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PREFACE

Preface

Pharmacology is a fascinating and multifaceted discipline that impacts both our professional careers and personal lives. The study of pharmacology covers a broad spectrum of diverse yet interrelated topics, such as botany, molecular chemistry, research, clinical observation, toxicology and patient education. Medical pharmacology is a unique synthesis of basic pharmacology with clinical pharmacology and pharmacotherapeutics. It is both a basic and an applied science. It forms the backbone of rational therapeutics. Whereas the medical student and the prescribing physician are primarily concerned with the applied aspects, correct and skilful application of drugs is impossible without a proper understanding of their basic pharmacology. The purpose of this note book is not merely to be a source of information in basic pharmacology, but also to present the background and context in which different classes of drugs have been developed and are used. This note book deals with drug interaction with living organism, drug dosage forms and biological effects of drugs. Along with the development of new drug delivery systems. In fact all those persons involved in new drug discovery, dug mechanism of action and its effect. Theoretical pharmacology touches upon common regularities of interactions of drugs with an organism. Experimental pharmacology investigates drugs influence on the organism of animals. Clinical pharmacology examines drugs influence on the organism of patient. Pharmacotherapy studies the use of medicaments for cure of a concrete illness. Some branches of pharmacology are different sciences: phytotherapy, toxicology, vitaminology, endocrinology, and chemotherapy. Pharmacology is closely connected with pharmacy. Pharmacology is based on the advances of physics, chemistry, biology, biochemistry, physiology for the explanation of drugs mechanism of action. Pharmacology is the basis for therapy and other clinical disciplines. The pharmacological effect is the changes of metabolism and function of cells.

CHAPTER 01

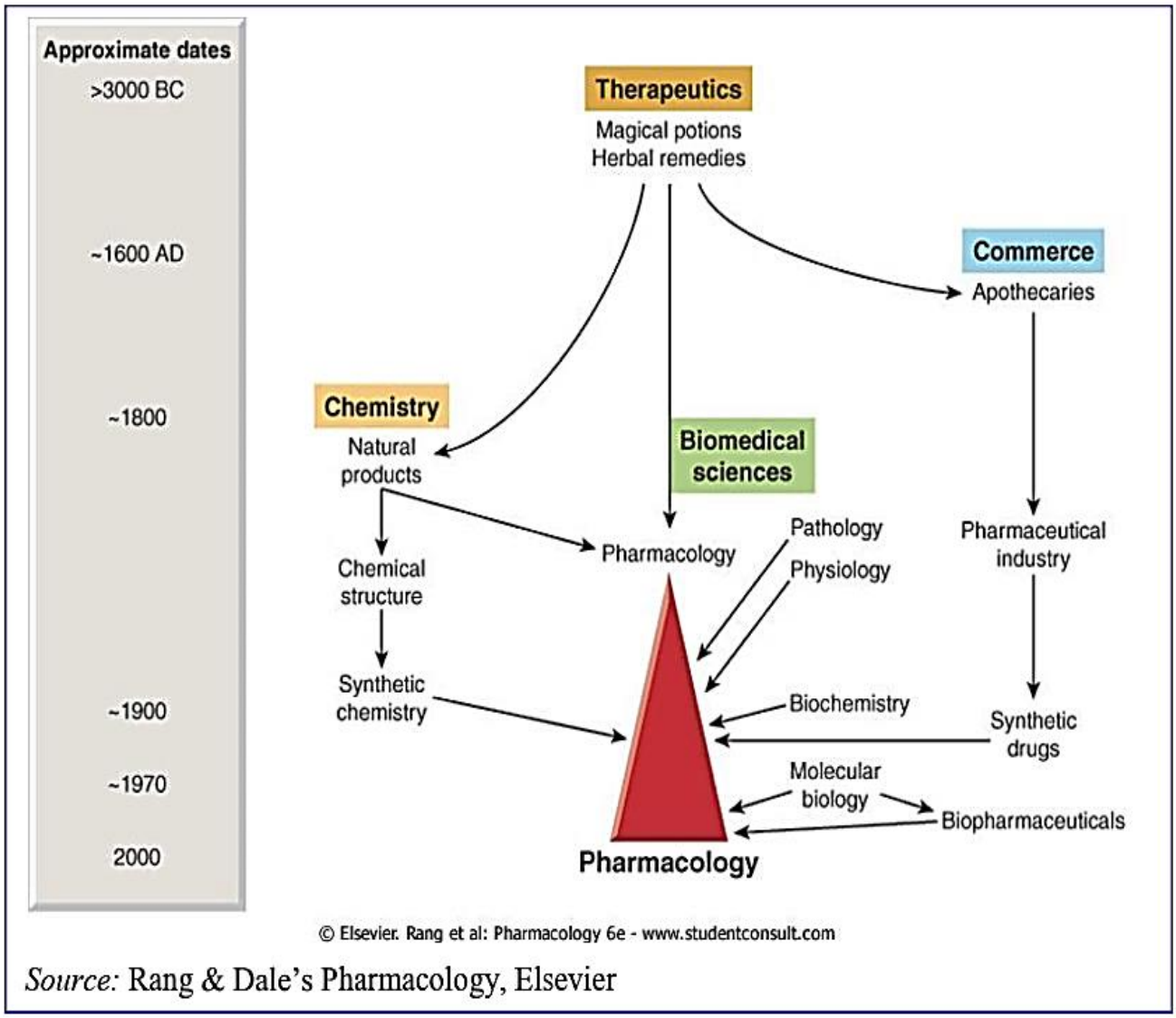
1. History and development of pharmacology

Early in human history a natural bond formed between religion and the use of drugs. Those who became most proficient in the use of drugs to treat disease were the “mediators” between this world and the spirit world, namely, the priests, shamans, holy persons, witches, and soothsayers. Much of their power within the community was derived from the cures that they could effect with drugs. It was believed that the sick were possessed by demons and that health could be restored by identifying the demon and finding a way to cast it out.

Originally, religion dominated its partnership with therapeutics, and divine intervention was called upon for every treatment. However, the use of drugs to effect cures led to a profound change in both religious thought and structure. As more became known about the effects of drugs, the importance of divine intervention began to recede, and the treatment of patients effectively became a province of the priest rather than the gods whom the priest served. This process lead to a growing understanding of the curative powers of natural products and a decreasing reliance on supernatural intervention and forever altered the relationship between humanity and its gods. Furthermore, when the priests began to apply the information learned from treating one patient to the treatment of other patients, there was a recognition that a regularity prevailed in the natural world independent of supernatural whim or will. Therapeutics thus evolved from its roots in magic to a foundation in experience. This was the cornerstone for the formation of a sciencebased practice of medicine (**Figure 1**).

1.1. Definition

Pharmacology is the science about drugs. It studies their properties and use. The main task of pharmacology is to create new more effective medicinal drugs for treatment and prophylaxis of diseases. Pharmacology is integrated into the system of medical and biological sciences (**Figure 2**). It receives necessary information from chemistry, biochemistry, genetics, microbiology, immunology etc. At the same time, pharmacology is the ground of the pharmacotherapy in all branches of the clinical medicine.



Source: Rang & Dale's Pharmacology, Elsevier

Figure 1. The development of pharmacology

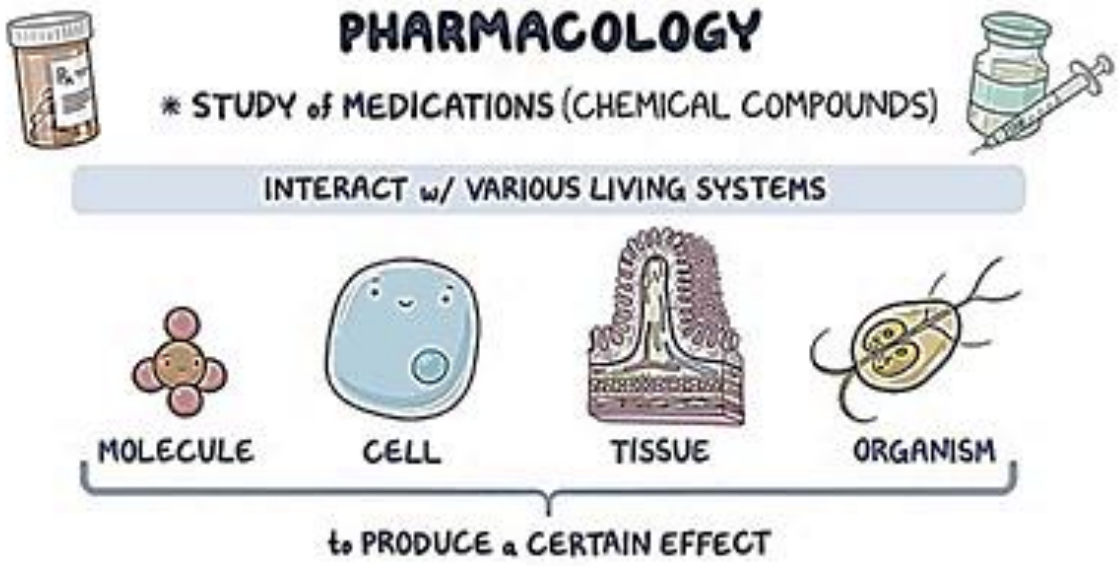


Figure 2. Main task of pharmacology

Pharmacology is the science that deals with the drugs regarding classification, pharmacokinetics, pharmacodynamics, side effects and therapeutic uses. Pharmacology studies the effects of drugs and how they exert their effects for exemple:

- ✓ Acetylsalicylic acid (ASA) or Aspirin can reduce inflammation, pain and fever. It inhibit the action of a human cell membrane enzyme known as cyclooxygenase
- ✓ Penicillin cures certain bacterial infections disrupt the synthesis of cell walls in susceptible ν bacterial strains by inhibiting a key enzyme.

1.2. Drug history and development

The world's oldest known pharmacological or therapeutic writings come from India and China. The earliest Indian records are the Vedas. Although there are medical descriptions in Rigveda (3000 B.C). It was Charaka, a renowned ancient Indian physician, and later Sushruta and Vagbhata, who described various medicinal preparations included in Ayurveda, Charaka described about 300 herbal drugs and classified them according to their effects. The Chinese material medica 'Pan Tsao' was probably written in (2735 B.C) and contained many plant and metallic preparations and a few animal products. Modern medicine is considered to date from Hippocrates, a Greek physician (450 B.C), who for the first time introduced the concept of disease as a pathologic process and tried to organize the science of medicine on the basis of observation, analysis and deduction.

➢ The oldest writings of medicinal agents belonged to Ancient India, closely followed by **Chinese** and **Egyptian** literatures.

➢ **Rigveda**, the oldest records of civilization (3000 BC) describes the value of medicinal herbs.

➢ **Ayurveda**, the oldest system of medicine, which is very popular in these days also, recommends herbal remedies and animal origin products for treatment of disease in man and animals. Charaka, Sushruta and Vaghbata pioneered in Ayurveda. Nakula, one of the Pandavas followed sound principles of animal husbandry and veterinary science.

➢ The earliest written compilation of drugs is the **Chinese** Herbal Formulary (Materia Medica) "**Pen Tsao**" which was written by **Emperor Shen Nung** (2700 BC). It contains many vegetables, metallic and animal products as remedies.

➢ The oldest record of **Egyptian drug codification** is the **Kahun Papyrus** (2000 BC). It deals with veterinary medicine and uterine disease of women and contains a number of prescriptions. The **Ebers Papyrus** (1550 BC) is a compilation of number of disease conditions and 829 prescriptions for medicaments employed in Egyptian medicine.

➢ **Hippocrates** (460–375 BC), a Greek physician and a great teacher of medicine advocated little use of drugs, maintained very high ethical standards of practice ("Above all, do no harm") and attempted to treat diseases based on four elements of nature i.e. water, fire, air and earth. Combination of these elements gave rise to four humours of the body related to a scale of life from most alive to dead. They are – Blood (Sanguine temperament), Phlegm (Phlegmatic), Yellow Bile or Urine (Bilious) and Black Bile (Melancholic). Treatment consisted of attempting to balance these humours by replenishment of deficiencies or removing excesses. Thus arose the practices of bleeding, purging and sweating.

➢ **Aristotle** (384–322 BC) gave scientific basis for medicine who recorded numerous observations on animals.

➢ **Theophrastus** (380–287 BC), a pupil of Aristotle, classified systematically medicinal herbs on the basis of their individual characteristics rather than their recommended use in treatment.

➢ **Dioscorides** (77), a surgeon, compiled and improved the work of Theophrastus and wrote the **First Materia Medica** which consisted of **6 volumes** and described 600 plants. Drugs were discussed from the standpoint of name, source, identification, test for adulteration, preparation of dosage form, what it would do and for what conditions it would be used.

➢ Following the fall of Roman Empire, Europe entered the dark ages, during which time there was little advancement in intellectual development. Custodian of knowledge and medical thought during this period were found in Muslims. An intellectual Persian writer, **Geber Ibn Hajar** (702-765) classified drugs and poisons of his time and stated that difference between a drug and a poison was just a matter of dosage. Any drug can be toxic if given in large enough amounts.

➢ The spirit of enquiry was reestablished in Europe during Renaissance. A German person **Valerius Cordus** (1514–1544) compiled **First Pharmacopoeia**.

➢ During 17th and 18th centuries, drug trade flourished and medical experimentation began. Drugs like cinchona (Quinine), coffee, tea, cocoa (methylxanthines), curare, digitalis and a variety of alkaloids were discovered.

➢ **William Withering** (1741–1799) worked on digitalis in the treatment of dropsy (due to congestive heart failure, CHF).

➢ **Edward Jenner** (1749–1823) gave principle of prophylactic immunization against small pox and first described anaphylaxis.

➢ **William Harvey** (1578–1657) discovered circulation of blood and indicated that drugs were distributed to various body parts via blood.

➢ **Christopher Wren** (1632–1723) made first intravenous injection in a dog.

➢ **Alexander Wood** (1817–1884) devised hypodermic syringe and needle.

➢ **Friedrich Surtner** (1783–1841) isolated morphine from opium and named it after the Roman God of sleep, "Morpheus".

➢ **Claude Bernard** (1813–1878) and **James Blake** (1814 - 1893) established the foundations of modern pharmacology. They worked on dose response relationship, drug disposition in the body, mechanism of action of drugs and structure activity relationship (SAR).

➢ **Rudolph Buchheim** (1820–1879) established the first laboratory for pharmacology at University of Dorpat, Estonia.

➢ **John J. Abel** (1857–1938) who is regarded as the Father of Pharmacology in USA, established Departments of Pharmacology at University of Michigan and at John Hopkins University. He also founded reputed journals like Journal of Biological Chemistry and Journal of Pharmacology and Experimental Therapeutics.

➢ During 20th Century, the science of Pharmacology flourished in the medical and pharmacy schools, and focus of leadership shifted from Europe to USA (due to two world wars and emergence of USA as industrial power). The science of

pharmacology developed exponentially thereafter due to emergence of Organic Chemistry:

- ***Herbs***

The word herb comes from the Latin word '*herba'* meaning grass, green stalks or blades. In general use, herbs are plants with savory or aromatic properties that are used for in medicine, flavoring food or as fragrances. Herbs have a variety of uses including medicinal and in some cases, spiritual. The term "herb" differs between culinary herbs and medicinal herbs; in medicinal or spiritual use, any parts of the plant might be considered as "herbs", including leaves, roots, flowers, seeds, root bark, inner bark (and cambium), resin and pericarp. Herbs have long been used as the basis of traditional Chinese herbal medicine, with usage dating as far back as the first century CE and far before. In India, the Ayurveda medicinal system is based on herbs. Which plant parts (flower, fruit, root, leaves stem, bark and seed) contain medicinal properties that are called herbs.

- ***Medicine***

Medicine is the science and practice of the diagnosis, treatment, and prevention of disease or a drug or other preparation for the treatment or prevention of disease. Medicine encompasses a variety of health care practices evolved to maintain and restore health by the prevention and treatment of illness. Contemporary medicine applies biomedical sciences, biomedical research, genetics and medical technology to diagnose, treat and prevent injury and disease.

- ***Ayurvedic medicine***

The word "ayurveda" is Sanskrit, A*yurveda*, meaning knowledge of life and longevity. Ayurvedic medicine is one of the world's oldest holistic healing systems. It was developed more than 3,000 years ago in India. It's based on the belief that health and wellness depend on a delicate balance between the mind, body, and spirit. Ayurveda names seven basic tissues, which are plasma, blood, muscles, fat, bone, marrow and semen. Ayurveda has historically divided bodily substances into five classical elements (Sanskrit *panchabhuta*, viz. earth, water, fire, air and ether. Ayurveda also names three elemental substances (called Vata, Pitta and Kapha). Ayurveda has eight ways to diagnose illness, called pulse, urine, stool, tongue, speech, touch, vision and appearance. After all it is a type of traditional Hindu medicine system that treats illness/disease using a combination of food, herbs and breathing exercise.

- ***Homeopathy***

The term "homeopathy" was coined by Hahnemann (respected doctor in Germany) and derived from two Greek words that mean “like disease”. Homeopathy is a system of alternative medicine created in 1796 by Samuel Hahnemann, based on his doctrine of *like cures like.* Homeopathy is an alternative medical practice in which extremely dilute amounts of certain natural substances are used to treat various ailments. It is a medical system based on the belief that the body can cure itself. Those who practice it use tiny amounts of natural substances, like plants and minerals. It is a system of treating disease or disease like condition, where we have using a very small amount of the drug/ chemical substance/compound in high amount, which cause the disease or disease like condition.

- ***Allopathy***

(A western system of medicine, Western-American culture). The term "allopathy" was coined in 1842 by C.F. Samuel Hahnemann. The system of medical practice which treats disease by the use of remedies which produce effects different from those produced by the disease under treatment. Allopathic medicine refers to the practice of traditional or conventional Western medicine.The term allopathic medicine is most often used to contrast conventional medicine with alternative medicine or homeopathy.

- ***Drugs***

It is the single active chemical entity/compound/substance in a medicine that is used for diagnosis/treatment/cure /prevention of a disease (allergy, cancer, tuberculosis, analgesic & AIDS etc). This disease oriented definition of drug does not including contraceptives or improvement of health. The WHO (1966) has given a more comprehensive definition-“Drug is any substance or product that is used or is intended/consumption/intake to be used to modify/change or explore physiological system or pathological states for the benefit of the recipients.

1.3. Generality about the drugs

A drug can be defined as a chemical substance of known structure, other than a nutrient or an essential dietary ingredient, which when administered to a living organism, produces a biological effect. Drugs may be synthetic chemicals, chemicals obtained from plants or animals or products of genetic engineering. According to **WHO**, “Drug is any substance or product other than food that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient”.

1.3.1. Drug development

Drug development includes many stages. It is very difficult and expensive. The process starts with the synthesis of novel chemical compounds or obtaining of medicinal substances from various sources (plants, animal tissues, microbial cultures, human cells). The next stage of drug development is preclinical testing with biochemical pharmacological investigations, toxicological investigations, study of pharmacokinetics and pharmaceutical technology (methods of drug formulation). Clinical testing starts with:

1. ***Phase I*** during this phase the future drug is studied on healthy subjects and seeks to determine whether effects observed in animal experiments also occur in humans.
2. In ***Phase II*** potential drug is tested on selected patients for therapeutic effecacy in those diseases for which it is intended.
3. In ***Phase III*** the drug is tested on large groups of patients and compared with standard treatments.

During clinical trials many drugs are revealed to be unusable. It is known that only one new drug remains from approximately 10000 newly synthesized substances.

The decision to approve a new drug is made by a National Regulatory Body. Following approval, the new drug may be marketed under a trade name.

1.4. Nature and sources of drugs

A drug can be defined as a chemical substance of known structure, other than a nutrient or an essential dietary ingredient, which when administered to a living organism, produces a biological effect. Drugs may be synthetic chemicals, chemicals obtained from plants or animals or products of genetic engineering.

According to WHO, "Drug is any substance or product other than food that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient".

(To use the word 'drug' intending only a harmful, dangerous or addictive substance is to abuse a respectable and useful word.).

The various sources of drugs are:

1.4.1. Drugs from plant sources

The ancient or original sources of drugs are the plants collectively known as medicinal plants. All parts of the medicinal plants have therapeutic values.

Root	:	Sarpgandha
Rhizome	:	Ginger, Haldi
Bark	:	Cinchona, Catechu, Acacia
Leaves	:	Atropine, Cocaine, Physostigmine
Flowers	:	Digitalis, Chrysenthemum
Fruits	:	Papaya, Anise
Seeds	:	Nux vomica, Kali mirchi, Methi

1.4.2. Drugs from animal sources

Hormones	:	Oxytocin, Insulin, Thyroxine, Gonadotrophins
Vitamins	:	Cod or shark liver oil (Rich sources of Vitamin A & D)
Antisera	:	Antisnake venom, Canine distemper antiserum etc.
Others	:	Heparin, Liver extract, Immunoglobulins, Blood/Plasma.

1.4.3. Drugs from microbial sources

Fungi/ Actinomycetes and Bacteria	:	Sources of antibiotics (penicillin, streptomycin, gentamicin, neomycin etc.)
Viruses/ Bacteria	:	Preparation of vaccines
Yeasts	:	Dried yeast as source of Vitamin B-complex

1.4.4. Drugs from mineral sources: (Inorganic salts)

Antacid	:	Magnesium oxide, Sodium bicarbonate
Purgative	:	Magnesium sulphate
Expectorant:		Potassium iodide
Diuretic	:	Potassium nitrate
Haematinic :		Ferrous sulphate
Hypothyroidism:		Iodine
Mineral oils :		Liquid paraffin (Laxative effect) – Long term administration interferes with Vitamin A & D, Calcium and Phosphorus absorption.

1.4.5. Synthetic drugs

Majority of the current day dugs are from synthetic source or laboratory sources. Examples are :

- Antipyretics
- Barbiturates
- Tranquillizers
- Anti-inflammatory drugs
- Anaesthetics
- Antiseptics
- Antiprotozoals
- Antihistamines etc.

1.4.6. Semi-synthetic drugs:

Examples are :

- Agonists and antagonists of morphine
- Dihydrostreptomycin – from streptomycin
- Semi-synthetic penicillins – from penicillin.

1.5. Drug nomenclature

When a new drug is synthesized, it is first assigned a code or number (usually identifying with its inventor, manufacturer/ pharmaceutical company). If it is found promising after clinical evaluation, the manufacturer wants to put it in the market; the new drug is given a generic name to designate its pharmacological class (nonproprietary name). If the new drug gets official recognition by drug regulatory authority, its manufacturer gives it a proprietary or trade name.

- Composition of Drugs: Inorganic drugs have simple formula, whereas organic drugs have a complex one. The most active amongst drugs are those containing alkaloids and glycosides:

1) Inorganic drugs (Acids, Bases and Salts).
2) Organic drugs (Alkaloids, glycosides, tannins, saponins etc).

✓ **Chemical name:** IUPAC name, generally long and hard to remember.

- Generic, Official, Approved or Trivial name:

✓ The chemical is entered in pharmacopoeias under this name.
✓ The chemical compound is known throughout the world by this generic name.
✓ Approved names are generally used by researchers and non-clinical teachers.

-Proprietary, Brand or Trade name:

✓ One chemical compound can have several proprietary names.
✓ Even one proprietary name may not contain single chemical.
✓ Manufacturers and clinicians prefer to use brand names.

Examples:

Chemical name	*Generic name*	*Trade name*
3,4-dihydroxyphenylethanolmethylamine	Epinephrine	Adrenaline
Acetylsalicylic acid	Aspirin	Ecosprin

1.6. Drug concentration and effect

Drug therapy is intended to result in a particular pharmacologic response of desired intensity and duration while avoiding adverse drug reactions. The relationship between the administered dose and the clinical response has been investigated for some drugs using a pharmacokinetic/pharmacodynamic (PK/PD) modeling approach, which is generally based on the plasma concentration-response relationship. For other drugs, a simpler relationship between the concentration and effect in an idealized in vitro system is modeled mathematically to conceptualize receptor occupancy and drug response. The model assumes that the drug interacts reversibly with its receptor and produces an effect proportional to the number of receptors occupied, up to a maximal effect when all receptors are occupied. The reaction scheme for the model is:

$$\text{Drug (D)} + \text{Receptor (R)} \underset{k_1}{\overset{k_2}{\leftrightarrow}} \text{DR} \rightarrow \text{Effect}$$

in which k_2 and k1 are rate constants. The relationship between effect and the concentration of free drug for the model is given by the Hill equation, which can be written as:

$$E = \frac{E_{max} \times C_n}{EC_{50} + C_n}$$

in which E is the effect observed at concentration C, Emax is the maximal response that can be produced by the drug (efficacy), EC50 is the concentration of drug that produces 50% of maximal effect (potency), and the Hill coefficient n is the slope of the log10 concentrationeffect relationship (sensitivity). The above equation describes a rectangular hyperbola when response (y-axis) is plotted against concentration (x-axis). However, dose- or concentration-response data is generally plotted as drug effect (y-axis) against log10 dose or concentration (x-axis). The transformation yields a sigmoidal curve that allows the potency of different drugs to be readily compared. In addition, the effect of drugs used at therapeutic concentrations commonly falls on the portion of the sigmoidal curve that is approximately linear, ie, between 20 % and 80 % of maximal effect. This makes for easier interpretation of the plotted data.

1.6.1. Types of drugs doses

The ***dose*** is the amount of drug administered into the body. The dose may be:

1. single (for single administration),
2. daily (for the day of treatment),
3. total (for the course of treatment).

- ✓ Therapeutic (minimal, average, maximal) – the dose which has therapeutic action.
- ✓ Toxic (minimal, average, maximal) –the dose which causes toxic action
- ✓ Mortal (the dose which causes the death of animals in experiments)
- ✓ Striking dose (a large dose at the start of treatment),
- ✓ Supporting dose (an individual dose for supporting a therapeutic effect during long-term treatment).

1.6.2. Agonists and antagonists drugs

An agonist is a drug that binds to receptors and thereby alters (stabilizes) the proportion of receptors in the active conformation, resulting in a biologic response. A full agonist results in a maximal response by occupying all or a fraction of receptors. A partial agonist results in less than a maximal response even when the drug occupies all of the receptors. There are four types of drug antagonism. Chemical antagonism involves chemical interaction between a drug and either a chemical or another drug leading to a reduced or nil response. Physiologic antagonism occurs when two drugs acting on different receptors and pathways exert opposing actions on the same physiologic system.

Pharmacokinetic antagonism is the result of one drug suppressing the effect of a second drug by reducing its absorption, altering its distribution, or increasing its rate of elimination. Pharmacologic antagonism occurs when the antagonist inhibits the effect of a full or partial agonist by acting on the same pathway but not necessarily on the same receptor. Pharmacologic antagonists comprise three subcategories. A reversible competitive antagonist results in inhibition that can be overcome by increasing the concentration of agonist. The presence of a reversible competitive antagonist causes a parallel rightward shift of the log concentration-effect curve of the agonist without altering Emax or EC_{50}. An irreversible competitive antagonist also involves competition between agonist and antagonist for the same receptors, but stronger binding forces prevent the effect of the antagonist being fully reversed, even at high agonist concentrations. The presence of an irreversible competitive antagonist causes a rightward shift of the log concentration-effect curve of the agonist that generally

displays decreased slope and reduced maximum effect. A noncompetitive antagonist inhibits agonist activity by blocking one of the sequential reactions between receptor activation and the pharmacologic response. Noncompetitive antagonism is generally reversible but can be irreversible. Noncompetitive antagonists and irreversible competitive antagonists cause similar perturbations in the log concentrationeffect curve of agonists. Isolated tissue experiments are used to distinguish the two subcategories, because noncompetitive antagonists are generally reversible.

Agonists, but not antagonists, elicit an effect even when they bind to the same site on the same receptor. An explanation is provided by both structural and functional studies, which indicate that receptors exist in at least two conformations, active and inactive, and these are in equilibrium. Because agonists have a higher affinity for the receptor's active conformation, agonists drive the equilibrium to the active state, thereby activating the receptor. Conversely, antagonists have a higher affinity for the receptor's inactive conformation and push the equilibrium to the inactive state, producing no effect. The concept of spare receptors explains a maximum response being achieved when only a fraction of the total number of receptors is occupied. For example, an action potential and maximal twitch of muscle fibers is elicited when 0.13% of the total number of receptors at a skeletal neuromuscular junction is simultaneously activated. From a functional perspective, spare receptors are significant, because they increase both the sensitivity and speed of a tissue's responsiveness to a ligand.

1.6.3. Structure–activity relationships

Structure-activity relationships are exploited in drug design, because small changes in chemical structure can produce profound changes in potency. For example, the substitution of a proton by a methyl group accounts for codeine being ~1,000 times less potent than morphine in its action on opioid receptors.

1.7. Pharmacological introduction

Pharmacology is the science of drugs (Greek: *Pharmacon*—drug; *logos*—discourse in). In a broad sense, it deals with interaction of exogenously (outer side of body) administered chemical molecules with living systems, or any single chemical substance which can produce a biological response is a 'drug'. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purposes (**Figure 3**).

Figure 3. An illustration showing some of the scopes and interests of pharmacology.

Pharmacology is also interested in creating newer and more effective medicinal drugs for the treatment of the various forms of diseases in living organisms including humans. Pharmacology cares about these therapeutic compounds **on a molecular level**, how do drugs interact with cell receptors? How do their mechanisms achieve the therapeutic effect? As we've seen in the history and evolution of pharmacology, we see that it is based on the advances of physics, chemistry, biology, biochemistry, physiology, it is as if we can say it is the "essential oil" of other sciences, and it makes the basis for therapy and other clinical disciplines. The science of pharmacology includes three major divisions: theoretical (general), experimental, and clinical, the definition of pharmacology is therefore furthermore expanded and divided into branches and divisions that specialize in certain aspects of this science, or even forming new sciences stemming from pharmacology (**Figure 4**).

Figure 4. Bowl of hygieia, symbol of pharmacy and pharmacology

1.7.1. Types of pharmacology

The two main divisions of pharmacology are pharmacodynamics and pharmacokinetics **(Figure 5):**

Figure 5. "Pharmacologyprism" illustration on pharmacokenetics and pharmacodynamics

- **Pharmacodynamics**

  (Greek: *Dynamis*—power) what the drug does to the body. This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/macromolecular levels. **For excemple:** Adrenaline → interaction with adrenoceptors → G protein mediated stimulation of cell membrane bound adenylyl cyclase → increased intracellular cyclic 3′,5′AMP → cardiac stimulation, hepatic glycogenolysis and hyperglycaemia, etc.

- **Pharmacokinetics:-**

  (Greek: *Kinesis*—movement) what the body does to the drug. This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug. **For excemple:** paracetamol is rapidly and almost completely absorbed orally attaining peak blood levels at 30–60 min; 25% bound to plasma proteins, widely and almost uniformly distributed in the body (volume of distribution ~ 1L/kg); extensively metabolized in the liver, primarily by Glucuronide and sulfate conjugation into

inactive metabolites which are excreted in urine; has a plasma half life (t½) of 2–3 hours and a clearance value of 5 ml/kg/min

1.7.2. Branches of pharmacology

Pharmacology is an integral part of the medical and biological sciences, as it derives from and adds to chemistry, biochemistry, genetic sciences, microbiology, immunology...etc. It is logical for this broad field of study to have branches and divisions that are specific and more specialized in certain aspects of said disciplines.

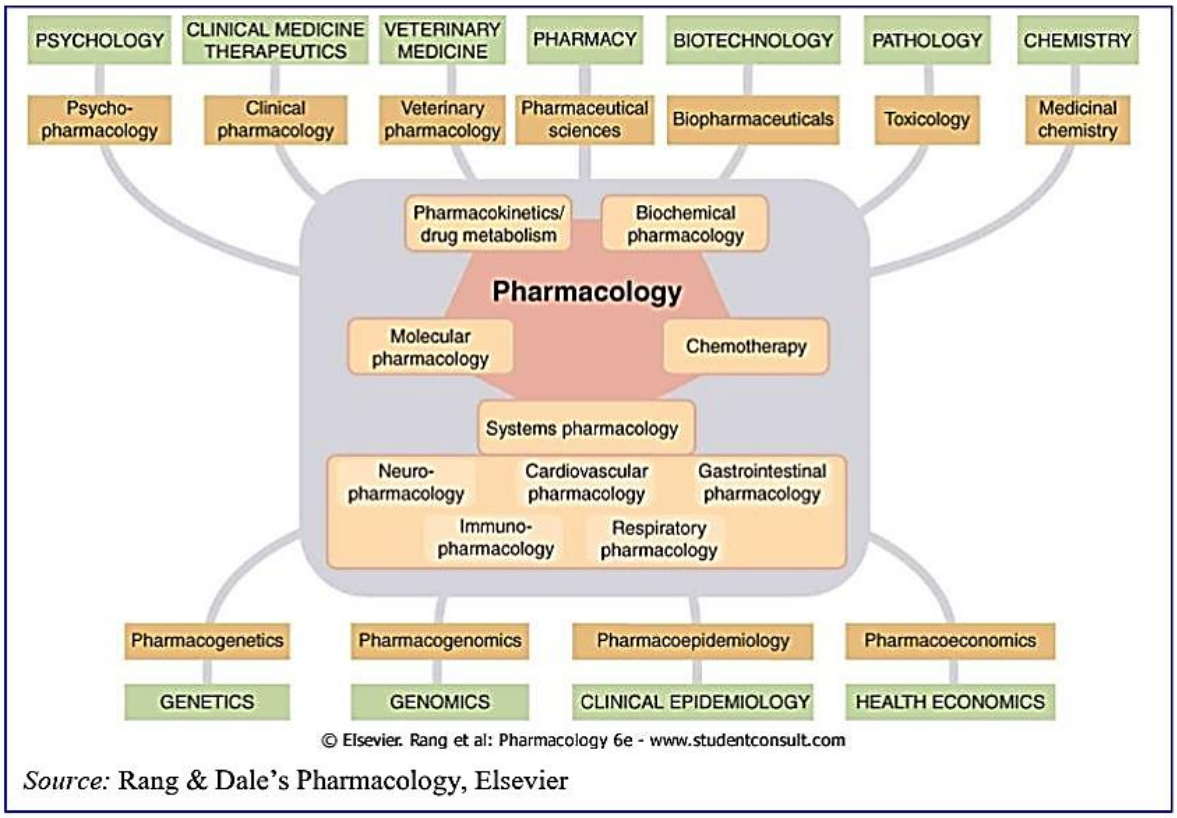


Figure 3. Pharmacology today with its various subdivisions. Interface disciplines (**brown boxes**) link pharmacology to other mainstream biomedical disciplines (**green boxes**)

Some other important aspects of pharmacology are:

- ***Pharmacotherapeutics***

  It is the scientific study of drugs together with knowledge of the disease for its prevention, mitigation or cure. Selection of the most appropriate drug, dosage and duration of treatment taking into account the specific features of a patient are a part of pharmacotherapeutics.

- ***Clinical pharmacology***

It is the scientific study of drugs (both old and new) in man. It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers and in patients. The aim of clinical pharmacology is to generate data for optimum use of drugs and the practice of 'evidence based medicine'.

- ***Chemotherapy***

It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/malignant cell with no/minimal effects on the host cells. Drugs in general, can thus be divided into:

1- **Pharmacodynamic agents:** these are designed to have pharmacodynamic effects in the recipient.

2- **Chemotherapeutic agents:** these are designed to inhibit/kill invading parasite/malignant cell and have no/minimal pharmacodynamic effects in the recipient.

- ***Pharmacy***

It is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs to man or animals (**Figure 6**). It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances. The large scale manufacture of drugs is called *Pharmaceutics*. It is primarily a technological science.

Figure 6. Photograph of some formulations of drugs

- ***Toxicology***

  It is the scientific study of drugs poisonous effect and other chemicals (household, environmental pollutant, industrial, agricultural, homicidal) with emphasis on detection, prevention and treatment of poisonings. It also includes the study of adverse effects of drugs, since the same substance can be a drug or a poison, depending on the dose.

- ***Metrology***

  It is the study of weights and measures as applied to preparation and administration of drugs.

- ***Materia medica***

  It is an obsolete didactic (instructive) subject that was concerned with pharmacy, posology, pharmacognosy and indications for therapeutic use of drugs. This subject was purely descriptive in nature and has been replaced in the modern veterinary medical curriculum by the science of comparative pharmacology.

- ***Posology***

  It is the study of medicine dosage (**Figure 7**).

  1- **Dose:** A dose is the quantity of medication to be administered at one time.
  2- **Dosage:** It refers to determination and regulation of doses.
  3- ***Loading dose:*** It is one or series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly.
  4- ***Maintenance dose:*** It is a series of relatively small doses that follow the loading dose in order to maintain an effective concentration in the bio-phase.

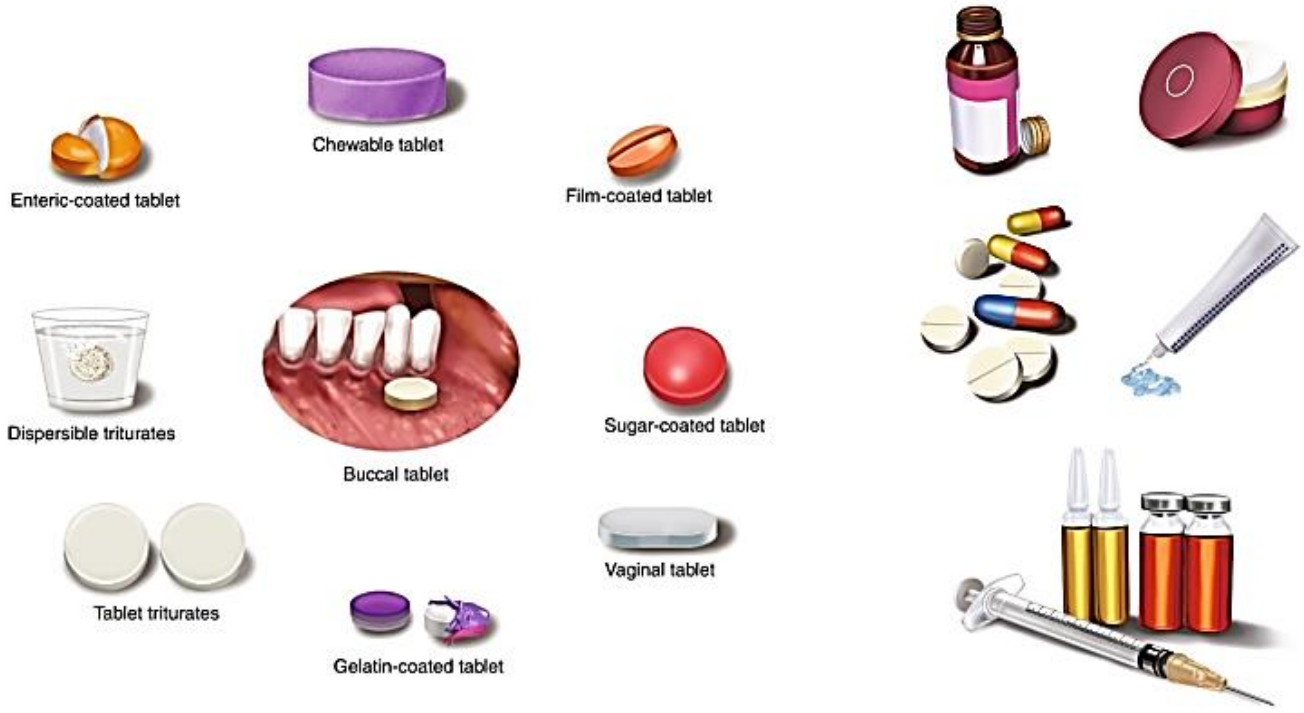


Figure 7. Some Dosage forms of drugs.

- **C*omparative pharmacology***

  It deals with the study of variation in drug effects in different species of animals.

- ***Neutraceuticals***

  These are nutritional products which allegedly have some therapeutic value in addition to their scientifically recognized nutritional content.

- ***Biotechnology***

  Originally, this was the production of drugs or other useful products by biological means (e.g. antibiotic production from microorganisms or production of monoclonal antibodies). Currently in the biomedical sphere, biotechnology refers mainly to the use of recombinant DNA technology for a wide variety of purposes, including the manufacture of therapeutic proteins, diagnostics, genotyping, production of transgenic animals, etc. The many non-medical applications include agriculture, forensics, environmental sciences, etc.

- ***Pharmacogenetics***

  This is the study of genetic influences on responses to drugs. Originally, pharmacogenetics focused on familial idiosyncratic drug reactions, where

affected individuals show an abnormal-usually adverse-response to a class of drug. It now covers broader variations in drug response, where the genetic basis is more complex.

- ***Pharmacogenomics***

  This recent term overlaps with pharmacogenetics, describing the use of genetic information to guide the choice of drug therapy on an individual basis. The underlying principle is that differences between individuals in their response to therapeutic drugs can be predicted from their genetic make-up.

- ***Pharmacoepidemiology***

  This is the study of drug effects at the population level. It is concerned with the variability of drug effects between individuals in a population, and between populations.

- **Pharmacoeconomics**

  This branch of health economics aims to quantify in economic terms the cost and benefit of drugs used therapeutically.

- **Nanotechnology**

  Nanotechnology is the study and use of structures between 1 nanometer (nm) and 100 nanometers in size. Nanotechnology is the study of phenomena and fine-tuning of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale. The applications of nanotechnology to pharmacology are biochips, nanosensors, bioreactors, neural stem cells, immune nanoparticles, biodegradable polymers, and convection-enhanced drug delivery in the diagnostics and treatment of diseases.

CHAPTER 02

2. Routes of drug administration

Drugs are used via **administering** them, in one or many of the diverse and various forms of **doses**, and via one or more of the many ”routes of administration” to the biological system, for an optimal delivery and to assure a good bioavailability this can be done in multiple ways. Different administering routes have different dose types and each comes with advantages and disadvantages, the common routes and forms of doses as shown in **Figure 8.** Route of administration **is an important determinant of the rate and efficiency of absorption.**

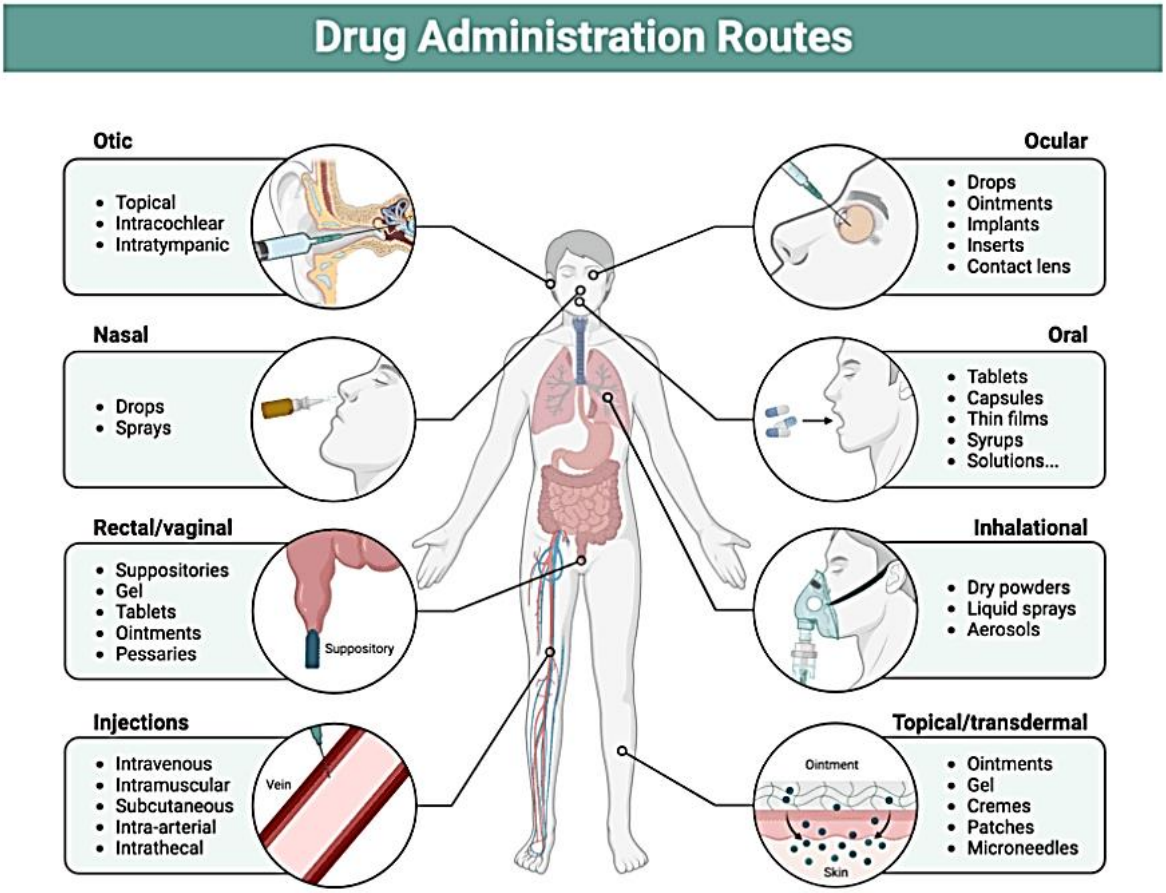


Figure 8. The various routes of administration illustrated

2.1. Factor affecting routes of drug administration

Factor affecting choice of route are:

- Physical and chemical properties of the drug (solid/liquid/gas, solubility, stability, pH, irritancy).
- Site of desired action-localized and approachable generalized and not approachable
- Rate and extent of absorption of the drug from different routes.

- Effect of digestive juices and first pass metabolism on the drug.
- Rapidity with which the response is desired (routine treatment or emergency).

2.2. Introduction of routes of drug administration

Routes or way, passes and administration or management. The routes of administration are depends on drug and as well as patients related factors. Routs of drugs administration are divided into enteral routs (through the gut), parenteral routs (not through the gut), and topical application for local action (**table 1**).

Table 1. Routs of drugs administration

Enteral routs	Parenteral routs	Topical application
1. Sublingual (under the tongue) 2. Oral (by mouth, per os) 3. Rectal (in rectum)	1. Injections 2. Inhalations (through the respiratory pathways) 3. Intranasal 4. Transcutaneous	1. On the surface of skin 2. On the surface of mucous membrane

2.2.1. Enteral routes

Enteral routes are the most common routes of administration. Examples of enteral routes are peroral, rectal, sublingual, subbuccal, and duodenal.

- Advantages of enteral administration. An alimentary route is physiological, generally the safest route of administration. The delivery of the drug into the circulation is slow after oral administration, so that rapid, high blood levels are avoided and adverse effects are less likely. The dosage forms available for alimentary administration are convenient and do not require sterile technique.
- Disadvantages of alimentary administration. It is not convenient for the first aid. The main disadvantage is that the rate of absorption varies. It becomes a problem if a small range in blood levels separates a drug desired therapeutic effect from its toxic ones. Irritation of mucosal surfaces can occur. A patient compliance is not ensured. With peroral administration of some drugs extensive hepatic metabolism may

occur before a drug reaches its site of action. This is known as a first-pass effect. Passage through the liver and the resulting initial hepatic metabolism are avoided by administering the drug sublingually. But only some drugs may penetrate through mucose surfaces.

2.1.2. Parenteral routes.

The main merit is that the medicine bypasses the alimentary tract. Examples of parenteral routes: intravenous, intramuscular, subcutaneous, intraperitoneal, intra-arterial, intrathecal, transdermal, intranasal, and inhalational etc.

- ***Advantages of parenteral administration:*** A drug gets to the site of action faster, providing a rapid response, which may be required in an emergency. The dose can often be more accurately delivered. Parenteral administration can be used when the alimentary route is not feasible (e.g. when a patient is unconscious). Large volumes can be delivered intravenously.
- ***Disadvantages of parenteral administration:*** More rapid absorption can lead to increased adverse effects. A sterile formulation and an aseptic technique are required. Local irritation may occur at the site of injection. Parenteral administration is not suitable for insoluble substances. Parenteral administration may lead to HIV infection and phlebitis.

2.2.3. Topical administration

Topical administration is useful in the treatment of patients with local conditions; with topical administration there is usually little systemic absorption. Drugs can be applied to various mucouse membranes and skin. Inhalation provides a rapid access to circulation; it is the common route of administration for gaseous and volatile drugs. It is managed well. In the case of inhalation there may occur allergic reaction and any disease may be aggravated.The routes can be divided into two classes: **local routes** and **systemic routes**:

2.3. Local routes

The local routes of administration are: topical route**,** deeper tissues and arterial supply:

2.3.1. Topical route

This refers to external/(outer surface of body) application of the drug to the surface for localized action. It is often more convenient or suitable as well as encouraging to the patient. These are another two types: **a)** Skin and **b)** Mucus membrane

a. Skin

Drug is applied as cream, lotion, ointment, jelly, paste, powder, dressing and spray etc

b. Mucus membrane

The dosage form depends on the site:

Mouth and pharynx-	Paints, lozenges, mouth washes, gargles.
Eyes, ear and nose-	Drops, ointment, irrigation, nasal spray.
Gastrointestinal tract GIT)-	Non-absorbable drugs given orally e.g. magnesium Hydroxide, sucralfate, neomycin.
Bronchi and lungs-	Volatile liquid, gases and fine powder (Aerosols and salbutamol etc).
Urethra-	Jelly (lidocaine), ointment and irrigating solutions.
Vaginal-	Tablet, inserts, cream, powder, douches.
Anal canal-	Ointment, suppositories.

2.3.2. Deeper tissues

In this routes, drug is apply for certain deep areas can be approached by using a syringe and needle, but the drug systemic absorption is very slow/minimum or absent, e.g. Intraarticular injection (hydrocortisone acetate), Intrathecal injection (lignocaine, amphotericin B).

2.3.3. Arterial supply

It is used for close intra-arterial injection, where the drug injected for contrast media in angiography. In this route anticancer drugs can be infused in femoral or brachial artery to localize the effect for limb malignancies.

2.4. Systemic routes

The drug administered through systemic routes is intended/reaches to be absorbed into blood and distributed all over the body, including the site of action, through circulation, these are various types. **A.** Oral**, b.** Sublingual (SI) Buccal**, c.** Nasal**, d.** Inhalation**, e.** Rectal**, f.**Cutaneous**, g.** Parenteral**.**

a- Oral

Oral route is the oldest and commonest mode of drug administration. It is safer more convenient or suitable, does not need assistance, non-invasive, often painless, the medicament

need not be sterile and so is cheaper. Both solid (tablet, capsule, powder etc) and liquid (syrups, emulsion, suspension, elixirs, solution etc) dosage forms can be given orally.

-Observation: **there are some limitation of oral route of administration:**

- Action is slower and thus not suitable for emergencies.
- Unpalatable drugs (paraldehyde) are difficult to administer, drug may be filled in capsules to circumvent this.
- May cause nausea and vomiting (emetine).
- Cannot be used for uncooperative/unconscious/vomiting patient.
- Certain drugs are not absorbed (streptomycin).
- Other are destroyed by digestive juices (penicillin, Insulin) or in liver (nitroglycerin, testosterone, lignocaine).
- Easy to intake for administration and no need of any maintenance.

b. Sublingual (SI) Buccal

The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa. Only lipid soluble and non-irritating drugs can be administered in this route. Absorption is relatively rapid and action can be produced in minutes. The chief advantage is that liver is bypassed and drugs with high first pass metabolism with absorbed directly into systemic circulation. For exemple: nitroglycerine, isoprenaline, clonidine.

c. Nasal

The mucus membrane of the nose can readily absorb many drugs, digestive juices and liver are bypassed. However only certain drugs like posterior pituitary powder and desmopressin applied as a snuff or spray or nebulized solution have been used by this route.

d. Inhalation

Volatile liquids and gases are given by in this route for systemic action, e. g. general anesthetics, amyl nitrite. Absorption takes place from the vast surface of alveoli and action is very rapid or fast. Thus in this route controlled administration is possible with moment to moment adjustment.

e. Rectal

Certain irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect. This route can also be used, when the patient is having recurrent vomiting. In this route absorption is slower, irregular and often unpredictable. Rectal inflammation can be cure by best result from irritant drugs in this route, e. g. Indomethacin, paraldehyde, diazepam, aminophylline etc.

f. Cutaneous

Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption and the liver is also bypassed. The drug can be applied over specified area of skin. Transdermal therapeutic system- these are recently developed devices in the form of adhesive patches of various shapes and sizes (5-20 cm^2). Which deliver the contained drug at a constant rate into systemic circulation via the stratum corneum. The drug is delivered at the skin surface by diffusion for percutaneous absorption into circulation. Transdermal patches of nitroglycerine, nicotine and estradiol are available in India, while those of isosorbide dinitrate, hyoscine and clonidine are available in other countries.

g. Parenteral

This doses form refers to administration by injection directly into the tissue, fluid or blood without having to cross the intestinal mucosa. In this route action is faster and surer (valuable in emergencies). Gastric irritation and vomiting are not provoked. The routes of administration in this class are: **1.** Intradermal**, 2.** Subcutaneous **(S.C), 3.** Intramuscular, **4.** Intravenous**, 5.** Intraarticular**, 6.** Intra-arterial**, 7.** Intrathecal**, 8.** Intracisternal**, 9.** Intracardiac**, 10.** Intracameral**, 11.** Intrasynovial.

1. **Intradermal**

   The drug is injected/projected into the skin dermis and epidermis layer. The volume of injection usually between 0.1-0.2 ml. this route used for skin raising a bleb (e. g BCG vaccine, sensitivity tests) or scarring/multiple puncture of the epidermis through a drop of the drug is done. This route is employed for specific purposes only.

2. **Hypodermic or subcutaneous**

   The drugs is deposited in the loose subcutaneous tissue, which is richly supplied by nerves (irritant drugs can’t be injected this route) but is less vascular (absorption is

slower than intramuscular). Onlysmall volumes can be injected s.c. Self injection is possible in this route because deep penetration isnot needed. The route should be avoided in shock patients who are vasoconstricted absorption will bedelayed. The volume of injected drugs usually between 0.5-1.0 ml.

3. **Intramuscular**

   The drug is injected in one of the large skeletal muscles deltoid, triceps, gluteus maximus, rectus femoris etc. It is less painful, but self injection is often impracticable because deep penetration is needed. Intramuscular injections should be avoided in anticoagulant treated patients, because it can produce local haematoma. The volume rarely exceeds 2.0 mL.

4. **Intravenous**

   The drug is injected as a bolus (Greek: - bolos-lump) or infused slowly over hours in one of the superficial veins. The drug reaches directly into the blood stream and effects are produced immediately (suitable for emergency). Only aqueous solutions are to be injected i. v and there are no depot preparations for this route. The dose of the drug required is smallest (bioavailability is 100%) and even large volumes can be infused. The volumes of such injection can vary from 1.0-500 ml. some time it is more than 500 ml also.

5. **Intraarticular**

   The drug is injected in certain deep areas, where the systemic absorption is slow. The drug is used in this route into knee, elbow and solder joint.

6. I**ntra-arterial**

   The close intra-arterial injection is used for contrast media in angiography, anticancer drugs can be infused/used in femoral or brachial artery to localize the effect for limb malignancies. The drug is injected into artery terminating in target area.

7. **Intrathecal**

   Into the subarachnoid space surrounding spinal cord which contains cerebro-spinal cord, which contains cerebro-spinal fluid. Injection are generally made in the filum terminale area. Volumes up to 10 ml can be injected.

8. **Intracisternal:** Into the cistern containing cerebro-spinal fluid.

9. **Intracardiac:** Into the heart chamber.

10. Intracameral: Into the eye ball.

11. Intrasynovial: Into a joint fluid area.

2.5. Fate of drugs in the body

After administration drug is absorbed and enter the blood. Then it is transported with blood and distributed in the body. After that drug is biotransformated and excreted. These processes results in drugs' inactivation and elimination (**Figure 9**).

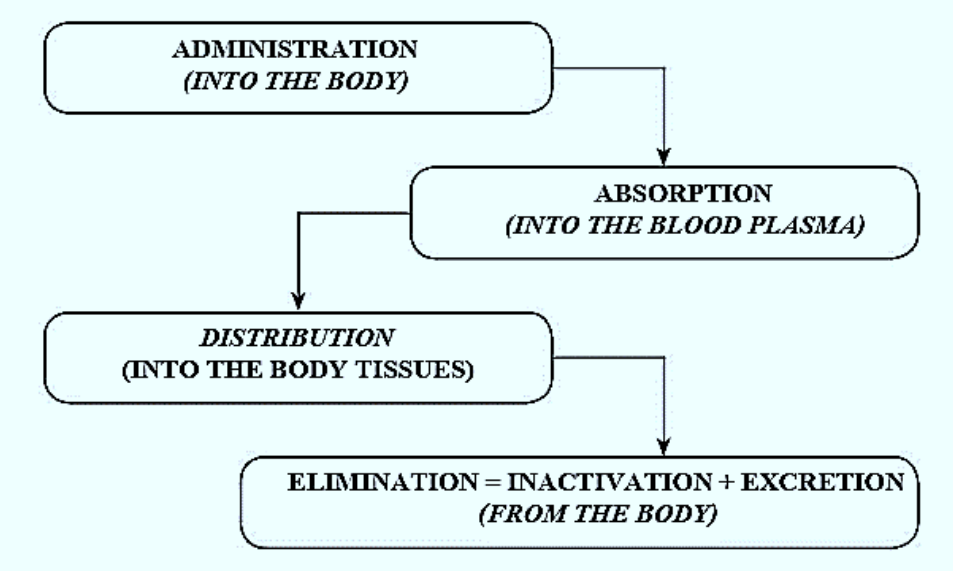


Figure 9. Schematic representation of drug absorption, distribution, and elimination

Absorption is the enter of a drug into the blood from the site of administration. **First pass metabolism** can occur with orally administered drugs. Drugs admin-istered orally are fist exposed to the liver and may be extensively metabolized before reaching the rest of the body Drugs administered enter directly into the systemic circulation and has direct access to the rest of the **body.** During the absorption drug crosses cell membranes. There are such kinds of this crossing as passive diffusion, filtration, active transport, and endocytosis (**Figure 10**).

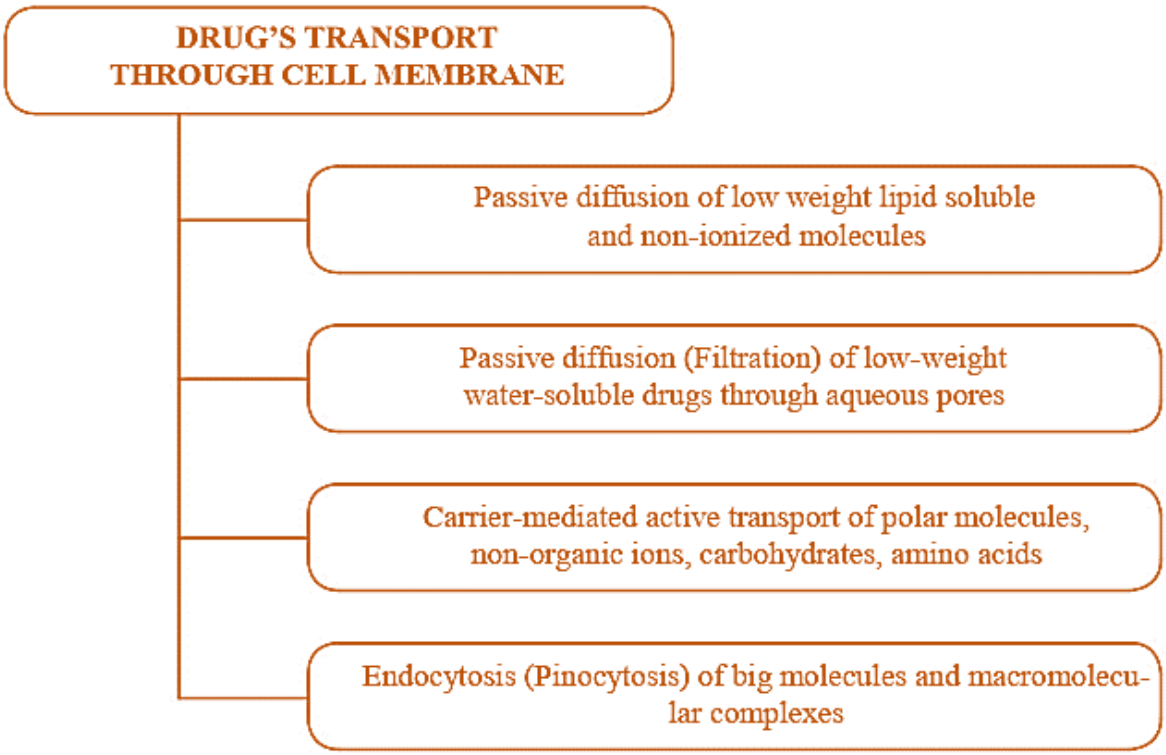


Figure 10. Schematic representation of a drug crossing through the cell membrane.

Passive diffusion is directed down concentration gradient (**Figure 11**). It does not require energy or carrier and is not saturable. Facilitated diffusion (or filtration) also is down gradient and energy independent, but needs carrier and is saturable. Active transport is against gradient, needs energy ATP and carrier, it is saturable.

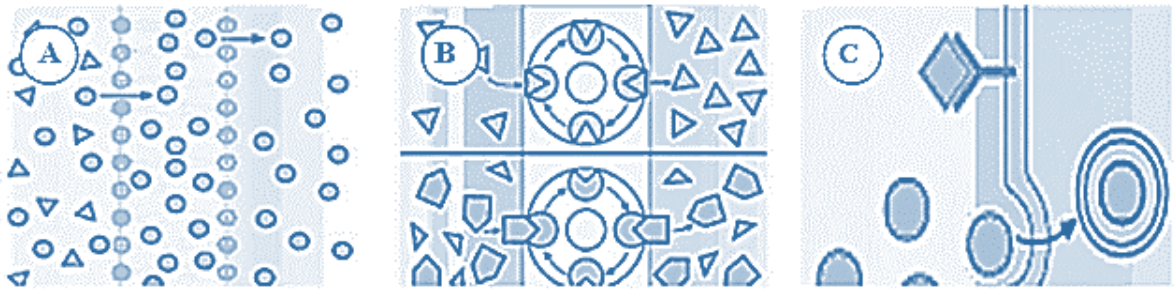


Figure 11. Passive diffusion (A), active transport (B), and endocytosis (C).

2.5.1. Factors affecting drug absorption

Factors affecting drug absorption are:

- **Solubility** of a drug in water and lipid affects absorption.
- **Dosage** affects the drug concentration at its site of action and, thus, greatly influences a biologic response to a drug. The larger the dose, the greater the effect, until a maximum effect is achieved. This is called a **dose-response relationship**.
- A **route of administration** affects the area of absorbing surface available to a drug. Drugs are absorbed more quickly from large surface areas. After any route of administration except intravenous administration the absorption of most drugs follows **first-order (exponential) kinetics**; thus, a constant *fraction* of drug is absorbed. After intravenous administration a constant *amount* (i.e. 100%) of a drug isabsorbed. After absorption or injection drugs may be distributed into interstitial or cellular fluids.

2.5.2. Factors influencing absorption

Factors influencing absorption are:

- Chemical structure
- Water- or lipid-solubility
- Ionization
- A medicinal form
- The route of administration
- State of tissues in the site of administration.

2.5.3. Drugs transport in the organism

Drugs transport in the body is realized: by proteins of the plasma (e.g. aspirin, sulfa drugs, hormonal preparations, iron) by lipoproteins of the plasma (e.g. vitamin A, vitamin D) by blood cells (e.g. antibiotics-macrolides) by the water fraction of the plasma (e.g. ions of sodium and potassium, glucose) .

2.5.4. Drugs distribution

Distribution is the process by which a drug leaves the blood stream and enters the intersticium (extracellular fluid or the cells of the tissues) Distribution depends on: The drug structure. The binding of drugs to plasma proteins. The blood flow The capillary permeability (blood-tissue barriers, e.g. the blood-brain barrier, placental barrier).

The transfer of drugs into the brain is regulated by the blood-brain barrier. The capillary membrane between the plasma and brain cells is much less permeable to water-soluble drugs than is the membrane between plasma and other tissues. The blood vessels of the fetus and mother are separated by a number of tissue layers that collectively constitute the placental barrier. Drugs that traverse this barrier will reach the fetal circulation. The placental barrier, like the bloodbrain barrier, does not prevent transport of all drugs but is selective, and factors that regulate passage of drugs through any membrane are applicable here.

Drug distribution may be uniform and nonuniform. Once in the circulatory system, some drugs can **bind** nonspecifically and reversibly to various **plasma proteins**; that is, to albumin or globulins. In this case, a bound and free drug reaches equilibrium. Only a **free drug** exerts a biologic effect; a bound drug stays in the vascular space, and is not metabolized or eliminated. Some areas of a body (e.g. the brain) are not readily accessible to drugs due to **anatomic barriers** (haematoencephalic etc.). The placenta also provides a barrier to some drugs. The drugs may be **sequestered** in storage depots; for example, lipid-soluble rugs in a fatty tissue. Factors modifying the **distribution** of a drug to a particular region of the body: physical and chemical characteristics of the drug (lipid to water partition coefficient); the velocity of blood circulation and cardiac output; capillary permeability in various tissues; lipid content of the tissue; binding to plasma proteins and tissues; disposition to tissues.

2.5.5. Biotransformation of drugs

Biotransformation is metabolism of drugs in the body. The main organ for drugs metabolism is the liver. Biotransformation is realized in two stages (**Figure 12**).

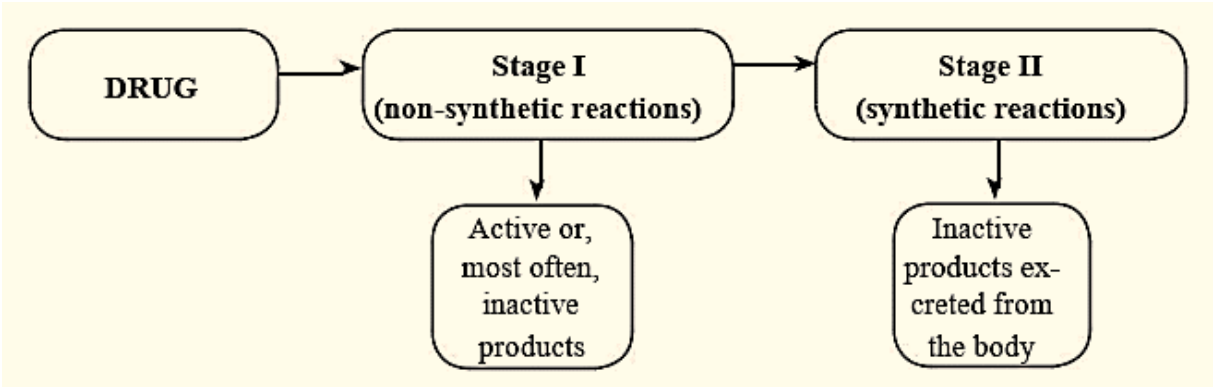


Figure 12. Stages of drugs biotransformation.

- ***Stage I*** reactions are non-synthetic and include oxidation, reduction, hydrolysis. Microsomal oxidation/reduction with participation of enzymes of cytochrome P-450

system is an important way of biotransformation of many drugs. The result of stage I is the formation of active or inactive products which enter the stage II reactions.

- ***Stage II*** reactions are synthetic (conjugation with glucuronic and sulfuric acids, methylation, acethylation). They lead to the formation of inactve metabolits excreted from the body. Drugs which increase the activity of microsomal enzymes in the liver are named the ***inductors of microsomal oxidation*** (e.g. phenobarbital, chlorpromazine). Drugs which decrease the activity of microsomal enzymes in the liver are named the ***inhibitors of microsomal oxidation*** (e.g. metronidazole).

Drug metabolism/biotransformation is the process of a chemical alteration of drugs in a body. The main principles are: a liver is a major site of metabolism for many drugs or other xenobiotics, but other organs, such as lungs, kidneys and adrenal glands can also metabolize drugs. Many lipid-soluble, weak organic acids or bases are not readily eliminated from a body and must be conjugated or metabolized to compounds which are more polar and less lipid-soluble before being excreted. Metabolism results in **inactivation** of a compound (e.g. morphini hydrochloridum). Some drugs are **activated** by metabolism. Some of these substances are called **prodrugs** (e.g. enalaprilum). Some drugs become more toxic by biotransformation.

2.5.6. Main pathways of drugs excretion

Drug excretion is the process of elimination of a drug or metabolite from a body. Elimination of drugs from the blood follows exponential (a first-order) kinetics. The elimination process can be saturated after high doses of some drugs and elimination will then follow a zero-order kinetics. Ethanol is a prototypic example. For drugs which are eliminated by a first-order kinetics, the fractional change in the amount of a drug in plasma or blood per unit of time is expressed by the half-life (t1/2), or by the elimination rate constant (k), which is equal to 0.693/t1/2**.** Routes of elimination. A kidney is the most important organ for excretion of drugs. Excretion of drugs and their metabolites into urine involves three processes: Glomerular filtration. Water-soluble and polar compounds are filtrated under hydrostatic pressure unable to diffuse back into circulation. Drugs dissolved in blood plasma are excreted in this way.

- ✓ ***Active tubular secretion:*** Mechanisms for active tubular secretion exist in the proximal tubule. Drugs such as organic acids (e.g. quinine sulfas) are transported by these systems.

- ✓ ***Passive tubular reabsorption:*** is typical for lipophylic nonpolar drugs. Biliary tract and faeces are important routes of excretion for some drugs which are metabolized in a liver (e.g. digitoxinum). Drugs and their metabolites can also be eliminated with expired air, sweat, saliva, tears, and breast milk. Drugs eliminated through these routes tend to be lipidsoluble and nonionized.

Excretion is the process by which drug leaves the body. Drugs are excreted:

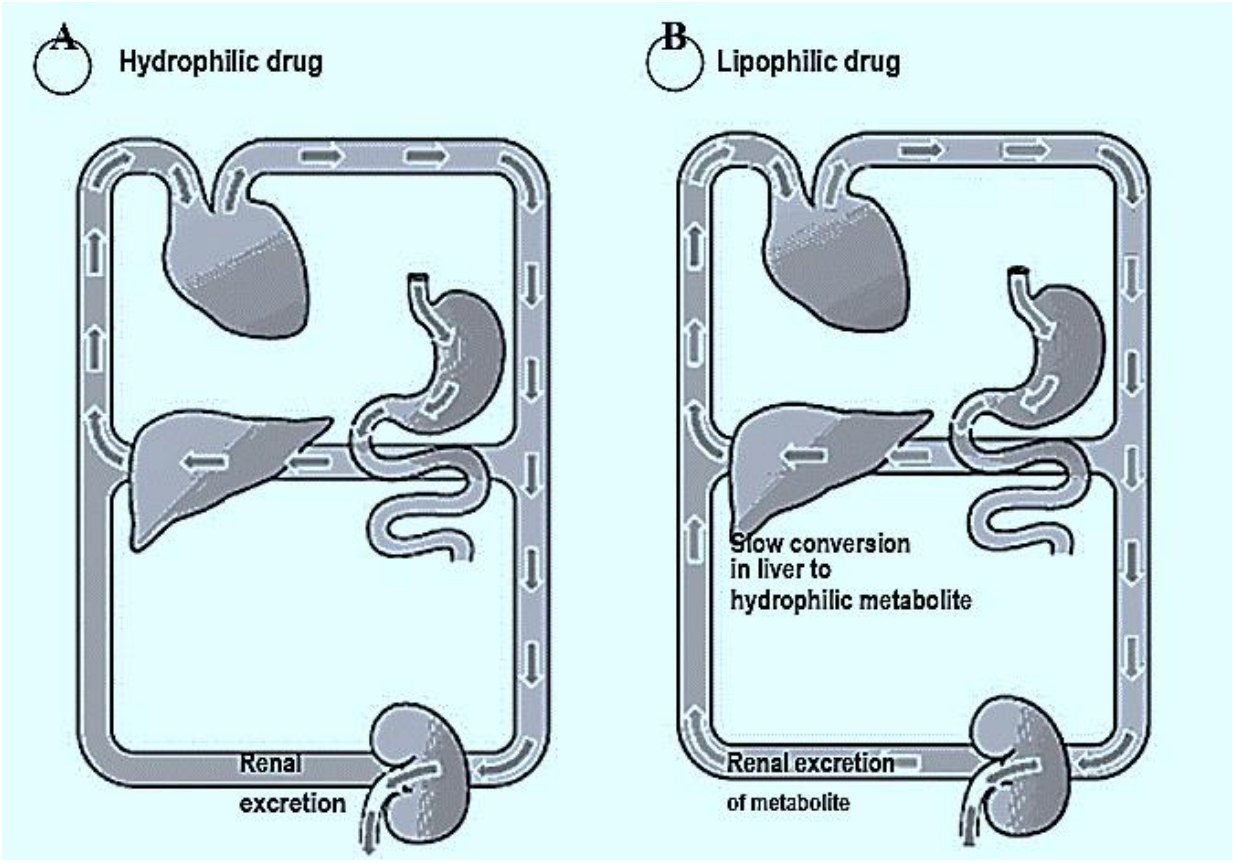


Figure 12. Renal excretion of hydrophilic (A) and lipophilic drugs (B)

Drugs and their metabolites enter primary urine by glomerular filtration and active secretion in proximal tubules (**Figure 13**). After that lipid soluble and unionized drugs are reabsorbed in distal tubules. Ionized, lipid-insoluble substances stay in urine and are excreted.

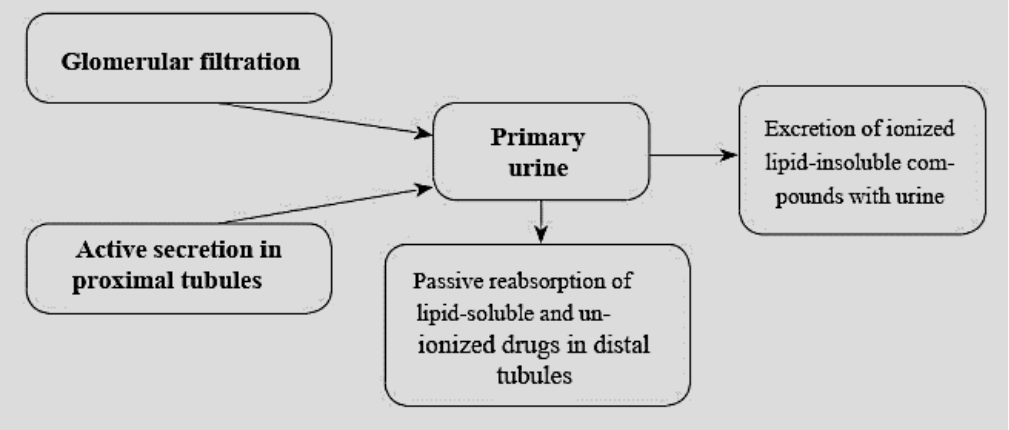


Figure 13. Drugs elimination in the kidney

2.6. Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation. Factors that influence bioavailability are solubility of a drug, nature of a drug, chemical instability, first-pass hepatic metabolism. The rate and amount of unchanged drug absorption into body, through different site of administration (oral and subcutaneous) into systemic circulation/target organ (blood, tissue, fluid & organ) is called bioavailability. Is one of the principal pharmacokinetic properties of drugs. When a drug is administered intravenously, its bioavailability is 100%, however, when a drug is administered by other routes (such as orally), its bioavailability generally decreases (due to incomplete absorption and first-pass metabolism) or may vary from patient to patient. The measurement of bioavailability **by: a.** Pharmacokinetics and **b.** pharmacokinetics

a. Pharmacodynamics

This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug.

b. Pharmacodynamics

This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/sub cellular/macromolecular levels,

CHAPTER 03

3. Pharmacokinetics

Pharmacokinetics is the mathematical description of the rate and extent of uptake, distribution of drugs in the body. The following are the most commonly measured pharmacokinetic metrics. Some of them are measured directly (maximal and minimal concentration, time to reach maximal concentration), other ones are calculated (volume of distribution, elimination half-life, elimination rate constant, area under the curve, clearance, bioavailability).

- ***Drug transport:*** The movement of drug molecules in the body is subject to absorption, distribution, and excretion.

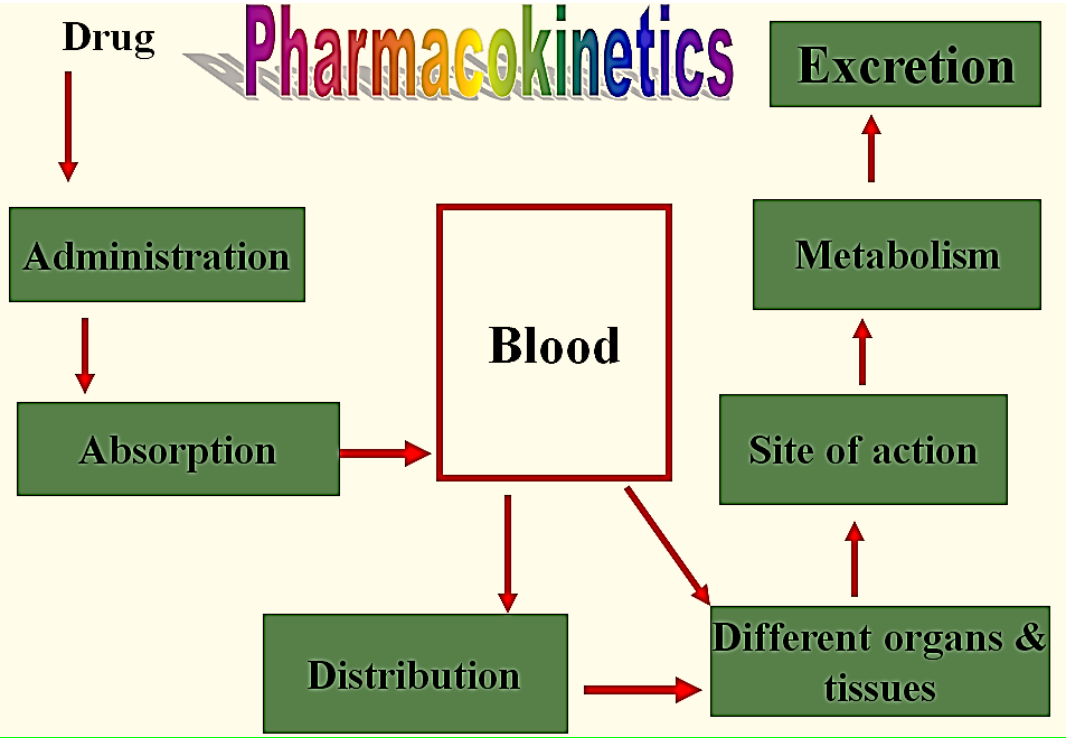


Figure 14. Pharmacokinetics

Pharmacokinetics is the quantitative study of drug movement in through and out of the body. Intensity of response is related to concentration of drug at the site of action, which in turn is dependent on its pharmacokinetic properties (**Figure 14**). All pharmacokinetic process involves transport of drug across biological membranes.

3.1. Biological membrane

This is a bilayer (about 100 A° thick) of phospholipid and cholesterol molecules, the polar groups (glyceryl phosphate attached to ethanolamine/choline or hydroxyl group of cholesterol) as shown in **Figure 15**.

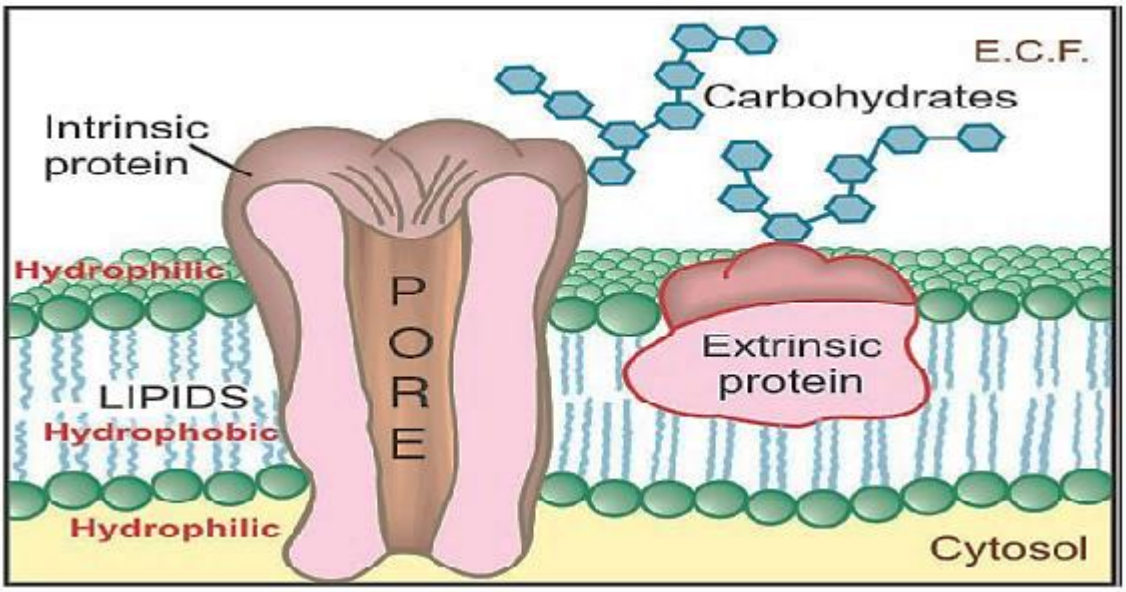


Figure 15. Structure of the organisation of biological membrane

Drugs can cross cellular membranes by various mechanisms. The mechanisms of absorption are similar to the mechanisms of membrane transport: passive diffusion, carrier-mediated diffusion, filtration, active transport, or pinocytosis. Being a bimolecular lipid layer, the cell membrane can also act as a barrier to some drugs (**Figure 16**).

Drugs are transport across the biological membranes by two ways: **1. Passive diffusion and filtration**, **2. Specialized transport**

1. Passive diffusion

Most compounds penetrate into cells by diffusing as the **unionized moiety** through the lipid membrane. Factors affecting the passage of a molecule through a membrane are the molecule's size and charge, the lipid-water partition coefficient, and the concentration gradient. The two types of passive drug transport are: **a. simple diffusion** and **b. filtration.**

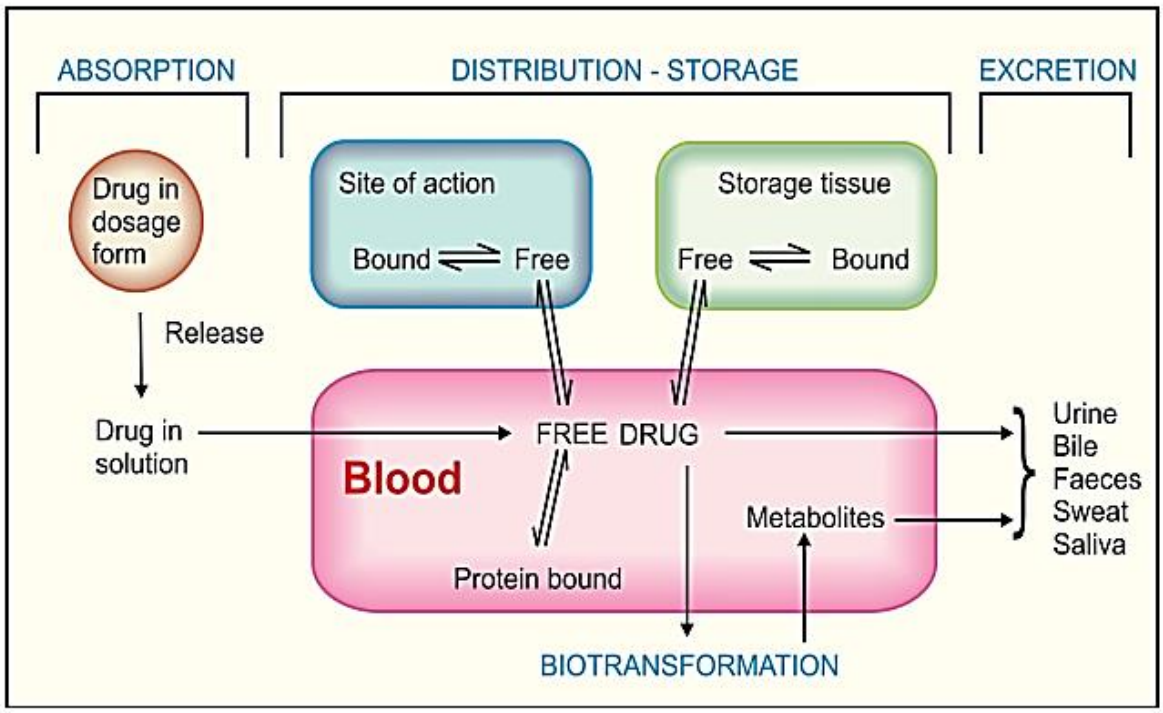


Figure 16. Schematic depiction of pharmacokinetic processes

a. Simple diffusion

Simple diffusion is characteristic of organic acids and alkaline. The greater the concentration gradient, the greater the rate of absorption. The larger the absorbing surface, the greater the drug flux. The diffusion constant is directly proportional to the temperature and is inversely related to the molecular size. The greater the lipid-water partition coefficient, the greater the drug flux. In simple diffusion, molecules cross the lipid membrane in an uncharged form. The pH of the medium affects the absorption and excretion of a passively diffused drug. Acidum acetylsalicylicum and other weak acids are best absorbed in the stomach because of its acidic environment. Alkalinic drugs are best absorbed in the small intestine, which has a higher pH.

b. Filtration

Filtration is a character of urea pure. Water, ions, and some polar and no polar molecules of low molecular weight can diffuse through membranes, suggesting that pores or channels may exist. The capillaries of some vascular beds (e.g. in the kidney) have large pores, which permit the passage of molecules as large as proteins.

2. Specialized transport

This can be carrier mediated or by pinocytosis:

a. Carrier transport

The drug combines with a carrier present in the membrane and the complex then translocates from one face of the membrane to the other. The host membranes/protein serves as carrier or transporters for ions, nutrients, metabolites, transmitters etc across the membrane. Carrier transport is specific, saturable and competitively inhibited by analogues which utilize the same carrier. This is of **two types**:

- ***Active transport***

  This movement process occurs against the concentration gradient and is inhibited by metabolic poisons. Where energy is requires for electrochemical gradient from lower to higher concentration e. g. levodopa and methyldopa.

- ***Facilitated diffusion***

  This proceeds more rapidly than simple diffusion and translocates even nondiffusible substrates, there is no need of energy for the transports of drugs and the transports also goes to direction of electrochemical gradient from higher to lower concentration.

b. Pinocytosis

It is the process of transport across the cell in a particulate form by formation of vesicles (small & hollow bag like structure in body). This is applicable to proteins and other big molecules, and contributes little to transport of most drugs.

- ***Simple passive/lipid diffusion***

  The drug diffuses across the membrane in the direction of its higher concentration to lower concentration gradient. Lipid soluble (water insoluble) drugs diffuse by dissolving in the lipoidal matrix of the membrane on this way.

- ***Filtration/aqueous diffusion***

  Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces. Water soluble (lipid insoluble) drug across biological membrane by filtration (lower concentration to higher concentration gradient) if their molecular size is smaller than the diameter of the pores (**Figure 17**).

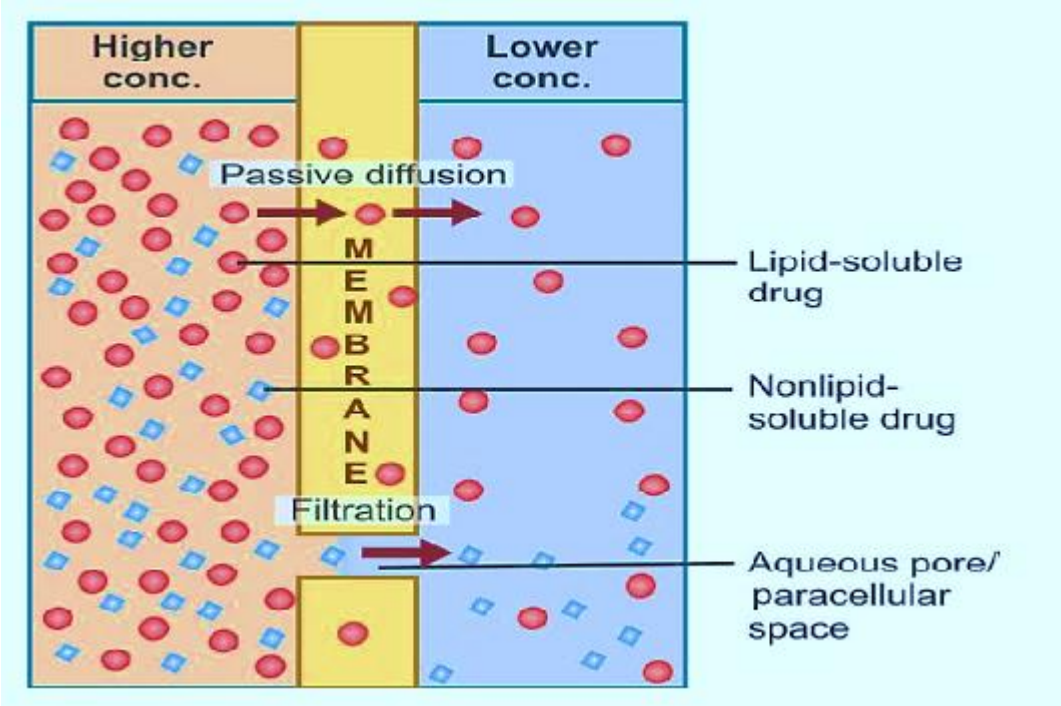


Figure 17. Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

3.2. Absorption

Absorption derived from (Absorb means, intake or accept & formation means process). Generally, absorption, the process of solid, liquid, gas or other substance being taken in any route that is called absorption e. g. plant absorb oxygen. In pharmacological definition absorption is movement of the unchanged drug from its site of administration (oral, IV, IM, topical and skin etc) into the systemic circulation (blood, fluid and tissue, etc):

a. Enternal route

By these routes the drug is the epithelial lining of the gastrointestinal tract, sublingual or buccal and also rectal. No ionized lipid soluble drugs are readily absorbed from stomach as well as intestine at rates proportional to their lipid: water partition coefficient.

b. Parenteral route

Par-beyond, enternal-intestinal, by these routes the drug is deposited directly in the vein, blood, fluid and tissue, in the vicinity of the capillaries (e. g. Intravenous, Intramuscular, Intradermal, Intraspinal and Intraarticular etc) lipid soluble drugs pass readily across the whole surface of the capillary endothelium.

c. Topical route

In these routes (skin, eye, ear, nose, inhalation, cornea, mucus membrane and intravaginal) the systemic absorption after topical application depends primarily on lipid solubility of drugs. The factors affecting GI absorption of a drug are:

1. Physicochemical factors

Including factors relating to the physical and chemical properties of the drug and dosage form characteristics and pharmaceutical ingredients:

- ✓ Drug solubility and dissolution rate
- ✓ Particle size and effective surface area
- ✓ Polymorphism and amorphism
- ✓ Salt form of the drug
- ✓ Pseudo polymorphism (hydrate/solvates)
- ✓ Lipophilicity of the drug
- ✓ pKa of the drug and gastrointestinal pH
- ✓ drug stability
- ✓ Stereochemical nature of the drug

2. Pharmaceutical factors

- ✓ Buffer
- ✓ Pharmaceutical ingredients (excipients/adjuvant)
- ✓ Nature and type of dosage form
- ✓ Product age and storage condition

3. Biological factors

- ✓ Age
- ✓ Sex (male/female)
- ✓ Species (man/animal/insect)
- ✓ Disease state
- ✓ Route of drug administration
- ✓ Gastrointestinal pH

3.2.1. Factor affecting absorption

These are some another factor, which is played a major role in absorption:

- ✓ **Aqueous solubility**

  Solid dosage form drugs given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.

- ✓ **Concentration**

  Drug given as concentrated solution is absorbed faster than from dilute solution.

- ✓ **Area of absorbing surface**

  Larger is the surface area, faster is the absorption.

- ✓ **Vascularity of the absorbing surface**

  Blood circulation removes the drug from the site of absorption and maintains the concentration gradient across the absorbing surface.

- ✓ **Route of administration**

  This affects drug absorption, because each route has its own peculiarities e. g. oral, topical and subcutaneous.

3.3. Distribution

Once a drug has been absorbed into the systemic circulation (vascular compartment), it is then capable of reaching any target organ by the process of distribution. The volume of distribution (V_d) reflects the extent to which a drug is partitioned between plasma and various other tissue compartments. Thus, the V_d is low for drugs that are retained within the vascular compartment and high for drugs that are highly distributed to adipose tissue and various other tissue compartment.

Distribution provides information on the extent/amount and time course of tissue accumulation and the elimination of drug and/or its metabolites. The disposition of drug into the organs and tissues via circulation depends upon the nature of the drug. The more lipophilic the drug is, the better will be the distribution into the organs and tissues. After absorption of drugs enters or passes through the various body fluid compartments such as blood, plasma, tissue and fluid, which is called distribution. On the other way it is a reversible transfer of drugs between one compartment to anther compartment. Distribution carried out by the one

compartment is blood or plasma and another compartment is extra vascular fluids and other body tissues (**Figure 18**).

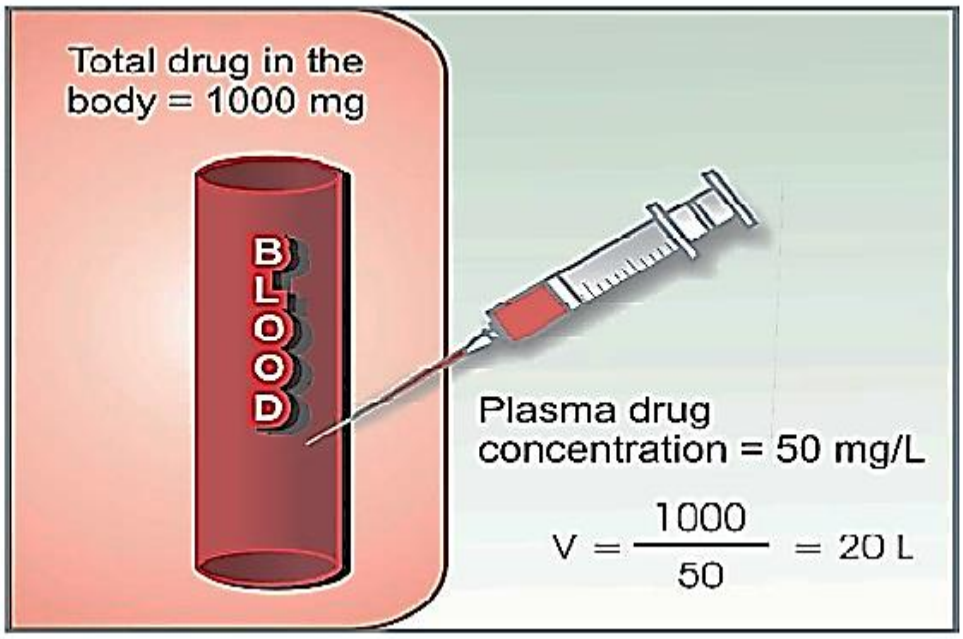


Figure 18. Illustration of the concept of apparent volume of distribution (V). In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L.

- **Volume of distribution**

  The volume of distribution (V_d), also known as apparent volume of distribution, is a pharmacological, theoretical volume that the total amount of administered drug would have to provide the same concentration as it is in blood plasma. If the amount of drug (X) and the resulting concentration (C) are known, then the volume of distribution (V_d) can be calculated using the simplified equations.

$X = V_d/C$, Where X = amount of drug in body, V_d = volume of distribution, C = plasma concentration.

The interaction of drugs and protein complex formation is called protein binding of drug, it is two types: **a)** Intracellular/primary receptor**, b)** Extracellular/secondary/silent receptor

a. Intracellular/primary receptor

The drugs bound with cell protein, which may be drug receptor and such binding show a pharmacological response and such receptor, which bind/interact with drug called primary receptor.

b. Extracellular/Secondary/Silent receptor

The drugs bind to extracellular protein, which is not show a pharmacological response that is called secondary or silent receptor. The most silent or secondary receptor of extracellular protein is plasma protein (particularly albumin). A drug in the body can interact with several tissue components of which are generally the macromolecules, proteins, DNA and adipose. Binding of drug are **two types**:

- **Binding of drug to blood components**

  The plasma protein and blood cells are a complex form of blood but these are separately bind with drugs and produces different pharmacological effects on these components.

  - **Plasma protein drug binding:**

    It is a reversible process of drug interaction, where the interaction of drugs and plasma proteins (human albumin serum, α acid glycoprotein, lipoprotein and α_1-α_2 globulin) complex formation is called plasma protein drug binding. The plasma proteins bound drug nor metabolized nor excreted or nor pharmacologically active and these are not show a pharmacological response.

- **Binding of drug to extra vascular tissues**

  A drug can bind to one or more of the several tissue components. The drugs bind to extra vascular tissue are Liver>kidney>lungs>muscle>intestine other are skin, eye, hair, bone, fat. Several example of extravascular tissue drug binding are:

  - **Liver:** As stated earlier, epoxides of a number of halogenated hydrocarbons and paracetamol bind irreversibly to liver tissues resulting in hepatotoxicity.
  - **Lungs:** Basic drugs like Imipramine, chlorpromazine and antihistamines accumulate in lungs.
  - **Kidney:** Metallothionin, a protein present in kidney, binds to heavy metals such as lead, mercury and cadmium and results in their renal accumulation and toxicity.
  - **Skin:** Chloroquine and phenothiazines accumulate in skin by interacting with melanin.
  - **Eyes:** The retinal pigments of the eye also contain melanin. Binding of chloroquine and phenothiazines to it is responsible for retinopathy.
  - **Hairs:** Arsenicals, chloroquine and phenothiazines are reported to deposit in hair shafts.

- **Bones:** Tetracycline is a well known example of a drug that binds to bones and teeth. Administration of this antibiotic to infants or children during odontogenesis results in permanent brown yellow discoloration of teeth. Lead is known to replace calcium from bones and cause their brittleness.
- **Fats:** Lipophilic drugs such as thiopental and the pesticide DDT accumulate in adipose tissue by partitioning into it. Receptors have stated that adipose localization of drugs is a result of binding competition between adipose and non adipose tissue (lean tissues like muscles, skin and viscera) and not partitioning.
- **Nucleic acids:** Molecular components of cells such as DNA interact strongly with drugs like chloroquine and quinacrine resulting in distortion of its double helical structure.

3.3.1. Factor affecting drugs distribution are:

a. Physiochemical properties of drug

- ✓ Particle size
- ✓ Aqueous/lipid solubility
- ✓ pKa value of drug
- ✓ Diffusion of drug
- ✓ pH
- ✓ Mass

b. Pharmaceutical factor

- ✓ Lipid : water partition
- ✓ Drug interaction
- ✓ Coefficient of the drug
- ✓ Binding of drug to blood components

c. Biological factors

- ✓ Organ/tissue size
- ✓ Age
- ✓ Diet
- ✓ Obesity
- ✓ Pregnancy
- ✓ Degree of plasma protein binding

- ✓ Fat lean body mass ratio
- ✓ Disease state

3.3.2. Bioavailability

is the systemically available fraction of a drug. Bioavailability is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a medication is administered intravenously, its bioavailability is 100%. When the medication is administered via other routes, its bioavailability decreases. Absolute bioavailability compares the bioavailability of the active drug in systemic circulation following nonintravenous administration with the bioavailability of the same drug following intravenous ad-ministration. Relative bioavailability measures the bioavailability of a formulation of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. Relative bioavailability is one of the measures used to assess bioequivalence between two drug products.

a. ***Volume of distribution*** is the apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).

b. ***Elimination half-life*** is the time required for the concentration of the drug to reach half of its original value.

c. ***Steady state concentration*** is the concentration at stedy state, the situation where the overall intake of a drug is fairly in dynamic equilibrium with its elimination. Steady state is reached when a time of 4 to 5 times the half-life for a drug after regular dosing is started (**Figure 19**).

Area under the curve is the integral of the concentration-time curve after a single dose or in steady state. ***Clearance*** is the volume of plasma cleared of the drug per unit time.

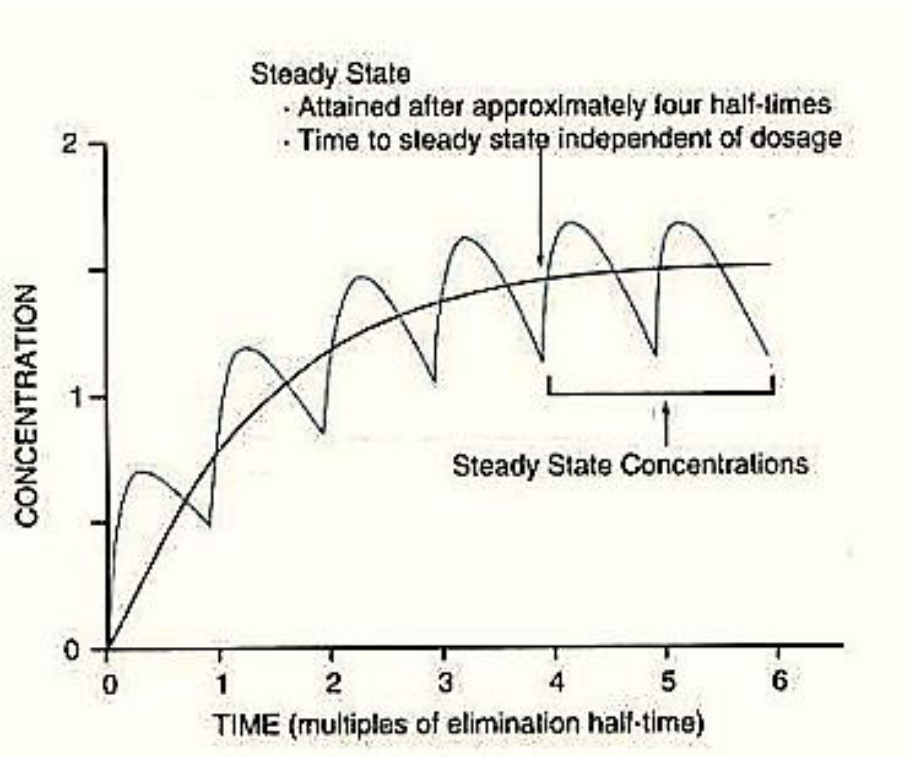


Figure 19. Steady state concentration.

3.4. Biotransformation

Although every tissue has some ability to metabolize drugs, the liver is the principal organ of drug metabolism. Other tissues that display considerable activity include the gastrointestinal tract, the lungs, the skin, the kidneys, and the brain. After oral administration, many drugs (eg, isoproterenol, meperidine, pentazocine, morphine) are absorbed intact from the small intestine and transported first via the portal system to the liver, where they undergo extensive metabolism.

Most metabolic biotransformations occur at some point between absorption of the drug into the general circulation and its renal elimination. A few transformations occur in the intestinal lumen or intestinal wall. In general, all of these reactions can be assigned to one of two major categories called **phase I** and **phase II reactions** (**Figure 19**).

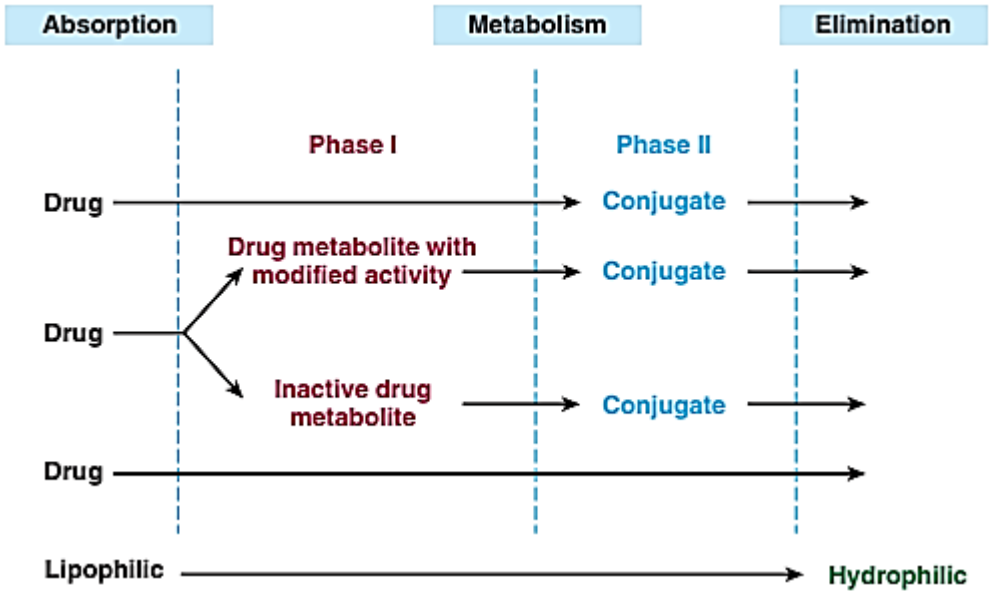


Figure 19. Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I reactions.

Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (OH, NH_2, SH). Often these metabolites are inactive, although in some instances activity is only modified or even enhanced. If phase I metabolites are sufficiently polar, they may be readily excreted. However, many phase I products are not eliminated rapidly and undergo a subsequent reaction in which an endogenous substrate such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid combines with the newly incorporated functional group to form a highly polar conjugate. Such conjugation or synthetic reactions are the hallmarks of phase II metabolism. A great variety of drugs undergo these sequential biotransformation reactions, although in some instances the parent drug may already possess a functional group that may form a conjugate directly. For example, the hydrazide moiety of isoniazid is known to form an *N*-acetyl conjugate in a phase II reaction. This conjugate is then a substrate for a phase I type reaction, namely, hydrolysis to isonicotinic acid (**Figure 20**). Thus, phase II reactions may actually precede phase I reactions.

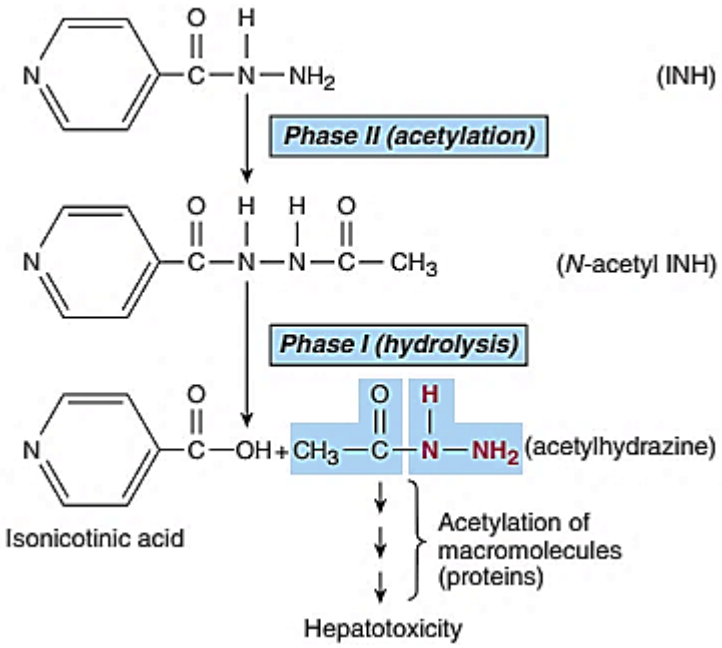


Figure 20. Phase II activation of isoniazid (INH) to a hepatotoxic metabolite

Although drug biotransformation in vivo can occur by spontaneous, noncatalyzed chemical reactions, most transformations are catalyzed by specific cellular enzymes. At the subcellular level, these enzymes may be located in the endoplasmic reticulum (ER), mitochondria, cytosol, lysosomes, or even the nuclear envelope or plasma membrane (**Figure 21**).

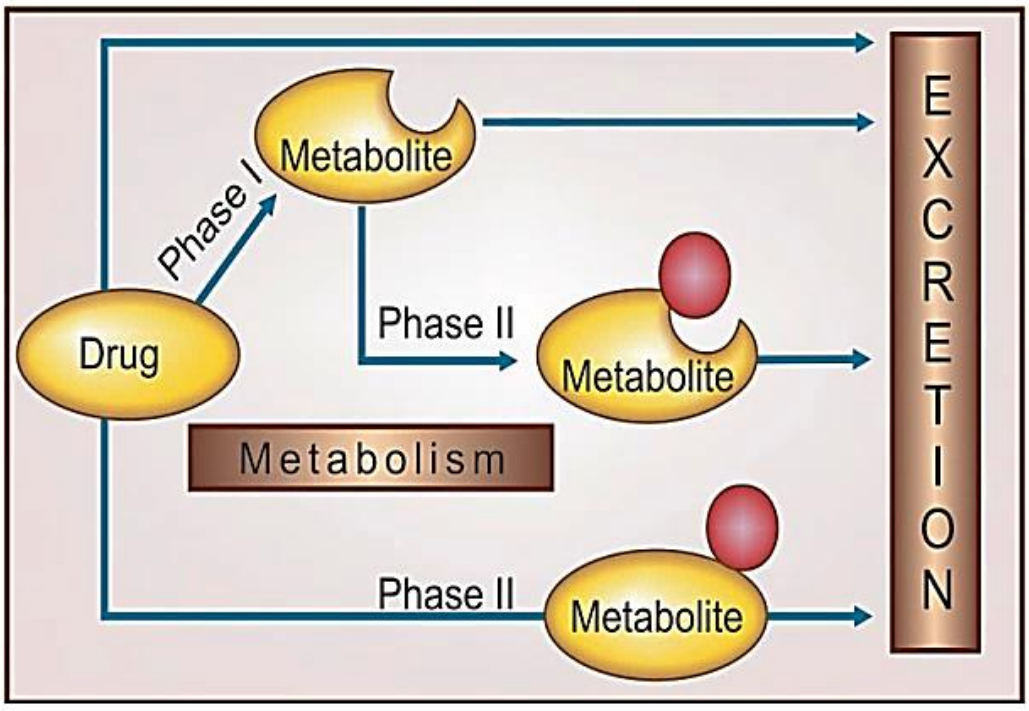


Figure 21. Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

3.4.1. Factor affecting metabolism

Factor affecting drugs metabolism are:

a. Physiochemical properties of drugs

- ✓ Induction and inhibition of drug metabolizing enzymes
- ✓ Environmental chemicals

b. Biological factors

- ✓ Species differences
- ✓ Strain differences
- ✓ Sex differences
- ✓ Age
- ✓ Diet
- ✓ Pregnancy
- ✓ Hormonal imbalance
- ✓ Disease states

3.5. Excretion

Excretion derived from 'Excrete', which means to pass out solid or liquid waste material from the body or pass out the waste material internal phase to external environmental condition.). Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

a. Urine: The kidney is responsible for excreting all water soluble substances. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion.

b. Faeces: Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids, organic bases, other lipophilic drugs and steroids by distinct nonspecific active transport mechanisms. Relatively larger molecules are preferentially eliminated in the bile..

c. Exhaled air: Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its

partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.

c. Saliva and sweat: These are of minor importance for drug excretion. Lithium, pot. iodide, rifampicin and heavy metals are present in these secretions in significant amounts. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

d. Milk: The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. However, the total amount of drug reaching the infant through breast feeding is generally small and majority of drugs can be given to lactating mothers without ill effects on the infant.

3.5.1. Nephron :A basic functional unit of kidney, each kidney contains 1 million nephron. Nephron is a coil like cell present in kidney, which are filtered the blood and separate the water and blood through tubular cell. Drugs and their metabolites are removed from the body is called excretion or it is an irreversible loss of drug from body, where the drug metabolites transfer from internal to external environment. These are categorized in two types: **a.** Renal, **b.** Non-renal.

a. Renal

All most all drugs and their metabolites are excreted by kidney. The kidney is responsible for excreting all water soluble, non-volatile, small size and metabolized slowly substances/drugs. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion (**Figure 22**).

Net renal excretion = (Glomerular filtration + Tubular secretion) – tubular reabsorption

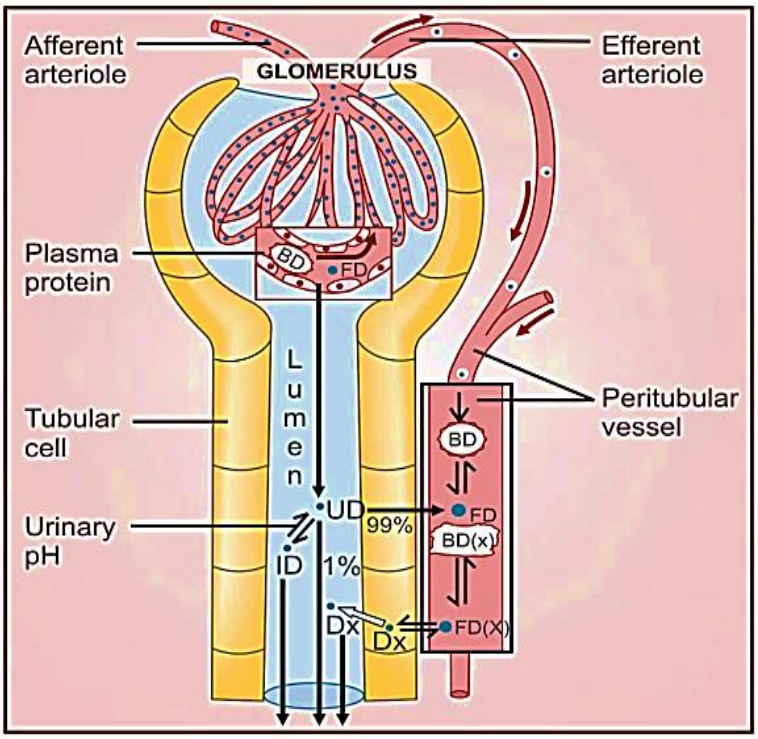


Figure 22. Schematic depiction of glomerular filtration, tubular reabsorption and tubular secretion of drugs FD—free drug; BD—bound drug; UD—unionized drug; ID—ionized drug; Dx—actively secreted organic acid (or base) drug

- ✓ **Urine:** Urine excreted by through the kidney. It is the most important channel of excretion for majority of drugs. All most all drugs and their metabolites are excreted by the kidney to some extent or the other. Agents that are excreted in urine are, water soluble, non-volatile and small in molecular size (less than 500 Daltons).
- ✓ **Kidney:** The processes which determine the elimination/excretion of a drug in the urine are:
    - ✓ **Glomerular filtration/Passive glomerular filtration:** Only the unbound fraction of unionized drugs is filtered at the glomerulus, but they are reabsorbed by diffusion back from tubular lumen into the cells lining the tubules. Glomerular capillaries have pores larger than usual; all nonprotein bound drug (whether lipid-soluble or insoluble) presented to the glomerulus is filtered. Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow. Glomerular filtration rate (g.f.r.), normally ~ 120 ml/min, declines progressively after the age of 50, and is low in renal failure.

- ✓ **Active tubular secretion:** Many weak acids (anionic substances) and weak bases (cationic substances) are actively secreted by proximal tubules by carrier mediated systems involving transporters such as p-glycoprotein and the multidrug resistance associated protein type 2 (MRP2). This is the active transfer of organic acids and bases by two separate classes of relatively nonspecific transporters (OAT and OCT) which operate in the proximal tubules.
    - **Organic acid transport:** (through OATP) operates for penicillin, probenecid, uric acid, salicylates, indomethacin, sulfinpyrazone, nitrofurantoin, methotrexate, drug glucuronides and sulfates, etc.
    - **Organic base transport:** (through OCT) operates for thiazides, amiloride, triamterene, furosemide, quinine, procainamide, choline, cimetidine, etc.
- ✓ **Passive tubular reabsorption:** This occurs by passive diffusion and depends on lipid solubility and ionization of the drug at the existing urinary pH. Lipid-soluble drugs filtered at the glomerulus back diffuse in the tubules because 99% of glomerular filtrate is reabsorbed, but nonlipid-soluble and highly ionized drugs are unable to do so. Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized:
    - Weak bases ionize more and are less reabsorbed in acidic urine.
    - Weak acids ionize more and are less reabsorbed in alkaline urine.

b. Non-renal

These routes are not depends upon the kidney and their metabolites are excreted by different another organ e. g. skin, intestine, lungs, milk etc.

- ✓ **Skin:** Arsenic and heavy metals like mercury and excreted in small quantities through the skin. Arsenic gets incorporated in the hair follicle on prolonged administration. This phenomenon is used for detection of arsenic poisoning.

- ✓ **Intestine:** Heavy metals are excreted through the intestine and can produce intestinal ulceration. Laxatives like cascara and senna, which act mainly on the large bowel are partly excreted into that area from the blood stream, after their absorption from the small intestine.

- ✓ **Lungs:** Volatile general anesthetics and certain other drugs like paraldehyde and alcohol are partially excreted by the lungs.

- ✓ **Milk:** The excretion of drug in milk is not important for the mother, but the suckling (who intake the milk) infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. As such more lipid soluble and less protein bound drugs cross better. However the total amount of drug reaching the infant through breast feeding is generally small and majority of the drugs can be given to lactating mothers without ill effects on the infant.

- ✓ **Faeces:** Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids (especially drug glucuronides by OATP and MRP2).

- ✓ **Exhaled air:** Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility.

- ✓ **Saliva and sweat:** Certain drugs like iodides and metallic salts are excreted in the saliva. These are of minor importance for drug excretion.

- ✓ **Bile:** Drugs such as phenolphthalein deoxycycline and cefoperazone appear in high concentration in the bile. Such drugs may get repeatedly reabsorbed from the intestine and reexcreted in bile, for excreting a prolonged action.

3.5.2. Factor affecting excretion

- ✓ Physiochemical properties of drugs
- ✓ Plasma concentration of the drug
- ✓ Distribution & binding characteristics of the drug
- ✓ Urine pH
- ✓ Blood flow to the kidney
- ✓ Drug interaction
- ✓ Biological factors: Age, diet, pregnancy, hormonal imbalance, disease states.

CHAPTER 04

4. Pharmacodynamics

Pharmacodynamics refers to the relationship between drug concentrations at the site of action and the resulting effect, including the time course and intensity of therapeutic and its adverse effects. Pharmacodynamics is the study of drug effects. It starts with describing what the drugs pharmacological and biochemical effect; when it reaches the site of action in body and goes on to explain how they do it. The site of drug action or where a drug acts, and the mechanism of drug action or how a drug acts, are the two fundamental and complex problems in pharmacodynamics. Modification of the action of one drug by another drug is also an aspect of pharmacodynamics. **Pharmacodynamics** is the section of pharmacology which studies how the drug acts on the body. It describes:

- ✓ Effects
- ✓ The mechanism of action
- ✓ Drugs interactions
- ✓ Doses
- ✓ Dose-effect dependence
- ✓ Factors influencing a drug action.

Pharmacodenamic involves how the drugs act on target cells to alter cellular function.

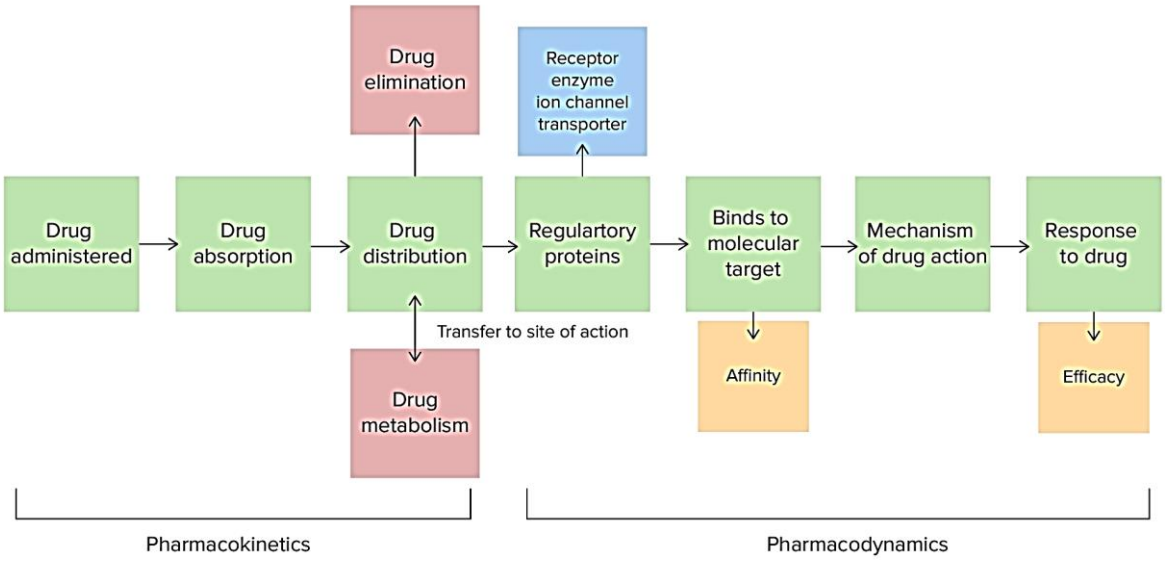


Figure 23. Pharmacodynamics

Many drugs are similar to or have similar chemical groups to the naturally occurring chemical and have the ability to bind onto a receptor where one of two things can happen- either the receptor will respond or it will be blocked.

4.1. Types of drugs doses

The **dose** is the amount of drug administered into the body. The dose may be: **single** (for single administration), **daily** (for the day of treatment), **total** (for the course of treatment).

- **Effect of repeated doses:** If the time interval between doses is less than four of its half lives a drug accumulates in a body. In this case the total body stores of the drug increase exponentially to a plateau. This plateau is known as a **steady-state concentration.**

4.1.1. Drugs interaction

Drugs interaction is the action of one drug on another one (**Table 2**).

Table 2. Two types of drugs interaction

Pharmaceutical (before the administration, outside the body)	***Pharmacological*** (after the administration, inside the body)
1. Physical (changes in agregate state of drugs) 2. Chemical (chemical reactions between the drugs).	1. Pharmacokinetic (interaction during absorption, distribution, biotransformation, and excretion) 2. Pharmacodynamic (intraction in tissues during binding to receptors).

4.1.2. Types of drugs action

Drugs action is displayed as changes in the function of organs and systems. There are such types of drugs action: local (in the site of administration), resorptive (after the absorption into the blood) direct (in the organ with target cells), indirect (in other organs, but due to the action on the target organ), reflexive (by reflexes) non-selective (on all cells), selective (on celected cells and tissues) reversible (with restoration to the initial state after the elimination of the drug), irreversible (without the restoration to the initial state after the elimination of the drug) main effects (for which the drug is used), side-effects (unwanted effects of a therapeutic dose of the drug).

4.1.3. Principles of drug action

Drugs do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity. However, this alone can have profound medicinal as well as toxicological impact. The basic types of drug action can be broadly classed as:

a. **Stimulation:** Increase in the activity of specialized cells is called stimulation e.g. adrenaline stimulates heart, pilocarpine stimulates salivary glands. However, excessive stimulation may ultimately lead to depression.
b. **Depression:** Decrease in the activity of specialized cells is called depression e. g. quinidine depresses the myocardium (Heart chamber cell) while barbiturates depress the central nervous system, omeprazole depresses gastric acid secretion.
c. **Irritation:** The term irritation indicates that a drug produces adverse effects on the growth, nutrition and morphology of living tissues. It produces changes in the cellular structure and can produce inflammation, corrosion and necrosis of cells. This may result in diminution or loss of function. The cellular changes produced are:
    - Astringent effect
    - Dehydration
d. **Replacement:** Drugs may be used as replacement when the production of endogenous substances is reduced. This replacement finds an important application in the treatment of hormonal deficiencies, e.g. levodopa in parkinsonism, insulin in diabetes mellitus, iron in anemia.
e. **Cytotoxic:** Damage to the cell wall or the nucleus e. g. anticancer drugs. Selective cytotoxic action on invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure/palliation of infections and neoplasms, e.g. penicillin, chloroquine, zidovudine, cyclophosphamide, etc.

4.1.4. Mechanisms of action

Mechanisms of action are events in cells caused by the drug. Medicinal substances realize their action by:

- changing of the enzymes activity (e.g. neostigmine as acethylcholinesterase inhibitor) interaction with receptors (e.g. atropine as M-cholinoblocker)
- influence on ion channels (e.g. local anesthetics)
- influence on the transport systems the antimetabolic mechanism (e.g. methotrexate as folate antagonist)
- the action at the genes level (e.g. anti-cancer drugs).

Most drugs interact with macromolecular components (called receptors**)** of a cell or an organism to begin biochemical and physiologic changes which causes drugs observed effects, or response, or primary pharmacological reaction. Receptors bind ligands and transduce signals. A drug is called an **agonist** if it interacts with specific receptor, causes its

conformation biochemical reactions, produces some of the effects of endogenous compounds. Agonists (e.g. acetylcholine) have intrinsic activity. Intrinsic activity is a drug ability to stimulate receptor and cause specific effects. An **antagonist** is a drug which has no intrinsic activity, even when it can reduce or abolish the effect of an agonist, protect from neuromediators and hormones action. Examples of pure antagonists are atropine sulfas and tubocurarini chloridum, which inhibit the effect of acetylcholine. If antagonists occupy the same receptors as agonists they are called concurrent antagonists (e.g. atropini sulfas). If antagonists occupy other sites of macromolecules which do not belong to a specific receptor they are called nonconcurent antagonists. Some drugs (e.g. nalorphini hydrochloridum) are agonists-antagonists or synergoantagonists; they have some intrinsic activity and may activate one type of receptors and block another one. There are drugs which may not cause a response by interacting with receptors. These drugs may combine with small molecules or ions found in a body. Drug or its effects are being used as synonyms. It is useful to term the initial consequences of drug cell interaction as action of the drug; the events that follow are called drug effects. A drug may act by virtue of its:

a. Physical action

- ✓ **Colour:** A pleasant colour may exert a psychological effect e. g. tincture of cardamom.
- ✓ **Physical mass:** Compounds like agar and psyllium seeds absorb water when administered orally and swell in size.
- ✓ **Smell:** Volatile oils like peppermint oil are used to mask the unpleasant smell of mixtures.
- ✓ **Taste:** Compounds with a bitter taste reflexly increase the flow of hydrochloric acid in the stomach and improve the appetite.
- ✓ **Osmolality:** Osmotic diuretics like mannitol, osmotic purgatives like magnesium sulfate.
- ✓ **Adsorption:** Kaolin and activated charcoal in the treatment of diarrhea.
- ✓ **Soothing-demulcent:** Syrups as pharyngeal demulcents in the treatment of cough, calamine lotion in eczema.
- ✓ **Reduction in surface tension:** Cationic surfactants like certrimide for cleaning the skin.
- ✓ **Electric charge:** Heparin a strongly acidic compound exerts its anticoagulant effect by virtue of its negative charge.
- ✓ **Radioactivity:** 131I in the treatment of hyperthyroidism.

- ✓ **Radio-opacity:** Barium sulphate as barium meal organic iodine compounds for the visualization of the urinary and biliary tracts.

b. Chemical action

- ✓ **Acidity or alkalinity:** Antacids in the treatment of peptic ulcer.
- ✓ **Chelation:** The chelating agent forms a ring structure with the molecules of lead, copper and other metals. This ring structure is non toxic and water soluble and is excreted in the urine.

c. Through enzymes: Almost all biological reactions are carried out under catalytic influence of enzymes. Drugs can either increase or decrease the rate of enzymatically mediated reactions.

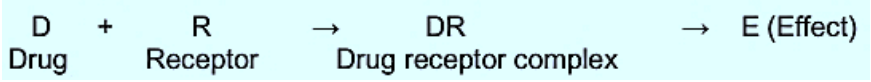
- ✓ **Stimulation:** Drugs may act by either increasing the rate of enzymatically mediated chemical reactions in the body is called enzyme stimulation. Thus, stimulation of enzymes by drugs, that are truly foreign substances, is unusual. Enzyme stimulation is relevant to some natural metabolites only, e.g. adrenaline stimulates adenylyl cyclase, pyridoxine acts as a cofactor and increases decarboxylase activity.
- ✓ **Enzyme inhibition:** Some chemicals (heavy metal salts, strong acids and alkalies, formaldehyde, phenol, etc.) denature proteins and inhibit all enzymes non-selectively. However, selective inhibition of a particular enzyme is a common mode of drug action. Such inhibition is either competitive or noncompetitive e.g. denaturing by alcohol or heavy metals or specific, inhibition of carbonic anhydase by acetazolamide and that of angiotensin converting enzyme (ACE) by captopril. It is occurs and commonly two types specific and non-specific.
    - o **Specific:** Where drug inhibition process carried out by a specific (selectively only one enzyme) enzyme without affecting anther enzymes, that is called specific inhibition, these are another **two types**:
        1. **Competitive** *(equilibrium type):* When drug competes with normal substrate or coenzyme for the catalytic binding site of the enzyme so that the product is not formed or a nonfunctional product is formed and a new equilibrium is achieved in the presence of the drug.
        2. **Non-competitive** *(non-equilibrium type) :* A *non-equilibrium type* of enzyme inhibitor reacts with adjacent site and not with the catalytic site or enzyme site and enzymes loses his catalytic enzymatic properties.

- **Non-specific:** When tertiary structure nature enzymes are comes in the contact of drugs and their chemical compounds, they inhibit the enzymatical process that is called non-specific inhibition.

d- Through receptor

Many drugs act by binding to specific protein macromolecules in the cell membrane or in the cytosol and regulate the cell function by altering enzyme activity, permeability to ions, conformational features or genetic material in the nucleus.

- ✓ **Receptor:** It is defined as a macromolecule or protein interact/attached/binding with drugs that is called receptors. Though, in a broad sense all types of target biomolecules, including the effectors (enzymes, channels, transporters, etc.) with which a drug can bind to produce its action have been denoted as 'receptors'. It is therefore better to reserve the term 'receptor' for purely regulatory macromolecules, which combine with and mediate the action of signal molecules including drugs.
- ✓ **Nature of receptor:** Receptors are regulatory macromolecules and mostly protein through nucleic acid may also serve as receptor.
- ✓ **Receptor theory:** After studying quantitative aspects of drug action, Clark (1937), propounded a theory of drug action based on occupation of receptors by specific drugs and that the pace of a cellular function can be altered by interaction of these receptors with drugs which, in fact, are small molecular ligands. He perceived the interaction between the two molecular species, *viz.* drug (*D)* and receptor (*R*) to be governed by the law of mass action, and the effect (*E*) to be a direct function of the drug receptor complex (*DR*) formed:



The following terms are used in describing drug-receptor interaction:

- **Affinity:** It is the ability of drugs to combine with receptor, which is called affinity.
- **Intrinsic activity (Efficacy):** It is the ability of drugs to activate the receptor, which is called efficacy.
- **Agonist:** An agents or drugs, which activate a receptor to produce an effect similar to that of the physiological signal molecule.
- **Competitive antagonists:** Competitive antagonists have affinity but no intrinsic activity (IA = 0), e.g. propranolol, atropine, chlorpheniramine, naloxone.

- **Inverse agonist:** An agents or drugs, which activates a receptor to produce an effect in the opposite direction to that of the agonist (**Figure 24**).
- **Antagonist:** An agents or drugs, which prevents the action of an agonist on a receptor or the subsequent response, but does not have any effect of its own.
- **Partial agonist:** An agents or drugs, which activates a receptor to produce sub maximal effect but antagonizes the action of a full agonist.
- **Ligand:** (Latin: *ligare*—to bind) any molecule or drugs, which attaches selectively to particular receptors or sites. The term only indicates affinity or ability to bind without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.

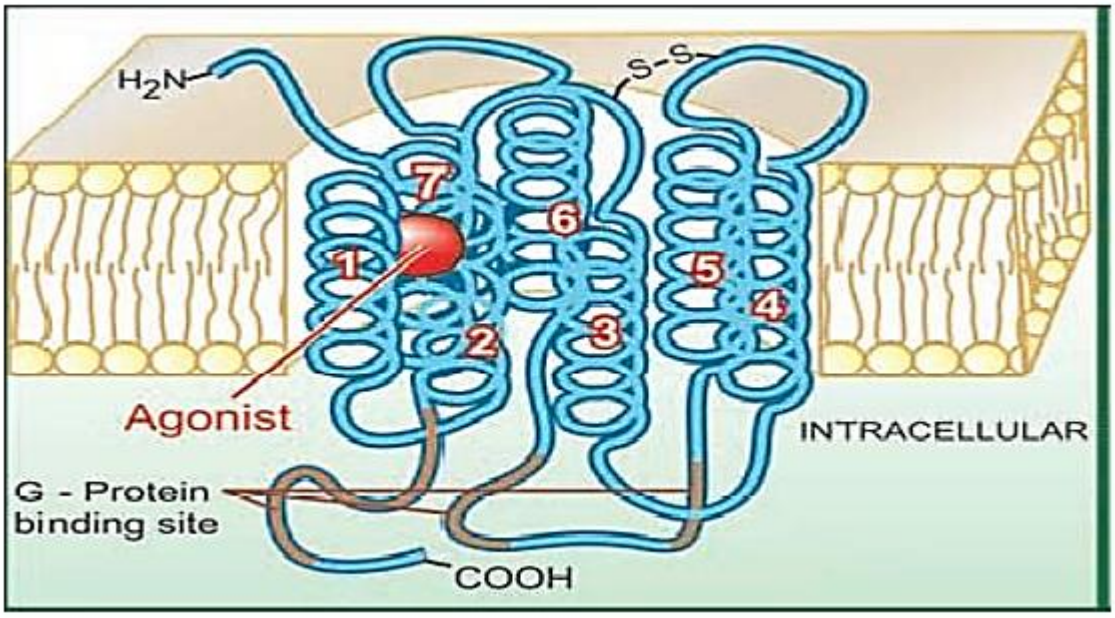


Figure 24. Diagrammatic representation of G-protein coupled receptor molecule

4.1.5. Factors influencing drug action

Factors influencing drug action are the age, weight, gender, physiological state, illness, genetic factors. Genetic factors represent an important source of interindividual variation in drug response. Relatively few adverse drug effects with a pharmacodynamic basis are known, and most of the well characterised inherited traits take the form of genetic polymorphisms of drug metabolism. Monogenic control of N-acetylation, S-methylation and cytochrome P450-catalysed oxidation of drugs can have important clinical consequences. Individuals who inherit an impaired ability to perform one or more of these reactions may be at increased risk of concentration-related toxicity. ***Pharmacogenetics*** is the study of inherited genetic

differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects. The term pharmacogenetics is often used interchangeably with the term ***pharmacogenomics*** which also investigates the role of genetic differences in relation to drug response and drug behaviour through examination of genes, gene products, and inter- and intra individual variation in gene expression and function.

4.3. Effects of repeated doses of drugs

- **Accumulation** (material and functional): is the accumulation of the drug or its effects (e.g, material accumulation of digitoxin, functional accumulation of antidepressants).
- **Tolerance** (habituation): is a decrease of drug's action after its repeated admin-istration (e.g, tolerance to hypnotics, alcohol, nitroglycerine, laxatives).
- **Tachyphylaxis:** is the rapid form of tolerance developing during the first day of treatment (e.g, tachyphylaxis to ephedrine).
- **Drug dependence:** is irresistible aspiration to take the drug for euphoria or improvement of condition.

There are two types of drug dependence:

- ***Physical dependence:*** if the patent wants to take the drug for altering general state and mood. It is characterized by abstinence. ***Abstinence*** is a phenomena of deprivation. Ethyl alcohol and narcotic analgesics may cause physical dependence.
- ***Psychological dependence:*** if the patient wants to take the drug for altering the mood (for euphoria). Such kind of drug dependence is caused by psychomotor stimulants.

CHAPTER 05

5. Active principles of medicinal plants

The medicinal value of plants or crude preparations of medicinal plants is due to presence of a variety of pharmacologically active principles, such as alkaloids (**Figure 25**), glycosides, oils, resins, oleoresins, gums, saponins, tannins etc.

5.1. Alkaloids

- ✓ Basic, nitrogenous substances.
- ✓ Insoluble in water, less soluble in alcohol, soluble in ether, chloroform and oils.
- ✓ Form water soluble crystalline salts with acids.
- ✓ Alkaloids consisting of oxygen are solids**.** (e.g. Atropine, reserpine, emetine, morphine, strychnine, quinine etc.)
- ✓ Alkaloids without oxygen are liquids**.** (e.g. Nicotine, pilocarpine, lobeline etc.)
- ✓ Mostly derived from plants. Exception – Epinephrine (obtained from adrenal medulla).

Alkaloid	Source	Action
Atropine	*Atropa belladonna*	Anticholinergic
Arecholine	*Areca catechu*	Cholinergic
Caffeine	*Coffea arabica*	Cortical & CVS stimulant
Cocaine	*Erythroxylon cocoa*	Local anaesthetic & CNS stimulant
Emetine	*Cephalis ipecacuanha*	Reflex emetic
Morphine	*Papaver somniferum*	Narcotic analgesic
Nicotine	*Nicotiana tabacum*	Ganglionic stimulant/ blocker
Physostigmine	*Physostigma venenosum*	Anti-AChE
Reserpine	*Rauwolfia serpentina*	Antihypertensive
Strychnine	*Strychnos nuxvomica*	Spinal stimulant/ convulsant

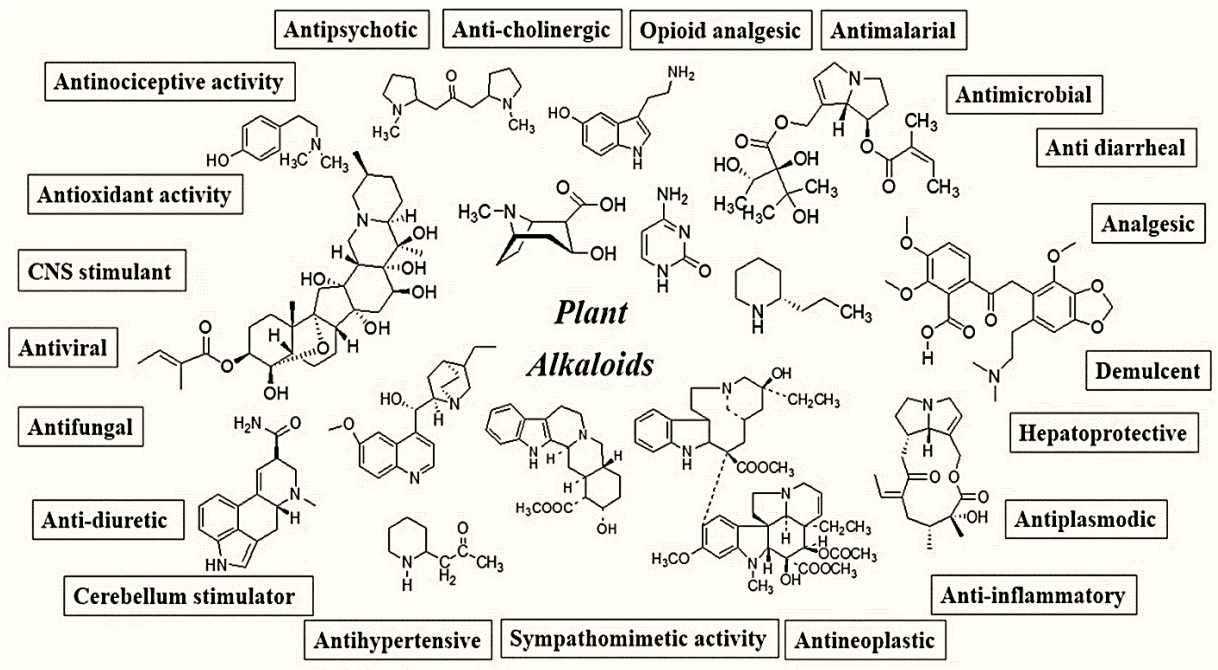


Figure 25. Plant alkaloids

5.2. Glycosides

- ✓ Compounds containing a sugar (glycone) and a non-sugar (aglycone or genin) part joined together through an ester linkage. So, these are **sugar esters.**
- ✓ The pharmacological action resides in the aglycone/ genin.
- ✓ Glycone part determines solubility, tissue permeability and duration of action of aglycone.
- ✓ Glycosides do not form salt with acids. On acid, alkali or enzyme hydrolysis, the glycosides break into two parts i.e. glycone and aglycone. **For excemples:**

Category	Glycoside	Source
Cardiac glycosides	Digitoxin, Gitoxin, Digoxin & Gitalin	*Digitalis lanata/ purpurea* (leaves)
	Strophanthin	*Strophanthus gratus* (seeds)
	Ouabain	*Urginea maritima* (bulb)
Cyanogenic glycosides	Amygdalin	*Prunus amygdalus*
	Dhurrin	*Sorghum vulgare*
	Linamarin	*Linum usitatissimum*
Miscellaneous glycosides	Mangeferin (Hepatoprotective/ Antioxidant)	*Manfifera indica* (Leaves, fruit)
	Swertiamarin (Cardiotonic/ Hepatoprotective)	*Swertia chirata* (Stem, leaves)

5.3. Oils

These are of two types: Fixed oils and Volatile oils.

a. Fixed oils

- ✓ These are glycerides of oleic, palmitic and stearic acids.
- ✓ Many fixed oils have food value (i.e. cooking oils). e.g. corn, ground nut, sunflower, mustard, soybean, coconut, palm oils etc.
- ✓ Cooking oils are pharmacologically inert and serve as vehicle for fat soluble vitamins.
- ✓ Some others have pharmacological actions. Examples :

Fixed oils	Source	Pharmacological action
Castor oil	*Ricinus communis*	Purgative
Linseed oil	*Linum usitatissimum*	Demulcent, vehicle, purgative
Croton oil	*Croton tiglium*	Drastic purgative

b. Volatile oils

Also known as **Aromatic, Essential, Ethereal** or **Flavouring oils**. These have no food value.

- ✓ These are volatile and emit characteristic odour while evaporation.
- ✓ Most of these have medicinal values. Examples are:

Volatile oils	Source	Pharmacological action
Eucalyptus oil	*Eucalyptus globulus*	Expectorant, Rubefacient
Ginger oil	*Zingiber officinale*	Stomachic, Carminative
Turpentine oil	*Cedrus deodara*	Counterirritant, Astringent
Clove oil	*Eugenia caryophyllus*	Analgesic, Antiseptic
Pippermint oil	*Mentha piperata*	Antiseptic, Antiemetic
Asafoetida oil	*Ferula foetida*	Carminative, Anthelmintic

5.4. Resins

- ✓ These are brittle, amorphous compounds formed from oxidation or polymerization of terpene components of volatile oils.
- ✓ These are insoluble in water, soluble in alcohol and other organic solvents.
- ✓ Form soap with alkali. Examples:

Resin	Source	Pharmacological action
Colophonium	Residue left after distillation of crude turpentine	Antiseptic, styptic, astringent
Podophylline	Dried rhizome & root of *Podophyllum emodi*	Purgative, sialic, cholagogue, antimitotic (anticancer).

These are mixtures of volatile oils, gums and resins. Example :

Oleoresin	Source	Pharmacological action
Asafoetida	Secretion from root of *Ferula foetida*	Carminative, antispasmodic

Balsams are also considered as oleoresins. These contain an aromatic acid, resin and volatile oil. Examples:

Balsam	Source	Pharmacological action
Balsam of Tolu	Secretion from trunk of *Myroxylon toluiferum*	Expectorant, antiseptic
Balsam of Peru	Secretion from trunk of *Myroxylon pereoie*	Antiseptic, acaricide

5.5. Gums

- ✓ These are polysaccharide secretory products of plants capable of forming thick mucilaginous colloids when mixed with water.
- ✓ Gums are pharmacologically inert with no systemic effects, but exert demulcent action on surfaces and are mainly used as suspending or emulsifying agents in pharmacy.

Gums	Source	Pharmacological action
Agar	Colloidal carbohydrate from sea weeds	Bulk purgative
Gum acacia	*Acacia senegal*	Demulcent, emulsifier
Gum arabica	*Acacia arabica*	Demulcent, emulsifier
Gum tragacanth	*Astragalus gummifier*	Demulcent, emulsifier

5.6. Saponins

- ✓ These are non-nitrogenous substances soluble in water which form foam or froth when shaken with water.
- ✓ Saponins upon hydrolysis, split into a sugar and a non-sugar (sapogenin), hence considered as a sub-class of glycosides.
- ✓ Saponins cause haemolysis of blood. Examples – Quillaris, Senega etc.

5.7. Tannins

- ✓ These are water soluble, non-nitrogenous plant constituents having characteristic astringent action (precipitation of protein) upon mucous membrane.
- ✓ These exert a protective action on the mucosa (GI) against irritants.
- ✓ Tannins also inactivate alkaloidal poisons.

Tannins	Source	Pharmacological action
Catechu	*Uncaria gambier*	Astringent, Precipitates alkaloids
Kino	*Pterocarpus marsupium*	Astringent, Precipitates alkaloids
Galla (Galls)	*Quercus infectoria*	Astringent, Antiseptic, Antisialic.

CHAPTER 06

6. Main groups of active substances

Drugs are chemicals which when administered to living organisms produce a biological effect. The term antibiotic was derived from the word “antibiosis”, which literally means “against life”. Antibiotics, in the past, were considered to be organic compounds produced by one microorganism which are toxic to other microorganisms by selectively killing or inhibiting the growth of other microorganisms. In modern terms, this definition includes antimicrobials produced through synthetic means partly (semi-synthetic) or wholly (synthetic). Some antibiotics are able to kill bacteria completely while some only inhibit their growth. Bactericidal are those that kill bacteria while bacteriostatic are those that inhibit bacterial growth.

6.1. Antibiotics

Antibiotics are substances produced by microbes for their antagonism with other microorganisms. Antagonism of microbes is named antibiosis. Antibiosis was studied by L. Paster and I. Mechnikov. The first antibiotic was penicillin. It was discovered by A. Fleming in 1928. The second antibiotic streptomycin was discovered by S. Waksman. He also proposed the name “antibiotics”. The term antibiotic has its origin in the word antibiosis (i.e. against life). Antibiotics are chemical substances obtained from various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms and eventually may destroy them. The probable points of difference amongst the antibiotics may be physical, chemical, pharmacological properties, antibacterial spectra, and mechanism of action. They have made it possible to cure diseases caused by bacteria, such as pneumonia, tuberculosis, and meningitis, and they save the lives of millions of people around the world.

-Antibiotics are divided:

According to the type of action

- ✓ Bactericidal
- ✓ bacteriostatic.

According to the spectrum of action

- ✓ antibiotics of a wide spectrum (with Gram (+) and Gram (-) coverage including Gram (-) bacilli)

- ✓ antibiotics of a narrow spectrum of action (with a limited list of microbes, Gram (+) and Gram (-) coverage without Gram (-) bacilli, only Gram (+), or only Gram (-) coverage).

-According to the clinical use

- ✓ basis antibiotics (antibiotics of choice) (the most effective antibiotics which are used at the start of treatment)
- ✓ alternative antibiotics (preparations which are used for the replacement of basis antibiotics in the case of microbial resistance or patient's hypersensitivity).

6.1.1. Main principles of the therapy by antibiotics

Therapy with antibiotics must be put into practice according to some common rules concerning both microorganism and macroorganism. These rules (principles) are:

- ✓ An early beginning of treatment The choice of an antibiotic according to its spectrum of action.
- ✓ The choice of an antibiotic according to the sensitivity of microbes in a definite patient
- ✓ The use of a wide spectrum antibiotic if the cause of infection is unknown
- ✓ The duration of the treatment no less than 5-7 days
- ✓ The usage of big doses of antibiotics
- ✓ The supporting of the therapeutic concentration of the drug in the organism Combination of antibiotics with one another, as well as with drugs from other groups
- ✓ The discontinuation of the treatment after the normalization of a clinical status and body temperature
- ✓ Allergic test at the start of treatment
- ✓ Attention to the age, physiological status of the patient, concomitant diseases, the location and severity of infection.

6.1.2. Common antibiotics side-effects

- ✓ Allergy, an anaphylactic shock. For prevention – an allergic test before the first administration of the drug
- ✓ A direct toxic influence

- ✓ Endotoxic reactions. They display as an increase in body temperature and intoxication resulting from the liberation of endotoxins from microbes destroyed by antibiotic
- ✓ Dysbacteriasis. It is the inhibition of normal microflora in the human body accompanied by activation of Candida fungi. For prevention – to take antifungal drugs (nystatin, itraconazole) together with a wide spectrum antibiotics.

6.1.3. Classification

A. Inhibitors of cell wall synthesis

- ✓ Penicillins
- ✓ Cephalosporins
- ✓ Carbapenems and monobactams
- ✓ Glycopeptides

B. Protein synthesis inhibitors acting on ribosomal subunits 30S

- ✓ Aminoglycosides
- ✓ Tetracyclines

C. Protein synthesis inhibitors acting on ribosomal subunits 50S

- ✓ Macrolides and azalides
- ✓ Chloramphenicols
- ✓ Lincosamides

D. Antibiotics which disturb functions of nucleic acids

- ✓ Rifampicins

E. Antibiotics which disturb the structure and functions of cell membranes

- ✓ Polyenes
- ✓ Cyclic polypeptides (polymyxins)

The main commun antibiotic drugs are shown in **figure 26** and the main classes of antibiotics in **Table 3**.

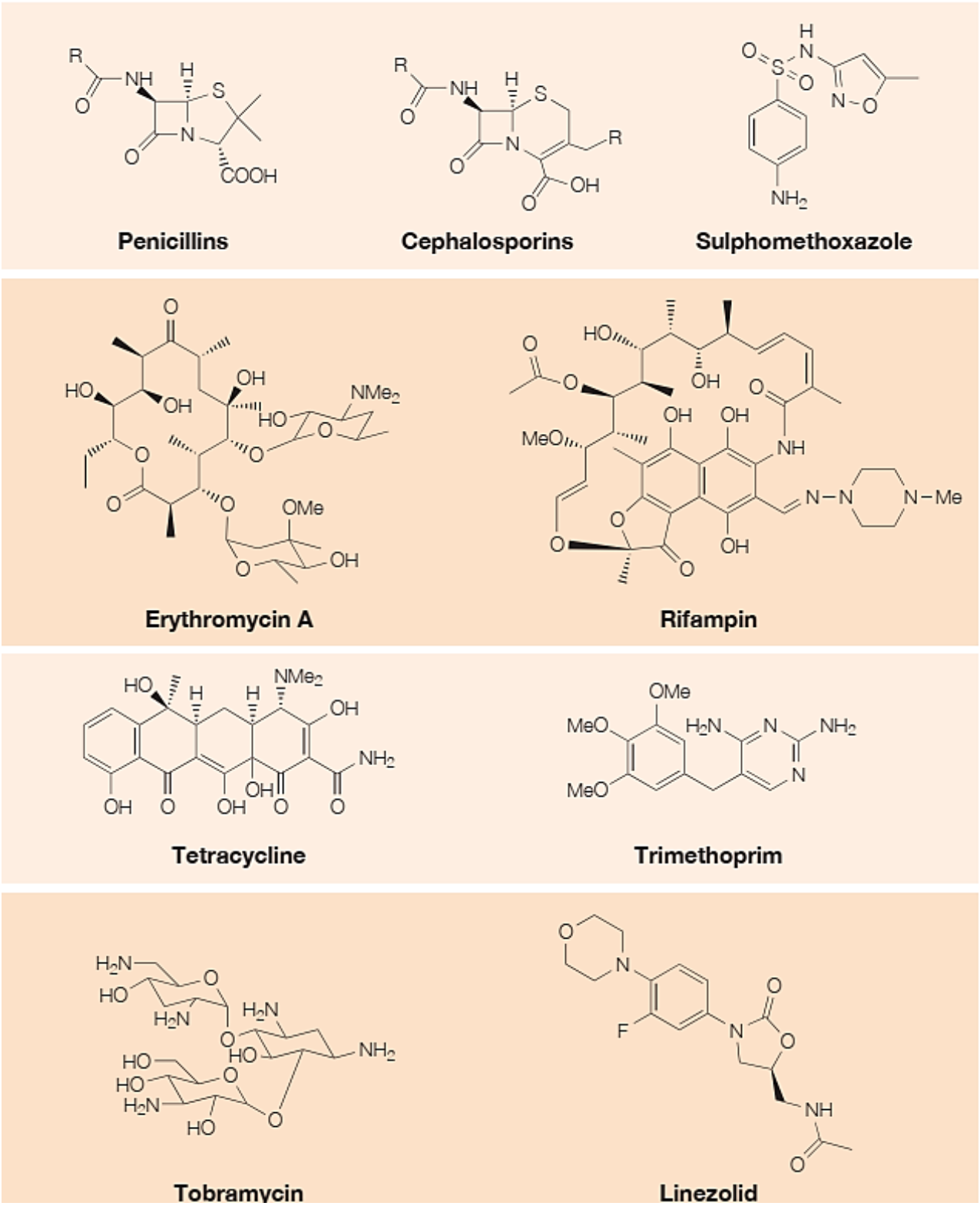


Figure 26. Classification based on chemical structure

Table 2. Main classes of antibiotics

Class	Examples
β-Lactams	
Penicillins	Penicillin G, penicillin V, methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, mezlocillin, piperacillin, azlocillin, temocillin
Cephalosporins	
First generation	Cepalothin, cephapirin, cephradine, cephaloridine, cefazolin
Second generation	Cefamandole, cefuroxime, cephalexin, cefprozil, cefaclor, loracarbef, cefoxitin, cefmetazole
Third generation	Cefotaxime, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime, cefixime, cefpodoxime, ceftibuten, cefdinir
Fourth generation	Cefpirome, cefepime
Carbapenems	Imipenem, meropenem
Monobactams	Astreonam
β-Lactamase inhibitors	Clavulanate, sulbactam, tazobactam
Aminoglycosides	Streptomycin, neomycin, kanamycin, paromycin, gentamicin, tobramycin, amikacin, netilmicin, spectinomycin, sisomicin, dibekalin, isepamicin
Tetracyclines	Tetracycline, chlortetracycline, demeclocycline, minocycline, oxytetracycline, methacycline, doxycycline
Rifamycins	Rifampicin (also called rifampin), rifapentine, rifabutin, bezoxazinorifamycin, rifaximin
Macrolides	Erythromycin, azithromycin, clarithromycin
Lincosamides	Lincomycin, clindamycin
Glycopeptides	Vancomycin, teicoplanin
Streptogramins	Quinupristin, dafloprístin
Sulphonamides	Sulphanilamide, *para*-aminobenzoic acid, sulfadiazine, sulfisoxazole, sulfamethoxazole, sulfathalidine
Oxazolidinones	Linezolid
Quinolones	Nalidixic acid, oxolinic acid, norfloxacin, pefloxacin, enoxacin, ofloxacin/levofloxacin, ciprofloxacin, temafloxacin, lomefloxacin, fleroxacin, grepafloxacin, sparfloxacin, trovafloxacin, clinafloxacin, gatifloxacin, moxifloxacin, sitafloxacin
Others	Metronidazole, polymyxin, trimethoprim

6.2. Antiseptics

Antimicrobial agents are drugs for the treatment and prevention of infection diseases. They are divided into disinfectants, antiseptics, and chemotherapeutics (**figure 27**). ***Disinfectants*** realize their antimicrobial properties in the environment outside the body. ***Antiseptics*** act on the surface of the body. ***Chemotherapeutics*** produce an antimicrobial effect inside the body.

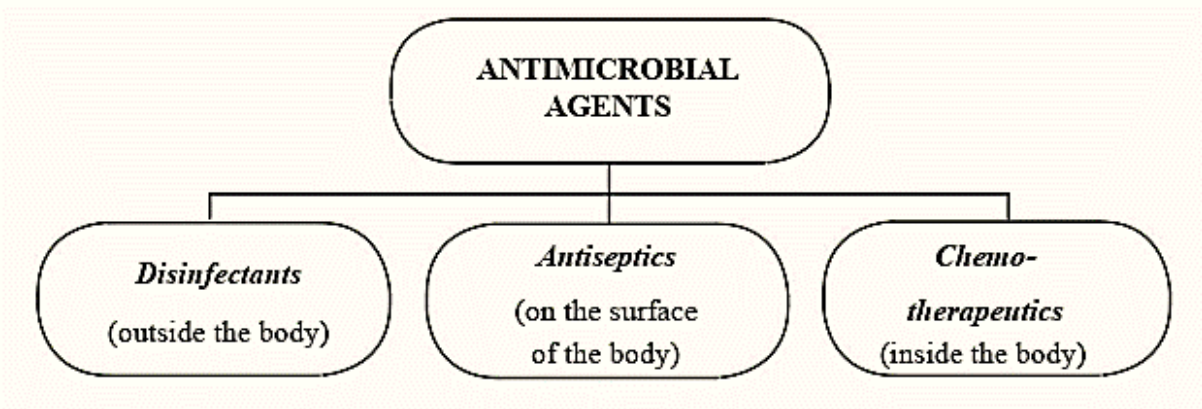


Figure 27. Main classes of antimicrobial agents.

Antimicrobial drugs may have a bactericidal or bacteriostatic type of action (**figure 28**). Antimicrobial drugs of a ***bactericidal action*** produce death of microbes. ***Bacteriostatic drugs*** stop the growth and replication of bacteria and then the immune system destroys such microbes.

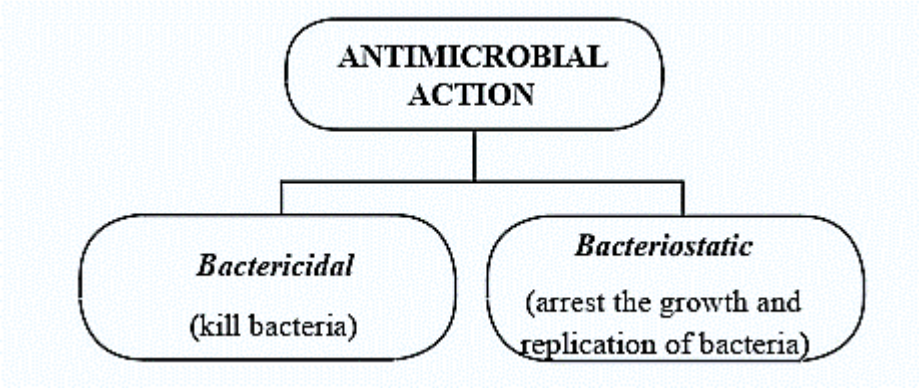


Figure 28. Types of antimicrobial action.

6.2.1. Antiseptics and disinfectants

Good antiseptic and disinfectant should meet such demands as:

- ✓ Bactericidal action
- ✓ Chemical stability
- ✓ A rapid action

- ✓ Lack of absorption
- ✓ Low toxicity
- ✓ Efficacy in the presence of different organic substrates, such as pus, blood, sputum
- ✓ The absence of allergic properties
- ✓ The absence of irritability.

There are 3 main mechanisms of an antimicrobial action of antiseptics and disinfectants:

- ✓ The denaturation of bacterial proteins, including enzymes
- ✓ The oxidation of bacterial protoplasma (cytoplasma)
- ✓ Changing of bacterial membrane properties and an increase in its permeability

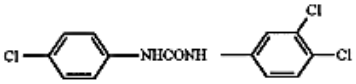
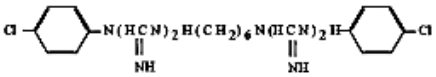
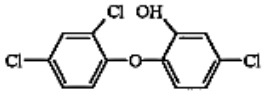
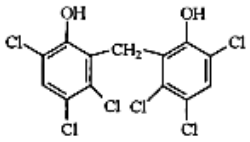
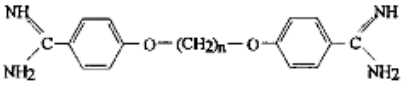
Antiseptics and disinfectants are used extensively in hospitals and other health care settings for a variety of topical and hard-surface applications (**Table 4-5**). In particular, they are an essential part of infection control practices and aid in the prevention of nosocomial infections (277, 454). Mounting concerns over the potential for microbial contamination and infection risks in the food and general consumer markets have also led to increased use of antiseptics and disinfectants by the general public. A wide variety of active chemical agents (or "biocides") are found in these products, many of which have been used for hundreds of years for antisepsis, disinfection, and preservation .

Despite this, less is known about the mode of action of these active agents than about antibiotics. In general, biocides have a broader spectrum of activity than antibiotics, and, while antibiotics tend to have specific intracellular targets, biocides may have multiple targets. The widespread use of antiseptic and disinfectant products has prompted some speculation on the development of microbial resistance, in particular crossresistance to antibiotics. This review considers what is known about the mode of action of, and mechanisms of microbial resistance to, antiseptics and disinfectants and attempts, wherever possible, to relate current knowledge to the clinical environment.

Table 4. The main antiseptics drugs

A. Inorganic substances	*B. Organic substances*
1. Halogens	1. Aldehydes
– Iodine (5% alcohol solution)	– Formaldehyde (Formalinum)
– Povidone- iodine	– Hexamethylentetraminum (Methenamine)
– Ioddicerin	2. Alcohols
– Chloramine B	– Ethyl alcohol (Spiritus aethylicus)
– Chlorhexidine (Hibitane)	3. Phenol derivatives
2. Oxidizing agents	– Phenol (Phenolum purum, Carbolic acid)
– Hydrogen peroxide	– Resorcinol
– Potassium permanganate	4. Dyes
3. Metallic salts	– Methylene blue (Methylenum coeruleum)
– Mercury dichloridum	– Brilliant green (Viride nitens)
– Yellow mercury oxide	– Etacridine lactate
– Silver nitrate	5. Detergents
– Copper sulfate	– Etonium
– Zinc sulfate	– Decamethoxine
– Zinc oxide	– Miramistin
4. Acids and alkalis	6. Tar, resins, products of petroleum
– Boric acid	– Birch tar (Pix liquida Betulae)
– Salicylic acid	– Ichthyol
– Solution of ammonia	– Liniment by Vishnevsky
	Nitrofuran derivatives
	– Nitrofurasone (Furacilinum)
	Antiseptics from medicinal plants
	– Chlorophylipt
	– Novoimanin
	Combined preparations
	– Sterillium
	– Cutasept

Table 5. Chemical structures and uses of biocides in antiseptics and disinfectants

Alcohols	Ethanol	$CH_3 — CHOH$	Antisepsis
	Isopropanol	CH_3 CH_3 — CHOH	Disinfection
			Preservation
Aldehydes	Glutaraldehyde	$OH — CCH_2CH_2CH_2C — HO$	Disinfection
	Formaldehyde	$H — C — HO$	Sterilization
			Preservation
Anilides	General structure	$C_6H_5.NH.COR$	Antisepsis
	Triclocarban		
Biguanides	Chlorhexidine		Antisepsis
			Antiplaque agents
	Alexidine, polymeric biguanides		Preservation
			Disinfection
Bisphenols	Triclosan		Antisepsis
	Hexachlorophene		Antiplaque agents
			Deodorants
			Preservation
Diamidines	Propamidine		Antisepsis
			Preservation
	Dibromopropamidine		

6.3. Hormones

Hormones are substances produced by endocrinal glands into blood which achieve humoral regulation of body functions. ***Hormonal preparations*** are medicinal forms of hormones used for treatment of diseases.

Anti-hormones are drugs which decrease effects of hormones by the inhibition of their secretion or binding to hormonal receptors. Hormonal drugs are divided into several groups by their origin and clinical properties (**figure 29**). They may be classified according to the mode of action and chemical structure.

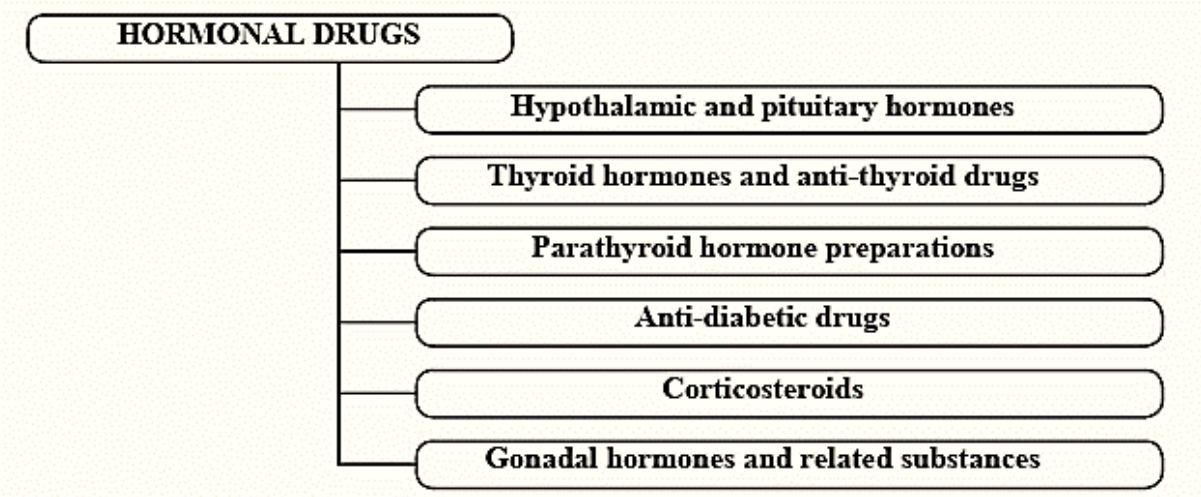


Figure 29. Main groups of hormonal preparations.

6.3.1. Classification of hormones according to the mode of action

A. *Kinetic hormones* (oxytocin, vasopressin)

B. *Morphogenous hormones* (somatotropin, thyroid hormones) *Metabolic hormones*

6.3.2. Common mechanisms of action

Hormones exert their effects through different mechanisms: by binding to the cell surface receptors (oxytocin, vasopressin, corticotro-pin, insulin, etc.). Hormones acting on the cell membrane receptors realize their effects by the alteration of the intracellular cAMP (e.g. hypothalamic and anterior pituitary hormones), by Ca^{++} and the generation of inositol-phospate/ diacilglycerol (e.g. posterior pituitary hormones), or by a direct transmembrane activation of tyrosine kinase (e.g. insulin) by binding to intracellular cytoplasmic receptors

(glucocorticoids, mineral- corticoids, estrogens, progestins, androgens) by interaction with nuclear receptors (thyroxine, triiodthyronine).

The Hormone's level in the blood is regulated according to the principle of "back-cross" (**figure 30**).

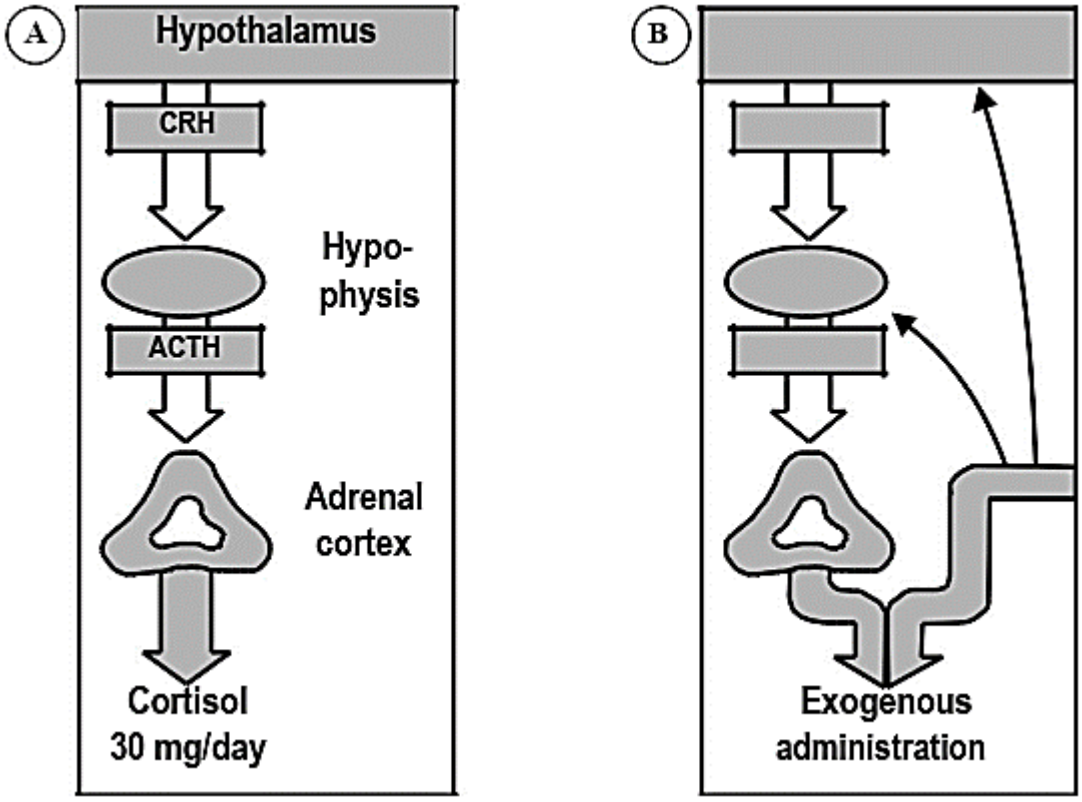


Figure 30. Back-cross regulation of cortisol production: **A** – cortisol production under normal condition; **B** – a decrease in cortisol production with a cortisol dose < daily production.

6.3.3. Types of hormonal therapy

Hormonal therapy is the therapy by hormonal preparations. There are such types of hormonal therapy:

- ✓ Replacement therapy, which is the use of hormonal drugs for the hypofunc-tion of the endocrinal gland (e.g. insulin for diabetes mellitus)
- ✓ Patogenesis therapy, which is the use of hormonal preparations for diseases unconnected with hormones deficit (e.g. insulin for cachexia)
- ✓ Pharmacodynamic therapy is the usage of non-hormonal properties of hormones (e.g. steroid Viadrilum for IV anesthesia)

- ✓ Stimulation therapy is the usage of hormones of the anterior pituitary for the stimulation of peripheral glands (e.g. corticotropin after the withdrawal of corticosteroids).
- ✓ Antihormonal therapy is the usage of anti-hormones (e.g. methimazole for hyperthyroidism).

6.3.4. Principles of hormonal therapy

An individual selection of the dose for each patient (e.g. 1IU of insulin for utilization of 3-5g of sugar excreted with urine per day) Taking into account of biological rhythms (e.g. glucocorticoids are more effective in the morning when it's their peak concentration in the organism) A long-term treatment, sometimes during the whole life (e.g. insulin for type 1 diabetes mellitus) Gradual abolishing Stimulation therapy at the end of treatment (e.g. corticotropin before the abolishing of glucocorticoids (**figure 30**).

6.4. Vitamins and their preparations

Vitamins are organic substances essential for normal metabolism. They are the normal components of diet and must be supplied in very small quantities. A russian scientist N. Lunin discovered vitamins (1880). Holand Ch. Echman supposed that rice husk contained substance for the prevention and treatment of disease beri-beri (vitamin B1) (1897). A polish scientist K. Funk separated this substance from rice husk and proposed the name "vitamin".

-*Vitamins preparations* are medicinal forms of vitamins used for the prophylaxis and treatment of diseases.

6.4.1. Distinguishes between membrane-tropic and enzyme-tropic vitamins

Division of vitamins into groups is based on their biochemical properties and participation in biological processes. Some common characteristics make it possible to speak about membrane-tropic and enzyme-tropic vitamins (table 6)

Table 6. Distinguishes between groups of vitamins

Membrane-tropic vitamins	Enzyme-tropic vitamins
1. Are fat and water-soluble substances 2. Have a requirement of 100 mg per day 3. Are components of cell membranes 4. Are not phosphorilized 5. Take part in the forming and protection of cells membranes 6. May cause hypervitaminosis	1. Are only water-soluble substances 2. Have a requirement of 1-10 mg per day 3. Are components of enzymes (co-enzymes) 4. Are phosphorilized 5. Take part in biochemical reactions 6. Don't cause hypervitaminosis

6.4.2. Vitamin deficiency

- ✓ ***Avitaminosis*** is a specific deficiency syndrome caused by the absence of particular vitamin. It is occurred very rarely.
- ✓ ***Hypovitaminosis*** is a specific deficiency syndrome caused by the deficit of particular vitamin. It is often occurred. There are two types of hypovitaminoses: exogeneous and endogeneous (**figure 31**). Exogeneous hypovitaminosis is caused by factors outside the body, e.g. deficit of vitamin in the diet or poor nutrition. Endogeneous hypovitaminosis is caused by factors inside the organism and is divided into physiological and pathological.

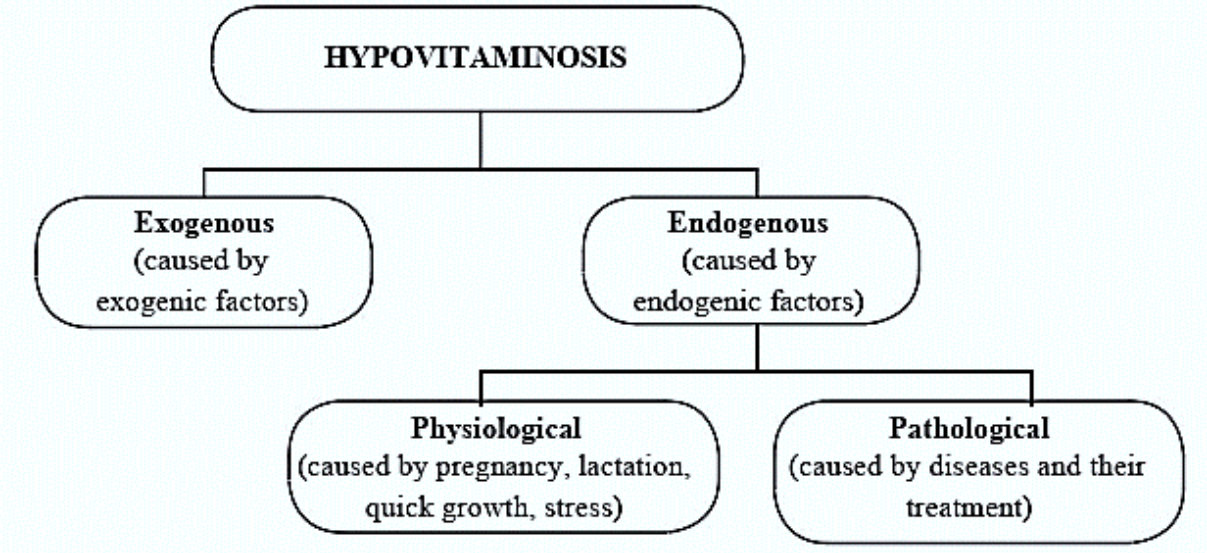


Figure 31. Types of hypovitaminosis.

a. Antivitamins

Antivitamins are substances which decrease a vitamins action. There are three groups of antivitamins:

- ✓ antimetabolites which are chemical analogues of vitamins (e.g. Neodicumarinum is an antivitamin of naphthoquinon; isoniazid is an antivitamin of pyridoxine; methotrexate is an antivitamin of the folic acid)
- ✓ enzymes which destroy vitamins (e.g. thiaminase, ascorbinase)
- ✓ substances which increase the utilization of vitamin (e.g. antiatherosclerotic drug Linaetholum increases the utilization of vitamin E).

b. Hypervitaminosis

Hypervitaminosis is the overdose of a vitamin preparation. Most of vitamins are comparatively safe, but vitamins A and D can cause seri-ous toxic effects. Hypervitaminosis may be acute and chronic.

6.4.3. Vitamins therapy

Vitamins therapy is the therapy by vitamins preparations. Vitamins therapy is divided into three types (**figure 32**):

- ✓ specific replacement therapy which is the use of vitamins for the treatment of hypo- and avitaminosis (e.g. the ascorbic acid is for the treatment of scurvy; thiamine – for beri-beri)
- ✓ pharmacodynamic therapy which is the use of vitamins for diseases nonconnected with vitamins deficit (e.g. the use of the ascorbic acid to treat wounds and infections)
- ✓ adaptation therapy which is the use of vitamins for the improvement of non-specific resistance and adaptation (e.g. the use of the ascorbic acid, tocopherol acetate, and multivitamins preparations in healthy persons under the conditions of stress or physical overstrain).

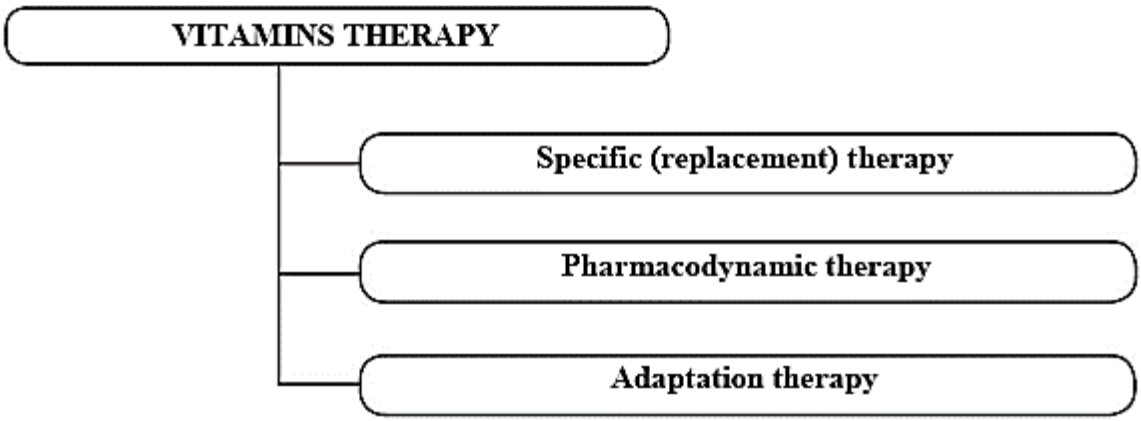


Figure 32. The types of vitamins therapy.

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