Pharmacology for Public Health Students

NURAHMED M
(Bpharm, MSc. In Pharmacology)

General Pharmacology



Adrenalin®

1:1000

1 mg/ml

30 ml

Nicorette®



2 mg

Antilirium®

IM/IV



1 mg/ml



Regitine®

IM/IV

5 mg vial

Atrovent®



14 g

Betachron®



60 mg 80 mg 120 mg 160 mg

Isuprel®



1 mg/5 mL

Brevibloc®



100 mg/10 ml



2.5 g/10 ml



Enlon®

IM/IV

10 mg/ml

"perhaps the greatest feature which distinguish man from other animals is his desire to take medicines"

(Sir William Osler)

Objectives

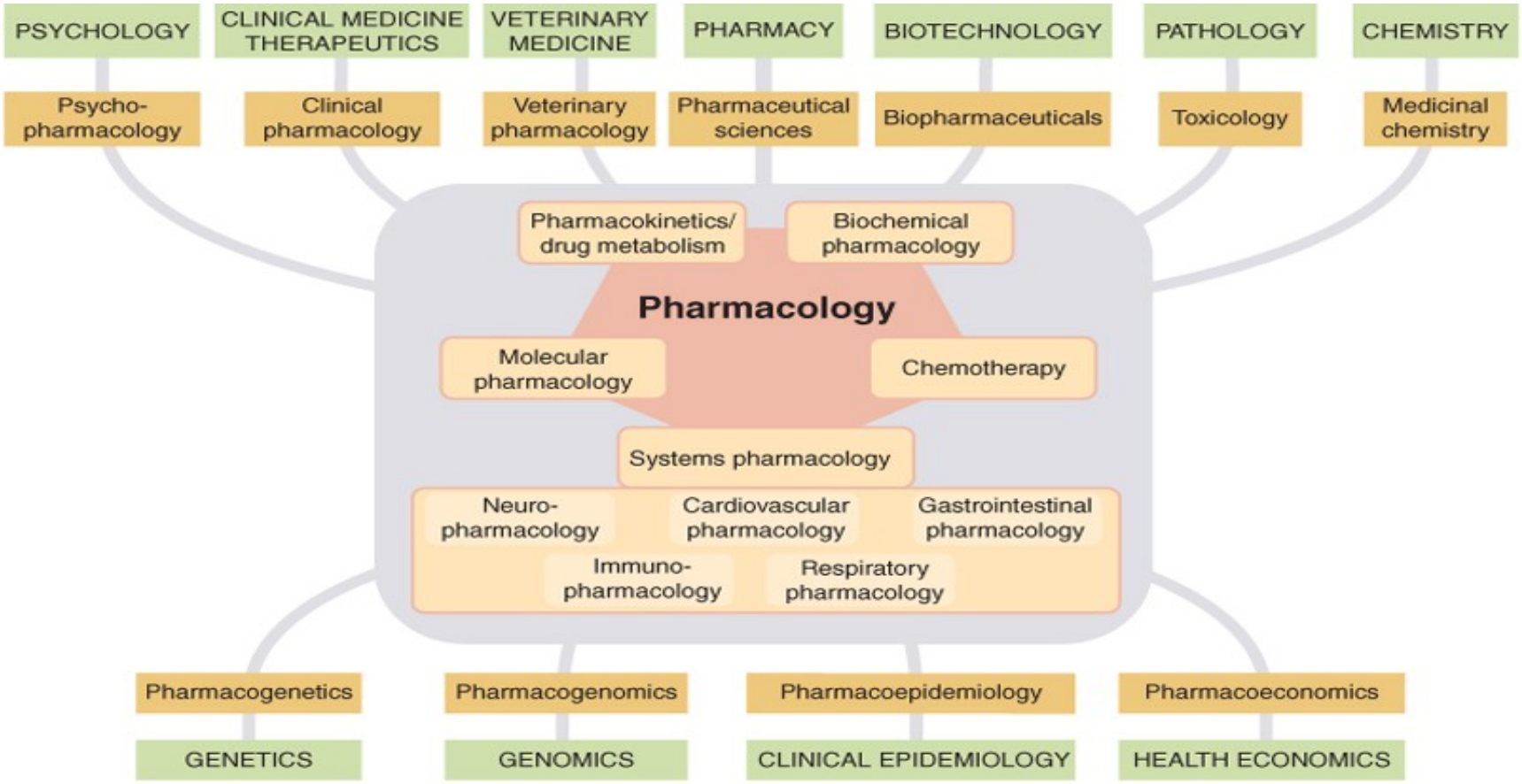
After completing this topic the students will be able to:

- ✓define pharmacology, medical pharmacology, toxicology, drug, poisons and toxins.
- ✓mention the branches of pharmacology.
- ✓list sources of drugs
- ✓describe drug development stages
- ✓differentiate between different drug names

Introduction

- **Pharmacology** came from the Greek words “Pharmacon” meaning drug and “logos” meaning discourse in
- **Pharmacology** is the study of substances:
  - ✓ that interact with living systems through chemical processes; especially by binding to regulatory molecules and activating or inhibiting normal body processes.
- These substances may be chemicals administered:
  - ✓ to achieve a beneficial therapeutic effect on some process within the patient or
  - ✓ for their toxic effects on regulatory processes in parasites infecting the patient.

- Boundaries of pharmacology are not sharply defined nor are they constant



Ctnd…

- **Medical pharmacology** is the science of substances used to:
  - ✓ Prevent, diagnose and treat disease
  - **Toxicology** is the branch of pharmacology which deals with the undesirable effects of chemicals on living systems
- **Poisons** are drugs that have almost exclusively harmful effects.
- **Toxins** are usually defined as poisons of biologic origin
- **Pharmacotherapeutics**: Use of drugs in prevention & Rx of disease.
- **Chemotherapy**: effect of drugs on microorganisms, parasites and neoplastic cells living & multiplying in living organism

Drug and Medicine

- **Drug:-** a chemical substance of known structure, other than a nutrient or an essential dietary ingredient, when administered to living organism, produce a biological effect
- **Medicine:-** a chemical preparation which usually but not necessary contain one or more drugs
  - Substance that have medical importance or therapeutic values
  - Mostly, Drug + additives

Sources of drugs

Drug is a substance which is used for:

- Diagnosis of disease
- Prevention of disease
- Treatment or palliation (relief of symptoms) of disease
- Prevention of pregnancy (i.e. contraception)
- Maintenance of optimal health

Ctnd…

Drugs are obtained from:

a. Minerals

- Liquid paraffin
- magnesium sulfate
- magnesium trisilicate
- kaolin, etc.

b. Animals

- Insulin
- thyroid extract
- heparin and
- antitoxin sera, etc.

Ctnd…

c. Plants

- morphine
- digoxin
- atropine
- castor oil, etc.

d. Synthetic source

- aspirin
- sulphonamides
- paracetamol
- zidovudine, etc.

Ctnd…

e. Microorganisms

- penicillin
- streptomycin and
- many other antibiotics

f. Genetic engineering

- human insulin
- human growth hormone etc.

Drug nomenclature

- Any drug can have three types of names:
- Existence of many names for each drug causes lamentable & confusing situation
  - Nonproprietary/generic name
  - Brand name/Proprietary/trademark/trade name
  - Chemical names

❖Generic, or non-proprietary, name;

- ✓ Proposed by the company that first developed the drug and Accepted or approved by international body
- ✓ Product must have this name
- ✓ only one generic name for a drug
- ✓ Serves as an important and unique designation for the active ingredient.
- ✓ Much shorter, easier to remember and pronounceable

❖Brand name/Proprietary/trademark/trade name

- Brand name: name by manufacture company
  - Vary from company to company
  - Several name for single drug

- More commonly, a company uses different brand names in different countries for the same drug, or two countries may market the same substance under different brand names.

- May occur have letter Informative specially absorption, disintegration…

- The difference b/n generic product and brand product is only the additives but not active ingredient

➢ **Chemical Name** : interest of chemists

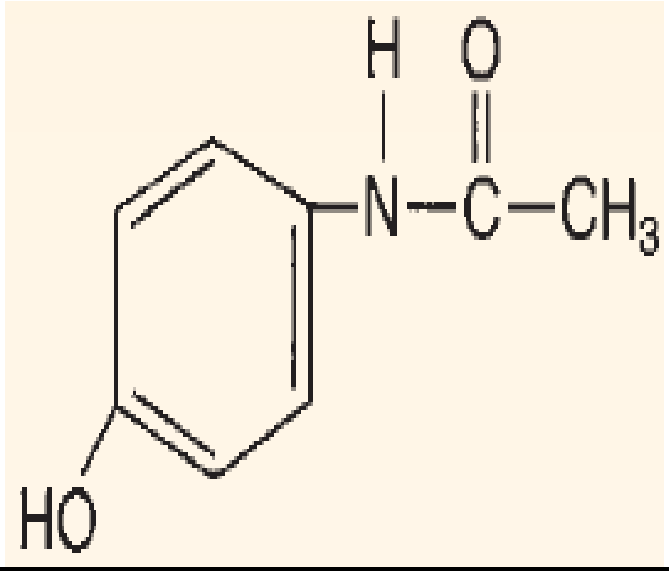
indicate the chemical entity present in the drug

- We employ drug names in two ways:

o for written and verbal communications about drugs

o to put labels to identify the medications present in containers

Which name is better to recommend in prescribing drugs?



Type of drug name	Examples
Chemical name	N-acetyl-para-aminophenol
Generic name	Paracetamol
Trade name	Panadol, Tylenol, Dapa, Valadol, Valorin, Helenol, etc

Stages of New Drug Development

- is an expensive and lengthy process
- the testing of new drugs has two principal steps:
  1. **Preclinical testing**
  2. **Clinical testing**

1. Preclinical testing

- In animals (different species)
- Evaluated for toxicities, pharmacokinetic properties, and potentially useful biologic effects
- May take 1 to 5 years
- When sufficient, the drug developer may apply to the FDA for permission to begin testing in humans

2. Clinical testing

- Done with humans
- Occur in four phases
- The first three phases are done before a new drug is marketed
- The fourth phase is done after marketing has begun.

Phase I

- conducted in normal volunteers(20-50)
- designed to test
- tolerable dose and duration of action
- to monitor toxicity
- to carry out kinetic studies

Phase II

- tested in patients
- to determine efficacy ,dose level and to establish that treatment offers some benefits
- usually a few hundred (100-500) for 3-6 months
- studied in great detail under close supervision (controlled clinical trial)

Phase III

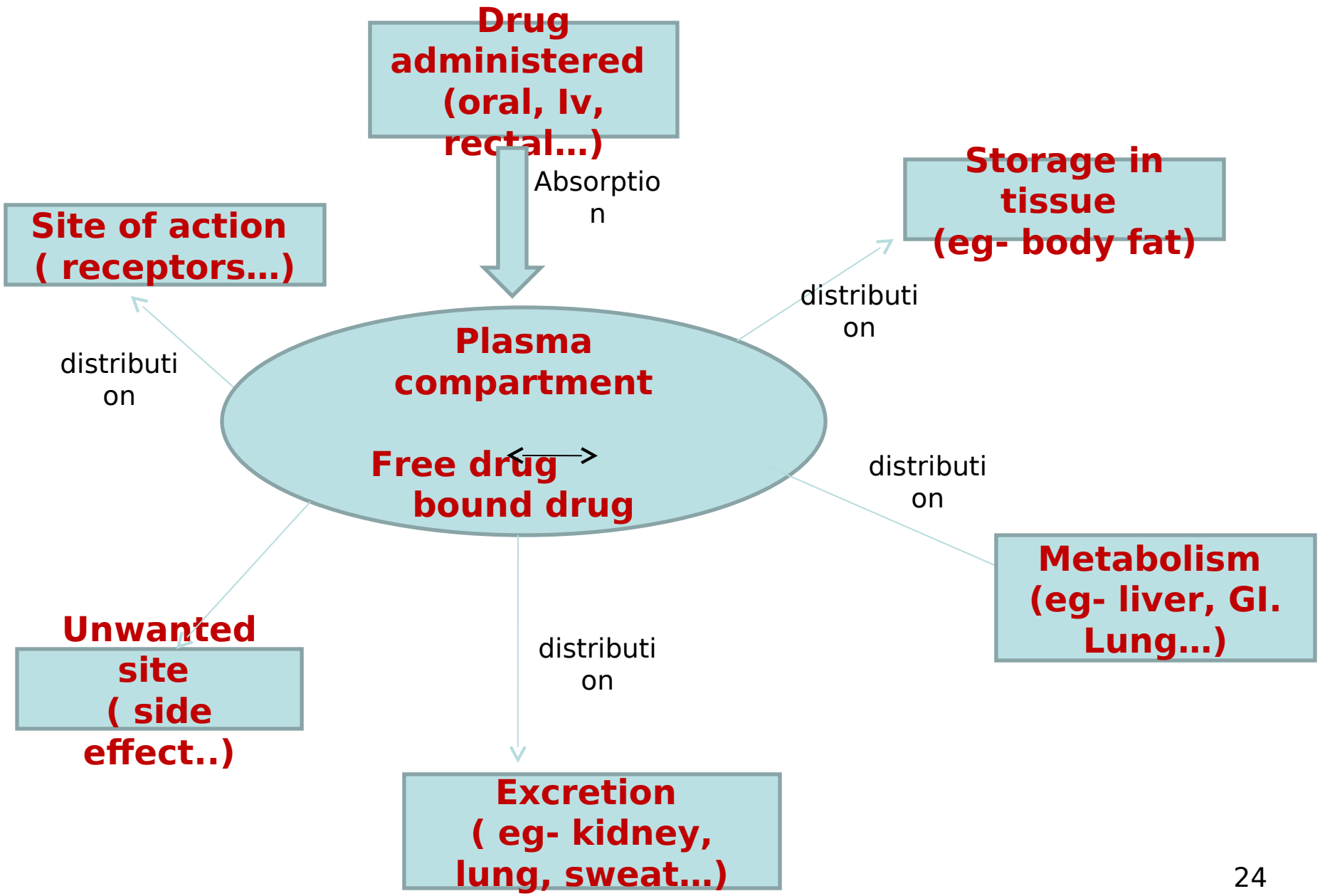
- Done in increased number (up to 2000 patients) of patients

Phase IV

- Post marketing surveillance
- Report about safety & efficacy
- Renewal or cancellation of the product depends on comment of review

Fate of administered drug

- Most drugs after administered to the body they undergo 2 major process
- **Pharmacokinetics process**:- process that involve absorption, distribution, metabolism, excretion.
- **Pharmacodynamics process**:- process that involve receptor – drug interaction which determines types and selectivity of the drug effect and quantitative determination of drug effect


Drug administered (oral, Iv, rectal…)
Absorptio n
Site of action (receptors…)
Storage in tissue (eg- body fat)
distributi on
distributi on
Plasma compartment
Free drug
bound drug
distributi on
Metabolism (eg- liver, GI. Lung…)
Unwanted site (side effect..)
distributi on
Excretion (eg- kidney, lung, sweat…)

Pharmacokinetics

- Pharmacokinetics:
  - Pharmaco: drug
  - Kinetics: motion
- Action of body on drug/ how body handles drugs
- Pharmacokinetics: deals with absorption, distribution, metabolism and excretion of drugs.
- To produce its characteristic effects, a drug must be present in appropriate concentration at its site of action.
- Concentration at the site of action depends on absorption, distribution, binding or localization in tissues, biotransformation, and excretion.
- All the pharmacokinetic processes involve passage of drug through membranes.

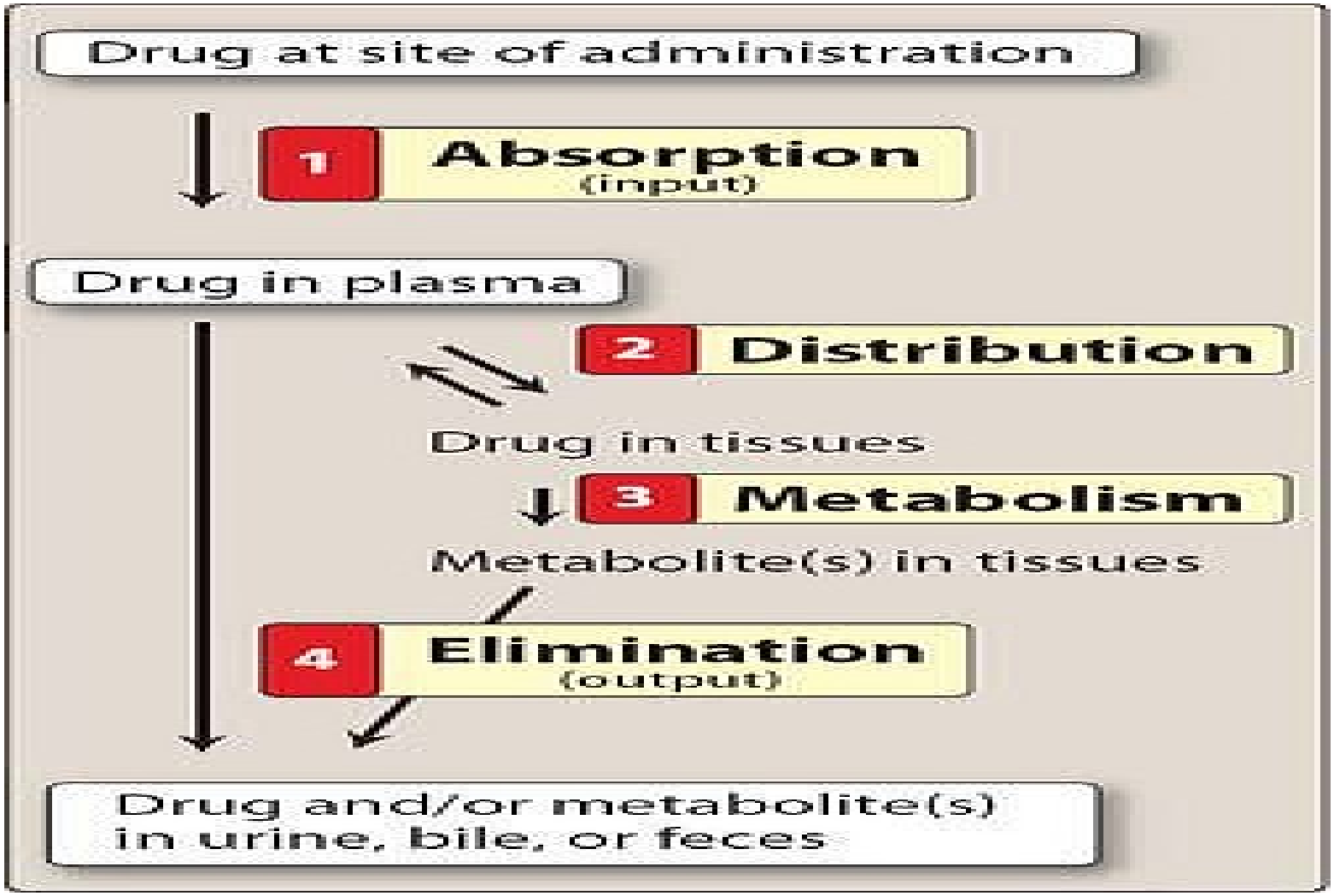
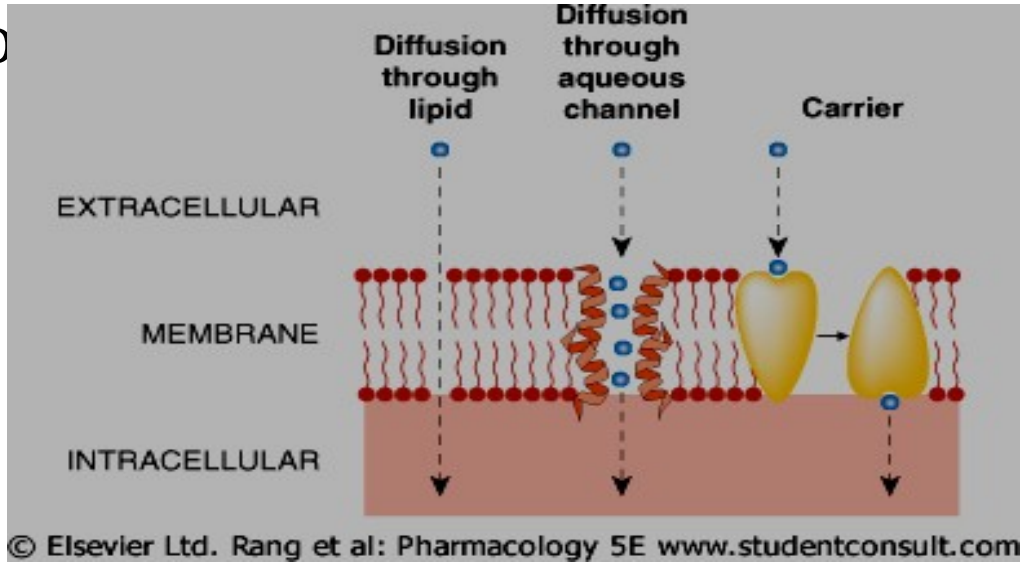


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

- There are four main ways by which small molecules cross cell membranes:
  - diffusing directly through the lipid
  - diffusing through aqueous pores
  - transmembrane carrier proteins that bind a molecule on one side of the membrane then changes conformation and releases it on the other
  - by endocyto



Passive diffusion

- The major mechanism for absorption of drugs.
- Not need energy
- The driving force for this process is the concentration gradient or electrochemical gradient
- **Fick's first law of diffusion:** drug molecules diffuse from a region of higher concentration to one of lower concentration until equilibrium is attained

Filtration or Pore Transport

- Is passage through the water filled pores in membranes
- It is accelerated by the hydrodynamic flow of water occurring under hydrostatic or osmotic pressure gradient
- Drug should be water soluble and of smaller molecular size than the diameter of the pores.
- Na+, glucose, caffeine

Carrier Mediated Transport

- Involves binding of the drug to specific receptors on the membrane for translocation into the cytoplasm
- Characteristics of carrier mediated transport
  - ✓ Selectivity
  - ✓ Competitive inhibition by chemical congeners
  - ✓ Requires energy
  - ✓ Saturability
  - ✓ Movement against electrochemical gradient
  - **Active transport:** when movement is against concentration gradient and Need energy e.g. levodopa and methyldopa from the gut
  - **Facilitated diffusion:** movement of drugs is along concentration gradient but in a much faster rate than simple diffusion and Not need energy e.g. levodopa & aminoacid into brain

cont’d

4. Phagocytosis & pinocytosis

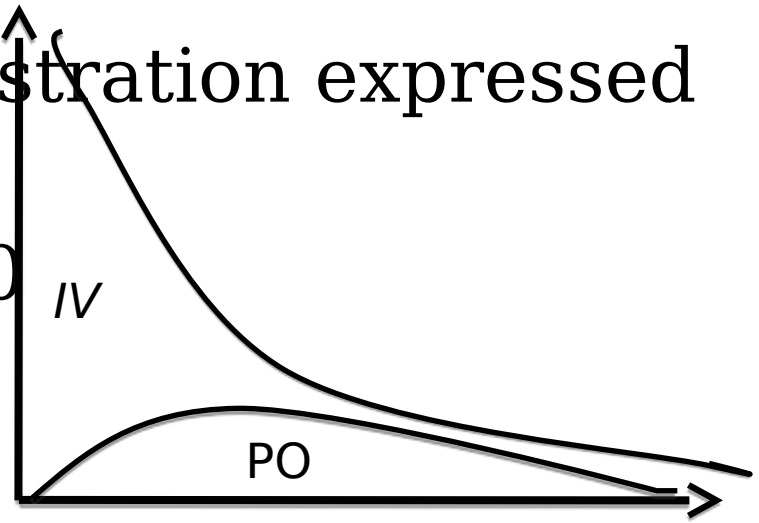
- Process by which large molecules are engulfed by the cell membrane forming a vesicle & releases them intracellular.
  - E.g. protein, toxin

Absorption

- **Absorption** Is the movement of drug from its site of administration into the central compartment, blood
- **Bioavailability(BA):-** is the fraction amount of drug passed in to the blood stream intact
  - ✓ Rate and relative amount of drugs reaching the blood not being changed
- Drug with good absorption – have better BA
- Route of drug administration affect the extent of absorption and hence affect bioavailability

- BA vary with different route of administration
  - Bioavailability is expressed in percentage
  - Bioavailability is 100% for drugs given IV.
- Factor affecting BA(F):-
  - Extent of absorption
  - First pass effect
- BA (F) from PO administration expressed as;

$$BA(F) = \frac{[AUC]_{po}}{[AUC]_{iv}} \times 100$$



Factors That Modify Absorption

- Drug solubility at the site of absorption
- Dosage form
- Local condition at the site of action
- Drug concentration at the site of absorption
- Circulation to the site of absorption
- Area of the absorbing surface
- The route of administration

Routes of administration

- **Enteral**
  - Oral, rectal, sublingual, buccal
- **Parenteral**
  - Intramuscular, subcutaneous, intravenous, intra arterial
- Inhalation
- Topical

Enteral

- **Oral route**
  - Involve many step before absorption(dissolution, disintegration)
- **Advantage**
  - Most convenient, safest
  - Most economical
  - Reverse of dose management is easily done(how?)
- **Disadvantage**
  - Irritation to GI(N&V)
  - High first pass effect
    - Some drug destructed by GI flora(digoxin), enzyme(insulin), p^H (penicillin)
    - Liver metabolism(highly enzymatic)
    - ✓ BA from PO < 1 --- b/c absorption
  - Not given for unconscious, uncooperative, vomiting patients
  - Slow onset of action
  - Irregular absorption (drug- food interaction)
    - Better to take the food and drug In at least 30 minute

- IV
- **Advantage**
  - Fast onset of action(emergency case)
  - 100 % BA
  - Better for drug with irritation effect
- **Disadvantage**
  - Pain, not convenient(d/t self administration)
  - Expensive
  - Only sterilized solution used
  - Difficult to manage dose dumping
  - No local action
- **Inhalation**
  - Absorption of inhalants mainly depend on particle size
  - Dosage must be aerosol, volatile liquids, gas
- Advantage
  - Used for both local action (asthma),and systemic action (general anesthetic)
  - Have rapid onset of action
  - Minimum FPE

- **Disadvantage**
  - d/t to put drug in aerosol, volatile or gas state
  - Poor ability to regulate the dose
  - Irritation of the pulmonary mucosa

o **Rectal**

- **Advantage**
  - For certain irritant and unpleasant drugs
  - For unconscious and uncooperative patients
  - FPE is minimal by 50% from PO
- **Disadvantage**
  - Unreliable and unpredictable absorption
  - Uncomfortable/not convenient and embarrassing

o **Topical application**

- Application could be on mucous, skin or the eye
- Mucous membrane include conjunctiva, nasopharynx, oropharynx, vagina …

Drug distribution

- Process by which a drug reversibly leaves the blood stream & enters the interstitium and/or cells of the tissues

Factors affecting drug distribution

I. Plasma protein binding

- Drug in systemic circulation exist as bound and unbound form
- Drug ordinarily bind with plasma protein in reversible fashion and in dynamic equilibrium

$$D + P \rightarrow [DP] \rightarrow D + P$$

  - As free drugs leave the systemic circulation the bound drug dissociate
    - Albumin[acidic drugs]
    - α-glycoprotein [basic drugs]

II. Tissue uptake

- Drugs will not always be uniformly distributed to and retained by body tissues; some drug will be either considerably higher or considerably lower in particular tissues: due to tissue different affinity

- Adipose tissue : drugs with extreme lipid solubility (excellent lipid water partition coefficient)
  - May result :–
    - decrease therapeutic activity (eg thiopental)
    - Prolonged activity (eg fat depot preparation)
    - Toxicity (eg-DDT)

- Kidney : contain proteins, methallothionein, that has high affinity for metals
  - Cadmium, Lead, Mercury accumulation -----toxicity

- Eye – drugs which have affinity for retinal pigment, melanin, accumulate in the eye
  - Chlorpromazine (other phenothiazine) and chloroquine--- accumulate in eye
- Bone- TTC, Lead, Cisplatin
  - TTC accumulation may cause dysplasia, poor bone development
  - Lead accumulation result bone brittleness (displace Ca^{2+})
  - Slow release of toxic effect may occur from lead and cisplatine accumulation
- Teeth –TTC accumulation result yellow- brown discoloration of teeth
- Liver – Chloroquine
- Generally tissue accumulation of drug may have
  - Advantageous effect ---(target tissue therapy eg Chloroquine, iodine: sustained release effect, eg fat depot)
  - Disadvantageous effect---mainly toxicity

III. Physiological barrier

- Blood brain barrier (BBB)
- Transfer of drug to brain is regulated by BBB

Not pass BBB
-- ionized drug
-- Lipid insoluble drugs
-- Bound drug

Cross BBB
--unionized drug
-- small size drug
-- unbound drug

- Inflammation such as due to meningitis or encephalitis increase the permeability of BBB so permeating the passage of ionized , lipid soluble drugs.
  - Eg:- penicillin and ampicillin – not cross BBB (highly ionized) but inflammation– they can pass BBB --used for antibiotic effect centrally
- Pgp transport system: ↓ the concentration of some drugs in CNS
  - Pump back to systemic circulation

- **Placenta barrier**

- Blood vessel of mother and fetus separated by PBB
- Highly polar and ionized drugs do not cross placenta readily
- Drugs with high lipid solubility shouldn't give pregnant mother
  - Eg TTC –accumulate in bone and teeth of neonate—↓development of bone and teeth
  - Chloramphenicol –cause gray baby syndrome
- Drug cross PBB and cause fetal abnormalities called teratogenic drug

IV. **Rate of blood flow**

brain, kidney, liver & lung- highly perfused

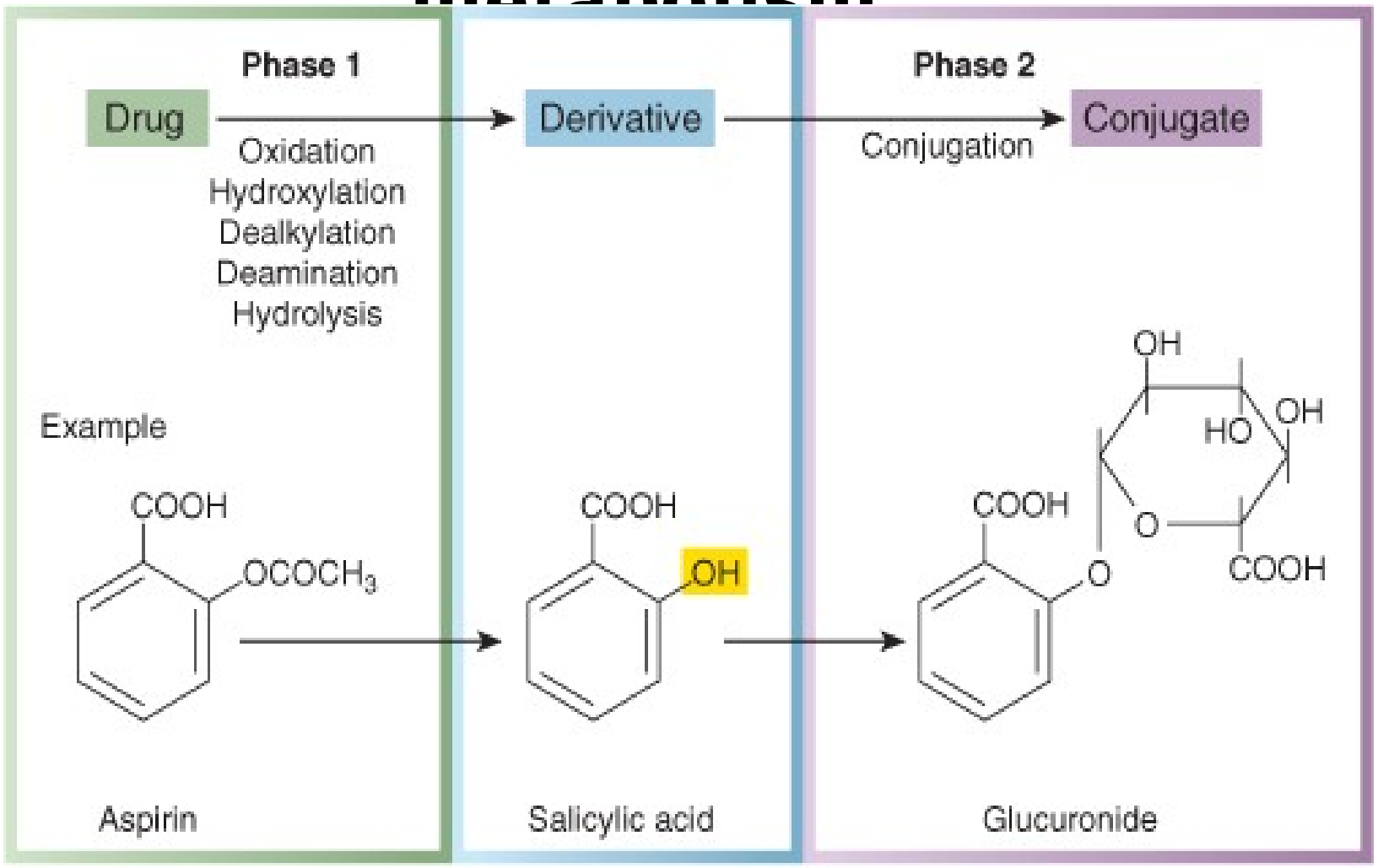
- **C. Drug biotransformation** is a process by which drugs are chemically changed in the body to facilitate excretion of drugs by rendering them more polar or by conjugating them with highly polar molecules.
- Every tissue has some ability to metabolize drugs (i.e. GI tract, lungs, skin, kidneys); however, the liver is the principal organ for drug metabolism
- Biotransformation may lead to one of the following:
  - Inactivation of parent drug –eg Phenobarbital
  - Conversion of drug to its toxic metabolite—eg paracetamole
  - Conversion of inactive drug (prodrug) to more active drug—eg levodopa
  - Maintenance of activity – eg diazepam

Pattern of Biotransformation

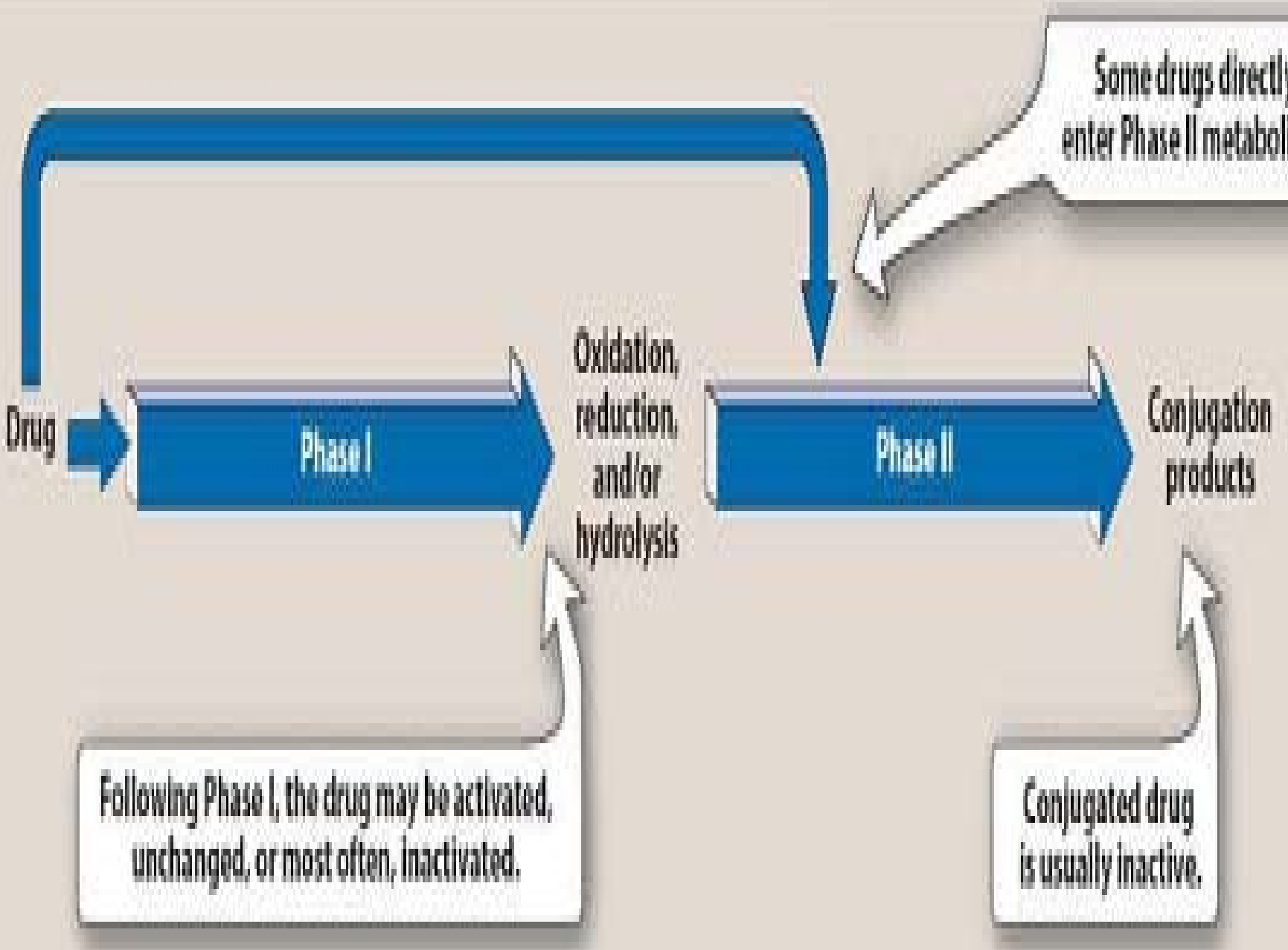
- Biotransformation reactions are classified as phase I and phase II reactions
- **Phase I** (functionalization or non-synthetic) reactions
  - Introduce or expose a functional group on the parent drug.
  - Generally result in the loss of pharmacological activity, although there are examples of retention, enhancement or alteration of activity.
  - If not excreted rapidly, the products of phase I biotransformation undergo phase II conjugation reaction.
  - Prominent reactions in this category include ***oxidation, reduction*** and ***hydrolysi***s

- **Phase II** (conjugation or synthetic) reactions
  - Lead to the formation of a covalent linkage between a functional group on the parent compound with endogenous substrates (***glucuronic acid, sulfate, amino acids, glutathione or acetate***).
  - Form highly polar conjugates which are generally inactive and are rapidly excreted in the urine or feces
  - Is a saturable process
  - Higher molecular weight conjugated metabolites are mostly excreted in the bile

The two phases of drug metabolism



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Some drugs directly enter Phase II metabolism.
Drug
Phase I
Oxidation, reduction, and/or hydrolysis
Phase II
Conjugation products
Following Phase I, the drug may be activated, unchanged, or most often, inactivated.
Conjugated drug is usually inactive.

Enzyme Induction

- An increased synthesis of CYP450 and hence increased rate of biotransformation.
- Induction brings about decreased bioavailability of parent drug and increased concentration of metabolite
  - Phenobarbitone: nonselective
  - DDT: induces cyp1A1
  - E.g. Induction of metabolism of ethinylestradiol by Rifampicin and phenobarbitone

Enzyme Inhibition

- Competition between two or more drugs for metabolizing enzyme may lead to a decrease in the metabolism of one of these agents
- Some drugs bind tightly to the Cytochrome P450 heme iron and reduce the metabolizing activity of the enzymes.
  - Cimetidine -Ketoconazole
  - Erythromycin -Chloramphenicol
- It results in elevated levels of the parent drug and hence prolonged pharmacological effect and an increased incidence of drug-induced toxicity.

Factors Affecting Drug Biotransformation

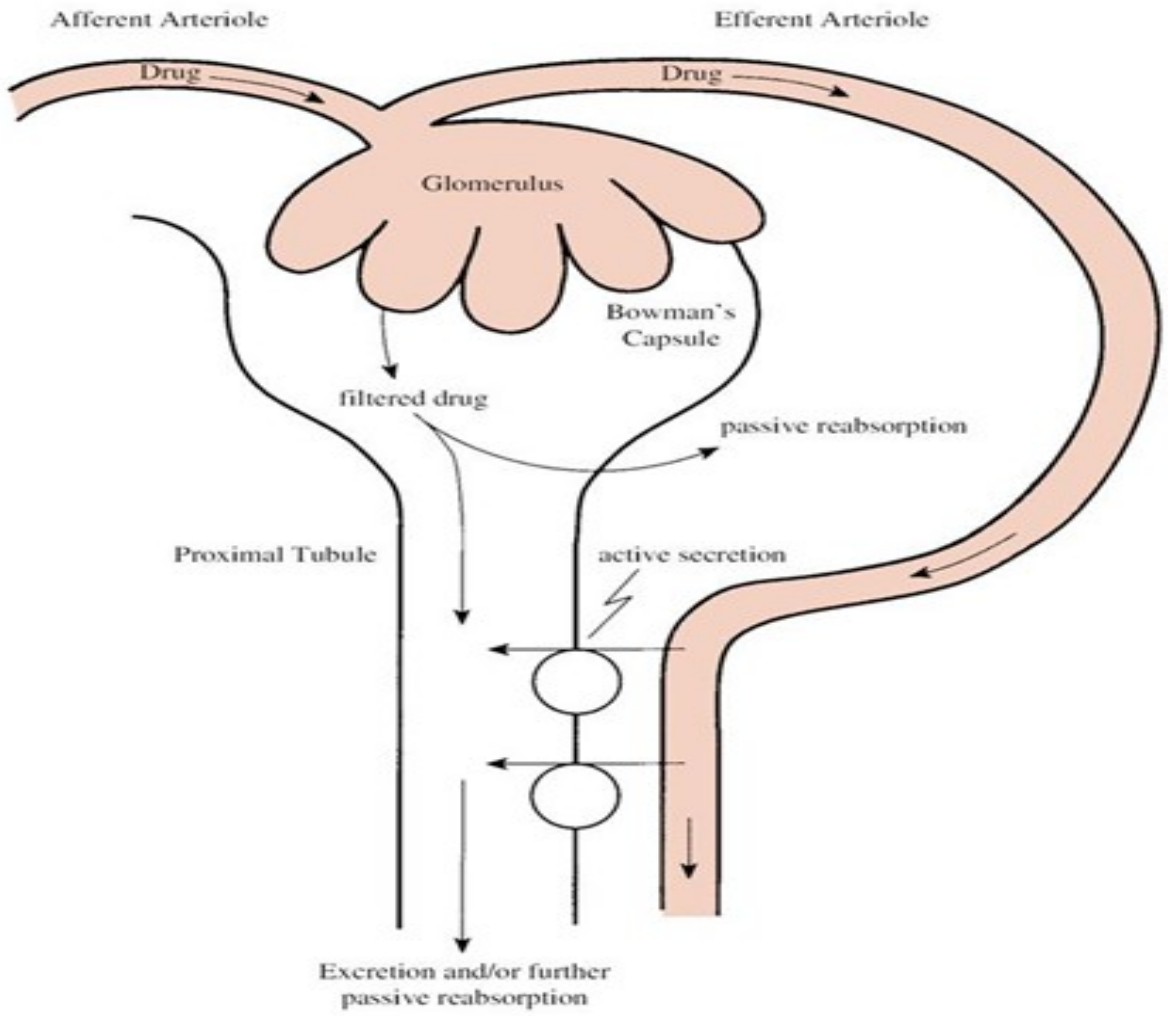
- Genetic polymorphism
- Disease conditions especially of the major drug metabolizing sites.
- Age
- Predisposing factors to enzyme induction or inhibition.

Excretion

- Drug excretion is the elimination (passage out) of a systemically absorbed drug from the body in the form of metabolites or unchanged drug.
- The kidneys are the main organ of excretion of drugs and their metabolites.
- Other routes of drug elimination:
  - lungs: for volatile substances
  - Sweat: for volatile oils
  - Bile and colon (for conjugated large molecular weight drug or metabolite)
  - Saliva
  - tears

Renal Excretion (water soluble substances)

- Renal excretion?
  - Principal organ for most drug removal especially for water soluble and non volatile drug
  - Excretion of drug through kidney involve 3 steps
    - Glomerular filtration
    - Tubular secretion
    - Tubular reabsorption


Afferent Arteriole
Efferent Arteriole
Drug
Drug
Glomerulus
Bowman's Capsule
filtered drug
passive reabsorption
Proximal Tubule
active secretion
Excretion and/or further passive reabsorption

Dosage forms of drugs

- A dosage form of a drug is the form of preparation designed for administration to the body for the purpose of diagnosis, prophylaxis and treatment.
- After development of a specific chemical entity for its pharmacological effects, it is formulated in a form that is suitable for administration and even efficacy and for the stability of the drug itself.
- There are different dosage form designs intended for the various routes of administration.

Solid dosage forms

- Tablets:
  - tablets are solid dosage forms containing the active ingredient with or without suitable diluents
  - They may be coated or uncoated.
  - Coating is intended to mask the contents of the tablet
    - Enteric coated: intended for intestinal medications without getting disintegrated in the stomach.
    - Non-enteric coated: intended to mask the unpleasant odour and taste of a drug.

- Capsules
  - Are solid dosage forms which the solid or liquid drug is enclosed in a hard or soft soluble gelatin shell to mask its bad taste and odour. They are intended for internal use.
- Suppositories
  - Are solid dosage forms with various sizes and shape for administration into body cavities (rectum, vagina, and urethra)
  - Rectal suppositories are conical or bullet shaped, vaginal suppositories spherical, and urethral suppositories pencil shaped.

Semi-solid dosage forms

- Syrups
  - Syrups are semi-solid, viscous, sticky preparations containing medicinal substance dissolved in a concentrated sugar solution.
- Ointments
  - Are semi-solid preparations containing the medicinal agent intended for use for application on skin or mucous membranes
- Creams
  - Creams are emulsions for external use as protective or emollients to soften and sooth.
- Pastes
  - Are semi-solid dosage forms of heavy consistency.

Liquid dosage forms

- Solutions
  - Are liquid preparations prepared by dissolving active medicinal substance in a solvent. It can be for internal or external use.
  - For internal use solutions
    - Tinctures: hydroalcoholic or alcoholic solution of vegetable material or chemical substance. They can also be used for external purpose.
    - Elixirs: hydroalcoholic preparations flavoured and sweetened with or without active substance.
    - Injectables

- Injectables are sterile preparations for Parenteral route. They may be labeled as
  - “for injection”: a sterile powder prepacked in a vial which on the addition of a suitable vehicle forms a clear solution.
  - “injection”: a ready made sterile liquid preparation in an ampoule or vial.
  - “sterile suspension”: a ready made suspension for parenteral uses, but not for intravenous or intrathecal injection.
  - “sterile for suspension”: a sterile powder prepacked in a vial which on addition of a sterile vehicle is made into a suspension for Parenteral uses, but not for intravenous or intrathecal injection.

- For external use solutions
  - **Drops**: are aqueous preparations intended for topical administration to the nose, throat, eye or ear. Eye drops should be clear and sterile aqueous solutions, adjusted to a suitable pH and osmotic pressure.
  - **Gargles:** are aqueous solution used to treat disease of the pharynx or nasopharynx and as deodorant or antiseptic.
  - Enemas: are aqueous solutions to be placed in the rectum to evacuate the bowel or to bring about local or systemic therapeutic action.

- Suspensions
  - Suspensions are preparations containing drugs, uniformly dispersed with the help of a dispersing agent. Every suspension should have a label “shake well before use”
  - Suspensions include
    - Emulsions: preparations consisting of two non-miscible liquids, with an emulsifying agent. They may be used for both internal and external use.
    - Mixtures: preparation of any solid material suspended in a liquid, and intended for internal use.
    - Lotion: an aqueous suspension to be applied without friction, for soothing, cleansing or antiseptic action on the skin.

Dosage regimen

- Dosage regimen is a systematic way of drug administration. There are two types: constant and variant dosing
- Constant dosing is employed only for safe and affordable drugs
- Variant dosing includes
  - **A loading dose** in one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. It is desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half lives) is long relative to the temporal demands of the condition being treated.

- **Maintenance dose**: is a dose administered to maintain the target concentration of a drug. The amount is equivalent to daily excreted dose.