

Pharmacodynamics & Pharmacokinetics



Pharmacology ...

The interaction of
chemical substances
(drugs) with living
organisms (humans)



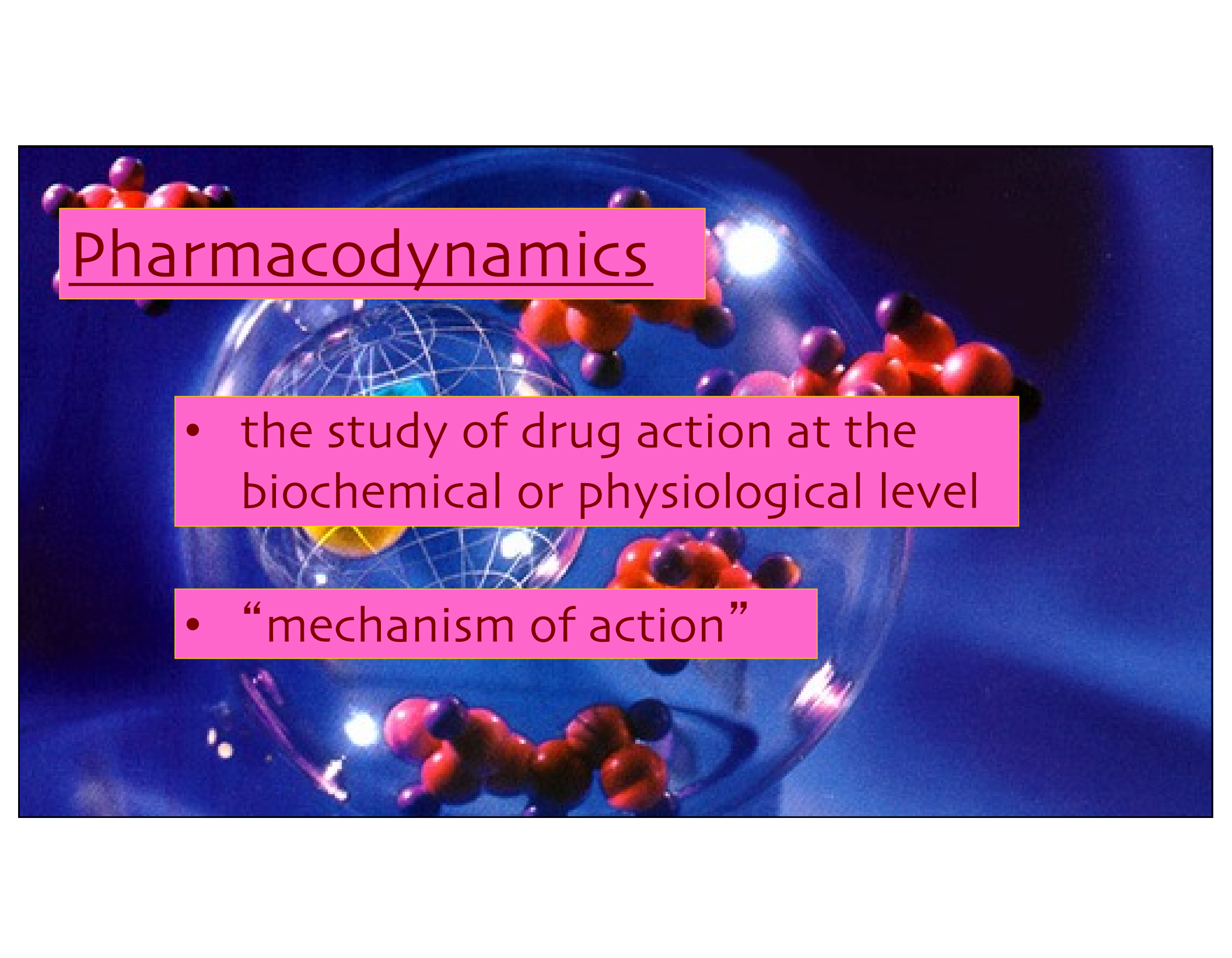
Pharmacology ...

- consists of (1) pharmacodynamics and (2) pharmacokinetics

“pharmaco” = drugs

“dynamics” = dynamics

“kinetics” = movement



Pharmacodynamics

- the study of drug action at the biochemical or physiological level
- “mechanism of action”

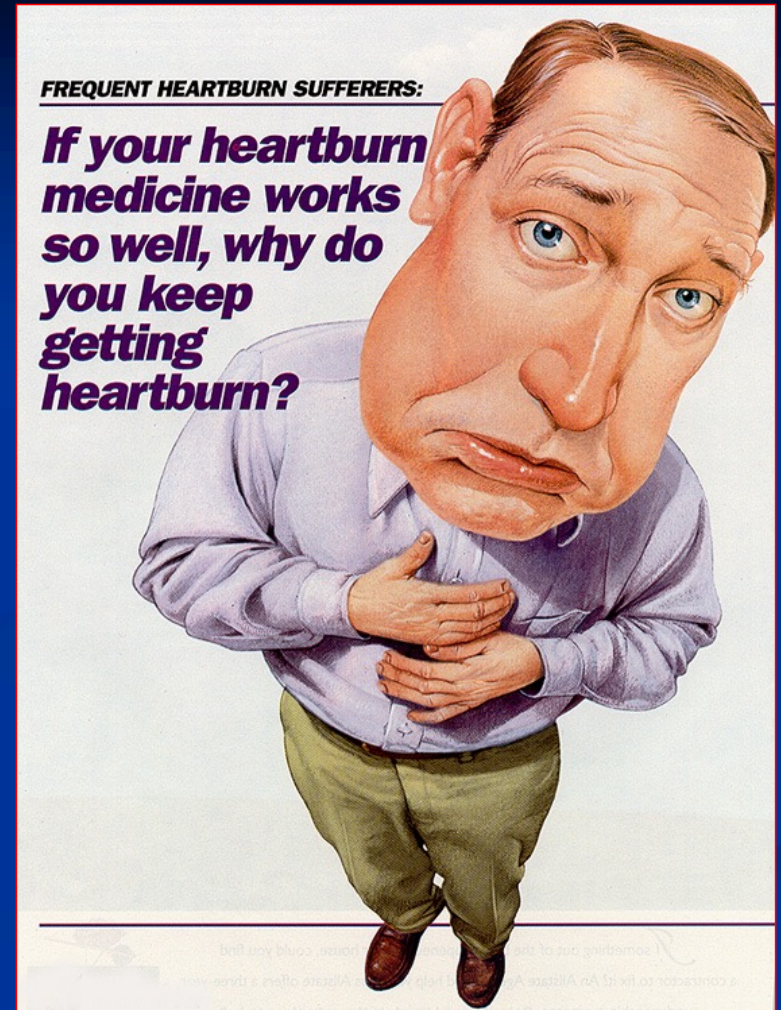
Pharmacokinetics ...

- study of how drugs:
 - (1) enter the body
 - (2) reach site of action
 - (3) are eliminated from the body

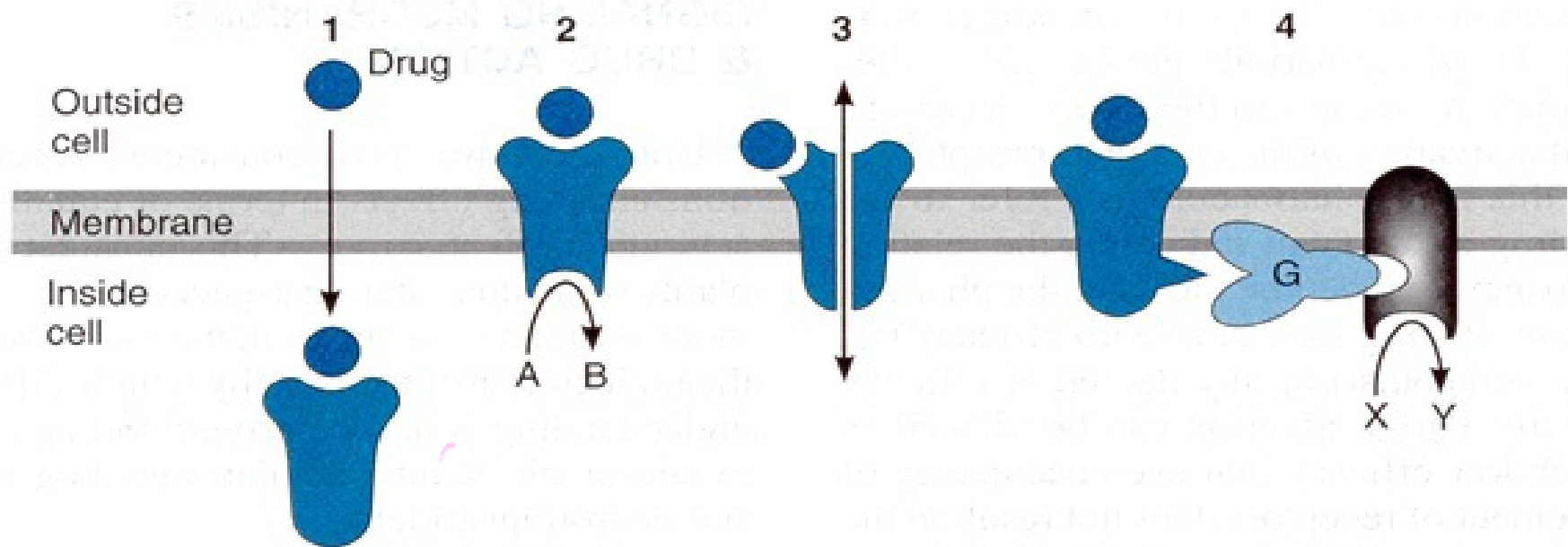


Pharmacodynamics

A. Drugs that change the environment of cells ...

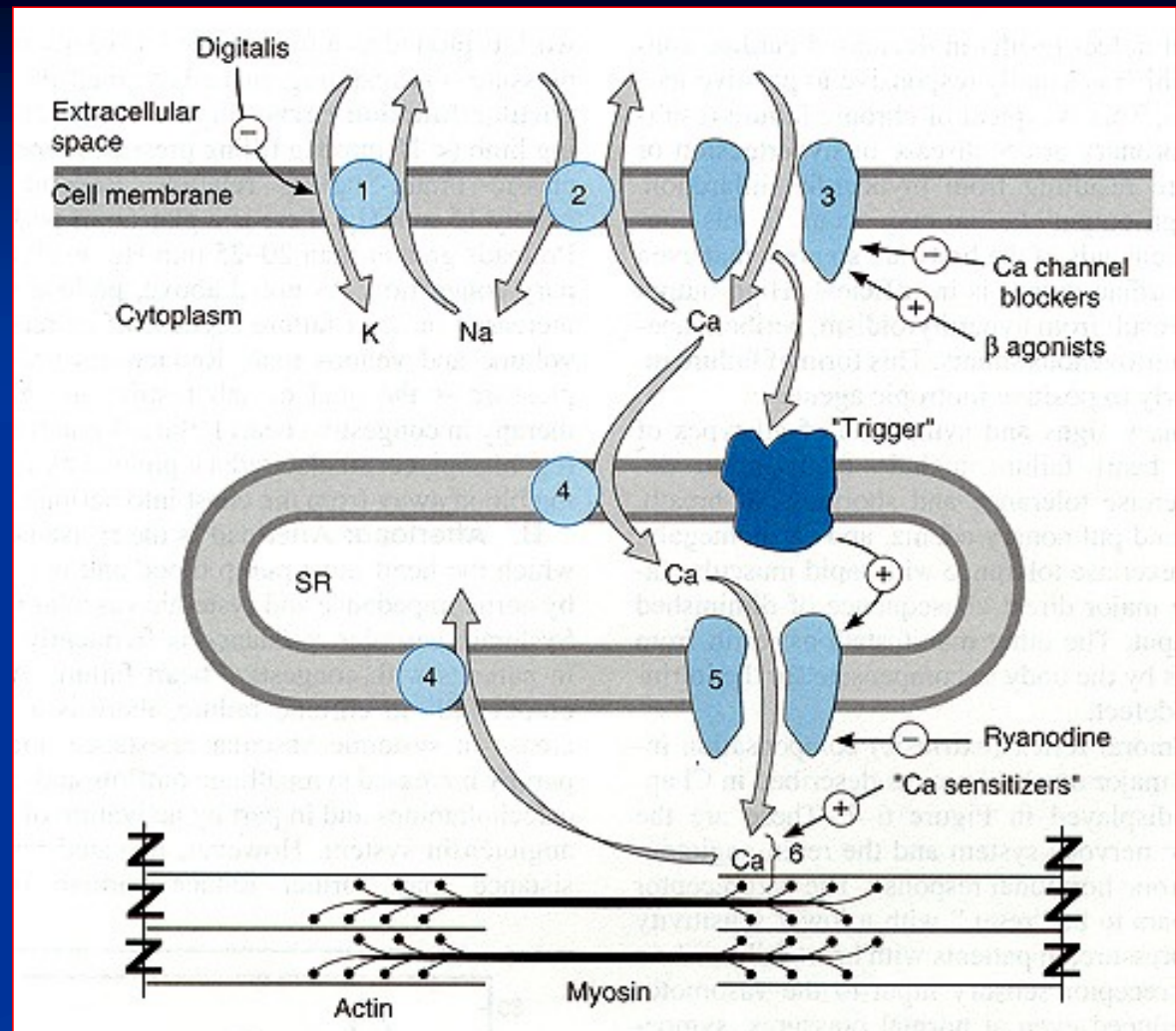


B. Drugs which selectively bind to receptors on cell membranes → alter cellular physiology

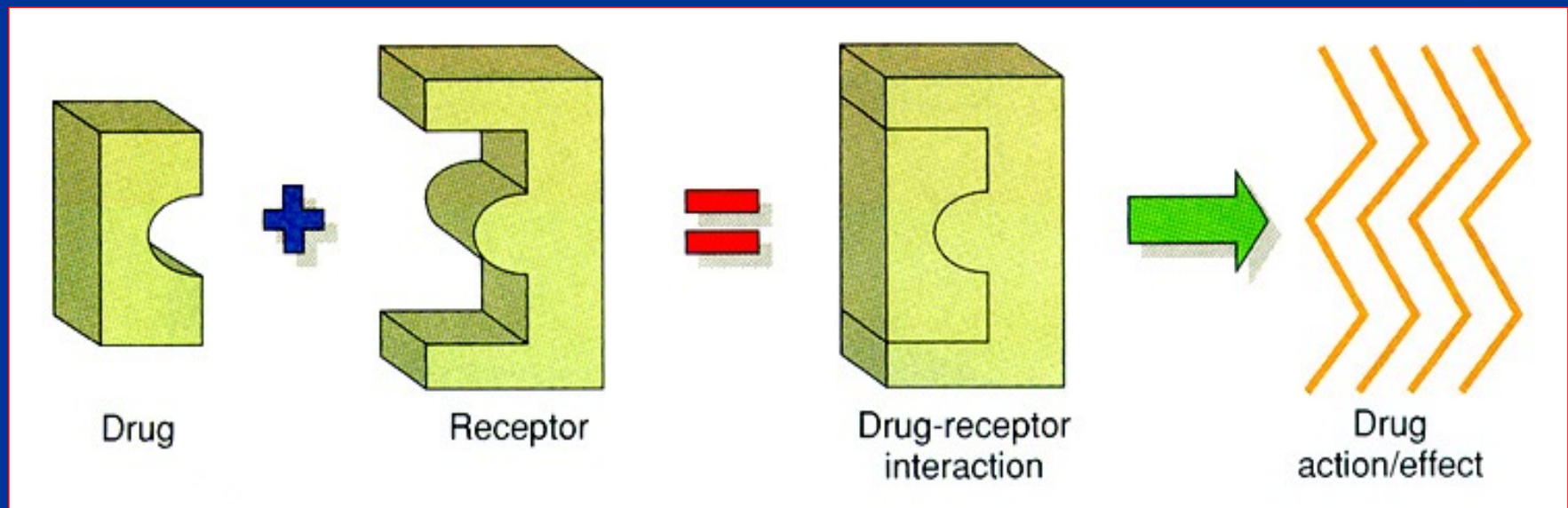


Example of Drug-Receptor Interaction:

Digoxin (Digitalis)



Definition: Agonist is a drug which binds to a specific receptor and produces a physiological effect by stimulating the receptor.



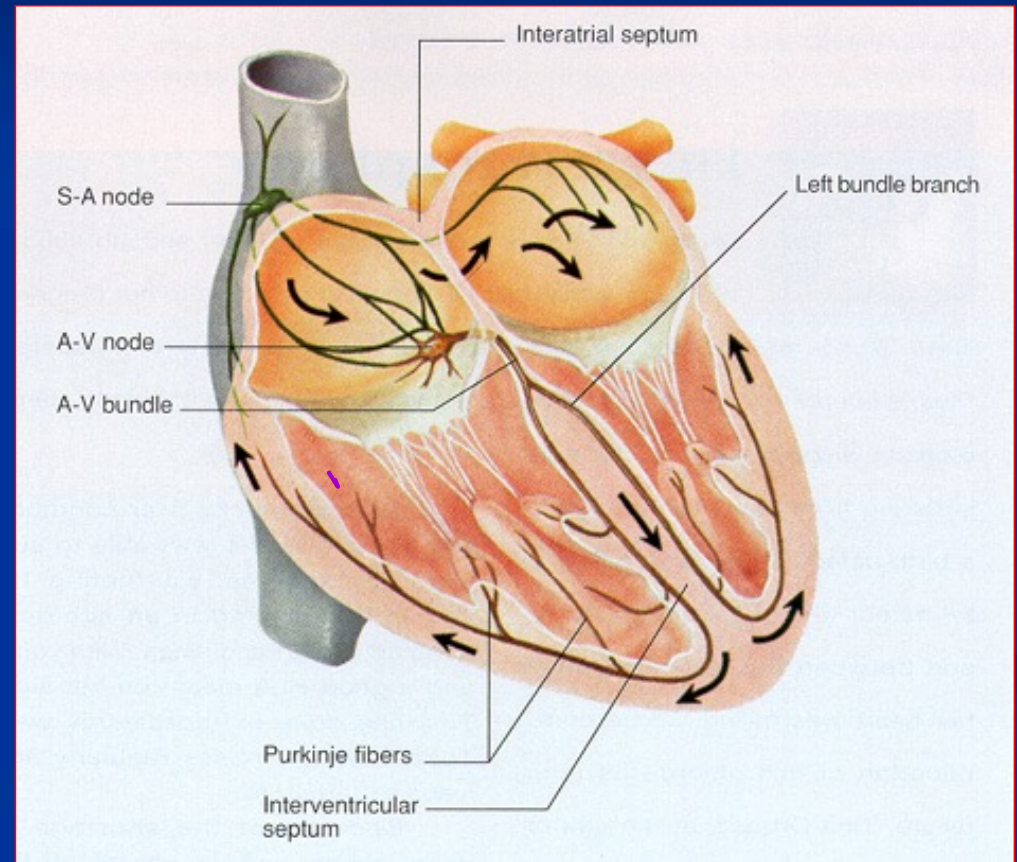
Agonist (Example)

Norepinephrine (NE)

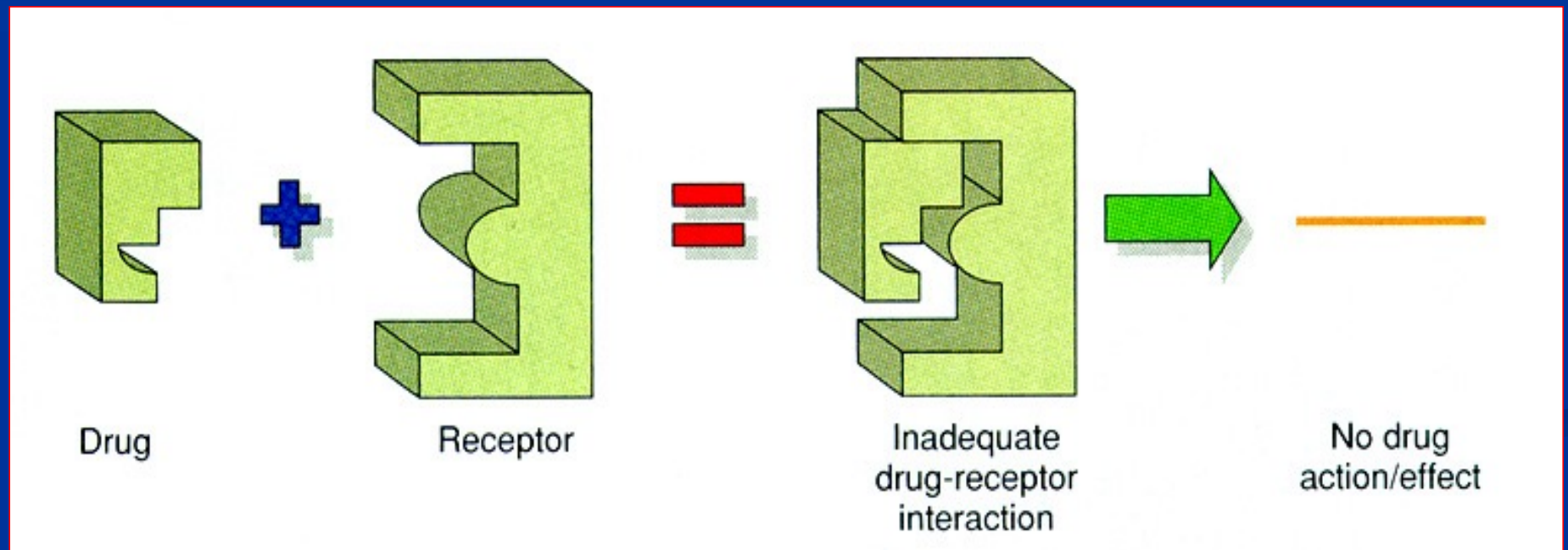
NE: stimulates beta-1
receptors on the SA
node

→ increases HR

→ increases BP



Definition: Antagonist is a drug which binds to a specific receptor and blocks other substances from stimulating the receptor.



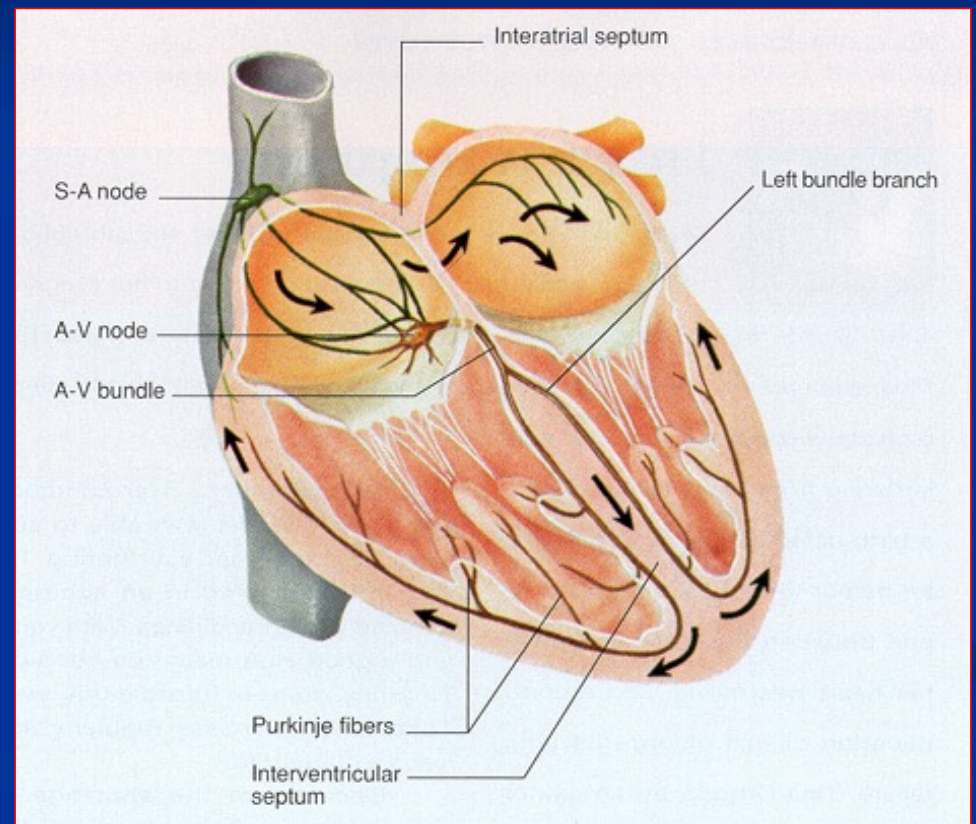
Antagonist (Example)

Propranolol (Inderal)

Propranolol: blocks beta-1 receptors on the SA node

→ decreases HR

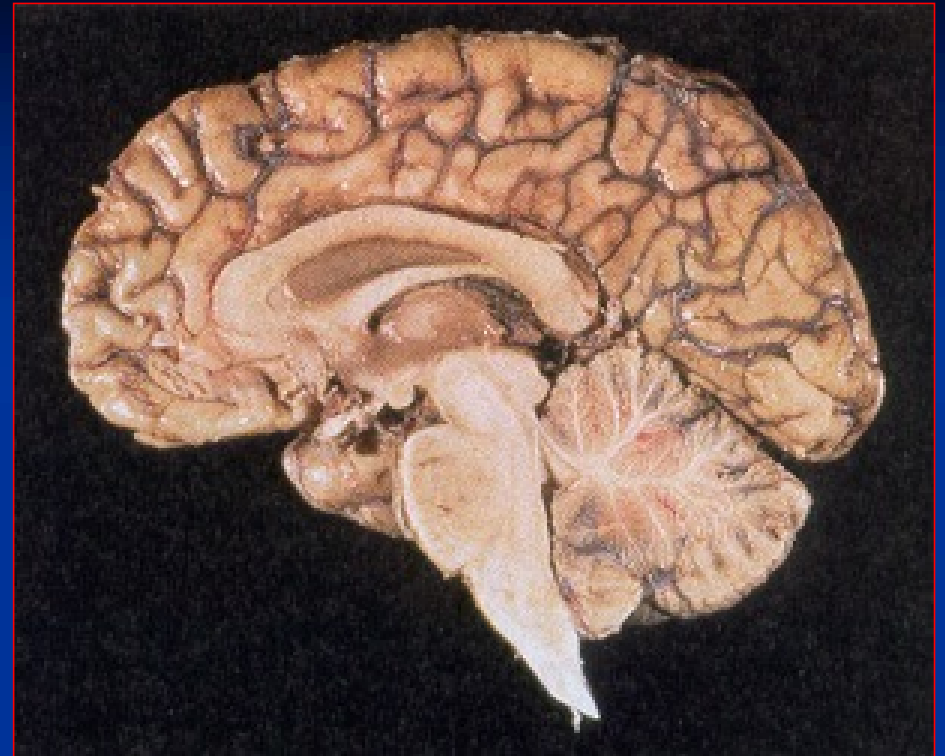
→ decreases BP



Antagonist (Example)

Naloxone (Narcan)

Naloxone blocks mu-opioid receptors in the respiratory center of the medulla oblongata



→ reverses respiratory depression in opioid overdose due to heroin, morphine, and other narcotics

New Classification: Inverse Agonist

Diphenhydramine (Benadryl)

Diphenhydramine binds to histamine receptors and induces a conformational change in the receptor

- prevents histamine from binding to its H-1 receptor
- prevents allergic reactions and symptoms



Receptor Binding Characteristics

a. affinity: drug ability to bind to its receptor

- agonist → affinity
- antagonist → affinity

b. efficacy: drug ability to stimulate its receptor

- agonist → efficacy
- antagonist → no efficacy

Competitive Inhibition

morphine (agonist) $\leftrightarrow$ naloxone (antagonist)

diazepam (agonist) $\leftrightarrow$ flumazenil (antagonist)

acetylcholine (agonist) $\leftrightarrow$ atropine (antagonist)

naloxone (Narcan): mu-opioid receptor antagonist

flumazenil (Romazicon): benzodiazepine (GABA) receptor antagonist

diazepam (Valium): benzodiazepine (GABA) receptor agonist

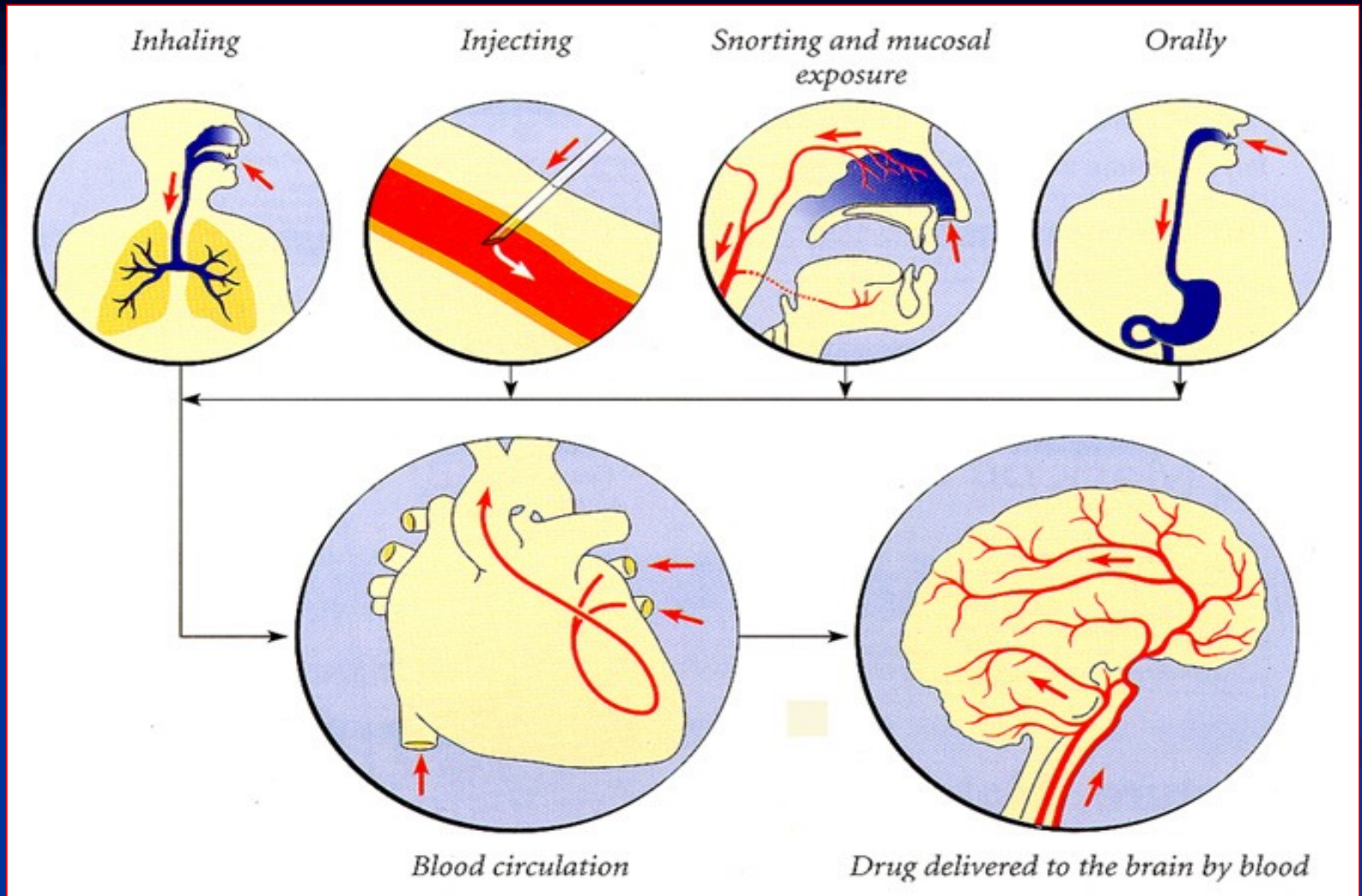
acetylcholine (ACh): cholinergic (muscarinic) receptor agonist

Pharmacokinetics consists of 4 phases:

- (a) • drug absorption
- (b) • drug distribution
- (c) • drug metabolism
- (d) • drug elimination
- (e) all of the above

$$C_p(t) = UDF(t) * I(t)$$

A b s o r p t i o n



Oral (PO)

drug is ingested



absorbed from
stomach / intestine



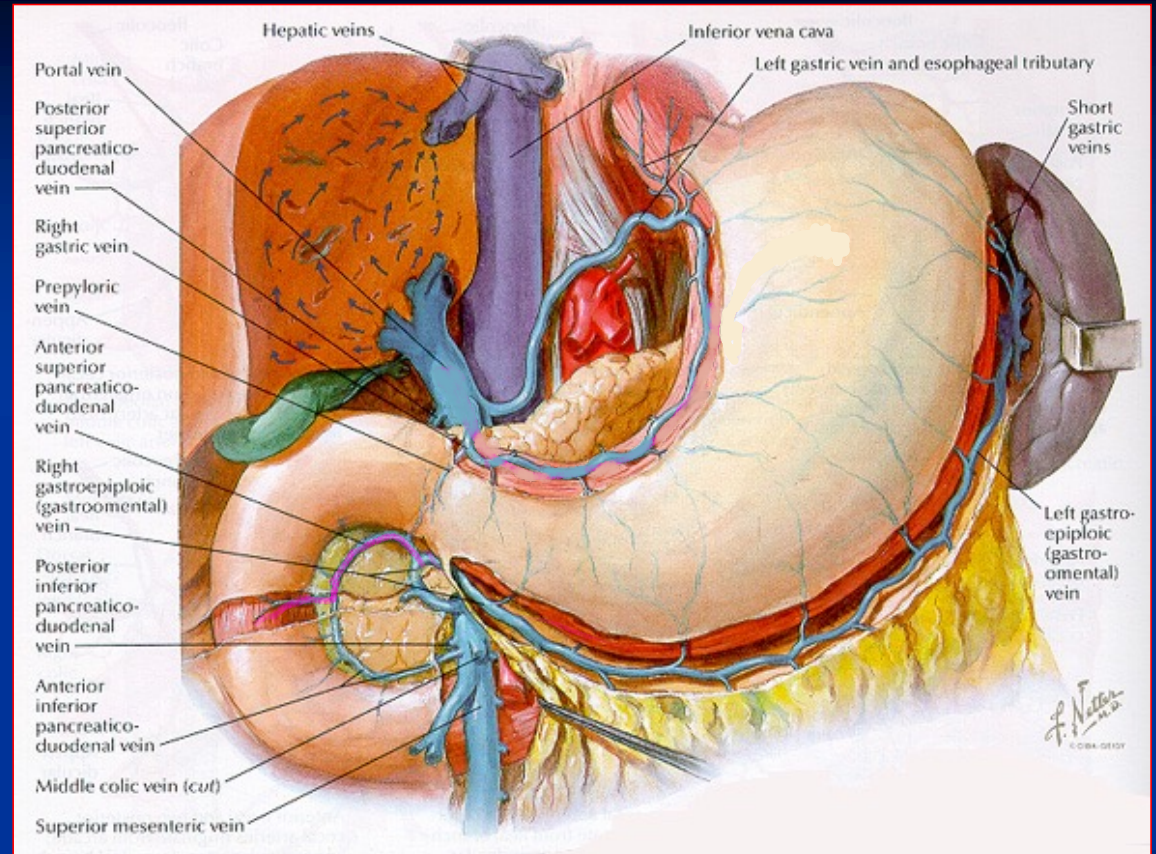
enters hepatic
portal system



liver

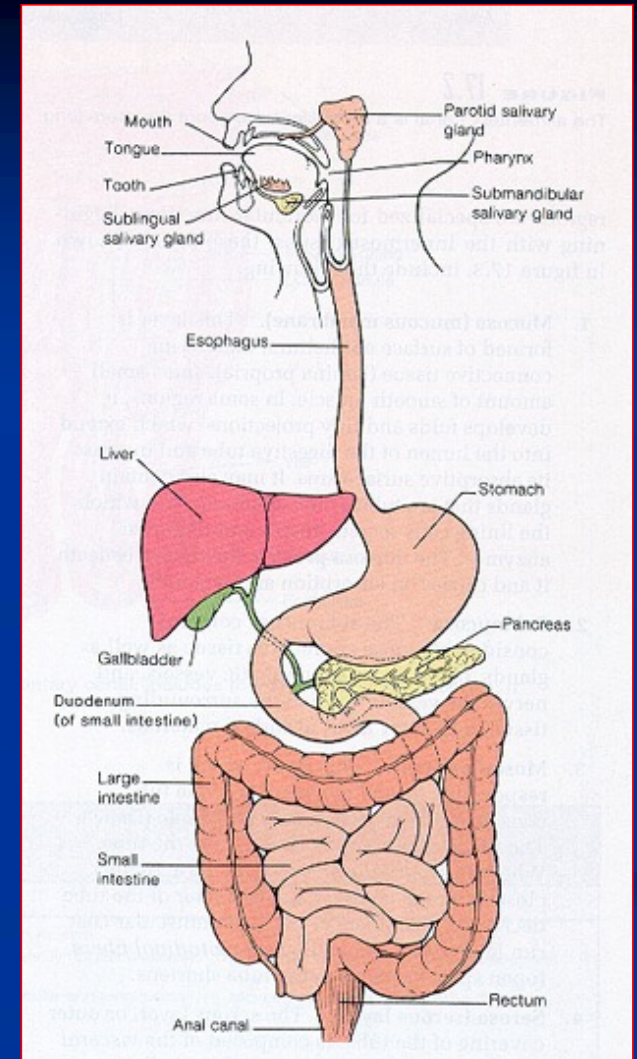


drug enters general circulation



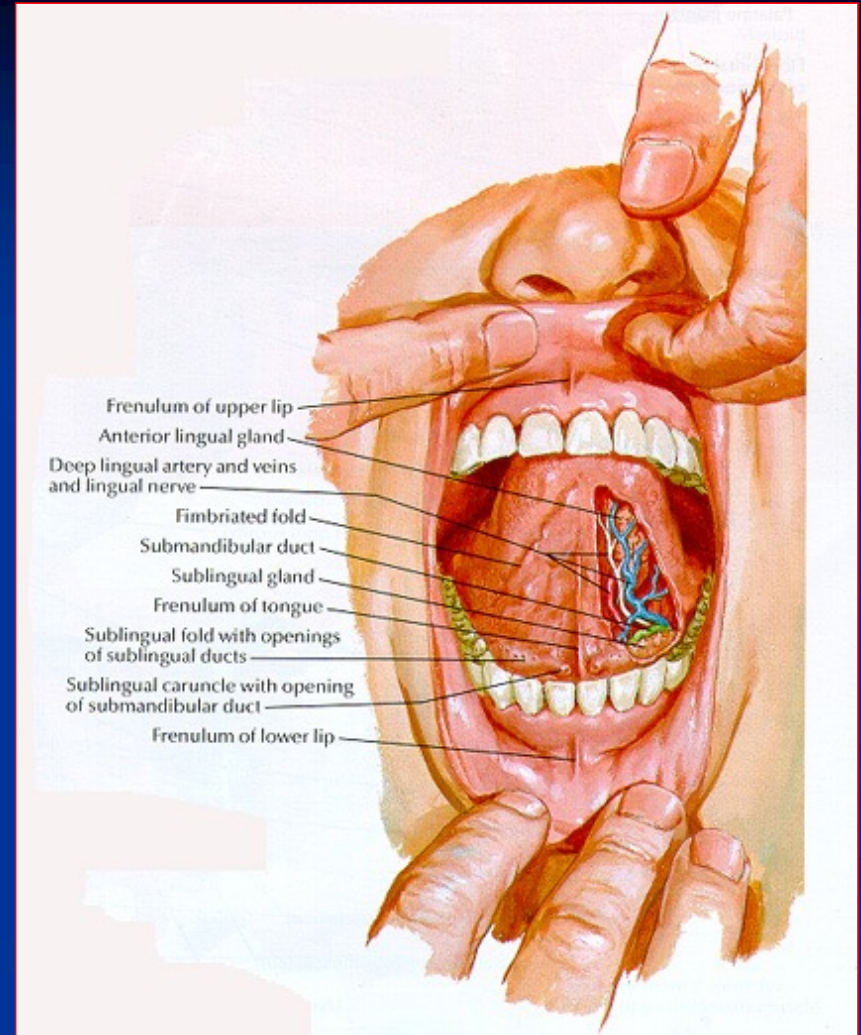
Oral (cont.)

- oral route is convenient and economical
- once absorbed into the bloodstream, the drug enters the liver, where it may be metabolized (“first-pass effect”)



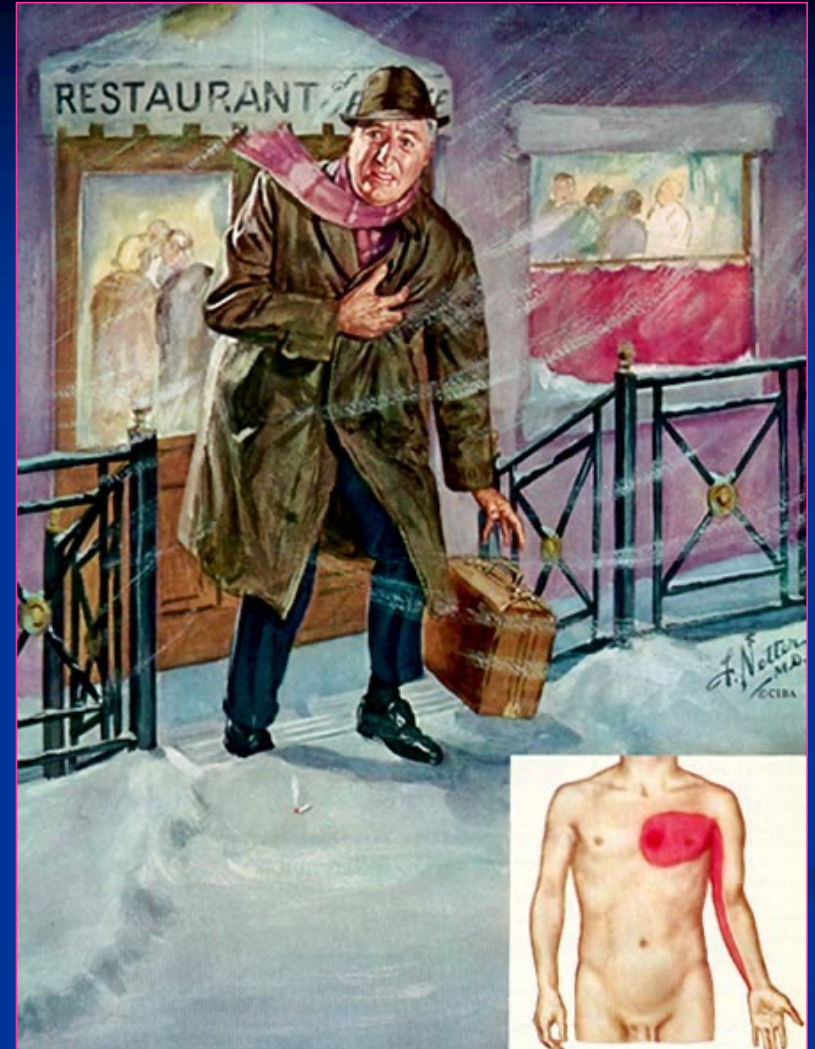
Sublingual

- drug is dissolved and absorbed under the tongue

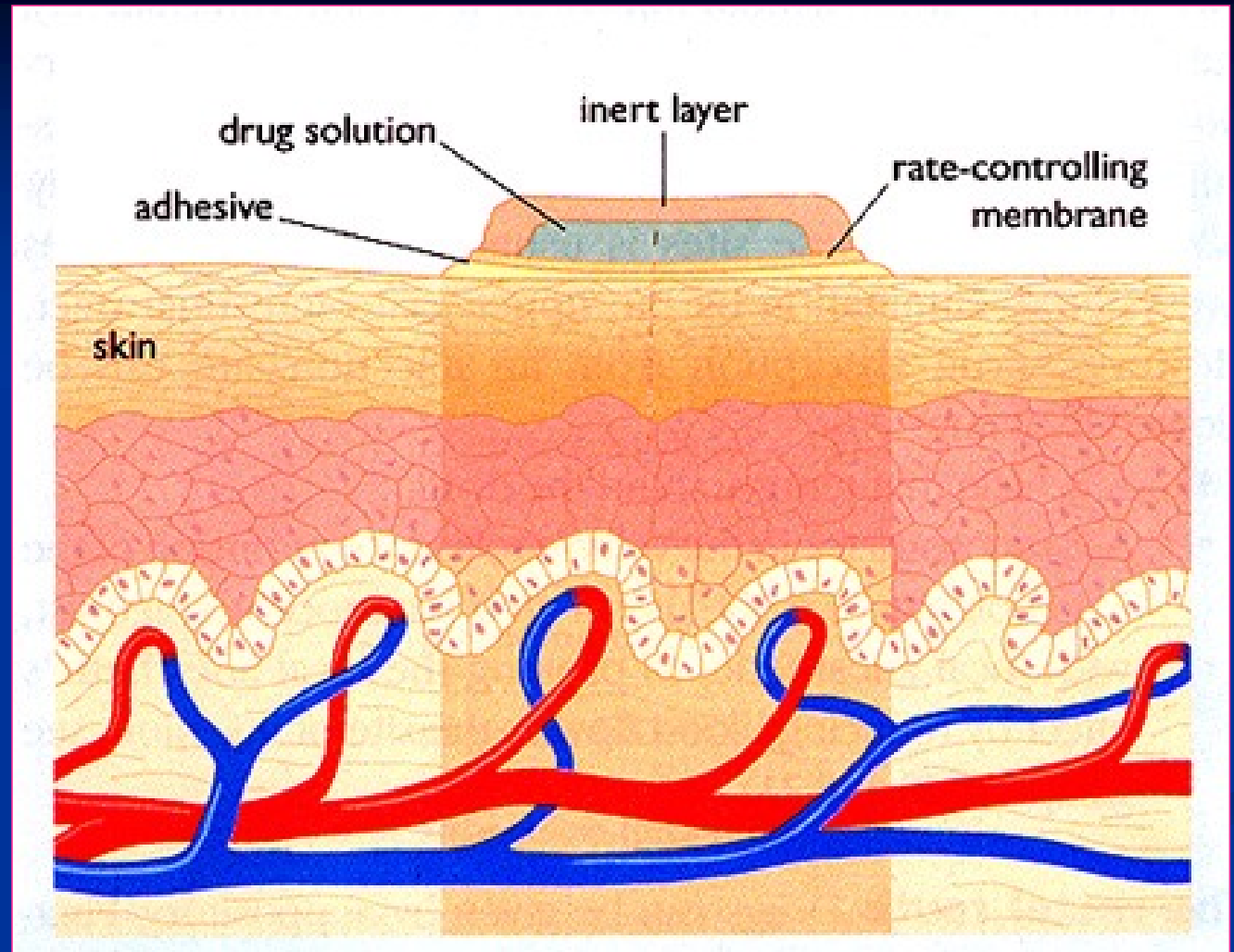


Sublingual

Example: Nitroglycerin SL

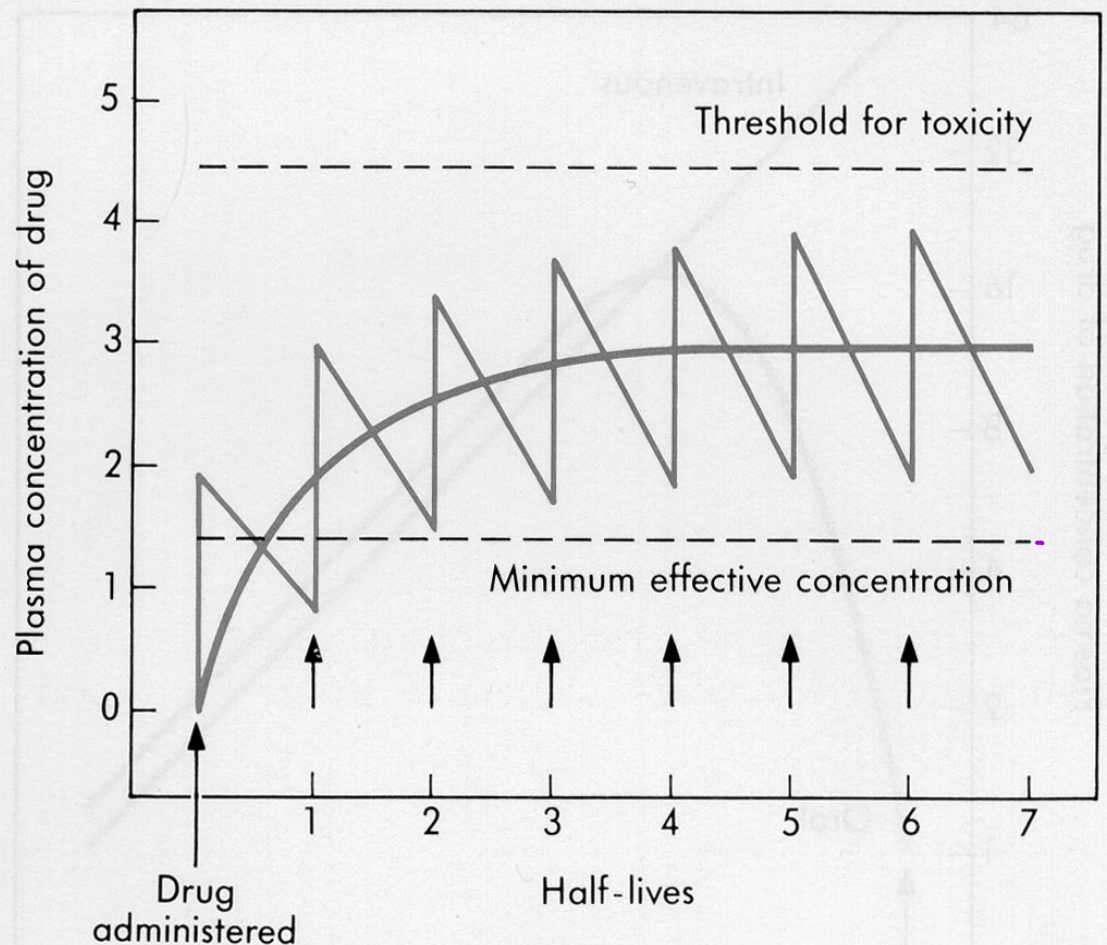
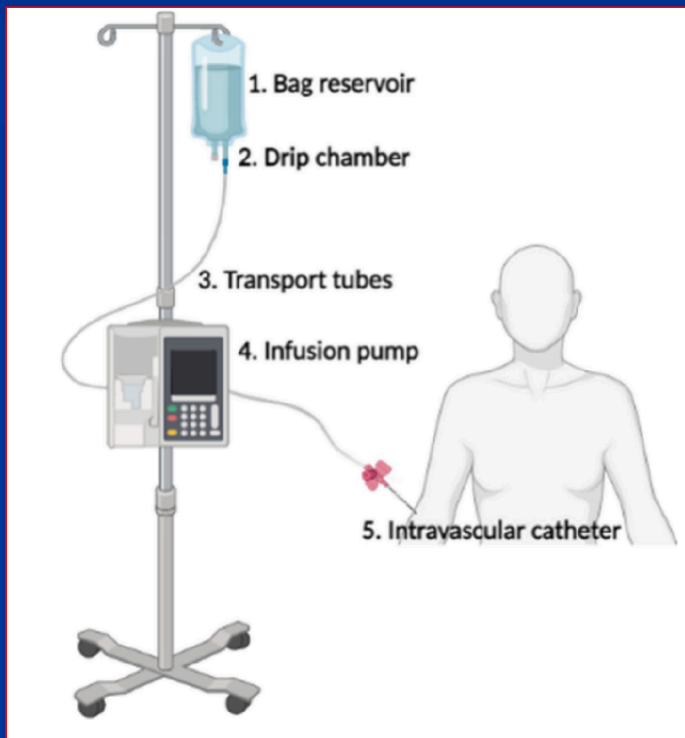


T r a n s d e r m a l



Transdermal

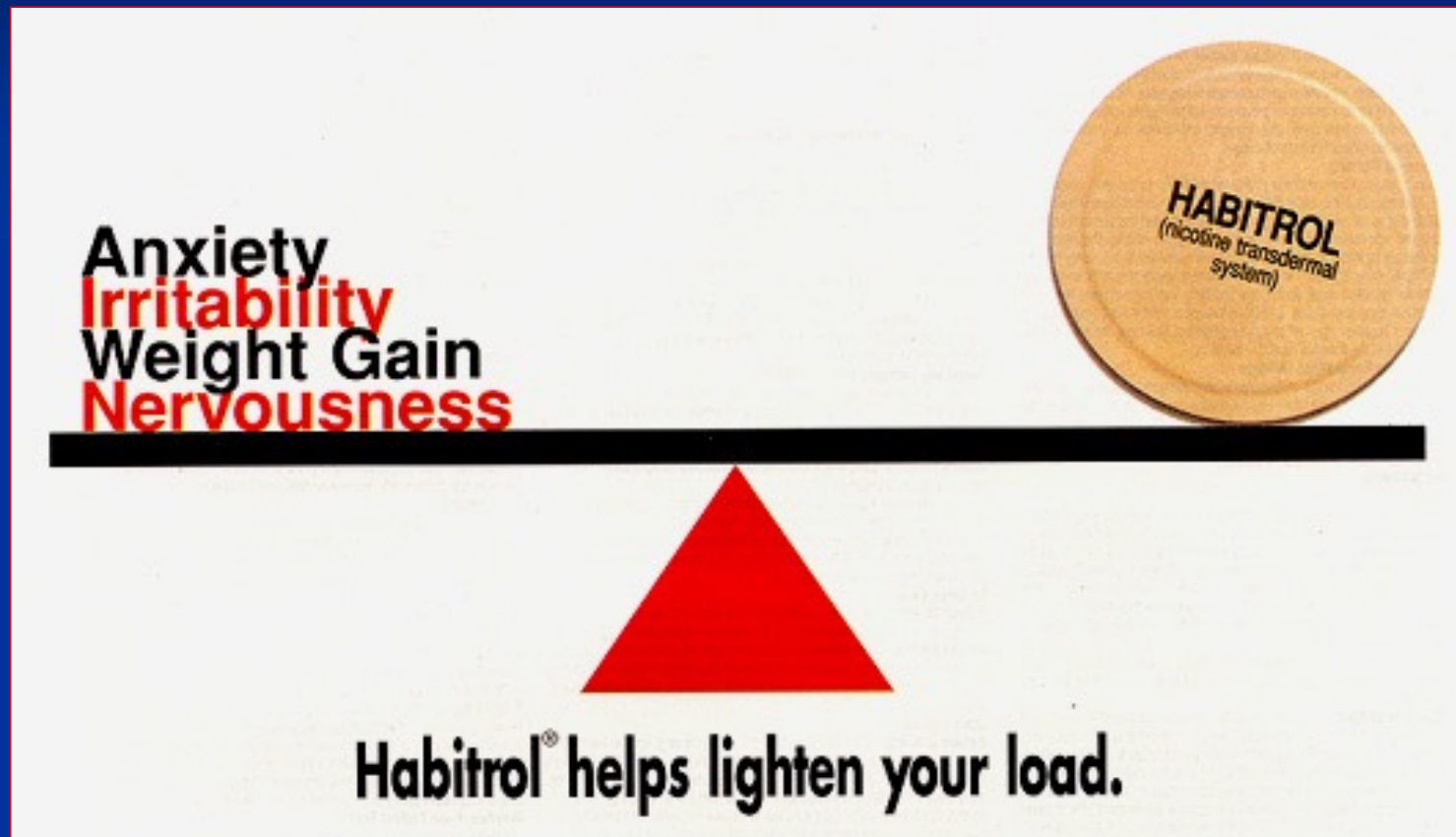
Continuous vs Intermittent Drug Dosing Regimens



Transdermal (cont.)

- drug patch provides continuous drug dosing
- local skin irritation may occur
- drug enters the general circulation before passing through the liver

Example: Transdermal Nicotine Patch



Transdermal (cont.)

Example:
Duragesic
(Fentanyl)
Patch

NDC 50458-036-05 One (100µg/h) System

DURAGESIC® 100µg/h 
(FENTANYL TRANSDERMAL SYSTEM)

In vivo delivery of 100µg/h fentanyl for 72 hours

NOT FOR ACUTE OR POSTOPERATIVE USE

Each transdermal system contains:
10mg fentanyl and 0.4ml alcohol USP

Caution: Federal law prohibits dispensing without prescription.

WARNING: May be habit-forming.


01461014

 **JANSSEN**
PHARMACEUTICA

ATTENTION:
Only for use by
patient for whom
prescribed.

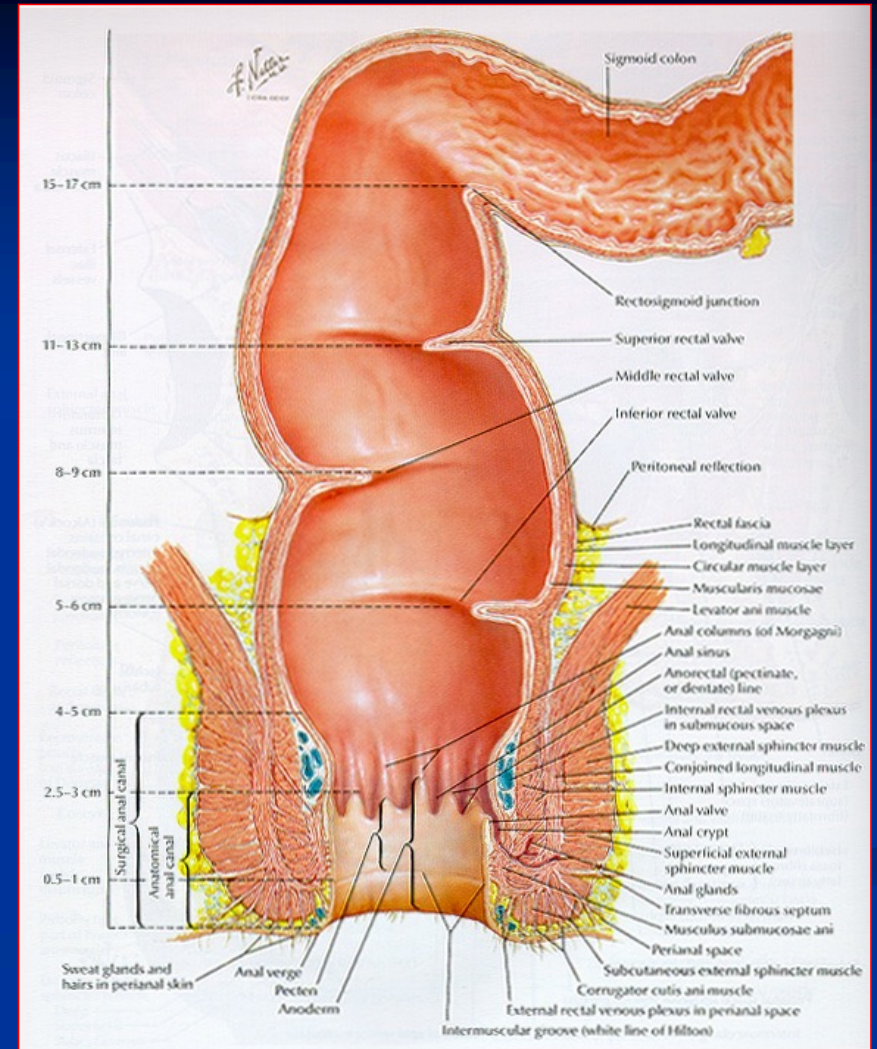
Transdermal (cont.)

Example:
Androderm
(testosterone)
Patch



Rectal

Example: Acetaminophen (Tylenol) suppository

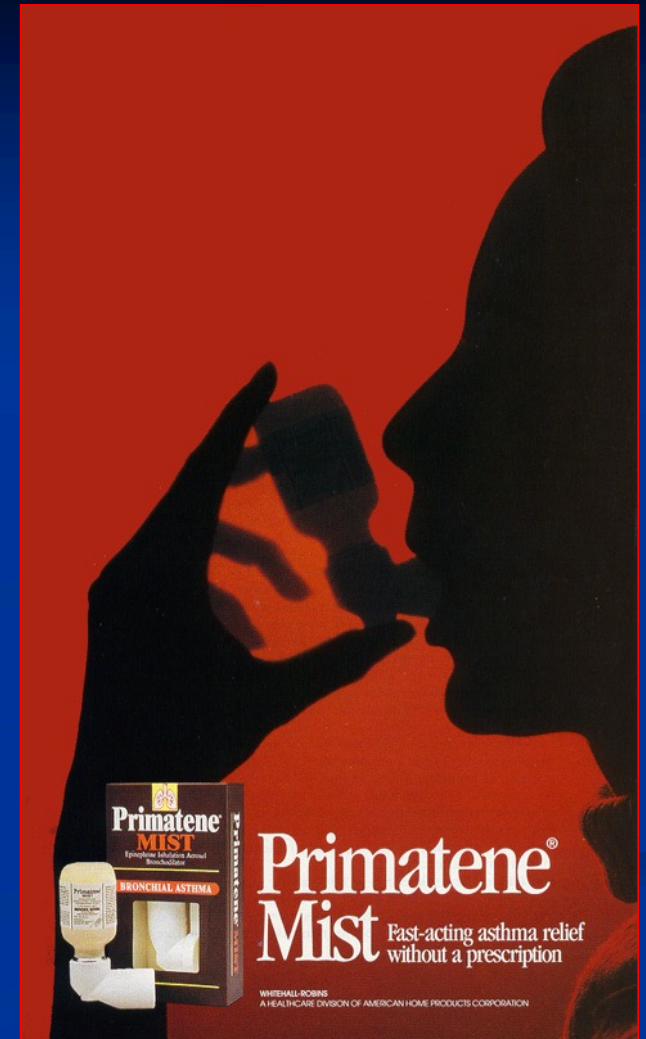


Rectal (cont.)

- rectal route is convenient in unconscious or vomiting patients
- disadvantage: drug may be incompletely or erratically absorbed

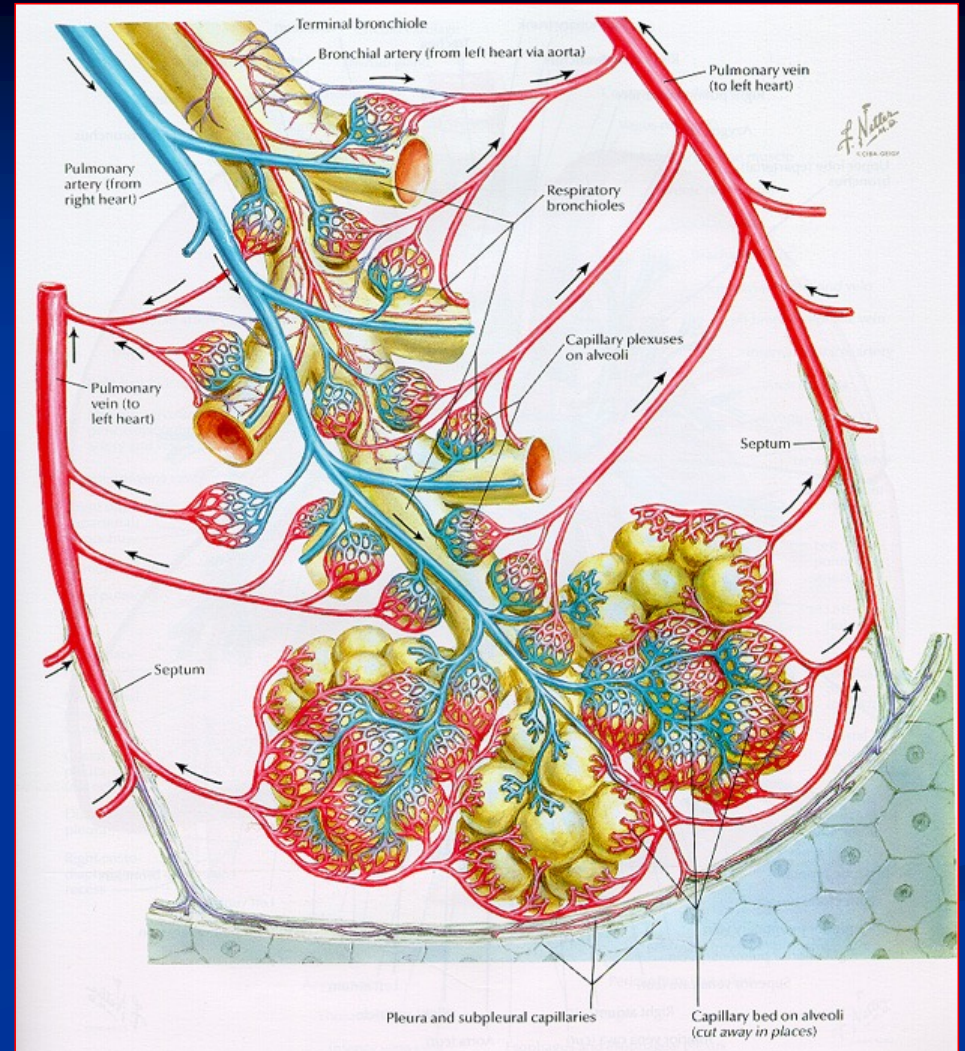
Inhalational

- drug is inhaled as a gas or aerosol into the lungs where it either exert a localized effect on lungs (e.g., bronchodilation) or

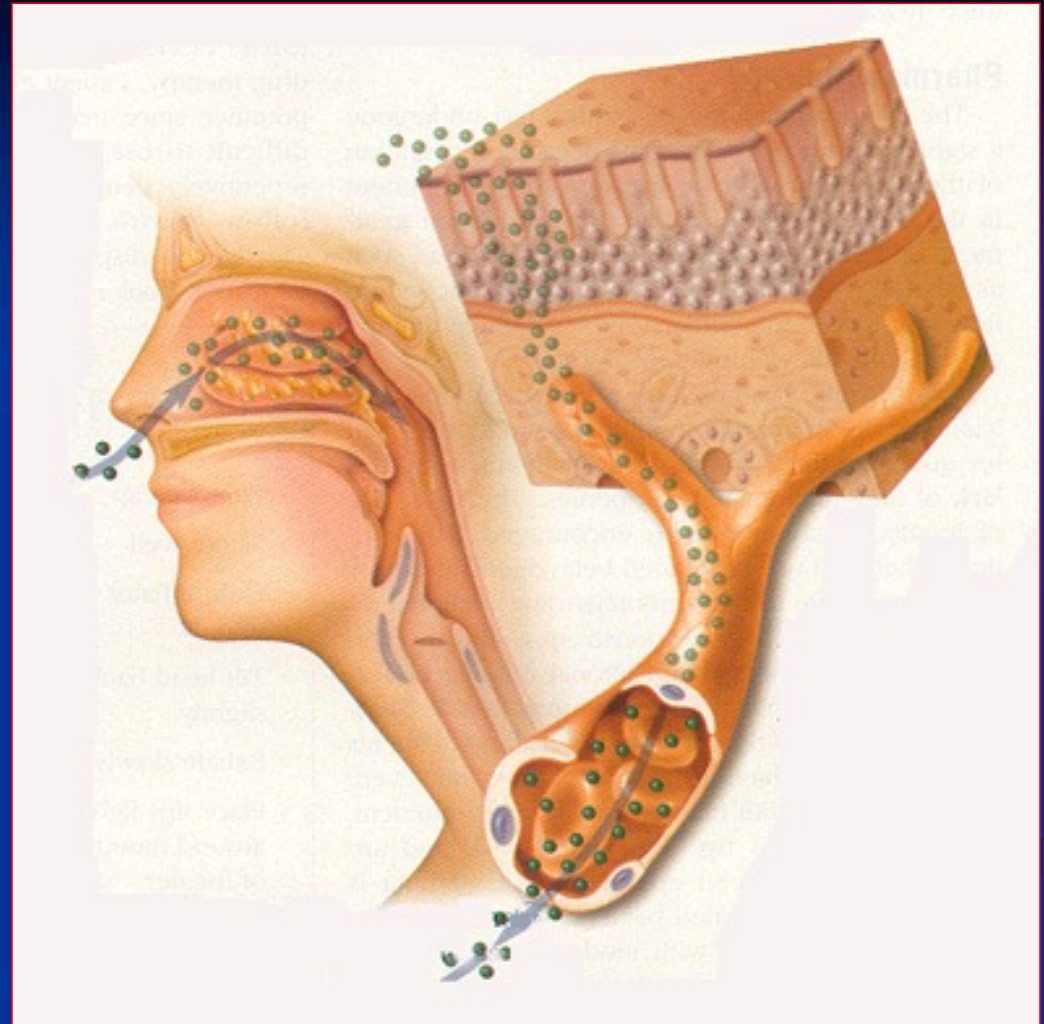


... the drug enters the bloodstream through the lungs

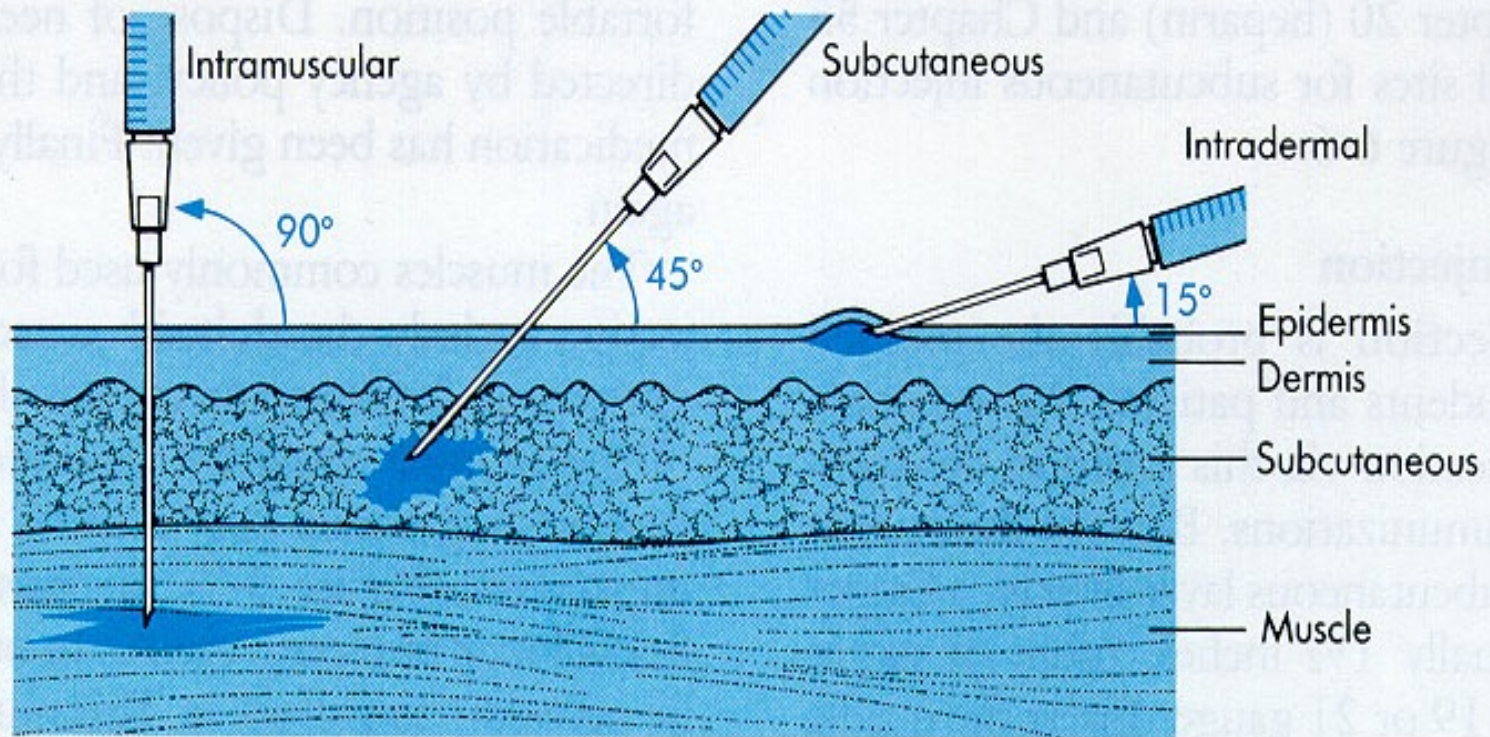
- inhaled drug produces a rapid onset since it enters the general circulation shortly after being inhaled



Intranasal



Parenteral route (IV, IM, & SC)



Parenteral route (cont.)

- advantages:
 - drug response: IV > IM > SC
 - avoids unpredictable absorption processes of GI tract
 - useful in unconscious or uncooperative patients



Parenteral (cont.)

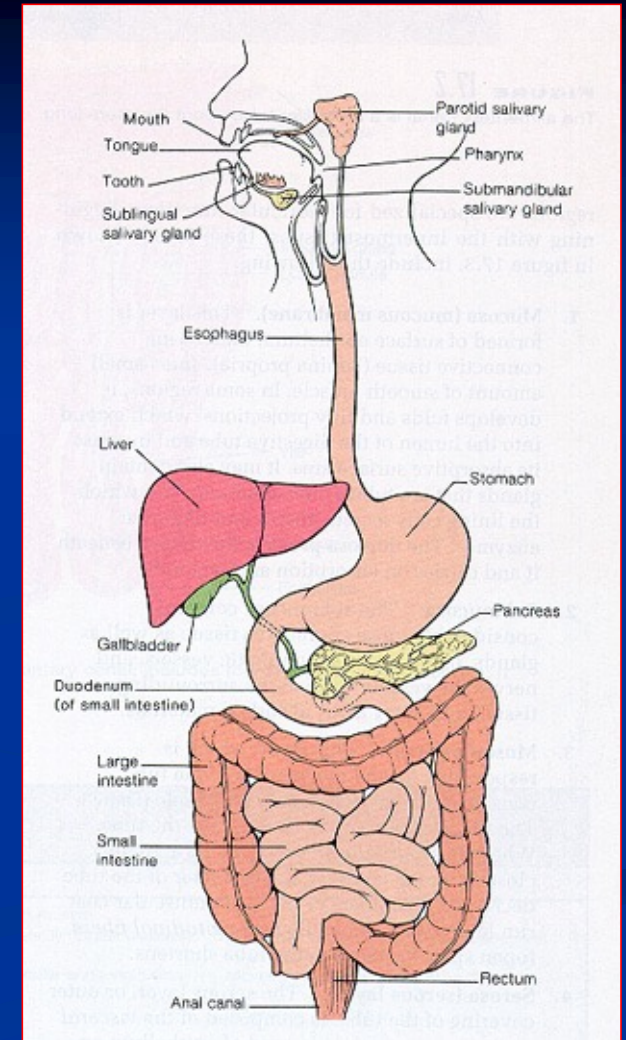
- disadvantages:
 - requires sterile conditions to prevent infections
 - more costly than other routes of administration
 - once injected, a drug cannot be retrieved
 - pain at injection site

Drug Distribution

- general rule: small and highly lipophilic drug molecules penetrate cell membranes, capillaries, and physiological barriers (i.e., placenta, blood-brain-barrier, etc...) more readily than larger, polar (non-lipophilic) drug molecules

Characteristics of Drug Absorption (GI tract)

- a. drugs must be relatively lipid-soluble to pass through the membranes of the GI tract
- b. drugs either exist in lipid-soluble form or non-lipid soluble form depending on their pH environment



Characteristics of Drug Absorption (GI tract)

- pH environment changes along the GI tract:
 - stomach (highly acidic)
 - small intestine (slightly alkaline)

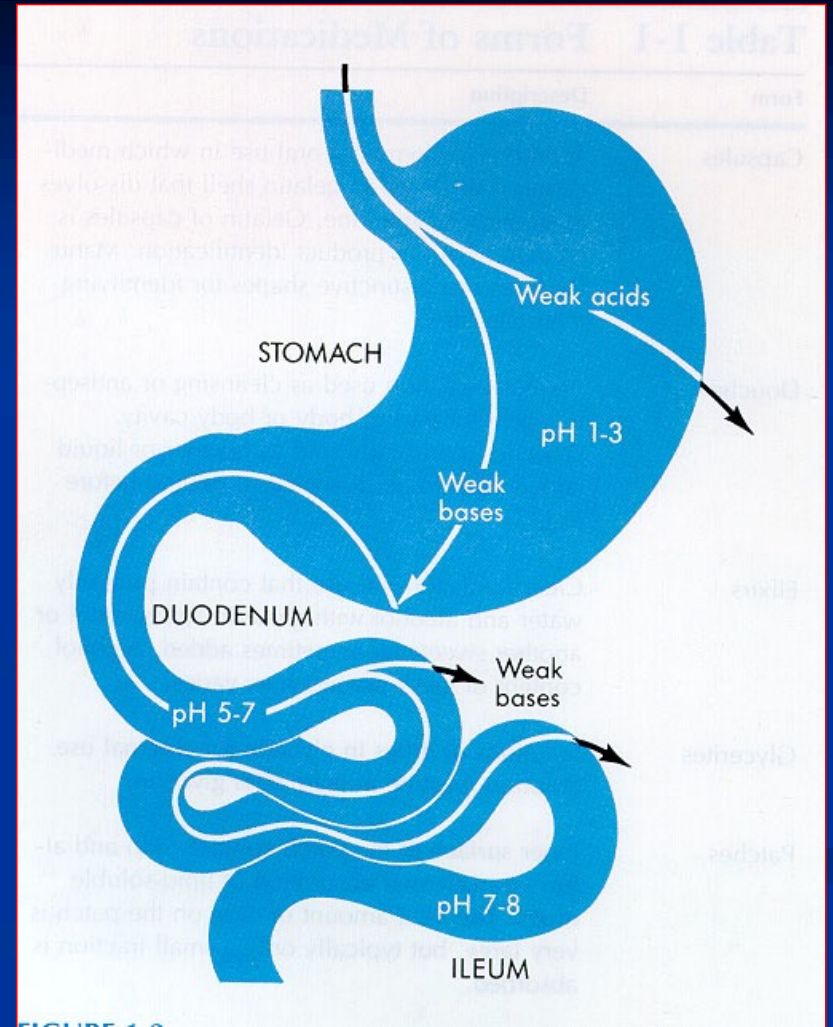


FIGURE 1-2

Bioavailability

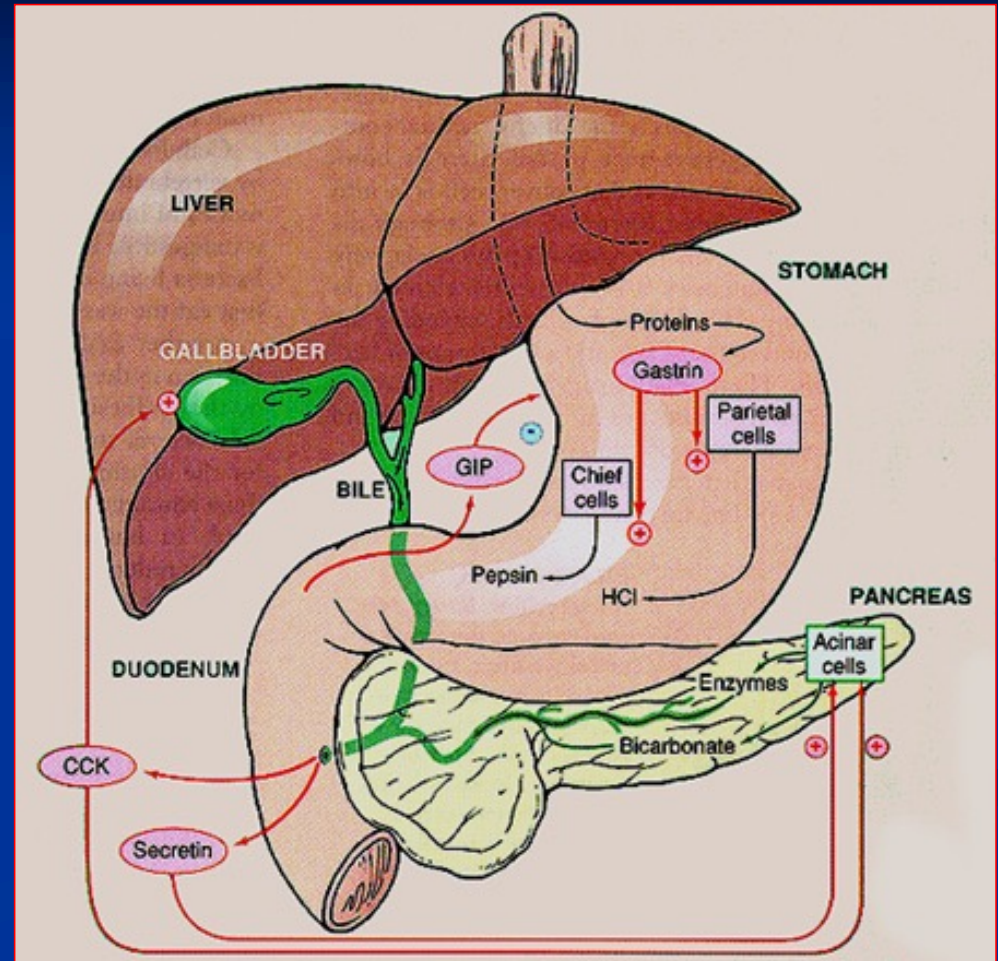
- describes what proportion of the administered drug is available to produce a pharmacologic response
- factors influencing bioavailability:
 - drug dissolution
 - inert ingredients (binders, disintegrators, lubricants, buffers, etc...)

Factors influencing bioavailability: GI Tract

- presence of food may affect dissolution and absorption of drugs
 - Tetracycline (TCN) + dairy products
 - TCN binds to calcium
 - unabsorbed TCN excreted in feces

ii. GI tract (cont.)

- achlorohydria
 - deficiency in pancreatic and intestinal secretions
- prevents dissolution of enteric-coated tablets

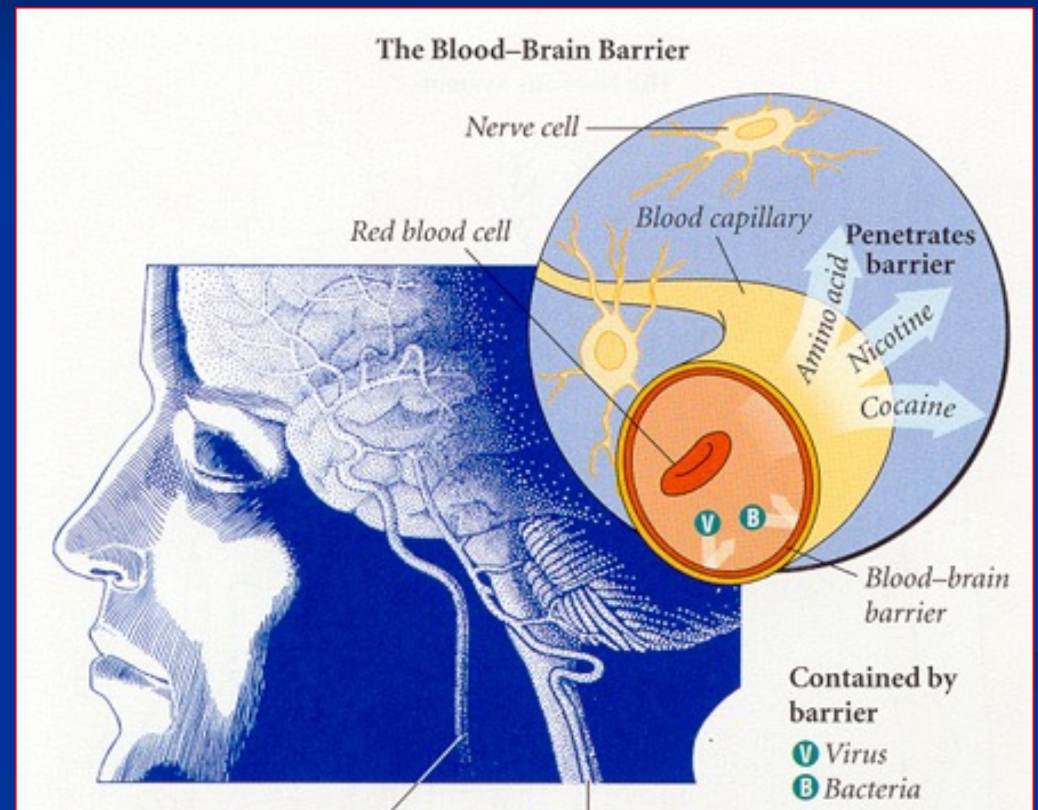


Drug Distribution (cont.)

- the degree to drug distribution depends on the physical and chemical properties of a drug and its ability to penetrate cell membranes, capillaries, blood-brain barrier, placenta, etc....

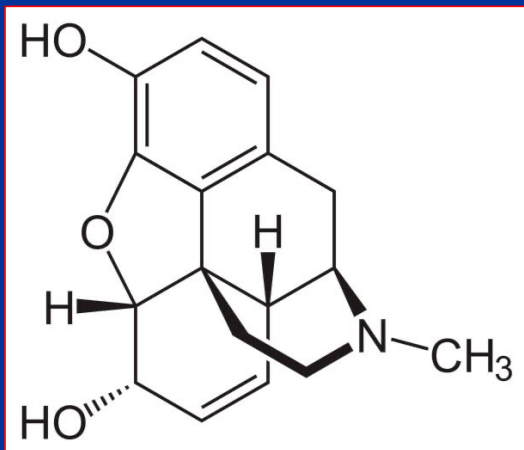
Blood-Brain-Barrier (BBB)

- only lipid-soluble drugs and very small molecules are capable of crossing the BBB to exert an effect on the brain



Blood-Brain-Barrier (cont.)

- heroin crosses the BBB more readily than morphine because of its greater lipid solubility factor



Morphine



Mexican "tar" Heroin

TO OPEN LIFT FLAP
TO CLOSE INSERT FLAP INTO CARTON

M-407 NDC 0024-1261-02
NSN 6505-00-149-0113

10 Carpuject®
Sterile Cartridge-Needle Units

(Each with Sterile 22 Gauge 1 1/4 Inch Needle
and Partially-Filled Cartridge of Medication)

DETECTO-SEAL® PAK Tamper Detection Package

**Morphine
Sulfate
Injection, USP**

Warning: May be habit forming.

10 mg/1 mL
10 mg per mL

NOT FOR INTRATHECAL OR EPIDURAL USE.
While admixture of drugs in the same
container is generally not recommended,
each cartridge is only partially-filled based
upon product volume to permit mixture with
other sterile materials in accordance with the
best judgment of the physician. (Incompatible
with soluble barbiturates, prochlorperazine,
and promethazine.)

Caution: Federal law prohibits
dispensing without prescription.

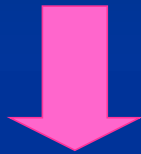
sanofi WINTHROP

Drug Distribution: Plasma Protein Binding

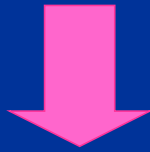
- many drugs bind to plasma reversibly with plasma proteins (e.g., albumin)
 - only unbound or “free” drug may:
 - diffuse through capillary walls
 - produce a pharmacological effect
 - be metabolized
 - be excreted

Plasma Protein Binding (cont.)

“free” drug $\leftrightarrow$ protein-bound drug



circulating drug reservoir



prolongs the action of drugs

Plasma Protein Binding and Drug-Drug Interactions

Aspirin (ASA)



ASA displaces warfarin from albumin binding site



increase in “free” warfarin drug levels



increases risk of bleeding

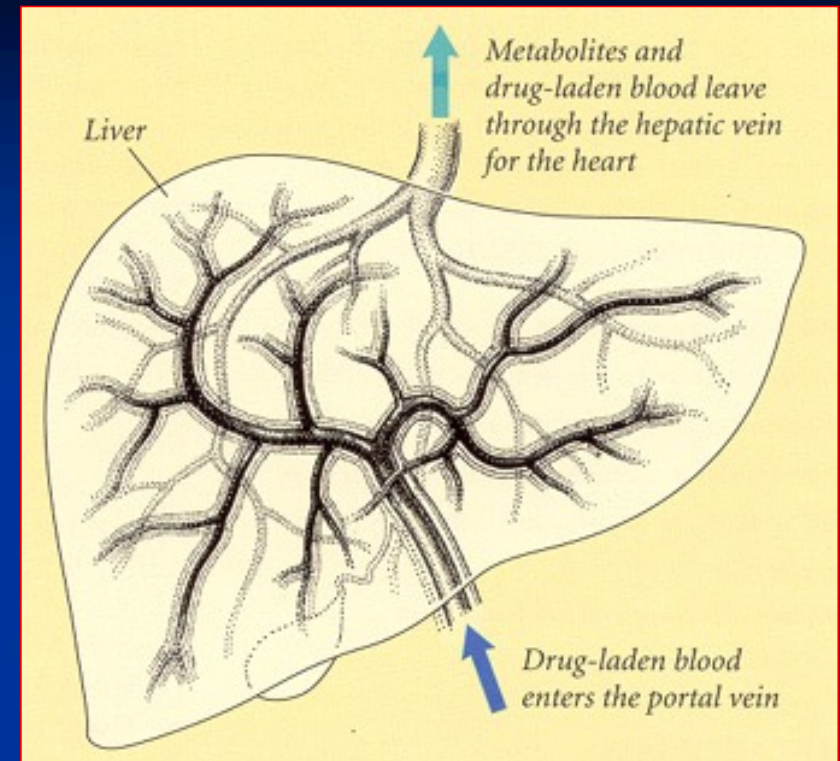
- Warfarin (Coumadin) is an anticoagulant.
- Aspirin (ASA) is an antiplatelet drug.

Tissue Trapping

- certain tissues (e.g., adipose tissue) are capable of trapping or storing drugs temporarily or permanently, converting them into “inactive” form
- when drugs leave the tissue-binding site, they become active again

Drug Biotransformation (Drug Metabolism)

- the liver is the major organ responsible for metabolizing drugs
- the liver converts lipid-soluble drugs to water-soluble drug → excreted by kidneys

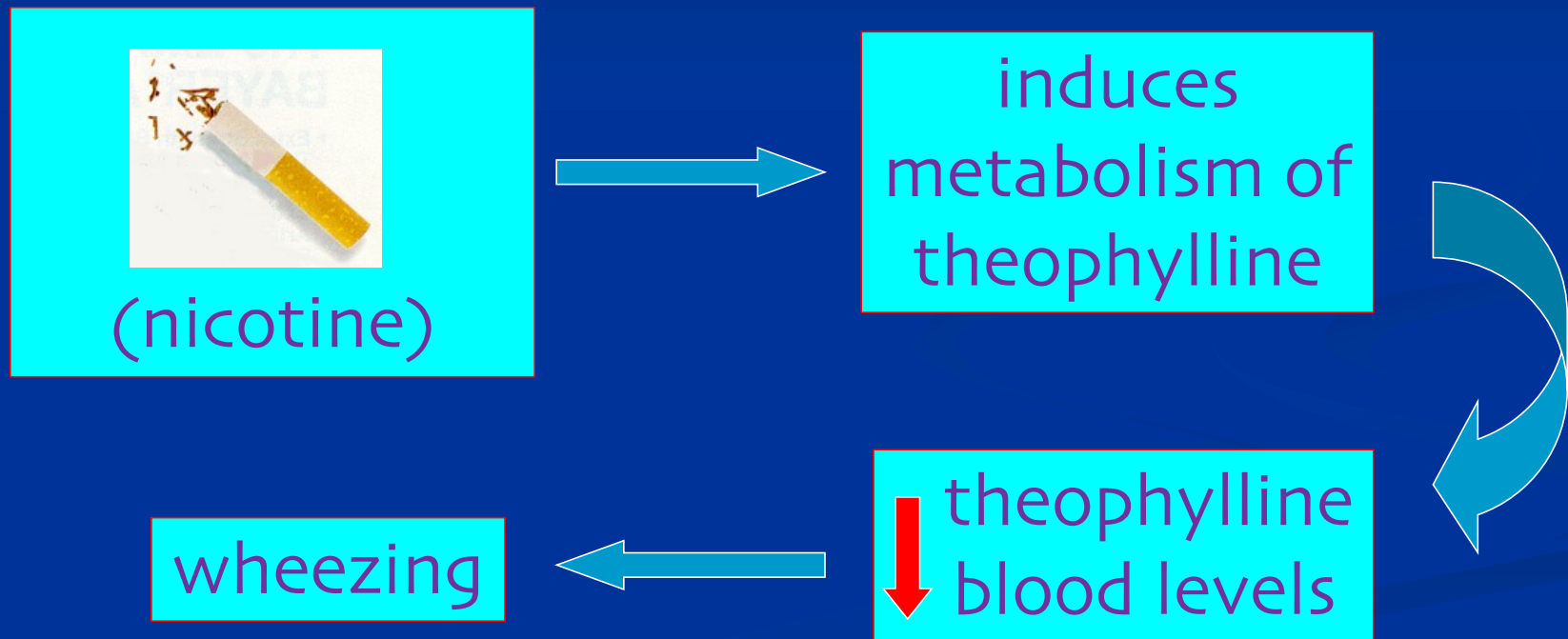


“First-Pass Effect” of the Liver

- the “first-pass effect” of the liver inactivates potentially harmful chemicals and drugs before being distributed in the general circulation throughout the body

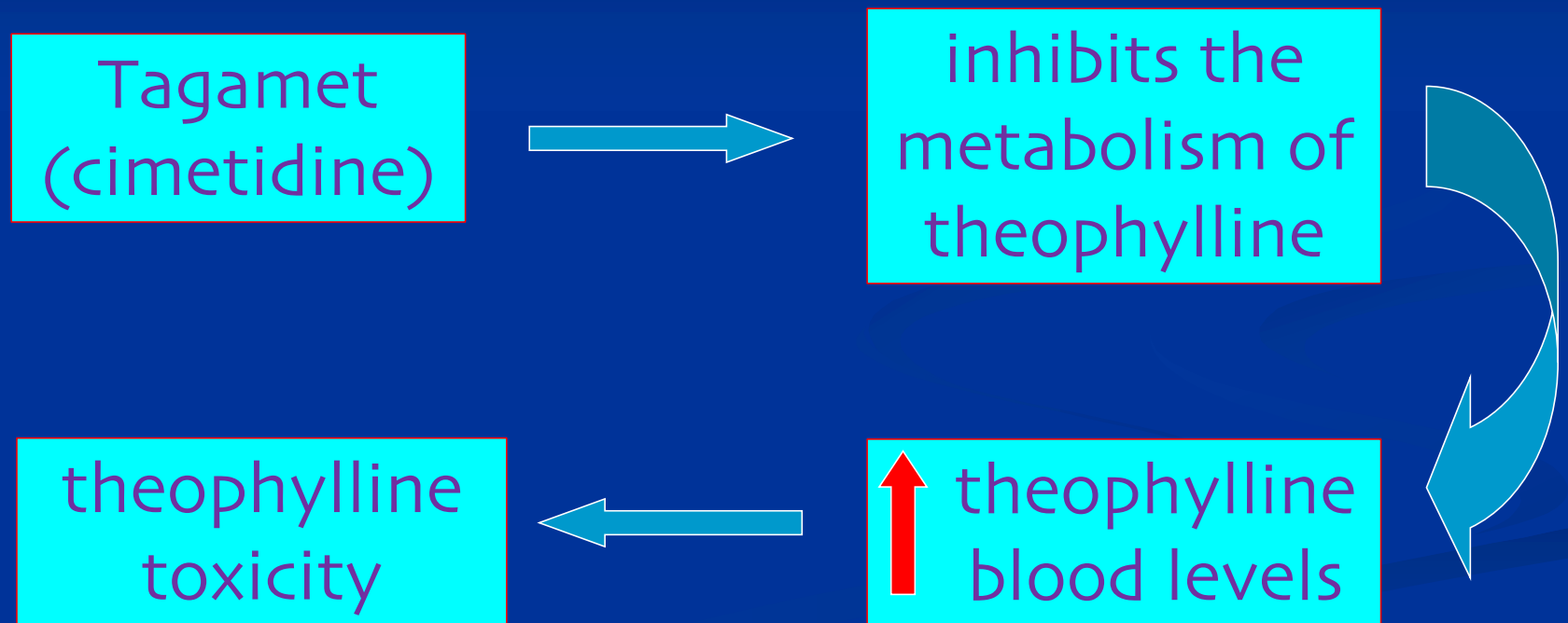
Induction / Inhibition of Drug Metabolism (Liver)

i. induction of enzymes (metabolism)



Induction / Inhibition of Drug Metabolism (Liver)

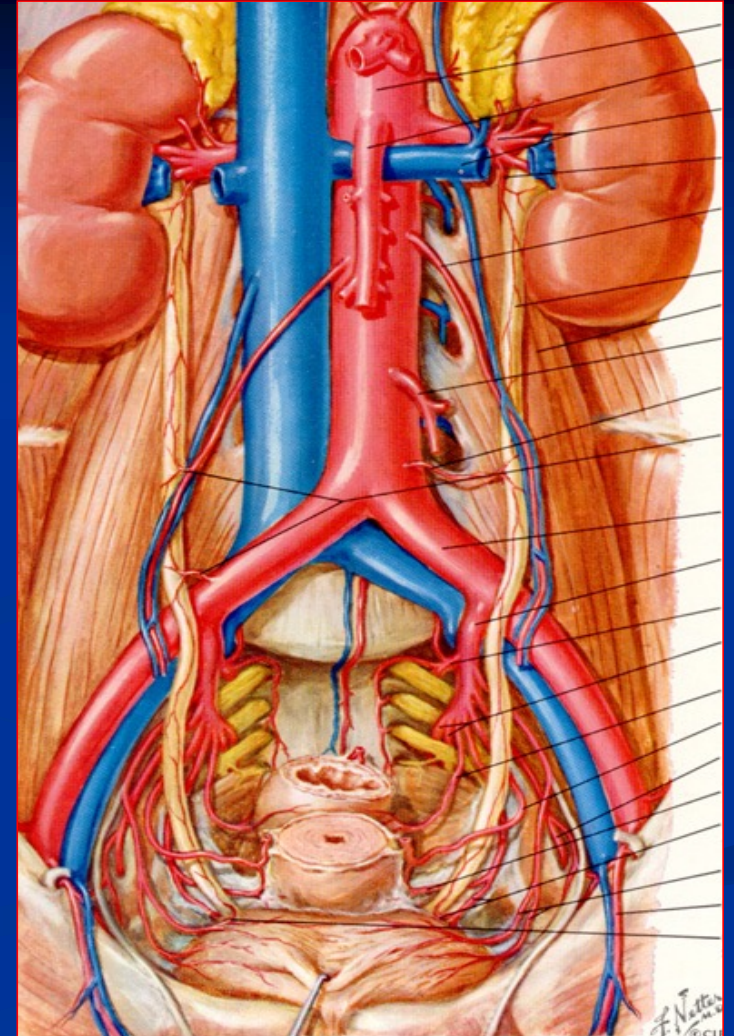
ii. inhibition of enzymes (metabolism)



Drug Elimination (Kidneys)

- it is estimated that kidney function decreases by 10% per decade of life after 20 years of age

$$\text{CrCl (ml/min)} = \frac{(140 - \text{Age}) \times \text{IBW}}{\text{sCr} \times 72}$$



Elimination of Drugs in the Feces

(a) metabolized drug → bile → feces

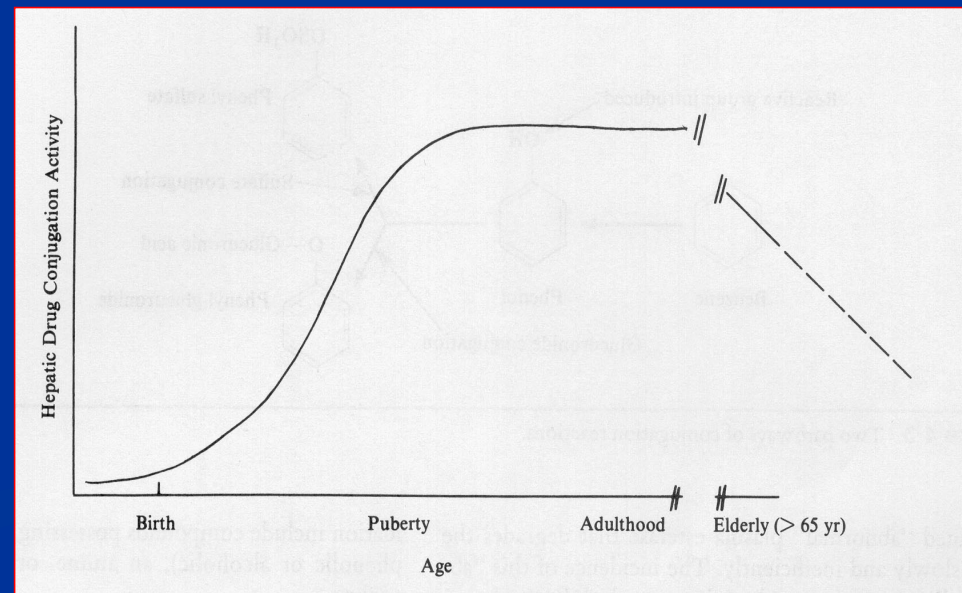
(b) enterohepatic recirculation

- metabolized drug is secreted in bile
 - enters small intestine
 - reabsorbed and returns to liver
 - secreted in bile

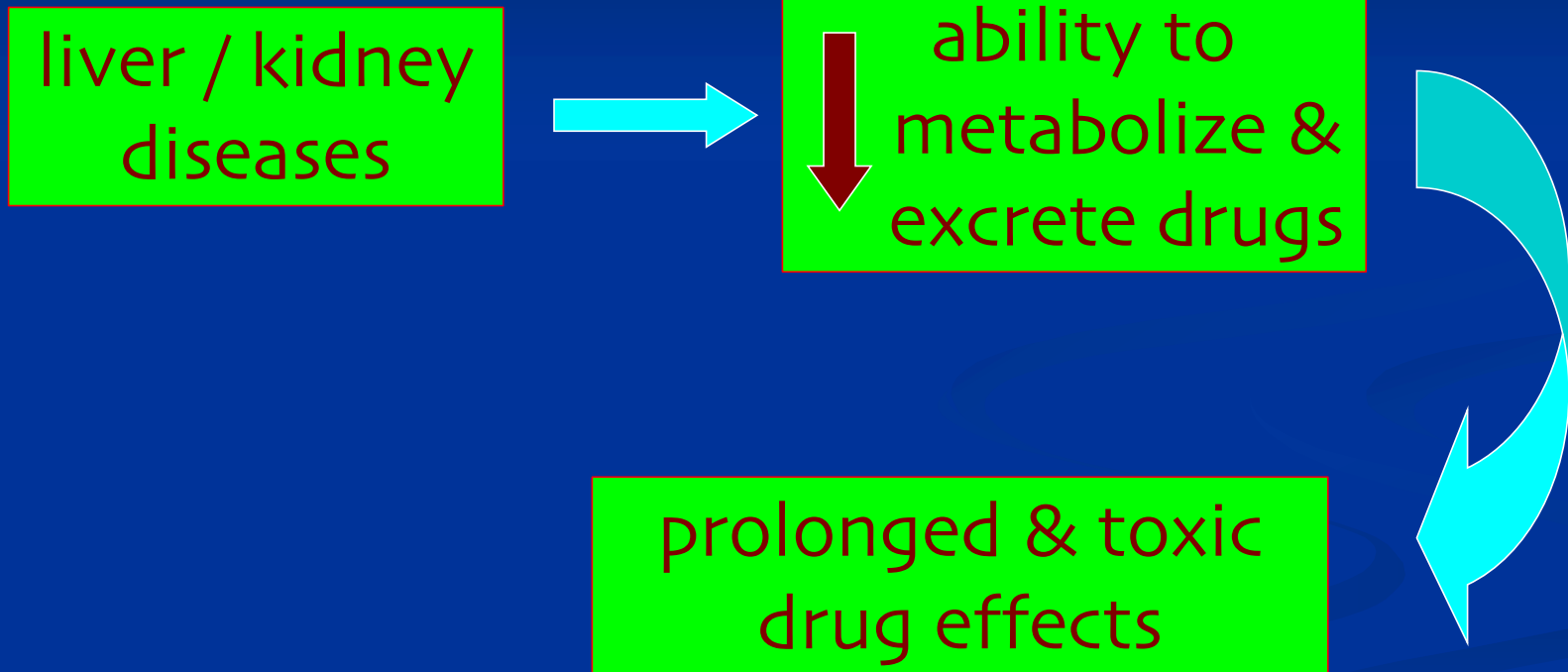
Drug Elimination & Age Considerations

- infants → underdeveloped ability to metabolize and excrete drugs
- elderly → impaired ability to metabolize and excrete drugs

Drug Metabolism (Liver) and Age Considerations



Disease & Drug Elimination Rates



Summary:

Pharmacodynamics & Pharmacokinetics

