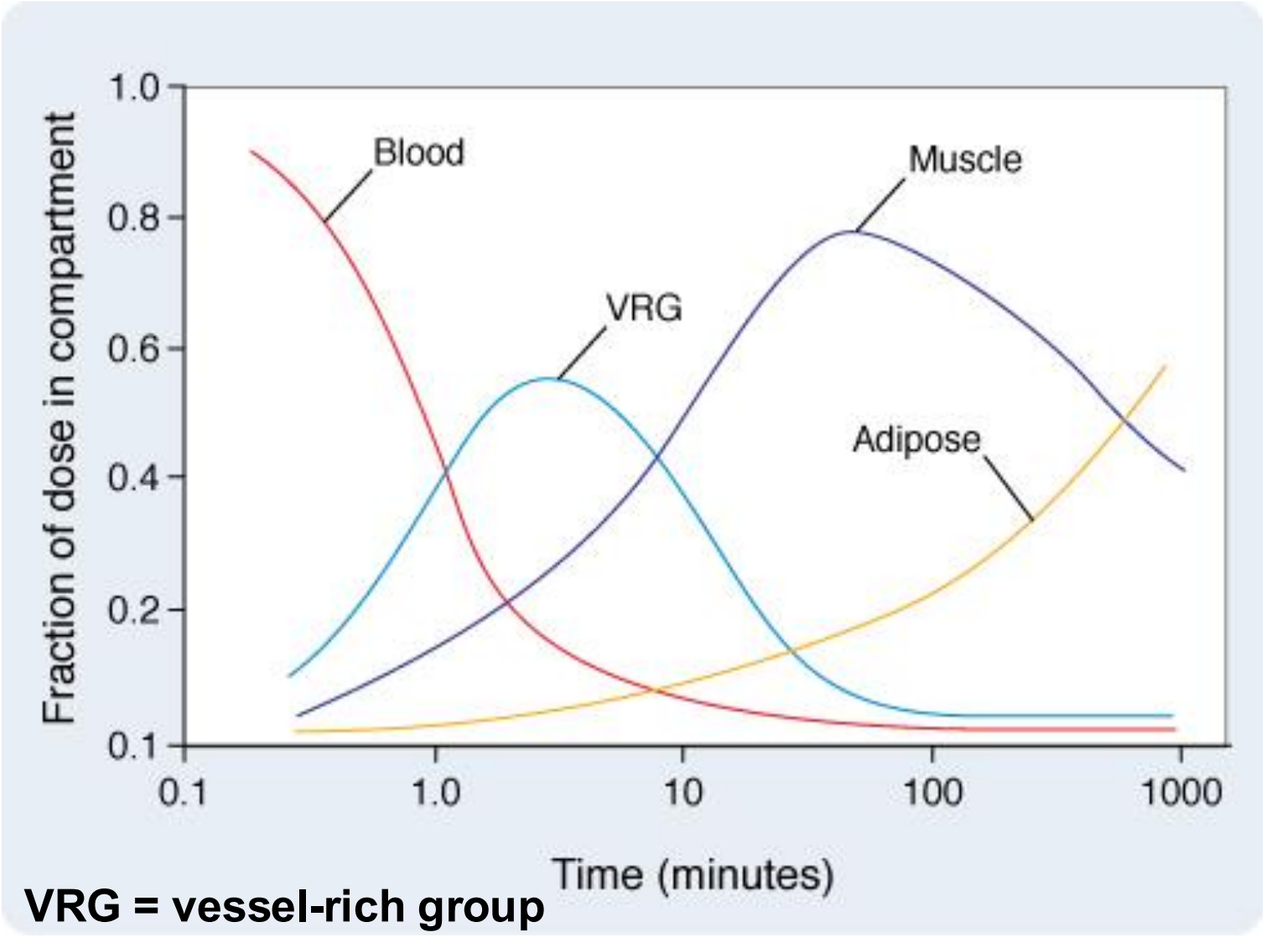
It is an apparent (theoretical) volume that represents a drug's propensity to remain in plasma or distribute to other tissue compartments.

It is a calculated parameter.

LWW Health Library

From: **3 Pharmacokinetics**
Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy Fourth Edition, 4e, 2017

Four-compartment model of drug distribution.



VRG = vessel-rich group

Multi-compartment model:

Drug concentration in a sample varies over time as the drug distributes around the body.

The drug concentration in a sample immediately after IV bolus will produce a different V_d value than a sample taken several hours later.

1. **Initial distribution phase**

- Highly-perfused organs – brain, kidney, liver, heart – receive most of the drug

2. **Second distribution phase**

- Delivery to muscle, most viscera, skin, and fat is slower
- May require minutes to several hours before the concentration of drug in tissue is in equilibrium with that in blood
- Involves far larger fraction of body mass relative to initial phase

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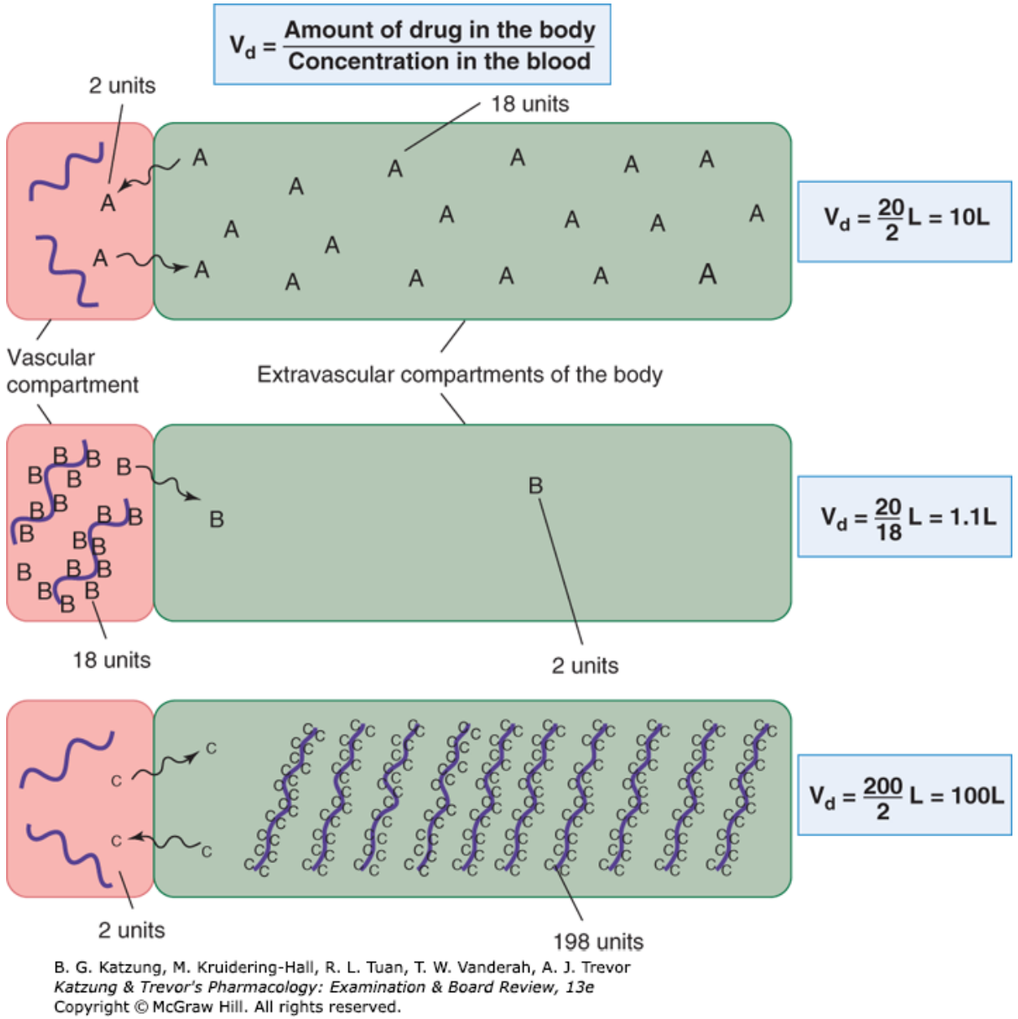

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- Drug A diffuses freely between the 2 compartments.
- Drug B binds avidly to plasma proteins (wavy lines).

  The drug is retained in plasma compartment → low *V*d
- Drug C binds avidly to molecules in peripheral tissues.
  - Low concentration in blood
  - High *V*d
  - Larger total dose is required to achieve measurable plasma concentrations

Effect of drug binding on volume of distribution. Drug A diffuses freely between the 2 compartments and does not bind to macromolecules (heavy wavy lines) in the vascular (volume 1 L) or the extravascular compartments (volume 5 L) of the hypothetical organism in the diagram. With 20 units of the drug in the body, the steady-state distribution leaves a blood concentration of 2 units/L. Drug B, on the other hand, binds avidly to proteins in the blood. At equilibrium, only 2 units of the total are present in the extravascular volume, leaving 18 units still in the blood. In each case, the total amount of drug in the body is the same (20 units), but the apparent volumes of distribution are very different. Drug C is avidly bound to molecules in peripheral tissues, so that a larger total dose (200 units) is required to achieve measurable plasma concentrations. At equilibrium, 198 units are found in the peripheral tissues and only 2 units in the plasma, so that the calculated volume of distribution is greater than the physical volume of the system.

Citation: Chapter 3 Pharmacokinetics, Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. *Katzung & Trevor's Pharmacology: Examination & Board Review, 13e;* 2021 Figure 3-1. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255304212 Accessed: August 23, 2021
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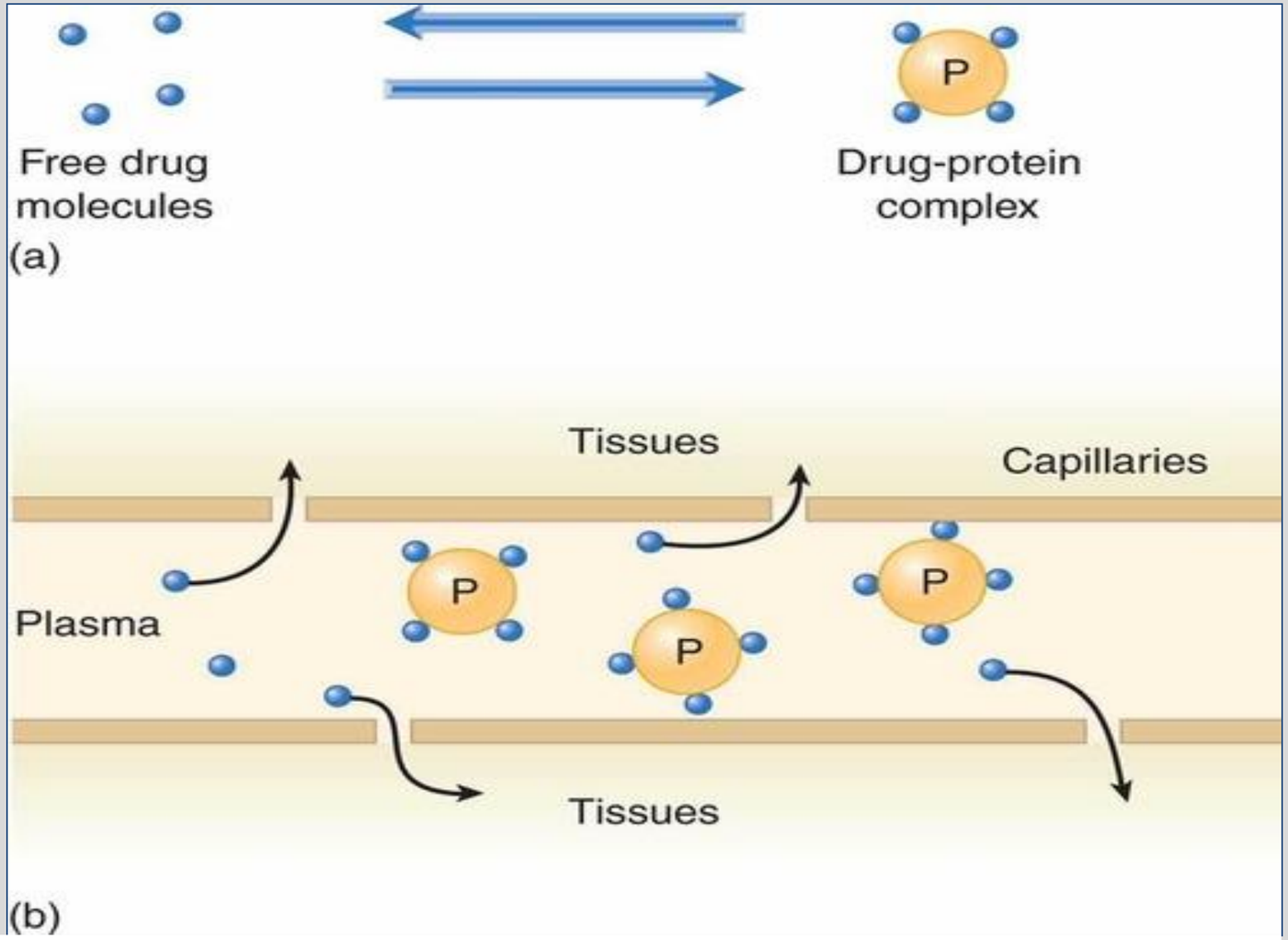
When plasma protein binding is reversible, a chemical equilibrium exists between bound and unbound drug.

drug + protein ⇆ protein-drug complex



Processes that lower the free drug concentration lead to rapid dissociation of drug from the drug-protein complex, thereby reestablishing equilibrium between bound and free drug.

Figure: http://quizlet.com/19545630/pharmacology-4-pharmacokinetics-objectives-flash-cards/

- The plasma concentration is a function of the rate of input of the drug (by absorption) into the plasma, the rate of distribution into other tissues, and the rate of elimination.
- If the rate of input is known, the remaining processes are well described by two primary parameters: **apparent volume of distribution (V_d)** and **clearance (CL).** These parameters are unique for a particular drug and a particular patient but have average values in large populations that can be used to predict drug concentrations.
- Clearance of a drug is the factor that predicts the rate of elimination in relation to the drug concentration.
- Volume of distribution is the proportionality constant that relates the total amount of drug in the body to the plasma concentration at a given time.

After completing the preparation materials, students should be able to:

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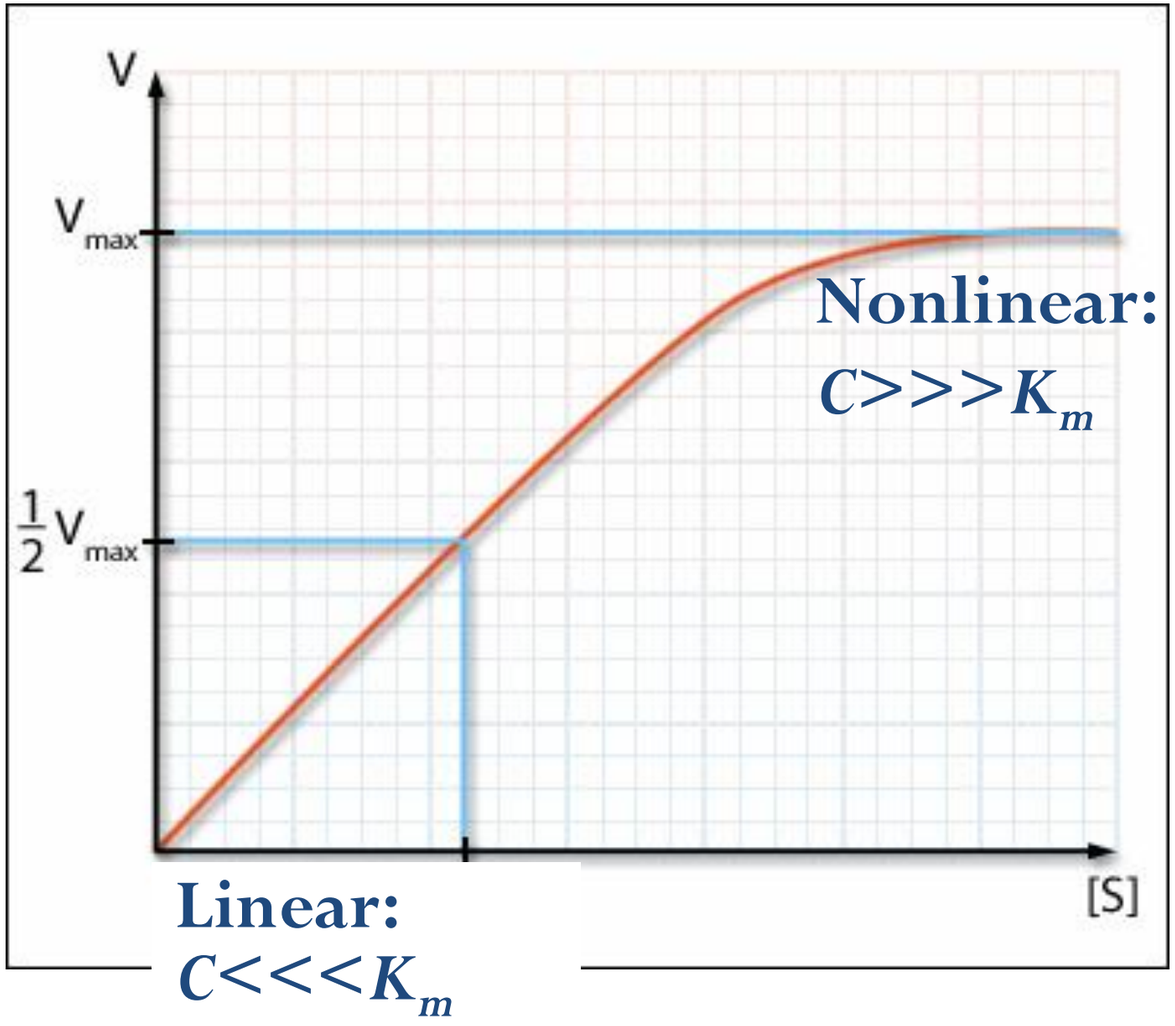
https://premiumbasicsciences-lwwhealthlibrary-com.nyit.idm.oclc.org/content.aspx?sectionid=253324942&bookid=3222

Zero-order kinetics: Clearance mechanisms become saturated – the rate of metabolism remains constant – a constant amount (not fraction) of drug is metabolized per unit of time. Dangerously elevated drug concentration can result.



$$\text{Rate of Elimination} = \frac{V_{max} \times C}{K_m + C}$$

$$Css = \frac{\text{Dosing rate} \times K_m}{V_{max} - \text{Dosing rate}}$$

As dosing rate approaches V_{max},

V_{max} – dosing rate approaches zero → disproportionate increase in concentration.

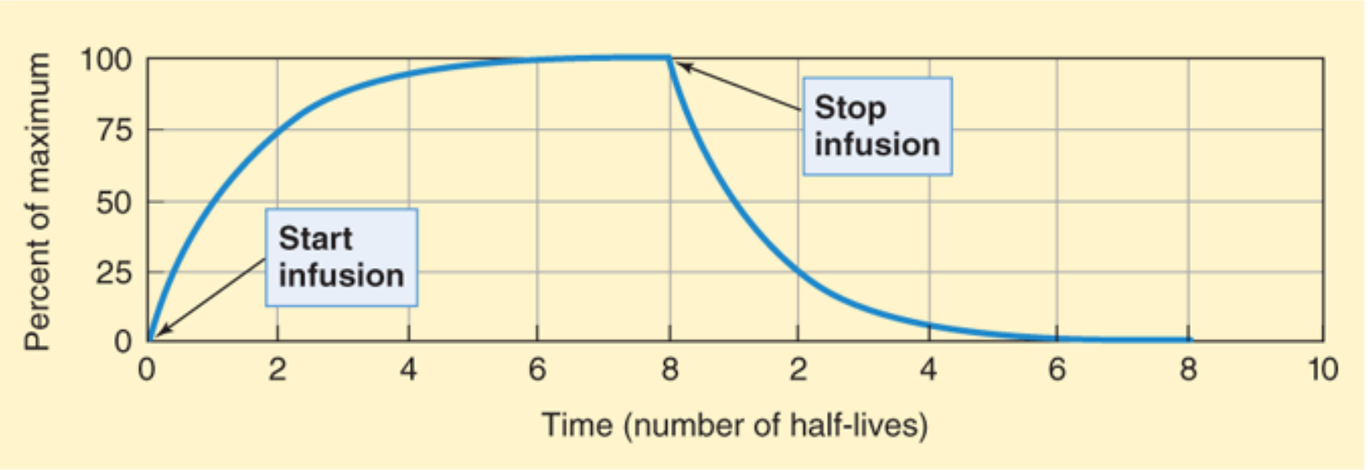
At C >> K_m elimination rate is almost independent of concentration.

K_m is the concentration of substrate at which enzyme activity is at half maximal – ½ Vmax.

Continuous administration results in drug accumulation until the rate of drug going in = rate going out.

After that point, no additional accumulation occurs.

Dynamic equilibrium – steady state – is reached.



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4 half-lives is the time required …

- to approach steady state and full effects to be seen, and
- for drug to be removed from the body by elimination

1 t½ → 50%
2 t½ → 75%
3 t½ → 87.5%
4 t½ → ~94%

Plasma concentration (plotted as percentage of maximum) of a drug given by constant intravenous infusion for 8 half-lives and then stopped. The concentration rises smoothly with time and always reaches 50% of steady state after 1 half-life, 75% after 2 half-lives, 87.5% after 3 half-lives, and so on. The decline in concentration after stopping drug administration follows the same type of curve: 50% is left after 1 half-life, 25% after 2 half-lives, and so on. The asymptotic approach to steady state on both increasing and decreasing limbs of the curve is characteristic of drugs that have first-order kinetics.

Citation: Chapter 3 Pharmacokinetics, Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. *Katzung & Trevor's Pharmacology: Examination & Board Review, 13e;* 2021, Figure 3-3. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255304212 Accessed: August 30, 2021
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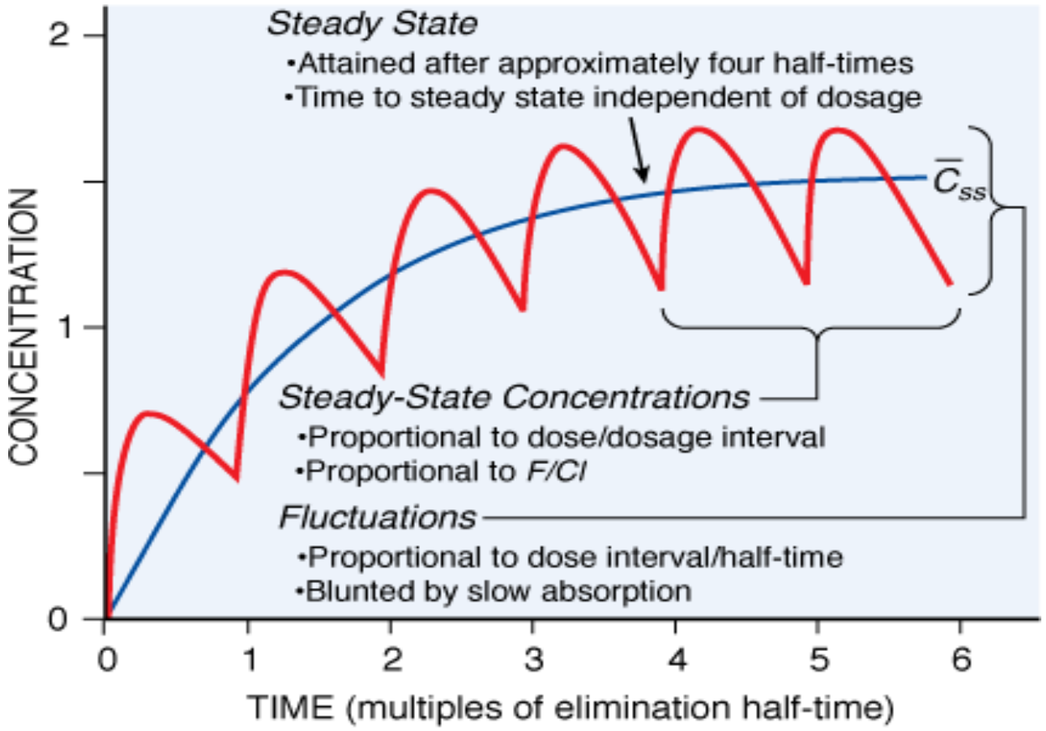
Drug accumulation with a continuous or intermittent dosing rate is based on the fundamental principle of clearance:

- Clearance = the volume of blood from which a drug is removed per unit of time (in mL/min or L/h)
- Clearance relates the rate of elimination to the plasma concentration (in μg/mL or mg/L)

$$\text{dosing rate} \times F = CL \times C_p$$

- Clearance of a particular drug remains constant although the actual amount of drug in the clearance volume varies with the plasma drug concentration.



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

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The legend for this figure is in the notes section of the PowerPoint slide.

Steady state:

Rate of drug elimination = Rate of drug administration

when drug is administered at a constant rate.

Citation: Chapter 2 Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017, Figure 2-7. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=166182905 Accessed: August 23, 2021

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