# PHARMACOKINETICS

## The Absorption, Distribution, and Excretion of Drugs

## O B J E C T I V E S:

- Explain the meaning of the terms absorption, distribution, metabolism, and excretion.
- List two physiologic factors that can alter each of the processes of absorption, distribution, and excretion.
- Explain how bioavailability can impact drug response and product selection.
- Compare the roles of passive diffusion and carrier-mediated transport in drug absorption.
- Describe two types of drug interaction and explain how they might affect drug response and safety

## What is **ABSORPTION:**

After administration of drug accept local route the drug entered the blood circulation the total amount of drug circulation but only a part of drug reaches blood circulation Bioavailability is amount of drug entering blood circulation for intravenous injection Bioavailability is 100% for maximum effect of drug should be absorbed parental route as more Bioavailability then oral route.

# TYPES OF ABSORBTION:

1) Simple diffusion: It is also called passive diffusion as the cell membrane is not involved in the across and does not require healthy it is by direction crosses where rate of absorption dependant on concentration across the cell membrane it is simple passage of drug through cell membrane by passive diffusion. Eg. Alcohol, urea etc. and the cell is made up of lipid by layer lipid soluble un-ionised drug are readily absorbed by passive diffusion.

2)ACTIVE TRANSPORT: It is special crosses required in energy it involves combination of drug with a carrier molecule forming a complex and dissociate towards the other side carrier molecule returns to original side again combining with drug molecule and release the drug other side till complete the drug absorbed as need energy is called active transport.

3)Pinocytosis: It is seen in unicellular organism like amoeba. In this process the cell is takes up fluid from its surrounding.

# FACTOR AFFECTING RATE OF ABSORPTION:

1.Physical state of drug: liquides are better absorbed then solid and soluble drugs are more readily absorbed then insoluble drugs.

2. Partical size: smaller partical size greatter is the absorption for GIT.

3. Concentration: higher the concentration more flux occurs across the membrane. The rate is less affected than the extent of absorption

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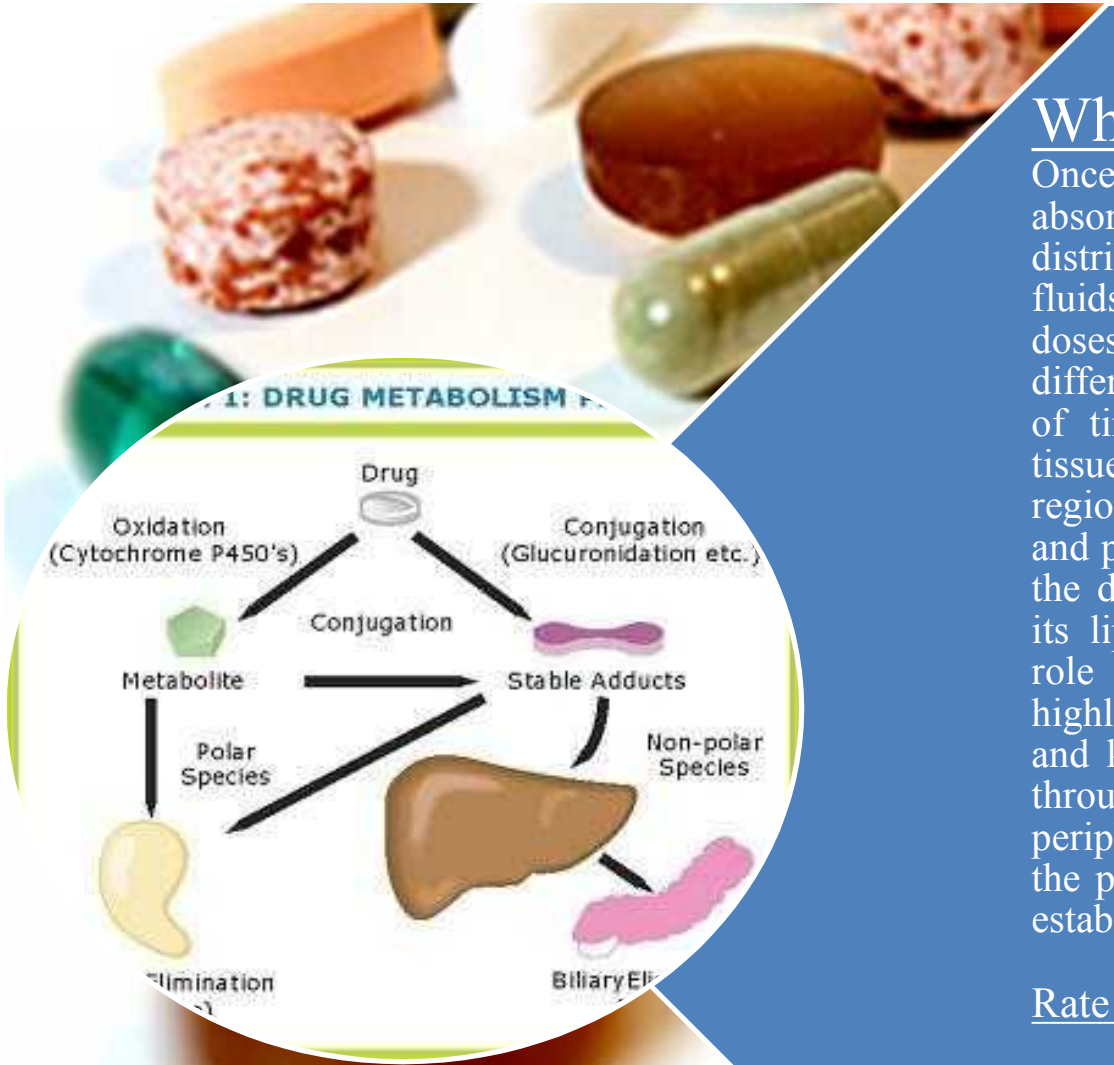
4. Area of Absorptive Surface: Area of absorptive surface affects oral as well as other routes. Most of the drugs are given orally because of the large area of absorptive surface, so that greater absorption occurs. Intestinal resection decreases the surface area leading to a decreased absorption. Similarly, when the topically acting drugs are applied on a large surface area, they are better absorbed.

5.Functioning of GIT: Increase peristalsis movement decrease rate of absorption as drug no remain in GIT for long time.

6.PH of the drug: Acidic pH favors acidic drug absorption while basic pH is better for basic drugs.

7. Formulation: When the drugs are formed, apart from the active form some inert substances are included. These are the diluents, excipients and the binders. Normally they are inert, but if they interact, they can change the bioavailability. Examples include Na+ which can interact to decrease the absorption.




# What is Distribution of drug?

Once a drug enters into systemic circulation by absorption or direct administration, it must be distributed into interstitial and intracellular fluids. Each organ or tissue can receive different doses of the drug and the drug can remain in the different organs or tissues for a varying amount of time. The distribution of a drug between tissues is dependent on vascular permeability, regional blood flow, cardiac output and perfusion rate of the tissue and the ability of the drug to bind tissue andplasma proteins and its lipid solubility. pH partition plays a major role as well. The drug is easily distributed in highly perfused organs such as the liver, heart and kidney. It is distributed in small quantities through less perfused tisses like muscle, fat and peripheral organs. The drug can be moved from the plasma to the tissue until the equilibrium is established (for unbound drug present in plasma).

Rate or metabolism of drug :

It is divided into 2 main categories:

a) Non-synthetic reaction: where the drugs undergoes oxidation reduction hydrolysis etc.
b) Synthetic reaction: In which drug combine with small molecule like glucouronic acid for combination.

# metabolism

# What is excreation of drug:

After metabolism the drug excreate the major route of excreation as :

**01) KIDNEY**: The drugs i.e. entered by kidney through glomeruler filtration tubular secretion and passive diffusion for acidic drugs media should be basic and for basic drug media should be

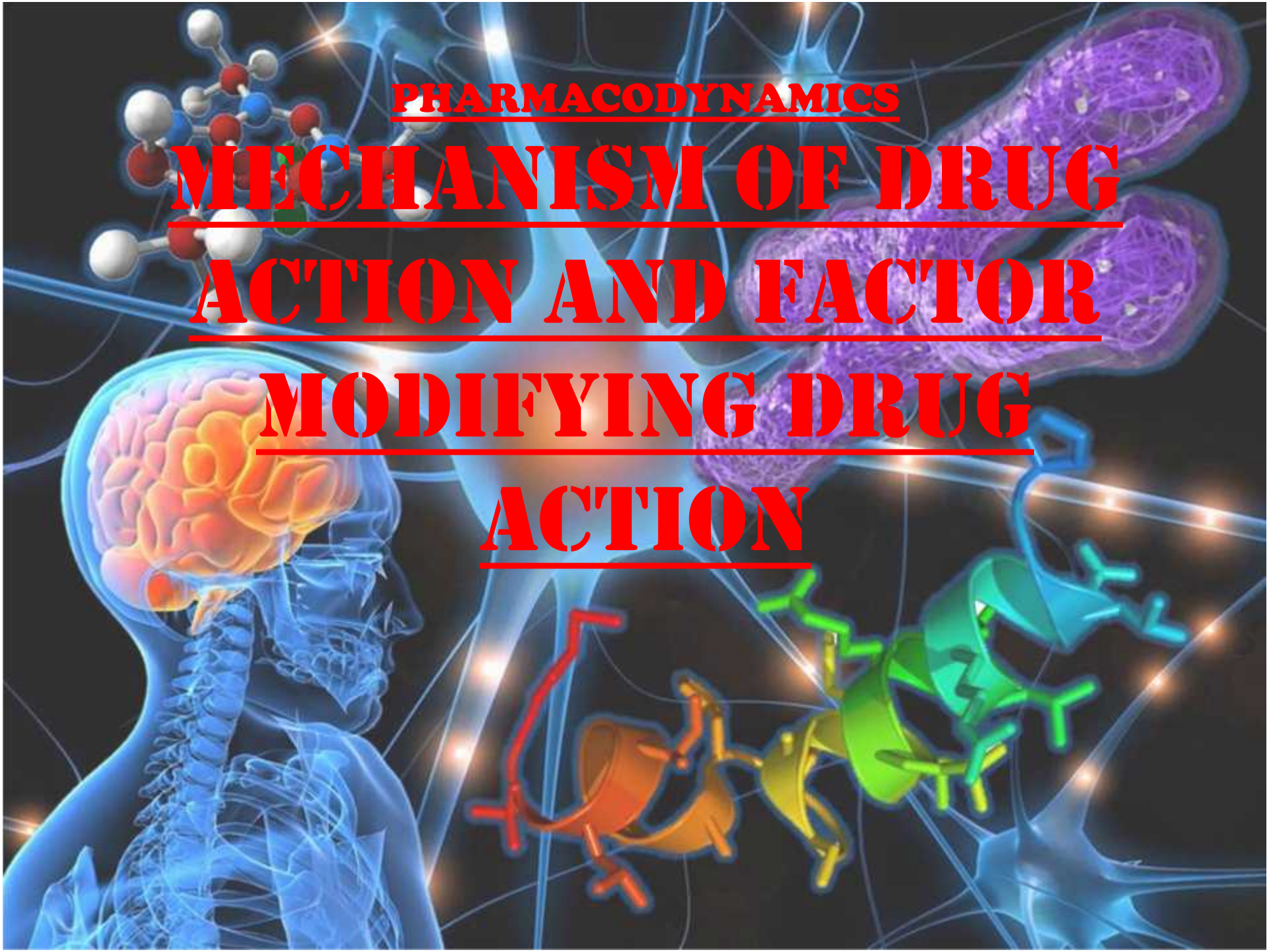
**02) LUNGS** : acidic usually gasses inhale volatile anaesthetics, volatile oil, alcohol, excreted by this route.

**03) INTESTINE**: Purgative like senna anthelmentics like heavy metal excreated by this route.

**04) SKIN**: heavy metal like arsenic lead get deposited in hair folical causing skin rashes .

**05) SALIVA AND MILK**: Antibiotics self drug and any other are excreted in milk.

**06) BILE**: Certain drugs like Erythromycin enter the enterohepatic cycle or excreted by bile the dose of such drugs is very important as the drugs is rapidly absorbed leading the toxicity.


PHARMACODYNAMICS
MECHANISM OF DRUG ACTION AND FACTOR MODIFYING DRUG ACTION

# IT IS MECHANISM OF ACTION OR ACTUAL EFFECT OF DRUG.

## Various types of drug action:

**1) Stimulation:** It is increase in activity of special cell eg. Caffein stimulates cerebral cortex

**2) Depression:** Decrease in normal activity in special cell. Eg. Depression of CNS

**3) Irritation:** drug show effect irritation of certain cell eg. Senna which is irritate purgative.

**4) Replacement:** usually when dificiency in body eg. Insulin is used in treatment of Diabetes

**5) Physical Action**: Some drug Act in pure mechanical way because of their physical properties eg. Kaolin admisnistered in dysentry for its absorption properties

**6) Chemical effect:** Some drugs show their effect because of some chemical reaction. Eg. Antacid which are bases neutralise the stomach acidic .

# Mechanism of drug action

In pharmacology the term **mechanism of action** (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor. Receptor sites have specific affinities for drugs based on the chemical structure of the drug, as well as the specific action that occurs there. Drugs that do not bind to receptors produce their corresponding therapeutic effect by simply interacting with chemical or physical properties in the body. Common examples of drugs that work in this way are antacids and laxatives.

For example, the mechanism of action of aspirin involves irreversible inhibition of the enzyme cyclooxygenase, therefore suppressing the production ofprostaglandins and thromboxanes, thereby reducing pain and inflammation. However, some drug mechanisms of action are still unknown. For example, phenytoin is used to treat symptoms of epileptic seizures, but the mechanism by which this is achieved is still unknown, despite the drug's having been in use for many years.

In comparison, a mode of action (MoA) describes functional or anatomical changes, at the cellular level, resulting from the exposure of a living organism to a substance.

# Factors Modifying Action Of Drugs:

## Various factor as follow:

### 1) Age:

The adult dose is for people between 18 and 60 years of age. The tissues of an infant & child are highly sensitive to large number of drugs. Children under 12 yrs require fraction of adult dose because:

Drug metabolizing enzyme system is inefficient in them (Glucuronidation takes 3 months to develop)

Their barriers are not fully developed (BBB, blood aqueous barrier), thus are more sensitive to CNS stimulants. All parts of the body are affected by the drug.

Infants have an immature renal tubular transport system. Penicillin, streptomycin and amino glycosides are not administered.

After one year of age, elimination by kidneys is increased.

Hepatic metabolizing capacity is also under developed. Chloramphenicol may cause grey baby syndrome.

### 2)Sex:

Testosterone increases the rate of biotransformation of drugs.

Decreased metabolism of some drugs in female (Diazepam) occurs. Females are more susceptible to autonomic drugs (estrogen inhibits choline esterase). Drugs used for ulcer may cause increased prolactin.

During menstruation, salicylates and strong purgatives should be avoided as they may increase bleeding.

### 3)Body weight:

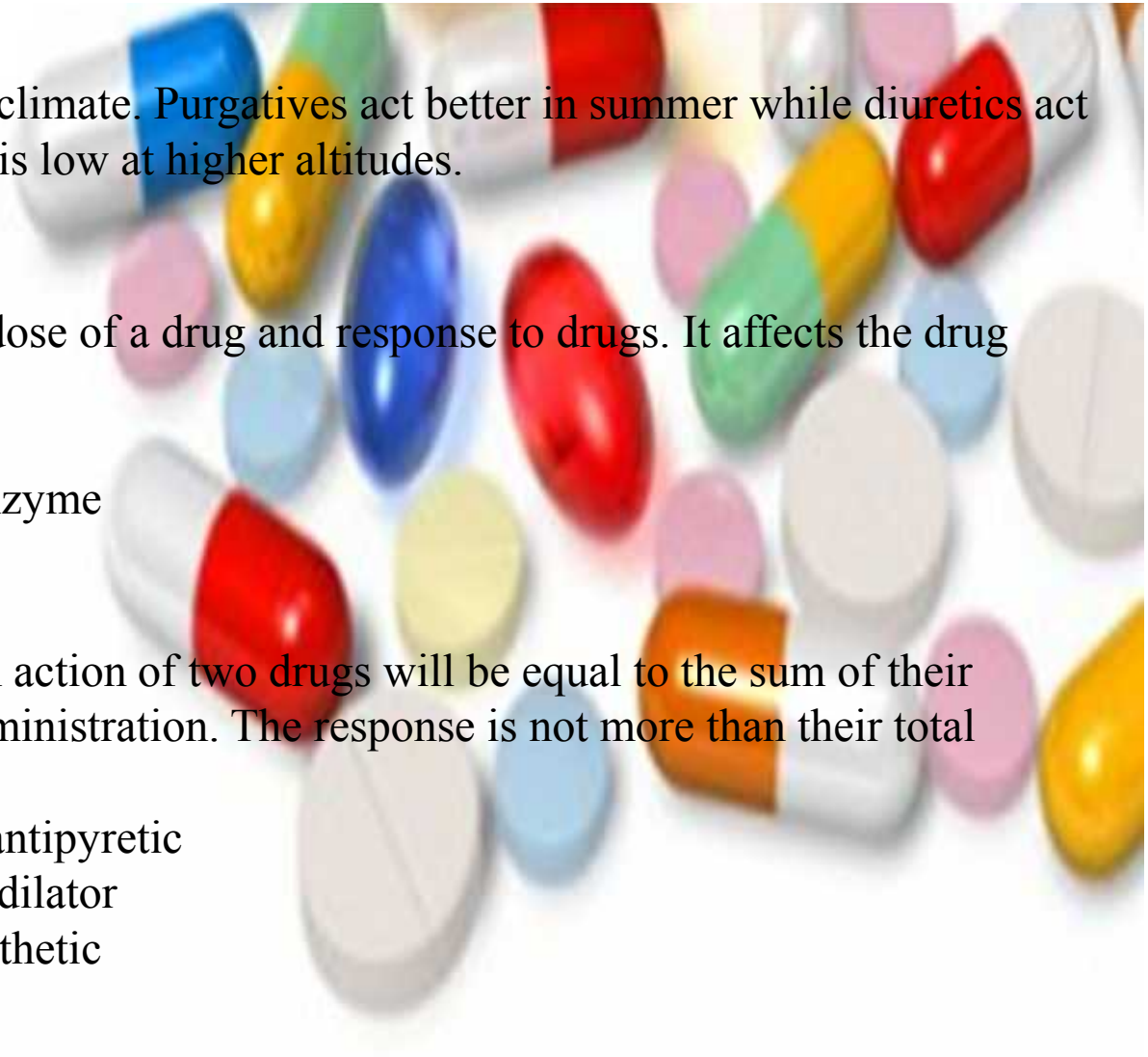
Dose is given per kg body weight. Average muscular weight is between 50 and 100 kg, with 70 kg being the average.

### 4)Route of Administration:

Some drugs are incompletely absorbed after oral intake, when given intravenously; their dose has to be reduced. Examples include morphine and magnesium sulphate. Magnesium sulphate when given orally is osmotic purgative, but its 20% solution is injected intravenously to control the convulsions in eclampsia of pregnancy.

### 5)Time of Administration:

Hypnotics (producing sleep) act better when administered at night and smaller doses are required. Amonoglycosides like streptomycin when given intravenously cause neuromuscular blockage, which is not observed after intramuscular injection.



## 6)Climate

Metabolism is low in hot and humid climate. Purgatives act better in summer while diuretics act better in winters. Oxidation of drugs is low at higher altitudes.

## 7)Genetic Factors

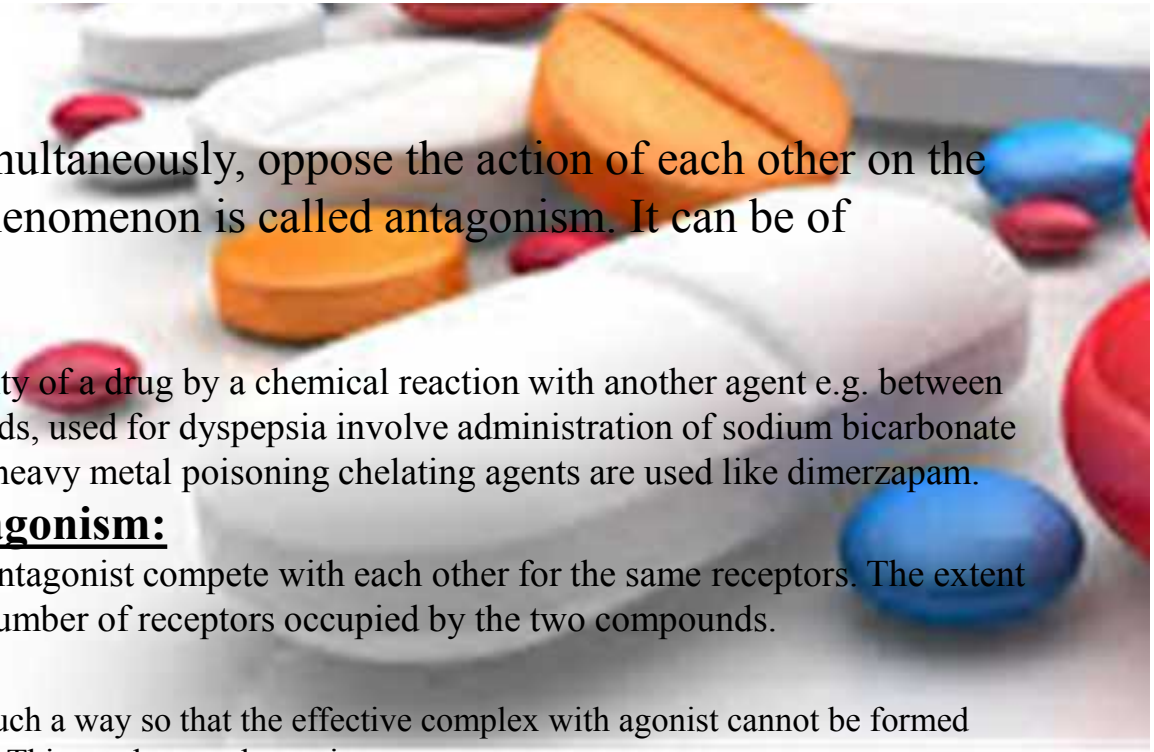
Genetic abnormalities influence the dose of a drug and response to drugs. It affects the drug response in individuals at 2 levels.
At the level of receptors
At the level of drugs metabolizing enzyme

## 8)Additive Effect

In this case the total pharmacological action of two drugs will be equal to the sum of their individual effect on simultaneous administration. The response is not more than their total algebraic sum. e.g.
Aspirin + paracetamol as analgesic/ antipyretic
Ephedrine + theophylline as bronchodilator
Nitrous oxide + ether as general anesthetic
Antihypertensive drugs
Cardiac stimulants.

## 9) Synergism

Synergism is the facilitation/potentiation of pharmacological response by concomitant use of two drugs.



## 10) Antagonism

When two drugs, administered simultaneously, oppose the action of each other on the same physiological system, the phenomenon is called antagonism. It can be of following 4 types.

## 1.Chemical antagonism:

It involves reduction of the biological activity of a drug by a chemical reaction with another agent e.g. between acids and alkalies: BAL and arsenic. Antacids, used for dyspepsia involve administration of sodium bicarbonate to react with hydrochloric acid. In cases of heavy metal poisoning chelating agents are used like dimerzapam.

## 2.Competitive or reversible antagonism:

In this type of antagonism the agonist and antagonist compete with each other for the same receptors. The extent of antagonism will depend on the relative number of receptors occupied by the two compounds.

## 3. Non competitive antagonism:

Here an antagonist inactivates the receptor in such a way so that the effective complex with agonist cannot be formed irrespective of the concentration of the agonist. This can happen by various ways:

The antagonist might combine at the same site in such a way that even higher concentration of the agonist can not displace it.

The antagonist might combine at a different site of R in such a way that agonist is unable to initiate characteristic biological response

The antagonist might itself induce a certain change in R so that the reactivity of the receptor site where agonist should interact is abolished.

## 4.Physiological antagonism:

In this interaction of two drugs, both are agonists, so they act at different receptor sites. They antagonize the action of each other because they produce opposite actions. Classical example of physiological antagonism is adrenalin and histamine. Former causes bronchodilatation while later broncho Constriction. So adrenalin is a life saving drug in anaphylaxis.

## 11)Emotional factor:

in mentally disturbed patient the drug effect can be variable even placibos are used sometimes.

## 12) Metabolic disorder:

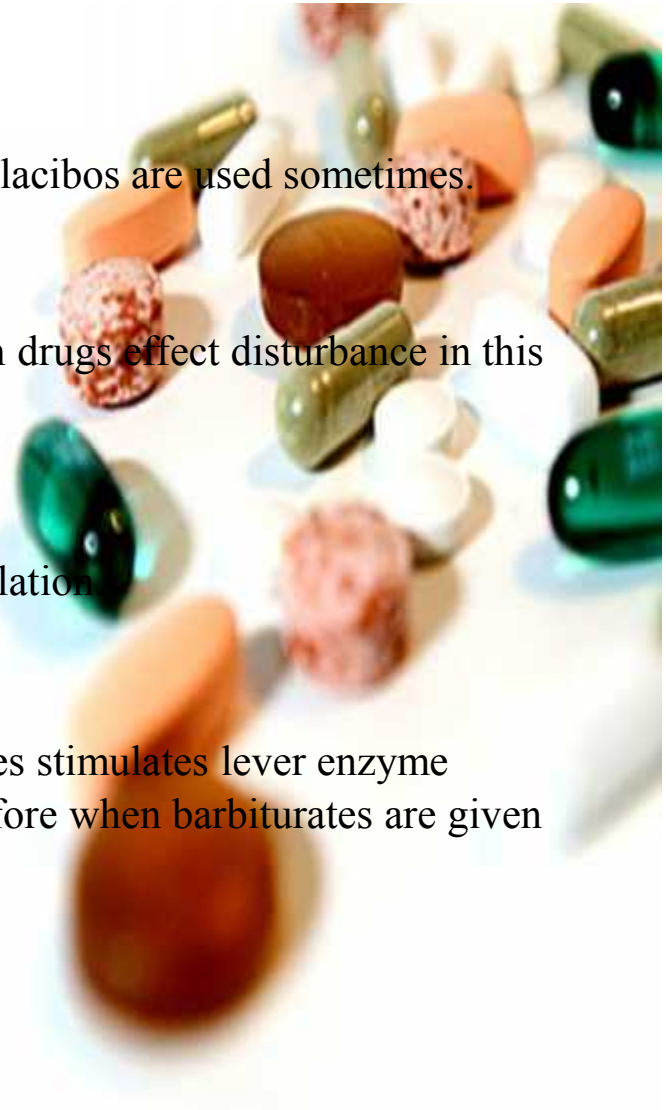
Electrolyte water and acid base balance is important for maximum drugs effect disturbance in this balance may ulter drug effect

## 13) Accumulation :

Repited administration of drug accumulate in body called accumulation

## 14) Other drug therapy :

Effect of other drug may modify eg. Phenobarbitone or barbiturates stimulates lever enzyme Hence metabolic drug increase decreasing duration of action therefore when barbiturates are given other dug the duration is decrease.



# 15)Drug Tolerance:

Resistance to normal therapeutic dose of drug, producing lesser response to normal therapeutic dose is known as tolerance. This is acquired character. Examples include morphine, person is initially responsive, if continued, changes occur at cellular and pharmacokinetic level, reducing the action. Thus one has to increase the dose of drug to overcome.

**It is of 3 types**

**A] true tolerance**: It is seen by all routes

It is of 2 types

**a. Natural tolerance**: seen by birth

It is of 2 types

**1. Species tolerance**: seen particular species only

**2. Racial tolerance**: it seen in particular race of human.

**b. Acquired tolerance** : it is of 2 types

**a. Tissue tolerance**: It seen in particular tissue and not in complete body .

**b. Cross tolerance**: When a person becomes tolerated to a particular drug belonging to a class it becomes to tolerant to complete class this called cross tolerance

**B] Pseudo tolerance**: is the need to increase dosage that is not due to**tolerance**, but due to other factors. such as: disease progression, new disease, increased physical activity, lack of compliance, change in. medication, drug interaction, addiction, and deviant behavior

## 16)Tachyphylaxis:

A decrease in response to a drug due to prior exposure to the agent, which may be countered by increasing the dose. Tachyphylaxis has been reported in some women taking subcutaneous hormo ne-replacement therapy, in
whom menopausal symptoms recur in the face of normal serum oestrogen levels.

## 17) Drug dependence:

When a person habitutes to a particular thing is called dependants .
There are two types of drug dependence.

**A. Physical dependence:**

If the drug is withdrown physical disturbance called withdraw symptoms are seen

**B. Psychological dependence:**

This kind of dependence is characterized by emotional and mental preoccupation with the drug's effects and by a persistent craving for it.
The symptoms displayed are not physical symptoms. Craving seems to be the most common withdrawal symptom.
Psychological dependence is usually manifested by compulsive drug-taking, but the frequency and pattern of use can differ considerably from one individual to another.

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