After completing preparation material, students should be able to:

1. Explain the phase 1 and phase 2 metabolic reactions and give examples of the actions of specific cytochrome P450 enzymes and transferases involved in drug biotransformation.
2. Relate the mechanisms of enzyme induction and inhibition and their effects on systemic drug concentrations.
3. Differentiate first-pass effect and enterohepatic circulation and explain the clinical relevance of each by giving examples.
4. Explain the three distinct processes that influence the concentration of drug and/or metabolites excreted in urine.
5. Correlate genetic factors and nongenetic variables in the individual patient to variations in the rate and extent of absorption, distribution, metabolism and excretion.

Links

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Scholar Rx Bricks: (Required)

General Principles

Pharmacology: Foundations and Frameworks https://exchange.scholarrx.com/brick/pharmacology-foundations-and-frameworks

Pharmacokinetics: Drug Transport and Diffusion https://exchange.scholarrx.com/brick/drug-transport-and-diffusion

Pharmacokinetics: Drug Administration, Metabolism, and Excretion https://exchange.scholarrx.com/brick/drug-administration-metabolism-and-excretion

Cell and Molecular Biology: Cellular Biology

Transport Across Membranes https://exchange.scholarrx.com/brick/transport-across-membranes

Cell Signaling https://exchange.scholarrx.com/brick/cell-signaling

TEXTBOOK

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 1: Introduction > The Nature of Drugs > General Principles of Pharmacology https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281746718

REVIEW BOOKS HAVE PRACTICE QUESTIONS

Access Medicine Katzung's Pharmacology Examination and Board Review, 14e, 2024
Chapter 1: Introduction > The Nature of Drugs
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285588535

LWW Health Library Premier 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

Key points: What you need to know and understand

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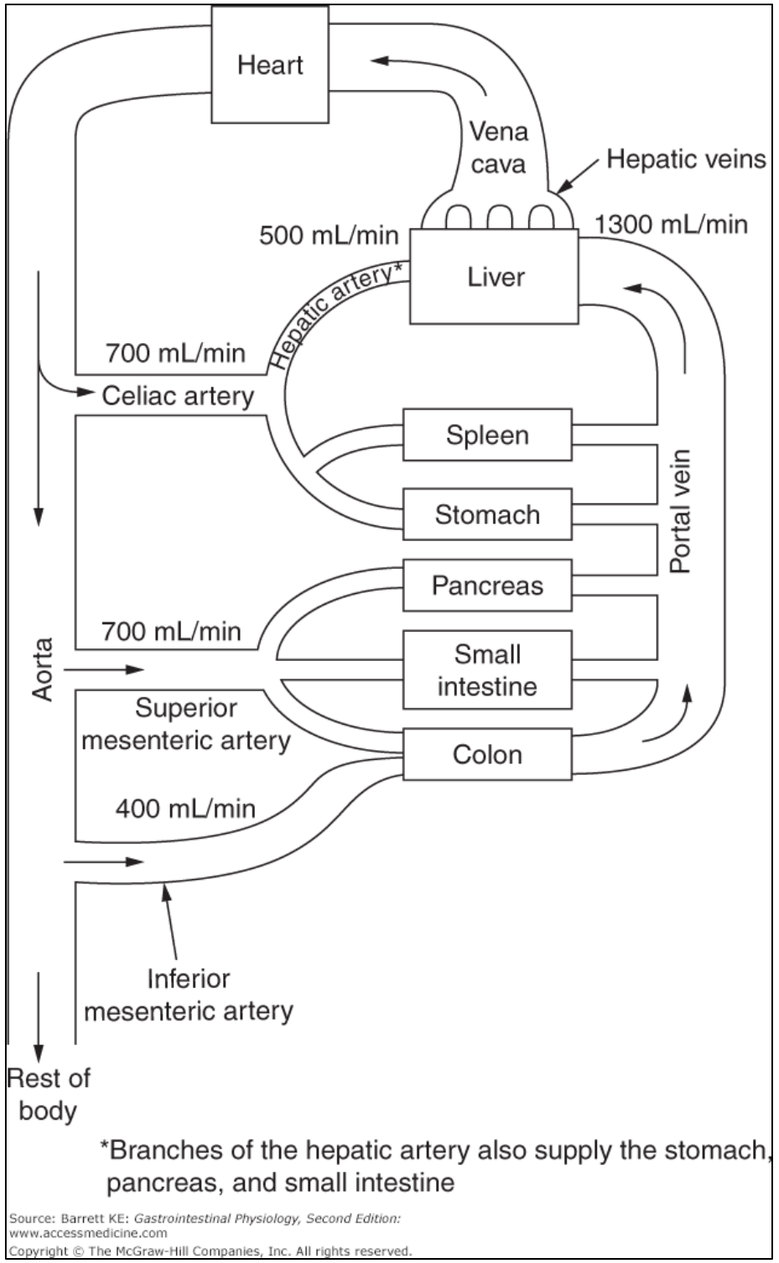
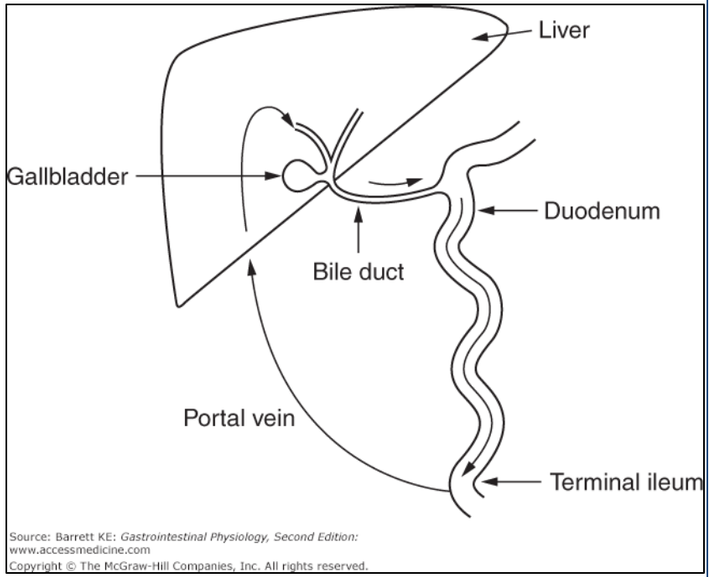
Please see Pharmacokinetics ADME Part 1 for the key points to know and understand about metabolism and excretion (slided 15-17).

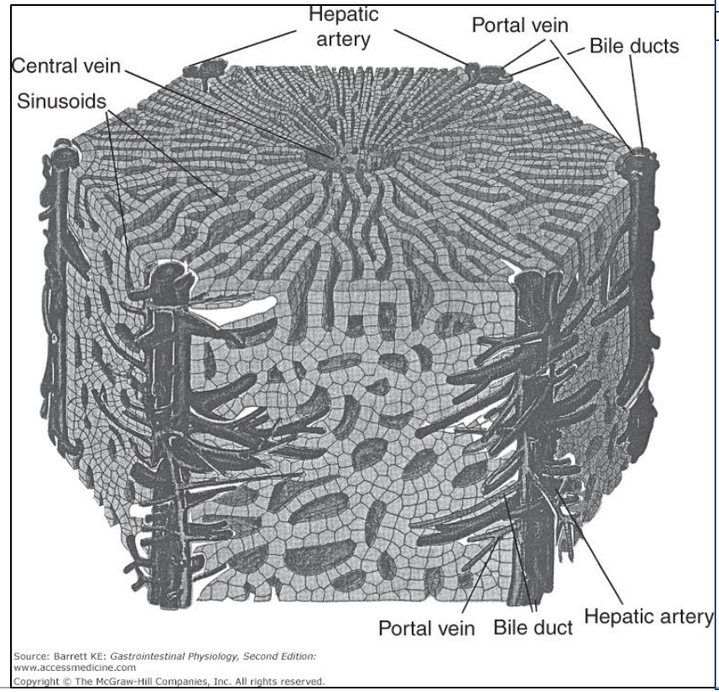
Schematic of the splanchnic circulation under fasting conditions.

Note that even during fasting, the liver receives the majority of its blood supply via the portal vein.





Schematic of the enterohepatic circulation of conjugated bile acids. Bile acids secreted by hepatocytes enter the bile and flow through the biliary system to the duodenum. Conjugated bile acids are selectively reabsorbed in the terminal ileum, and flow through the portal vein back to the liver to be reabsorbed by hepatocytes and resecreted.



Arrangement of blood vessels, bile ducts, and hepatocytes to form the liver lobule. Branches of the portal vein and hepatic artery run parallel to bile ducts in the so-called portal triads. Blood percolates through sinusoids arranged between the hepatocytes, to be collected eventually in the central vein.
(From Ross MH, Reith EJ. Histology. A Text and Atlas. New York: Harper and Row; 1985.)

Citation: Chapter 10. Functional Anatomy of the Liver and Biliary System, Barrett KE. *Gastrointestinal Physiology, 2e;* 2014. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=691&sectionid=45431411 Accessed: July 13, 2021
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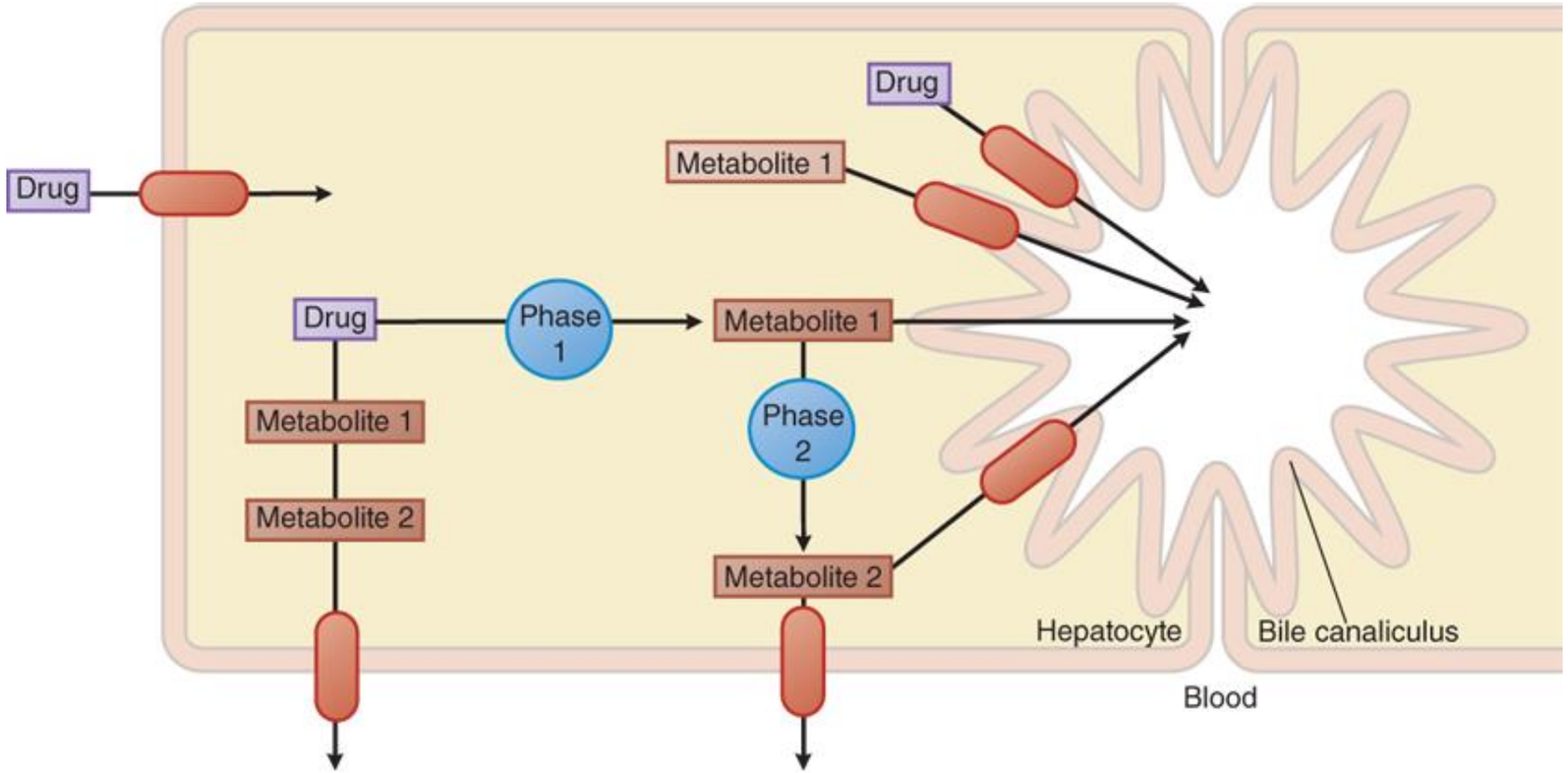
Drugs may be biotransformed into inactive, active, or toxic metabolites or more hydrophilic, readily excretable products.



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:
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Phase 1 reactions include oxidation, reduction, and hydrolysis.
Phase 1 reactions unmask a polar functional group that alters the biological properties of the drug. The drug may be inactivated (most often) or activated. Drugs may also pass through unchanged.

Phase 2 conjugation reactions transfer an endogenous molecule to the substrate (i.e. drug or phase 1 product) producing a hydrophilic metabolite that is almost always inactive.

Hepatic drug transporters. Membrane transporters (red ovals with arrows) work in concert with phase 1 and phase 2 drug-metabolizing enzymes in the hepatocyte to mediate the uptake and efflux of drugs and their metabolites.

Citation: Chapter 4 Membrane Transporters and Drug Response, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition;* 2023 Figure 4-2. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=267774770 Accessed: June 07, 2024
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First-pass metabolism (first-pass effect)

1) Initially, enzymes in the epithelial cells of the GI tract metabolize drug.

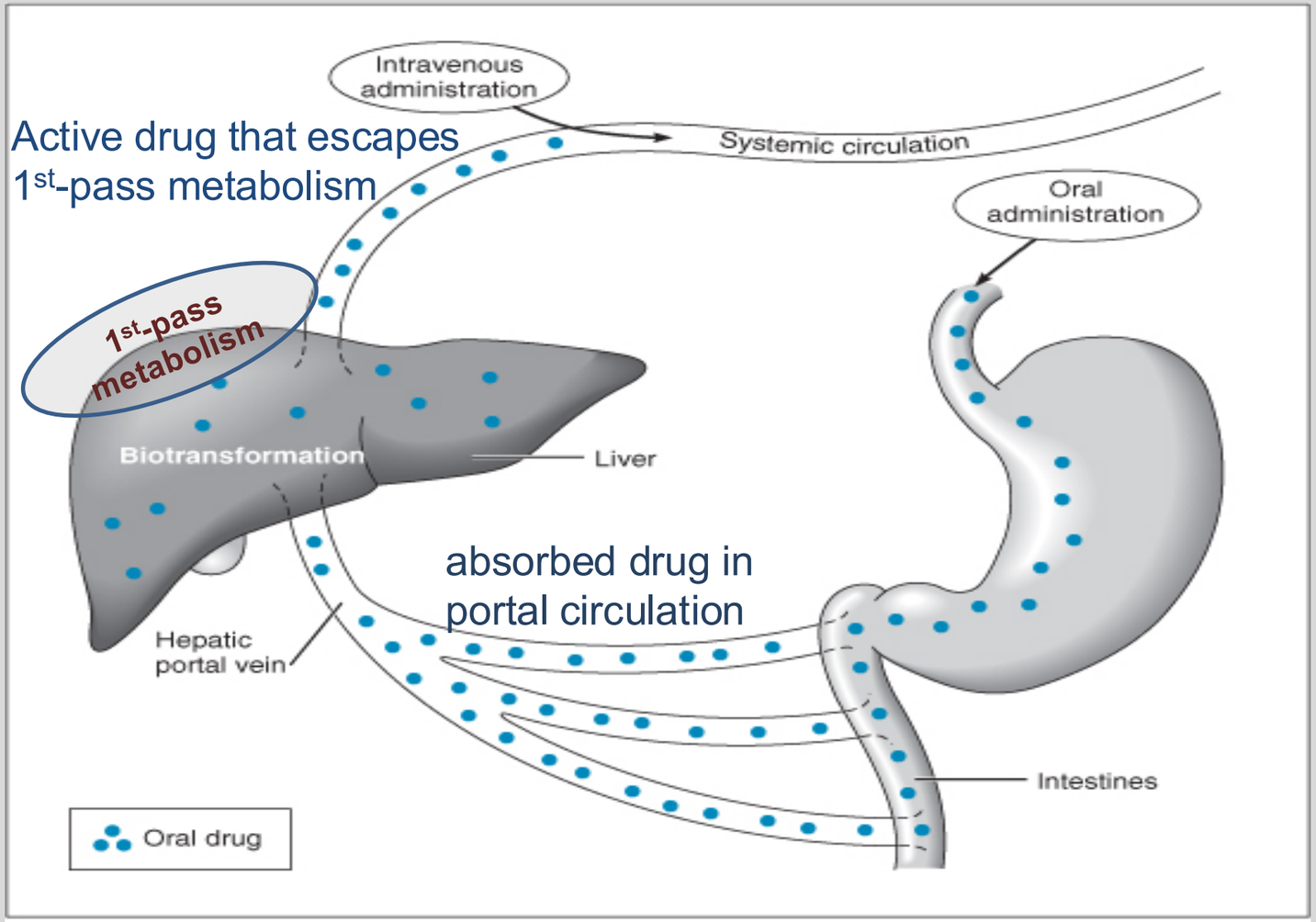
2) Absorbed drug → portal circulation → first-pass through the liver

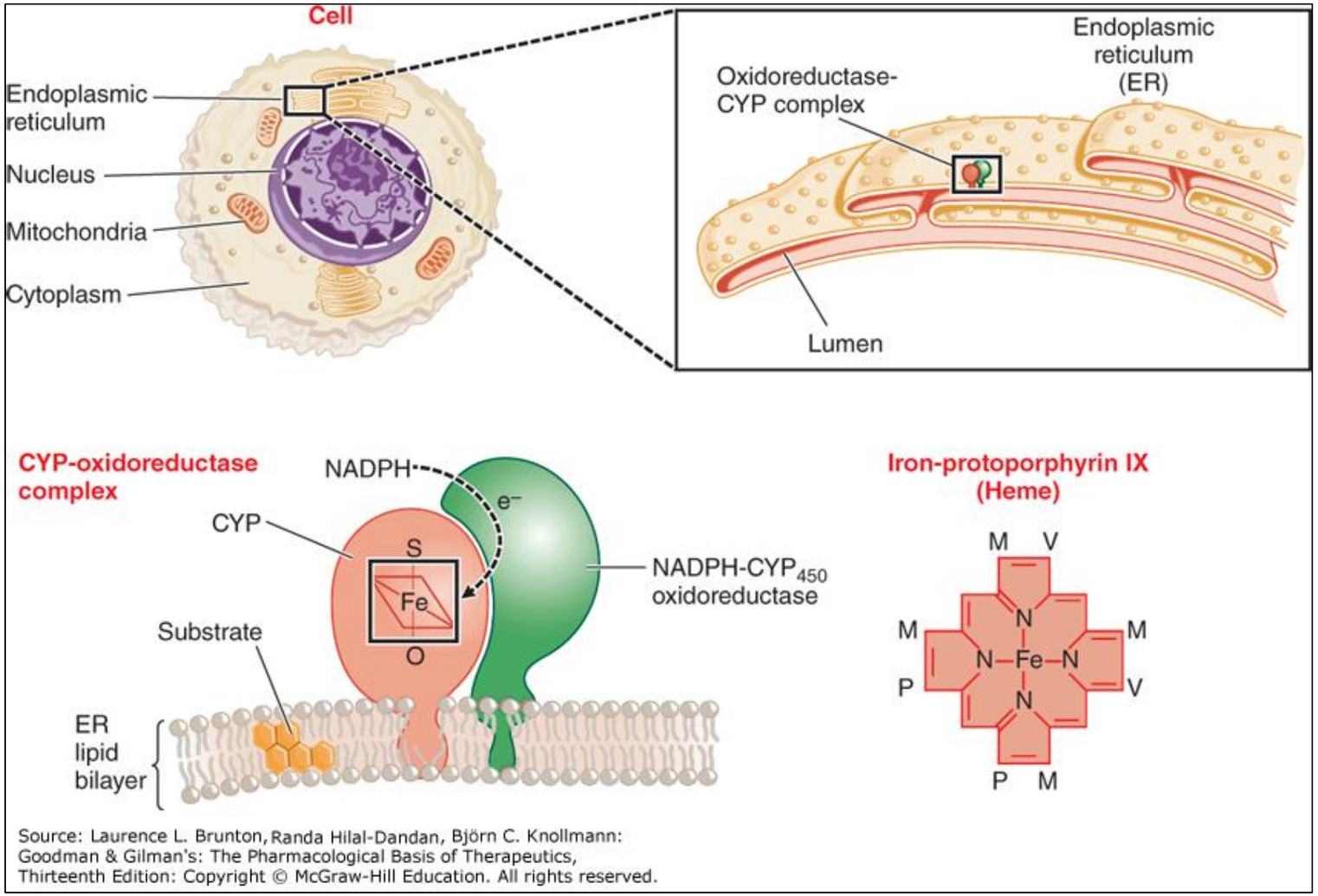
Drug can undergo significant metabolism.

3) Bioavailability:

Active (unmetabolized) drug enters systemic circulation.

Active drug that escapes first-pass metabolism is metabolized on subsequent passes through the liver until the active drug is eliminated.





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.

- CYPs are embedded in the phospholipid bilayer of the ER. Most of the enzyme is located on the cytosolic surface of the ER.
- A second enzyme, NADPH-CYP oxidoreductase, transfers electrons to the CYP where it can, in the presence of O_2, oxidize xenobiotic substrates, many of which are hydrophobic and dissolved in the ER. A single NADPH-CYP oxidoreductase species transfers electrons to all CYP isoforms in the ER.
- Each CYP contains a molecule of iron-protoporphyrin IX (heme) that functions to bind and activate O_2.

Location of CYPs in the cell. Increasingly microscopic levels of detail are shown, sequentially expanding the areas within the black boxes.

Substituents on the porphyrin ring are methyl (M), propionyl (P), and vinyl (V) groups.

Citation: Chapter 6 Drug Metabolism, Brunton LL, Hilal-Dandan R, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e;* 2017 .Figure 6-2
Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=167889421 Accessed: July 13, 2021
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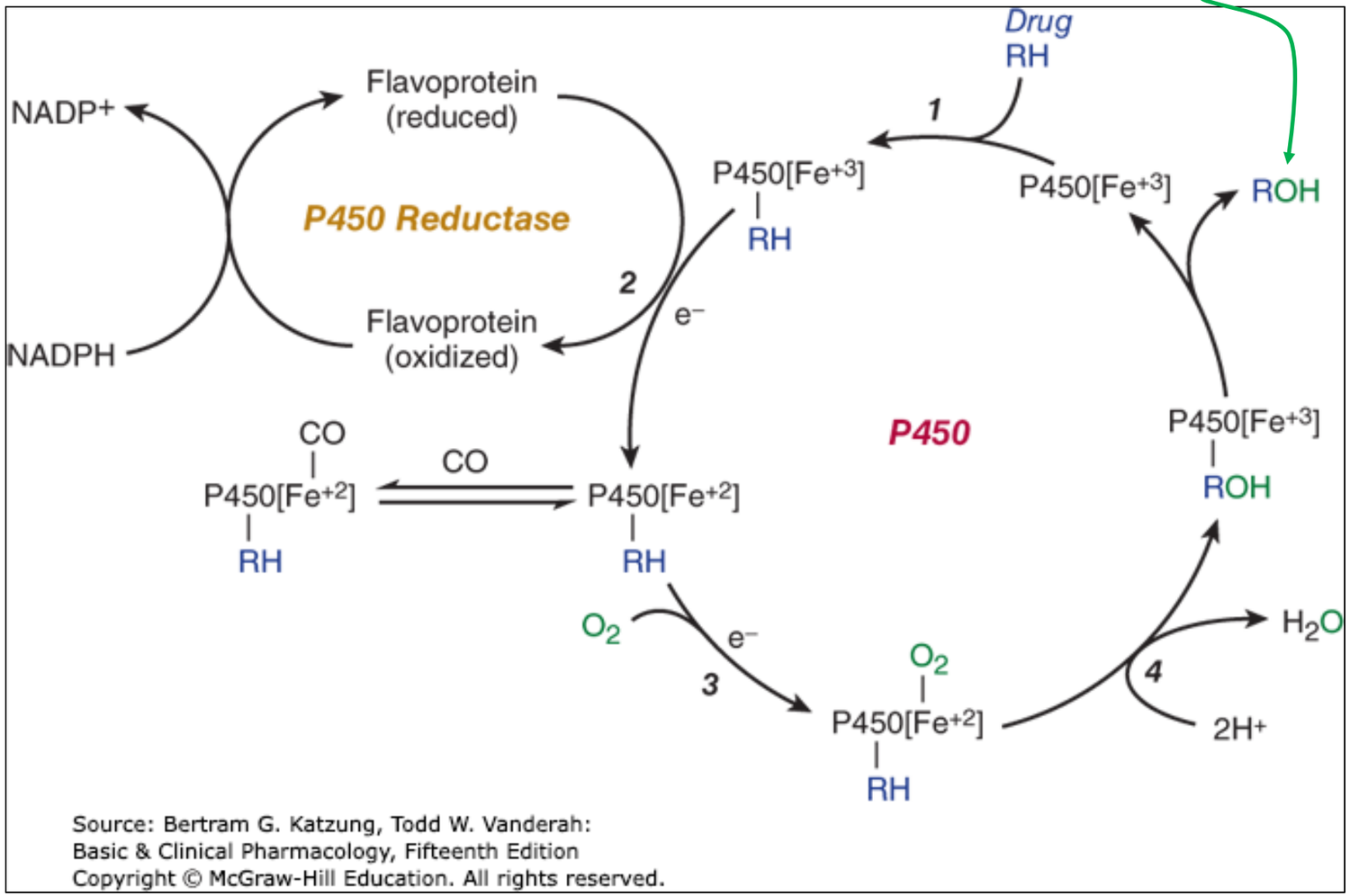
Drug + O_2 + NADPH + H^+ → Drug product$_{\text{oxygen incorporated}}$ + H_2O + $NADP^+$



Source: Bertram G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, Fifteenth Edition
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Cytochrome P450 cycle in drug oxidations. e^-, electron; RH, parent drug; ROH, oxidized metabolite.

1 oxygen molecule, O_2, is consumed per molecule of substrate.

1 atom of oxygen in the product and 1 atom of oxygen as H_2O.

High potential for drug interactions:

CYPs are subject to inhibition and induction (by increased expression of the enzymes).

Citation: Chapter 4 Drug Biotransformation, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021. Figure 4-3 Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250594466 Accessed: July 13, 2021
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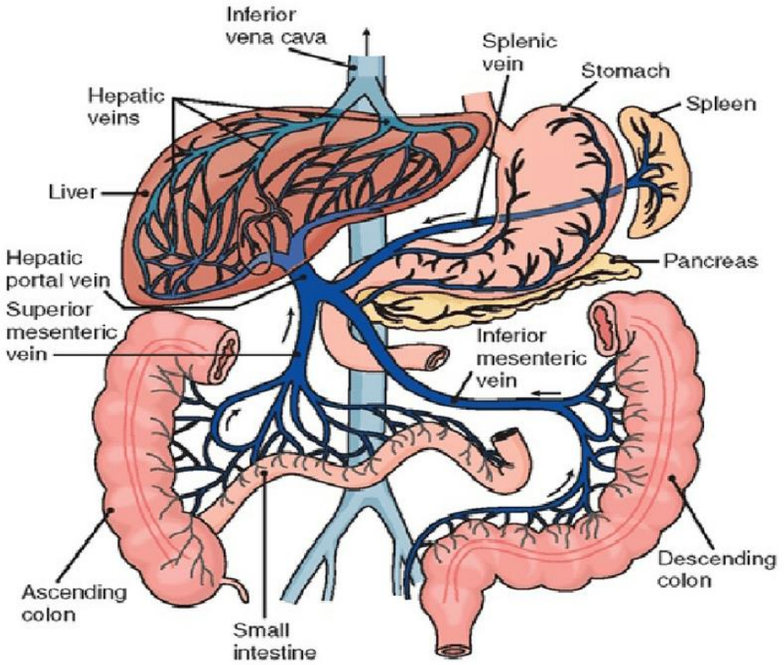
Check your knowledge of CYP metabolism: Fill in the blanks

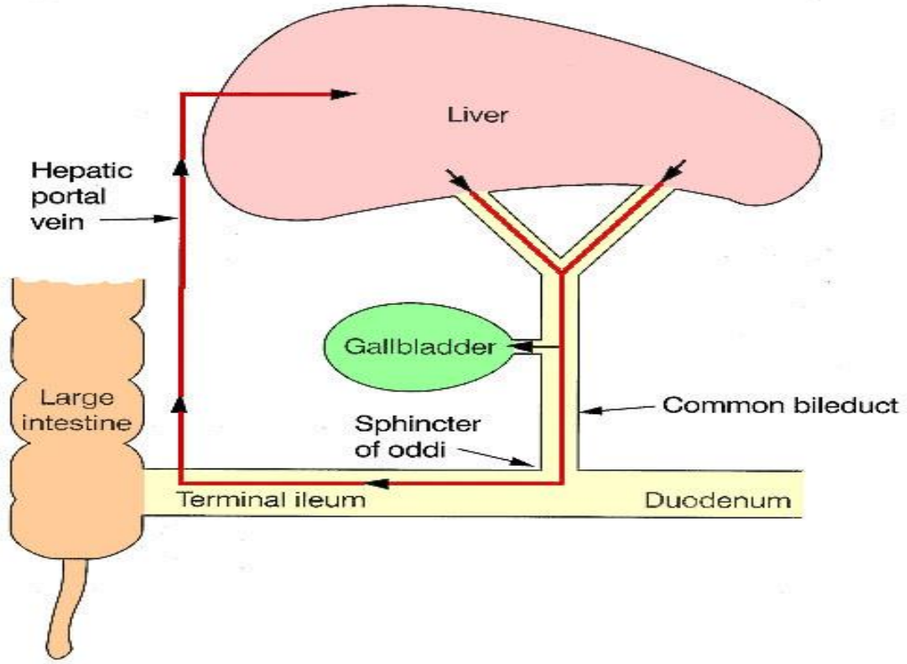
CYP metabolism requires what three elements?	
CYPs are susceptible to alterations in rates of drug elimination by what?	
How do these alterations potentially affect patient care?	
How is a knowledge of clinically relevant pharmacokinetic properties of drugs essential for patient care?	

The right drug in the right dose for the right duration
→ optimal outcomes = optimization of therapy

Enterohepatic Circulation of Glucuronide Metabolites



https://www.researchgate.net/figure/Hepatic-Portal-Circulation_fig1_268212871

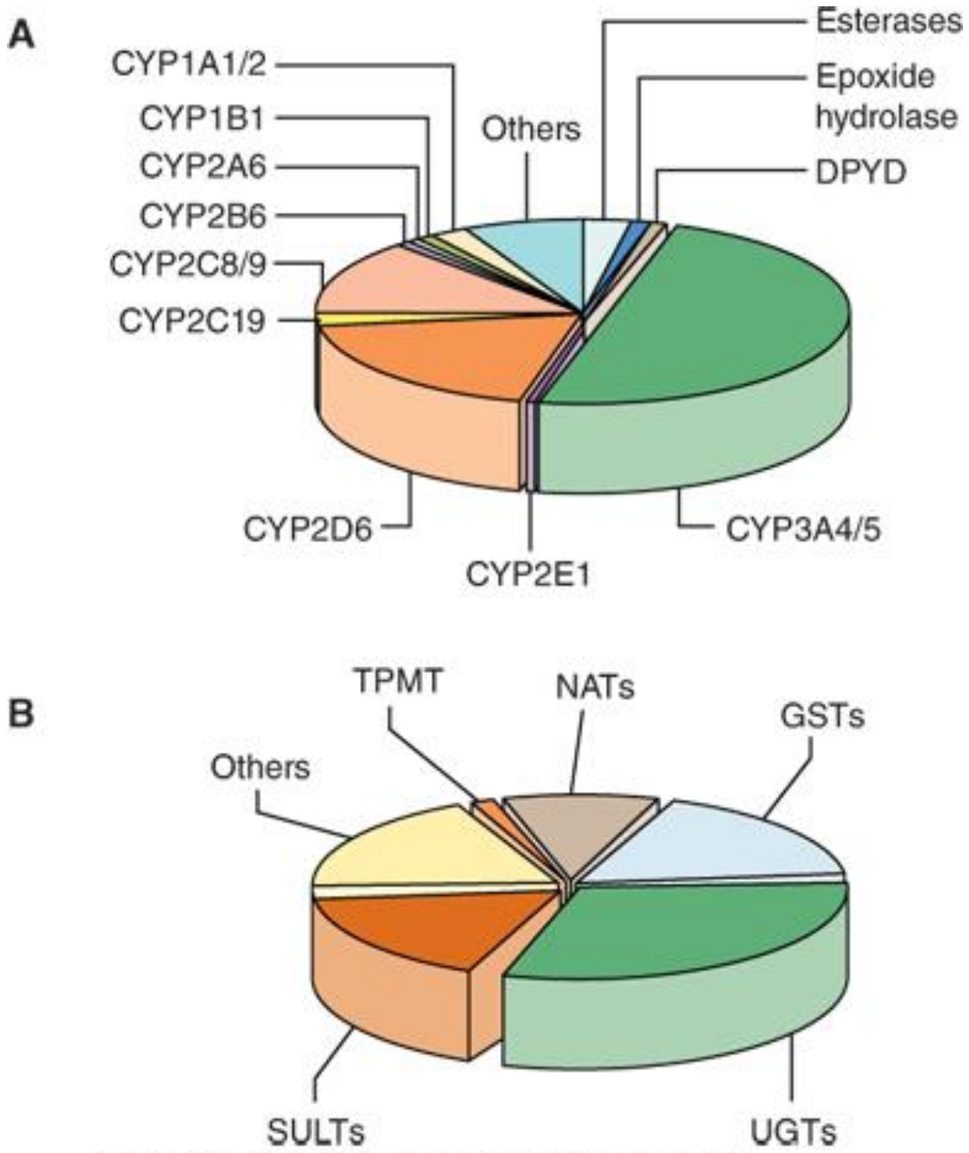


http://www.nurseprescriber.co.uk/education/visual_lib/vl_basicpharm.htm

Drug is swallowed → drug is absorbed from small intestine → portal vein → liver → glucuronide metab → gall bladder

THEN…

1. Glucuronide metabolites excreted in bile are transported to the duodenum along with the bile
2. β-glucuronidase of intestinal bacteria flora cleave drug conjugates
3. Liberates the drug into the intestinal lumen
4. Passive diffusion of the free drug through intestinal epithelium → drug reenters the portal circulation → back to the liver



Source: Bertram G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, Fifteenth Edition
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A. Relative contributions of various cytochrome P450 isoforms.

B. Relative contributions of various phase 2 transferases.

Many drugs are metabolized by two or more of these pathways.

Note that two pathways CYP3A4/5 and UGT are involved in the metabolism of the majority of drugs in clinical use.

DPYD, dihydropyrimidine dehydrogenase;
GST, glutathione-S-transferase;
NAT, N-acetyltransferase;
SULT, sulfotransferase;
TPMT, thiopurine methyltransferase;
UGT, UDP-glucuronosyltransferase.

Citation: Chapter 4 Drug Biotransformation, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021. Figure 4-4. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250594466 Accessed: July 13, 2021
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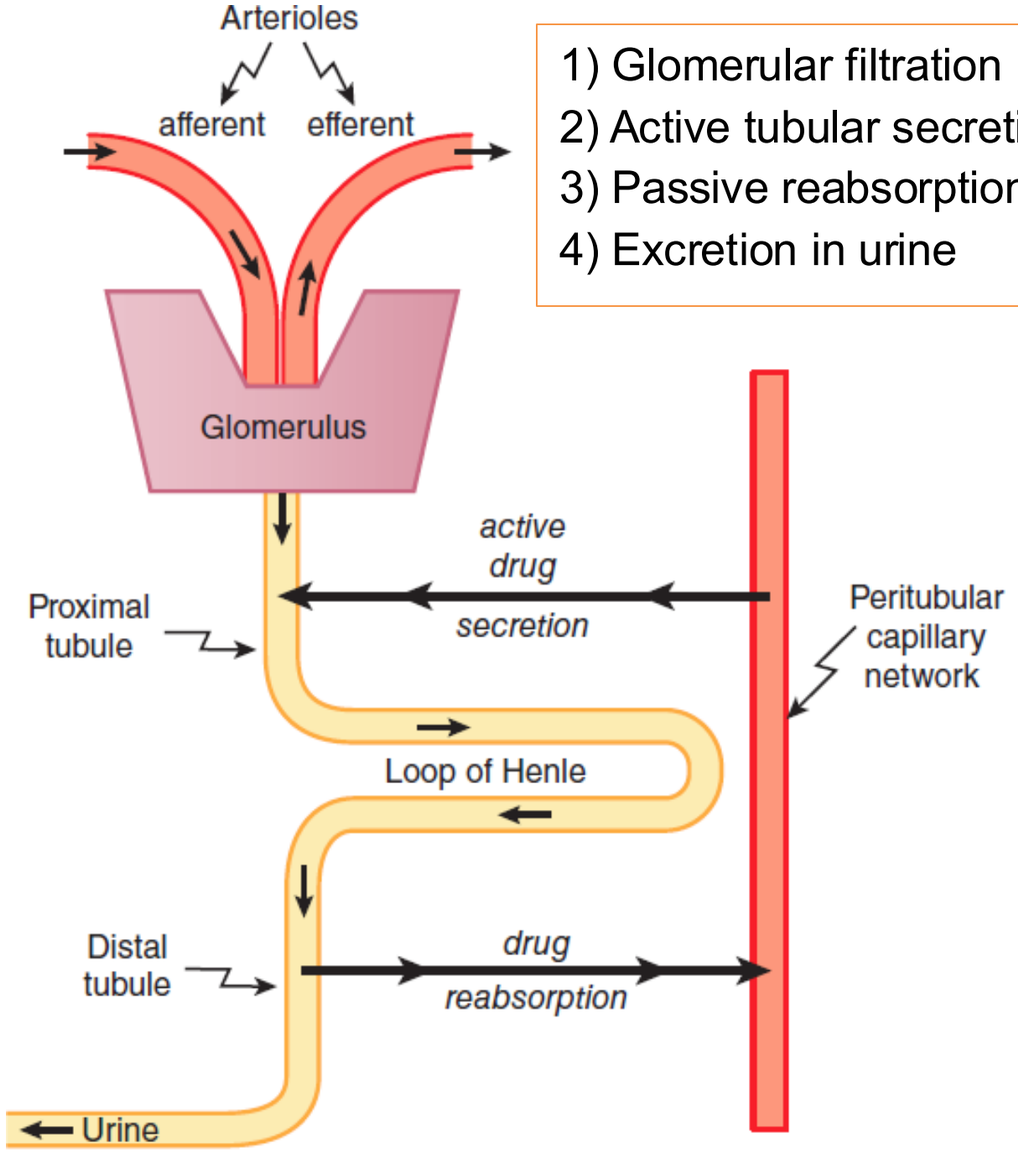

1) Glomerular filtration
2) Active tubular secretion
3) Passive reabsorption
4) Excretion in urine

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,
- actively secreted into the proximal tubule,
- passively reabsorbed from the distal tubular fluid back into the systemic circulation,
- and collected in the urine.

Membrane transporters, OAT, OCT, MDR1 (P-gp), and MRP2, among others mediate secretion into the proximal tubule.

Reabsorption of compounds from the distal tubular fluid (generally acidic) is pH sensitive:

Ionizable drugs are subject to ion trapping.

Altering urinary pH to favor ionization can enhance excretion of charged species.

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. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=166182905
Accessed: July 13, 2021
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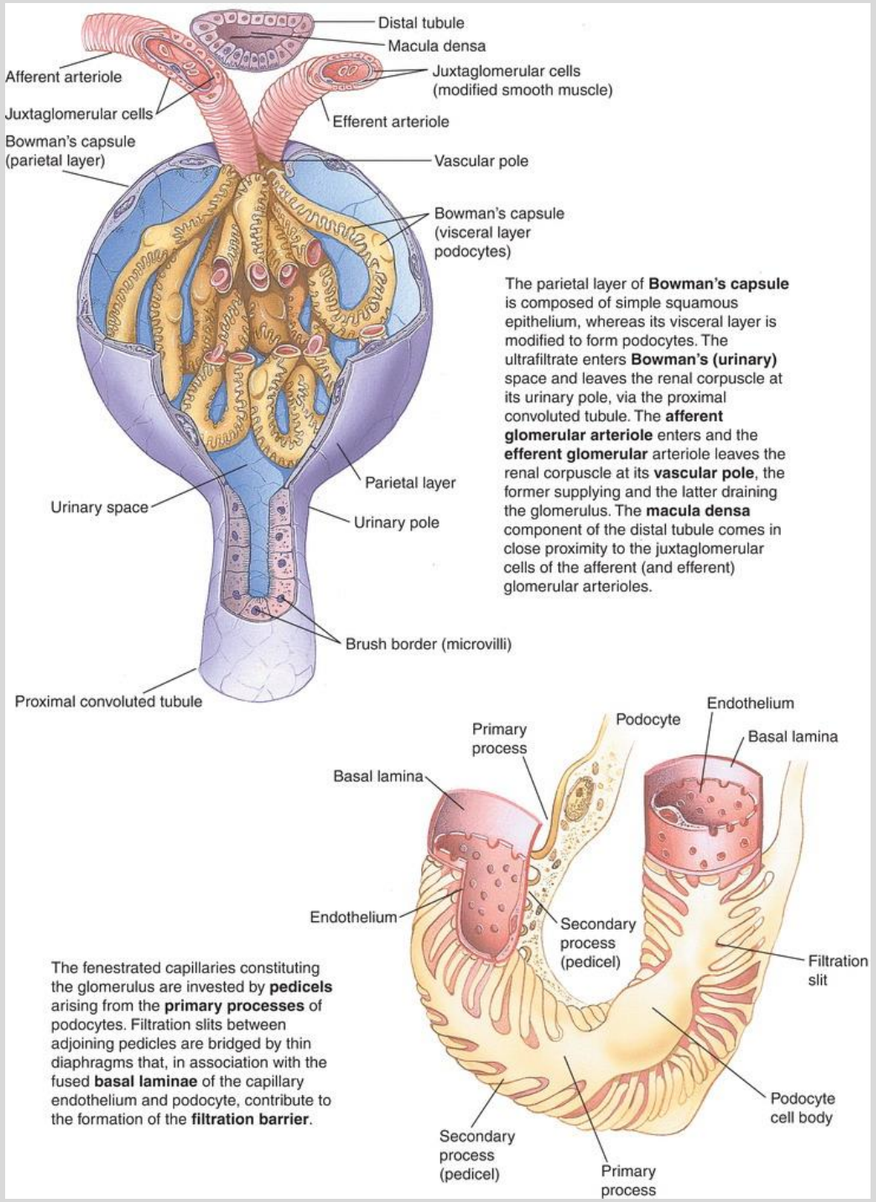
Assessment of kidney function is necessary for the safe use of drugs.



- The glomerulus is the tuft of capillaries at the beginning of each nephron (the functional units of the kidney).
- The glomerulus filters the plasma. The filtrate contains inorganic ions and low molecular weight organic solutes in the same concentrations as in plasma.
- Selectivity of the filtration barrier is crucial for renal function.

THE TAKEAWAY

- The glomerular filtration rate (GFR) is a determinant of renal function. GFR is a useful measure of renal function (although there are limitations).
  - GFR = sum of functioning nephrons →
  - Rough measure of the number of functioning nephrons

LWW Health Libraries Color Atlas and Text of Histology, 7e; Chapter 16: Urinary System, Figure 16-2 Renal Corpuscle

The older patient and the neonate:

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Changes in the older patient that can impact drug therapy:

- Multiple concurrent diseases, such as:

  hypertension, heart disease, arthritis, osteoporosis, cancer, prostate disease
- ↓ Intestinal motility and ↓ blood flow
- ↓ Muscle mass and ↑ total body fat
- ↓ Kidney function
- ↓ Liver function
- General structural and functional changes in the brain

The neonate: Immature ADME processes alter absorption, distribution, metabolism, and excretion:

- Blood flow, GI function influences absorption
- Higher percentage of water, low muscle mass, low total body fat
- Lower plasma protein binding capacity
- Low activity of drug metabolism enzymes and transporters
- Low GFR, reduced kidney function

Drug excretion

- Most drugs are excreted in urine, either as the parent compound (unchanged drug) or as metabolites with polar characteristics. Minor routes of excretion include sweat, saliva, tears, skin, hair, and breast milk.
- The processes involved in renal elimination are glomerular filtration, active tubular secretion, and passive tubular reabsorption (lipophilic drugs). Only free drug molecules (not bound to plasma proteins) are filtered by the glomerulus.
- The concentration of drug excreted in urine results from the amount of drug introduced to the nephrons by glomerular filtration and secretion in the proximal tubule, minus the amount reabsorbed in the distal tubule. Inter-individual variations can affect the rate and extent of drug elimination.
- Serum creatinine and creatinine clearance are biomarkers of renal function. They are used to estimate the glomerular filtration rate (GFR) in the assessment of kidney function for the individual patient.

Answers to the CYP metabolism Fill in the blanks

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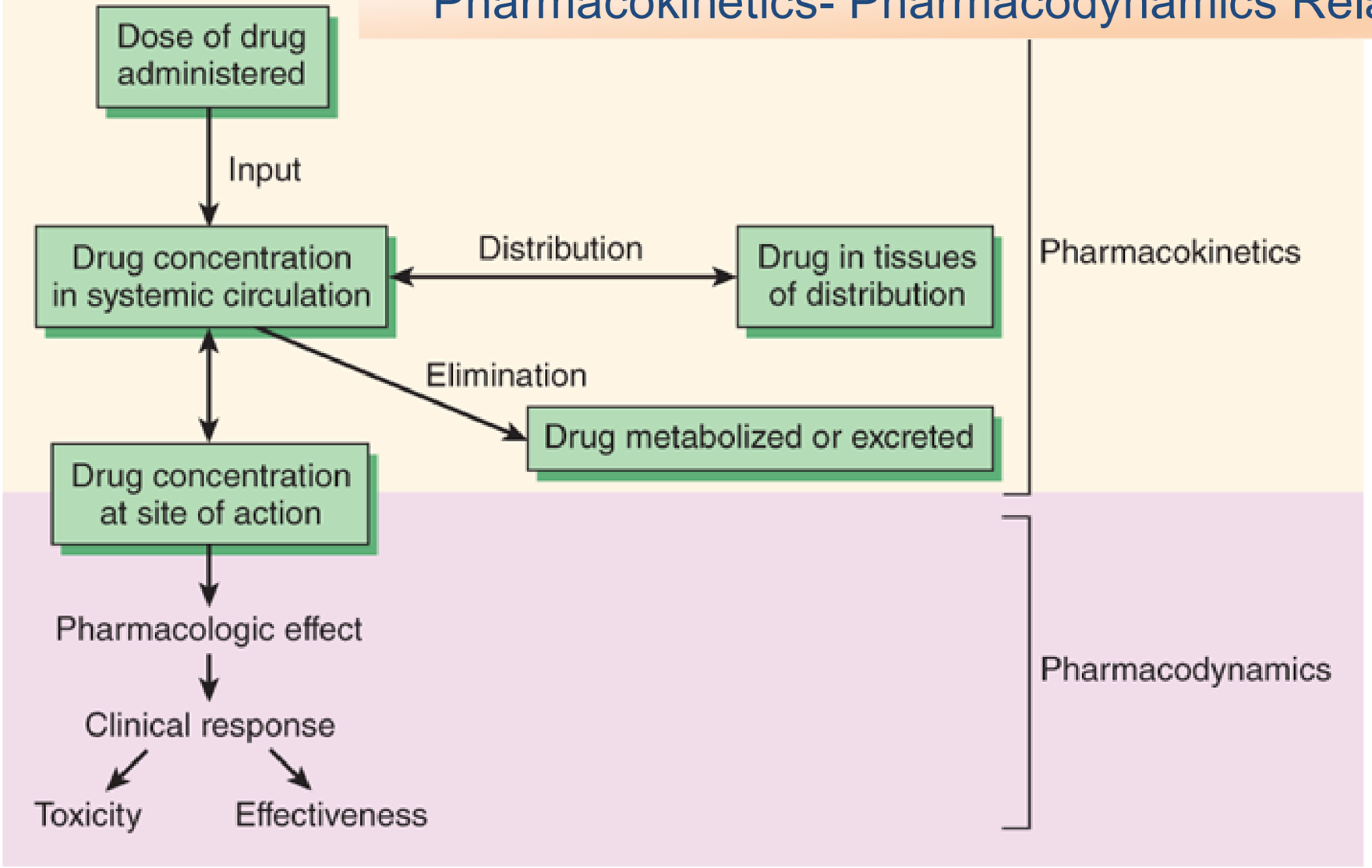
CYP metabolism requires what three elements?	heme, NADPH (reducing agent), and oxygen CYP 450 enzymes are monooxygenases.
CYPs are susceptible to alterations in rates of drug elimination by what?	Inhibition or induction of CYPs and by pharmacogenetic variabilities
How do these alterations potentially affect patient care?	Alterations in plasma drug concentrations can lead to increased potential for toxicity (inhibition or underfunctioning enzyme) or reduced efficacy (induction or ultrarapidly functioning enzyme)
How is a knowledge of clinically relevant pharmacokinetic properties of drugs essential for patient care?	Mechanisms of drug interactions and effects of organ function on plasma drug levels

The right drug in the right dose for the right duration
→ optimal outcomes = optimization of therapy

https://www.dreamstime.com/illustration/patients.html

Understanding and employing pharmacokinetic principles can increase the probability of therapeutic success and reduce the occurrence of adverse drug effects in the body for the **optimization of drug therapy in the individual patient**.

Pharmacokinetics- Pharmacodynamics Relationship



Source: Bertram G. Katzung, Todd W. Vanderah:
Basic & Clinical Pharmacology, Fifteenth Edition
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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.**
Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250594300 Accessed: July 12, 2021
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After completing preparation material, students should be able to:

1. List the factors influencing the concentration, effect and time course of drug action.
2. Describe the mechanisms of drug permeation across physiologic barriers and give examples of passive diffusion and active transport mechanisms.
3. Explain the pH-dependent behavior of weak acids and weak bases as described by the Henderson-Hasselbalch equation and give examples of drug transport across membranes and the clinical application of ion trapping.
4. Compare and contrast the advantages and disadvantages of the various routes of drug administration.
5. Summarize the processes of, and barriers to, distribution of drugs to extracellular fluids and tissues, including binding to plasma proteins and tissue macromolecules.

mechanisms, mechanisms, mechanisms

Links

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Scholar Rx Bricks: (Required)

General Principles

Pharmacology: Foundations and Frameworks https://exchange.scholarrx.com/brick/pharmacology-foundations-and-frameworks

Pharmacokinetics: Drug Transport and Diffusion https://exchange.scholarrx.com/brick/drug-transport-and-diffusion

Pharmacokinetics: Drug Administration, Metabolism, and Excretion https://exchange.scholarrx.com/brick/drug-administration-metabolism-and-excretion

Cell and Molecular Biology: Cellular Biology

Transport Across Membranes https://exchange.scholarrx.com/brick/transport-across-membranesCell Signaling https://exchange.scholarrx.com/brick/cell-signaling

TEXTBOOK

Access Medicine Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 1: Introduction > The Nature of Drugs > General Principles of Pharmacology https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281746718

REVIEW BOOKS HAVE PRACTICE QUESTIONS

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Chapter 1: Introduction > The Nature of Drugs
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LWW Health Library Premier 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

Questions help learning. Questions help to master a topic.

1. **Guided Reading Questions** are intended to help you identify what you NEED to know.
   - Other information in the reading provides context to help you understand concepts within the big picture.
2. **Practice Questions** are for your own assessment of your learning – for applying what you have learned in the context of clinical case vignettes.
   - Practicing through case vignettes will help you bridge pharmacology science and pharmacotherapeutics (clinical concepts).
3. **Write down your own questions** as you study. This practice helps you identify where you are strong and where you weak so you can focus your efforts.

Brown, Roediger, and McDaniel. *Make It Stick The Science of Successful Learning*. Belknap Press of Harvard University Press, 2014

Definitions:
Terms you need to know to understand pharmacokinetics

Absorption	Phase 1 metabolism	Weak acid
Distribution	Phase 2 metabolism	Weak base
Elimination	Cytochrome P450 (CYP) enzymes	Lipid:water partition coefficient
Metabolism	Transferases	Concentration gradient
Biotransformation	First-pass effect	Ion trapping
Excretion	Enterohepatic circulation	Passive diffusion
Bioavailability	Glomerular filtration	Aqueous diffusion
Bioequivalence	Glomerular filtration rate (GFR)	Paracellular transport
Redistribution	Tubular secretion	Facilitated transport
Xenobiotic	Reabsorption	Active transport
Central compartment	Serum creatinine	Endocytosis | Exocytosis
Plasma protein binding	ABC superfamily (transporters)	SLC superfamily (transporters)
Tissue reservoirs	P-glycoprotein (efflux transporter)	

Key points: What you need to know (and understand):

- DEFINITIONS of terms
- Physicochemical characteristics of a drug determine its ability to permeate physiologic barriers.
- The major processes involved in pharmacokinetics are absorption, distribution, metabolism, and excretion (ADME processes).
- Aqueous diffusion is the passive movement of molecules through watery extracellular and intracellular spaces.
- Lipid diffusion is the passive diffusion of drugs across lipid bilayers of cell membranes and other lipid barriers.
- The concentration gradient drives diffusion. Fick's law predicts the rate of movement of molecules across a barrier.
- Drugs that do not readily diffuse through membranes may be transported across barriers by transporter molecules – channels, facilitated carriers, and active transporters and, to a minor extent by endocytosis. Transporters have a maximum capacity – they are saturable.

What you need to know (and understand):

- Many drugs are weak acids and weak bases. The pH of the medium determines the fraction of the molecules in the charged (ionized hydrophilic) form and the fraction in the nonionized state. The nonionized forms can readily pass through lipid bilayers by passive diffusion, whereas the ionized forms cannot.
- If the pKa of the drug and the pH of the environment are known, the ratio of the concentrations of the weak acid or weak base in the ionized and nonionized states can be calculated using the Henderson-Hasselbalch equation.
- Weak acids are not ionized when they are protonated (HA). Weak bases are ionized when they are protonated (BH^+).
- The Henderson-Hasselbalch relationship is clinically important when it is necessary to estimate or alter the partition of drugs between compartments of differing pH, such as the blood and urine. Altering the pH of the urine can trap the ionized form in the urine (“ion trapping”) and increase the rate and extent of drug excretion in the urine.

What you need to know (and understand):

- A drug must be absorbed from its site of administration, unless it is injected directly into the blood stream (vascular compartment).
- The rate and efficiency of absorption differ depending on the route of administration and the drug's physicochemical properties. There are advantages and disadvantages of each route of administration (listed in the summary of this PowerPoint).
- The bioavailability of a drug is the fraction of the dose that reaches the systemic circulation.
- Blood flow influences the rate of uptake of a drug. The solubility of a drug in tissue influences the concentration of drug in extracellular fluid (for example, the brain has a high lipid content and rapidly dissolves a high concentration of lipid soluble drugs).
- Binding to plasma proteins tends to increase concentration of the drug in the blood. Binding to inert extravascular tissue macromolecules tends to increase concentration in the tissues and decrease concentration in the blood.

What you need to know (and understand):

- Drug elimination is the sum of the processes removing active drug from the body. The liver is the primary organ of metabolism, but extrahepatic metabolism can occur in many organs. The kidney is the primary organ of excretion of drug and metabolites, but other organs are also involved.
- Drug metabolism (biotransformation) that converts a drug to biologically inactive metabolites terminates the action of the drug. Drug metabolism may convert an active drug to active metabolites or to toxic metabolites.
- Metabolism of an inactive prodrug converts it to an active drug molecule.
- Some drugs given orally are highly metabolized in the gut and/or liver before reaching the systemic circulation, resulting in low bioavailability. This is called the first-pass effect or first-pass metabolism.
- Some drugs are not modified in the body (not metabolized). They are excreted as unchanged drug.

What you need to know (and understand):

- Two processes are involved in the hepatic metabolism (biotransformation) of drugs, known as phase 1 and phase 2 metabolism.
- Enzymes of phase 1 metabolic reactions catalyze the oxidation, reduction, and hydrolysis of exogenous molecules (xenobiotics), as well as endogenous molecules, by exposing a polar functional group. The cytochrome P450 mixed-function oxidases (CYPs) are the predominant enzymes involved in oxidative metabolism.
- Enzymes (transferases) of phase 2 metabolic reactions catalyze the transfer of a functional group from an endogenous cofactor onto a nonpolar drug or metabolite, resulting in a hydrophilic drug conjugate that is readily excreted. Phase 2 metabolites are largely inactive, with a few exceptions.
- Some drug conjugates, especially glucuronide conjugates, undergo biliary excretion and enterohepatic circulation.

  In biliary excretion, drug molecules or drug metabolites are secreted from the liver into the biliary system. When the person eats a fatty meal, the drug or metabolite is released into the gut along with the bile acids. The drug travels through the intestine and may be reabsorbed in the terminal ileum (enterohepatic circulation) or excreted in the feces.

What you need to know (and understand):

- The processes influencing the renal excretion of drugs and metabolites are glomerular filtration of unbound drug dissolved in plasma, active tubular secretion of many diverse molecules into the proximal tubule of the nephron, and passive reabsorption of lipid soluble drugs in the distal tubule.
- The dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients because of individual differences in drug distribution and rates of drug metabolism and elimination.
- These differences are determined by genetic factors and non-genetic variables, such as age, sex, liver size, liver function, circadian rhythm, body temperature, and nutritional and environmental factors, including concomitant exposure to inducers or inhibitors of drug metabolism.

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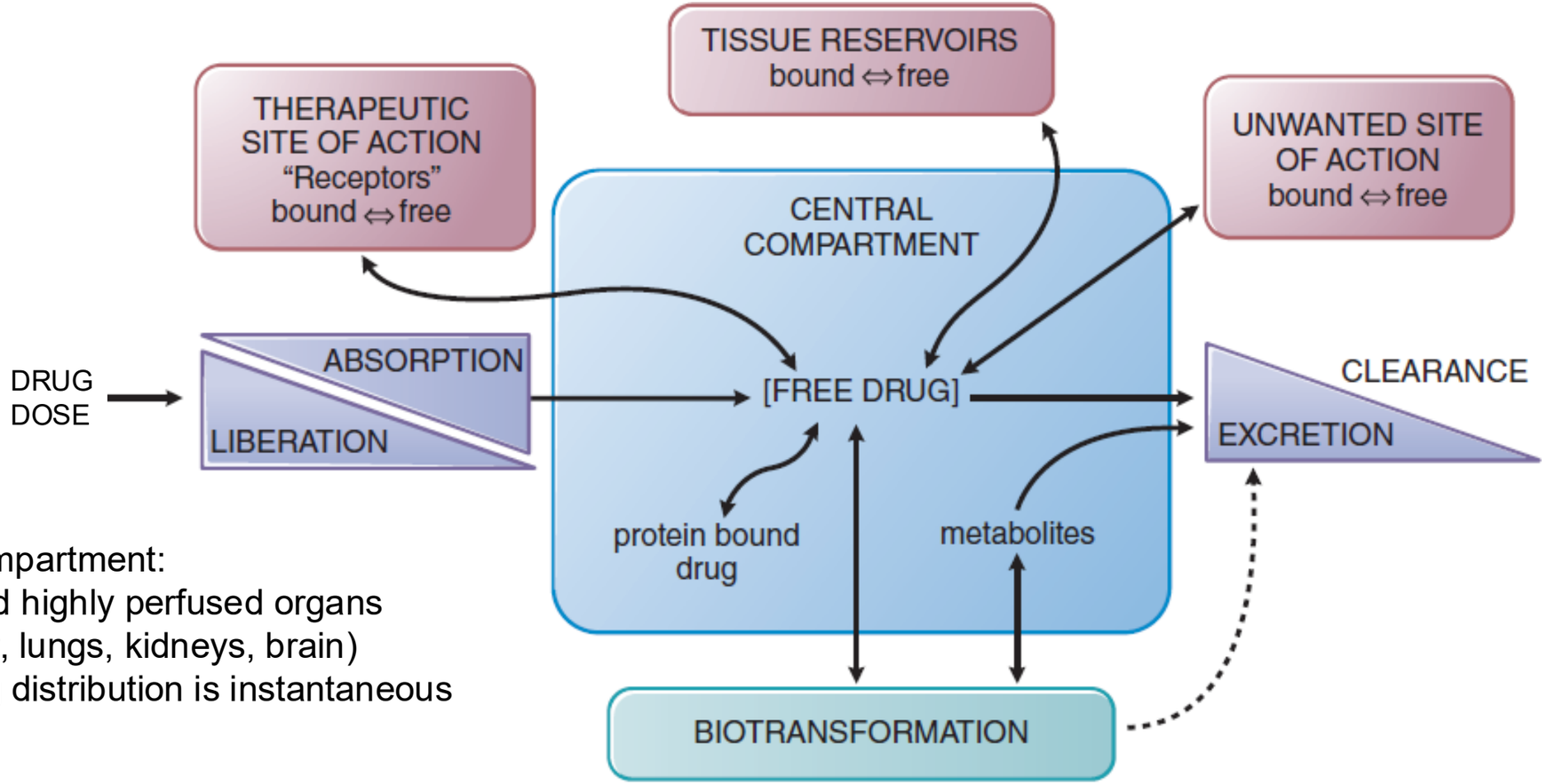
Outline

Topics presented in this video are:

- Drug absorption
- Weak acids, weak bases, and the Henderson-Hasselbalch equation.
- Ion trapping
- Routes of administration (a brief mention)
- Drug distribution
- Plasma protein binding and tissue reservoirs.

Topics presented in ScholarRx Bricks:

- Passive diffusion of drug across physiologic barriers and Fick's law.
- Weak acids, weak bases, and the Henderson-Hasselbalch relationships.
- Ion trapping
- Transport across membranes
- Routes of administration



Central compartment:
Plasma and highly perfused organs
(liver, heart, lungs, kidneys, brain)
where drug distribution is instantaneous

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.

The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action. Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

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**. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=166182905 Accessed: July 12, 2021
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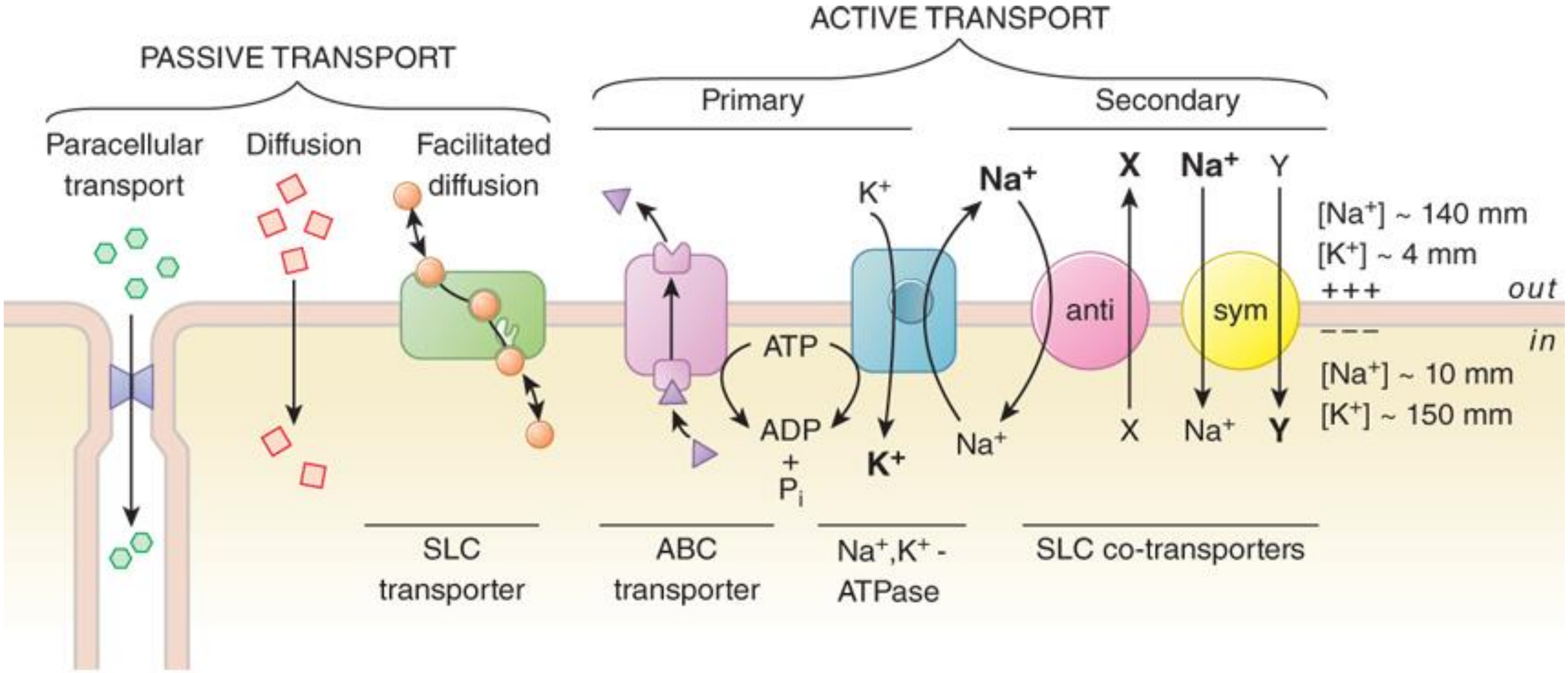
A useful drug must be able to…..

- Withstand digestive fluids and enzymes (drugs administered to the GI tract).
- Cross physiological barriers.
- Survive metabolic processes and achieve therapeutic concentrations of active drug in the systemic circulation.
- Distribute to the site of action.
- Exit the site of action after providing the specific effect of the drug.
- Undergo elimination:
  - metabolism to inactive metabolites, which terminates the drug's effects,
  - excretion of unchanged drug and active metabolites (and, of course, inactive metabolites).



Source: Laurence L. Brunton, Björn C. Knollmann:
Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:
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Drugs move across membrane and cellular barriers in a variety of ways.

Citation: Chapter 2 Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition;* 2023, Figure 2-2. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=267905627
Accessed: June 07, 2024
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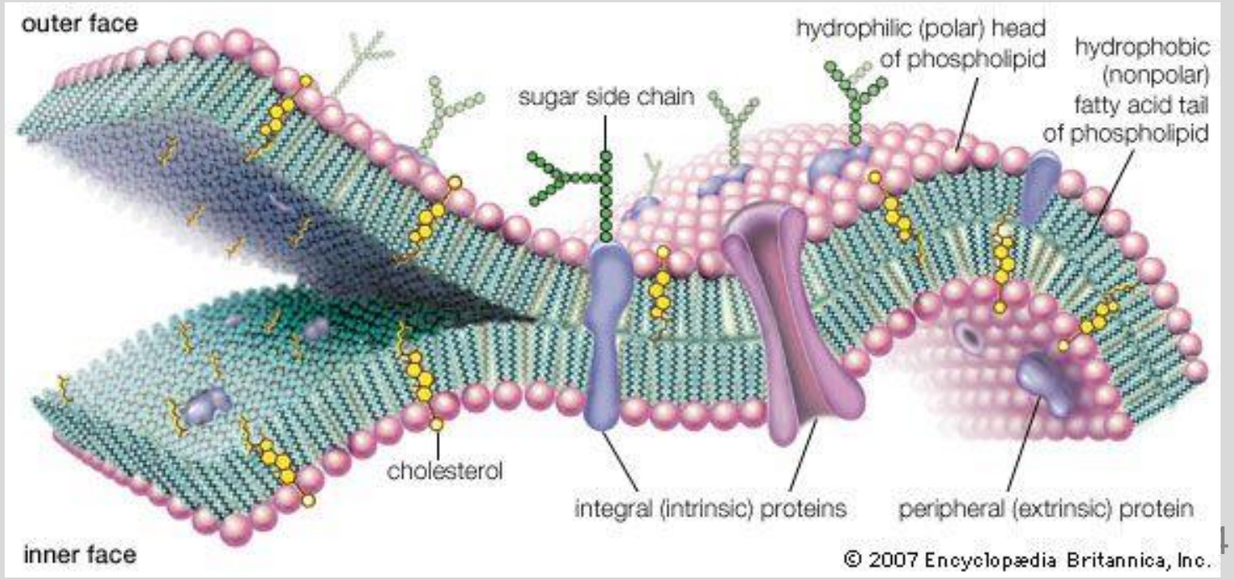
Passive Diffusion of Lipid-Soluble Drugs Across Cell Membranes

The concentration gradient drives drug diffusion.

Rate and extent of flow are influenced by the:

- Magnitude of the concentration gradient across the membrane
- Lipid-water partition coefficient of the drug
- Membrane surface area exposed to the drug
- Membrane permeability
- Membrane thickness

🔑 **Passive diffusion of drugs is not energy-dependent and not saturable.**

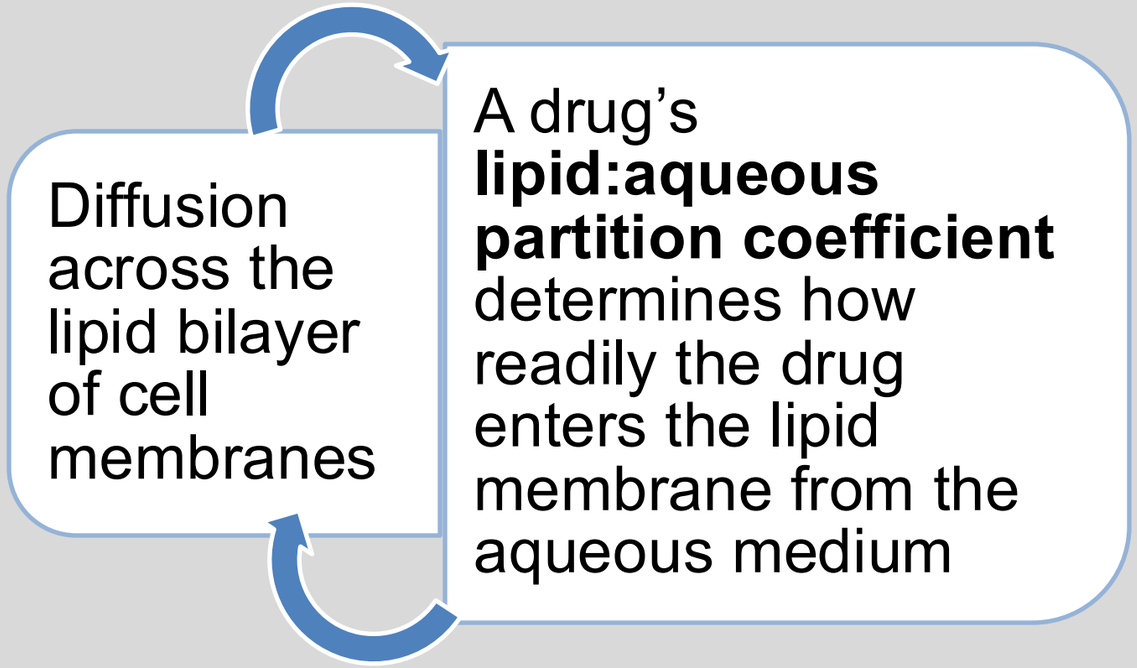


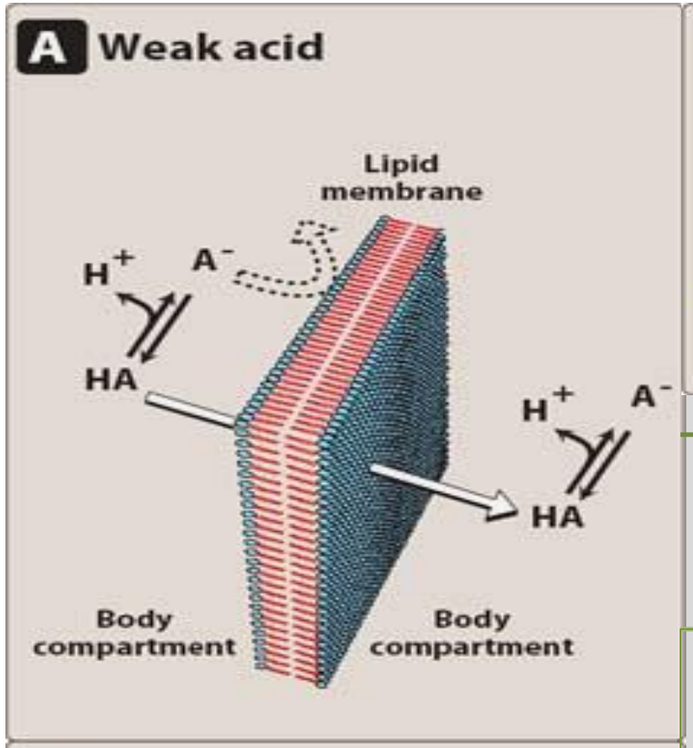
Fick's law of diffusion predicts the rate of the movement of molecules across a physiologic barrier

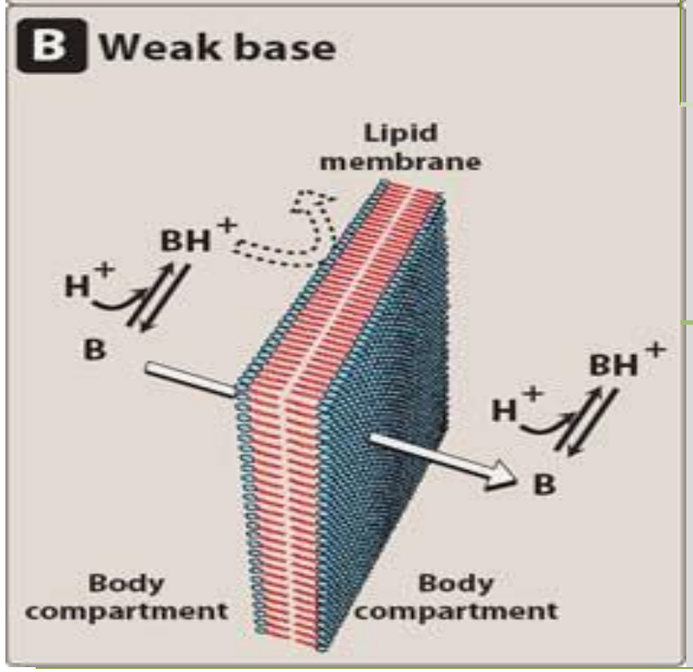
A solute will move from a region of high concentration to a region of low concentration across a concentration gradient.

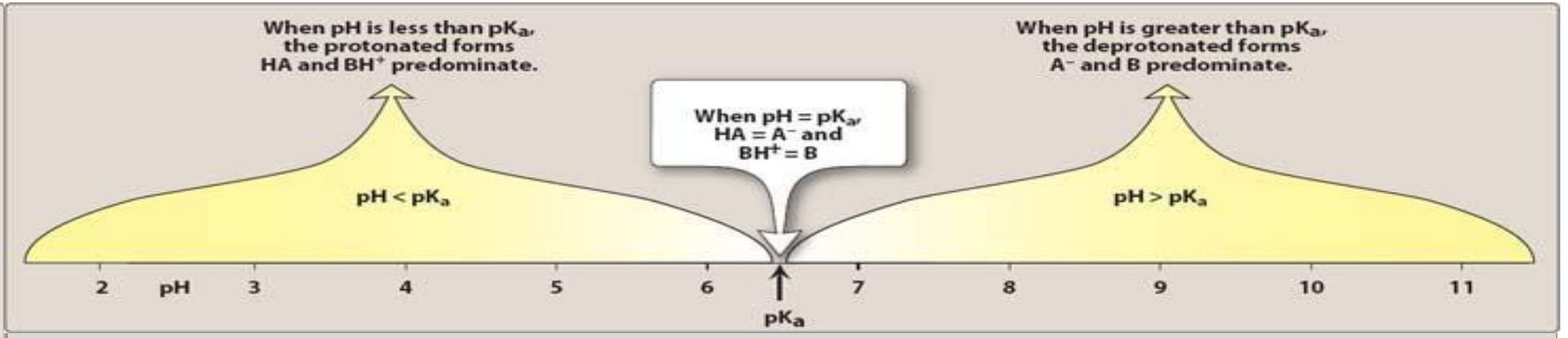
$$\text{Diffusion flux} = \underset{\text{(molecules per unit time)}}{C1 - C2} \times \underset{\text{(concentration gradient)}}{\frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}}$$

- C1: higher concentration
- C2: lower concentration
- Area: cross-sectional area of the diffusion path
- Permeability coefficient: a measure of the mobility of the drug molecules in the medium of the diffusion path
- Thickness: The thickness of the diffusion path









Nonionized molecules *diffuse readily* across the cell membrane

Ionized molecules have low lipid solubility and are less able to penetrate lipid membrane.

Weak acids release H+ forming the charged anion A^-

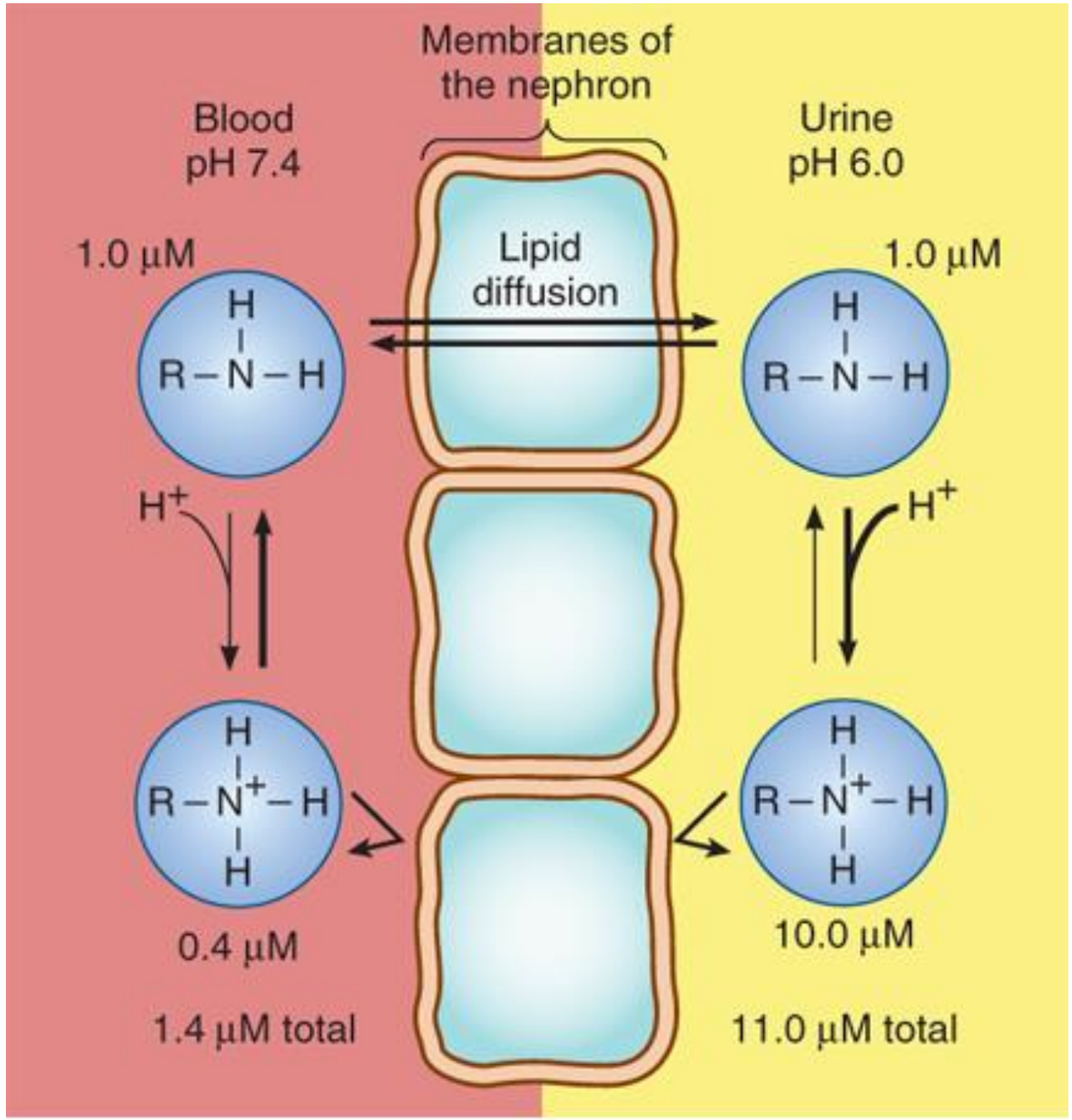
$$HA \leftrightarrows H^+ + A^-$$

Weak bases (B) combine with $H^+ \rightarrow$ charged form

$$B + H^+ \leftrightarrows BH^+$$

Loss of the proton produces the uncharged base B.

Lippincott Illustrated Reviews: Pharmacology, Figures 1.7 and 1.8



Source: M. Kruidering-Hall, B. G. Katzung, R. L. Tuan, T. W. Vanderah: Katzung's Pharmacology Examination & Board Review, 14th Edition
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Ion Trapping: The clinical importance of the Henderson-Hasselbalch relationship for altering the partition of drugs between compartments of differing pH – the blood and urine in this example.

The nonionized, uncharged form diffuses readily across the lipid barriers of the nephron. Thus, this form may reach equal concentrations in the blood and urine (at steady state).

The ionized form does not diffuse as readily because of protonation in the blood and the urine.

Example: Pyrimethamine, a weak base of pK_a 7.0

- At blood pH, only 0.4 µmol of the protonated species will be present for each 1.0 µmol of the unprotonated form. The total concentration in the blood will thus be 1.4 µmol/L.
- In the urine at pH 6.0, 10 µmol of the nondiffusible ionized form will be present for each 1.0 µmol of the unprotonated, diffusible form. Therefore, the total urine concentration (11 µmol/L) may be almost 8 times higher than the blood concentration.

Citation: Chapter 1 Introduction, Kruidering-Hall M, Katzung BG, Tuan R, Vanderah TW. *Katzung's Pharmacology Examination & Board Review, 14th Edition;* 2024, Figure 1-2. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3461&sectionid=285588535 Accessed: June 10, 2024
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SLC superfamily

- ***S****o****l****ute* ***c****arrier*

Carrier proteins and Channels

- Facilitated diffusion down a concentration gradient
- Energy not required

Secondary active transporters

- One substance (ie Na^+) moving down its concentration gradient supplies the energy for the movement of another substance.

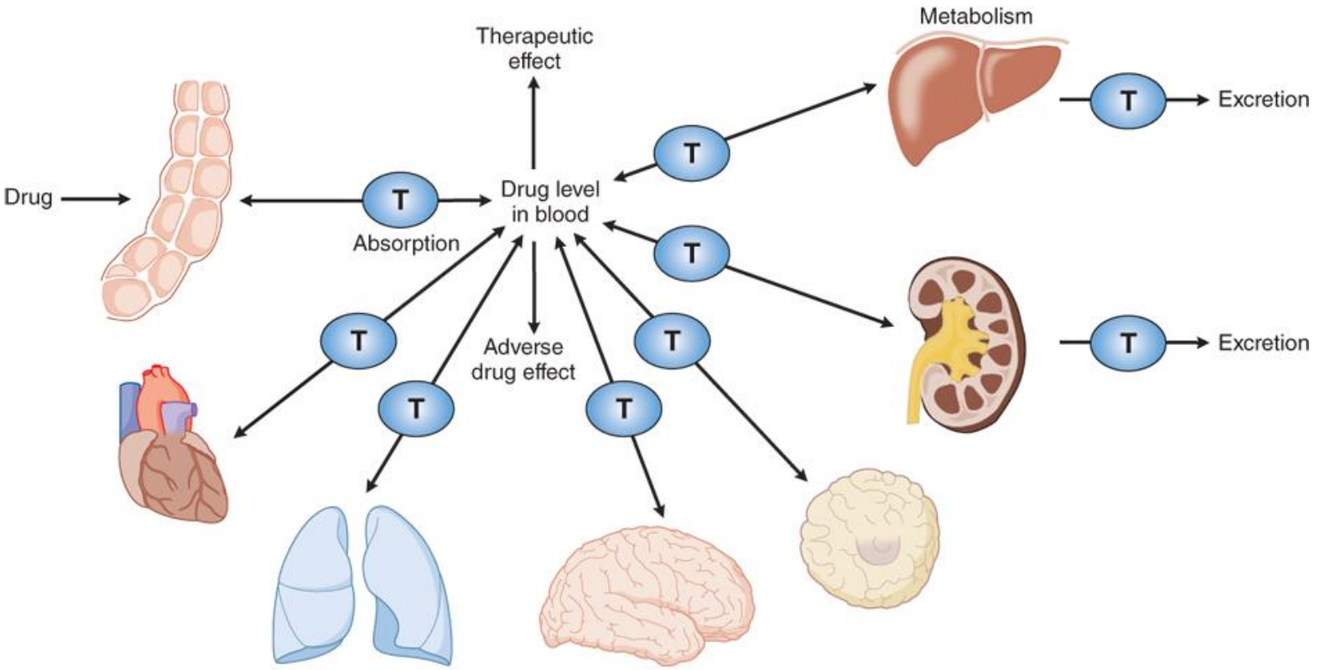
ABC superfamily

- ***A****TP-****b****inding* ***c****assette*

Primary active transport

- ATP hydrolysis, catalyzed by **ATPase**, supplies energy for active transport against a concentration gradient.
- Active efflux of xenobiotics

Xenobiotic: substance foreign to the body



Source: Laurence L. Brunton, Björn C. Knollmann: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:*
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Membrane transporters in pharmacokinetic pathways.
Membrane transporters (T) play roles in pharmacokinetic pathways (drug absorption, distribution, metabolism, and excretion), thereby setting systemic drug levels.
Drug levels often drive therapeutic and adverse drug effects.

Citation: Chapter 4 Membrane Transporters and Drug Response, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14th Edition;* 2023, Figure 4-1. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=267774770 Accessed: June 17, 2024
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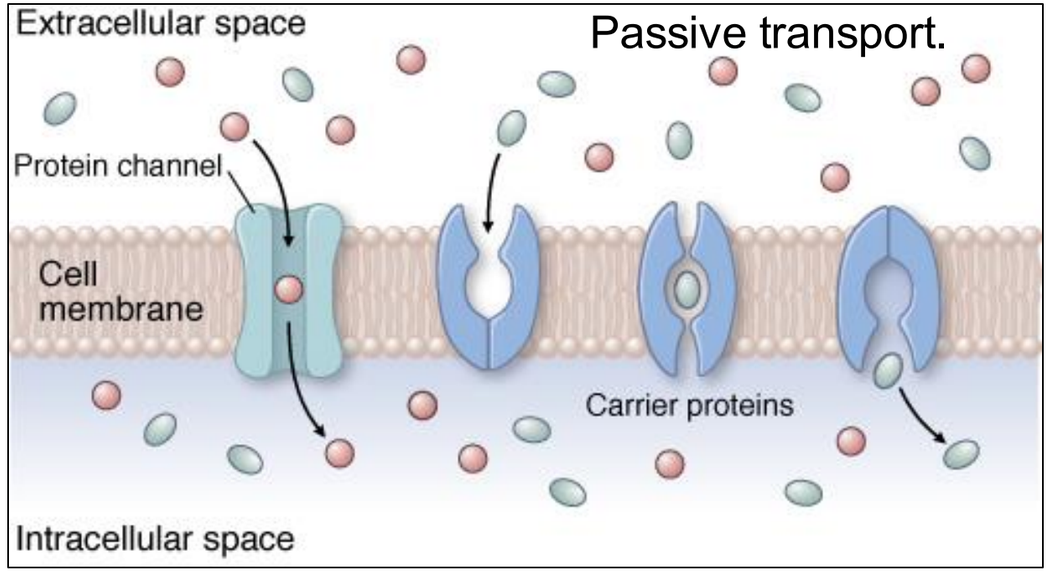
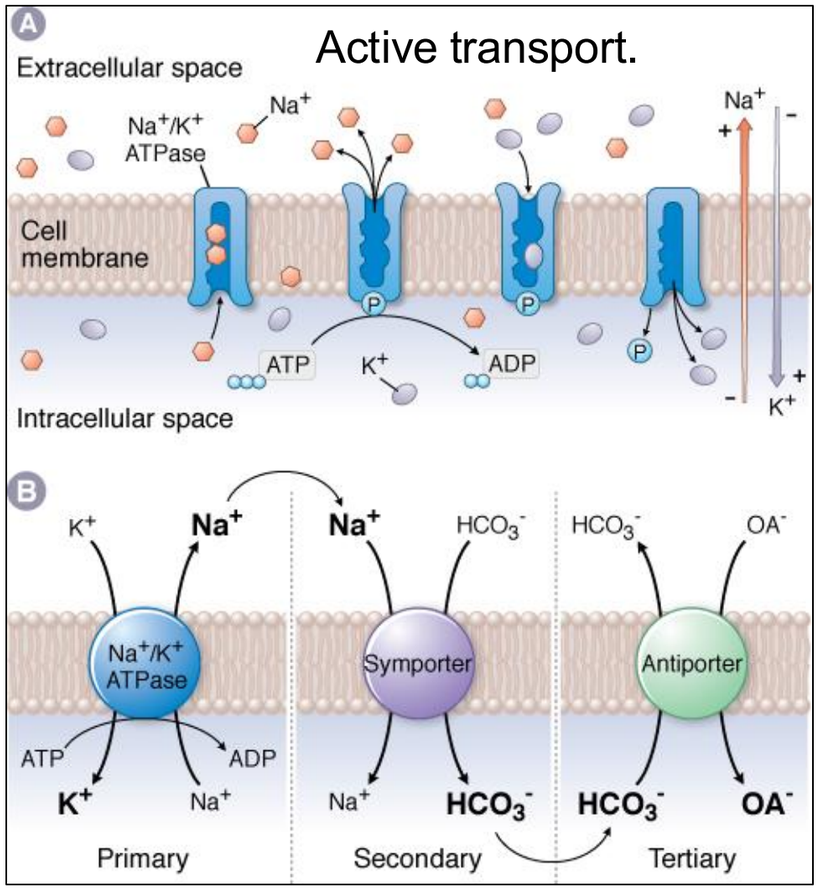
From: **5 Drug Transporters**
Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy Fourth Edition, 4e, 2017



Passive transport: Channels and carrier proteins facilitate the transport of substrates (e.g. drugs) down their concentration gradient.

This process does not require energy.



Active transport: Carrier proteins transport substances against their concentration gradient, which requires energy.

Primary active transport is powered by ATP hydrolysis (ATPase).

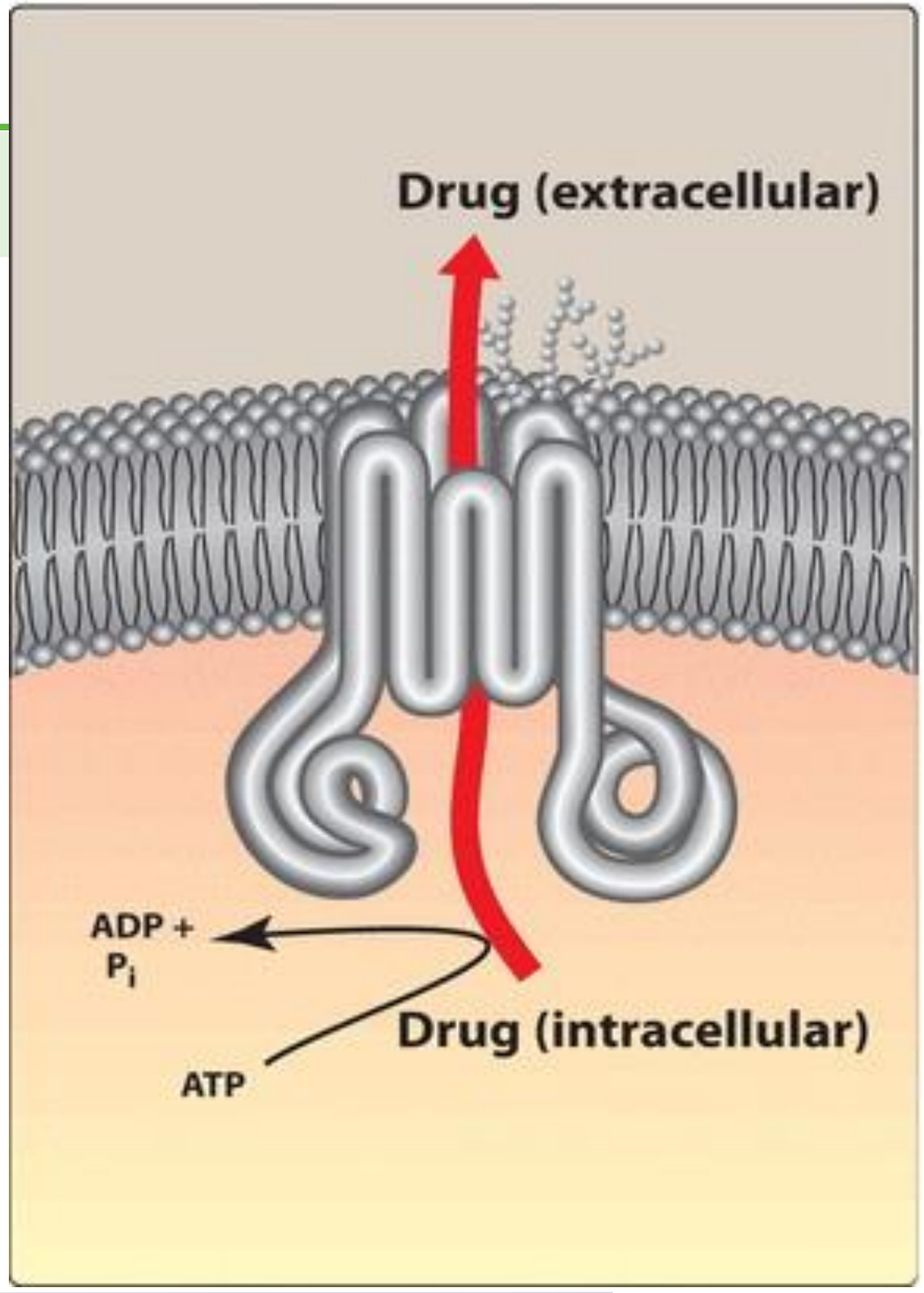
Secondary active transport is powered by energy stored in electrochemical gradients.

Figure 5-3: Passive Transport and Figure 5-4 Active Transport

From: **1 Pharmacokinetics**
Lippincott® Illustrated Reviews: Pharmacology, 8e, 2023

The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping (active efflux) of drugs from the cell.

- P-glycoprotein is located on the apical side of plasma membranes.
- P-gp is constitutively expressed in the intestine, liver, kidney, brain capillaries, placenta, and other tissues.
- P-gp is also expressed on tumor cells and confers multidrug resistance.

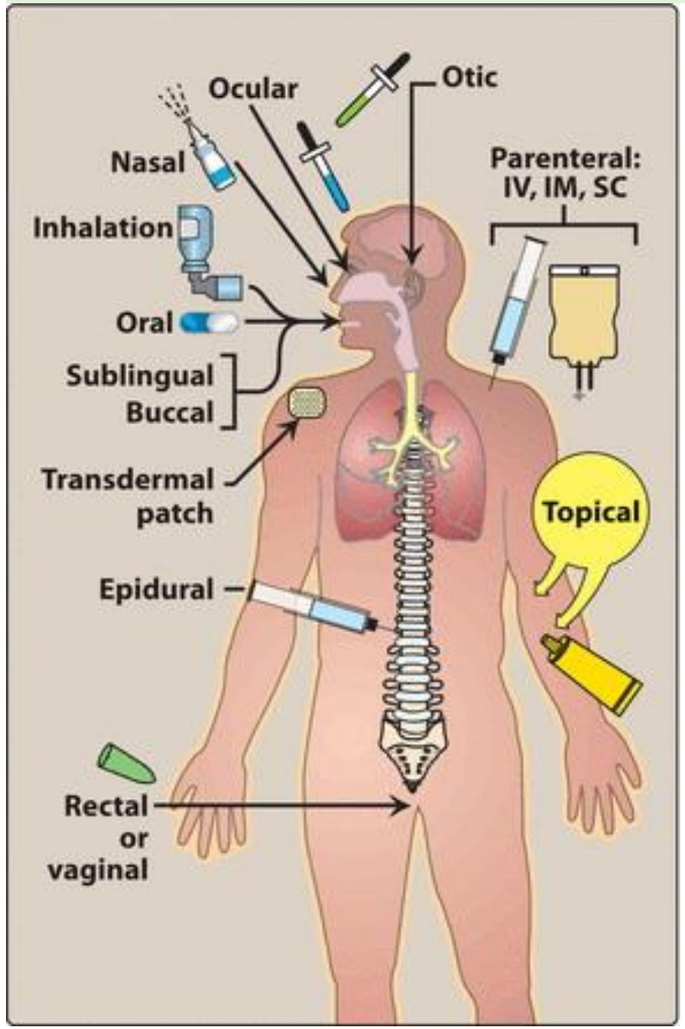


P-glycoprotein (P-gp) is also known as MDR1, multidrug resistance protein 1.

Check your knowledge

1. What physicochemical property determines the ability of a drug to passively diffuse through lipid membranes?
2. By what mechanism can a hydrophilic drug cross physiologic barriers?
3. For drugs that are weak acids and weak bases, why is the pH of biologic fluid clinically important?

From: **1 Pharmacokinetics**
Lippincott® Illustrated Reviews: Pharmacology, 7e, 2019



Routes of Administration

- Selection of the route is determined by the properties of the drug and therapeutic objective (rapid onset, long-term use, etc.).

Commonly used routes of drug administration.

Routes of Administration

Enteral

- Oral, sublingual, buccal
- Enteral tube
- Rectal

⇒ *Clinical correlate:* The upper small intestine is the major site of oral drug absorption.

Parenteral:

Common routes:

- Intravenous (IV)
- Intramuscular (IM)
- Subcutaneous (subQ)
- Intrathecal (IT)

Alternative routes:

- Intradermal
- Intra-osseous
- Intra-arterial
- Intraventricular

Transdermal / Transmucosal

- Drug delivery through the skin or mucosa to the systemic circulation

Topical: Application for local effect

- skin
- eyes, ears
- lungs (oral inhalation)
- gut (oral, nonabsorbed drugs)

*** Advantages and disadvantages of each route are listed in the summary section of this PowerPoint.**

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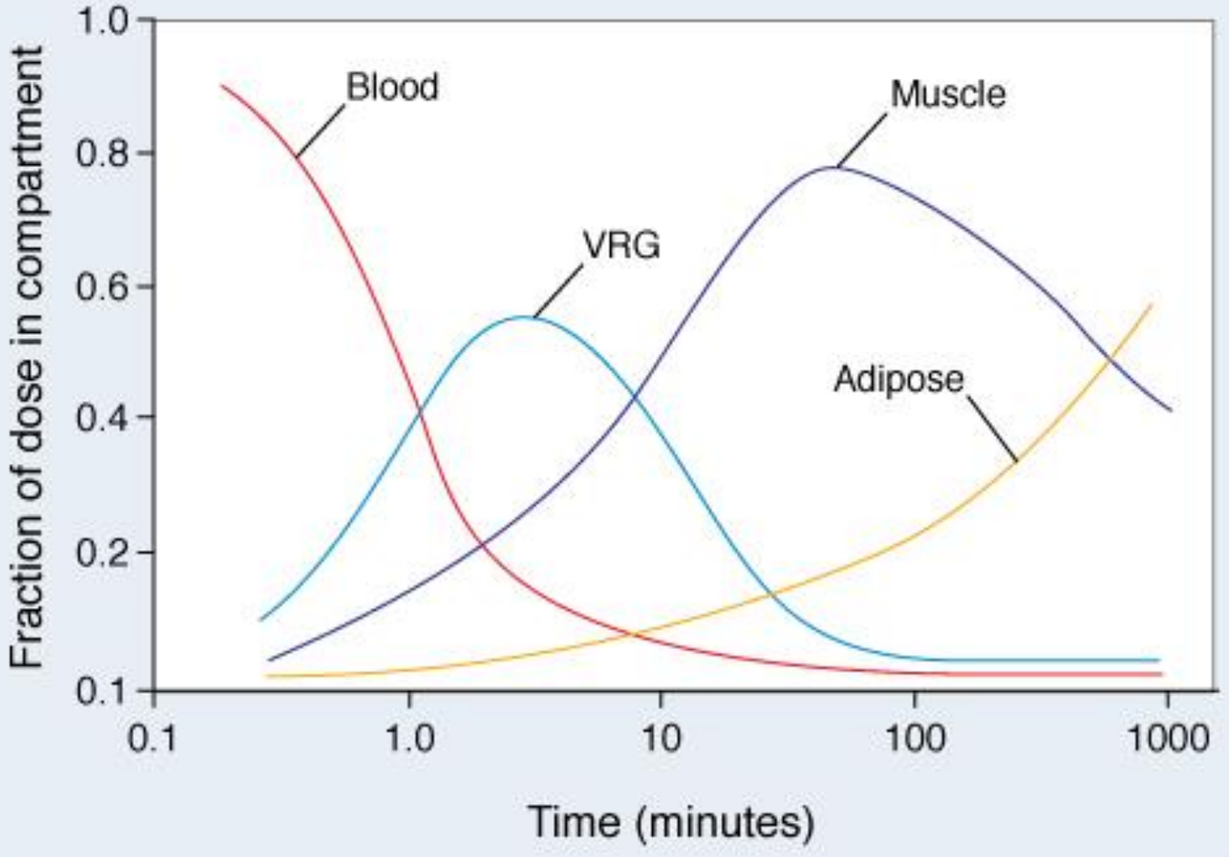
From: **3 Pharmacokinetics**

Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy Fourth Edition, 4e, 2017



VRG vessel-rich group: Highly-perfused organs

Four-compartment model of drug distribution.

Tissue compartments vary in the rate and capacity of drug accumulation.

Redistribution:

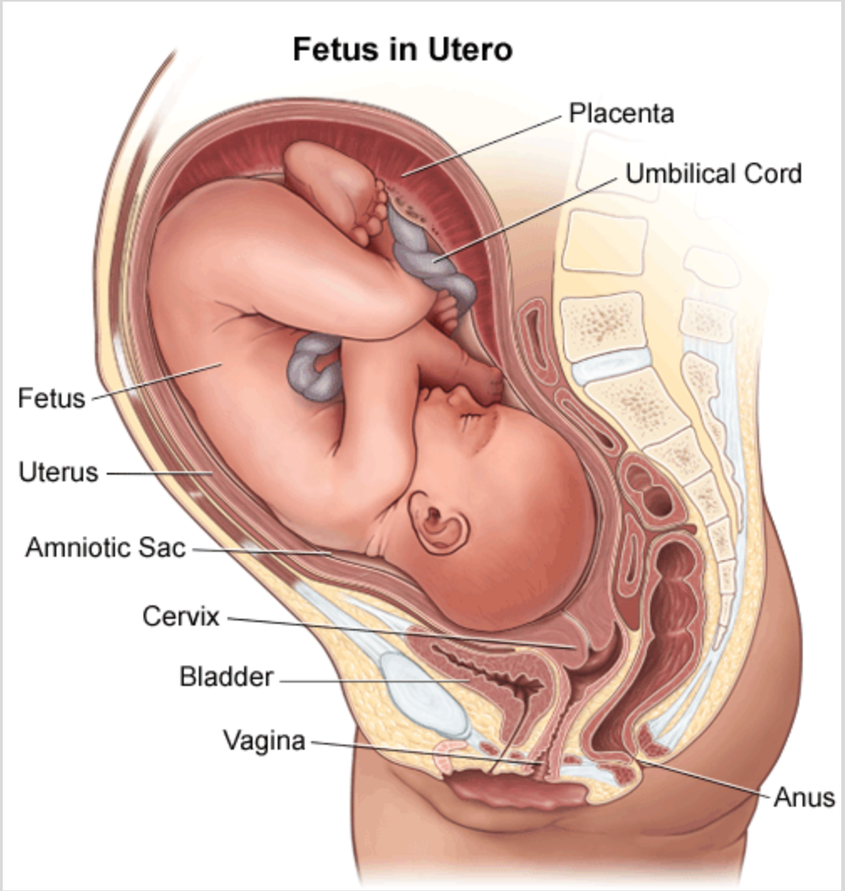
The change in plasma drug concentration significant enough to alter or terminate the CNS effect of the drug.

This phenomenon occurs primarily when one dose of *highly lipid-soluble drug* acting on the brain (i.e. anesthetic) is administered rapidly by intravenous injection or by inhalation.

The drug rapidly distributes to the CNS, moves down its concentration gradient into the CNS tissues, and produces it effect. The drug then moves back into the blood as it is then taken up by the less vascular tissues, which terminates the CNS effect.

Placental transfer of drugs across the placenta may cause anomalies in the developing fetus.

- General determinants are lipid solubility and extent of protein binding.
- The fetal plasma is slightly more acidic than that of the mother (pH 7.0 to 7.2 compared to 7.4), so that ion trapping of basic drugs occurs.
- P-glycoprotein and other export transporters form the blood-placenta barrier and function to limit fetal exposure to potentially toxic substances.



https://www.stanfordchildrens.org/en/topic/default?id=anatomy-fetus-in-utero-85-P01189

When plasma and tissue protein binding is reversible, a chemical equilibrium exists between bound and unbound drug.

As the concentration of free drug decreases due to elimination, drug molecules rapidly dissociate from the drug-protein complex, which maintains the free-drug concentration at a constant fraction.

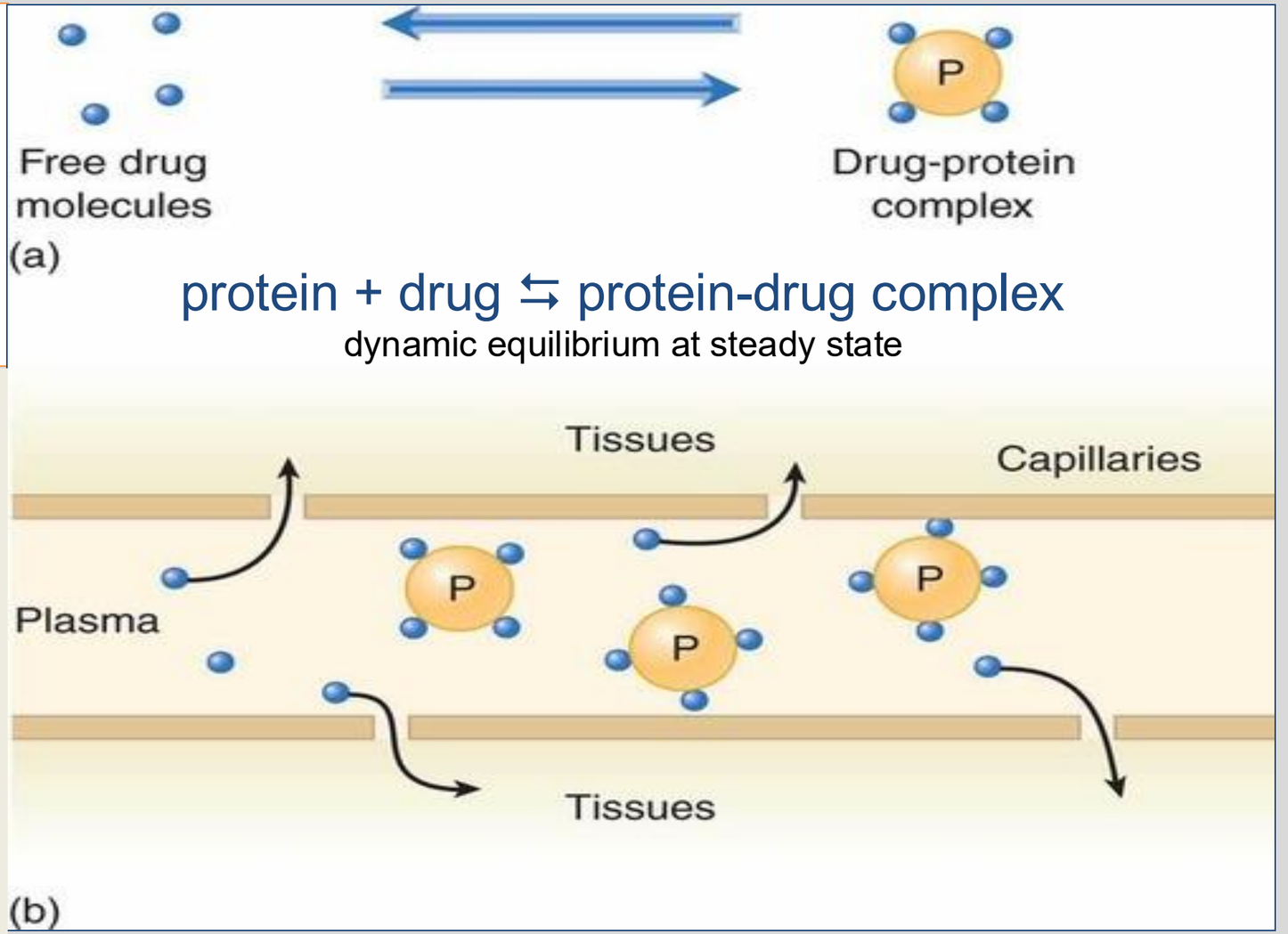


Figure: http://quizlet.com/19545630/pharmacology-4-pharmacokinetics-objectives-flash-cards/

Pharmacokinetics processes link drug dose to concentration in biologic fluids and determine the time course and intensity of drug action.

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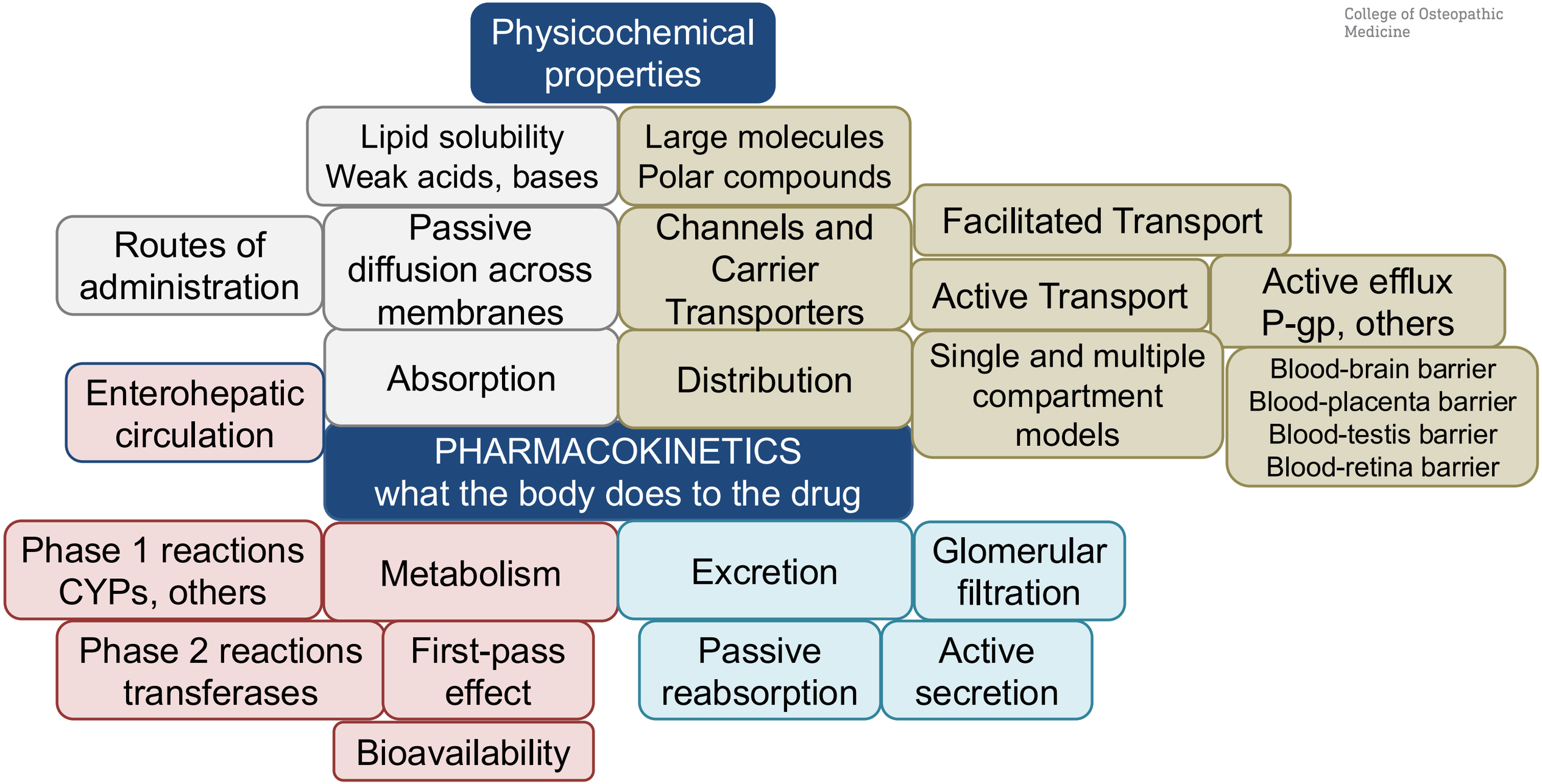

Summary: Physicochemical characteristics and drug permeation of physiologic barriers

- The physicochemical characteristics of a drug determine its ability to withstand digestive fluids and enzymes and be absorbed from the GI tract, cross physiologic barriers, survive metabolic processes, distribute to the site of action in therapeutic concentrations, exit the site of action, and be eliminated.
- Drugs move along their concentration gradients by passive diffusion across the lipid bilayer of cell membranes or by carrier-mediated transport. Drugs may also be pumped out by energy-dependent active transport. Very large or lipid insoluble drugs may enter / exit cells by endocytosis/pinocytosis and exocytosis.

Summary: Passive diffusion of drug molecules

- The rate and extent of flow of drug molecules are influenced by the magnitude of the concentration gradient across the membrane, lipid-water partition coefficient, and membrane surface area, thickness, and permeability.
- Weak acids and weak bases are present in solution as both the non-ionized and ionized species. The non-ionized molecules usually are more lipid soluble and can diffuse readily across the cell membrane, whereas ionized molecules usually are less able to penetrate the lipid membrane because of their low lipid solubility. Transmembrane distribution is determined by the drug's pK_a and the pH gradient across the membrane.

Summary: Administration and Distribution

- Different routes of administration are used in clinical medicine for various reasons, such as convenience, rapid onset of action, maximizing concentration at the site of action, avoiding the first-pass effect, and minimizing adverse effects.
- The rate and extent of drug distribution are determined by physicochemical properties of the drug, and the physiologic factors of cardiac output, regional blood flow, capillary permeability, and tissue volume. Extensive binding to inert proteins and other macromolecules may slow the rate at which a drug reaches the site of action and may prolong the duration of action.

Route (Bioavailability)	Absorption Pattern	Utility	Limitations and Precautions
Oral (enteral) (<5-100%)	Variable Affected by on many factors	Safest, most convenient and economical route of administration	• Limited absorption; potentially erratic and incomplete • Food may affect absorption • Drugs may be metabolized before reaching systemic circulation CYPs (esp. CYP3A4/5) are present in intestinal epithelial cells. • GI irritation • Patients self-administer so adherence to therapy is necessary for therapeutic outcomes
Oral: Controlled release formulations (variable bioavailability)	Slow, sustained absorption over extended time period (8-24 hours usually)	• Decrease dosing frequency • Decrease incidence and/or intensity of adverse effects (lower peak concentrations) • Therapeutic levels maintained within the therapeutic window (elimination of troughs in concentration) • Therapeutic effect maintained overnight • Useful for drugs with short half-life • Improved patient compliance	• Variable systemic concentrations • “Dose dumping”: failure of the formulation so that the total dose is absorbed at once, resulting in toxicity (rare occurrence) • Abuse of the higher dose, controlled release narcotics (eg, oxycodone) by crushing the tablet and snorting the full dose of the drug

Answers to the Question

1. What physicochemical property determines the ability of a drug to passively diffuse through lipid membranes?

- The lipid-water coefficient of a drug (the ratio of the concentration of the drug in the lipid and aqueous phases) determines how readily the drug molecule moves across lipid membranes. Lipid soluble drugs passively diffuse through the lipid membranes (not saturable). The rate of transfer across the membranes from an area of higher concentration to lower concentration is directly proportional to the lipid-water coefficient.

2. By what mechanism can a hydrophilic drug cross physiologic barriers?

- A hydrophilic drug can cross physiologic barriers via transport proteins – passive diffusion or facilitated transport down the concentration gradient or by energy-using active transport. Transporters are saturable – full occupation of transporters $\rightarrow$ maximum rate of transfer.

3. For drugs that are weak acids and weak bases, why is the pH of biologic fluid clinically important?

- Weak acids and weak bases either gain or lose electrical charge-bearing protons depending on their pKa and the pH of the medium. Only the uncharged form of the drug will passively diffuse across the lipid bilayer, while the charged form does not. This is called ion trapping. Manipulation of urine pH may be appropriated for increasing the rate of excretion by ion trapping of certain drugs, such as toxic concentrations of salicylates.