

Introduction pharmacology

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PhD of Molecular Pharmacology

The optimum goal

Pharmacology is a keystone for a prescribing doctor, as they can impact proper dosage, what time a drug should be taken, and how a drug should be delivered.

Drug Naming

- **Chemical Name** - describe chemical structure (rarely seen in medical literature)
- **Generic Name** - a name assigned to drug that can be used by anyone (not proprietary)
- **Trade Name** - Proprietary name given to the drug by the manufacturer

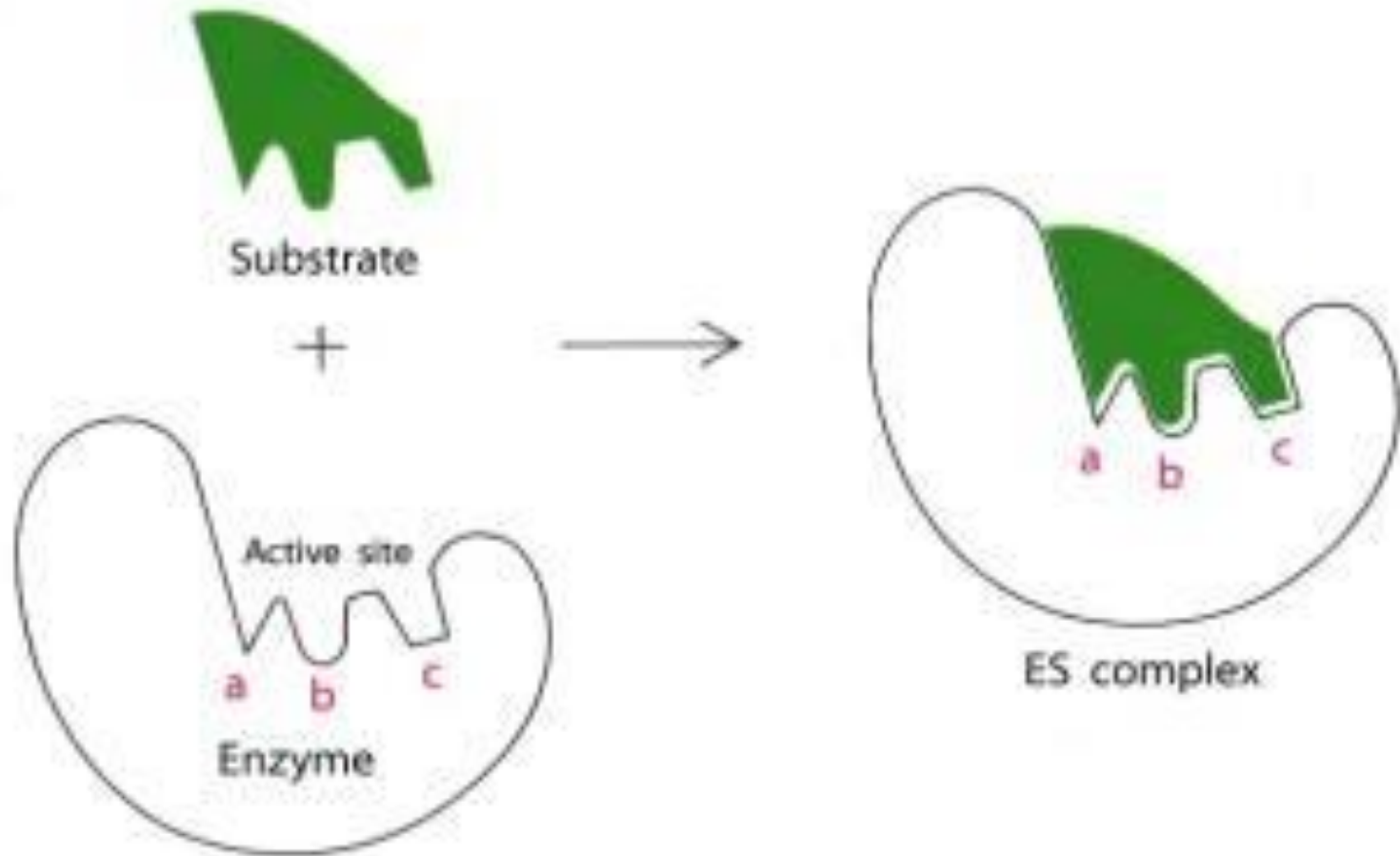
Table 1-1

EXAMPLES OF DRUG NOMENCLATURE

Chemical	Generic (Nonproprietary)	Trade/Brand-Name (Proprietary)
<i>N</i> -Acetyl- <i>p</i> -aminophenol	Acetaminophen	Tylenol, Panadol, many others
3,4-Dihydroxyphenyl-L-alanine	Levodopa	Larodopa
5,5-Phenylethylbarbituric acid	Phenobarbital	Luminal, Eskabarb
7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2 <i>H</i> -1,4-benzodiazepin-2-one	Diazepam	Valium

Over the counter????

Model of Drug/Receptor Binding

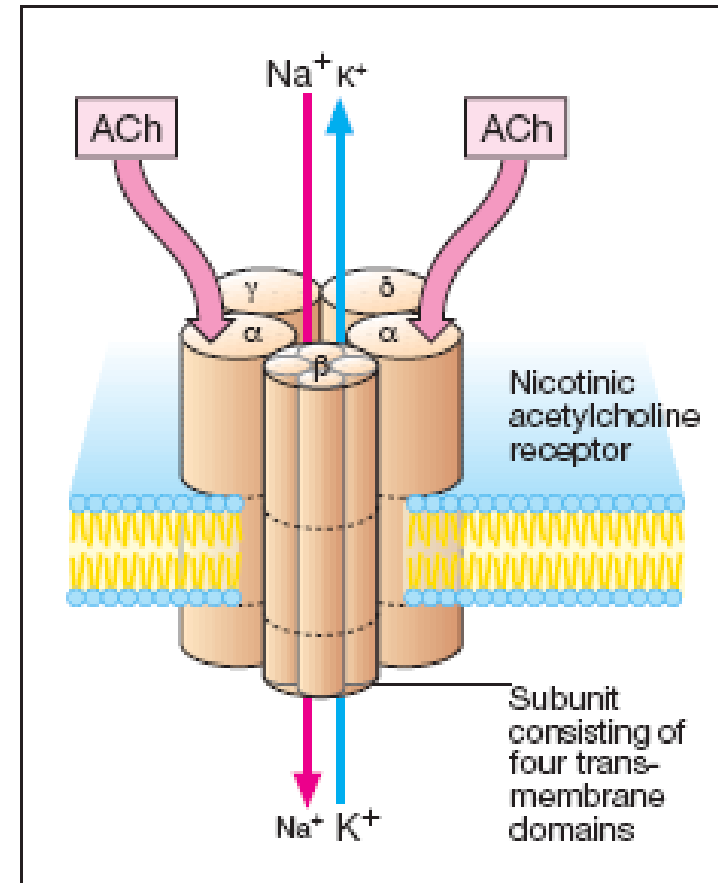
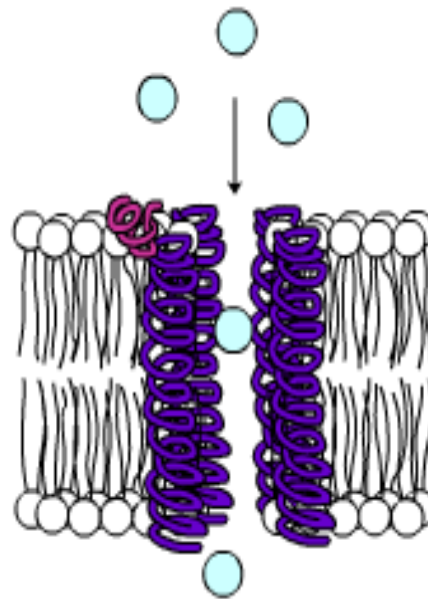
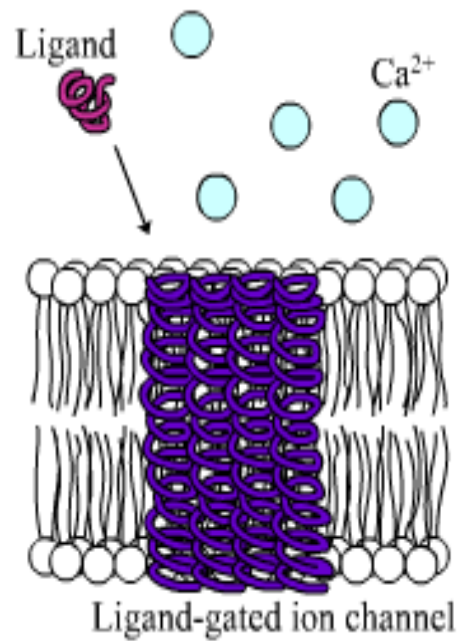


Major receptor families

- **Ligand-gated ion channels**
- **G protein-coupled receptors**
- **Enzyme-linked receptors**
- **Intercellular receptors**

Ligand-gated ion channels

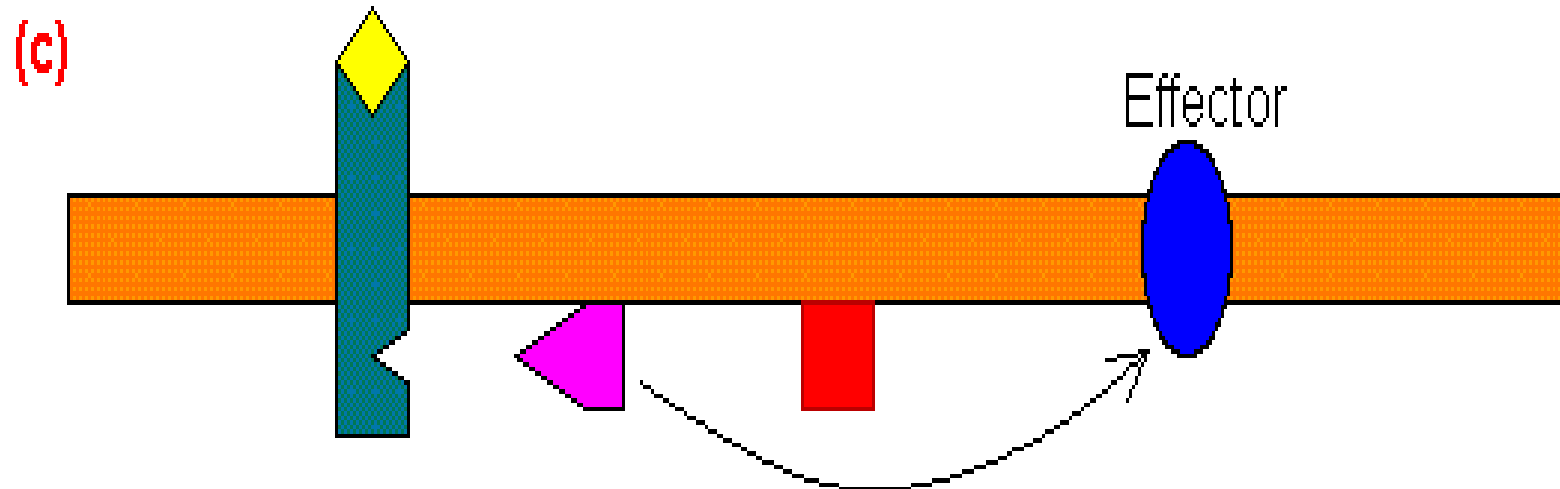
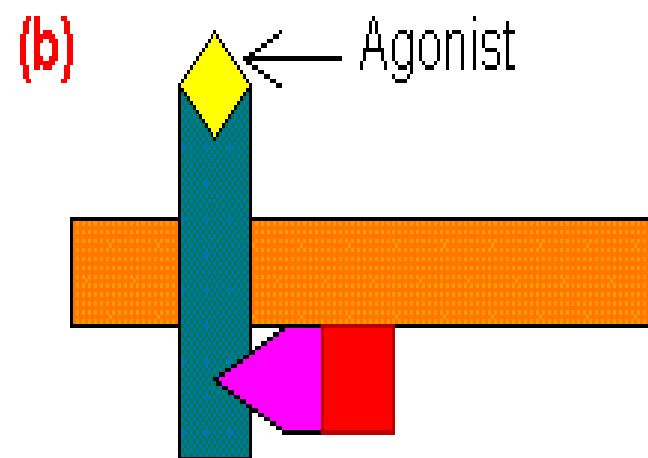
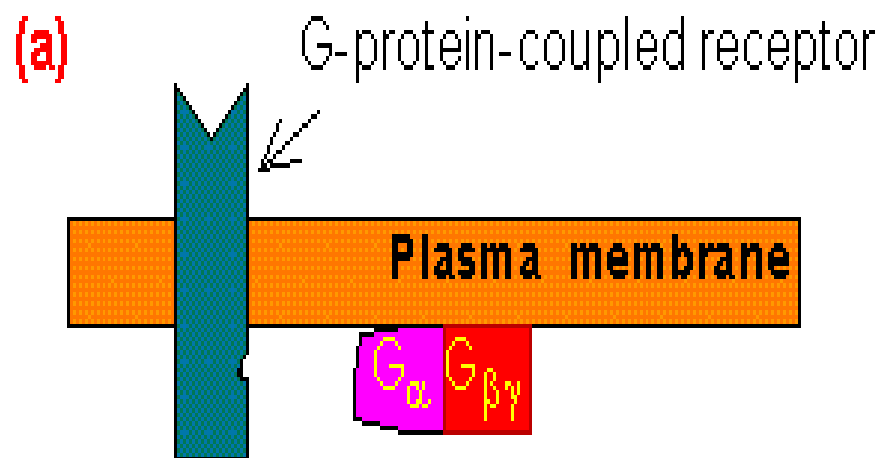
- Responsible for regulation of the flow of ions channels across cell membranes.
- Regulated by binding of a ligand to the channels.
- The best example being the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle



B. Ligand-gated ion channel

G protein-coupled receptors

- Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins.
- Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors depend on the G proteins) mediate their action on cells.



Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme.
- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein.
- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch.

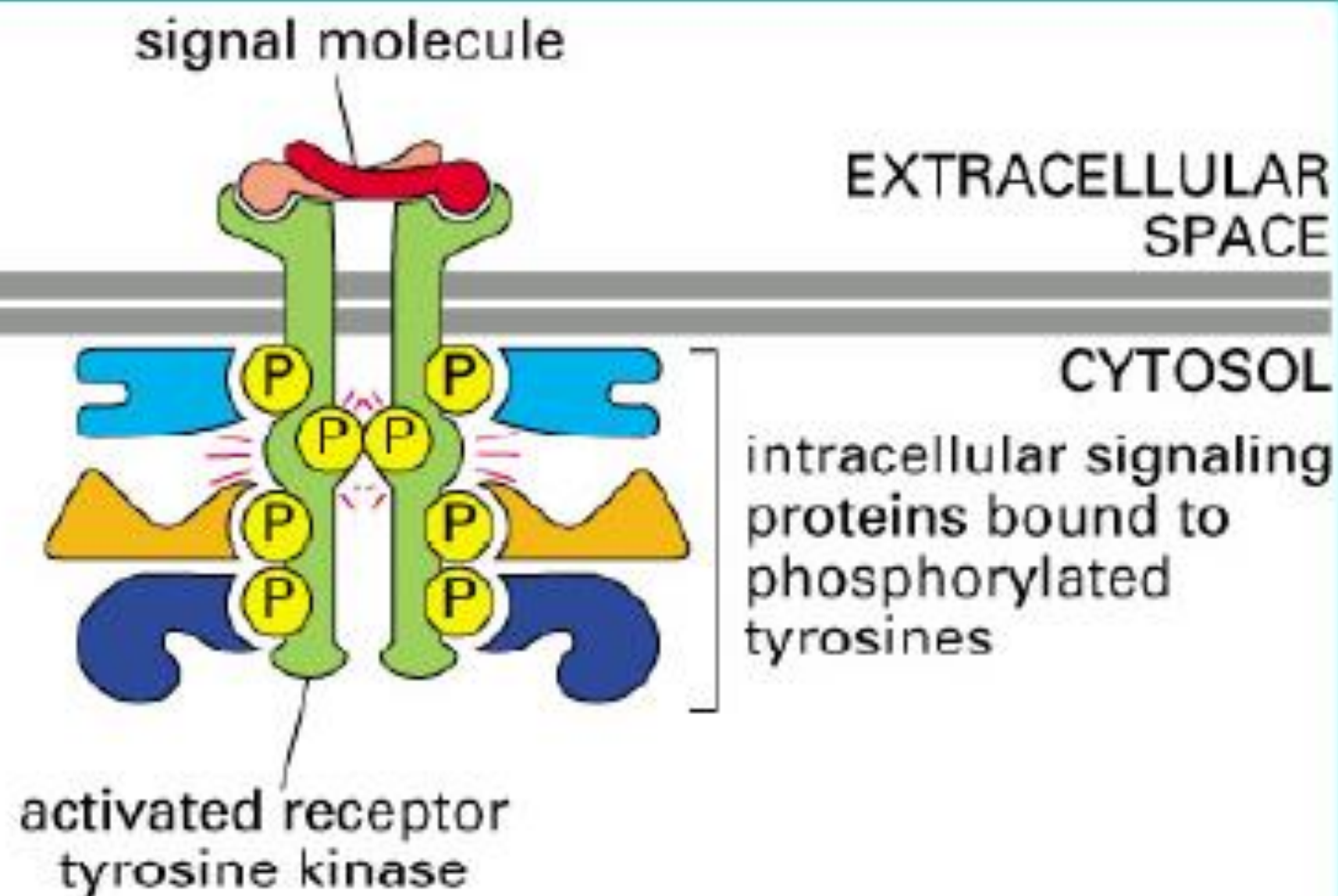
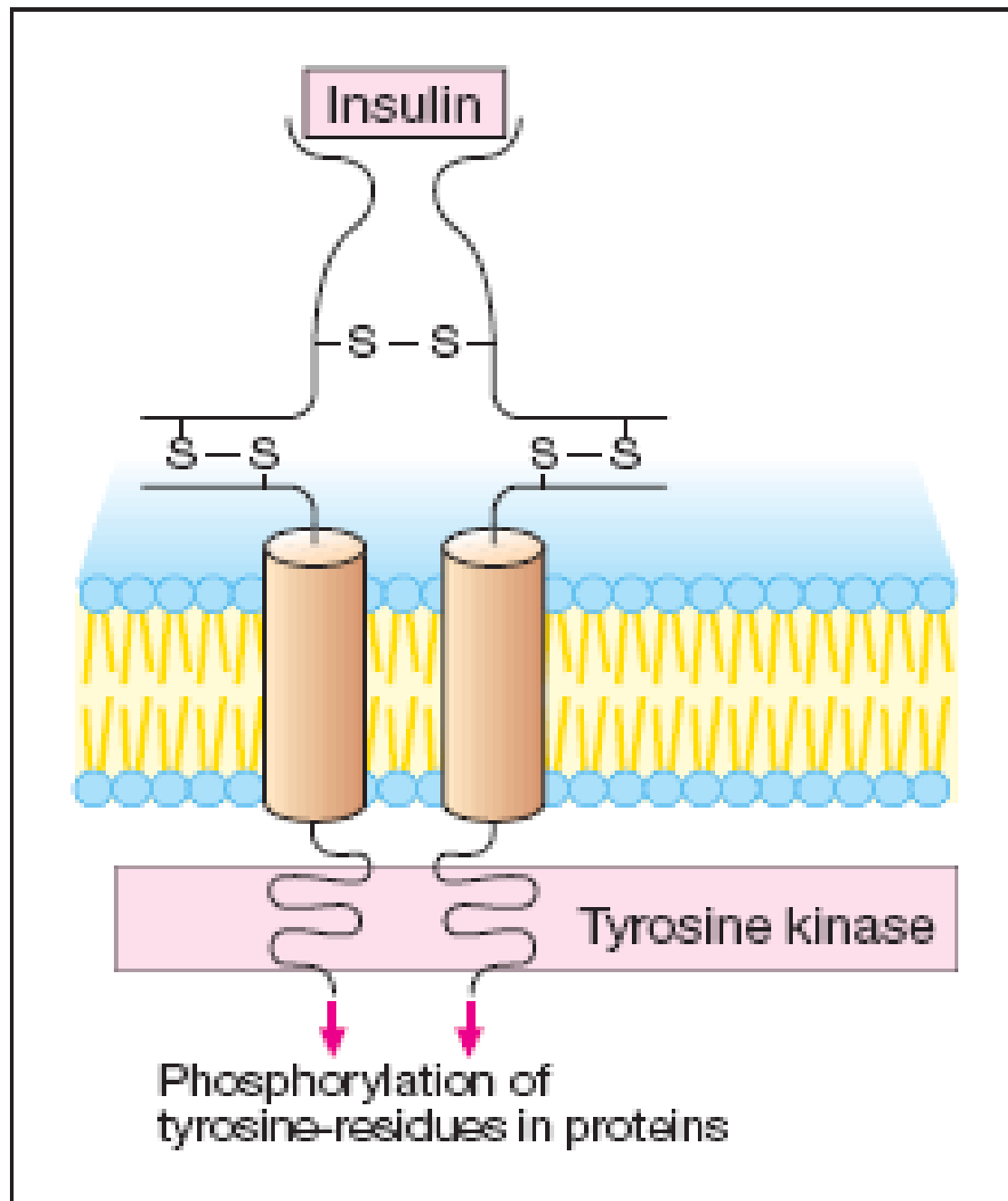


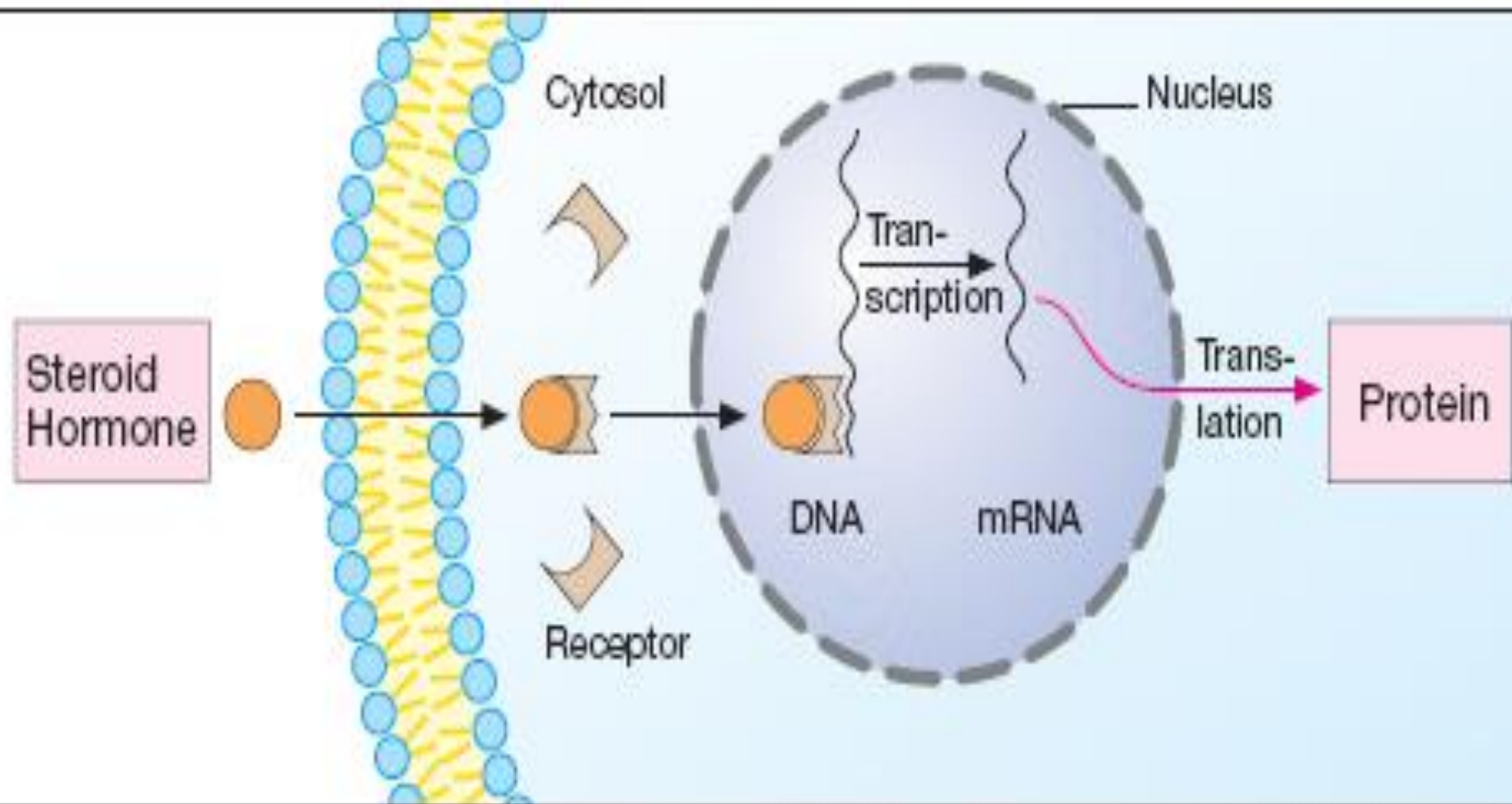
Figure 15-52. Molecular Biology of the Cell, 4th Edition.



C. Ligand-regulated enzyme

Intercellular receptors

- In this family the ligand must diffuse into the cell to interact with the receptors.
- Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes.
- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression.



D. Protein synthesis-regulating receptor

Dose response relationships

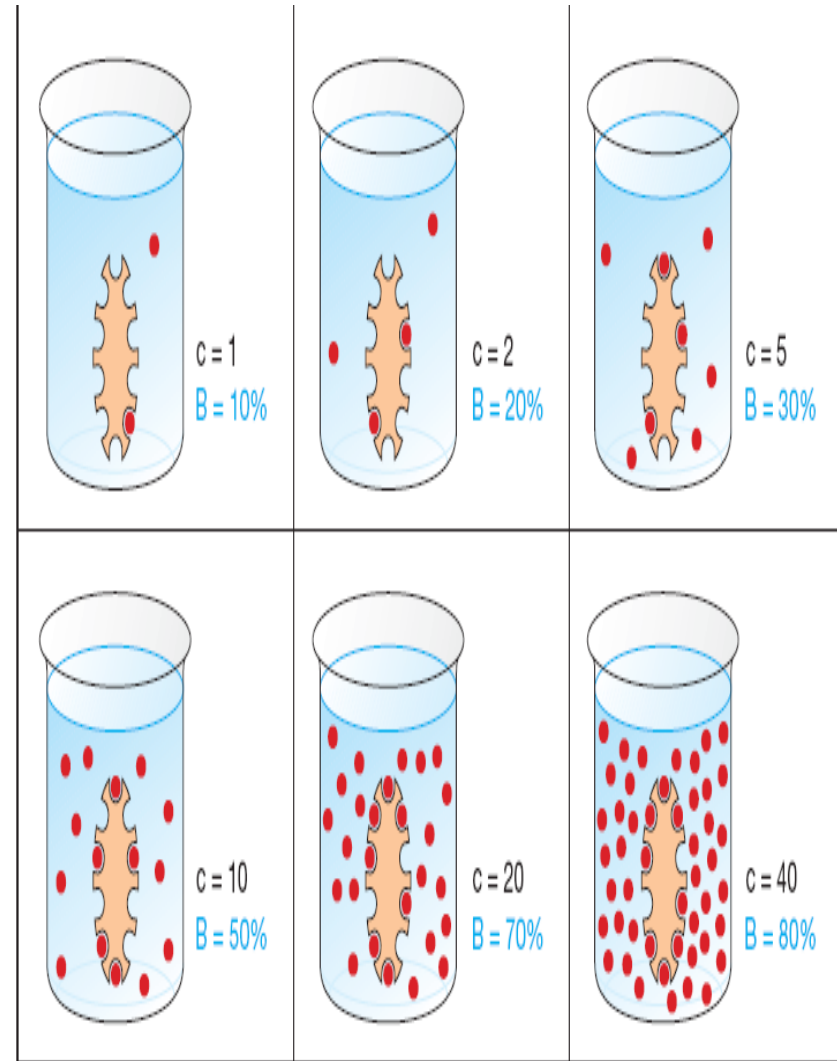
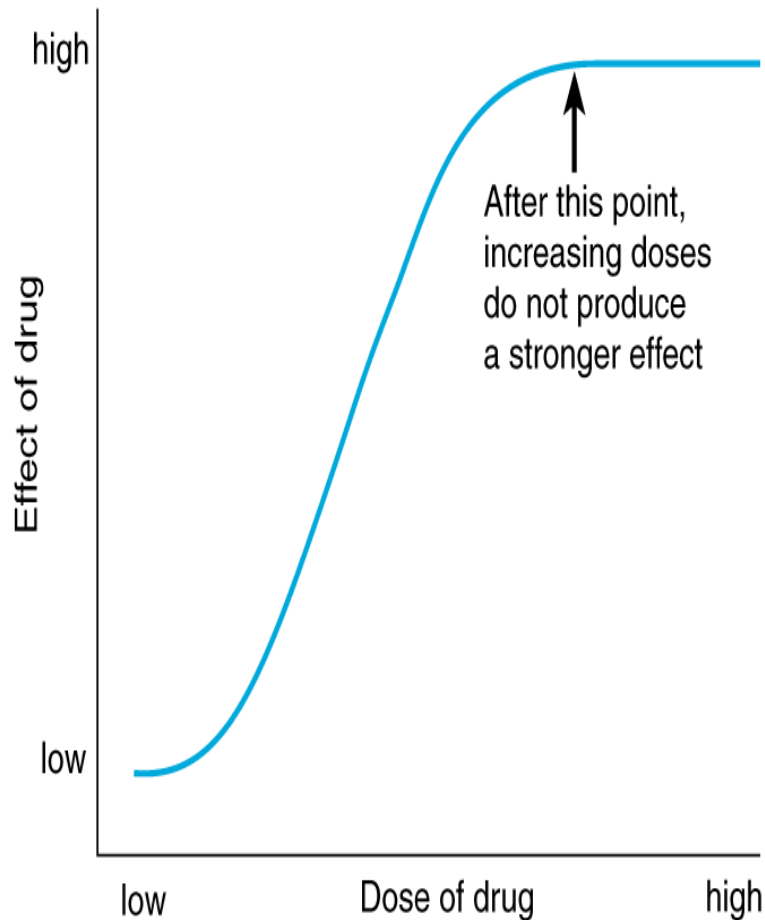
- Graduated dose-response relations

As the dose administered to single subject or isolated tissue is increased, the pharmacologic effect will also increase.

At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or E_{max} .

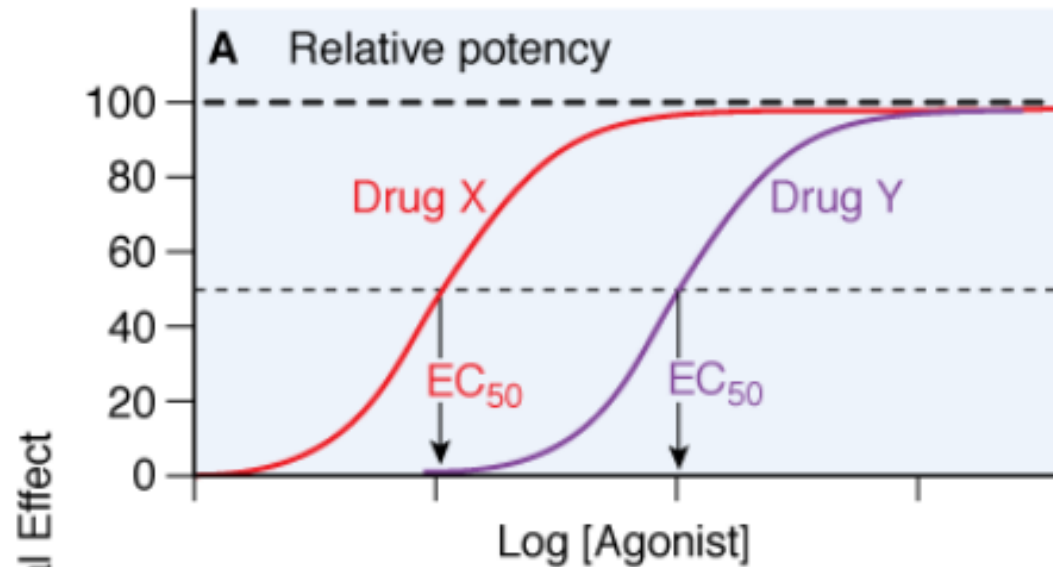
Graduate dose-response curve

► Dose-Response Curve

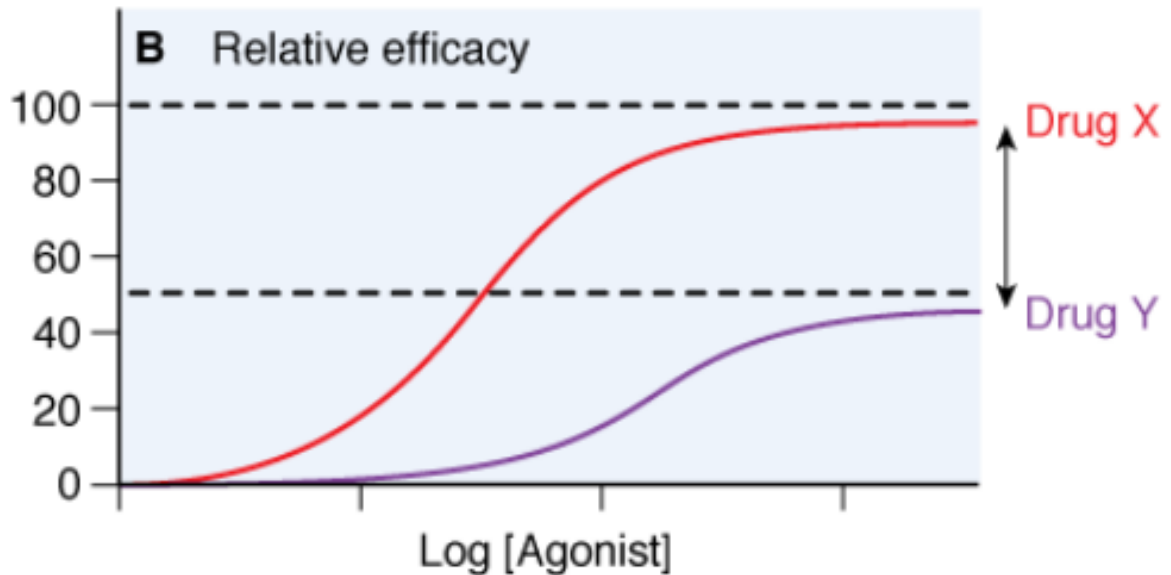


Log dose response curve

The smaller the EC_{50} , the greater the potency.



Efficacy is indicated by the height of the log dose response



Antagonism between drugs

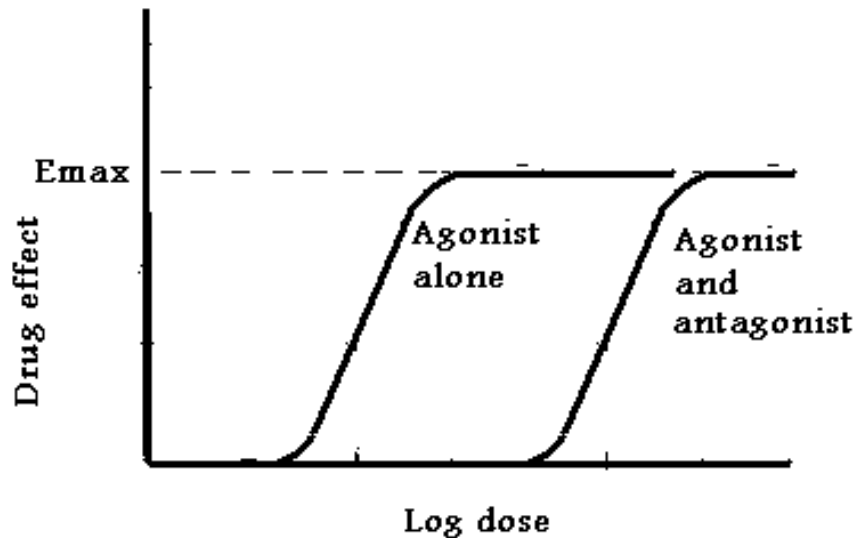
- A. Pharmacologic antagonism: occurs when an antagonist prevent an agonist from interacting with its receptors to produce an effect, and it can be either competitive or noncompetitive.

Competitive antagonist compete with agonist in a reversible fashion in the receptors. The log dose-response curve is shifted to the right, indicating that a higher concentration of agonist is necessary to achieve the response.

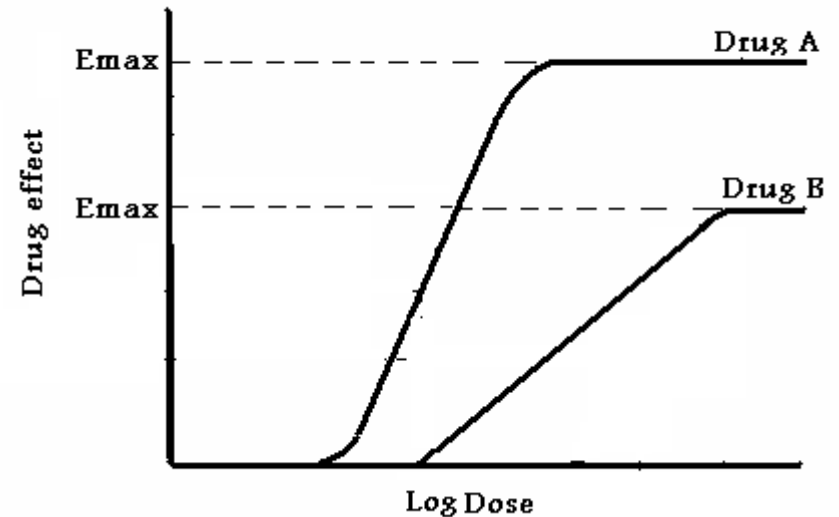
Noncompetitive antagonist binds irreversibly to the receptors site or to another side that inhibit the response to the agonist. And no matter how much agonist is given, the action of the antagonist can not overcome. The shift in the log response curve in this case is a nonparallel shift.

Shift in the log-dose response

Competitive antagonist



Noncompetitive antagonist



Antagonism between drugs

- B. Physiologic Antagonist: here the drugs act independently on two different receptors, and exemplified by one drug acting on the sympathetic nervous system causing the heart rate to increase and causing vasoconstriction; while another drug acting on the parasympathetic nervous system decrease the heart rate and causes vasodilation.
- C. Chemical antagonist (Antagonism by neutralization):
Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

Enhancement of drug effects

A. Additive drug effect occurs if two drugs with the same effect, when given together produce an effect that is equal in magnitude to the sum of the effect.

$$E_{AB} = E_A + E_B$$

$$1 + 1 = 2$$

B. Synergic drug effect occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually.

$$E_{AB} > E_A + E_B$$

$$1 + 1 > 2$$

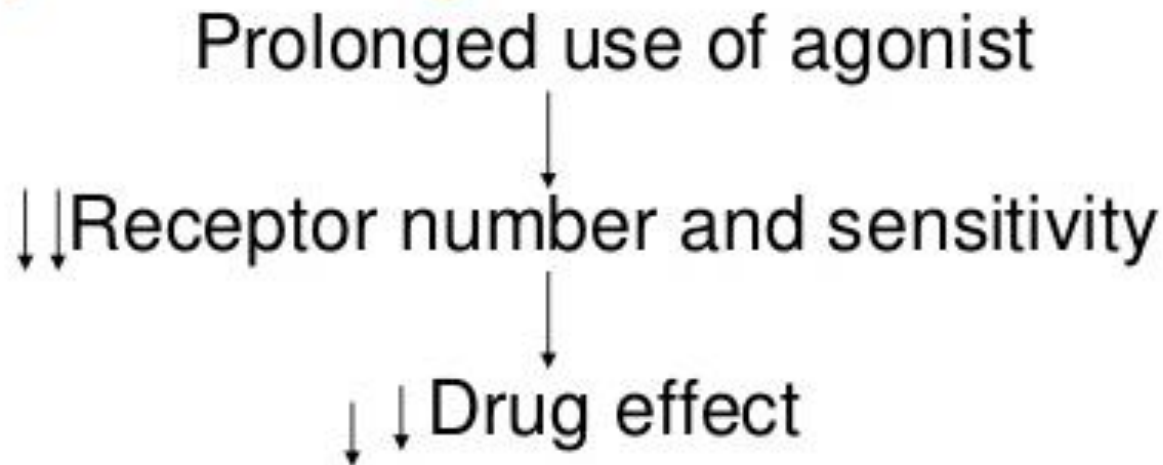
C. Potentiation drug effect occurs if a drug lacking an effect of its own increase the effect of a second active drug.

$$E_{AB} > E_A + E_B$$

$$0 + 1 > 2$$

Receptor are in dynamic state

- The affinity of the response to drugs is not fixed. It alters according to situation.
- Receptor down regulation:



Ex: Chronic use of salbutamol down regulates β_2 adrenergic receptors.

- Receptor up regulation:

Prolonged use of antagonist



↑↑ Receptor number and sensitivity



???? Drug effect

- Ex:- propranolol is stopped after prolonged use, produce withdrawal symptoms. Rise BP, induce of angina.

Therapeutic index and margin of safety

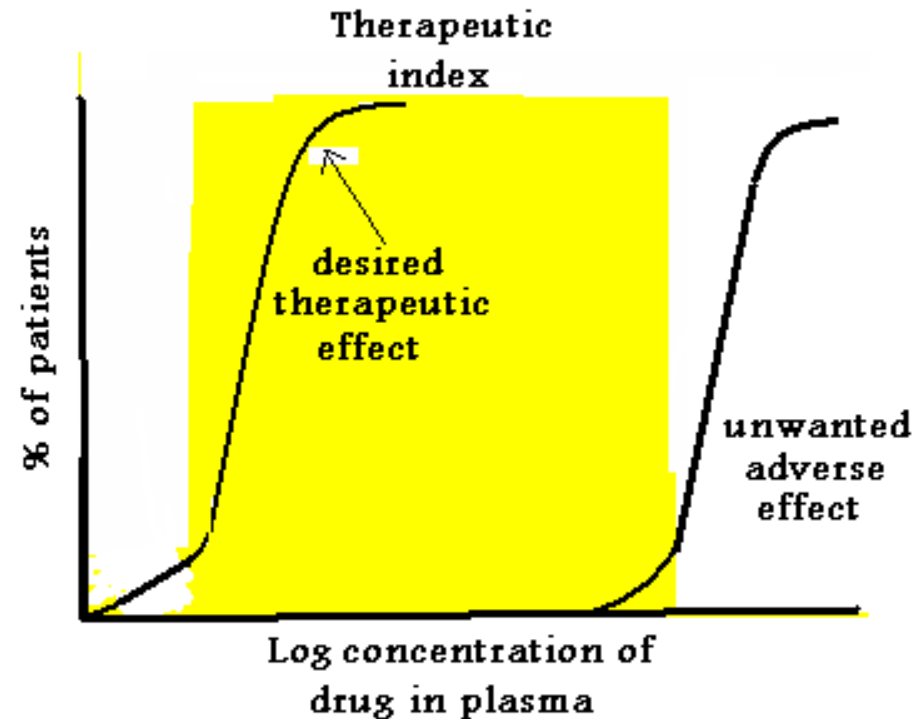
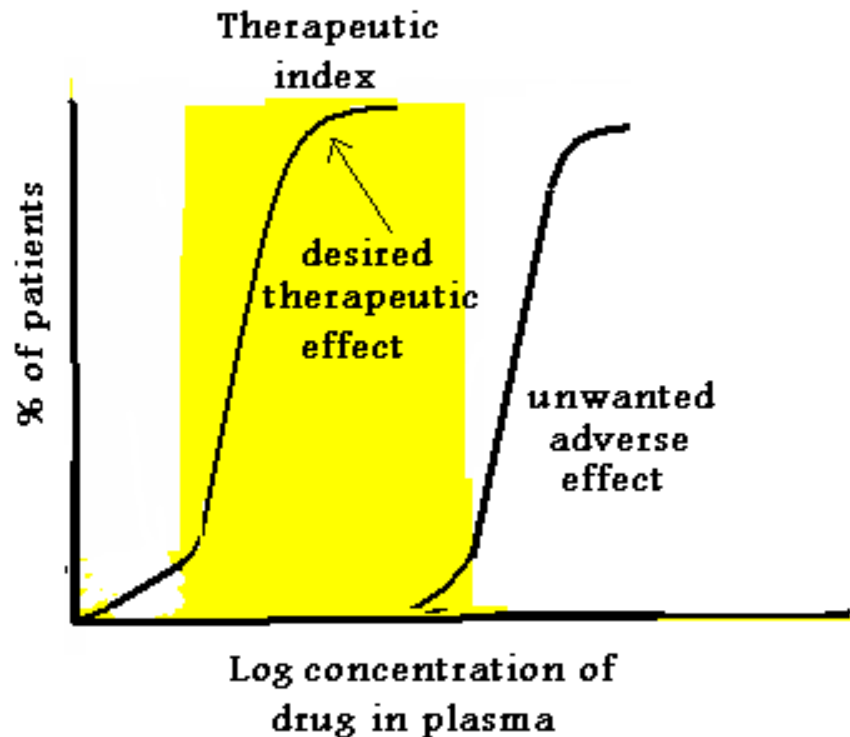
Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals:

$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD₅₀ is the minimum dose that is toxic for 50% of the population, and ED₅₀ is the minimum dose that is effective for 50% of the population.

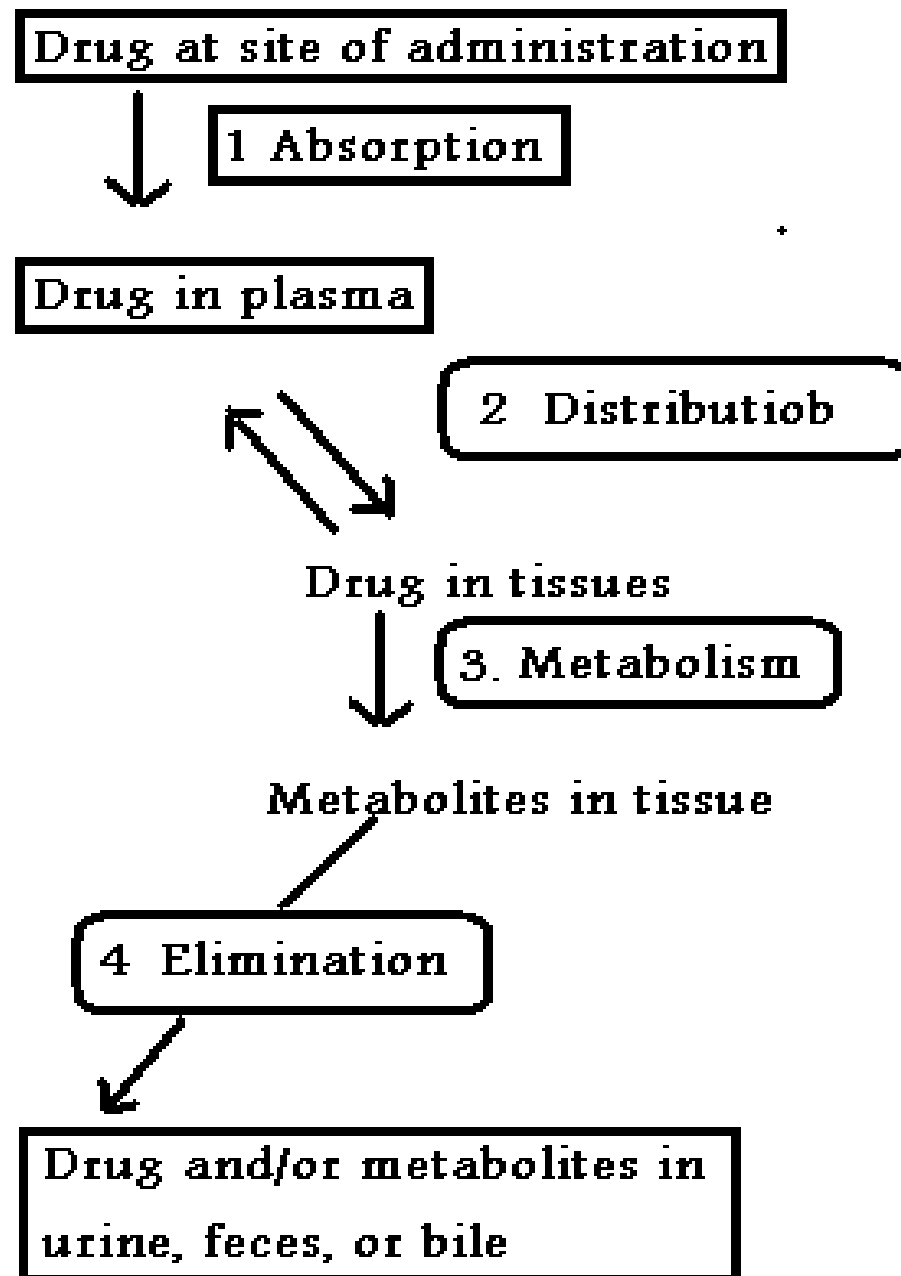
Ideally the TD₅₀ Should be a much higher dose than the ED₅₀ so that the therapeutic index would be large.

Therapeutic index and margin of safety



- Cyclosporine – 100-400ng/ml
- Carbamazepine- 4-10µg/ml
- Digoxin- 0.8-2ng/ml
- Phenytoin – 10-20µg/ml
- Quinidine- 2-6µg/ml

Pharmacokinetics



Drug transport

- the movement of drug molecules in the body affect the absorption, distribution, and elimination.
- Drug can cross cellular membrane by:
Passive diffusion or by an active transport.

a. passive diffusion.

Lipid diffusion of un-ionised molecules, Majority of drugs gain access to the body by this mechanism.

Size and charge, the lipid-water partition coefficient being the most important factors.

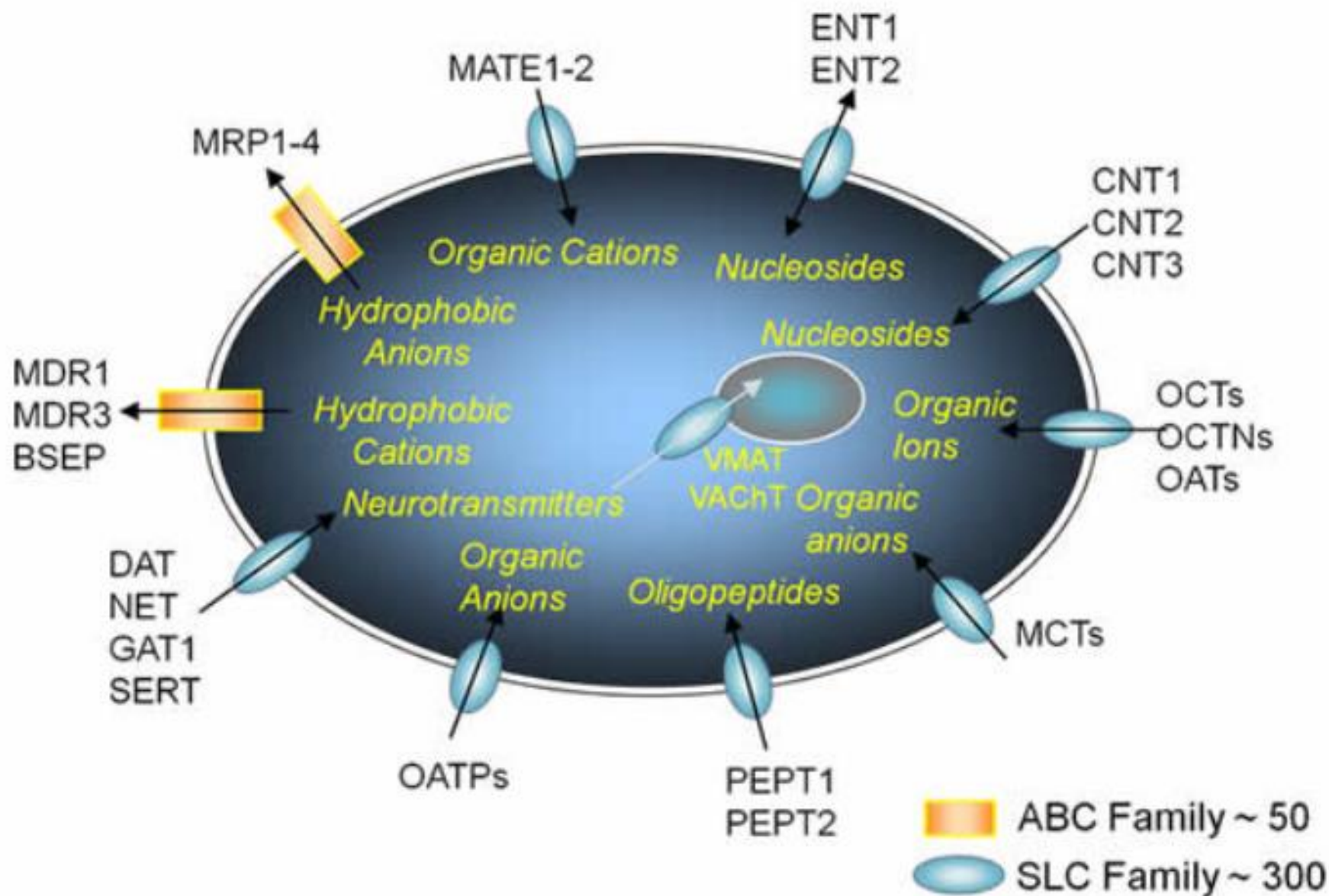
Does not require metabolic energy.

Drug transport

b. Active transport:

- Movement through the membrane is facilitated by a macromolecules.
- Selective for chemical structure and it is saturable process
- A few drugs that closely resemble the naturally occurring metabolites are transport by this process
- Need metabolic energy and can transports molecules against a concentration gradient.

Selected Membrane Transporters in Human Genome



Relevance of Drug Transporters

- Modulation of transporter function through inhibition or induction could result in changes in drug absorption, distribution and excretion--drug-drug interactions.
- A source of inter-individual variability in drug response
- A source for nonlinear kinetics

P-gp

- FDA concept paper on drug interactions recommends that new drug candidates be evaluated as substrates, inhibitors, and inducers of Pgp to assess the potential for clinical drug-drug interactions.

Clinical Study: P-gp Mediated DDI Involving Loperamide and Quinidine

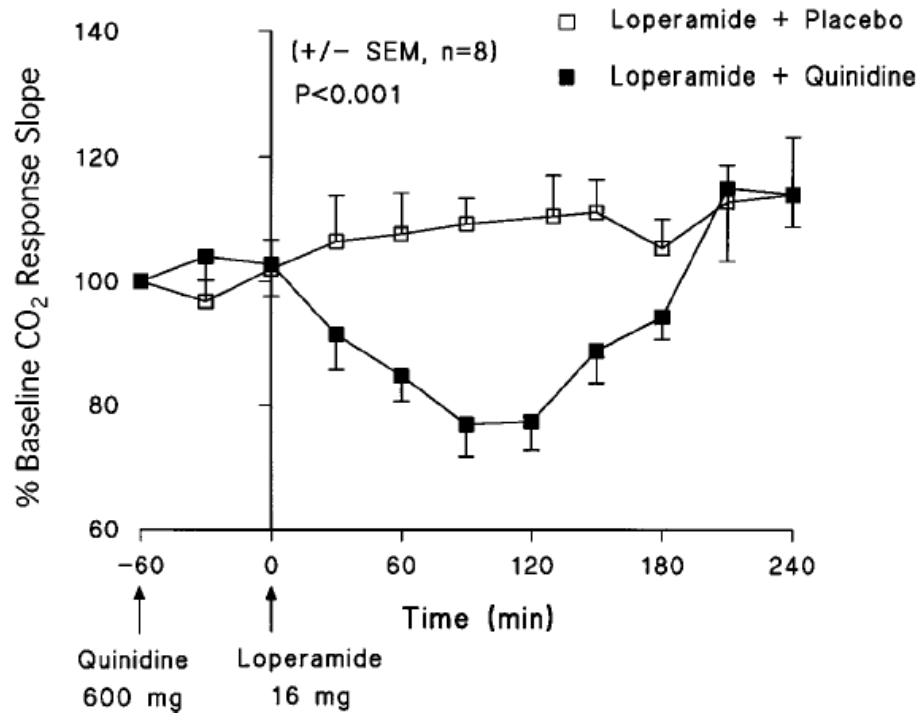


Fig 2. Effect of quinidine on slope of the carbon dioxide response curve after administration of loperamide after placebo (*open boxes*) or quinidine (*solid boxes*).

LOP: potent opiate/anti-diarrheal; no CNS effects at normal doses

When LOP (16 mg) given with QND (600 mg) AUC increased ~2.5 fold

Respiratory depression produced by LOP only when co-administered with QND

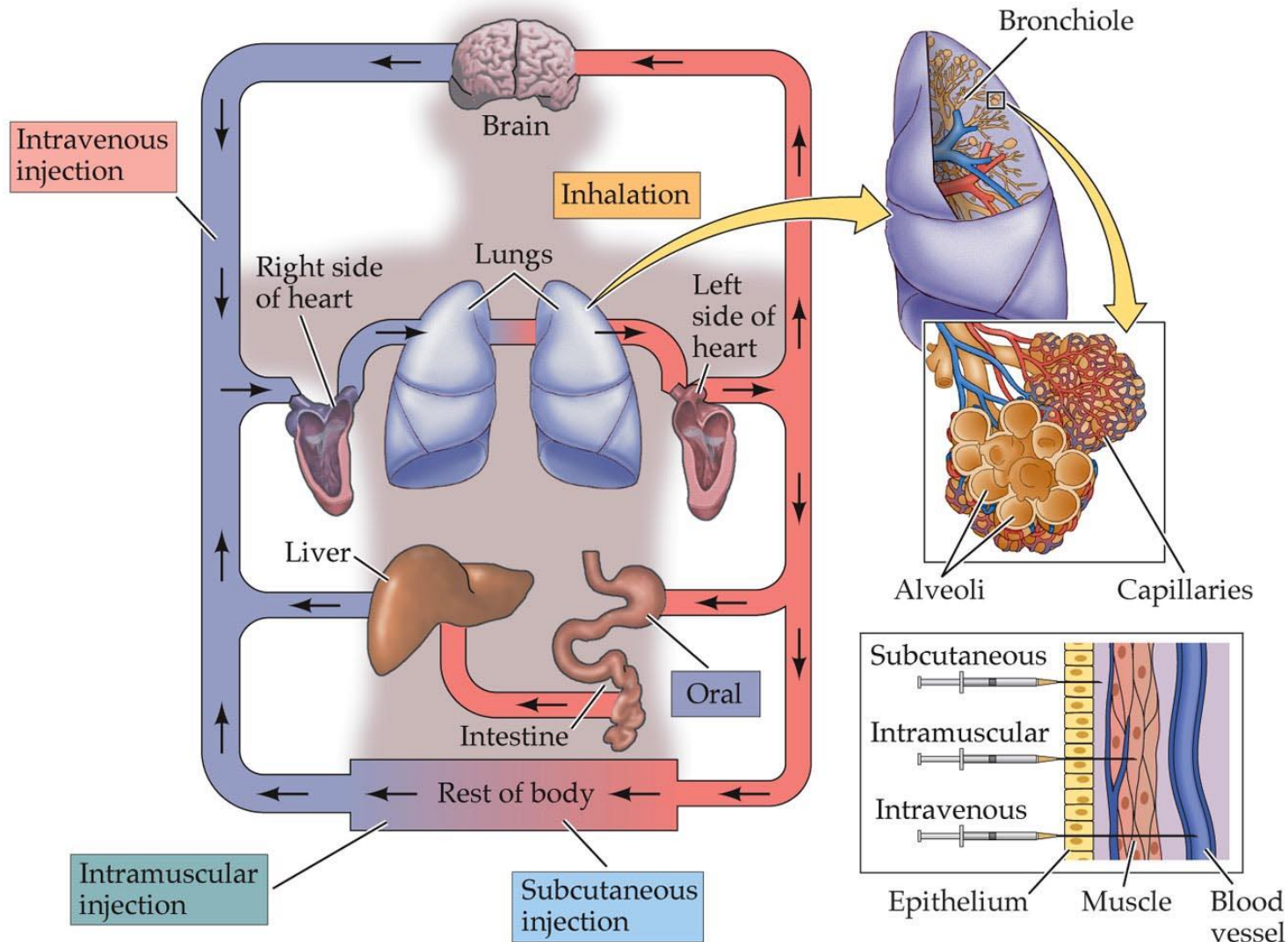
Authors conclude: QND inhibited the P-gp mediated efflux of LOP at the BBB

Example of transporter mediated DDI with potential for toxic effect in humans

Route of administration

- An important determinant of the rate and efficiency of absorption, divided into three category:
 - a. Alimentary routes, such as oral, rectal, and sublingual.
 - b. Parenteral routes, such as intravenous, intramuscular, subcutaneous, and Intrathecal.
 - c. Miscellaneous routes, such as
 - 1. topical administration, useful in treatment of local conditions
 - 2. inhalation, provides a rapid access to circulation.

Routes of Administration



Oral

- Oral routes is the most common, but it is the most **variable** and involve most **complication** to the tissue, mainly the stomach acidity and **first pass effect at the liver**.
- The delivery of the drug into circulation is slow after oral Administration, so that rapid and high blood levels are avoided and adverse effect are less likely.
- Oral route consider the safest and the most convenient for the patient.
- The main disadvantages are the absorption variation and irritation of mucosal surfaces.

Sublingual route:

Some drugs are taken as smaller tablets which are held under the tongue (**sublingual tablet**).

E.g **Nitroglycerin**, as a softer sublingual tablet [**2 min disintegration time**], may be used for the rapid relief of angina.

Advantages

- 1- Avoid hepatic first pass-**
- 2- Rapid absorption** - Because of the good blood supply to the area, absorption is usually quite rapid.
- 3- Drug stability** - pH in mouth relatively neutral.



Rectal route:



Most commonly by suppository.

Advantages

1- By-pass liver - Some of the veins draining the rectum lead directly to the general circulation, thus by-passing the liver. Reduced first-pass effect.

2- Useful - This route may be most useful for patients unable to take drugs orally (unconscious patients) or with younger children.

- if patient is nauseous or vomiting

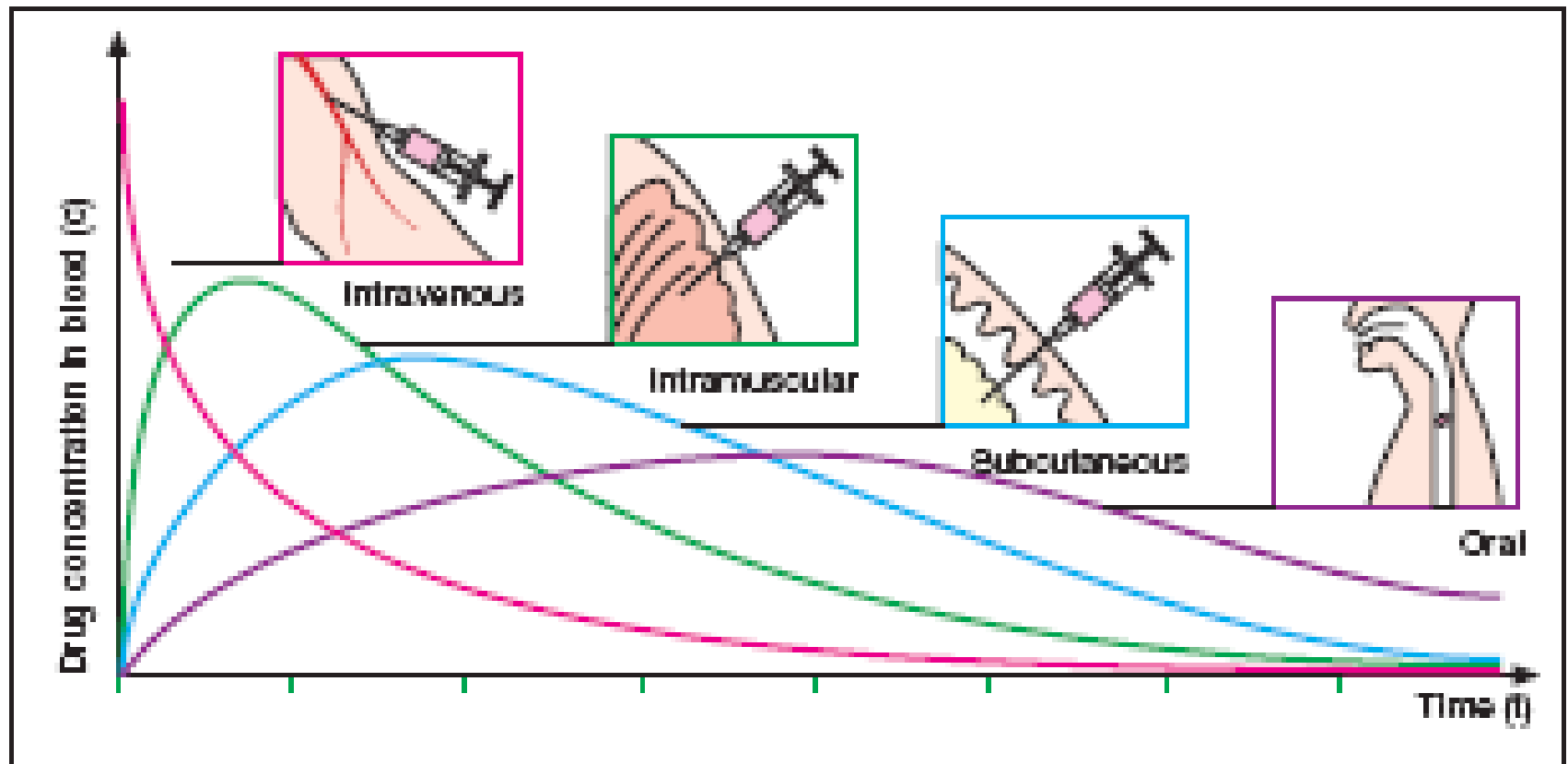
Parenteral routes (Injections)

When to use this routes and mainly INJECTIONS

- A. drug is poorly absorbed through mucous membranes
- B. to avoid first-pass inactivation in the liver
- C. to avoid uncertainty about amount absorbed
- D. to give a rapid response
- E. the drug causes vomiting

The main disadvantages are

- a. More rapid absorption may lead to increase adverse effect
- b. A sterile formulation and aseptic techniques are required



B. Mode of application and time course of drug concentration

Drug absorption

Is the rate at which a drug leaves the site of administration and the extent to which this occur.

the Physical factors influencing absorption are :

- A. Blood flow to the absorption site: intestine absorption is more favorable over that from the stomach because the blood flow to the intestine is much greater than the flow to the stomach.
- B. Total surface area available for absorption: Small intestine is the principal region of absorption of orally administered drugs, because the intestine has a surface rich in microvilli.
- C. Contact time at the absorption surface
The rate of transit through the stomach and intestine is an obvious rate limiting factor in absorption. For example, if a drug moves through the GI tract very quickly, as in severe diarrhea, it is not well absorbed.

Bioavailability

- Is the fraction of administered drugs that reaches the systemic circulation.
- Expressed as the fraction of the administered drug that gain access to the systemic circulation.
- For example if 100 mg of a drug administered orally and 70 mg are absorbed unchanged, the bioavailability is 70%.

Bioavailability

- Factors that influence bioavailability:

1. first-pass hepatic metabolism

Drugs are first carried in the portal circulation to the liver where they may be metabolized.

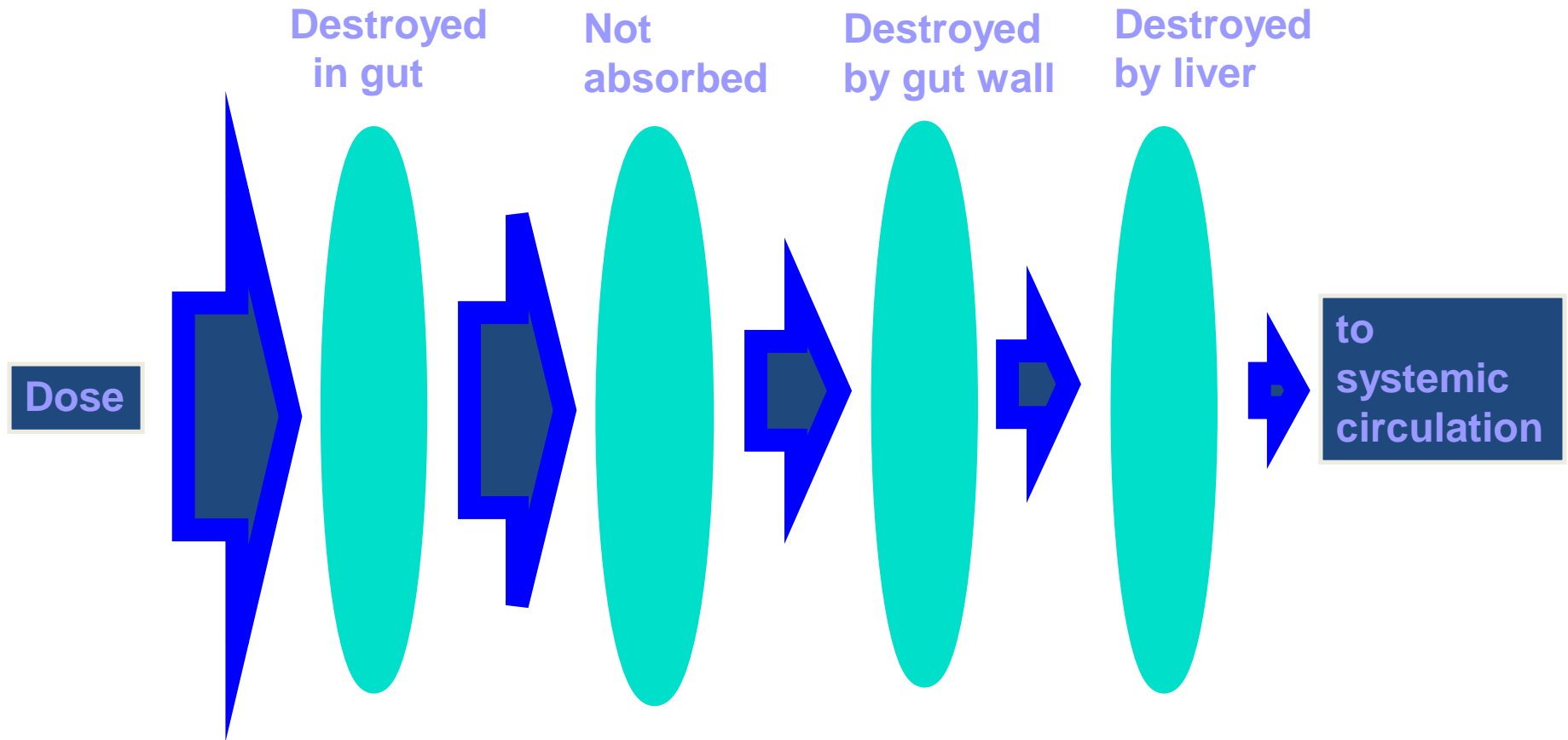
Loss of drug by this passage through the liver is termed THE FIRST-PASS EFFECT.

This can be very significant and may result in virtually complete elimination of the original drug.

2. solubility of the drug:

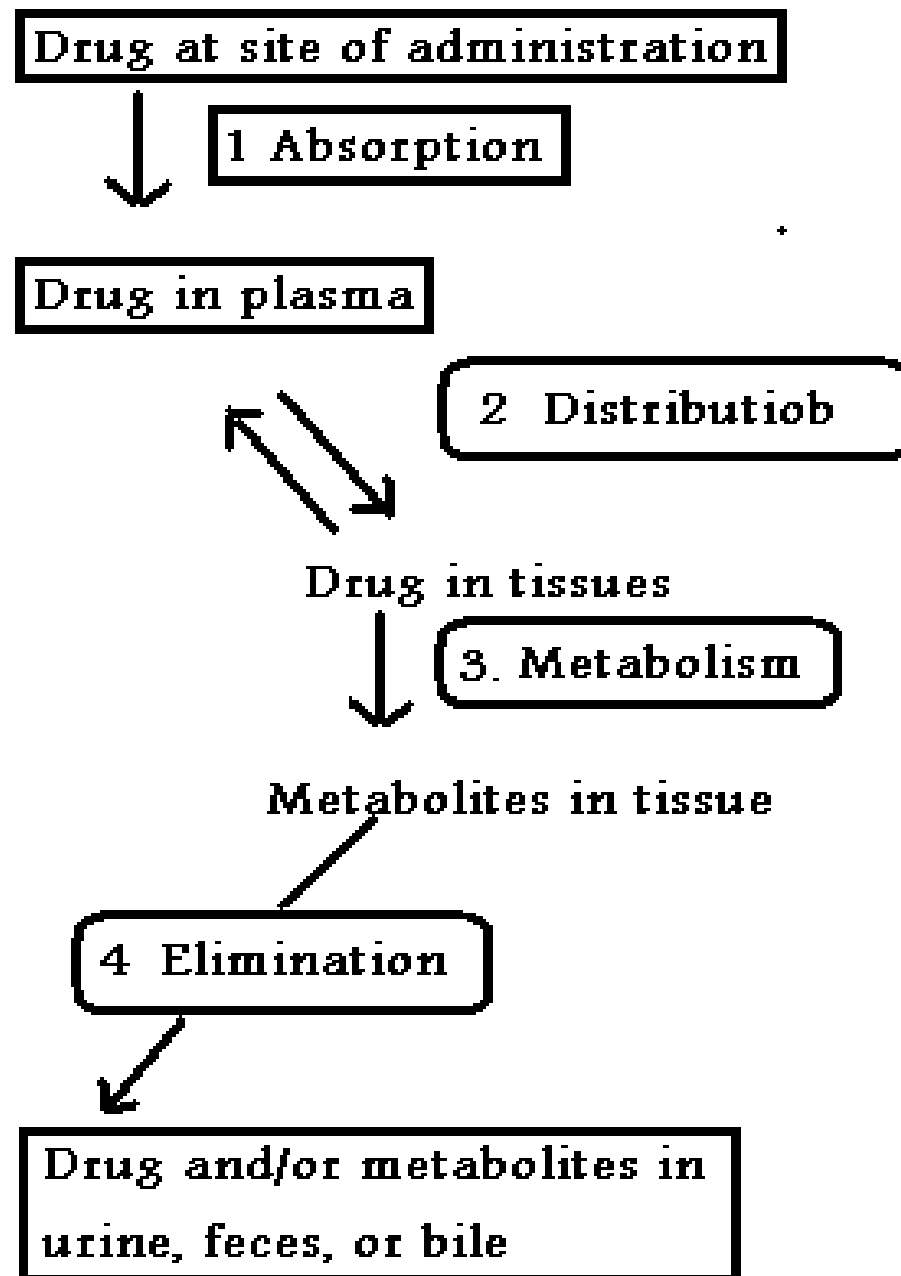
Very hydrophilic drugs are poorly absorbed, because of their inability to cross the lipid rich membrane.

First Pass Metabolism



- **Bioavailability: the fraction of the administered dose reaching the systemic circulation**

Pharmacokinetics



Distribution

- Once the drug enters the body, it distribute into one of three functional compartments:
 - A. Plasma: has very large molecular weight or bind extensively to the plasma proteins. So the drug is effectively trapped with the plasma (vascular) compartment.

In this case the drug will distribute in a volume that is about 6% of the body weight.

for example, in 70 kg individual, agents of this type, such as Heparin, will distribute in 4 L of body fluids.

Distribution

- A. Extracellular: has low molecular weight but it is hydrophilic, it can move through the endothelial junctions but cannot cross the membrane to enter the cells.

So drugs like aminoglycosides, will distribute into a volume equal to the sum of the plasma water and the interstitial fluids (14 L in a 70 kg individual)

- B. Total body water: has low molecular weight and hydrophobic, here the drug moves through the membranes into the cells. Here the drug will distribute into a volume of about 60% of the body weight (42 L in a 70 kg individual).

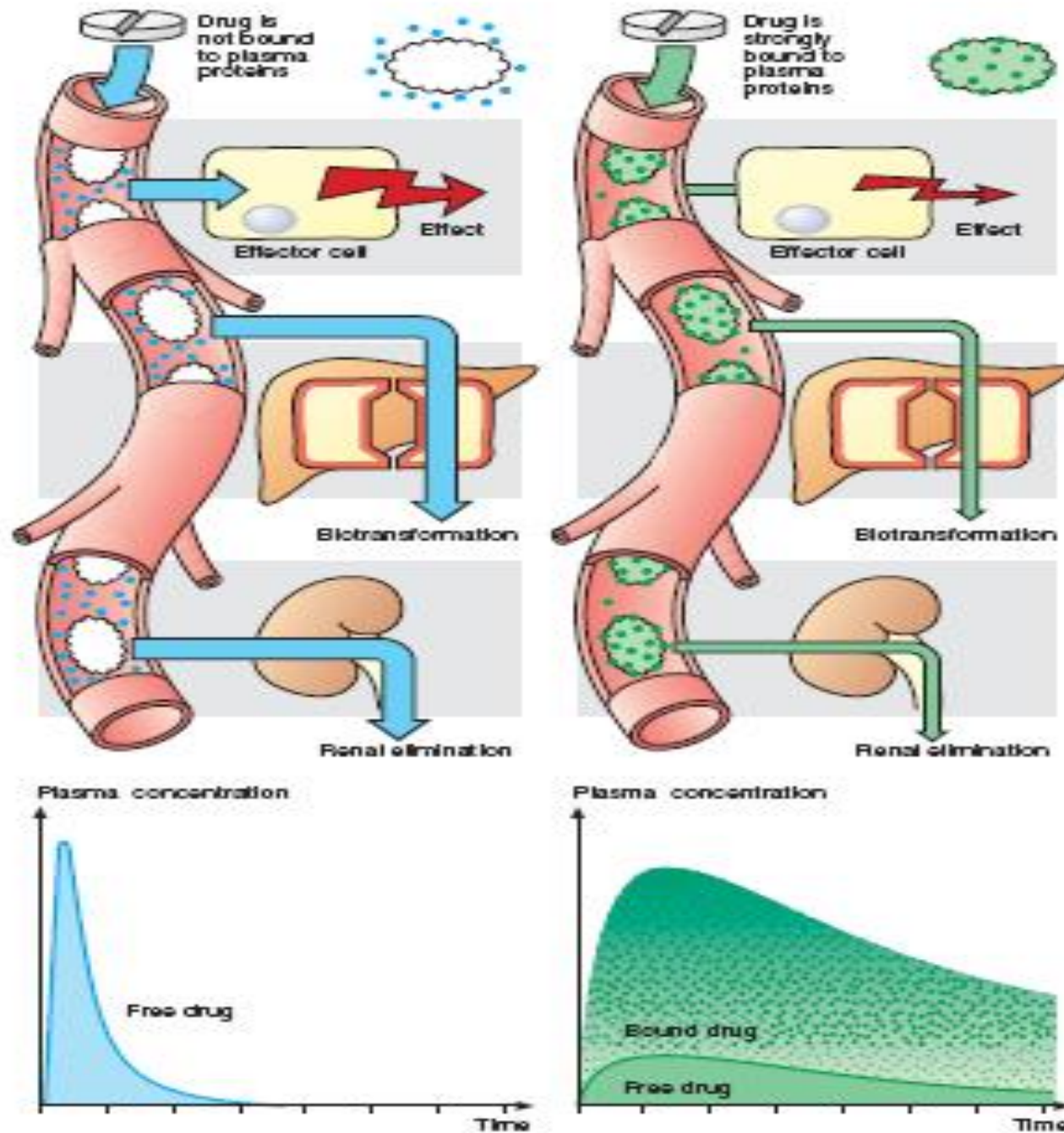
note: Some drugs, lipid soluble ones, stored in the fatty tissue in an equilibrium with free circulating drug

Distribution

- Some areas of the body (e.g. the brain, the placenta) are not accessible to drugs due to anatomic barriers,
- The capillary membrane between the plasma and brain cells is much less permeable than is the membrane between plasma and another tissue.
- Therefore the transfer of drugs into the brain is regulated by what is called “blood brain barrier”
 - 1.it is only permeable to lipophilic agents
 2. impermeable to ionic hydrophilic agents
 3. Amino acids, glucose etc have specific uptake systems

DRUG BINDING TO PLASMA ALBUMEN

- Some drugs bind nonspecifically and reversibly to various plasma proteins, albumin and globulins, in which the bound and free drug reach equilibrium, and only the free drug exerts a biological effect.
- In general albumen binding reduces pharmacological activity but prolongs duration of action in a way dependent on affinity, binding capacity and rate of dissociation.
- This type of agents have a high affinity for albumen and are not bound to any significant extent by other constituents of the tissues.



A. Importance of protein binding for intensity and duration of drug effect

DRUG BINDING TO PLASMA ALBUMEN

- Binding is reversible and is dominated by electrostatic, hydrogen bonding and hydrophobic interactions.
- There are several binding sites on albumen. Lipophilic drugs are strongly bound.
- Drug interactions occur on albumen by the displacement of one drug by another. Can raise dose of some drugs to toxic levels.
- For example Anticoagulants (Warfarin) can be displaced by the anti-inflammatory agents Phenylbutazone.

Pharmacokinetics

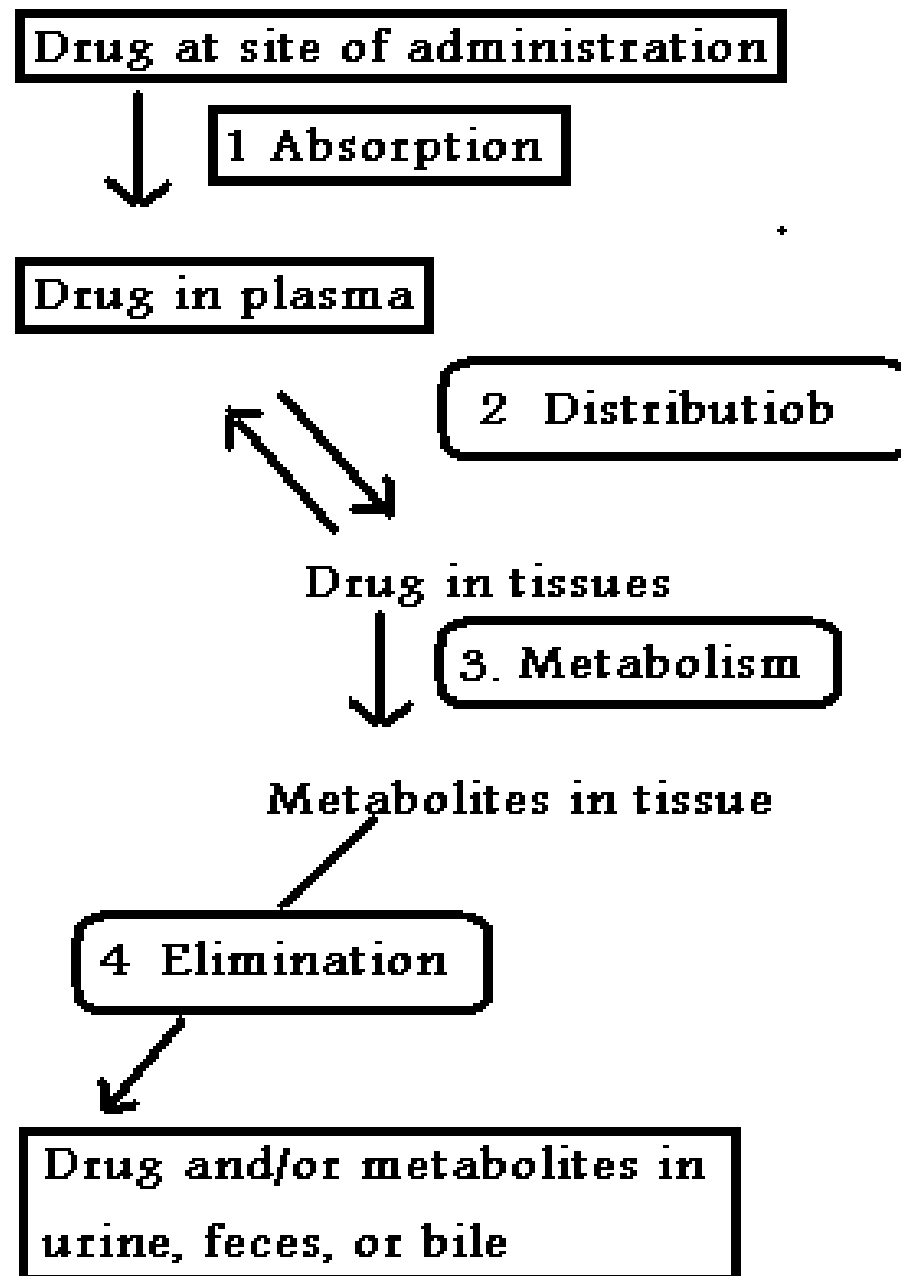
Adults >65 years old

- Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution
- Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin
 - Serum levels may go up due to decreased volume of distribution
- Fat soluble: diazepam, thiopental, trazadone
 - Half life increased with increase in body fat

Pediatric Distribution

- Body Composition
 - ↑ total body water & extracellular fluid
 - ↓ adipose tissue & skeletal muscle
- Protein Binding
 - albumin, bilirubin, α_1 -acid glycoprotein
- Tissue Binding
 - compositional changes

Pharmacokinetics



Metabolism

- The liver is the major site of metabolism for many drugs, but other organs, such as lungs and kidney can also metabolize drugs.
- Many lipid soluble drugs are not readily eliminated from the body and must be conjugated or metabolized to compounds that are more polar and less lipid soluble before being excreted.
- Metabolism often, but not always, results in inactivation of the compounds.
- Some drugs are activated by metabolism, these substances called prodrugs.

Phase I metabolism

- Drug metabolism occur in two phases:
- Phase I reactions function (e.g., oxidation, reduction, hydrolysis) alter chemical reactivity and increase water solubility.
- Phase I reaction frequently catalysis by the cytochrome P450 system (also called microsomal mixed function oxidase).



- To date, 12 unique isoforms of this enzymatic system (CYP 2D6, CYP3A4) have been identified to play a role in human drug metabolism.

Phase II metabolism

- If the metabolite from phase I is polar enough it will be excreted by the kidney, But if it is still lipophilic to be retained in the kidney, a subsequent Phase II metabolism will take place.
- Phase II consists of conjugation reaction with endogenous substances, such as, glucuronic acid, sulfuric acid, or an amino acid.
- Results in polar and usually more water soluble compounds.

CYP family of enzymes

- Found in liver, small intestine, lungs, kidneys, placenta
- Consists of > 50 isoforms
- Major source of catalytic activity for drug oxidation
- It's been estimated that 90% or more of human drug oxidation can be attributed to 6 main enzymes:
 - CYP1A2 • CYP2D6
 - CYP2C9 • CYP2E1
 - CYP2C19 • CYP3A4
- *In different people and different populations, activity of CYP oxidases differs.*

Cytochrome P450 system

- Cytochrome P450 system dependant enzymes are important target for drug interaction because they can be induced or inhibited by certain drugs.
- Cytochrome enzymes Inducers like rifampin and carbamazepine are capable of increasing the synthesis of one or more of isoforms. For example, Rifambin significantly decreases the plasma concentration of HIV protease inhibitors.
- Cytochrome enzymes inhibitors, omeprazole inhibits three CYP isoforms that are responsible for warfarine metabolism, leading in an elevation in the warfarin concentration, and so greater inhibition of coagulation, leading in more risk of serious bleeding reaction,

Interaction of citrus juices with felodipine and nifedipine

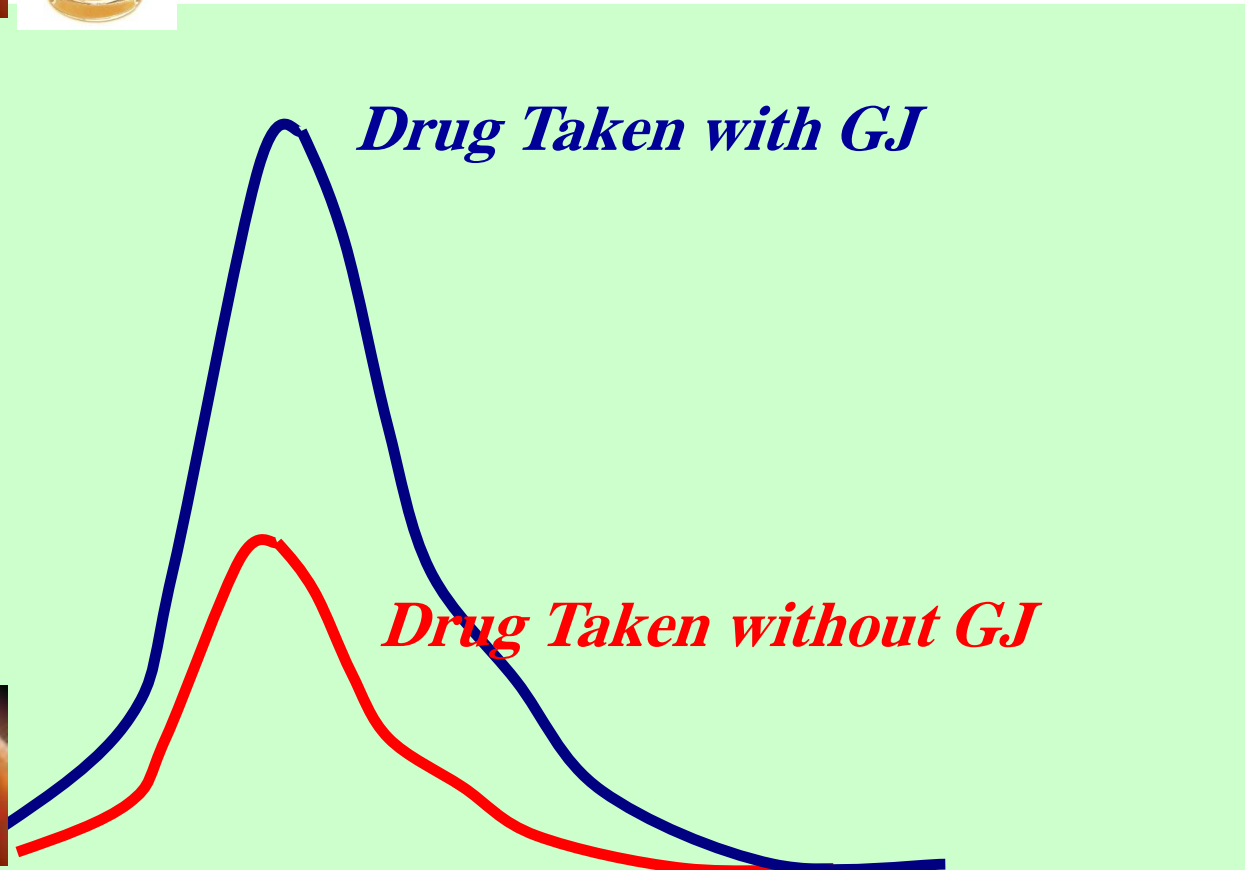
DAVID G. BAILEY J. DAVID SPENCE
CLAUDIO MUNOZ J. MALCOLM O. ARNOLD

Six men with borderline hypertension took felodipine 5 mg with water, grapefruit juice, or orange juice. The mean felodipine bioavailability with grapefruit juice was 284 (range 164–469)% of that with water. The dehydrofelodipine/felodipine AUC ratio was lower, diastolic blood pressure lower, and heart rate higher with grapefruit juice than with water. Vasodilatation-related side-effects were more frequent. Orange juice had no such effects. Six healthy men took nifedipine 10 mg with water or grapefruit juice; the bioavailability with grapefruit juice was 134 (108–169)% of that with water.

Lancet 1991; 337: 268–69.



Drug Blood Concentration (AUC)



Time

Some drugs influenced by grapefruit juice

Drug	AUC increase
felodipine	~ 3 fold
cisapride	~ 1.4 fold
cyclosporine	~ 1.5 fold
saquinavir	~ 2 fold
terfenadine	~ 2.5 fold
buspirone	~ 9 fold
lovastatin/simvastatin	~ 10 fold

CYP isoforms vary with age

- For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life.
- Carbamazepine (3A4) clearance faster in children than adults – requires higher doses.

Elimination

- It is a process in which drugs are transferred from the internal to the external environment.
- Occur via a number of routes , the most important being through the kidney into the urine.
- Other routes include the bile, intestine, lung, or milk in nursing mother.
- Drugs eliminated through these routes tend to be lipid soluble and unionized.

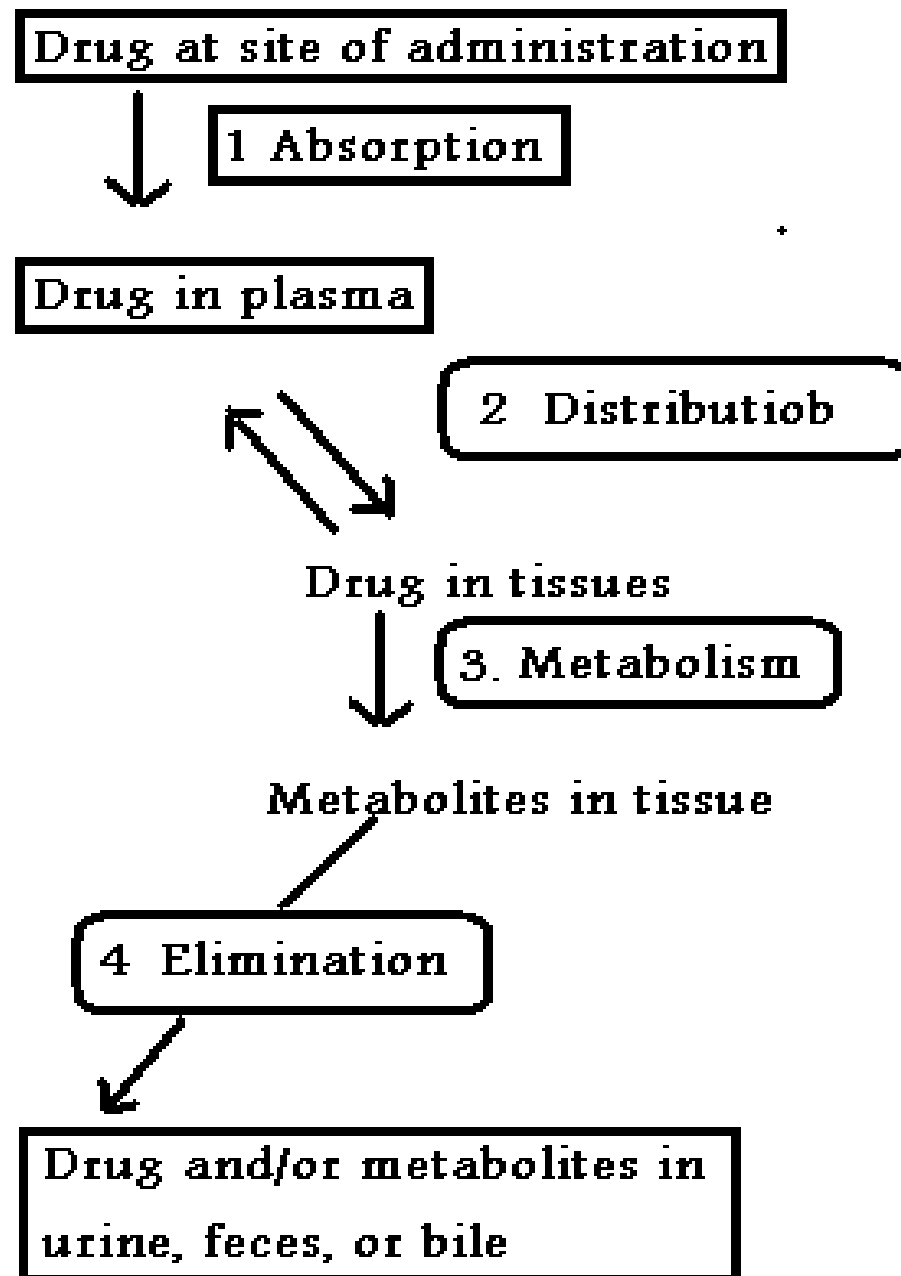
Example: Creatinine Clearance vs. Age

<u>Age</u>	<u>Scr</u>	<u>CrCl</u>
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
 - More available drug
- Immature liver/kidneys
 - Liver often metabolizes more slowly
 - Kidneys may excrete more slowly

Pharmacokinetics



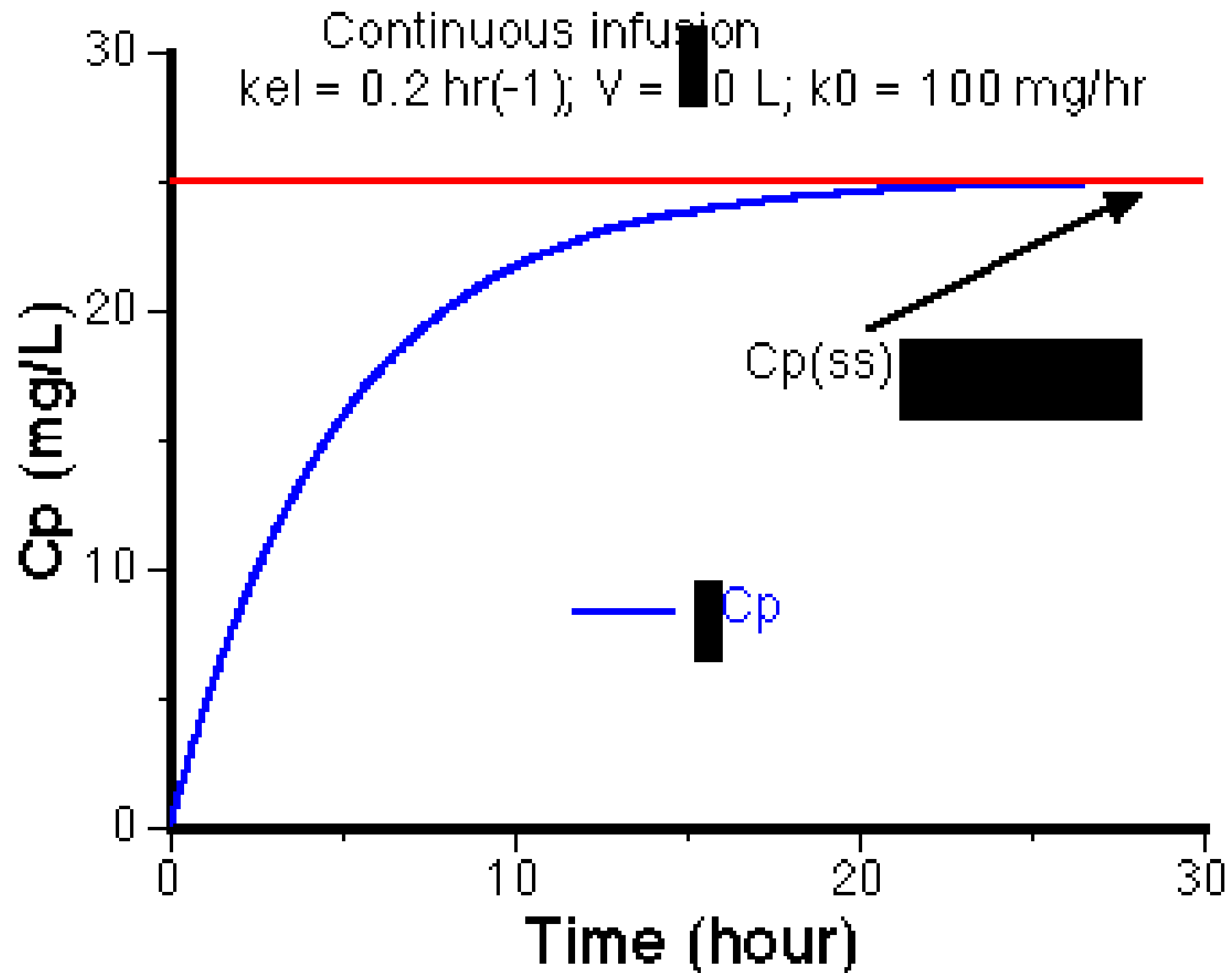
Half-life of elimination

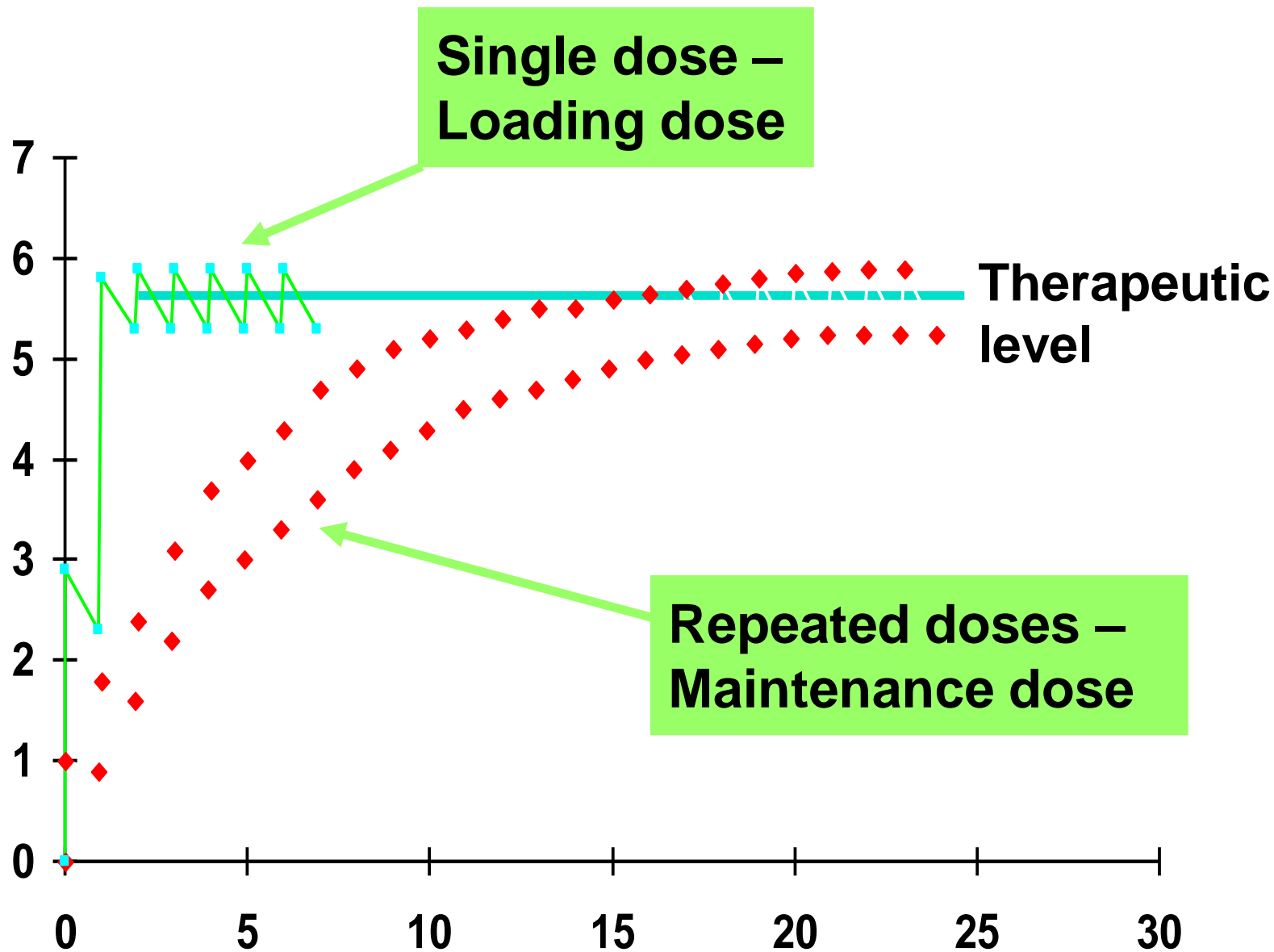
- Time for plasma conc. to decrease by half.
- Useful in estimating:
 - time to reach steady state concentration.
 - - time for plasma concentration to fall after dosing is stopped.
- On continuous steady administration of a drug, plasma concentration will rise fast at first then more slowly and reach a plateau, where:

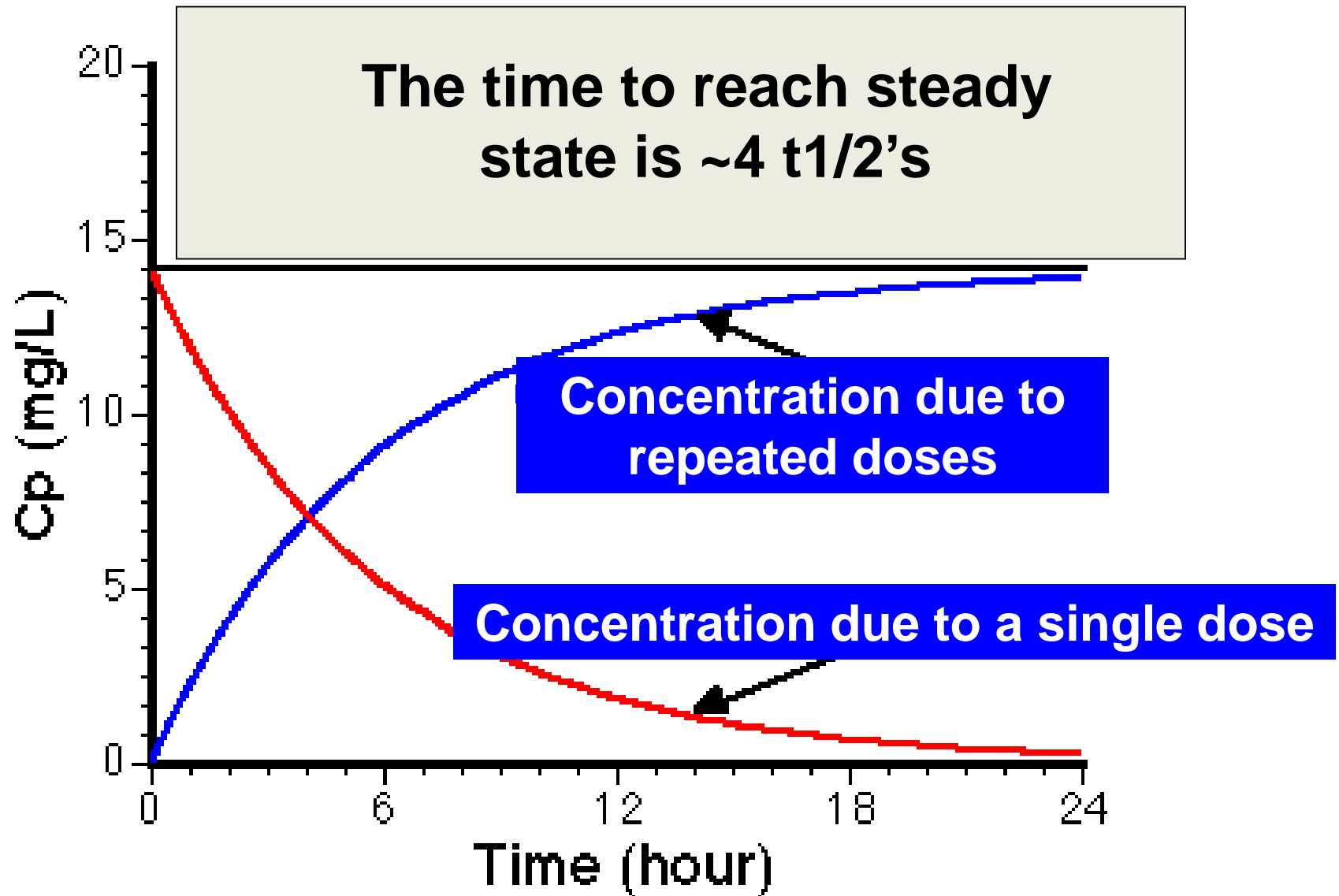
rate of administration = rate of elimination

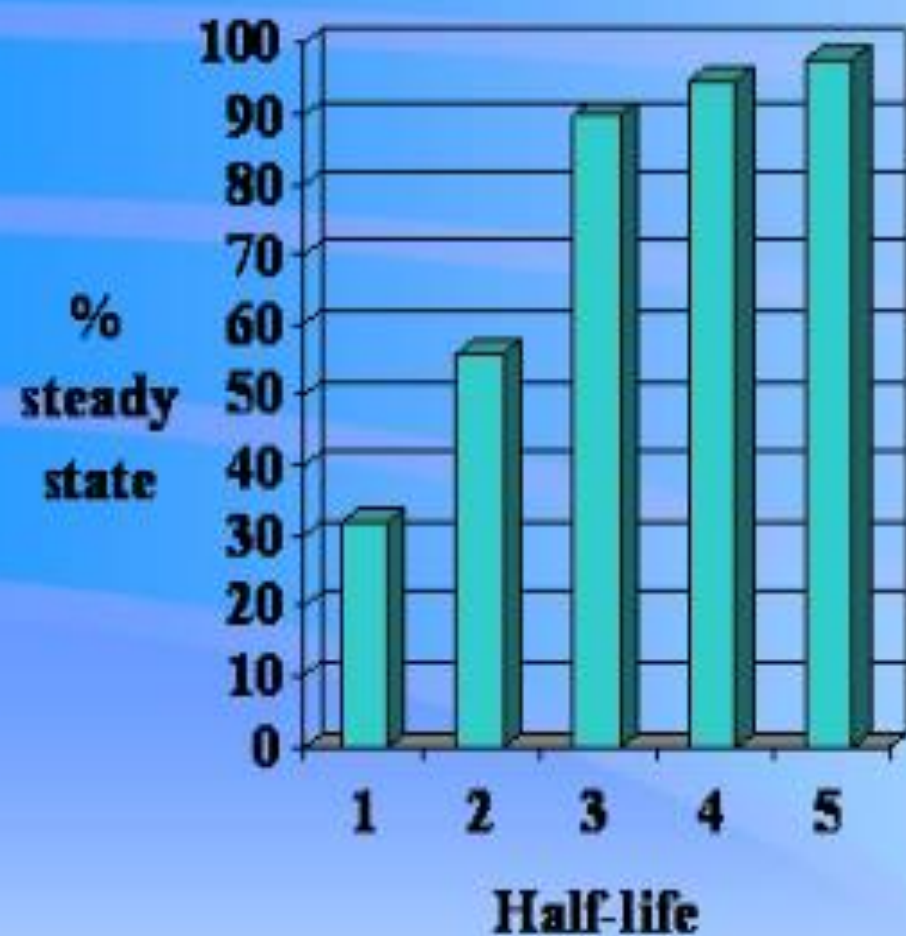
ie. steady state is reached.

Constant Rate of Administration (i.v.)

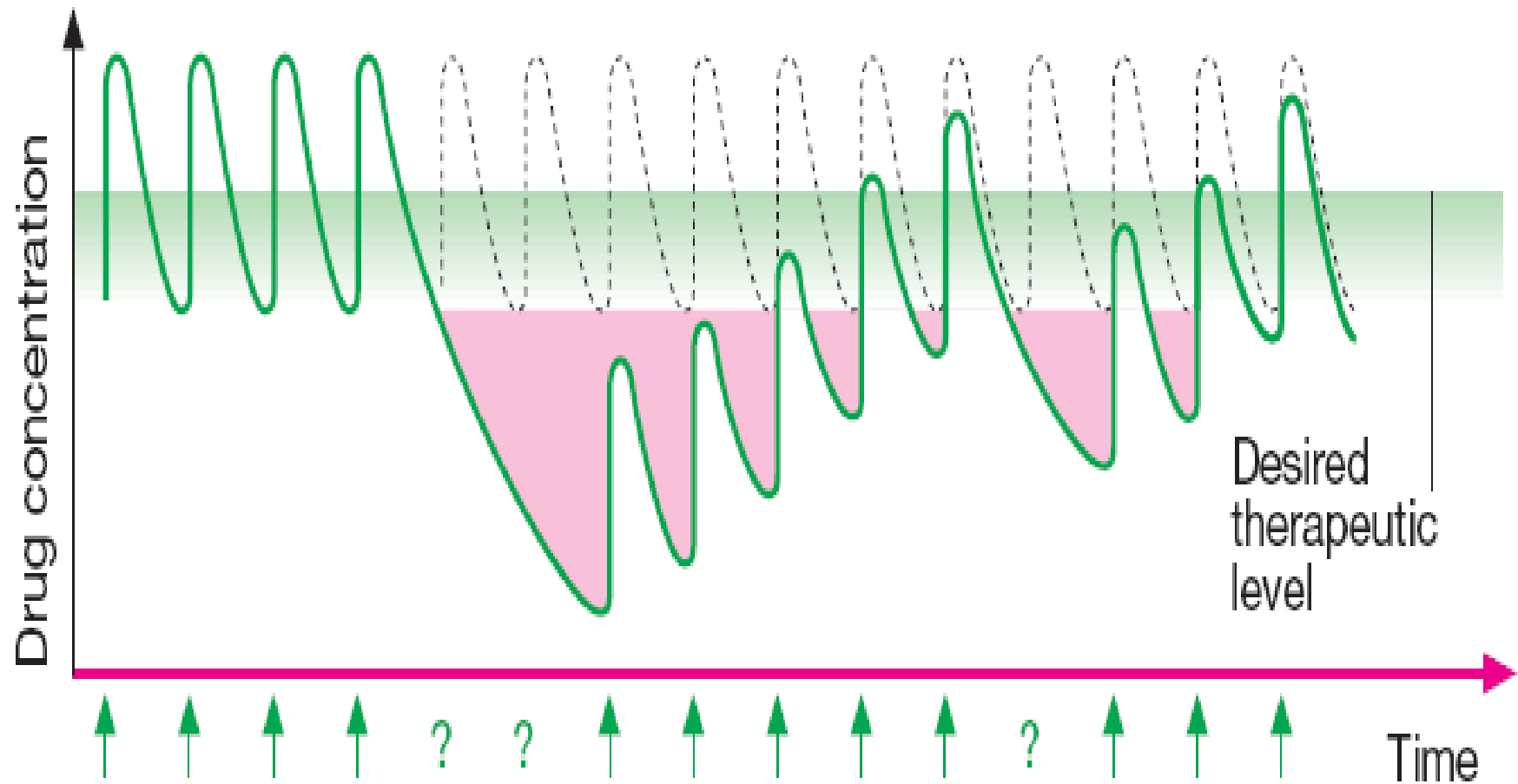








- Half-life = time required for serum plasma concentrations to decrease by one-half (50%)
- 4-5 half-lives to reach steady state



Time course of drug concentration with irregular intake

Drug-drug interaction

- When two drugs taken together, there is a possibility that the drugs will interact with each other to cause unanticipated effect. Usually increase or decrease in the desired therapeutic effect.
- Drug-drug interaction can occur in the following sites
 1. at the site of absorption, tetracycline is not absorbed from the GI tract if calcium product present in the stomach.
 2. during biotransformation (CYP 450).
 3. At the site of action, drug antagonism.

Drug-drug interaction

3. During excretion, digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.
4. During distribution, aspirin competes with methotrexate for protein binding sites, and because aspirine is more competitive for the sites, resulting in increased release of methotrexate and so increase toxicity to tissues.

REMEMBER

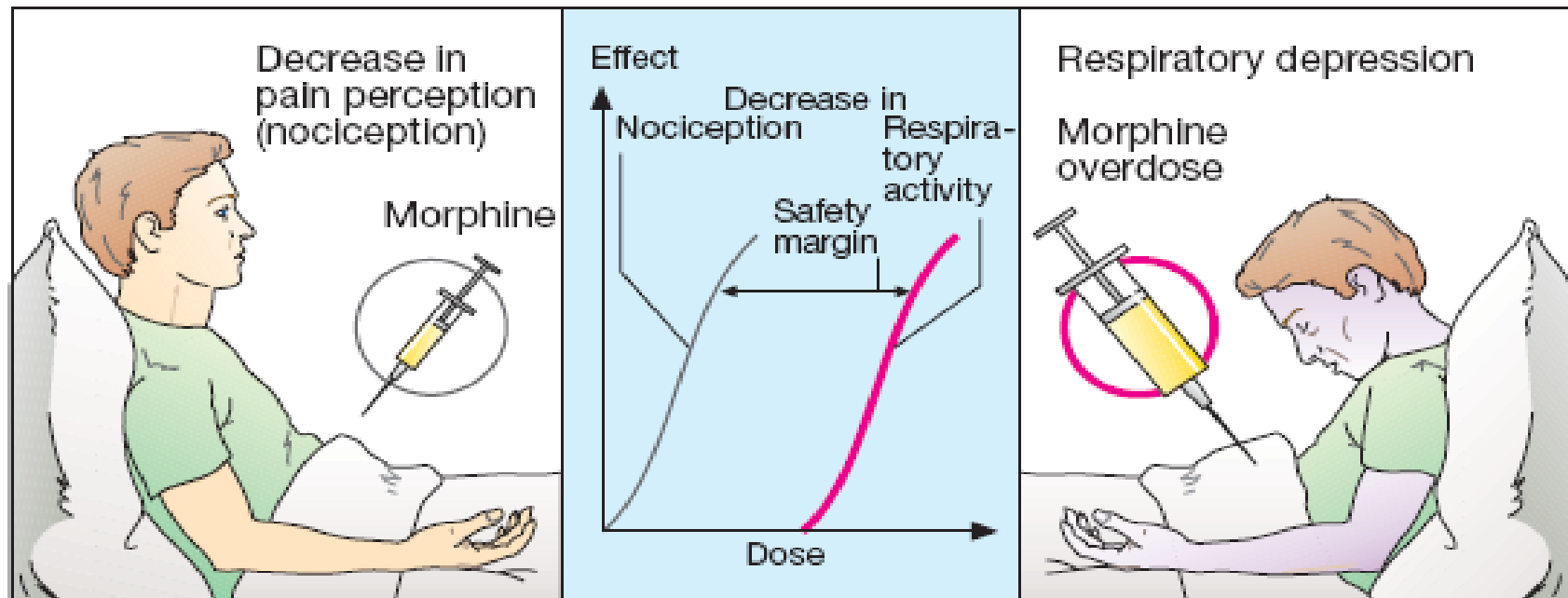
No drug produces a
single effect!!!

Adverse effect

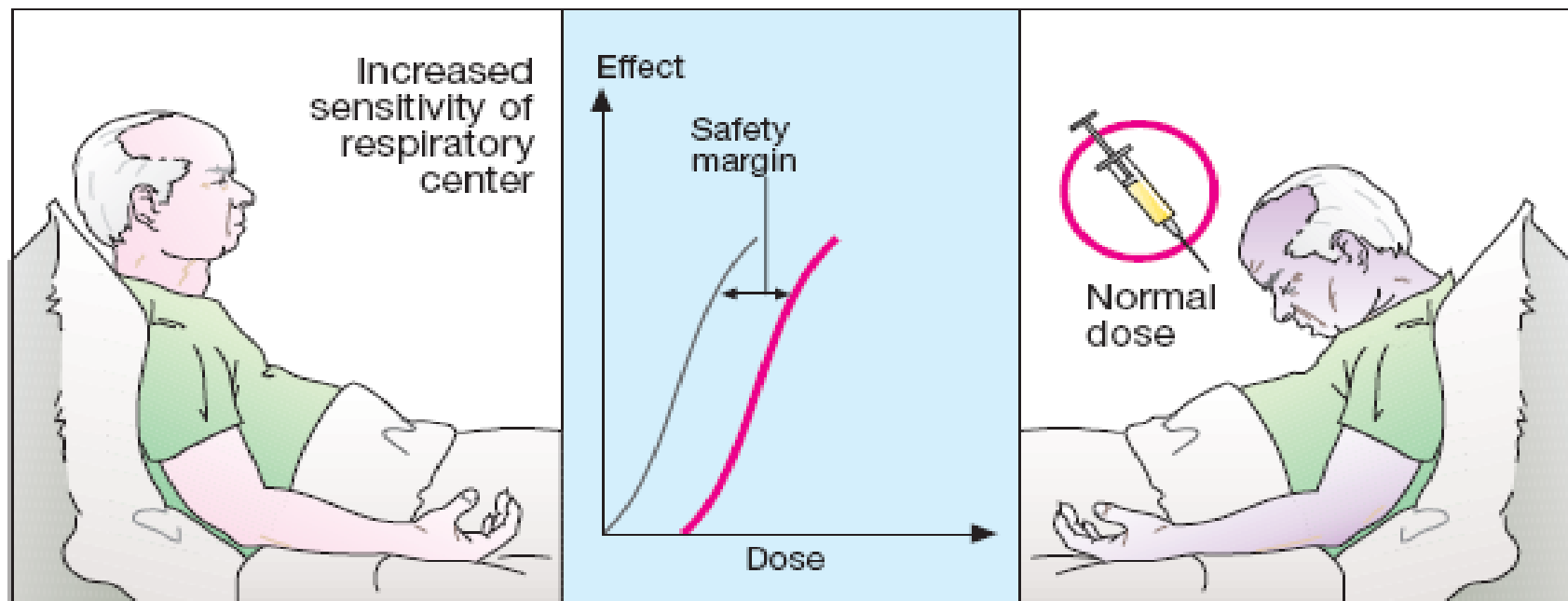
- Adverse effect are undesired effect that may be unpleasant or even dangerous they can occur for many reasons:
 1. The drug may have other effects on the body besides the therapeutic effect.
 2. The patient is sensitive to the drug.
 3. The patient is taking too much or too little of the drug.
- the nurse, as the most frequently administers medications, must be constantly alert for sign of drug reactions of various types.

Adverse effect

- With every drug use, unwanted effects must be taken into account before prescribing a drug, the physician should therefore assess the **risk: benefit ratio**.
- In this, knowledge of principal and adverse effects is a prerequisite.



A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

Adverse effect

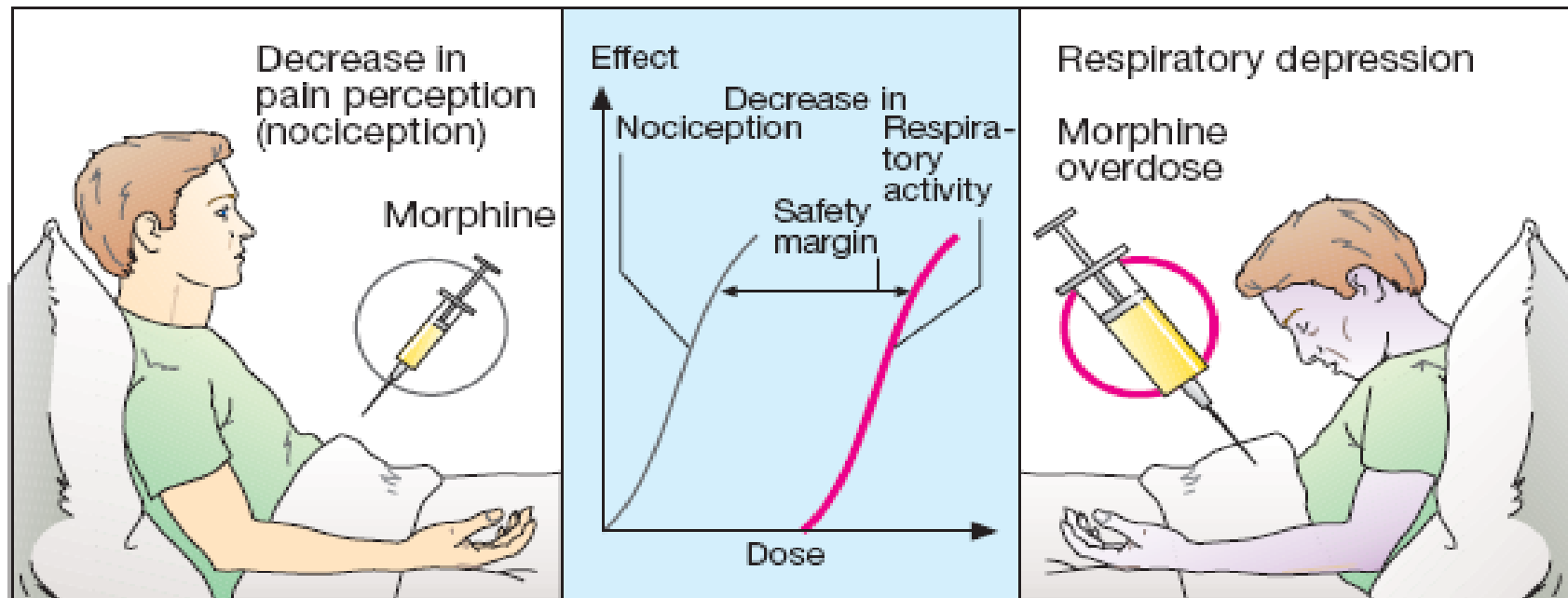
- **Type A—Exaggerated pharmacological response**
 - Pharmacodynamic (e.g., bronchospasm from beta-blockers)
 - Toxic (e.g., deafness from aminoglycoside overdose)
- **Type B—Nonpharmacological, often allergic, response**
 - Medicine-induced diseases (e.g., antibiotic-associated colitis)
 - Allergic reactions (e.g., penicillin anaphylaxis)
 - Idiosyncratic reactions (e.g., aplastic anemia with chloramphenicol)

Adverse effect

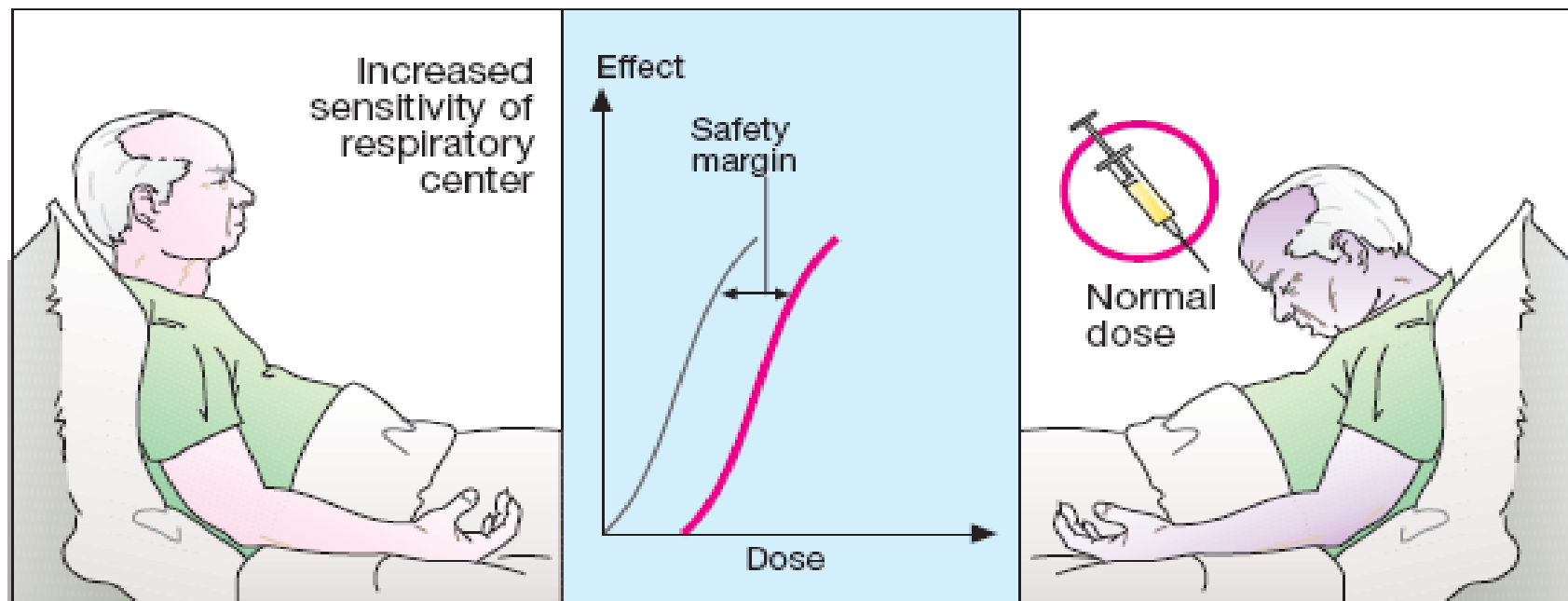
- **Type C—Continuous or long term (time related)**
 - Osteoporosis with oral steroids
- **Type D—Delayed (lag time)**
 - Teratogenic effects with anticonvulsants or lisinopril
- **Type E—Ending of use (withdrawal)**
 - Withdrawal syndrome with benzodiazepines
- **Type F—Failure of efficacy (no response)**
 - Resistance to antimicrobials

Risk Factors for Adverse Drug Reactions

- Simultaneous use of several different drugs
 - Drug-drug interactions
- Very young, or very old in age
- Pregnancy
- Breast Feeding
- Hereditary Factors
- Disease states which may effect drug absorption, metabolism, and/or elimination



A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

risk: benefit ratio

With every drug use, unwanted effects must be taken into account. Before prescribing a drug, the physician should therefore assess the

risk: benefit ratio.

In this, knowledge of principal and adverse effects is a prerequisite.

COMMUNICATING WITH THE PATIENT

- **SPEAKING CLEARLY AND SLOWLY IS VERY IMPORTANT**
- **BE AWARE OF THE DIFFERENT LANGUAGES AND CULTURES.**
- **PATIENTS WILL SOMETIMES HAVE A DIFFERENT MEANING THAN THE PERSON TEACHING THE INFORMATION.**

Hints

- **Balance between over-prescription and under-prescription.**
- **Avoid a pill for every ill.**
- **Always consider non pharmacological therapy.**

Three STEPS IN PLANNING TO GIVE A MEDICATION

1. Decide the reason or goal for giving the medication
2. Learn specific information about the medication:
 - a. The desired action of the drug
 - b. Side effects that may develop
 - c. The usual dosage, route, and frequency
 - d. Situations in which the drug should not be given(contraindications)
 - e. Drug interactions (What is the influence of another drug given at the same time?)
3. Develop a teaching plan for the patient:
 - a. What the patient needs to know about the medication's action and side effects
 - b. What the patient needs to know about the administration of the medication
 - c. What the patient needs to report to the nurse or physician about the medication.

Variation in drug responses

Sources of individual variation

Each patient is unique in ability to respond and to how they each respond, but formation of "IDEAL DRUG" will lessen this variation

- Age- very important factor
- Sex- due to hormonal differences
- Weight- less effective and longer lasting in obese individuals (storage in fat)
- Kidney & liver functions - elimination of drug
- Genetic variables- tolerance, allergy (though not always genetic)

Geriatrics

Adults >65 years old

- Fastest growing population in US
- 20% of hospitalizations for those >65 are due to medications they're taking

Pharmacokinetics

- **Decrease in total body water and increase in total body fat affects volume of distribution**
- **Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin**
 - **Serum levels may go up due to decreased volume of distribution**
- **Fat soluble: diazepam, thiopental, trazadone**
 - **Half life increased with increase in body fat**

Metabolism

- Oxidative metabolism through cytochrome P450 system does decrease with aging,
- resulting in a decreased clearance of drugs

Excretion and Elimination

- GFR generally declines with aging, but is extremely variable
 - 30% have little change
 - 30% have moderate decrease
 - 30% have severe decrease
- Serum creatinine is an unreliable marker, why????
- If accuracy needed, do Cr Cl

Example: Creatinine Clearance vs. Age

Age

CrCl

30

65

50

53

70

41

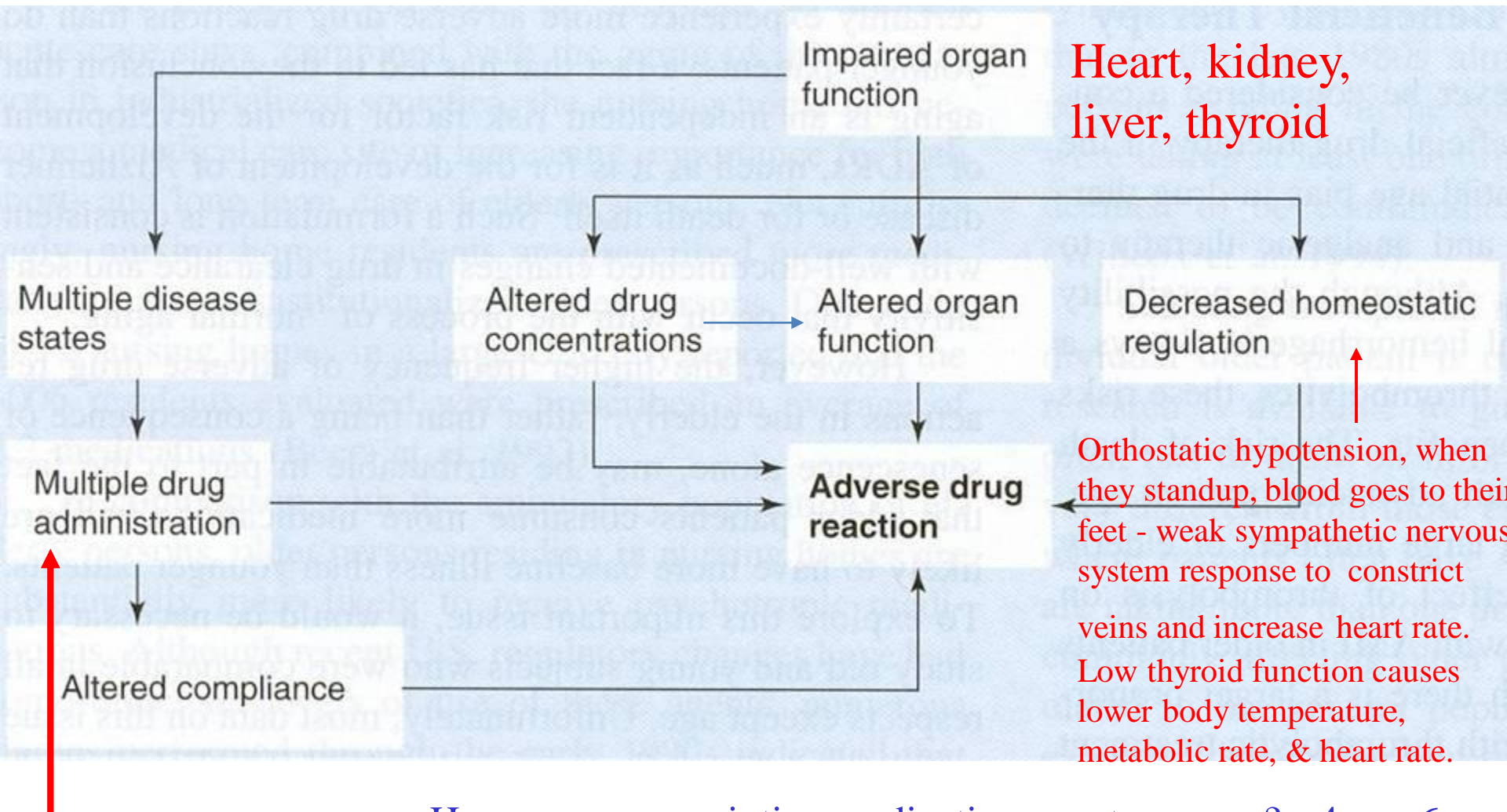
90

30

Pharmacodynamics (PD)

- Age-related changes:
 - ↑↑ sensitivity to sedation and psychomotor impairment with benzodiazepines
 - ↑↑ level and duration of pain relief with narcotic agents
 - ↑↑ drowsiness and lateral sway with alcohol
 - ↓↓ HR response to beta-blockers
 - ↑↑ sensitivity to anti-cholinergic agents
 - ↑↑ cardiac sensitivity to digoxin

Factors contributing to adverse drug reactions in elderly patients



Polypharmacy

How many prescription medications are too many? >4 or >6
Many elderly people receive 12 medications per day

Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
 - More available drug
- Immature liver/kidneys
 - Liver often metabolizes more slowly
 - Kidneys may excrete more slowly

Pediatric Dosing

- Traditionally, for less frequently used drugs, extrapolation is done from adult dose on a weight or surface area basis.

Problems

- Absorption may be more or less than adult
- Clearance of some drugs in children is affected by maturation,
 - Cytochrome P450 enzyme system matures over time
 - Glomerular filtration changes over time
- Drug targets may vary with age
- **“Children are not Small Adults”**

Examples

- CYP isoforms vary with age:
For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life
- Carbamazepine (3A4) clearance faster in children than adults
– requires higher doses

SPECIAL CONSIDERATIONS IN PREGNANT AND BREASTFEEDING WOMEN

- IN PREGNANCY, THE DRUG IS REALLY GOING TO TWO PEOPLE, SO YOU MUST CONSIDER HOW THE DRUG MAY AFFECT THE GROWING FETUS.
- IMPORTANT FOR WOMEN TO AVOID AS MANY DRUGS AS POSSIBLE UNLESS ORDERED BY THE PHYSICIAN.
- TERATOGENIC—DRUGS THAT ARE LIKELY TO CAUSE MALFORMATIONS OR DAMAGE IN THE EMBRYO OR FETUS.
- THESE TYPE OF DRUGS SHOULD BE AVOIDED.

Drug efficacy is questioned..

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BBC SPORT

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Drugs 'don't work on many people'

A senior executive at Europe's largest drug maker has admitted most prescription medicines don't work for most people, it is reported.

Allen Roses, of GlaxoSmithKline, is quoted in a national newspaper as saying more than 90% of drugs only work in 30-50% of people.

He said: "Drugs on the market work, but they don't work in everybody."

Mr Roses, an expert in genetics, said new developments should help tailor drugs more specifically.

At present, pharmaceutical companies adopt a "one-drug-fits-all" policy.

But Mr Roses said refinements in genetic technology should make it possible to identify more precisely those people who were likely to benefit from a drug.



Drugs may be more specifically targeted

SEE ALSO:

- ▶ [Ethics backing for tailored drugs](#)
23 Sep 03 | Health
- ▶ [DNA chip gives drug advice](#)
14 Apr 03 | Health

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- ▶ [GlaxoSmithKline](#)
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PATIENTS CAN RESPOND DIFFERENTLY TO THE SAME MEDICINE

HYPERTENSION DRUGS

ACE Inhibitors

10-30%



HEART FAILURE DRUGS

Beta Blockers

15-25%



ANTI-DEPRESSANTS

20-50%



CHOLESTEROL DRUGS

Statins

30-70%



ASTHMA DRUGS

Beta-2-agonists

40-70%



Percentage of the patient population for which any particular drug is ineffective

Definitions

- **Pharmacogenetics** is the study of the effects of a drug in relation to a single or defined set of genes.
- **Pharmacogenomics** is the study of the effect of a drug in relation to the functions and interactions of all the genes in the genome.

The goal



rational means to optimize drug therapy
and ensure maximum efficacy with
minimal side effects.

Example

- African hypertensive



diuretics



ACEI and β -blockers.

- Combination of isosorbide dinitrate and hydralazine in blacks with heart failure.

the first race-based prescription drug in the United States.

(FDA) then approved (BiDil)

What is Personalized Medicine?

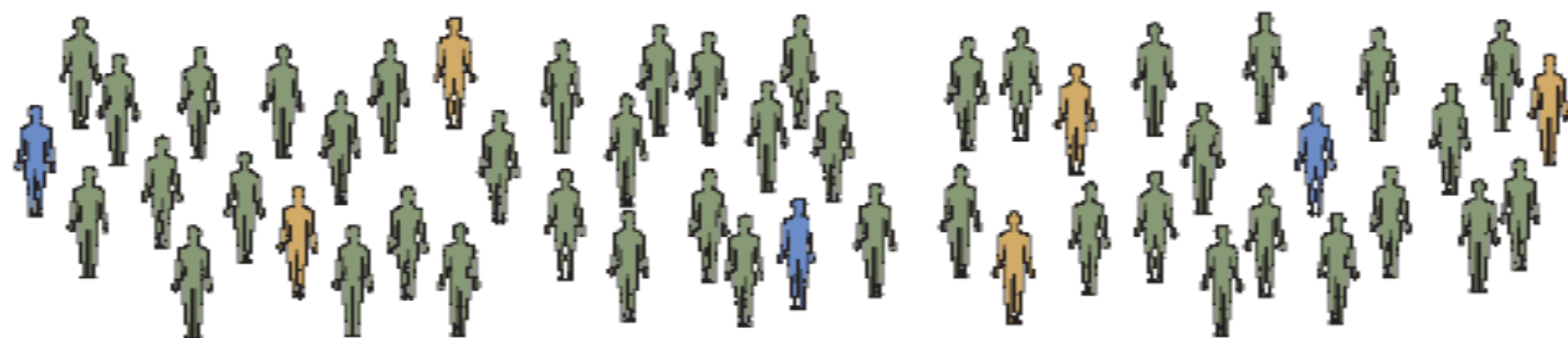
Personalized medicines simply means the prescription of specific treatments and therapeutics best suited for an individual's genetic makeup

Personalized Medicine will enable doctors to:

Use medications and other treatments that would work best for each individual

Avoid medications that would cause an individual to have bad side effects

Different patients receiving the same medicine



GCCC**A**CCTC

Treat patients genetically
predisposed to respond well.



GCCC**G**CCTC

Screen out patients likely to experience
adverse events or lack of efficacy



What are SNPs

- Single Nucleotide Polymorphisms
 - A SNP is a site of the DNA in which a single base-pair varies from person to person
 - They are the most common form of genetic variation in the human genome (frequency of >1%)

The basis of Genetic Diversity...



- Different arrangements of NUCLEOTIDES in a nucleic acid (DNA) provides the key to DIVERSITY among living organisms.

Genetic Factors Determining Drug Response

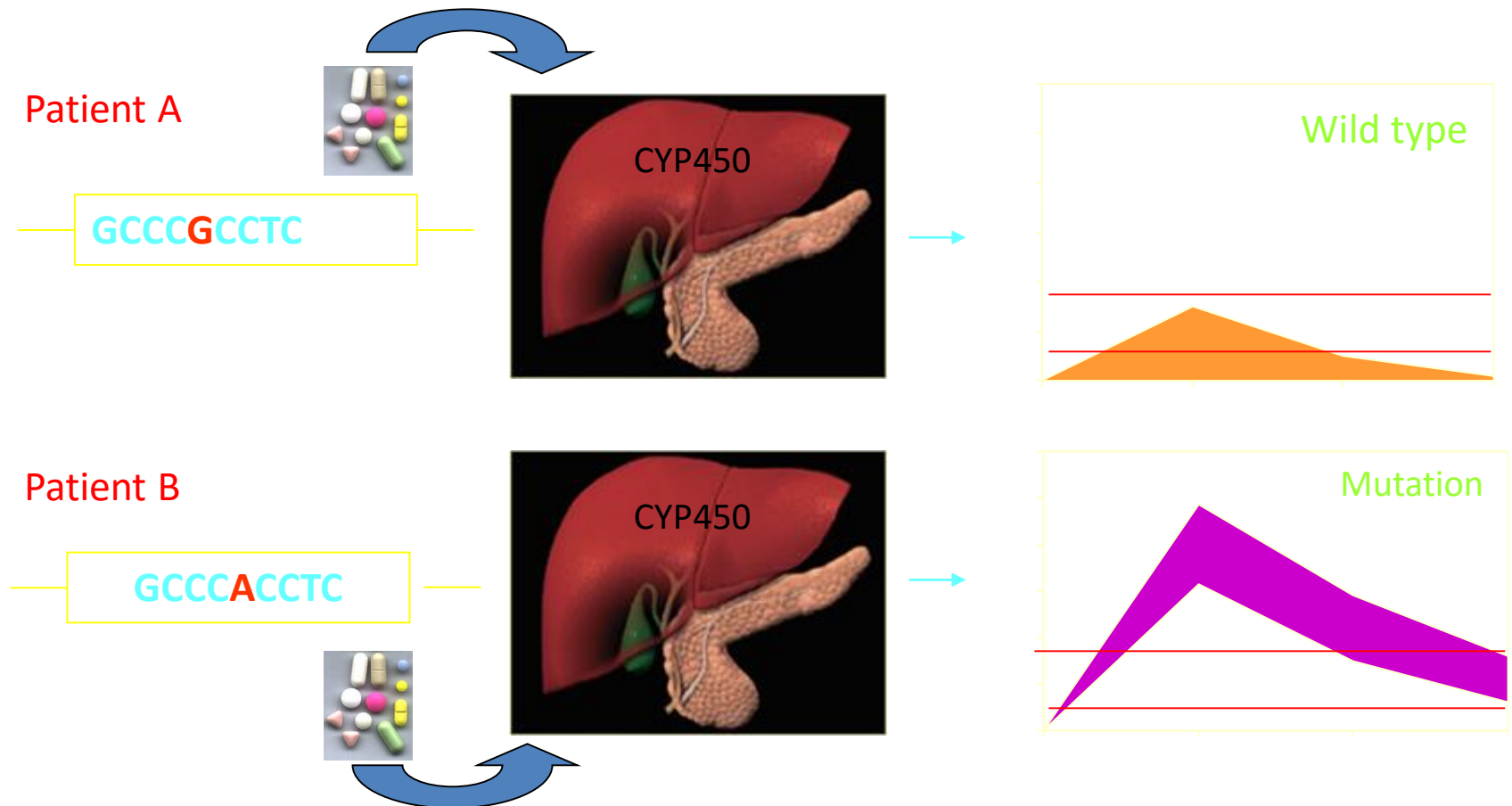
Polymorphisms
in Drug
Receptors
(e.g. β 2AR)

Polymorphisms
in Drug
Transporters
(e.g. MDR1)

Polymorphisms
in Drug
Metabolizing
Enzymes
(e.g. CYP2D6)

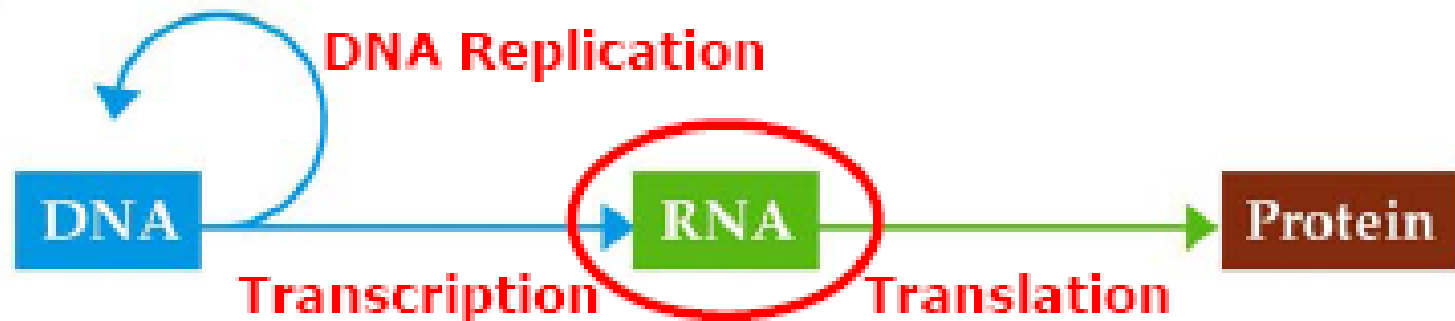
Pharmacogenetics and Drug Metabolism

Same dose but different plasma concentrations



The Central Dogma

The Flow of Information: DNA → RNA → Protein



- A gene is expressed in two steps:
 - DNA is transcribed to RNA
 - Then RNA is translated into protein

GENE

- **A code made up of pairs of bases carried on the DNA molecule.**
- **Each DNA molecule contains many genes.**
- **The basic physical and functional units of heredity**
- **Genes vary in size and exon content**
- **has regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.**

GENE

- Each chromosome carries a couple of thousand genes
- Many of these are common to all human beings.

99.9% of your DNA is identical to everyone else's.

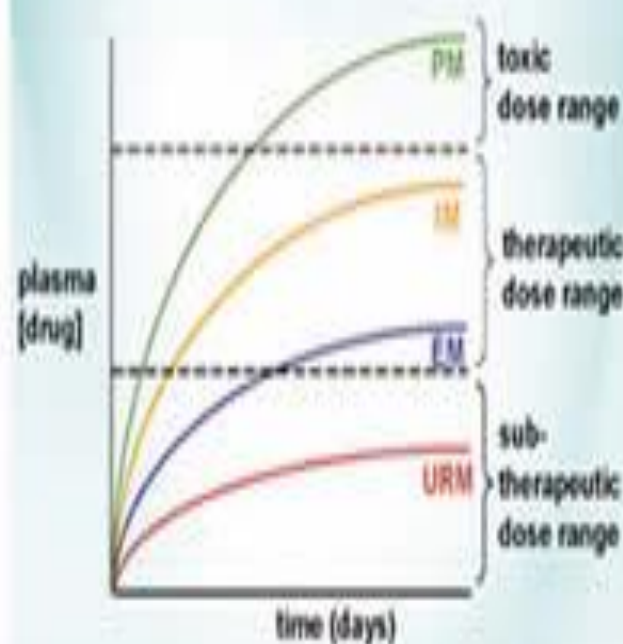
- The remaining 0.1% influences the differences between us
 - height, hair color and susceptibility to a particular disease
 - And so on

What drugs

1. Drug with narrow therapeutic range
eg; theophylline
2. Drug with life-threatening adverse effects
eg; warfarin
3. Drug therapies of which individual response can
badly be predicted
eg; antidepressant drugs
4. Drug therapies of which quick response is required
eg; analgesic drugs

Classification of Drug Metabolism

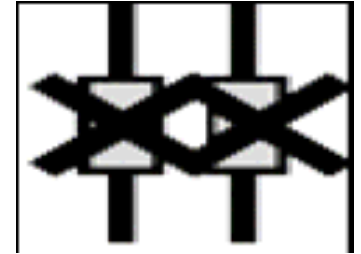
- Drug metabolism is arbitrarily classified into 3 or 4 classes, depending on the enzyme involved
- These classifications may represent genetic polymorphism or groups of polymorphism
- The classes include:
 - PM = poor metabolizers
 - IM = intermediate metabolizer
 - EM = extensive metabolizers
 - URM = ultrarapid metabolizers



Phenotypes of CYP450

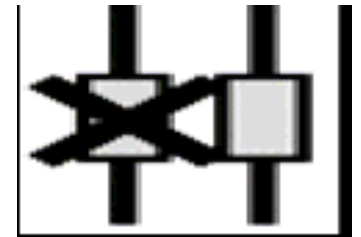
1. Poor metabolizer (PM)

- has low metabolic capacity
- has two mutant alleles



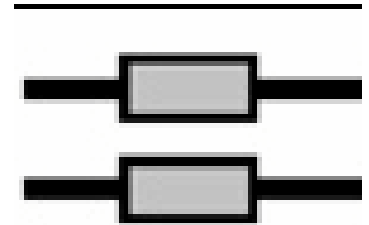
2. Intermediate metabolizer (IM)

- has metabolic capacity between PM and EM
- has one reduced activity allele and one null



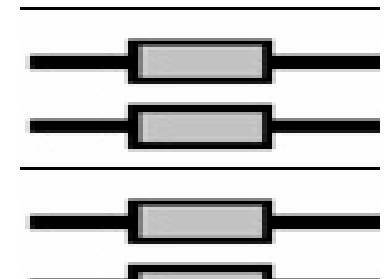
3. Extensive metabolizer (EM)

- has regular metabolic capacity
- has at least one and no more than two normal functioning alleles

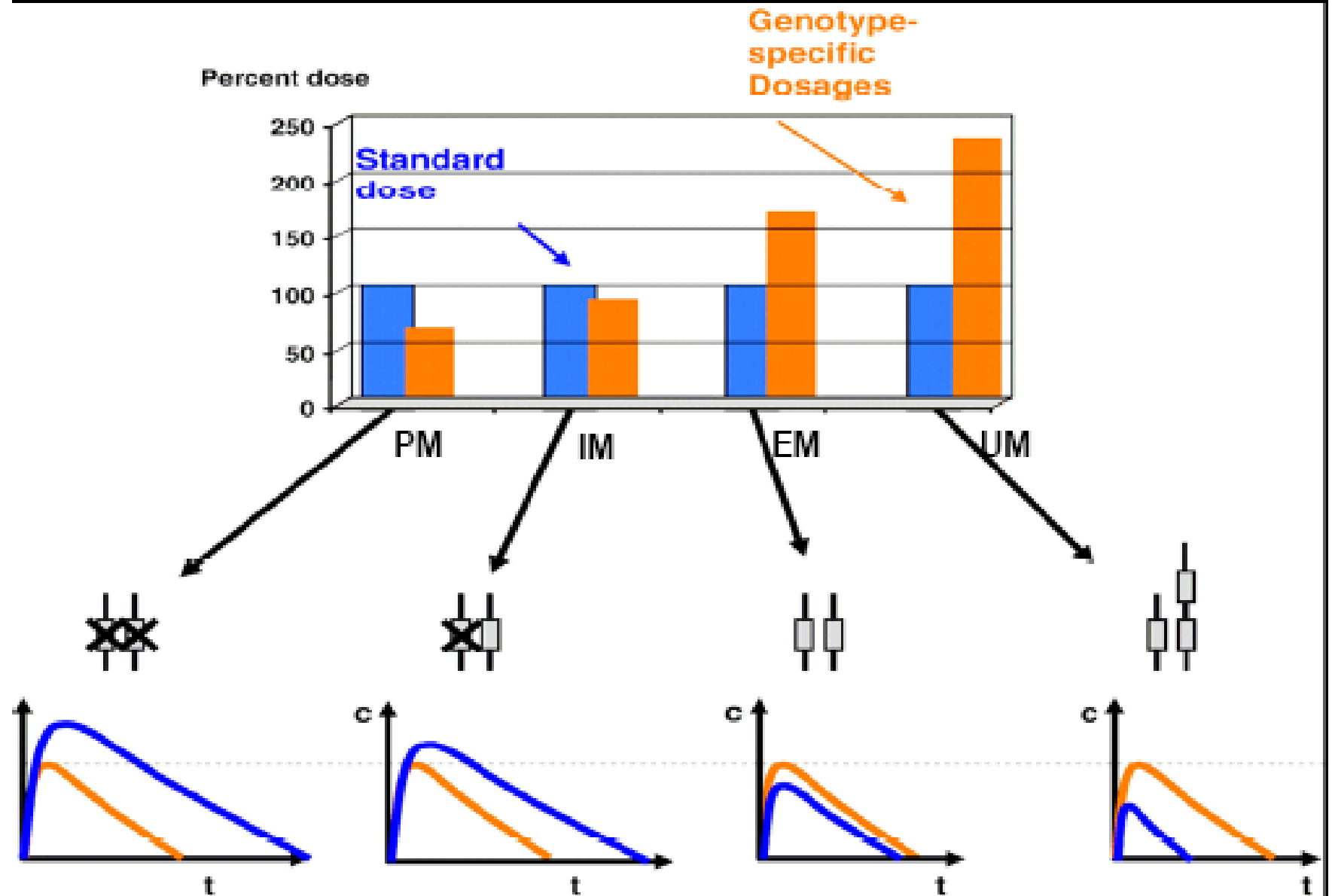


4. Ultrarapid metabolizer (UM)

- has higher metabolic capacity than EM
- has multiple copies of functional alleles



Dose Adjustment Based on Genotypic Differences



Phenotype	Active Drug (requires metabolism for detoxification such as CYP2C19 mediated metabolism of omeprazole)	Prodrug (requires metabolism for activity such as CYP2D6 mediated metabolism of codeine to morphine)
Poor	<ul style="list-style-type: none"> • Accumulation of drug may lead to adverse reactions • May require lower dose 	<ul style="list-style-type: none"> • Poor efficacy • Accumulation of prodrug
Extensive and or Ultrarapid	<ul style="list-style-type: none"> • Poor efficacy • May require higher dose or more frequent dosing 	<ul style="list-style-type: none"> • Good efficacy • May require lower dose

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

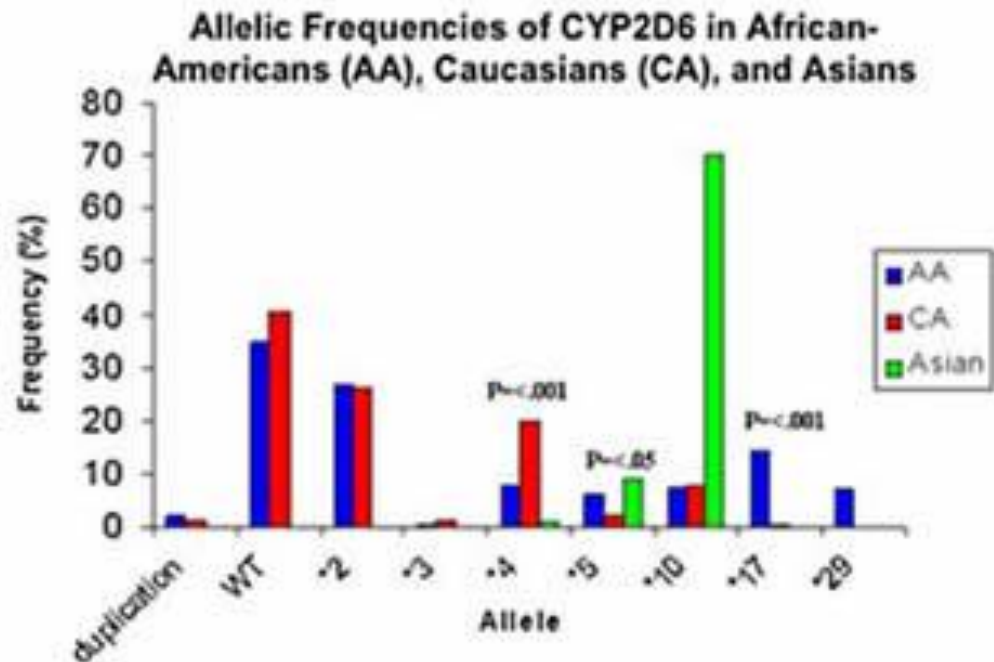
Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China ¹⁷	Debrisoquin ¹⁵ Sparteine ¹⁶ Nortriptyline ²³ Codeine ^{27,28}	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England ²⁹ (those homozygous for the *2 and *3 alleles)	Warfarin ^{29,30} Phenytoin ^{31,32}	Enhanced drug effect ²⁹⁻³²
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans ³³ 3.3% in Sweden 14.6% in China ¹⁷ 18% in Japan ³³	Omeprazole ^{34,35}	Enhanced drug effect ^{36,37}
Dihydropyrimidine dehydrogenase	Approximately 1% of population is heterozygous ³⁸	Fluorouracil ^{39,40}	Enhanced drug effect ^{39,40}
Butyrylcholinesterase (pseudocholinesterase)	Approximately 1 in 3500 Europeans ⁴¹	Succinylcholine ^{9,41}	Enhanced drug effect ^{9,41}

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

CYP2D6

- Discovered in the 1970s, one of the most widely studied polymorphisms in drug metabolism
- 2% of total liver CYP content
- Distribution of PM: 7% of Caucasians, 1% of Asians
- Involved in metabolism of several drugs
 - Psychotropic medications: tricyclic antidepressants, SSRIs, classical and atypical antipsychotics
 - Cardiovascular drugs
 - β -receptor antagonists: metoprolol, propranolol, timolol
 - Phenacetine
 - Codeine
 - Abused drugs

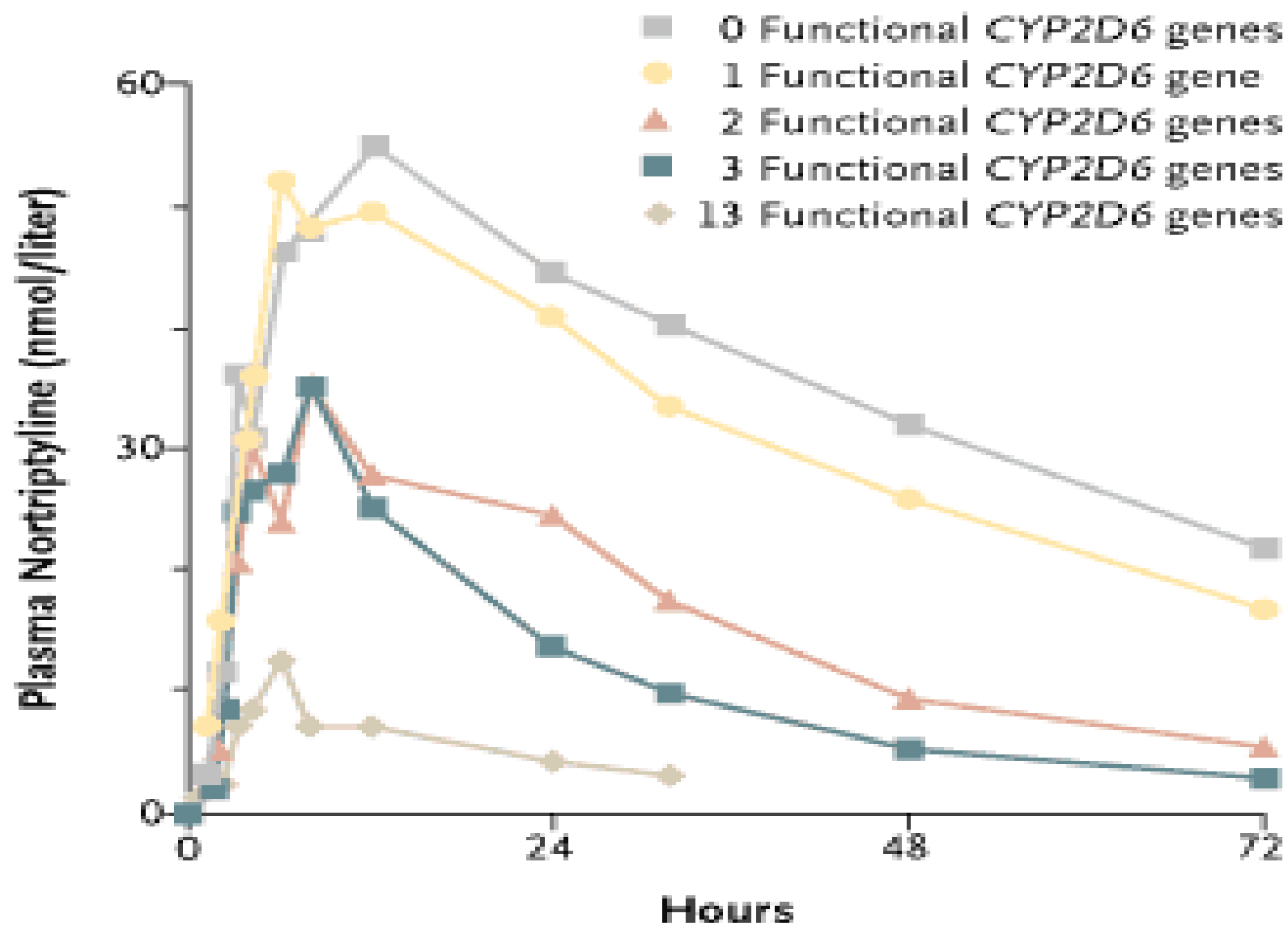
Ethnicity and distribution of CYP2D6 genotypes



Wan Y et al. Pharmacogenetics 2001, 11: 439-499.
Gaedigk A et al. Clin Pharmacol Ther. 2002
Jul; 72(1): 76-89.

CYP2D6

- More than 50 alleles, encoding enzymes with inactive / decreased / increased / normal catalytic function.
- Poor metabolisers
 - are at risk of drug toxicity even at standard doses, resulting in poor compliance
 - may also present with treatment resistance to prodrugs that require activation (codeine)
- Ultrarapid metabolisers:
 - delayed therapeutic response or treatment resistance (29% of Ethiopians carry multiplicated functional CYP2D6 alleles)





5-10% PMs

1-2% UMs

3.6% UMs

7-10% UMs

10% UMs

13% UMs

20% UMs

1-2% PMs

29% UMs

Springer



Information for Healthcare Professionals: Use of Codeine Products in Nursing Mothers

Update: The issues described in this communication have been addressed in product labeling (see [Drugs@FDA](#))

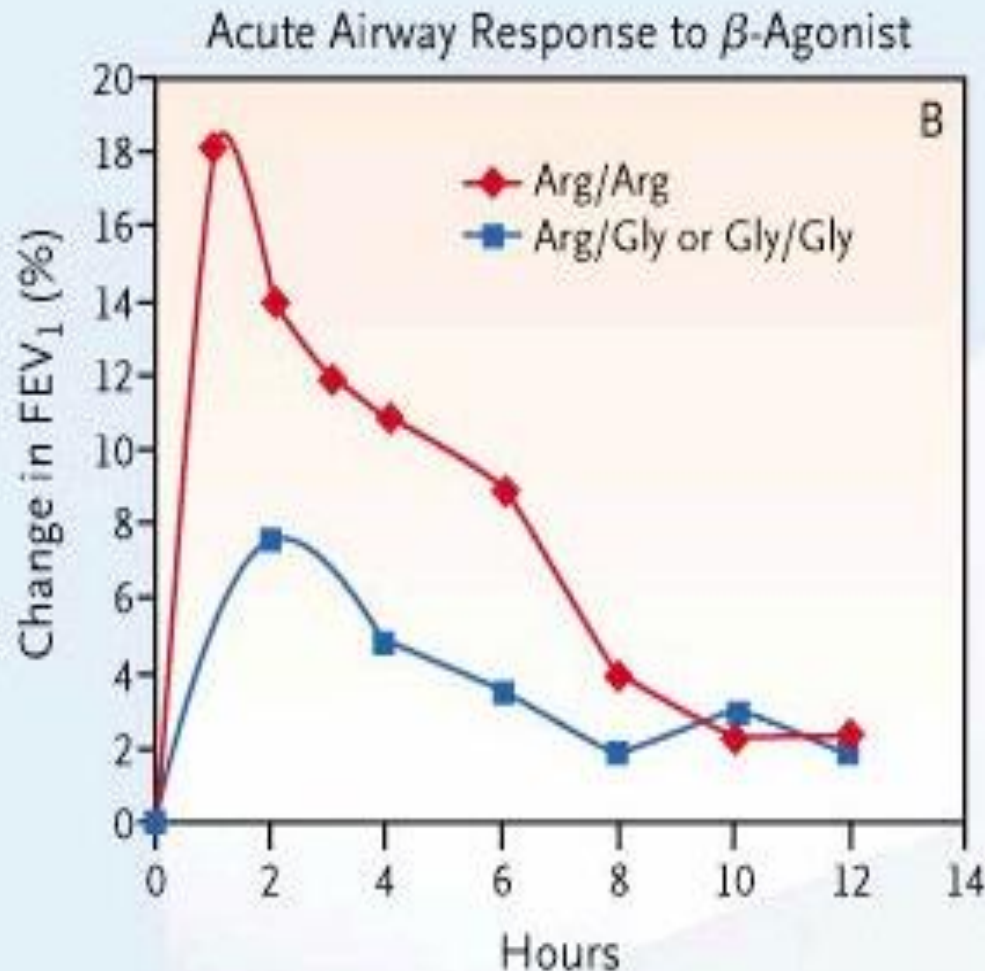
FDA Alert: [8/17/2007] FDA has important new information about a very rare, but serious, side effect in nursing infants whose mothers are taking codeine and are ultra-rapid metabolizers of codeine. These babies may be at increased risk for morphine overdose.

Pharmacogenomics

Drug Targets

- Direct protein target of drug
 - Receptor
 - Enzyme
- Proteins involved in pharmacologic response
 - Signal transduction proteins or downstream proteins

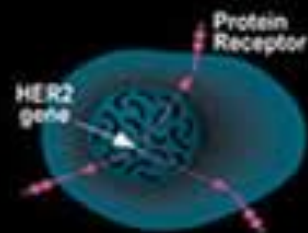
Beta-2 Polymorphisms and Response to Albuterol



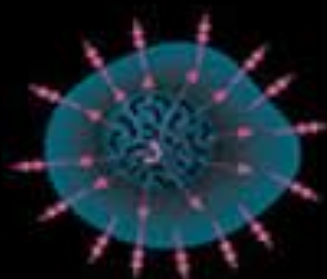
- Single 8 mg albuterol dose
- Albuterol-evoked increases in FEV₁ were higher and more rapid in Arg16 homozygotes compared with Gly carriers
- Codon 16 polymorphism is a determinant of bronchodilator response to albuterol

Lima JJ et al. Clin Pharmacol Ther 1999; 65: 519-25

Trastuzumab (Herceptin®)



In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.



In certain types of breast cancers, the Her-2 gene is over-expressing this cell surface receptor, contributing to cancerous cell growth.

This is the case in ~30% of breast cancers.



Herceptin (trastuzumab) is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.