**INTRODUCTION. THE CONCEPT OF GENERAL PHARMACOLOGY.**

**PHARMACOKINETICS AND PHARMACODYNAMICS.**

Pharmacology is the study of the therapeutic value and/or potential toxicity of chemical agents on biological systems.

It targets every aspect of the mechanisms for the chemical actions of both traditional and novel therapeutic agents.

Two important and interrelated areas: pharmacodynamic and pharmacokinetics.

1. Pharmacodynamic (what drug does with the body) are the study of the molecular, biochemical, and physiological effects of drugs on cellular systems and their mechanisms of action.
2. Pharmacokinetics (what body does with the drug) deals with the absorption, distribution, and excretion of drugs.

**Pharmacodynamic**

The effect of the drug on the body. Pharmacodynamics is the study of the relationship of drug concentration and the biologic effect (physiological or biochemical).

For most drugs, it is necessary to know the site of action and mechanism of action at the level of the organ, functional system, or tissue. For example, the drug effect may be localized to the brain, the neuromuscular junction, the heart, the kidney, etc. Often the mechanism of action can be described in biochemical or molecular terms. Most drugs exert effects on several organs or tissues, and have unwanted as well as therapeutic effects. There is a dose-response relationship for wanted and unwanted (toxic) effects.

Patient factors affect drug responses – age, weight, sex, diet, race, genetic factors, disease states, trauma, concurrent drugs, etc.

**Pharmacokinetics**

The effect of the body on the drug. To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Thus, it is important to know the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.

1. *Absorption* (oral or parenteral):

A drug must be absorbed and achieve adequate concentration at its site of action in order to produce its biological effects. Thus, when a drug is applied to a body surface (e.g., GI tract, skin, etc.), its rate of absorption will determine the time for its maximal concentration in plasma and at the receptor to produce its peak effect.

2. *Distribution*: The blood, total body water, extracellular, lymphatic and cerebrospinal fluids are involved in drug movement throughout the body. Depending upon its chemical and physical properties, the drug may be bound to plasma proteins or dissolved in body fat, delaying its progress to its sites of action or excretory mechanism.

3. *Metabolism*: This is how certain drugs are handled by the body in preparation for their elimination and includes the fate of drugs – biotransformation (e.g., hydrolysis, conjugation, oxidation-reduction).

4. *Excretion*: The kidney is the most important organ for drug excretion but the liver, lung and skin are also involved in drug elimination. Drugs excreted in feces are mostly derived from unabsorbed, orally ingested drugs or from metabolites excreted in the bile and not reabsorbed by the intestine. The physical and chemical properties, especially the degree of ionization of the drug, are important in the rate of excretion.

5. *Indications and Therapeutic Uses*: Emphasis is placed on the therapeutic use of drugs for the treatment of disease in clinical pharmacology, internal medicine and therapeutics. There are specific clinic disorders or disease entities for which a given drug may be prescribed and the physician must weigh the potential benefit of drug use against the risks of adverse effects.

6. Contraindications and Factors (e.g., liver disease) May Modify Drug Action: Where detoxification of the drug by the liver is important. It is important to know that the presence of disease or organ pathology may influence the actions of a drug. Conditions such as age, pregnancy, concomitant administration of other drugs and disease may alter the patient's response to a given drug.

7. Bioavailability: The fraction of drug administered which is actually absorbed and reaches the systemic circulation following oral dosing. Preparations of the same drug by different manufacturers may have a different bioavailability.

8. Prescription writing: It is important that the physician write clear, error-free directions for the drug provider (pharmacist) and for the patient. Physicians must guard against prescribing too many drugs, or preparations of little value. Drugs of unproven clinical value should be avoided, as well as potentially toxic agents if drugs equally effective but less dangerous are available. Risk-benefit and cost-benefit should be considered. Drugs may be prescribed by generic name, since often a less expensive drug product can be obtained in this way. A particular manufacturer may be specified if the physician has reason to believe a better or more reliable preparation is available from that manufacturer.

**ROUTES OF ADMINISTRATION**

A. Enteral

Enteral administration {administering a drug by mouth) is the most common, convenient, and economical method of drug administration. The drug may be swallowed, allowing oral delivery, or it may be placed under the tongue {sublingual) or between the gums and cheek {buccal), facilitating direct absorption into the bloodstream.

1. Oral: Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

a. Enteric-coated preparations: An enteric coating is a chemical envelope that protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs {for example, omeprazole) that are acid labile, and for drugs that are irritating to the stomach, such as aspirin.

b. Extended-release preparations: Extended-release {abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral morphine is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

2. Sublingual/buccal: The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal {GI) environment, and avoidance of first-pass metabolism {see discussion of first-pass metabolism below).

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, heparin) or unstable in the GI tract (for example, insulin). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fear, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, subcutaneous, and intradermal.

1. Intravenous (IV): IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker rocuronium. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

2. Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

3. Subcutaneous (SC): Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur.

4. Intradermal (ID): The ID route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route.

C. Other

1. Oral inhalation and nasal preparations: Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. Intrathecal/intraventricular: The blood-brain barrier typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid.

3. Topical: Topical application is used when a local effect of the drug is desired.

4. Transdermal: This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch. The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application, as well as the lipid solubility of the drug.

5. Rectal: Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.

**DRUG ABSORPTION**

A. Biologic Factors

1. Membrane structure and function

The cell membrane is a semipermeable lipoid sieve containing numerous aqueous channels, as well as a variety of specialized carrier molecules.

a. For most tissues, passive aqueous diffusion through channels occurs only for molecules less than 150-200 MW. A notable exception is the endothelial capillary lining, whose relatively large pores allow molecules of 20-30,000 to pass. However, the capillaries of most of the brain lack these large pores.

b. Passive lipid diffusion is probably the most important absorptive mechanism. Lipid-soluble drugs dissolve in the membrane, and are driven through by a concentration gradient across the membrane.

c. Carrier-mediated facilitated transport occurs for some drugs, particularly those which are analogs of endogenous compounds for which there already exist specific membrane carrier systems. For example, methotrexate, an anticancer drug which is structurally similar to folic acid, is actively transported by the folate membrane transport system.

2. Local blood flow is a strong determinant of the rate of absorption because it continuously maintains the concentration gradient necessary for passive diffusion to occur. For orally administered drugs, remember that the blood supply draining the gut passes through the liver before reaching the systemic circulation. Since the liver is a major site of drug metabolism, this first-pass effect may reduce the amount of drug reaching the target tissue. In some cases, the first-pass effect results in metabolic activation of an inert pro-drug.

3. Gastric emptying times vary among patients and contribute significantly to intersubject variability in drug absorption.

4. Drug binding

Many drugs will bind strongly to proteins in the blood or to food substances in the gut. Binding to plasma proteins will increase the rate of passive absorption by maintaining the concentration gradient of free drug. For many drugs, the gastrointestinal absorption rate, but not the extent of absorption, is reduced by the presence of food in the gut. Some drugs are not affected by food, while the absorption of a third group of drugs is enhanced by food (bile secretion by liver in response to food in GI tract increases drug absorption). Some drugs are irritating and should be administered with meals to reduce adverse effects.

B. Physicochemical Factors: pH Partition Theory

1. Background review

The simplest definition of an acid is that it is a substance, charged or uncharged, that liberates hydrogen ions (H+) in solution. A base is a substance that can bind H+ and remove them from solution. Strong acids, strong bases, as well as strong electrolytes are essentially completely ionized in aqueous solution. Weak acids and weak bases are only partially ionized in aqueous solution and yield a mixture of the undissociated compound and ions.

Ion trapping

The influence of pH on transfer of drugs across membranes.

Most drugs are too large to pass through membrane channels and must diffuse through the lipid portion of the cell membrane. Nonionized drug molecules are readily lipid-soluble, while ionized molecules are lipophobic and are insoluble.

The distribution of a drug across the cell membrane is usually determined by its pKa and the pHs on both sides of a membrane. The difference of pH across a membrane influences the total concentration of drug on either side, since, by diffusion, at equilibrium the concentration of nonionized drug will be the same on either side.

For example, let's consider the influence of pH on the distribution of a drug which is a weak acid (pKa = 4.4) between plasma (pH = 7.4) and gastric juice (pH = 1.4). The mucosa can be considered to be a simple lipid barrier.

**DRUG DISTRIBUTION**

Once in the blood, drugs are simultaneously distributed throughout the body and eliminated. Typically, distribution is much more rapid than elimination, is accomplished via the circulation, and is influenced by regional blood flow.

A. Compartments

1. Central Compartment

The central compartment includes the well-perfused organs and tissues (heart, blood, liver, brain and kidney) with which drug equilibrates rapidly.

2. Peripheral Compartment(s)

The peripheral compartment(s) include(s) those organs (e.g., adipose and skeletal muscle) which are less well-perfused, and with which drug therefore equilibrates more slowly. Redistribution from one compartment to another often alters the duration of effect at the target tissue. For example, thiopental, a highly lipid-soluble drug, induces anesthesia within seconds because of rapid equilibration between blood and brain. Despite the fact that the drug is slowly metabolized, however, the duration of anesthesia is short because of drug redistribution into adipose tissue, which can act as a storage site, or drug reservoir.

3. Special Compartments

Several special compartments deserve mention. Entry of drug into the cerebrospinal fluid (CSF) and central nervous system (CNS) is restricted by the structure of the capillaries and pericapillary glial cells (the choroid plexus is an exception). The blood-brain barrier limits the success of antibiotics, anticancer drugs and other agents used to treat CNS diseases. Drugs also have relatively poor access to pericardial fluid, bronchial secretions and fluid in the middle ear, thus making the treatment of infections in these regions difficult.

B. Protein Binding

Many drugs bind to plasma proteins. Weak acids and neutral drugs bind particularly to albumin, while basic drugs tend to bind to α-1-acid glycoprotein (orosomucoid). Some drugs even bind to red cell surface proteins.

1. Effects on drug distribution

Only that fraction of the plasma drug concentration which is freely circulating (i.e., unbound) can penetrate cell membranes. Protein binding thus decreases the net transfer of drug across membranes. Drug binding to plasma proteins is generally weak and rapidly reversible, however, so that protein-bound drug can be considered to be in a temporary storage compartment. The protein concentration of extravascular fluids (e.g., CSF, lymph, synovial fluid) is very low. Thus, at equilibrium (when the concentrations of free drug are equal), the total drug concentration in plasma is usually higher than that in extravascular fluid. The extent of protein binding must be considered in interpreting "blood levels" of drugs.

2. Effects on drug elimination

The effects of plasma protein binding on drug elimination are complex. For drugs excreted only by renal glomerular filtration, protein binding decreases the rate of elimination since only the free drug is filtered. For example, the rates of renal excretion of several tetracyclines are inversely related to their extent of plasma protein binding. Conversely, however, if drug is eliminated by hepatic metabolism or renal tubular secretion, plasma protein binding may promote drug elimination by increasing the rate that that drug is presented for elimination.

3. Tissue binding Binding to tissue proteins may cause local concentration of drug. For example, if a drug is bound more extensively at intracellular than at extracellular sites, the intracellular and extracellular concentrations of free drug may be equal or nearly so, but the total intracellular drug concentration may be much greater than the total extracellular concentration.

C. Apparent volume of distribution (AVD or Vd).

The volume of distribution, or more properly the apparent volume of distribution, is calculated from measurements of the total concentration of drug in the blood compartment after a single IV injection. Suppose that we injected someone IV with 100 mg of a drug, and measured the blood concentration of the drug repeatedly during the next several hours.

If the drug is assumed to follow two-compartment kinetics, the initial curvilinear portion of the data reflects the drug distribution phase, with drug moving from the blood into tissues. The linear portion of the curve reflects drug elimination. By extrapolation of the linear portion, we can find the blood concentration at time 0, had mixing between both compartments been instantaneous; it is 10 mg/ml. We can also calculate Vd, which is defined as:

$$Vd=\frac{amount of drug injected}{blood concentration at time 0}=\frac{100 mg}{10 mg/L}=10L$$

Vd does not represent a real volume, but rather indicates the size of the pool of body fluids that would be required if the drug were distributed equally throughout the body. Drug concentrations in body compartments will vary according to the physicochemical properties of the drug. Thus, Vd is a characteristic property of the drug rather than the patient, although disease states may influence Vd. If binding to plasma proteins is marked, most of the drug will be maintained within the intravascular compartment and Vd will be small. If there is extravascular binding, or storage in fat or other tissues, Vd will be large. For example, digoxin, a hydrophobic drug which distributes into fat and muscle, has a Vd of 640 liters (in a 70 kg man), approximately nine times the total volume of the man! The usefulness of the Vd concept will become more apparent when we discuss pharmacokinetics and perform calculations of blood levels of drugs. In general, acidic drugs bind to plasma proteins and have small Vds, while basic drugs tend to bind more

extensively to extravascular sites and have larger Vds. Vd may be influenced by disease states. For example, patients with chronic liver disease have lower serum albumin concentrations. Plasma protein binding will be reduced, leading to lower plasma drug concentrations and higher Vds.

**DRUG BIOTRANSFORMATION**

The body is exposed to a wide variety of foreign compounds, called xenobiotics. Exposure to some such compounds is unintentional (e.g., environmental or food substances), while others are deliberately used as drugs. The following discussion of drug biotransformation is applicable to all xenobiotics and to some endogenous compounds (e.g., steroids) as well.

The kidneys are capable of eliminating drugs which are low in molecular weight, or which are polar and fully ionized at physiologic pH. Most drugs do not fit these criteria, but rather are large, unionized or partially ionized, lipophilic molecules. The general goal of drug metabolism is to transform such compounds into more polar (i.e., more readily excretable) water-soluble products. For example, were it not for biotransformation to more water-soluble products, thiopental, a short-acting, lipophilic anesthetic, would have a half-life of more than 100 years! Imagine, without biotransformation reactions, anesthesiologists might grow old waiting for patients to wake up.

Most products of drug metabolism are less active than the parent compound. In some cases, however, metabolites may be responsible for toxic, mutagenic, teratogenic or carcinogenic effects. For example, overdoses of acetaminophen owe their hepatotoxicity to a minor metabolite, which reacts with liver proteins. In some cases, with metabolism of so-called prodrugs, metabolites are actually the active therapeutic compounds. The best example of a prodrug is cyclophosphamide, an inert compound that is metabolized by the liver into a highly active anticancer drug.

A. Sites of drug metabolism

1. At the organ level

The liver is the primary organ of drug metabolism. The gastrointestinal tract is the most important extrahepatic site. Some orally administered drugs (e.g., isoproterenol) are conjugated extensively in the intestinal epithelium, resulting in decreased bioavailability. The lung, kidney, intestine, skin and placenta can also carry out drug metabolizing reactions. Because of its enormous perfusion rate and its anatomic location with regard to the circulatory system, the lungs may exert a first-pass effect for drugs administered IV.

2. At the cellular level

Most enzymes involved in drug metabolism are located within the lipophilic membranes of the smooth endoplasmic reticulum (SER). When the SER is isolated in the laboratory by tissue homogenation and centrifugation, the SER membranes re-form into vesicles called microsomes. Since most of the enzymes carry out oxidation reactions, this SER complex is referred to as the microsomal mixed function oxidase (MFO) system.

3. At the biochemical level

Phase I reactions refer to those which convert a drug to a more polar compound by introducing or unmasking polar functional groups such as - OH, -NH2, or -SH. Some Phase I products are still not eliminated rapidly, and hence undergo Phase II reactions involving conjugation of the newly established polar group with endogenous compounds such as glucuronic acid, sulfuric acid, acetic acid, or amino acids (typically glycine). Glucuronide formation is the most common phase II reaction. Sometimes, 29 the parent drug may undergo phase II conjugation directly. In some cases, a drug may undergo a series of consecutive reactions resulting in the formation of dozens of metabolites.

Most phase I MFO biotransformation reactions are oxidative in nature and require a reducing agent (NADPH), molecular oxygen, and a complex of microsomal enzymes; the terminal oxidizing enzyme is called cytochrome P450, a hemoprotein so named because its carbon monoxide derivative absorbs light at 450 nm. We now know that cytochrome P450 is actually a family of enzymes which differ primarily with regard to their substrate specificities. Advances in molecular biology have led to the identification of more than 70 distinct P450 genes in various species.

The nomenclature of the P450 reductase gene products has become complex. Based upon their amino acid homologies, the P450 reductases have been grouped into families such that a cytochrome P450 from one family exhibits < 40% amino acid sequence identity to a cytochrome P450 in another gene family. Several of the gene families are further divided into subfamilies, denoted by letters A, B, C, etc.

B. Enzyme Induction

An interesting and important feature of the cytochrome P450 mixed function oxidase system is the ability of some xenobiotics to induce the synthesis of new enzyme. Microsomal enzyme induction is a complex and poorly understood process associated with an increase in liver weight, proliferation of the SER, and synthesis of P450 enzymes. For example, phenobarbital induces the P450IIB subfamily, while polycyclic aromatic hydrocarbons (e.g., found in cigarette smoke or charcoal broiled foods) induce the P450IA subfamily; these and other inducers are listed in Table 1, above. Obviously, the dose and frequency of drug administration required to achieve therapeutic drug concentrations in blood may vary enormously from person to person, depending upon the degree of exposure to microsomal inducers.

For example, consider patients who routinely ingest barbiturates or tranquilizers (P450 inducers) who must, for medical reasons, be treated with warfarin or dicumarol (oral anticoagulants). Because of a faster rate of drug metabolism, the dose of warfarin will need to be high. If the patient should for some reason discontinue the barbiturates, the blood level of warfarin will rise, perhaps leading to a bleeding disorder.

C. Enzyme Inhibition

Relatively few xenobiotics are known to inhibit microsomal enzymes. Some drugs are used therapeutically because they inhibit specific enzyme systems (e.g., monoamine oxidase inhibitors for depression, xanthine oxidase inhibitors for gout, etc.). Sometimes such drugs are not totally specific and inhibit other enzyme systems to some extent. However, cimetidine, a widely used anti-ulcer drug, is an important, potent inhibitor of microsomal drug metabolism which retards the metabolism of many other drugs, including warfarin and similar anticoagulants, theophylline and caffeine, phenobarbital, phenytoin, carbamazepine, propranolol, diazepam, and chlordiazepoxide. Other inhibitors are erythromycin and ketonazole. You will encounter these drugs later in the course. Grapefruit juice also inhibits CYP P450.

**DRUG ELIMINATION**

The kidney is the most important organ for the excretion of drugs and/or their metabolites. Some compounds are also excreted via bile, sweat, saliva, exhaled air, or milk, the latter a possible source of unwanted exposure in nursing infants. Drug excretion may involve one or more of the following processes.

A. Renal Glomerular Filtration

Glomeruli permit the passage of most drug molecules, but restrict the passage of protein-bound drugs. Changes in glomerular filtration rate affect the rate of elimination of drugs, which are primarily eliminated by filtration (e.g., digoxin, kanamycin).

B. Renal Tubular Secretion

The kidney can actively transport some drugs (e.g., dicloxacillin) against a concentration gradient, even if the drugs are protein-bound. (Actually, only free drug is transported, but the protein-drug complex rapidly dissociates.) A drug called probenecid competitively inhibits the tubular secretion of the penicillins, and may be used clinically to prolong the duration of effect of the penicillins.

C. Renal Tubular Reabsorption

Many drugs are passively reabsorbed in the distal renal tubules. Reabsorption is influenced by the same physicochemical factors that influence gastrointestinal absorption: nonionized, lipid-soluble drugs are extensively reabsorbed into 33 plasma, while ionized and polar molecules will remain in the renal filtrate and be excreted via urine. Thus, as in the gut, urine pH plays an important role, as does urine volume. Urine pH may vary widely from 4.5 to 8.0, may be influenced by diet, exercise, or disease, and tends to be lower during the day than at night. It is sometimes clinically useful, particularly in drug overdose cases, to alter the pH of the urine (of the patient). For drugs, which are weak acids, urine alkalinization favors the ionized form and promotes excretion. Alternatively, acidification promotes the renal clearance of weak bases.

D. Biliary Excretion

Comparatively little is known about hepatic drug elimination. Many drugs and metabolites are passed into the small intestine via bile and may undergo enterohepatic cycling. Recent studies have attempted to interrupt enterohepatic cycling of drugs, pesticides and heavy metals through the oral administration of non-absorbable, nonspecific adsorbents such as charcoal or cholestyramine. The results, generally a decrease in drug half-life, have been surprising in that they suggest that many more drugs undergo enterohepatic cycling than previously suspected.

Pharmacodynamics is how the drugs acts on the body. More the amount of drug the more intense is the drug action. The mode of action of the drug is the action at the cellular or molecular level. The therapeutic action is the end result of the drug action.

**A. Drug – Receptor Action**

A receptor is what the drug binds to, to cause a reaction or effect. If the drug fits exactly into the receptor then an excellent drug response results. It is these receptors that are responsible for the normal functioning of the body.

The enzyme converts the substrate into a product without interference. If a competitive drug is present then it will compete with the substrate for the active center of the enzyme. If the drug binds then it will not allow the substrate to bind, then the drug leaves the active center and this allows another drug molecule to bind or the substrate. In this case the enzyme is still active and enzyme action is much slower. E.g. Sulphonamides which are look alike of 4 benzoic acid used in the synthesis of folic acid.

In the case a non–competitive drug binds to the enzyme it will block any further activity. It causes a change in the 3D shape of the enzyme as the drug could have been bound to the remote site instead of the active site, since the shape of the enzyme would have changed it prevents any binding of the substrate.e.g. asprin or some MAOI Drugs that bind to a receptor and produce a biochemical or physiological change in the cell are called agonists, they mimic the substance in our body that would have actually bound to the receptor. E.g. Insulin.

Drugs that bind to a receptor but do not produce a biochemical or physiological change are called antagonist. These drugs block or stop what normally binds to a receptor. E.g. Narcan, as an antidote to a narcotic overdose. On binding to the receptor it does not produce a physiological response and does not allow morphine or heroin to bind to the receptor to stimulate a physiological response.

The receptor site can be a part of the cell and on the surface of the cell Or it can be within the cell (Intracellular), or it could even just be floating in the blood (like the coagulation enzymes).

Receptor is usually a protein. Partial agonists: when a transmitter binds to a receptor, bonding occurs between the drug and the receptor. There has to be complete congruity between the drug and the receptor for the reaction to proceed. This is known as a receptor fit. Some drugs do not fit exactly on the receptor and hence they stimulate a response but not as much as the natural receptor fit and this is termed as a partial agonist.

**Agonist and Antagonist Drugs**

Some drugs act as both agonist to one receptor and antagonist to another receptor. E.g. pentazocine which is a narcotic opioid. It will bind to one receptor and displace morphine and bind to other receptor associated with pain and produce an agonist effect by stimulating them.

**Drug Receptors**

1. Membrane solubility allows lipid soluble drugs to cross the cell membrane and bind to intracellular receptors e.g. NSAIDS, NRTI ( nucleotide analogue reverse transcriptase inhibitor) MAOI
2. Transmembrane proteins bind the drug at the extracellular site and binding activates an intracellular enzyme site e.g. Insulin
3. Transmembrane protein is linked to an enzyme via a G – protein e.g. Opioid drugs
4. The receptor is a transmembrane ion channel. E.g. Calcium channel blocker. The receptor can be located at several places in the body and this is what leads to producing side effects.

**B. Direct Physiological Action**

1.Chemical reaction: drugs work by simple chemical reactions. E.g. antacids, chelating agents.

2.Physical action: by some kind of physical mechanism e.g. osmosis, flatulence.

## Drug Interaction

A drug interaction is the phenomenon in which a substance or an external circumstance affects the action of the drug.

Interactions outside the body such as sunlight, moisture, reaction with the so called inert filler material, reaction with the containers, or mixing of a drug in a syringe can cause a so called chemical reaction and lead to decreased drug action.

Within the body, the drug may undergo interactions with many factors such as:

**Interaction in the Gastrointestinal Tract**

The amount of drug absorbed from the gastrointestinal (GI) tract determines the blood plasma level of the drug better known as bioavailability. If the bioavailability is reduced it will lead to the fact that the drug cannot achieve its mec and as a result there will be decreased therapeutic effect. Sometimes the converse is also true. E.g. tetracycline taken with calcium compounds has decreased bioavailability. Iron is better absorbed as ferrous then ferric and hence should be taken with an antioxidant like vit C. Some drugs prevent the absorption of other fat soluble vitamins leading to a deficiency. There can also be interaction between the drug and food which may not be favorable.

**Interactions after Absorption**

Usually occurs when drugs are administered concurrently. Many of these interactions between the drugs and the enzyme of the liver can alter the amount of time the drug is present in the system.

Some drug interactions can prove to be beneficial and is known as synergism : two types: additional or summation and potentiation.

Liver enzyme and drug interaction: Inside the liver cells there are vesicles called microsomes which contain the relevant enzyme for metabolism. Cytochrome P450 has many isoforms. An isoform is when there is the same enzyme with a small change in its structure which makes it have different substrate specificity.

**Drug–Drug Interaction**

Drug A can intensify the effect of drug B = Potentiation = increased therapeutic effect or an increase in the adverse reaction.

Drug A inhibits the effect of drug B = Inhibitoy = reduced therapeutic effect or reduced adverse reaction.

**Food Drug interaction**

A drug molecule can interact with food ingested at the same time. This can decrease the rate of absorption, or even increase drug toxicity. Timing of administration of drug with food is often important. For e.g. tetracycline gets inactivated with calcium and therefore it is advisable not to take tetracycline with calcium-rich foods such as milk.

**Affinity, Specificity, Efficacy, Potency**

***Affinity:*** is defined as the extent of binding of a drug to a receptor, the greater the affinity the more the binding and consequently more the action

***Specificity:*** defined as the ability of the drug to produce an action at the specific site

***Efficacy:***is the ability of the drug to produce an effect at the receptor

***Potency:*** is defined as the relative amount of drug that has to be present to produce a desired effect. The more potent a drug the lesser it has to be administered.

## Factors Affecting Drug Response

1. Age: either very young or very old may not be able to process the drug efficiently.
2. Gender: different body compositions and the amt of fat to lean tissue can influence the action of drugs as well as its passage through the body.
3. Body weight: Increased body weight might lead to an increased amount of drug that needs to be taken to achieve the same response.
4. Body surface area: determined by the use of a nomogram.
5. Basal Metabolic rate: high BMR: rapid metabolism and elimination of the drug.
6. Genetic factors: differences in the genetic composition of the different patients. E.g. fast and slow acetylators.
7. Placebo effect: Placebo = dosage that contains no pharmacologicaly active ingredient. Placebo effect = effect elicited by administration of virtually any drug whether it is pharmacologically active or not.
8. Tolerance
9. Pathological status : disease. GI Tract illness will affect oral medicines whereas parental absorption of drugs can be affected by a circulatory shock, peripheral vascular illness and cardiac failure.
10. Drug interaction. Different drug interaction may affect the absorption, metabolism, distribution and elimination of the drug.
11. Habits
12. Effects of exercise.
13. Effects of diet: food in the gut will prove to be competition for the drug and hence the amount of drug would actually be lowered. Lipid soluble drugs are less affected as compared to water soluble drugs. The activity of the microsomal enzyme cytochrome P450 depends on the amount of minerals and vitamins present. It needs vitamins A, B1 and B2 , essential fatty acids, proteins and minerals like copper, zinc and calcium for proper functioning. If there is an imbalance in any of the above there is an imbalance in the activity of the enzyme.
14. Effects of pregnancy.