

## SCOPE OF PHARMACOLOGY

- A. History** - It is of intellectual interest to the physician to know how drugs are discovered and developed. Often in the past, this was based on folklore or intelligent observation (e.g. digitalis leaf, penicillin). Nowadays, new drugs are mostly developed by the organic chemist working with a pharmacologist, increasingly from basic knowledge about key molecular targets. Usually some sort of biological screen is used to select among organic molecules for optimum pharmacological activity.
1. **Francois Magendie (1783-1855)**, a French physiologist laid down the dictum "Facts and facts alone are the basis of science." Experimental procedures with animals are the testing grounds for determination of drug action.
  2. **Claude Bernard (1813-1878)** worked in Magendie's lab, investigated the plant extract curare and proposed a site of action for this agent.
  3. **Rudolph Buchheim (1820-1879)**. In 1847 Buchheim established the first laboratory devoted to experimental pharmacology in the basement of his home in Dorpat which is known as the cradle of experimental pharmacology.
  4. **Oswald Schmiedeberg (1838-1921)**. In 1872 Schmiedeberg set up an institute of pharmacology in Strasbourg, France (Germany at that time) which became a mecca for students who were interest in pharmacological problems.
  5. **J.N. Langley (1852-1925 and Sir Henry Dale (1875-1968)** pioneered pharmacology in England, taking a physiological approach.
  6. **John J. Abel (1857-1938)** established the first chair of pharmacology in the U.S.A. (U. Michigan, 1891) after training in Germany. Able went to Johns Hopkins in 1893, and trained many U.S. pharmacologists. He is known as "The Father of American Pharmacology".
  7. The second world war was the impetus for accelerated research in pharmacology (the war time antimalarial program) in the U.S., and introduced strong analytical and synthetic chemical approaches.
- B. Chemistry** - Chemical structures of drugs can provide information about mechanism of action, pharmacokinetics, stability, and metabolic fate.
1. **Structure-Activity Relationship** - A modification of the chemical structure of a drug may accentuate or diminish its pharmacological effects, often providing clues as to the mechanism of action. A picture

of the biological reactive site (the receptor) can be developed in such studies. Also, drugs are metabolized by body systems, which may convert the parent drug to a more active or a less active form. The drug structure can be modified to enhance or diminish the rate of metabolic conversion.

2. **Sites of Action** - The organ or cellular target of drug action.
  3. **Drug Receptors** - Macromolecules in cells or cell membranes with which drugs interact to exert their effects. Usually the interacting forces are reversible ionic and Van der Waals bonds of relatively low energy, but sometimes covalent bonds are formed (e.g. organophosphate insecticides).
- C. Pharmacodynamics** - The effect of the drug on the body. Pharmacodynamics is the study of the relationship of drug concentration and the biologic effect (physiological or biochemical). For most drugs it is necessary to know the site of action and mechanism of action at the level of the organ, functional system, or tissue. For example, the drug effect may be localized to the brain, the neuromuscular junction, the heart, the kidney, etc. Often the mechanism of action can be described in biochemical or molecular terms. Most drugs exert effects on several organs or tissues, and have unwanted as well as therapeutic effects. There is a dose-response relationship for wanted and unwanted (toxic) effects. Patient factors affect drug responses - age, weight, sex, diet, race, genetic factors, disease states, trauma, concurrent drugs, etc.
- D. Pharmacokinetics** - The effect of the body on the drug. To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Thus, it is important to know the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.
1. **Absorption** (oral or parenteral) - A drug must be absorbed and achieve adequate concentration at its site of action in order to produce its biological effects. Thus, when a drug is applied to a body surface (e.g., g.i. tract, skin, etc.), its rate of absorption will determine the time for its maximal concentration in plasma and at the receptor to produce its peak effect.
  2. **Distribution** - The blood, total body water, extracellular, lymphatic and cerebrospinal fluids are involved in drug movement throughout the body. Depending upon its chemical and physical properties, the drug may be bound to plasma proteins or dissolved in body fat, delaying its progress to its sites of action or excretory mechanism.

3. **Metabolism** - This is how certain drugs are handled by the body in preparation for their elimination and includes the fate of drugs-biotransformation (e.g., hydrolysis, conjugation, oxidation-reduction).
4. **Excretion** - The kidney is the most important organ for drug excretion but the liver, lung and skin are also involved in drug elimination. Drugs excreted in feces are mostly derived from unabsorbed, orally ingested drugs or from metabolites excreted in the bile and not reabsorbed by the intestine. The physical and chemical properties, especially the degree of ionization of the drug, are important in the rate of excretion.
5. **Biological Factors Modifying Pharmacokinetic Aspects** - Normal variations occur in population pharmacokinetic constants (absorption rates, elimination rates). Other factors include age, weight, obesity, edema, concurrent diseases, other drugs (various interactions including effects on protein binding or metabolic rate), diet, dose interval and route of administration, genetic variations in elimination rate.

#### **E. Clinical Pharmacology and Therapeutics**

1. **Indications and Therapeutic Uses** - Emphasis is placed on the therapeutic use of drugs for the treatment of disease in clinical pharmacology, internal medicine and therapeutics. There are specific clinic disorders or disease entities for which a given drug may be prescribed and the physician must weigh the potential benefit of drug use against the risks of adverse effects.
2. **Contraindications and Factors (e.g., liver disease) May Modify Drug Action** - where detoxification of the drug by the liver is important. It is important to know that the presence of disease or organ pathology may influence the actions of a drug. Conditions such as age, pregnancy, concomitant administration of other drugs and disease may alter the patient's response to a given drug.
3. **Posology** - Is an archaic term describing dosage regimens. Consideration of dosage schedules is a part of pharmacokinetics.
4. **Bioavailability** - The fraction of drug administered which is actually absorbed and reaches the systemic circulation following oral dosing. Preparations of the same drug by different manufacturers may have a different bioavailability.
5. **Prescription writing** - It is important that the physician write clear, error-free directions for the drug provider (pharmacist) and for the patient. Physicians must guard against prescribing too many drugs, or

preparations of little value. Drugs of unproven clinical value should be avoided, as well as potentially toxic agents if drugs equally effective but less dangerous are available. Risk-benefit and cost-benefit should be considered. Drugs may be prescribed by generic name, since often a less expensive drug product can be obtained in this way. A particular manufacturer may be specified if the physician has reason to believe a better or more reliable preparation is available from that manufacturer.

6. **Drug Nomenclature** - In addition to its formal chemical name, a new drug is usually assigned a code name by the pharmaceutical manufacturer. If the drug appears promising and the manufacturer wishes to place it on the market, a United States Adopted Name (USAN) is selected by the USAN Council which is sponsored by:

- 1) The American Medical Association
- 2) The American Pharmaceutical Association
- 3) The United States Pharmacopeial Convention

F. **Toxicology** - That aspect of pharmacology that deals with the adverse effects of chemical agents. Toxicology is concerned not only with drugs used in therapy but also with the other chemicals that may be responsible for household, environmental or industrial intoxication.

1. **Forensic Toxicology** - Addresses medicolegal aspects of the use of chemicals that are harmful to animals or man. Analytical chemistry and fundamental toxicological principles are hybridized to underlie this aspect of toxicology. Nonetheless accidental poisoning with drugs is a health problem of major significance. More than 1/4 of the fatalities and about 1/2 of all poisonings occur in children under 5 years of age. All common household articles that are poisonous should be made unavailable to children, and poisonous rodenticides and insecticides should not be placed in the home.

2. **Clinical Toxicology** - Focuses on toxic events that are caused by or are uniquely associated with drugs or other chemicals.

3. **Adverse Drug Reactions Toxicities and Side Effects** - No drug is free of toxic effects. Some untoward effects of drugs are trivial, but others are serious and may be fatal. Side effects often are predictable from a knowledge of the pharmacology of a particular drug. Examples of chemicals or drug-induced toxicities are given below:

a. **Allergic reactions** - The number of serious allergic reactions to drugs involving antigen-antibody reactions is low but when they occur the physician must have sufficient knowledge to manage these problems.

- b. **Blood dyscrasias** - These are very serious and sometimes fatal complications of drug therapy. They include: agranulocytosis, aplastic anemia, hemolytic anemia, thrombocytopenia and defects in clotting factors.
- c. **Hepatotoxicity and nephrotoxicity** - Because many chemicals and drugs are eliminated and metabolized by the liver and kidney, damage to these organs is seen commonly.
- d. **Teratogenic effects** - The thalidomide tragedy dramatically emphasized that drugs may adversely influence fetal development.
- e. **Behavioral toxicity** - This is a term used to describe suppression of normal anxiety, reduction in motivation, impairment of memory and learning, distortion of judgement, impairment of reflexes, adverse effects on mood, etc.
- f. **Drug dependence and drug abuse** - The repeated administration of some chemicals may lead to drug dependence. Drugs likely to be abused and upon which drug dependence may develop are the various psychopharmacological agents such as opiates, barbiturates, amphetamines, nicotine and ethanol. Dependence on tobacco (nicotine) is also well known.
- g. **Carcinogenesis** - Carcinogenesis is a delayed type of toxicity with a latency of many years.
- h. **Pharmacogenetic toxicities** - Certain genetically-predisposed individuals have a markedly toxic reaction to certain otherwise safe drugs. Examples are prolonged apnea after succinylcholine, or malignant hyperthermia associated with anesthetics.