FIRST EDITION

# Pocket SYSTEMIC AND CLINICAL PHARMACOLOGY FOR HEALTH SCIENCES

ORUIKOR GABRIEL JEREMIAH, DrPH

# POCKET

# SYSTEMIC AND CLINICAL

# PHARMACOLOGY

# FOR

# HEALTH SCIENCES

**First edition**

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# TABLE OF CONTENTS

## DEDICATION

I dedicate this to book to:

The first Love of my life, GOD the creator of all, who gave me this privilege to be a writer and my LOVELY wife, Dr. Mrs Gabriel Jeremiah, who always stood by me in everything good.

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# FOREWORD

Drugs are gotten from Animals, Plants and Minerals. By products of animals, including humans, are a source for drugs because they contain hormones that can be reclaimed and given to patients who need increased hormonal levels to maintain homeostasis. For example, Premarin is a drug that contains estrogen that is recovered from mare urine. This is used as hormonal therapy to manage menopausal symptoms. Insulin is another hormonal drug that is used to regulate blood sugar levels in patients with diabetes mellitus. Insulin can be recovered from humans using DNA technology.

A number of plants have medicinal qualities and have been used for centuries as natural remedies for injuries and illnesses. Pharmaceutical firms harvest these plants and transform them into drugs that have a specific purity and strength sufficient to treat diseases. An example of a drug that comes from a plant is digitalis. Digitalis is made from leaves of the foxglove plant and is used to treat congestive heart failure and cardiac arrhythmias

Basically, Clinical pharmacology is the science of drug use to manage illnesses in humans. General medical practitioners and Clinicians of all specialties prescribe drugs in their daily routines. Also, students in health sciences are expected to have sound knowledge in Clinical pharmacology because it form the basis of their studies. If drugs are not used properly in therapeutic practices, it become very dangerous for the effectiveness of the practice as lives would be in danger.

Dr. ORUIKOR GABRIEL JEREMIAH, decided to present a textbook that would summarize the practice of using drugs in a simple format to assist health sciences in the basic knowledge of drugs usage for humans.

The book entitle “POCKET SYSTEMIC AND CLINICAL PHARMACOLOGY FOR HEALTH SCIENCES FIRST EDITION” is well prepared to serve its vulnerable purpose of studies in clinical Pharmacology. However, this first edition does not cover all the pharmacology of the human systems, its selective which include: Drugs acting on GIT, RESPIRATORY SYSTEM, BLOOD, AND THE

NERVOUS SYSTEM. It's believed that subsequent editions would cover other systems.
The author also discussed the principles of basic Pharmacology and toxicology.
Its my pleasure to have a review of this book written by Dr ORUIKOR GABRIEL JEREMIAH. I place my thumb up on this for all health science and medical students to use this book because the approaches here in this book are simplified ,current and comprehensive.

PROFESSOR NADJIBOU DJIBRIL, PhD
- *Prof & Researcher in clinical pharmacology, University of Parakou*
- *Head of department in Drug research*
-*Specialist of cardiovascular emergencies*

# PREFACE

Drugs are the cornerstone of modern therapeutics. Nevertheless, it is well recognized among physicians and among the lay community that the outcome of drug therapy varies widely among individuals.

. Drug action is the physiochemical interaction between the drug molecule and molecules in the body that alters a physiological process of the body in one of three ways.

The goal of clinical pharmacology and its principal is for the safe and optimal use of available and new drugs. Drugs interact with specific target molecules to produce their beneficial and adverse effects. The chain of events between administration of a drug and production of these effects in the body can be divided into two important components, both of which contribute to variability in drug actions. The first component comprises the processes that determine drug delivery to, and removal from, molecular targets. The resultant description of the relationship between drug concentration and time is termed pharmacokinetics. The second component of variability in drug action comprises the processes that determine variability in drug actions despite equivalent drug delivery to effector drug sites.

Clinical .pharmacology is a science which prepare students in health sciences for adequate use of drugs in human to manage certain conditions. For example, Our body requires trace elements of minerals in order to maintain homeostasis. Minerals are inorganic crystal substances that are found naturally on earth. Patients lacking an adequate level of these materials may take specific mineral based drugs to raise the level of minerals. An iron supplement is a common mineral-based drug that is given to patients who suffer iron deficiency, a condition which can lead to fatigue. Iron is a natural metal that is an integral part of body proteins such as hemoglobin that carries oxygen throughout the body. Minerals are obtained from animal and plant sources.

In order to determine the suitable doses of these drugs for patients, clinical Pharmacology is very necessary.

I warmly recognize the fact that there has been the existence of Clinical Pharmacology textbooks for decades now by other eligible authors. But

most times, the volume and contexts are overstretched, making it incomprehensive for readers. This Pharmacology textbook "POCKET SYSTEMIC AND CLINICAL PHARMACOLOGY FOR HEALTH SCIENCES FIRST EDITION summarizes the principles of Pharmacology and toxicology, and clinical aspects of drugs usage in various systems in a comprehensive manner to enhance the understand and quick coverage of it.

It's worthy of note that this text book is birthed from other researched works by many authors and scholars in the field of Clinical Pharmacology.

Finally, I appreciate many of my superiors in this field who by their relentless efforts made ready a bridge to climb to this work of mine.

ORUIKOR GABRIEL JEREMIAH, DrPH

# CHAPTER ONE
# BASIC CONCEPTS OF CLINICAL PARMACOLOGY 1:

**Description of Basic terms in clinical Pharmacology**

- **Pharmacology** is the study of chemicals, drugs, on living tissues and how those chemicals help diagnose, treat, cure, and prevent disease or correct the pathophysiology of living tissues.
- **Clinical Pharmacology** is the science of substances used to prevent, diagnose and treat diseases. Pharmacology simply is the science of drugs.
- **Sustained release dosage form**: The drug release from sustained release dosage form exhibit a predetermined rate in order to maintain an approximately constant drug concentration in the body over a prolonged period. The rate of release of drug follows first-order kinetics. Usually, the drug content of one dose of SR dosage form is more than that of its conventional or immediate release dosage form.
- **Prolonged action dosage form:** In this type of dosage form the drug is released at a rate relatively slower rate, but for a long period; so that, the therapeutic action of the drug remains for an extended period. In this type of dosage form, one dose of the drug is released immediately after administration and later on, the second dose is released.
- **Extended-release dosage form**: If a dosage form reduces the frequency of dose at least by two-fold as compared to the frequency of administration of immediate release or conventional dosage form, the dosage form is said to be the extended release dosage form.Sustained-release, controlled-release, or long-acting dosage forms belong to this class.
- **Delayed release dosage form**: When a dosage form does not release the drug immediately after administration like immediate release or conventional dosage form but releases the drug in portions at a predetermined time or at times, it is called delayed

release dosage form. However, in some cases, a portion of the drug may be released immediately after administration.

- **Site-specific targeting**: These systems refer to targeting the release of a drug straight to a particular biological location. In this case, the target is adjacent to or in the diseased organ or tissue.
- **Side effects:** A drug can have a side effect in addition to its pharmaceutical response. A side effect is a physiologic effect other than the desired effect. Sometimes side effects are predictable and other times they are not and may be unrelated to the dosage.

Some side effects are desirable and others are undesirable. A severe undesirable side effect is referred to as an adverse reaction that occurs unintentionally when a normal dose of the drug is given to a patient. For example, an adverse reaction might be anaphylaxis (cardiovascular collapse) some adverse reactions are predictable by age and weight of the patient. Young children and the elderly are highly responsive to medications because of an immature or decline in hepatic and renal function. Body mass also influences the distribution and concentration of a drug. The dosage must be adjusted in proportion to body weight or body surface area. Drug effects can also be related to other factors. These include:

**i. Gender:** Women typically are smaller than men and have a different proportion of fat and water which affects absorption and distribution of the drug.

**ii. Environment:** Cold, heat, sensory deprivation or overload, and oxygen deprivation in high altitude create environmental factors that might interact with a drug.

- **Receptor targeting**: These systems refer to targeting a specific biological receptor.In this case, the target is the specific receptor for a drug within an organ or tissue.Site-specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.
- **Modified release dosage form:** The dosage forms, in which the rate of release of the drug and the time at which the release of the drug would take place are different from conventional type, are called modified release dosage form. An enteric coated tablet can be

considered as a common example of a modified release dosage form. For example, erythromycin gets decomposed in the stomach; hence it is formulated as an enteric coated tablet. The multi-layered tablet is a further advancement of the modified release delivery systems.

- **Immediate release dosage forms**: The conventional dosage forms belong to this class. The dosage form releases the drug present in it after administration to achieve rapid and complete systemic absorption. After absorption of the drug from the dosage form, plasma concentration of the drug starts decreasing according to its pharmacokinetic profile. Finally, the concentration falls below the minimum therapeutic concentration and therapeutic activity ceases.
- **Toxicology** is the branch of Pharmacology, which deals with the undesirable effects of chemicals on living systems from individual cells to complex ecosystems.
- **Pharmacokinetics** is the study of drug absorption, distribution, metabolism and excretion (ADME) – 'what the body does to the drug'.
- **Pharmacodynamics** is the study of effects of drugs on biological processes.
- **Dosage Form Design** What do we mean by dosage form? A dosage form is the form in which a drug substance can be administered to a patient. A tablet or a syrup is a dosage form.
- **Time of administration:** A drug might be influenced by the presence or absence of food in the patient's gastrointestinal tract or by the patient's corticosteroid secretion rhythm. In addition, circadian cycle, urinary excretion pattern, fluid intake, and drug metabolizing enzyme rhythms all might influence a drug's effect.
- **Pathologic state:** A drug can react differently if the patient is experiencing pain, anxiety, circulatory distress, or hepatic and/or renal dysfunction.
- **Tolerance:** The patient has a decreased physiologic response after repeated administration of the drug. This is common with tobacco, opium alkaloids, nitrites, and ethyl alcohol. The dosage must be increased to achieve the pharmaceutical response.

- **Drug dependence:** This can be either a physical or psychological dependency. With a physical dependency, the patient experiences an intense physical disturbance when the drug is withdrawn. With psychological dependency, the patient develops an emotional reliance on the drug.
- **Drug interaction:** The administration of one drug increases or decreases the pharmaceutical response of a previously administered drug.
- **Synergism:** A more desirable pharmaceutical response is achieved through the interaction of two drugs that are administered.
- **Potentiation:** Concurrent administration of two drugs increases the pharmaceutical response of one of those drugs.
- **Toxic effect:** This occurs when the administered drug exceeds the therapeutic range through an overdose or by the drug accumulating in the patient.
- **Tachyphylaxis:** The patient builds a tolerance to the drug due to the frequency in which the drug is administered. This occurs with narcotics, barbiturates, laxatives, and psychotropic agents. The patient may eventually need more of the drug to reach the desired effect.
- **Placebo effect:**The patient receives a psychological benefit from receiving a compound that has no pharmaceutical response. A third of patients taking a placebo experience the placebo effect.
- **Pharmacogenetic effect:**A drug varies from a predicted response because of the influence of a patient's genetic factors. Genetic factors can alter the metabolism of the drug and results in an enhanced or diminished pharmaceutical response.
- **Allergic reactions:** If the patient was previously sensitized to the drug, a drug might trigger the patient's immunologic mechanism that results in allergic symptoms. Antibodies are produced the first time the drug is introduced to the patient creating sensitivity to the drug. The next time the drug is given to the patient, the drug reacts with the antibodies and results in the production of histamine. Histamine causes allergic symptoms to occur. The patient should

not take any drug that causes the patient to have an allergic reaction. There are four types of allergic reactions. These are:

i. **Anaphylactic:** This is an immediate allergic reaction that can be fatal.
ii. **Cytotoxic reaction:** This is an autoimmune response that results in hemolytic anemia, thrombocytopenia, or lupus erythematosus (blood disorders). In some cases, it takes months for the reaction to dissipate.
iii. **Immune complex reaction:** This is referred to as serum sickness and results in angioedema, arthralgia (sore joints), fever, swollen lymph nodes, and splenomegaly (large spleen). The immune complex reaction can appear up to three weeks after the drug is administered.
iv. **Cell mediated:** This is an inflammatory skin reaction that is also known as delayed hypersensitivity. The strength of a drug action is determined by the dose administered to a patient and how frequently the dose is administered. The first dose is called a loading dose or priming dose and consists of a large concentration of the drug. Subsequent doses are called maintenance doses and consist of a normal concentration of the drug. Drug activity is divided into the pharmaceutic phase, pharmacokinetic phase; and the Pharmacodynamic phase. The pharmaceutic phase is the disintegration and dissolution of a drug taken orally. The pharmacokinetic phase is the mechanism used to absorb, distribute, and eliminate a drug. The pharmacodynamics is a drug's effect on the physiology of the cell and the mechanism that causes the pharmaceutical response. Drugs bind to receptors on the cell membrane called reactive cellular sites. Receptors are proteins, glycoproteins, proteolipids, or enzymes. Depending on the drug, binding either initiates a physiological response by the cell or blocks a cell's physiological response. A drug that causes a physiological response is called an agonist. A drug that blocks a physiological response is called an antagonist. The safety of a drug is identified by the drug's therapeutic index. A low therapeutic

index means a drug has a narrow margin of safety requiring that that the drug's peak level and trough levels be closely monitored. A high therapeutic index means a drug has a broad margin of safety and does not require frequent monitoring of the patient and the serum drug level.

- **Chemotherapy** is the treatment of systemic infection / malignancy with specific drugs that have selective toxicity for the infecting organism /malignant cell with no or minimal effects on the host cells:
- **Drug** is any substance that can bring about a change in biologic function of the body through its chemical action. Is the single active chemical entity present in a medicine that is used for diagnosis, prevention treatment / cure of a disease.

  Drugs are the cornerstone of modern therapeutics.

  Drugs may be solid, liquid or gas. Example of solid is paracetamol tablet and ampicillin capsules, liquid e.g propranolol and formaldehyde.

# CHAPTER TWO
# BASIC CONCEPTS OF CLINICAL PHARMACOLOGY TWO

## DRUGS AND SOURCES

**Plants:**
A number of plants have medicinal qualities and have been used for centuries as natural remedies for injuries and illnesses. Pharmaceutical firms harvest these plants and transform them into drugs that have a specific purity and strength sufficient to treat diseases. An example of a drug that comes from a plant is digitalis. Digitalis is made from leaves of the foxglove plant and is used to treat congestive heart failure and cardiac arrhythmias. Digitalis also strengthens the force of the contractions of the heart.

**Herbals:**
Herbals are non-woody plants. Some have medicinal qualities and are classified as a dietary supplement not a drug. Unlike drugs that are governed by the Food and Drug
Administration, dietary supplements are not tested or regulated and can be sold over-the-counter without a prescription. This lack of monitoring means there are no standards for purity and strength for herbals. Two packages of the same herbal distributed by the same company might have different purity and strength that makes the effect of the herb unreliable. There is no control over the manufacturing process and that can lead to contamination. The law prohibits distributors of herbals from claiming that a herbal can cure a disease. They can only state the effect of the herbal on the body. For example, the manufacturer can say that a herbal increases blood flow to the heart, but cannot say that the herb prevents heart disease. Herbals can lead to unwanted side effects and undesirable interactions with prescription drugs. For example, ginkgo inhibits platelet aggregation (grouping to form clots) if taken with coumadin, an anticoagulant. The result can be increased bleeding and stroke. Garlic interacts with protease inhibitors used to treat HIV

and decreases the effectiveness of the prescribed medication. The interaction of herbals with other drugs can be unpredictable and even dangerous. Healthcare providers should encourage patients to reveal any herbal preparations they are taking.

**Animals:**
By products of animals, including humans, are a source for drugs because they contain hormones that can be reclaimed and given to patients who need increased hormonal levels to maintain homeostasis. For example, Premarin is a drug that contains estrogen that is recovered from mare urine. This is used as hormonal therapy to manage menopausal symptoms. Insulin is another hormonal drug that is used to regulate blood sugar levels in patients with diabetes mellitus. Insulin can be recovered from humans using DNA technology

**Minerals:**
Our body requires trace elements of minerals in order to maintain homeostasis. Minerals are inorganic crystal substances that are found naturally on earth. Patients lacking an adequate level of these materials may take specific mineral based drugs to raise the level of minerals. For example, an iron supplement is a common mineral-based drug that is given to patients who suffer iron deficiency, a condition which can lead to fatigue. Iron is a natural metal that is an integral part of body proteins such
as hemoglobin that carries oxygen throughout the body. Minerals are obtained from animal and plant sources.

**4. Synthetic/chemical derivatives:**

Great strides in molecular biology and biochemistry enable scientists to create manmade drugs referred to as synthetic drugs. A synthetic drug is produced using chemical synthesis, which rearranges chemical derivatives to form a new compound. Sulfonamides are a common group of synthesized drugs that are used to treat many infections including bronchitis, pneumonia, and meningitis. Sulfonamides are designed to prevent the growth of bacteria.

**Drug Actions**

Drug action is the physiochemical interaction between the drug molecule and molecules in the body that alters a physiological process of the body in one of three ways.

1. **Replacement:** The drug replaces an existing physiological process such as Estrogen replacement.
2. **Interruption:** The drug interferes with a physiological process. This occurs when a antihypertensive (high blood pressure) drug interferes with the process that constricts blood vessels and may cause blood pressure to rise. The blood vessels remain dilated and pressures remain normal or drop.
3. **Potentiation:** The drug stimulates a physiological process as in the case of furosemide (Lasix) which is a diuretic and stimulates the kidneys to excrete urine.

   A drug action begins when the drug enters the body and is absorbed into the Blood stream where the drug is transported to receptor sites throughout the body. Once the drug hooks onto a receptor site, the drug's pharmacological response initiates. The pharmacological response is the therapeutic effect that makes the patient well. Drugs have multiple actions. These are the desired effect and effects other than the desirable effect. The desirable effect is what makes the patient well or prevents the disease or disorder. An effect other than the desirable effect is known as a side effect. Some side effects are desirable and others are undesirable. The strength of a drug action is determined by how much of the drug is given, (the dose) and how often the drug is given (the frequency). For example, a patient who has a sore throat can be given a large dose of an antibiotic—a loading dose— on the first day of treatment and a normal or maintenance dose for the next five days. Drug activity is divided into three phases. These are:

   i. **Pharmaceutic Phase:** This phase occurs after the drug is given and involves disintegration and dissolution of the dosage form.
   ii. **Pharmacokinetic Phase:** This is the way the drug is absorbed, distributed, and eliminated.

iii. **Pharmacodynamic Phase:** This is the effect the drug has on the body.

## 2.1 Pharmaceutic

The pharmaceutic phase is the form of the drug such as a tablet, capsule, liquid, elixirs, or syrups. The drug in solid form must disintegrate before dissolution, which is the process by which a drug goes into solution before it becomes available for absorption. Drugs contain an active ingredient and inactive ingredients. The active ingredient is the substance that causes the pharmaceutical response. The inactive ingredient, called excipient, is the substance that has no pharmaceutical response but helps in the delivery of the drug. These are fillers and inert substances that give the drug its shape and size. The coating around tiny particles of a capsule that causes a timed-release action of the drug is an inactive ingredient. Nearly 80% of all drugs are administered orally (P.O.) and are carried to the small intestine by the gastrointestinal tract where the drug is absorbed into the bloodstream. The time necessary for the drug to disintegrate and dissolve so it can be absorbed is called the rate limiting time. A drug has a higher rate limiting time if it is absorbed in acidic fluids rather than alkaline fluids. Children and the elderly have a lower pH in their GI tract and therefore drugs are absorbed more slowly than in a healthy adult. Some drugs are more effective if absorbed in the small intestine rather than the stomach. However, the stomach is more acidic than the small intestine. Therefore, pharmaceutical manufacturers place an enteric coating around the drug that resists disintegration in the stomach. The coating disintegrates in the alkaline environment of the small intestine. Enteric coating is also used to delay the onset of the pharmaceutical response and to prevent food in the stomach from interfering with the dissolution and absorption of the drug. The form of a drug influences the drug's pharmacokinetics and pharmacodynamics.

# CHAPTER THREE
# PRNCIPLES OF CLINICAL PHARMACOLOGY 1

## 3.1. Pharmacodynamics

The study of effects of drugs on biological processes is known as Pharmacodynamics. An example, the effects of a proton pump inhibitor and of a histamine H2 receptor antagonist (both drugs used for the treatment of peptic ulceration and other disorders related to gastric hyperacidity) on gastric PH can be demonstrated and compared. Many mediators would exert their effects as a result of high-affinity binding to specific receptors in plasma membranes or cell cytoplasm/nuclei.

There are two types of effects that a drug delivers. These are the primary effect and the secondary effect. The primary effect is the reason for which the drug is administered. The secondary effect is a side effect that may or may not be desirable. For example, diphenhydramine (Benadryl) is an antihistamine. Its primary effect is to treat symptoms of allergies. Its secondary effect is to depress the central nervous system causing drowsiness. The secondary effect is desirable if the patient needs bedrest, but undesirable if the patient is driving a car. A period of time passes after a drug is administered until the pharmaceutical response is realized. This is referred to as the drug's time response. There are three types of time responses: onset, peak, and duration. The onset time response is the time for the minimum concentration of drug to cause the initial pharmaceutical response. Some drugs reach the onset time in minutes while other drugs take days. The peak time response is when the drug reaches its highest blood or plasma concentration. Duration is the length of time that the drug maintains the pharmaceutical response. The response time is plotted on a time–response curve that shows the onset time response, the peak time response, and the duration. All three parameters are used when administering the drug in order to determine the therapeutic range and when the drug will become effective, when it will be most effective, and when the drug is no longer effective. It is also used to determine

when a drug is expected to reach a toxic level. For example, the time–response curve of an analgesic is used for pain management. Once the peak response time is reached, the effectiveness of the drug to block pain diminishes. The time–response curve indicates when the pharmaceutical response is no longer present requiring that an additional dose be administered to the patient.

**Principles of pharmacodynamics**

Once a drug accesses a molecular site of action, it alters the function of that molecular target, with the ultimate result of a drug effect that the patient or physician can perceive. For drugs used in the urgent treatment of acute symptoms, little or no delay is anticipated (or desired) between the drug-target interaction and the development of a clinical effect. Examples include vascular thrombosis, shock, malignant hypertension, status epilepticus, or arrhythmias. For many conditions, however, the indication for therapy is less urgent, and in fact a delay between the interaction of a drug with its pharmacologic target (s) and a clinical effect is common. Pharmacokinetic mechanisms that can contribute to such a delay include uptake into peripheral compartments or generation and accumulation of active metabolites. A common Pharmacodynamic mechanism is that the clinical effect develops as a downstream consequence of the initial molecular effect the drug produces. Thus, administration of a proton-pump inhibitor or an H2-receptor blocker produces an immediate increase in gastric pH but ulcer healing that is delayed. Cancer chemotherapy inevitably produces delayed therapeutic effects, often long after drug is undetectable in plasma and tissue. Translation of a molecular drug action to a clinical effect can thus be highly complex and dependent on the details of the pathologic state being treated. These complexities have made pharmacodynamics and its variability less amenable than pharmacokinetics to rigorous mathematical analysis. Nevertheless, some clinically important principles can be elucidated. A therapeutic drug effect assumes the presence of underlying pathophysiology. Thus, a drug may produce no action, or a different spectrum of actions, in unaffected individuals compared to patients. Further, concomitant disease can complicate

interpretation of response to drug therapy, especially adverse effects. For example, increasing dyspnea in a patient with chronic lung disease receiving amiodarone therapy could be due to drug, underlying disease, or an intercurrent cardiopulmonary problem. Thus the presence of chronic lung disease, and interpretation of the symptom of increasing dyspnea, is one factor that should be considered in selection of antiarrhythmic therapies. Similarly, high doses of anticonvulsants such as phenytoin may cause neurologic symptoms, which may be confused with the underlying neurologic disease.

The concept that a drug interacts with a specific molecular receptor does not imply that the drug effect will be constant over time, even if stable drug and metabolite concentrations are maintained. The drug receptor interaction occurs in a complex biologic milieu that itself can vary to modulate the drug effect. For example, ion channel blockade by drugs, an important anticonvulsant and antiarrhythmic effect, is often modulated by membrane potential, itself a function of factors such as extracellular potassium or Thus, the effects of these drugs may vary depending on the external milieu. Receptors may be up or down regulated by disease or by the drug itself. For example, B-adrenergic blockers up regulate B-receptor density during chronic therapy. While this effect does not usually result in resistance to the therapeutic effect of the drugs, it may produce severe B-agonist–mediated effects (such as hypertension or tachycardia) if the blocking drug is abruptly withdrawn.

**Receptor theory**

The pharmaceutical response is realized when a drug binds to a receptor on the cell membrane. These are referred to as reactive cellular sites. The activity of the drug is determined by the drug's ability to bind to a specific receptor. The better the fit, the more biologically active the drug. Receptors are proteins, glycoproteins, proteolipids, or enzymes. Depending on the drug, binding either initiates a physiological response by the cell or blocks a cell's physiological response. Receptors are classified into four families.

**1. Rapid-cell membrane-embedded enzymes:**
A drug binds to the surface of the cell causing an enzyme inside the cell to initiate a physiological response.

2. **Rapid-ligand-gated ion channels:**
The drug spans the cell membrane causing ion channels within the membrane to open resulting in the flow of primarily sodium and calcium ions into and out of the cell.

3. **Rapid-G protein-couple receptor systems:**
The drug binds with the receptor causing the G protein to bind with guanosine triphosphate (GTP). This in turn causes an enzyme inside the cell to initiate a physiological response or causes the opening of the ion channel.

4. **Prolonged-transcription factors:**
The drug binds to the transcription factors on the DNA within the nucleus of the cell and causes the transcript factor to undergo a physiological change. A drug that causes a physiological response is called an agonist and a drug that blocks a physiological response is referred to as an antagonist. The effect of an antagonist is determined by the inhibitory (I) action of the drug concentration on the receptor site. An inhibitory action of 50 (I50) indicates that the drug effectively inhibits the receptor response in 50% of the population. Agonists and antagonists lack specific and selective effects. They are called nonspecific and have non-specificity properties. Each receptor can produce a variety of physiologic responses. Cholinergic receptors are located in the bladder, heart, blood vessels, lungs, and eyes. A cholinergic stimulator or blocker will affect all of these sites. These drugs are called nonspecific or are said to have non-specificity properties. A drug that is given to stimulate the cholinergic receptors will decrease the heart rate and blood pressure, increase gastric acid secretion, constrict bronchioles, increase urinary bladder contraction, and constrict the pupils. The effects may be beneficial or harmful.

**Categories of drug action**

Drugs are categorized by the type of action it causes on the body. There are four types of responses:

**i. Stimulation or depression:** These are drugs that either increase or depress cellular activity.
**ii. Replacement:** These are drugs that replace an essential body compound such as insulin or estrogen.
**iii. Inhibition:** These drugs interfere with bacterial cell and limit bacterial growth or eliminate the bacteria, such as penicillin.
**Irritation:** These drugs irritate cells to cause a natural response that has a therapeutic effect such as a laxative that irritates the colon wall to increase movement of the colon resulting in defecation.

**Therapeutic index and therapeutic range**

Drugs have a pharmaceutical response as long as the dose remains within the drug's margin of safety. Some drugs have a broad margin of safety. This means that a patient can be given a wide range of dose levels without experiencing a toxic effect. Other drugs have a narrow margin of safety where a slightest change in the dose can result in an undesirable adverse side effect. The drug's Therapeutic Index (TI) identifies the margin of safety of the drug and is a ratio between the therapeutic dose in 50% of persons/animals and the lethal dose in 50% of animals. The therapeutic dose is notated as ED50 and the lethal dose in animals is noted as LD50. The closer that the ratio is to 1, the greater the danger of toxicity. TI = LD50/ED50.
Drugs that have a low TI are said to have a narrow margin of safety. These drugs require that levels in the plasma be monitored and adjustments are made to the dosage in order to prevent a toxic effect from occurring. The plasma drug levels must be within the therapeutic range, which is also known as the therapeutic window. The therapeutic range is between the minimum effective concentration (MEC) for obtaining the desired pharmaceutical response and the minimum toxic concentration (MTC). MEC is achieved by administering a loading dose, which is a large initial dose given to achieve a rapid plasma MEC.

**Peak and trough levels**

The plasma concentration of a drug must be monitored for drugs that have a narrow margin of safety or low therapeutic index. The

concentration is measured at two points. These are the peak drug level and the trough level. The peak drug level is the highest plasma concentration at a specific time. Peak levels indicate the rate a drug is absorbed in the body and is affected by the route used to administer the drug. Drugs administered intravenously have a fast peak drug level while a drug taken orally has a slow peak drug level because the drugs needs time to be absorbed and distributed. Blood samples are drawn at peak times based on the route used to administer the drug. This is usually 1⁄2 to 1 hr after drug administration. The trough level is the lowest plasma concentration of the drug and measures the rate at which the drug is eliminated. Blood should be drawn immediately before the next dose is given regardless of the route used to administer the drug.

### 3.2. Pharmacokinetics

This is the study of drug absorption, distribution, metabolism and excretion (ADME) – 'what the body does to the drug'. Understanding pharmacokinetic principles, combined with specific information regarding an individual drug and patient, underlies the individualized optimal use of the drug (e.g. choice of drug, route of administration, dose and dosing interval).

Pharmacokinetic modelling is based on drastically simplifying assumptions; but even so, it can be mathematically cumbersome, sadly rendering this important area unintelligible to many clinicians.

About 80% of all drugs are administered orally and flow through the gastrointestinal tract (GI) into the small intestine where the membrane of the intestine absorbs drug particles passing them into the bloodstream, where plasma circulates the particles, throughout the body. Drug molecules move to the intended site of action in the plasma but sometimes this journey can be limited because they have to get into the interior of a cell or body compartment through cell membranes. These membranes could be in the skin, the intestinal tract, or the intended site of action. Drug particles then attach themselves to receptor sites resulting in its therapeutic effect.

There are three ways in which drug particles are absorbed. These are:

1. **Passive diffusion:** Passive diffusion is the flow of drug particles from a high concentration to a low concentration. This is similar to how water flows downstream. There is no energy expended in passive diffusion because drug particles are moving along the natural flow.
2. **Active Diffusion:** Active diffusion is how drug particles swim upstream against the natural flow when there is a higher concentration of plasma than there is of drug particles. Drug particles don't have enough energy to go against the natural flow without help. Help comes from an enzyme or protein carrier that transports drug particles upstream across the membrane and into the plasma. The enzyme or protein carrier expends energy to move drug particles.
3. **Pinocytosis:** Pinocytosis is the process of engulfing the drug particle and pulling it across the membrane.

**Principles of pharmacokinetics**

The processes of absorption, distribution, metabolism, and elimination are collectively termed drug disposition. Drug disposition determine the concentration of drug delivered to target effector molecules. Mathematical analysis of these processes can define specific, and clinically useful, parameters that describe drug disposition. This approach allows prediction of how factors such as disease, concomitant drug therapy, or genetic variants affect these parameters, and how dosages therefore should be adjusted. In this way, the chances of under treatment due to low drug concentrations or adverse effects due to high drug concentrations can be minimized.

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treatment due to low drug concentrations or adverse effects due to high drug concentrations can be minimized.

**Absorption rate**

Absorption begins where the drug is administered. This can be by mouth, injection, through the skin, and many other sites. How quickly the drug becomes therapeutic will depend on how fast the drug is absorbed. How long the drug will be effective and how much drug is needed depends on the route of administration, the dose of the drug, and the dosage form (tablet, capsule, or liquid). The absorption rate of a drug is influenced by a number of factors that might increase or decrease the rate; this is similar to how more gasoline is used to drive at faster speeds. Absorption is affected by many factors that include pain, stress, hunger, fasting, food, and pH. Hot, solid, fatty foods can slow absorption such as eating a Big Mac before taking medication. Even exercise which is usually good for the body affects absorption of a drug. During exercise, circulation to the stomach is diverted to other areas of the body and drug absorption is decreased.

**Circulation**

Blood flow to the site of administration of the drug will help increase the rate of absorption. An area that has a lot of blood vessels and good circulation will help absorb the drug quickly and circulate it to the intended site. When a patient is in shock and has a low blood pressure due to decreased circulation (blood flow) drugs may not be absorbed very quickly.

**Route of Administration**

The rate at which drug particles are absorbed is determined by the amount of blood vessels there are in the area where the drug is administered. Drug particles are nearly instantaneously absorbed if the drug is injected intravenously (IV). A slower absorption rate occurs if the drug is administered intramuscularly (IM). The IM rate is dependent on the amount of blood vessels there are at the site of the injection. For

example, a drug is absorbed faster in the deltoid (arm) muscle than in the gluteal
(butt) muscle because there are more blood vessels in the deltoid muscle. Drugs injected in subcutaneous (SC) tissue are absorbed slower than those injected via IM injections because there are fewer blood vessels in subcutaneous tissues than in muscles.

**Solubility**

Drug particles dissolve in either lipid (fat) or water. Lipid-soluble drugs are absorbed more quickly than water-soluble drugs because membranes in the GI tract are composed of lipids making those membranes a perfect highway for lipid soluble drugs to move from the GI tract and into the bloodstream. However, membranes of the GI tract do not directly absorb large water-soluble molecules and a carrier must be used to transport the water-soluble drugs across the GI membrane and into the bloodstream. This additional step causes water soluble drugs to be absorbed more slowly than fat-soluble drugs.

**pH Level**

The pH level of a drug determines how easily drug particles will be absorbed in the GI tract. These drugs that are weak acid, such as aspirin and can pass rapidly across the GI tract membrane while weak base drugs, such as an antacid are absorbed more slowly than a weak acidic drug. Strong acids and bases destroy cells and are not absorbed. The concentration of the drug will also affect the rate of absorption. If a high concentration of the drug is given, it will tend to be absorbed more rapidly. Sometimes larger (loading or priming) doses of a drug may be given that will be more than the body can excrete. When this is done, the drug becomes therapeutic much faster. After the first large dose, small maintenance doses will help keep the therapeutic effect. The form (solid, liquid) the drug is given can affect the absorption
rate. Drugs can be processed when they are manufactured to add other ingredients that will help or hinder absorption.

**Bioavailability**

Not all drug particles reach the circulatory system. Some particles are misdirected or destroyed during the absorption process. For example, hydrochloric acid in the stomach destroys some drug particles before it can pass through the membrane and into the bloodstream. The percentage of a dose that reaches the blood stream is called the bioavailability of a drug. Typically, between 20% and 40% of drugs that are administered orally reach the blood stream. This is called the first pass effect and is the beginning of the metabolism of a drug that is given orally. After a drug is absorbed in the GI tract it is carried to the liver and metabolism occurs. Sometimes very little of the drug remains available for a therapeutic effect after the first pass.

Only drugs administered intravenously have a 100% bioavailability because they are directly injected into the vein. Pharmaceutical manufacturers must consider bioavailability when determining the dose for a drug. For example, the dose for a drug administered PO (orally) might be 4 times higher than if the same drug is administered intravenously.

There are a number of factors that alter bioavailability. These are:

i. **Form:** Tablet, capsule, slow-release, liquid, transdermal patch, suppository, and inhalation.
ii. **Route:** PO (mouth), topical, parenteral, and rectal.
iii. **GI:** The ability of the mucosa (lining) in the GI tract impacts the ability to absorb drug particles and the ability to move food through the digestive tract.
iv. **Food:** Drug particles for some drugs are better absorbed if they are taken with certain foods, while other foods slow down or block absorption.
v. **Drugs:** Some drugs increase or decrease another drug's absorption when both drugs are taken together.
vi. **Liver metabolism:** Liver dysfunction can prevent or delay the metabolism of a drug.
vii. **Concentration:** A higher portion of active ingredient in a dose increases the amount of drug particles that are absorbed.

viii. **Cell membrane:** Single layer cell membrane, such as those found in the intestine, increase absorption, while some drugs are absorbed more slowly in multiple-layers, such as skin.
ix. **Surface area:** A larger surface area, such as in the small intestine, absorbs drugs faster than a smaller area such as in the stomach.

**Drug concentration**

A drug contains an active ingredient, which produces the therapeutic effect, and other materials that give the drug form and protection. The percent of active ingredient in a dose is referred to as the drug concentration. There are generally two levels of concentrations. These are primary loading. Primary loading is a large concentration that is used to achieve a fast therapeutic effect such as the first dose of an antibiotic, and maintenance dose. Maintenance dose is a typical concentration of the drug that is used to provide an ongoing therapeutic effect such as subsequent doses of an antibiotic

**Distribution**

Once absorbed, drug particles are transported in blood plasma. These are referred to as "free" drugs because they are not bound to any receptor sites. Only free drugs can cause a pharmacological response. Drugs bind to proteins in plasma, usually albumin or globulins. These drug–protein complexes decrease the concentration of free drug in the circulation. This protein–drug molecule is too large to pass through the membrane of a blood vessel and is not available for therapeutic use. This process can be reversed when free drug is excreted from the body. The drug molecule is released from the protein and it becomes free drug and can be absorbed for use. Drugs affect areas of the body with good blood supply first, such as the heart, liver, kidney, and brain and then flow to areas with less blood supply, such as muscles and fat. Drugs accumulate in an area of the body and form a reservoir by binding to tissues. This is referred to as pooling. There are two types of pooling.
These are protein binding. Protein binding is when a drug binds to plasma proteins, and Tissue binding. Tissue binding are fat soluble drugs are stored in adipose (fat) tissue. Inderal (propranolol) is a heart

medication that is highly bound to and only about 7% of free drug is available for use at a time. Thiopental (Pentothal) is an anesthetic agent that is stored in fat tissue. In addition, some drugs, such as the antibiotic Tetracycline like to be stored in bones which can interfere with growth of fetal skeletal tissues and can discolor teeth if given to children under eight years of age. Distribution of drugs is affected by three factors:

**1. Level of Plasma Protein:**
A low level of plasma protein and albumin might not provide enough binding sites for drug particles. This results in a buildup of drugs which can reach a toxic level. This happens when there is liver or kidney disease or if the patient is malnourished resulting in low albumin levels (hypoalbuminemia). The elderly are prone to hypoalbuminemia. Healthcare professionals should monitor a patient's plasma protein and albumin levels and the protein-binding percentage of all drugs before administering drugs to the patient.

**2. Blood flow:**
There must be adequate blood flow to target areas of the body; otherwise, insufficient drug particles will reach affected parts of the body. Drugs can also be stored in fat, bones, muscle, and the eyes. Drugs that accumulate in fat are called lipid soluble and remain for about three hours because there is low blood flow in fat tissue. The body also has a blood–brain barrier that enables only lipid soluble drugs, such as general anesthetics and barbiturates which enters into the brain and cerebral spinal fluid (CSF). The only way for non-lipid soluble drugs to enter the brain
is if they are instilled intrathecally, which is, injected directly into the CSF, bypassing the blood-brain barrier.

**3. Competing Drugs:**
Two drugs administered simultaneously might compete for the same binding sites making some drug particles unable to find a binding site. The result is an accumulation of free drug that could reach toxic levels. Two drugs that are highly protein bound are Coumadin (warfarin) and

Inderal (propranolol). Inderal will compete for the protein sites. This can cause serious problems and can result in toxic levels of one or both of the drugs when increased amounts of free drug become available. Abscesses, exudates, body glands, and tumors hinder the distribution of drugs in the body. In addition, antibodies do not distribute well at abscess and exudates sites. The placenta metabolizes some drugs making then inactive and thereby protecting the fetus from drugs given to the mother. However, steroids, narcotics, anesthetics, and some antibiotics can penetrate the placental barrier and cause adverse effects to the fetus.

**Elimination**

Drugs accumulate in a reservoir and are gradually absorbed and eventually eliminated by the body. This metabolism is called biotransformation. Biotransformation occurs in the liver where enzymes inactivate a drug by changing it into more water-soluble compounds that can be excreted from the body. Elimination occurs mainly through the kidneys, although some drugs are also eliminated in bile, feces, lungs, sweat, and breast milk. Patients suffering from liver diseases are prone to drug toxicity because the diseased liver no longer metabolizes the drug sufficiently to allow elimination through the kidneys. The result is a buildup of the drug, which can eventually lead to a toxic effect on the body. The amount of time for half of the drug concentration to be eliminated from the body is called the drug's half-life and is a crucial measurement used to determine how often to administer a drug. Some drugs have a short half-life (less than 8 hours) while other drugs have a longer half-life (24 hours). For example, Digoxin has a half-life of 36 hours. This means it takes 5 to 7 days before there is a steady state of Digoxin in the serum.

Children and the elderly might be unable to absorb and/or eliminate drugs. This can result in toxicity should additional doses be given before the previous does is eliminated from the body. Free drugs, water-soluble drugs, and unchanged drugs are filtered by the kidneys and eliminated through urine. Protein-bound drugs do not filter through the

kidneys until the drug is released from the protein. The quantity of drugs that can be excreted by the kidneys is influenced by the pH of the urine, which normally is between 4.5 and 8.0. Acidic urine (4.5) eliminates weak base drugs; alkaline urine (8.0) eliminates weak acid drugs. The pH of urine can be altered to increase the elimination of certain drugs. For example, urine can be made more alkaline by giving the patient sodium bicarbonate or made more acidic by giving the patient high doses of vitamin C or ammonium chloride. Kidney disease decreases the glomerular filtration rate (GFR) and thereby reduces the quantity of drugs that can be eliminated by the kidneys. This can result in drug toxicity. A similar effect can be caused by a decrease in blood flow to the kidneys. Kidney function is tested by the creatinine clearance test. A decrease in GFR causes an increase in creatinine in serum and a decrease in creatinine in urine. The results of the creatinine clearance test vary with age and whenever there is decreased muscle mass. In some situations, it is important to reduce the excretion of a drug to prolong the drug's therapeutic effect, such as with penicillin. Giving the patient another drug, such as Probenecid, blocks excretion of penicillin. Drugs can be excreted artificially through the use of dialysis, which is a common treatment in certain drug overdoses. Drugs that are excreted by the kidneys can be eliminated using hemodialysis. These drugs include stimulants, depressants, and some non-narcotic analgesics. Drugs that are metabolized by the liver are secreted into bile and then passed through the intestines and eliminated in feces. During this process, the bloodstream might reabsorb fat-soluble drugs and return them to the liver where they are metabolized and eliminated by the kidneys. This is called the enterohepatic cycle. The lungs eliminate drugs that are intact and not metabolites such as gases and anesthetic drugs. The rate at which these drugs are eliminated corresponds to the respiratory rate. Some drugs, such as ethyl alcohol and paraldehyde, are excreted at multiple sites. A small amount is excreted by the lungs and the rest by the liver and the kidneys. Volatile drugs such as anesthetics and drugs that are metabolized to CO2 and H20 are excreted through the lungs. Sweat and salivary glands is not a major route of drug elimination because elimination depends on the diffusion of lipid-

soluble drugs through the epithelial cells of the glands. However, side effects of drugs, such as rashes and skin reactions, can be seen at these sites. Some intravenously administered drugs are excreted into saliva and cause the patient to taste the drug. Eventually, drugs that are excreted into saliva are swallowed, reabsorbed, and eliminated in urine. Many drugs or their metabolites are excreted in mammary glands. These include narcotics such as morphine and codeine. Diuretics and barbiturates, which are weak acids, are less concentrated in breast milk. However, even small amounts of drugs can accumulate causing an undesirable effect on infant receiving breast milk.

**The First pass effect**

The most common way drugs are administered is orally, by swallowing a pill. The drug is then absorbed into the GI tract and enters the portal circulation system where drug particles are transported through the portal vein into the liver where the drug is metabolized. This is referred to as the first pass effect. Not all drugs are metabolized in the liver. Some drugs bypass the first pass effect by sublingual administration (under the tongue) or buccal administration (between the gums and the cheek) where they are absorbed directly into the bloodstream from the mouth. These drugs do not enter the stomach where the hydrochloric acid might destroy drug particles. Other drugs go directly to the liver through the portal vein and also bypass the stomach. The drug is then metabolized in the liver and much of the drug may be eliminated and not available for a therapeutic effect. Sometimes this effect is so great that none of the drug is available for use if given by mouth. The drug must then be given in very high doses or parenterally (intramuscularly or intravenously) to bypass the liver.

# CHAPTER FOUR
# PRINCIPLES OF CLINICAL PHARMACOLOGY 2:

## DOSAGE FORMATION AND ROUTES OF DRUGS ADMINISTRATION

### DOSAGE FORMS

Drugs can be in various dosage forms for convenient and efficacious treatment of a disease. Different dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration. They are not usually administered as pure chemical substances, but are almost always given in formulated preparations, which could range from relatively simple solution to complex drug delivery systems through the use of appropriate additives or excipients in order to provide varied and specialized pharmaceutical functions.

Drugs can be presented in these forms: Capsules, Solutions emulsion, Suspensions Tablets, Suppositories.

### ROUTES OF DRUGS ADMINISTRATION

Drugs are administered through various routes such as oral, topical, parenteral, etc.

Among all these routes, the oral route is the most common, convenient and popular.

There are various reasons for such popularity. The most important and common reasons for their popularity are the convenience of administration, easy to carry and the ease of preparation on an industrial scale.

For simplicity, drugs are classified into two major routes, namely Enteral and Parenteral.

### ENTERAL

**i. Rectal**

The rectal route is usually used to administer drugs used in the cases of vomiting.

Rectal **diazepam** is useful for controlling status epilepticus in children. **Metronidazole** is well absorbed when administered rectally, and is less expensive than intravenous preparations. However, there are usually more reliable alternatives, and drugs that are given rectally can cause severe local irritation.

The sublingual and rectal routes of administration have the advantage that they prevent drug destruction by intestinal enzymes or by low pH in the stomach. The rectal route is also advantageous in cases when drug induces vomiting when given orally.

The following advantages have been claimed for the rectal route of administration of systemically active drugs:

1. Exposure to the acidity of the gastric juice and to digestive enzymes is avoided.
2. The portal circulation is partly bypassed, reducing presystemic (first pass) metabolism.
3. For patients who are unable to swallow or who are vomiting.

**ii. Oral**

Oral drug administration may be used to produce local effects within the gastro-intestinal tract. Examples include antacids, and sulphasalazine, which delivers 5-amino salicylic acid to the colon, thereby prolonging remission in patients with ulcerative colitis.

Oral preparations are usually given by month. It is the most common route of drug administration. It is the most variable too.

It involves the most complicated pathway to the tissues. For example, drugs are absorbed from the stomach but the duodenum is the major site of entry to the systemic circulation because of its larger absorptive surface (Most drugs absorbed from the gastro intestinal (G 1) tract enter the portal circulation and encounter the liver before they are distributed into th general circulation.

The presence of food in the stomach delays gastric emptying so drugs that are destroyed by acid (e.g. Ampicillin Capsules) become unavailable for absorption.

Other limitations of slow-release preparations are:Transit time through the small intestine is about six hours, so once daily dosing may lead to unacceptably low trough concentrations.

If the gut lumen is narrowed or intestinal transit is slow,as in the elderly, or due to other drugs (tricyclic
antidepressants, opiates), there is a danger of high local drug concentrations causing mucosal damage.

**Osmosin**, an osmotically released formulation of **indometacin**, had to be withdrawn because it caused bleeding and ulceration of the small intestine.

Overdose with sustained-release preparations is difficult to treat because of delayed drug absorption.

Sustained-release tablets should not be divided.

**ii. Bucal and lingual**

This is the placing of a drug under the tongue which allows a drug to diffuse into the capillary network and to enter the systemic circulation directly.

Drugs are administered to be retained in the mouth for local disorders of the pharynx or buccal mucosa, such as aphthous ulcers (**hydrocortisone** lozenges or **carbenoxolone** granules).

Sublingual administration has distinct advantages over oral administration (i.e. the drug to be swallowed) for drugs with pronounced presystemic metabolism, providing direct and rapid access to the systemic circulation, bypassing the intestine and liver. **Glyceryl trinitrate**, **buprenorphine** and **fentanyl** are given sublingually for this reason. **Glyceryl trinitrate** is taken either as a sublingual tablet or as a spray. Sublingual administration provides short-term effects which can be terminated by swallowing the tablet. Tablets for buccal absorption provide more sustained plasma concentrations, and are held in one spot between the lip and the gum until they have dissolved.

Drug administered in this manner bypasses the intestine and liver and thus avoids first pass metabolism.

**PARENTERAL**

This option is taken especially:

a. When a person cannot take anything by mouth

b. When a drug must be administered rapidly or in a precise or very high dose
c. When a drug is poorly or erratically absorbed from the digestive tract

Injection routes.

Administration by injection (parenteral administration) includes the following routes:

1. **Intrathecal route**, a needle is inserted between two vertebrae in the lower spine and into the space around the spinal cord. The drug is then injected into the spinal canal. A small amount of local anesthetic is often used to numb the injection site. This route is used when a drug is needed to produce rapid or local effects on the brain, spinal cord, or the layers of tissue covering them (meninges)—for example, to treat infections of these structures. Anesthetics and analgesics (such as morphine) are sometimes given this way.
2. **Subcutaneous route**, a needle is inserted into fatty tissue just beneath the skin. After a drug is injected, it then moves into small blood vessels (capillaries) and is carried away by the bloodstream. Alternatively, a drug reaches the bloodstream through the lymphatic vessels (see figure Lymphatic System: Helping Defend Against Infection). Protein drugs that are large in size, such as insulin, usually reach the bloodstream through the lymphatic vessels because these drugs move slowly from the tissues into capillaries. The subcutaneous route is used for many protein drugs because such drugs would be destroyed in the digestive tract if they were taken orally.

   Certain drugs (such as progestins used for hormonal birth control) may be given by inserting plastic capsules under the skin (implantation). Although this route of administration is rarely used, its main advantage is to provide a long-term therapeutic effect (for example, etonogestrel that is implanted for contraception may last up to 3 years).
3. Intravenous route, a needle is inserted directly into a vein. A solution containing the drug may be given in a single dose or by continuous infusion. For infusion, the solution is moved by gravity

(from a collapsible plastic bag) or, more commonly, by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm. Intravenous administration is the best way to deliver a precise dose quickly and in a well-controlled manner throughout the body. It is also used for irritating solutions, which would cause pain and damage tissues if given by subcutaneous or intramuscular injection. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection because inserting a needle or catheter into a vein may be difficult, especially if the person is obese.

When given intravenously, a drug is delivered immediately to the bloodstream and tends to take effect more quickly than when given by any other route. Consequently, health care practitioners closely monitor people who receive an intravenous injection for signs that the drug is working or is causing undesired side effects. Also, the effect of a drug given by this route tends to last for a shorter time. Therefore, some drugs must be given by continuous infusion to keep their effect constant.

4. **Intramuscular route** is preferred to the subcutaneous route when larger volumes of a drug product are needed. Because the muscles lie below the skin and fatty tissues, a longer needle is used. Drugs are usually injected into the muscle of the upper arm, thigh, or buttock. How quickly the drug is absorbed into the bloodstream depends, in part, on the blood supply to the muscle: The sparser the blood supply, the longer it takes for the drug to be absorbed.

## OTHER ROUTES

### Cutaneous route

Drugs applied to the skin are usually used for their local effects and thus are most commonly used to treat superficial skin disorders, such as psoriasis, eczema, skin infections (viral, bacterial, and fungal), itching, and dry skin. The drug is mixed with inactive substances. Depending on the consistency of the inactive substances, the formulation may be an

ointment, cream, lotion, solution, powder, or gel (see Topical Preparations).

**Transdermal route**

Some drugs are delivered body wide through a patch on the skin. These drugs are sometimes mixed with a chemical (such as alcohol) that enhances penetration through the skin into the bloodstream without any injection. Through a patch, the drug can be delivered slowly and continuously for many hours or days or even longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body because such drugs, if taken in other forms, would have to be taken frequently. However, patches may irritate the skin of some people. In addition, patches are limited by how quickly the drug can penetrate the skin. Only drugs to be given in relatively small daily doses can be given through patches. Examples of such drugs include nitroglycerin (for chest pain), scopolamine (for motion sickness), nicotine (for smoking cessation), clonidine (for high blood pressure), and fentanyl (for pain relief).

**Nasal route**

If a drug is to be breathed in and absorbed through the thin mucous membrane that lines the nasal passages, it must be transformed into tiny droplets in air (atomized). Once absorbed, the drug enters the bloodstream. Drugs administered by this route generally work quickly. Some of them irritate the nasal passages. Drugs that can be administered by the nasal route include nicotine (for smoking cessation), calcitonin (for osteoporosis), sumatriptan (for migraine headaches), and corticosteroids (for allergies).

**Inhalation route**

Drugs administered by inhalation through the mouth must be atomized into smaller droplets than those administered by the nasal route, so that the drugs can pass through the windpipe (trachea) and into the lungs. How deeply into the lungs they go depends on the size of the droplets.

Smaller droplets go deeper, which increases the amount of drug absorbed. Inside the lungs, they are absorbed into the bloodstream.
Relatively few drugs are administered this way because inhalation must be carefully monitored to ensure that a person receives the right amount of drug within a specified time. In addition, specialized equipment may be needed to give the drug by this route. Usually, this method is used to administer drugs that act specifically on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers (called inhalers), and to administer gases used for general anesthesia.

**Nebulization route**
Similar to the inhalation route, drugs given by nebulization must be aerosolized into small particles to reach the lungs. Nebulization requires the use of special devices, most commonly ultrasonic or jet nebulizer systems. Using the devices properly helps maximize the amount of drug delivered to the lungs. Drugs that are nebulized include tobramycin (for cystic fibrosis), pentamidine (for pneumonia caused by Pneumocystis jirovecii), and albuterol (for asthma attacks).

**Otic route**
Drugs used to treat ear inflammation and infection can be applied directly to the affected ears. Ear drops containing solutions or suspensions are typically applied only to the outer ear canal. Before applying ear drops, people should thoroughly clean the ear with a moist cloth and dry it. Unless the drugs are used for a long time or used too much, little of the drugs enter the bloodstream, so bodywide side effects are absent or minimal. Drugs that can be given by the otic route include hydrocortisone (to relieve inflammation), ciprofloxacin (to treat infection), and benzocaine (to numb the ear).

**Vaginal route**
Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, suppository, or ring. The drug is slowly absorbed through the vaginal wall. This route is often used to give estrogen to

women during menopause to relieve vaginal symptoms such as dryness, soreness, and redness.

**Ocular route**

Drugs used to treat eye disorders (such as glaucoma, conjunctivitis, and injuries) can be mixed with inactive substances to make a liquid, gel, or ointment so that they can be applied to the eye. Liquid eye drops are relatively easy to use but may run off the eye too quickly to be absorbed well. Gel and ointment formulations keep the drug in contact with the eye surface longer, but they may blur vision. Solid inserts, which release the drug continuously and slowly, are also available, but they may be hard to put in and keep in place.

Ocular drugs are almost always used for their local effects. For example, artificial tears are used to relieve dry eyes. Other drugs (for example, those used to treat glaucoma [see table Drugs Used to Treat Glaucoma], such as acetazolamide and betaxolol, and those used to dilate pupils, such as phenylephrine and tropicamide) produce a local effect (acting directly on the eyes) after they are absorbed through the cornea and conjunctiva. Some of these drugs then enter the bloodstream and may cause unwanted side effects on other parts of the body.

# CHAPTER FIVE
# PRINCIPLES OF CLINICAL PHARMACOLOGY 3:

## TOXICOLOGY

"All substances are poisons- the difference is in the dose". The above aphorism is attributed to Paracelsus. It illustrates that the potential for harm is widespread and all chemicals could be toxic but the degree of harm that a chemical can inflict on a human or any other living being depends on the dose or the degree of exposure as well as on other factors.

**Toxicology** is the branch of Pharmacology, which deals with the undesirable effects of chemicals on living systems from individual cells to complex ecosystems.

It is the study of poisonous effect of drugs and other chemicals with emphasis on detection, prevention and treatment of poisons.

### Classification

General toxins are classified according to their physical state, chemical groups or target organ damage. Here are some examples**.**

| S/NO | CATEGORY | EXAMPLES |
|---|---|---|
| 1. | Metals and metalloids | Arsenic, cadmium, lead, mercury, nickel, tin, etc |
| 2. | Inorganic compounds | Asbestos, carbon monoxide, hydrogen supplied. |
| 3. | Hydrocarbons (aliphatic) | Propane, butane, pentane, hexane |
| 4. | Hydrocarbons (aromatic) | Benzene, toluene, xylene, naphthalene |
| 5. | Aliphatic alcohols, ketones and acids | Ethanol, acetone, formaldehyde, acetic acid |
| 6. | Chlorinated organic compound | Tetrachlororethene, vinylchloride. |

| | | |
|---|---|---|
| | a. volatile<br>b. non-volatile | Pesticides such as chlordane and DDT, dibenzofurans. |
| 7. | Miscellanies organic compounds | Benzedine, aniline organophosphates. |

Also, poisons can be categorized based on their actions as:
(a) Corrosives- strong acids, strong alkalis, metallic salts.
(b) Irritants- organic, inorganic compounds.
(c) Systemic- cerebral, spinal, peripheral, CVS, asphyxiants.
(d) Miscellaneous- food poisoning and botulism.

**Ecology of Poisoning.**
Interaction between the host and the environment (including easy access to the poisonous substances) determines the magnitude of the problem.
Age- About 40% of all cases of accidental poisoning in children are reported in the second year of life; about 12% of the cases occur in the first and 20% in the third year. As the children start crawling and walking around 1 year, they become very active and try to explore unfamiliar objects by putting these into their mouth and testing these. Thus they expose themselves to accidental poisoning. Hyperactive male children are more prone to accidental poisoning.
**Large families:** In large families mother is often too occupied with household chores, is easily fatigued and often careless in storage of potentially poisonous household substances.
**Small accommodation**: it enhances poisoning.
Environment: Lead poisoning is common in children living in areas where there are workshops for automobile, lead storage batteries or for manufacture of lead typesets for printing presses. Caustic soda poisoning used to be observed frequently in children of families, which prepared washing soap for domestic or commercial purposes in their own houses. Insecticides, medicines, naphthalene balls and kerosene are common household things which are potential hazards.
Rural or Urban areas:

The pattern of poisoning varies in rural and urban areas due to exposures to different types of potential poisons. Snakebites are more common in those wandering in fields. Also pesticides are more common in rural set up. The poor are driven by starvation to experiment on roots and fruits thus leading to poisoning.
Time relationship:
Accidental poisoning is likely when normal routine in the house is disturbed such as during periodic house painting, packing and unpacking at the time of change of residence, going for vacation etc.

**Toxicokinetics**
This is a branch of toxicology that deals with how the body handles the toxins (poisons). There are basically five (5) toxicokinetic properties. They are absorption, distribution, metabolism or biotransformation, storage and excretion.

### 1.3.1 Absorption
As a general rule, fat soluble liquids are readily absorbed through the skin and fat soluble vapors are readily absorbed through the lungs. Notably these routes apply to organic solvents such as hexane, toluene and many others.
In the respiratory systems, toxins such as dust, fumes vapours are more readily absorbed. Water soluble toxins exert immediate effects in the respiratory system. Less soluble substances dissolves more slowly producing acute pneumonitis and pulmonary oedema.
As asphyxiants interrupt the supply of oxygen, simple asphyxiates e.g N2 displaces O2 in the air. Chemical asphyxiants like CO combines with Hb to form carboxyheemoglobin which hinders respiration. Determinants of efficacy of respiratory routes include airborne concentration and respiratory rate.
Determinants of efficacy of skin absorption are site, degrees of vascularization, and prior damage to the skim. Determinates of efficacy of gastrointestinal absorption include fasting state, action of gastic and pancreatic enzymes, portal circulation to the liver,

**Distribution**

The distribution of a toxic substance determines its concentration at a particular tissue and therefore the number and type of cells exposed to high concentrations of it. Water or fat solubility affects the distribution. For example, water soluble compounds of lead (Pb) are found (amongst other tissues) in the red blood cells, while fat solution ones concentrate in the central nervous of system (CNS).

The destination of toxins determined by

a. Ability to cross membrane barriers.

b. Concentration in the blood.

c. Affinity for particular body compartments.

Some toxic substances are transported by binding.

Heam --CO

RBC--PB

Albumin --Hg

Globulins --Fe, Zn

**1.3.2 Metabolism/ Biotrasisformation**

This is the breakdown of toxins into simpler moleles.

Processes involved in metabolism include oxidation, reduction, conjugation and hydrolysis.

The two usual organ that predominantly biotransforms toxic substances are liver and kidney.

Thus non – polar and therefore not water soluble organic compounds tend to be oxidized within the liver e.g

- tichloroethane oxidized to trichlorethanol trichloroacetaldelyde and trichloroacetic acid.

Metabolism or biotransformation does not necessarily result in less toxic compounds. For example benzene may be oxidized to an an exposide which then inflicts damage on the DNA in genes, i.e. it is genotoxic and thence carcinogenic.

### 1.3.4 Storage

This entails to what extent the metabolites are preserved in the body before being excreted.

Factors that affect degree of storage includes affinity e.g where naturally occurring elements with similar properties exist- Pb and Ca.

Fat soluble substances may be stored in adipose tissue e.g DDT, dieldrin.

Toxins can be mobilized from the stoles.

### 1.3.5 Excretion

The following are various roots of elimination of toxic or non- toxic metabolites.

a. Kidney especially water soluble substances.

b. Lungs especially fat soluble vapours e.g. alcohols, or gases such as carbon monoxide (CO).

c. Brest milk.

d. Sweet

e. Saliva.

## TOXICODYNAMICS.

This is a branch of toxicology that deals with what the poisons may do to the body.

Acute effects refers to the short term consequences of exposure. Chronic effects relate to a much longer time scale, while sub-acute are in between acute and chronic.

Effects are usually dose respondent.

The higher the exposure the worse it gets e.g irritant effect on the skin.

Examples of target organic responses are:

### LIVER

- Lapatocelluler damage e.g ethylalcohol, cyclophosphamide.
- Carcinogenic effects e.g aflatoxins, vinyl chloride monomers.

### KIDNEY

- Tubular damage e.g heavy metals like Pb. Cd and Hg,

**BLOOD**
- Acute responses (irritants, allergies).
- Chromic responses (fibrogenic dusts).

**CNS**
- Acute responses (solvents) e.g acetone, toluene causes headache, dizziness, confusion, narcosis.

**Chronic Responses**
- Pb – foot or wrist drop (motor neurone damage).
- Mn – damage to cerebellum (parkinsonism)
- ACH accumulates at parasympathetic nerve endings increased red cell cholinesterase causing weakness of muscles and paralysis including respiration which can lead to sudden death.

**Genetic**
**Carcinonoges**: - Benzene in high concentration can cause leukemias.
**Mutagens:** - Alkylating agents e.g mechlorethamine can lead to inherited defects by DNA damage.
**Teratogenes**: - Damage to featus, not necessarily damaging the mother e.g methyl intro nitroso-gnanidine (MNNG).

**DRUG POISONING AND MANAGEMENT**
**Iron Intoxication**
Ingestion of a number of tablets of ferrous sulphate may cause acute poisoning. Lethal dose is 300 mg/kg of iron. Severe vomiting and diarrhea occur. These may contain blood due to extensive gastrointestinal bleeding. The child may go into severe shock, hepatic and renal failure within a few hours or after a latent period of 1 to 2 days.
**Intervention**
Vomiting should be induced and stomach should be washed with sodium bicarbonate solution. Shock is corrected by infusion of fluids parenterally. Three mL of 7.5 percent sodium bicarbonate solution per kg of body weight are diluted with 3 times its volume of 5 percent

glucose solution and injected intravenously for treatment of acidosis. This dose may be repeated after an hour if acidosis is persisting.
Iron salts are chelated with desferrioxamine IV at 15mg/kg/hour until the serum iron is <300 mg/dL or till 24 hours after the child has stopped passing the characteristic 'vin rose' colored urine. Presence of 'vin rose' color to urine indicates significant poisoning.
**Salicylate Poisoning:** Ingestion of 150 mg/kg of salicylates causes intoxication. Salicylate level of 50-80 mg/dL causes moderate symptoms. Severe symptoms are associated with blood levels above 80 mg/dL.
Initially, there is a respiratory alkalosis, because of hyperventilation induced by sensitization of the respiratory center by salicylates. Kidneys compensate for this alkalsis by increasing the excretion of sodium and potassium bicarbonate Metabolic acidosis supervenes quickly due to disturbances of oxidative phosphorylation and reduction of hepatic glycogen with resultant ketonemia.

**Intervention**
The patients are treated with adequate replacement of fluids to restore renal function.
Urine is alkalinized by administering 1-2 mEq/kg of sodium bicarbonate at half hourly intervals for 4 hours to promote excretion of urine, because in alkaline urine, salicylates do not diffuse back into the tubular cells from the lumen. Potassium salts should be given (3-5 mEq/kg/day) to replace the potassium losses

**Paracetamol Poisoning**
It is safe in pharmacological doses. Overdosage may cause hepatic damage.
**Intervention**
Acetaminophen overdosage is treated with acetylcysteine to be used orally within 16 hours after ingestion in a loading dosage of 140 mg/kg diluted to 5 percent solution orally followed by 70 mg/kg q 4h for another 16 doses.

**Morphine (Opium) Poisoning**

Respiratory depression occurs and pupils are constricted; patients are excessively drowsy.

**Intervention**

Stomach wash is done. Specific antidote for opium poisoning is naloxone given IV in a dose of 0.03 mg/kg/dose. If there is no response in 2 minutes the same dose may be repeated. Naloxone can also be given by continuous infusion (20-40 microgram/kg/h). Analeptics may be used and oxygen is administered by inhalation.

**Isoniazid Poisoning**

Toxic effects of INH may be (i) directly due to the drug i.e., jaundice, SLE, arthralgias, altered sensorium, hemolysis and hypersensitivity reactions; or (ii) due to pyridoxine depletion i.e., convulsions, peripheral neuropathy, demyelination and inhibition of phenytoin metabolism. Lethal doses are>50 mg/kg.

**Intervention**

Gastric lavage is indicated. Patients are given 1 g of pyridoxine (vit. B6) for each gram of INH ingested. If amount of ingested INH is not known, administer 70 mg/kg of

pyridoxine intravenously. The dose may be repeated if seizures recur. Use diazepam or phenobarbitone to control seizures. In severe cases with seizures not responding to treatment hemodialysis may be necessary to save life.

**CHAPTER SIX**

# 6. 0. DRUGS USE IN NERVOUS SYSTEM MANAGEMENT

## 6.1. REVIEW OF BASIC ANATOMY AND PHYSIOLOGY OF THE NERVOUS SYSTEM

The sum total of the tissues that record and distribute information within a person, and does so by electrical and chemical means.

The nervous system has two distinct parts -- central and peripheral. The central part is made up of the brain and spinal cord. Together they are the central nervous system (CNS). The peripheral part of the nervous system is said to be peripheral because it is outside the CNS. The function of the peripheral nervous system is to transmit information back and forth between the CNS and the rest of the body.

The human nervous system contains approximately 10 billion nerve cells. These neurons are the basic building blocks of the nervous system. Neurons consist of the nerve cell body and various extensions from the cell body. These extensions, or processes, are the dendrites (branches off the cell that receive electrical impulses), the axon (the electrical wiring and conduit tube that conducts impulses), and specialized endings (terminal areas to transfer impulses to receivers on other nerves or muscles).

**Central Nervous system:** The central nervous system is that part of the nervous system that consists of the brain and spinal cord.

**The central nervous system (CNS)** is one of the two major divisions of the nervous system. The other is the peripheral nervous system (PNS) which is outside the brain and spinal cord.

The peripheral nervous system (PNS) connects the central nervous system (CNS) to sensory organs (such as the eye and ear), other organs of the body, muscles, blood vessels and glands. The peripheral nerves include the 12 cranial nerves, the spinal nerves and roots, and what are called the autonomic nerves that are concerned specifically with the regulation of the heart muscle, the muscles in blood vessel walls, and glands.

## 6.2. **Drugs and the Nervous system**

Active drugs on the central nervous system affect the functioning of the brain and spinal cord, exerting an action that can help cure or alleviate certain medical conditions, such as disease Alzheimer's disease, Parkinson's disease and depression as well as other conditions. In this family of drugs, also belong the active ingredients that help fight pain, as well as sedatives and muscle relaxants.

These drugs are included:

**Analgesics**: these are drugs used to relieve pain. The so-called narcotics, opium derivatives, act directly on the brain by binding to receptors involved in the perception of pain sensation and they can also be used as a sedative for coughs. The most popular among non-narcotic analgesics, NSAIDs, act instead on the synthesis of prostaglandins, which are important mediators of inflammation.

**General anesthetics:** they are used to prevent pain during surgery and act by inducing a state of unconsciousness.

**Anorectic**: they are used to reduce appetite because they act on an area of the brain that inhibits hunger, but they also apply in the case of keeping a person awake, accelerate the heart rate or increase the blood pressure.

**Anticonvulsants**: they are used to control seizures typical of epilepsy and work by reducing the excessive stimulation of the nervous system typically associated with this disorder. Their possible mechanisms of

action include the increased activity of the neurotransmitter GABA and the inhibition of calcium channels or of glutamate receptors. Sometimes they are also used to prevent and treat certain types of pain.

**Cholinergic agonists**: they are used to increase salivation in case of dry mouth. They act by stimulating the parasympathetic nervous system. Examples are ;direct-acting cholinergic agents include choline esters (acetylcholine, methacholine, carbachol, bethanechol) and alkaloids (muscarine, pilocarpine, cevimeline). ;Indirect-acting cholinergic agents increase the availability of acetylcholine at the cholinergic receptors. These include reversible agents (physostigmine, neostigmine, pyridostigmine, edrophonium, rivastigmine, donepezil, galantamine) and irreversible agents (echothiophate, parathion, malathion, diazinon, sarin, soman).

**Antidepressants**: they are used to treat depression, episodes of panic attacks, to combat obsessive-compulsive disorder as well as to prevent certain types of migraine and other forms of pain. The mechanism at the basis of their pain-killing effect has not yet been fully clarified, while the antidepressant action follows different paths depending on the molecule considered. Some, for example, maintain high levels of serotonin, the so-called "hormone of humor."

**Muscle relaxants**: they are used to relieve muscle spasms and sometimes, musculoskeletal pain or to relax the voluntary muscles during surgery. In the first case, their mechanism of action is based on the reduction of muscle tone; while in the second case, they act on the transmission of nerve impulses to the muscle.

**Sedatives and Anxiolytics**: they are used for the treatment of anxiety, panic attacks and insomnia and work by reducing the levels of several specific molecules in the brain.

**Antiemetics:** they are used to control vomiting and dizziness and act on brain receptors that trigger the urge to empty the stomach.

**Antipsychotics and tranquilizers**: they act by inhibiting the activity of specific nerve impulses and are used to treat psychosis.

**Drugs against Parkinson's disease**: they correct the alteration of chemical equilibrium of the brain that is typical of this disease, thus helping to alleviate the symptoms. In particular, anticholinergic agents (or acetylcholine antagonists) block the muscarinic receptors of the neurotransmitter acetylcholine, while dopaminergic agents replace the neurotransmitter dopamine or prevent their degradation.

**Medications against alcohol addiction**: these may act differently between them. Some, for example, reduce the desire to drink that leads to withdrawal symptoms, while others cause nausea and vomiting if taken with alcohol, and thus discourage its consumption.
**Stimulants of the central nervous system:** they are used in case of attention deficit disorder/hyperactivity disorder and narcolepsy. Their exact mechanism of action is not known.

**Hypnotic drugs:** they are used in case of insomnia. The two main classes are barbiturates and benzodiazepines. Both act by increasing the effect of the neurotransmitter GABA.

**Inhibitors of cholinesterase**: they are used to treat dementia in people with Alzheimer's disease. They act by increasing the activity of the nerves stimulated by the neurotransmitter acetylcholine.

# CHAPTER SEVEN
# BASIC ANATOMY AND PHYSIOLOGY OF THE RESPIRATORY SYSTEM

The major functions of the respiratory system can be divided in two categories:
Respiratory and non-respiratory. The first function is to carry out gas exchange.
Metabolizing tissues utilize oxygen and produce carbondioxide. The respiratory system must obtain oxygen from the environment and must eliminate carbondioxide produced by cellular metabolism. These processes must be coordinated so that the demand for oxygen is met and so that the carbondioxide that is produced is eliminated. The respiratory system is well designed to carry out gas exchange in an expeditious manner.
The respiratory system is also involved in non-respiratory functions. It participates in maintaining acid-base balance, since increase in Co2 in the body lead to increased H+ the lungs also metabolize naturally occurring compounds such as angiotensin, prostaglandins and epinephrine. The lungs are also responsible for protecting the body from inhaled particles.

**Function of the respiratory system:**
Function of the respiratory system is the exchange of O2 and CO2 between the external environment and cells of the body.

## 1.1 Functional anatomy of the respiratory system
Functionally, the respiratory air passages are divided into two zones: a conductive zone and a respiratory zone. The airway tree consists of a series of highly branched hollow tubes that decrease in diameter and become more numerous at each branching.
Trachea, the main airway in turn branches into two bronchi, one of which enters each lung. Within each lung, these bronchi branch many times into progressively smaller bronchi, which in turn branch into

terminal bronchioles analogous to twigs of a tree. The terminal bronchioles redivide to form respiratory bronchioles, which end as alveoli, analogous to leaves on a tree.

## STRUCTURES

### NOSE

The nose, consists of the external nose and the nasal cavity. The external nose is the visible structure that forms a prominent feature of the face.

The largest part of the external nose is composed of hyaline cartilage plates, and the bridge of the nose consists of bones.

The nasal cavity extends from the nares to the choanae.

The nostrils, are the external openings of the nasal cavity and the choanae are the openings into the pharynx.

The anterior part of the nasal cavity, just inside each nostrils, is the vestibule. The hard palate is a bony plate covered by a mucous membrane that forms the floor of the nasal cavity. It separates the nasal cavity from the oral cavity. The nasal septum is a partition of bone and cartilage dividing the nasal cavity into right and left parts. A deviated nasal septum occurs when the septum bulges to one side.

Three bony ridges, called conchae, resembling a conch shell), are present on the lateral walls on each side of the nasal cavity.

Beneath each concha is a passageway called a meatus.

Within the superior and middle meatus are openings from the various paranasal sinuses and the opening of a nasolacrimal duct is within each inferior meatus.

Sensory receptors for the sense of smell are found in the superior part of the nasal cavity. The lungs are the vital organs of respiration. Their main function is to oxygenate the blood by bringing inspired air into close relation with the venous blood in the pulmonary capillaries.

### PHARYNX

The hollow tube that is about 5 inches long and starts behind the nose and ends at the top of the trachea (windpipe) and esophagus. The

pharynx serves as a vestibule or entryway for the trachea and esophagus.
The pharynx is the common passageway of both the digestive and the respiratory systems.
It receives air from the nasal cavity and receives air, food, and drink from the oral cavity.
Inferiorly, the pharynx is connected to the respiratory system at the larynx and to the digestive system at the esophagus. The pharynx is divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx.

**LARYNX**

The larynx is located in the anterior part of the throat and extends from the base of the tongue to the trachea.
It is a passageway for air between the pharynx and the trachea. The larynx is connected by membranes and/or muscles superiorly to the hyoid bone and consists of an outer casing of nine cartilages connected to one another by muscles and ligaments.
Three of the nine cartilages are unpaired, and six of them form three pairs. The largest of the cartilages is the unpaired thyroid cartilage or Adam‘s apple.
The most inferior cartilage of the larynx is the unpaired cricoid cartilage, which forms the base of the larynx on which the other cartilages rest. The third unpaired cartilage is the epiglottis.
The larynx prevents the entry of swallowed materials into the lower respiratory tract and regulates the passage of air into and out of the lower respiratory tract.
During swallowing, the epiglottis tips posteriorly until it lies below the horizontal plane and covers the opening into the larynx.
Thus, food and liquid slide over the epiglottis toward the esophagus.
The most important event for preventing the entry of materials into the larynx, however, is the closure of the vestibular and vocal folds.
That is, the vestibular folds move medially and come together, as do the vocal folds.

The closure of the vestibular and vocal folds can also prevent the passage of air, as when a person holds his or her breath or increases air pressure within the lungs prior to coughing or sneezing.

**TRACHEA**

The trachea or wind pipe, is a membranous tube attached to the larynx. The trachea has an inside diameter of 12 mm and a length of 10–12 cm, descending from the larynx to the level of the fifth thoracic vertebra.

It consists of dense regular connective tissue and smooth muscle reinforced with 15–20 C-shaped pieces of hyaline cartilage. The cartilages support the anterior and lateral sides of the trachea.

They protect the trachea and maintain an open passageway for air.

The posterior wall of the trachea is devoid of cartilage; it contains an elastic ligamentousmembrane and bundles of smooth muscle called the trachealis muscle.

The esophagus lies immediately posterior to the cartilage-free posterior wall of the trachea.

**THE LUNGS**

The lungs are the principal organs of respiration.

Each lung is cone-shaped, with its base resting on the diaphragm and its apex extending superiorly to a point about 2.5 cm above the clavicle.

The right lung has three lobes called the superior, middle, and inferior lobes. The left lung has two lobes called the superior and inferior lobes.

The lobes of the lungs are separated by deep, prominent fissures on the surface of the lung.

Each lobe is divided into broncho-pulmonary segments separated from one another by connective tissue septa, but these separations are not visible as surface fissures.

Individual diseased bronchopulmonary segments can be surgically removed, leaving the rest of the lung relatively intact, because major blood vessels and bronchi do not cross the septa.

There are 9 broncho-pulmonary segments in the left lung and 10 in the right lung. The lungs are separated from each other by the mediastinum.

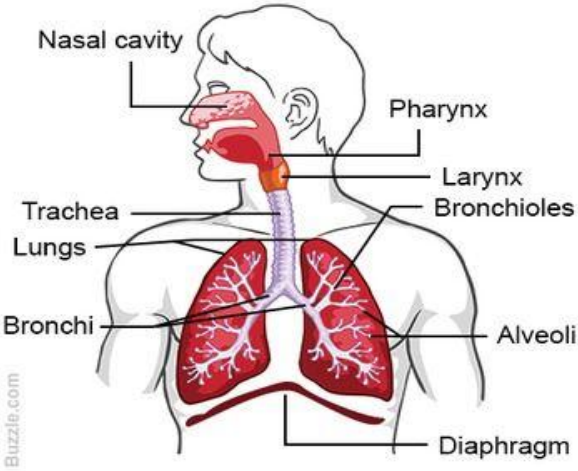
Each lung has:

An apex, the blunt superior end of the lung ascending above the level of the 1st rib into the root of the neck that is covered by cervical pleura.
A base, the concave inferior surface of the lung, opposite the apex, resting on and accommodating the ipsilateral dome of the diaphragm.
Two or three lobes, created by one or two fissures.
Three surfaces (costal, mediastinal, and diaphragmatic).
Three borders (anterior, inferior, and posterior).
The right lung features right oblique and horizontal fissures that divide it into three right lobes: superior, middle, and inferior.
The right lung is larger and heavier than the left, but it is shorter and wider because the right dome of the diaphragm is higher and the heart and pericardium bulge more to the left.
The anterior border of the right lung is relatively straight
The left lung has a single left oblique fissure dividing it into two left lobes, superior and inferior.
The anterior border of the left lung has a deep cardiac notch, an indentation consequent to the deviation of the apex of the heart to the left side. This notch primarily indents the anteroinferior aspect of the superior lobe. This indentation often shapes the most inferior and anterior part of the superior lobe into a thin, tongue-like process, the lingula (L. dim. of lingua,tongue), which extends below the cardiac notch and slides in and out of the costomediastinal recess during inspiration and expiration.

**BRONCHIAL TREE**

Beginning at the larynx, the walls of the airway are supported by horseshoe- or C-shaped rings of hyaline cartilage.
The sublaryngeal airway constitutes the tracheobronchial tree.
The trachea (described with the superior mediastinum, described in the previous subunit), located within the superior mediastinum, constitutes the trunk of the tree.
It bifurcates at the level of the transverse thoracic plane (or sternal angle) into main bronchi, one to each lung, passing inferolaterally to enter the lungs at the hila (singular = hilum)

The right main bronchus is wider, shorter, and runs more vertically than the left main bronchus as it passes directly to the hilum of the lung.
The left main bronchus passes inferolaterally, inferior to the arch of the aorta and anterior to the esophagus and thoracic aorta, to reach the hilum of the lung. Within the lungs, the bronchi branch in a constant fashion to form the branches of the tracheobronchial tree. Note that the branches of the tracheobronchial tree are components of the root of each lung (consisting of branches of the pulmonary artery and veins as well as the bronchi).
Each main (primary) bronchus divides into secondary lobar bronchi, two on the left and three on the right, each of which supplies a lobe of the lung. Each lobar bronchus divides into several tertiary segmental bronchi that supply the bronchopulmonary segments




*Respiratory system*

**I.2 Conducting zone**

The conducting zone includes all of the anatomical structures through which air passes before reaching the respiratory zone. The conducting zone includes all of the anatomical structures through which air passes before reaching the respiratory zone.
The conducting zone carries gas to and from the alveoli, i.e., it exchanges air between the alveoli and atmosphere. The conducting zone of the respiratory system, in summary consists of the following parts:

Mouth→ nose→ pharynx→ larynx→ trachea→ primary bronchi→ all successive branches of bronchioles including terminal bronchioles.

**Functions**

**1. Warming and humidification of the inspired air**

Regardless of the temperature and humidity of the atmosphere, when the inspired air reaches the respiratory zone it is at a body temperature of 37o C (body temperature) and it is saturated with water vapor. This ensures that a constant internal body temperature will be maintained and that delicate lung tissue will be protected from desiccation.

2. **Filtration and cleaning**

Mucous secreted by the cells of the conducting zone serves to trap small particles in the inspired air and thereby performs a filtration function. This mucus is moved along at a rate of 1-2cm/min by cilia projecting from the tops of the epithelial cells that line the Conducting zone. There are about 300 cilia per cell that bend in a coordinated fashion to move mucus toward the pharynx, where it can either be swallowed or expectorated. As a result of this filtration function, particles larger than about 6μm do not enter the respiratory zone of the lungs. The importance of this disease is evidenced by the disease called black lung, which occurs in miners who inhale too much carbon dust and therefore develop pulmonary fibrosis. The cleansing action of cilia and macrophages in the lungs is diminished by cigarette smoke.

**3. Distribute air to the gas exchange surface of the lung.**

- **Respiratory zone**

The respiratory zone includes the respiratory bronchioles (because they contain separate out pouching of alveoli) and the alveoli. Alveoli are tiny air sacs, having a diameter of 0.25-0.50mm. There are about 300-500 million alveoli in a lung. The numerous numbers of these structures provides a large surface area (60-80m2 or 760ft2) for diffusion of gases.

- **Pulmonary blood flow.**

Pulmonary blood flow is the cardiac output of the right heart. It is delivered to the lungs via the pulmonary artery. Pulmonary capillaries form dense network around the alveoli.

Pulmonary blood flow is not distributed evenly in the lungs because of gravitational effects. When a person is standing, blood flow is lowest at apex (top) and higher at base (bottom) of lungs. When a person is in supine (lying down), position gravitational effects disappear. As in other organs, regulation of blood flow is accomplished by altering arteriolar resistance

Bronchial circulation is the blood supply to the conducting airways & is a small fraction of total pulmonary blood flow.

## 1.3 Lung Volumes and Capacities

### I.3.1 Lung Volumes.

- **Tidal volume (TV) -** volume expired or inspired with each breath at rest
  Normal TV is 350-500 ml and includes volume that fills alveoli plus the volume that fills airways
- **Inspiratory reserve volume (IRV)-**additional volume of air inspired on maximal forced inspiration at the end of normal tidal inspiration.
  Normal IRV-3000ml
- **Expiratory reserve volume (ERV)**: Volume of air still be expired by forceful expiration after the end of normal tidal expiration.
  Normal value= 1100ml
- **Residual volume (RV):** Volume that remains in the lungs after maximum expiration, normal=1200ml.
  RV cannot be measured with spirometry

### I.3.2 Lung capacities

It is the addition of 2 or more volumes

- **Inspiratory capacity (IC)=**TV+ IRV= 3500ml
- **Functional residual capacity (FRC) =**ERV+RV =2400ml
- **Vital capacity (VC) =**IRV+ERV=4700ml
- **Total lung capacity (TLC**) =includes all lung volumes and capacity

=VC+RV=590ml

# CHAPTER EIGHT
# DRUGS USE FOR RESPIRATORY SYSTEM MANAGEMENT

## BRONCHODILATORS

These are the most frequently used inhaled medications. Bronchodilators can be subdivided into sympathomimetic (adrenergic) drugs and parasympatholytic (anticholinergic) drugs, as well as being classified as short acting or long acting. The adrenergic drugs stimulate the sympathetic nervous system, while anticholinergic drugs block the parasympathetic system. Adrenergic agents work to cause bronchodilation; anticholinergic drugs block bronchoconstriction. Short-acting drugs are effective for 4 to 6 hours and long-acting bronchodilators generally last about 12 hours.

- **Albuterol**

It is a commonly used bronchodilator and is a short-acting ß2-adrenergic agonist (SABA). Salmeterol is delivered in a dry-powder inhaler (DPI) and is a long-acting ß2-adrenergic agonist (LABA). Levalbuterol is the R enantiomer of racemic albuterol and is a frequently used inhaled drug for bronchodilation. This is a single-isomer drug (the other isomer has been removed). More single-isomer medications are being developed and released for use because these drugs tend to reduce adverse effects such as tremors and tachycardia.

Recently, formoterol was added to the list of adrenergic agents; it is a LABA. Formoterol is administered using a DPI. In October 2006, the US Food and Drug Administration approved the R-R enantiomer of formoterol for marketing as arformoterol. This drug is a single-isomer formulation indicated for use in chronic obstructive pulmonary disease (COPD). Arformoterol is not indicated for acute problems and is not approved for use in pediatric patients. It is administered twice daily and supplied as a 2-mL unit dose for nebulization. Each dose contains 15 µg of arformoterol with isotonic saline as the diluent. It should not be used in conjunction with any other LABA.

The SABA medications are used to provide short-term relief from the bronchospasm and shortness of breath most often associated with asthma and COPD. The LABA medications are for longer-lasting relief and are also useful in treating asthma and COPD. Rau lists 12 inhaled adrenergic bronchodilators. In the current practice of respiratory care, however, four or five of these are commonly administered.

- **Anticholinergic**

Medications provide relief from bronchospasm and shortness of breath. They can be used alone or in combination with SABA and LABA. They are frequently prescribed for patients with asthma or COPD. Of the anticholinergic drugs, respiratory therapists are probably most familiar with ipratropium. Ipratropium works at the muscarinic receptors and blocks transmission of the parasympathetic response. The combination of albuterol and ipratropium has a significantly better effect than one or the other alone. A newer formulation of this type of bronchodilator is tiotropium, which targets more specific muscarinic receptors. Tiotropium has a longer pharmacological half-life and promotes bronchodilation for 24 hours.

Many patients with congestive heart failure, coronary-artery disease, or hypertension take medications that block the ß1-receptors. These ß-blockers could also be termed sympatholytics. Upon the initial release of these drugs in the 1960s, physicians were advised to avoid using them to treat patients with COPD or asthma (due to the possibility of bronchospasm). As the ß-blocking drugs have become more specific to cardiac receptors, however, this potential problem has been eliminated, and the use of cardioselective ß-blockers has become common in patients who also have COPD or asthma.

**Corticosteroids**

Corticosteroids are anti-inflammatory glucocorticoids used primarily for patients with asthma, but they are of some use in COPD as well (particularly for patients with severe COPD and frequent exacerbations). Corticosteroids inhibit many of the cells involved in the inflammatory response (such as eosinophils, T-lymphocytes, mast cells, and dendritic cells and help to increase the diameter of the airways by reducing swelling. By inhaling these medications, patients minimize

many of their systemic adverse effects, which can include suppression of the hypothalamus, pituitary, and adrenal glands; osteoporosis; mood changes; fluid retention; hypertension; an increased white–blood-cell count and a shift in the normal differential; cushingoid appearance; and growth restriction.

Nonetheless, some adverse effects are associated with inhaled steroids. These include oral candidiasis, hoarseness and changes in the voice, and cough. These problems can be minimized through the use of a spacer with a metered-dose inhaler (MDI), along with brushing the teeth and gargling to help reduce residual medication in the oropharynx after using the inhaled medication. Recently developed inhaled steroids provide long-lasting drug coverage that does not require the patient to take multiple puffs from an inhaler, helping to increase compliance. Fluticasone, budesonide, and (most recently) mometasone have become popular as effective steroids that reduce the number of puffs needed; mometasone, for example, can be effective for some patients who use just a single puff of 220 µg in the evening. Some inhaled steroids developed earlier required as many as four to 10 puffs at a time to manage symptoms. Budesonide has an advantage over other steroids in that it can be nebulized; every other steroid used in the United States is available only as a DPI or MDI.

**Mast Cell Stabilizers and Anti-IgE Antibodies**

Nedocromil and cromolyn sodium are older, well-known drugs. Both work to stabilize mast cells and prohibit release of asthma-related chemical mediators such as histamine, leukotrienes, and cytokines from the mast cell. Both drugs are included in the 2002 National Asthma Education and Prevention Program (NAEPP) guidelines and the 2006 Global Initiative for Asthma (GINA) guidelines. The third drug in this category is omalizumab, which is injected subcutaneously every 2 to 4 weeks to treat patients with refractory, severe asthma. These three drugs are not used to treat COPD, since problems with mast cells do not appear to be part of its clinical picture.

Omalizumab stops immunoglobulin E (IgE) from binding to mast cells and basophils, thus preventing the release of chemical mediators. Patients must be more than 12 years old to use this drug, and

administration must be closely monitored for the first 2 hours after injection due to serious side effects, including anaphylaxis, the severe (and sometimes fatal) systemic reaction to an allergen. Patients who might be candidates for treatment with omalizumab must have their total serum IgE levels tested and their current body weight measured for the correct dose to be determined.

IgE levels do not need to be monitored after treatment starts; these levels actually increase during treatment, but they hardly influence inflammation because they are countered by the effects of omalizumab. Three groups of patients are considered to benefit most from using this medicine: those who are using high doses of inhaled steroids and are sensitive to perennial allergens such as dust mites, cockroaches, and pet dander; those who have frequent exacerbations; and those who comply poorly with their medication regimens and may have severe symptoms.

According to the GINA guidelines, the use of omalizumab should be considered for patients who have severe, uncontrolled asthma despite the regular use of inhaled steroids. Omalizumab should be considered an add-on medication; the other drugs being used should be continued as indicated by asthma severity.

**Leukotriene Receptor Antagonists**

Asthma patients use these medications to block the effects of leukotrienes as part of the inflammatory cascade. There are three drugs on the market that work in this area: zafirlukast, montelukast, and zileuton. Of the three, montelukast may be preferred. It is the only drug approved for children 2 or more years old (zafirlukast is approved for those older than 6; zileuton, for those 12 and older).

In addition, zileuton has an adverse effect involving liver toxicity, and the manufacturer recommends monitoring liver enzymes when it is used. These three agents are taken orally and are not used in treating respiratory disorders other than allergic responses and asthma.

**Antihistamines and Epinephrine**

There are numerous first-generation antihistamines such as diphenhydramine and chlorpheniramine on the market, and most are available over the counter. There are three notable second-generation drugs: loratadine, fexofenadine, and cetirizine. These are longer lasting

and less sedating than the first-generation drugs, so they are frequently used to treat allergies and asthma. All of them are supplied in pill form.
Anaphylaxis is treated using epinephrine, usually given intramuscularly or subcutaneously. Some patients with severe allergies carry a single-use injection of epinephrine for use in an allergic emergency.

**Respiratory Stimulants**

Drugs in this category include doxapram, progesterone, caffeine, and theophylline. Doxapram has been used primarily to help preterm infants who have apnea, but has also been somewhat helpful in older patients with sleep apnea and in COPD patients with acute respiratory failure. Likewise, progesterone, caffeine, and theophylline have been cited in the literature as having limited roles in stimulating the respiratory system. Although these medications bring about short-term apnea relief and increase ventilation, there are only limited data to support their routine use.

**Pulmonary Surfactants**

Treatment for neonates with immature pulmonary systems has included exogenous surfactant for many years. In 1990, colfosceril was approved for use, and it was followed by beractant in 1991. In 1998, calfactant was approved, followed by poractant alfa. Colfosceril is the only surfactant that is classified as synthetic; all the others are natural, with their ingredients taken from animals or humans through alveolar lavage or using amniotic fluid. All of the surfactant preparations are given via endotracheal-tube instillation, with varying dosage, handling, and instillation details.
Surfactant therapy has been studied in patients with acute lung injury (ALI) and/or adult respiratory distress syndrome (ARDS), with mixed results. Currently, there are two notable trials looking further into the use of exogenous surfactant in ALI/ARDS. One study is focusing on patients who had either aspiration or pneumonia as the underlying cause of ALI/ARDS, since part of the benefit of surfactant is its anti-inflammatory and antibacterial functions. Progression from direct lung injury to ALI/ARDS may be blunted or stopped by early initiation and longer duration of surfactant therapy. The second study is looking at

using surfactant lavage via bronchoscopy, reaching lung segments to clear damaging proteins.

**Antimicrobials and Antivirals**

Inhaled agents that fight infection include the antimicrobials pentamidine and tobramycin and the antivirals ribavirin and zanamivir. Pentamidine is used to prevent Pneumocystis carinii pneumonia in patients with AIDS. Tobramycin is used to treat Pseudomonas aeruginosa infections, mainly in patients with cystic fibrosis; it has also been used to fight P. aeruginosa in lung-transplant recipients. Ribavirin is used to treat severe infections caused by respiratory syncytial virus. Zanamivir is an antiviral agent used to treat influenza in adults. It has recently gained attention as the inhaled drug of choice to fight possible pandemic influenza.

**Other Agents**

Guaifenesin is a commonly used over-the-counter expectorant that is now being advertised heavily. This re-emphasis is curious, however, since the American College of Chest Physicians' evidence-based clinical practice guidelines on therapy to decrease cough frequency and/or intensity stated that guaifenesin was ineffective in enhancing cough clearance in patients with chronic bronchitis. The drug was not mentioned in any of the 15 ACCP recommendations on cough suppressants and pharmacological protussive therapy.

Varenicline is a medication for smoking cessation that it thought to bind to the nicotine receptors in the brain. When the nicotine receptors are tied up by varenicline, the pleasurable sensation associated with smoking is blunted. Beyond this desired effect, varenicline has several adverse effects that reinforce the desire to quit smoking, including nausea, headache, and sleeping/dreaming abnormalities.

In respiratory therapy, a few medications are considered drugs of choice. As resources for physicians and other prescribing clinicians, however, therapists should always be aware of new medications coming up through research channels. Likewise, they should be among the first to know about newly released pulmonary medications (including their indications, dosages, routes of administration, adverse effects, contraindications, and expected outcomes). Therapists should be

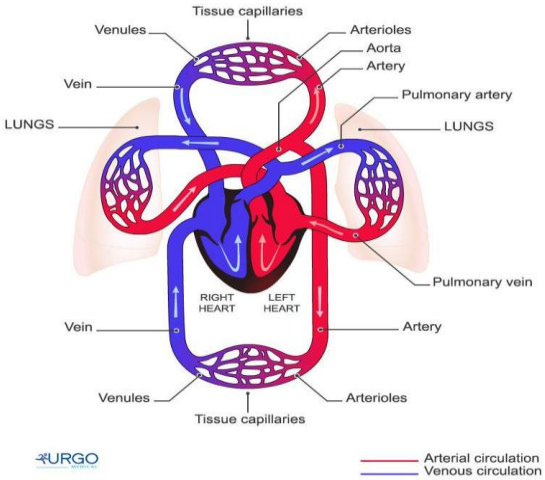
participating in research to verify the effectiveness of new drugs, and they should provide drug education for patients, families, and the other members of the health care team.

# CHAPTER NINE
# III. BLOOD PHYSIOLOGY

## III.1. The Blood

Blood is the vehicle for long-distance, bulk transport of materials between cells and the external environment or between themselves. Such transport of substances is essential for maintaining homeostasis. It transports substances from place to place, buffers PH changes, carries excess heat to the body surface for loss, plays a very crucial role in the body's defense against microbes and minimizes blood loss by evoking homeostatic responses when a blood vessel is injured. Cells need a constant supply of oxygen to execute energy-producing chemical reactions that produce carbon dioxide that must be eliminated continuously.

Blood is about 8% of total body weight and has an average volume of 5 liters in women and 5.5 in men. It is estimated that there are perhaps 60,000 miles of blood vessels in an adult. A very tiny portion of the cardiac output passes through each capillary, bringing oxygen, nutrients, and hormones to each cell and removing carbon dioxide and metabolic end products (waste products).



### III.2. Blood composition

Blood consists of erythrocytes, leukocytes, and platelets suspended in liquid called plasma. (Plasma= 5% of body weight). Because over 99% of the cells are

1 0 0 erythrocytes, the hematocrit, or packed cell volume (HCT or PCV), actually represents the total cell volume occupied by red cells. The white cells and platelet after centrifugation are packed in a thin, cream colored layer because they are colorless, the "buffy coat", on top of the packed red cell column. The hematocrit averages 42% for women, 45% for men, with average volume occupied by plasma being 58% for women and 55% for men.

### III.3. Blood Component Therapy

Components preparation allows better storage of individual components. E.g. red cells are stored at 1 to 6 C while platelets require room temperature. Factors from plasma can be concentrated Whole Blood.

Platelets and plasma are separated from the red cells shortly after donation, and plasma may be further fractionated. Each unit is 450-50 ml blood mixed with 63 ml anticoagulant and red cell preservative solution such as CPDA -1. Such preservatives include citrate, which binds with calcium, and phosphate, dextrose, and adenine, to improve red cell survival.

- **Packed Red Cells**: Most anemic should be transfused with packed red cells, after removing 80% of the plasma, so that the volume of the component is about 150 ml.
  One unit of packed red cells raises recipient's hematocrit by 3 percent.
- **White-cell-poor Red cells**
  Packed cell still contains WBC, which may cause development of HLA-antibodies in response to previous transfusions or pregnancy may have febrile transfusion reactions because of the presence of donor white cells. WBC can be removed by centrifugation, or with the use of special filters.

- **Washed Red Cells**
  Such preparations are needed for individuals who are IgA deficient and have had a life-threatening reaction to plasma containing IgA. The washing procedure also removes WBC. The washed red cells must be used within 24 hours to avoid growth of contaminating bacteria.
- **Frozen Red Cells**
  Packed red cells can be stored for 42 days. Membrane and metabolic changes occur to the red cells during this storage 1 - 60C. It is possible to freeze cells at –700C for as long as 10 years. Freezing requires the addition of glycerol, a cryoprotectant that enters the cells and limits the formation of intracellular crystals. Glycerol is removed before transfusion.
- **Platelets**
  Platelets are concentrated by centrifugation and stored at 20-240C since refrigeration destroys their ability to aggregate. Storage is allowed up to 5 days.
- **Granulocytes**
  Pheresis techniques are used to obtain concentrates of WBC from normal donors for treating severely neutropenic patients. Granulocytes must be transfused as soon as collected, since it is not possible to preserve their function by storage at any temperature. Granulocyte transfusions are frequently accompanied by fever and respiratory symptoms in the recipient; these reactions can often be fatal.
- **Fresh Frozen Plasma**
  FFP is used to correct severe coagulopathies due to multiple factor deficiencies. It is not practical for treating hemophilia A.
- **Cryoprecipitate**
  The preparation of cryoprecipitate concentrates factor VIII is used for treating hemophilia A and von Willebrnand's disease. The half-life of transfused factor VIII is 8 to 12 hours. Cryoprecipitate also corrects bleeding in uremia.

- **Clotting Factor Concentrate**
  Specific factors such as F VIII can be concentrated; factor IX has been made available by this method. It may cause thrombosis and DIC and so must be used with caution.
- **Albumin**
  It is used as a replacement fluid during plasma exchange. It is prepared by heating plasma at 600C over a long period to make it free from infections.

# CHAPTER TEN
# DRUGS USE FOR BLOOD MANAGEMENT

Drugs acting on the blood can be classified under these headings:

1. Anticoagulants
2. Hematinics
3. Hemostatics

## 1. Anticoagulants

Anticoagulants interfere either directly or indirectly with the clotting cascade. The following are some examples of anticoagulants:

- **Vitamin K antagonists (oral anticoagulants):**

They differ from heparin primarily in their duration of activity and magnitude of effect. Their primary importance has been because of their toxic rather than therapeutic effects. Therapeutic indications include oral long term treatment and prevention of recurrence of thrombotic conditions (eg, aortic or pulmonary thromboembolism and venous thrombosis) in cats, dogs, and horses.

There are several groups of vitamin K antagonists. They interfere with the hepatic synthesis of vitamin K–dependent clotting factors by blocking the reduction of vitamin K epoxide after clotting factor synthesis, thus effectively reducing the concentration of vitamin K. Their anticoagulant activity (and therefore therapeutic or toxic effect) is delayed for 8–12 hr after administration or accidental ingestion because of the persistence of factors synthesized before administration. Factor VII has the shortest half-life and is the first factor to become deficient.

The vitamin K antagonists are rapidly and completely absorbed after administration PO. Levels peak in 1 hr. They are almost totally protein bound in plasma, and their volume of distribution is limited to the plasma volume. They are metabolized by the liver to primary metabolites and then conjugated to glucuronides. They undergo an enterohepatic cycle. A variety of factors can increase the activity of these drugs, including hypoproteinemia, antimicrobial therapy, hepatic disease, hypermetabolic states, pregnancy, and the nephrotic syndrome.

The potential for drug interactions is significant. Because they are highly protein bound, they can be displaced by other drugs that are protein bound (eg, acetylsalicylic acid and phenylbutazone), and their anticoagulant effects can be increased to the point of toxicity. Drug interactions also are seen with other antihemostatics.

- **Heparin**

It is a heterogeneous mixture of sulfated (anionic) mucopolysaccharides named because of its initial discovery in high concentrations in the liver. It is prepared from porcine intestinal mucosa and bovine lung. It acts indirectly to facilitate endogenous anticoagulants, specifically antithrombin III and heparin cofactor II. These molecules form stable complexes with (and thus inactivate) clotting factors, especially thrombin. Heparin is released in its active form after inactivation of the clotting factor and thus can interact with other molecules. The effect is greater with low concentrations of heparin. Heparin is also antithrombotic due to binding to endothelial cell walls, thus impairing platelet aggregation and adhesion.

Clinical indications for heparin therapy include the prevention or treatment of venous or pulmonary embolism and embolization associated with atrial fibrillation. It is also used as an anticoagulant for diagnostic use and blood transfusions. Heparin is used in conjunction with blood and/or plasma to treat disseminated intravascular coagulation (DIC) and other hypercoagulable conditions. It has also been used to clear hyperlipidemia.

Heparin is available as a sodium or calcium salt. Absorption and distribution of heparin are limited by the large size and polarity of the molecule. Oral absorption is poor; hence, it is a parenteral anticoagulant. Although anticoagulant activity is first order, half-life of the drug is dose-dependent, steady-state concentrations are difficult to achieve, and pharmacokinetics vary among individuals. Heparin is metabolized by heparinase in the liver and by reticuloendothelial cells. Metabolites of heparinase activity are excreted in the urine. The half-life is prolonged in renal or hepatic failure.

Heparin can be given IV (either intermittently or as a constant infusion) or SC. Deep SC or intrafat injection prolongs persistence of therapeutic

concentrations. Large hematomas can develop after deep IM injection. High-dose heparin therapy (dogs: 150–250 U/kg, SC, tid; cats: 250–375 U/kg, SC, bid) has been recommended for established thromboembolism. Lower dosages (dogs and cats: 75 U/kg, SC, tid; horses: 25–100 U/kg, SC, tid) are indicated in management of DIC. Blood coagulation times (eg, activated partial thromboplastin time) should be monitored during therapy. Adverse effects and toxicities of heparin are limited to potential hemorrhage and, because heparin is a foreign protein, possible allergic reactions. Heparin is contraindicated in bleeding animals and in DIC unless replacement blood or plasma therapy is also given.

Low-molecular-weight heparins (LMWHs, eg, dalteparin and enoxaparin) are alternatives to "unfractionated heparin" and are used extensively in people as anticoagulants for various thromboembolic conditions. LMWHs differ from heparin in that the molecular weights are approximately one-tenth that of heparin, dosing can be once to twice daily in people, there is no need to monitor activated partial thromboplastin time, the risk of bleeding and thrombocytopenia is smaller, and the effect on thrombin is less than that of heparin. LMWHs target antifactor Xa activity. Limited efficacy, safety, and dosing data are available to guide use in veterinary medicine. However, a suggested dosage regimen for dalteparin in dogs and cats is 100–200 IU/kg, SC, once to twice daily, and a suggested dosage regimen for enoxaparin in dogs and cats is 1–2 mg/kg, SC, bid, while monitoring prothrombin time. Individual responses to LMWHs appear to be quite variable in cats.

- **Warfarin sodium**

It is the most commonly used therapeutic preparation. The dosage is 0.1–0.2 mg/kg/day, PO, for dogs and cats, and 0.067–0.167 mg/kg/day, PO, for horses. Toxicity, manifest as hemorrhage, is a major concern with vitamin K antagonists. Coagulation times (particularly prothrombin time), CBCs, and clinical evidence of bleeding (eg, occult blood in feces and urine) must be monitored carefully during warfarin therapy.

- **Fibrinolytic agents**

An increase the activity of plasmin (fibrinolysin), the endogenous compound responsible for dissolving clots. The inactive precursor of plasmin is plasminogen, which exists in two forms: plasma soluble form and fibrin (clot) bound form. Streptokinase and streptodornase are synthesized by streptococci and activate both forms of plasminogen. They are used locally as a powder, infusion, or irrigation in treatment of selected chronic wounds (eg, burns, ulcers, chronic eczemas, ear hematomas, otitis externa, osteomyelitis, chronic sinusitis, or other chronic lesions) that have not responded to other therapy. Tissue-type plasminogen activator (tPA) preferentially activates the fibrin-bound form of plasminogen. Unlike parenterally administered streptokinase, tPA does not induce a systemic proteolytic state. Selective clot lysis occurs without increasing circulating plasmin; thus, tPA has a lower risk of bleeding than does parenteral streptokinase. Although tPA has been used to treat aortic thromboembolism in cats (0.25–1 mg/kg/hr, IV, for a total dosage of 1–10 mg/kg), both the risk of death due to reperfusion (and release of toxic metabolites) and the expense of this genetically engineered product may limit its use.

- **Antithrombotic drugs**

They affect platelet activity, which is normally controlled by substances (such as prostaglandins) generated both outside and within the platelet. Platelet activity can be modulated by interacting with these substances. NSAIDs inhibit the formation of cyclooxygenase, the enzyme responsible for synthesis of prostaglandin products from arachidonic acid that has been released into cells and platelets. The formation of all prostaglandins is inhibited, including that of thromboxane, a potent platelet aggregator and vasoconstrictor. In addition to its inhibitory effects on cyclooxygenase, aspirin irreversibly acetylates thromboxane synthetase, the specific enzyme responsible for synthesis of thromboxane. Aspirin is a potent inhibitor of platelet activity; new platelets must be generated before the effects of aspirin on platelet activity disappear. At higher dosages, aspirin inhibits prostacyclin, a prostaglandin product that counteracts the thrombogenic effects of thromboxane. Thus, aspirin must be used cautiously for antiplatelet

effects. The antiplatelet dosage for dogs is 5–10 mg/kg, PO, every 24–48 hr, and for cats 80 mg, PO, every 48–72 hr. Clopidogrel is an antithrombotic agent used in small animals in treatment of autoimmune hemolytic anemia and in cats with aortic/pulmonary thromboembolism.

**2. Hematinics**

Anemia can be treated pharmacologically by providing components needed for RBC production, including hemoglobin synthesis, and by stimulating bone marrow formation of RBCs.

- **Vitamin B12**

It is essential for DNA synthesis. Deficiency causes inhibited nuclear maturation and division. RBC maturation arrest in the bone marrow leads to megaloblastic or pernicious anemia. Vitamin B12, a porphyrin-like compound consisting of a ring structure that contains centrally located cobalt, is derived from the diet and microbial synthesis in the GI tract. However, except for ruminants, microbial production occurs in the large intestine, from which vitamin B12 is not readily absorbed. Dietary deficiency of B12 is rare; deficiency usually results from poor absorption from the GI tract.

Vitamin B12 absorption is complex and depends on gastric acid, pepsin, and intrinsic factor secreted from gastric parietal cells or pancreatic duct cells. Intrinsic factor binds to and protects vitamin B12 from digestion. In this form, B12 binds to highly specific receptor sites in the brush border of the ileum, where it enters enterocytes by pinocytosis. Interference with its absorption in the ileum results in continuous depletion, although many months of defective absorption are necessary before deficiency develops. Vitamin B12 is bound in the plasma to transcobalamin. It is stored in large quantities in the liver and slowly released as needed. It is excreted into the bile but undergoes enterohepatic cycling.

Vitamin B12 (dogs: 100–200 mcg/day, PO or SC; cats: 50–100 mcg/day, PO or SC) is available in oral and parenteral preparations of cyanocobalamin. There are no significant toxicities associated with therapy. Indications for therapy are limited to cases of vitamin B12 malabsorption, such as ileectomy, gastrectomy, or deficiency malabsorption syndromes (eg, exocrine pancreatic insufficiency).

Chronic administration of H2-receptor blockers (cimetidine, ranitidine, famotidine) can also lead to vitamin B12 deficiency, because an acid environment is necessary for its absorption.

- **Folic acid**

It is needed for DNA and RNA synthesis. Anemia associated with folic acid deficiency is characterized as megaloblastic. Sources of folic acid in the diet include yeast, liver, kidney, and green vegetables, although it can also be formed by microbes. Folic acid is stored in the liver but not as avidly as vitamin B12. Because folic acid is destroyed by catabolic processes every day, serum levels decrease rapidly in the presence of deficient diets. Absorption of folic acid is not as sensitive as that of vitamin B12, although jejunal pathology can result in folate deficiency.
Folic acid (dogs: 5 mg/day, PO; cats: 2.5 mg/day, PO) is available in both oral and parenteral formulations. Significant toxicity is not associated with therapy. Indications for therapy include inadequate intake due to administration of selected drugs (eg, methotrexate, potentiated sulfa drugs, some anticonvulsants [eg, primidone and phenytoin]), liver disease, malabsorption, or other chronic debilitating diseases.

- **Iron**

It is necessary for hemoglobin formation. It is available in the diet either as a heme form, which is a small percentage of the total but readily absorbed, or a nonheme form. Absorption of the nonheme form is profoundly affected by diet. Iron is absorbed from the proximal jejunum, where it immediately combines in the enterocyte to the globulin transferrin. It is transported in the plasma in this form, but the binding is loose and iron can be easily transferred to tissues. Iron enters cells via specific receptors that interact with transferrin. In the cell, iron combines with the protein apoferritin to become ferritin, the soluble form of iron storage. Smaller quantities are also stored as the insoluble hemosiderin; the amount of this storage form increases when the total amount of iron in the body is much more than apoferritin can accommodate. There is no mechanism for the excretion of iron other than via the GI tract. GI elimination occurs by exfoliation of enterocytes

containing iron, biliary elimination, and elimination of dietary iron that has not been absorbed.

Indications for iron therapy are limited to treatment or prevention of iron deficiency (eg, blood loss, pregnancy). Iron is available in both oral and parenteral preparations. Oral preparations should be ferrous salts, such as sulfate (dogs: 100–300 mg/day; cats: 50–100 mg/day), gluconate, and fumarate. Therapy can be continued for several months to replenish body iron stores. Response to iron therapy can be assessed by monitoring circulating hemoglobin concentrations. Adverse effects are dose-related. Parenteral preparations are indicated for initial treatment of iron deficiency or if oral preparations cannot be tolerated or are not feasible (eg, in neonatal pigs). Iron dextrans can be given as a single IM injection (100 mg) at 2–4 days of age in newborn piglets. Toxicity may be seen and is manifest as pale skin, bloody diarrhea, and shock (see Iron Toxicosis in Newborn Pigs). When efficacy of parenteral preparations is compared, dextran complexes and hydrogenated dextrans are more effective than dextrins. Hemoglobin formation requires pyridoxine and the trace elements copper and cobalt (necessary for B12 synthesis by ruminal microflora). "Shotgun" preparations contain a combination of hematinic agents; the efficacy of such products is questionable. As with any hematinic preparation, provision of these compounds will be ineffective if the nutritional status of the animal is poor.

- **Epoetin alfa**

It is the synthetic form of the human glycoprotein erythropoietin (ERP). Epoetin alfa is indicated in treatment of anemia associated with chronic renal failure in dogs and cats. The initial dosage is 100 U/kg, SC, 3 times/wk for 4 mo, while monitoring PCV, followed by a maintenance dosage of 75–100 U/kg, SC, 2–3 times/wk. The most significant adverse effects in dogs and cats are development of antibodies to ERP, resistance to treatment, and worsening of anemia. Other potential adverse effects include iron deficiency, hypertension, fever, local cellulitis, arthralgia, mucocutaneous ulcers, polycythemia, and CNS disturbances (seizures).

- **Anabolic steroids**

They are compounds structurally related to testosterone that have similar protein-anabolic activity but minimal androgenic effects, such as masculinization. As part of their anabolic activity, these compounds increase the circulating RBC mass and possibly granulocytic mass. Clinical indications for use of anabolic steroids include chronic, nonregenerative anemias. Response to therapy is variable, and the time to clinical improvement is long, frequently ≥3 mo. The proposed mechanisms of action include increased ERP production via ERP-stimulating factor, differentiation of stem cells into ERP-stimulating factor-sensitive cells (eg, hemocytoblasts), and direct stimulation of erythroid-progenitor cells. The effect of anabolic steroids requires adequate ERP levels and sufficient cells in the bone marrow. Thus, the effectiveness of anabolic steroids in treating anemia may be limited, depending on the cause.

Anabolic steroids can be divided into two categories depending on the presence or absence of an alkyl group at the 17-carbon position. They are available as oral and parenteral preparations, including oil-based products intended for slow release. The absorption and disposition of anabolic steroids depend on the type of preparation and the animal species. Most are eliminated after hepatic metabolism. The alkylated products are more effectively absorbed when given PO and are more effective stimulants of bone marrow. Alkylated anabolic steroids include oxymetholone (dogs and cats: 1–5 mg/kg, PO, every 18–24 hr). Nonalkylated anabolic steroids include nandrolone decanoate (dogs: 1–1.5 mg/kg/wk, IM; cats: 1 mg/kg/wk, IM; horse: 1 mg/kg, IM, once every 4 wk). Boldenone undecylenate is approved for horses at 1.1 mg/kg, IM, every 3 wk. Adverse effects of anabolic steroids include sodium and water retention, virilization, and hepatotoxicity. The alkylated products are more hepatotoxic than the nonalkylated products, particularly in cats. Cholestatic liver damage develops early and can be significant but frequently is reversible.

**3. Hemostatics**

- **Lyophilized concentrates of one or more clotting factors**

They are available as topical or local hemostatics. Most act to provide an artificial factor or structural matrix that facilitates control of capillary bleeding. An intact hemostatic mechanism is necessary. These absorbable products are indicated for capillary oozing from small, superficial vessels. Concentrated factors include thromboplastin, thrombin (available as a powder, solution, or sponge), collagen, and fibrinogen. Artificial matrices include fibrin foam, absorbable gelatin sponge, and oxidized cellulose.

- **Astringents**

They act locally by precipitating proteins. These agents do not penetrate tissues and, thus, are restricted to surface cells. They can be damaging to surrounding tissues. Examples include ferric sulfate, silver nitrate, and tannic acid.

- **Epinephrine and norepinephrine**

They are hemostatics by virtue of their vasoconstrictive effects. They may be included in topical medications to decrease blood flow to the tissues, or applied intranasally in tampons to decrease epistaxis.

1. **Systemic hemostatics** include fresh blood or blood components administered to animals that have a coagulation factor deficiency. Examples include fresh plasma, fresh frozen plasma, cryoprecipitate, and platelet-rich plasma.
2. **Vitamin K** is a hemostatic only in instances of vitamin K deficiency. It is necessary for hepatic synthesis of coagulation factors II, VII, IX, and X. The principal indication is treatment of rodenticide toxicity, moldy sweet clover poisoning (dicumarol), and sulfaquinoxaline toxicity.

Vitamin K1 (phytonadione) is a plant form of vitamin K that is safer and more effective with more rapid restoration of coagulation factors than other analogues such as vitamin K3 (menadione). The preferred routes to administer phytonadione are SC and PO, although it can be given by slow IV (anaphylactic reactions have been reported) or IM injections. After IM administration, bleeding may occur at the injection site. The dosage regimen selected depends on the nature of the

anticoagulant toxicity. Vitamin K1 must be given as long as the anticoagulant is present in the body at toxic levels; this duration varies depending on the rodenticide. Second-generation coumarin derivatives or indanediones are potent and have long half-lives. Several weeks of vitamin K1 therapy may be necessary after ingestion of these long-acting rodenticides. Coagulation status should be monitored during therapy. The lag period after administration of phytonadione and synthesis of new clotting factors is 6–12 hr.

**Desmopressin** is a synthetic analogue of vasopressin and is used to treat diabetes insipidus. In animals with von Willebrand disease, desmopressin transiently increases von Willebrand factor and shortens bleeding time. It may be useful in dogs with von Willebrand disease (0.4 mcg/kg, SC; 1 mcg/kg, IV, diluted in 20 mL of saline and given over 10 min), to permit surgical procedures or control capillary bleeding.

# CHAPTER ELEVEN
# GASTROINTESTINAL ANATOMY AND PHYSIOLOGY

The GIT is made of these:

- The main organs
  1. Mouth
  2. Pharynx
  3. Esophagus
  4. Stomach
  5. Small Intestine
  6. Large Intestine
- Accessory Digestive Organs
  1. Teeth
  2. Salivary Glands
  3. Pancreas
  4. Liver
  5. Gallbladder

The GIT is responsible for the following:

- **Ingestion**
  Food must be placed into the mouth before it can be acted on; this is an active, voluntary process called ingestion.
- **Propulsion**
  If foods are to be processed by more than one digestive organ, they must be propelled from one organ to the next; swallowing is one example of food movement that depends largely on the propulsive process called peristalsis (involuntary, alternating waves of contraction and relaxation of the muscles in the organ wall).
- **Food breakdown**
  Mechanical digestion prepares food for further degradation by enzymes by physically fragmenting the foods into smaller pieces, and examples of mechanical digestion are: mixing of food in the

mouth by the tongue, churning of food in the stomach, and segmentation in the small intestine.

The sequence of steps in which the large food molecules are broken down into their building blocks by enzymes is called chemical digestion.

- **Absorption**

  Transport of digested end products from the lumen of the GI tract to the blood or lymph is absorption, and for absorption to happen, the digested foods must first enter the mucosal cells by active or passive transport processes.

- **Defecation**

  Defecation is the elimination of indigestible residues from the GI tract via the anus in the form of feces.

## 1. Anatomy of the Digestive System

The organs of the digestive system can be separated into two main groups: those forming the alimentary canal and the accessory digestive organs.

### 1.1 Organs of the Alimentary Canal

The alimentary canal, also called the gastrointestinal tract, is a continuous, hollow muscular tube that winds through the ventral body cavity and is open at both ends. Its organs include the following:

#### *1.1.2. Mouth*

Food enters the digestive tract through the mouth, or oral cavity, a mucous membrane-lined cavity.

- **Lips**; The lips (labia) protect its anterior opening.
- **Cheeks;** The cheeks form its lateral walls.
- **Palate**; The hard palate forms its anterior roof, and the soft palate forms its posterior roof.
- **Uvula**; The uvula is a fleshy finger-like projection of the soft palate, which extends inferiorly from the posterior edge of the soft palate.
- **Vestibule;** The space between the lips and the cheeks externally and the teeth and gums internally is the vestibule.

- **Oral cavity proper**; The area contained by the teeth is the oral cavity proper.
- **Tongue;** The muscular tongue occupies the floor of the mouth and has several bony attachments- two of these are to the hyoid bone and the styloid processes of the skull.
- **Lingual frenulum;** The lingual frenulum, a fold of mucous membrane, secures the tongue to the floor of the mouth and limits its posterior movements.
- **Palatine tonsils**; At the posterior end of the oral cavity are paired masses of lymphatic tissue, the palatine tonsils.
- **Lingual tonsil**; The lingual tonsils cover the base of the tongue just beyond.

### *1.1.3. Pharynx*

From the mouth, food passes posteriorly into the oropharynx and laryngopharynx.

- **Oropharynx**; The oropharynx is posterior to the oral cavity.
- **Laryngopharynx**; The laryngopharynx is continuous with the esophagus below; both of which are common passageways for food, fluids, and air.

### *1.1.4. Esophagus*

The esophagus or gullet, runs from the pharynx through the diaphragm to the stomach.

- **Size and function**; About 25 cm (10 inches) long, it is essentially a passageway that conducts food by peristalsis to the stomach.
- **Structure**; The walls of the alimentary canal organs from the esophagus to the large intestine are made up of the same four basic tissue layers or tunics.
- **Mucosa;** The mucosa is the innermost layer, a moist membrane that lines the cavity, or lumen, of the organ; it consists primarily of a surface epithelium, plus a small amount of connective tissue (lamina propria) and a scanty smooth muscle layer.

- **Submucosa;** The submucosa is found just beneath the mucosa; it is a soft connective tissue layer containing blood vessels, nerve endings, lymph nodules, and lymphatic vessels.
- **Muscularis externa**; The muscularis externa is a muscle layer typically made up of an inner circular layer and an outer longitudinal layer of smooth muscle cells.
- **Serosa**; The serosa is the outermost layer of the wall that consists of a single layer of flat serous fluid-producing cells, the visceral peritoneum.
- **Intrinsic nerve plexuses;** The alimentary canal wall contains two important intrinsic nerve plexuses- the submucosal nerve plexus and the myenteric nerve plexus, both of which are networks of nerve fibers that are actually part of the autonomic nervous system and help regulate the mobility and secretory activity of the GI tract organs.

### *1.1.5. Stomach*

Different regions of the stomach have been named, and they include the following:

- **Location**; The C-shaped stomach is on the left side of the abdominal cavity, nearly hidden by the liver and the diaphragm.
- **Function;** The stomach acts as a temporary "storage tank" for food as well as a site for food breakdown.
- **Cardiac region;** The cardiac region surrounds the cardioesophageal sphincter, through which food enters the stomach from the esophagus.
- **Fundus;** The fundus is the expanded part of the stomach lateral to the cardiac region.
- **Body;** The body is the midportion, and as it narrows inferiorly, it becomes the pyloric antrum, and then the funnel-shaped pylorus.
- **Pylorus**; The pylorus is the terminal part of the stomach and it is continuous with the small intestine through the pyloric sphincter or valve.

- **Size;** The stomach varies from 15 to 25 cm in length, but its diameter and volume depend on how much food it contains; when it is full, it can hold about 4 liters (1 gallon) of food, but when it is empty it collapses inward on itself.
- **Rugae;** The mucosa of the stomach is thrown into large folds called rugae when it is empty.
- **Greater curvature.** The convex lateral surface of the stomach is the greater curvature.
- **Lesser curvature;** The concave medial surface is the lesser curvature.
- **Lesser omentum**; The lesser omentum, a double layer of peritoneum, extends from the liver to the greater curvature.
- **Greater omentum;** The greater omentum, another extension of the peritoneum, drapes downward and covers the abdominal organs like a lacy apron before attaching to the posterior body wall, and is riddled with fat, which helps to insulate, cushion, and protect the abdominal organs.
- **Stomach mucosa;** The mucosa of the stomach is a simple columnar epithelium composed entirely of mucous cells that produce a protective layer of bicarbonate-rich alkaline mucus that clings to the stomach mucosa and protects the stomach wall from being damaged by acid and digested by enzymes.
- **Gastric glands;** This otherwise smooth lining is dotted with millions of deep gastric pits, which lead into gastric glands that secrete the solution called gastric juice.
- **Intrinsic factor;** Some stomach cells produce intrinsic factor, a substance needed for the absorption of vitamin b12 from the small intestine.
- **Chief cells**; The chief cells produce protein-digesting enzymes, mostly pepsinogens.
- **Parietal cells;** The parietal cells produce corrosive hydrochloric acid, which makes the stomach contents acidic and activates the enzymes.

- **Enteroendocrine cells**; The enteroendocrine cells produce local hormones such as gastrin, that are important to the digestive activities of the stomach.
- **Chyme;** After food has been processed, it resembles heavy cream and is called chyme.

### *1.1.6 Small Intestine*

The small intestine is the body's major digestive organ.

- **Location**; The small intestine is a muscular tube extending from the pyloric sphincter to the large intestine.
- **Size**; It is the longest section of the alimentary tube, with an average length of 2.5 to 7 m (8 to 20 feet) in a living person.
- **Subdivisions**; The small intestine has three subdivisions: the duodenum, the jejunum, and the ileum, which contribute 5 percent, nearly 40 percent, and almost 60 percent of the small intestine, respectively.
- **Ileocecal valve;** The ileum meets the large intestine at the ileocecal valve, which joins the large and small intestine.
- **Hepatopancreatic ampulla**; The main pancreatic and bile ducts join at the duodenum to form the flasklike hepatopancreatic ampulla, literally, the" liver-pacreatic-enlargement".
- **Duodenal papilla;** From there, the bile and pancreatic juice travel through the duodenal papilla and enter the duodenum together.
- **Microvilli;** Microvilli are tiny projections of the plasma membrane of the mucosa cells that give the cell surface a fuzzy appearance, sometimes referred to as the brush border; the plasma membranes bear enzymes (brush border enzymes) that complete the digestion of proteins and carbohydrates in the small intestine.
- **Villi;** Villi are fingerlike projections of the mucosa that give it a velvety appearance and feel, much like the soft nap of a towel.
- **Lacteal;** Within each villus is a rich capillary bed and a modified lymphatic capillary called a lacteal.

- **Circular folds;** Circular folds, also called plicae circulares, are deep folds of both mucosa and submucosa layers, and they do not disappear when food fills the small intestine.
- **Peyer's patches**; In contrast, local collections of lymphatic tissue found in the submucosa increase in number toward the end of the small intestine.

### *1.1.7. Large Intestine*

The large intestine is much larger in diameter than the small intestine but shorter in length.

- **Size;** About 1.5 m (5 feet) long, it extends from the ileocecal valve to the anus.
- **Functions;** Its major functions are to dry out indigestible food residue by absorbing water and to eliminate these residues from the body as feces.
- **Subdivisions**; It frames the small intestines on three sides and has the following subdivisions: cecum, appendix, colon, rectum, and anal canal.
- **Cecum;** The saclike cecum is the first part of the large intestine.
- **Appendix;** Hanging from the cecum is the wormlike appendix, a potential trouble spot because it is an ideal location for bacteria to accumulate and multiply.
- **Ascending colon;** The ascending colon travels up the right side of the abdominal cavity and makes a turn, the right colic (or hepatic) flexure, to travel across the abdominal cavity.
- **Transverse colon;** The ascending colon makes a turn and continuous to be the transverse colon as it travels across the abdominal cavity.
- **Descending colon;** It then turns again at the left colic (or splenic) flexure, and continues down the left side as the descending colon.
- **Sigmoid colon;** The intestine then enters the pelvis, where it becomes the S-shaped sigmoid colon.

- **Anal canal;** The anal canal ends at the anus which opens to the exterior.
- **External anal sphincter;** The anal canal has an external voluntary sphincter, the external anal sphincter, composed of skeletal muscle.
- **Internal involuntary sphincter**; The internal involuntary sphincter is formed by smooth muscles.

***Accessory Digestive Organs***

Other than the intestines and the stomach, the following are also part of the digestive system:

**a .Teeth;** The role the teeth play in food processing needs little introduction; we masticate, or chew, by opening and closing our jaws and moving them from side to side while continuously using our tongue to move the food between our teeth.

- **Function;** The teeth tear and grind the food, breaking it down into smaller fragments.
- **Deciduous teeth;** The first set of teeth is the deciduous teeth, also called baby teeth or milk teeth, and they begin to erupt around 6 months, and a baby has a full set (20 teeth) by the age of 2 years.
- **Permanent teeth**; As the second set of teeth, the deeper permanent teeth, enlarge and develop, the roots of the milk teeth are reabsorbed, and between the ages of 6 to 12 years they loosen and fall out.
- **Incisors;** The chisel-shaped incisors are adapted for cutting.
- **Canines;** The fanglike canines are for tearing and piercing.
- **Premolars and molars**; Premolars (bicuspids) and molars have broad crowns with round cusps (tips) and are best suited for grinding.
- **Crown;** The enamel-covered crown is the exposed part of the tooth above the gingiva or gum.
- **Enamel;** Enamel is the hardest substance in the body and is fairly brittle because it is heavily mineralized with calcium salts.

- **Root;** The outer surface of the root is covered by a substance called cementum, which attaches the tooth to the periodontal membrane (ligament).
- **Dentin;** Dentin, a bonelike material, underlies the enamel and forms the bulk of the tooth.
- **Pulp cavity;** It surrounds a central pulp cavity, which contains a number of structures (connective tissue, blood vessels, and nerve fibers) collectively called the pulp.
- **Root canal;** Where the pulp cavity extends into the root, it becomes the root canal, which provides a route for blood vessels, nerves, and other pulp structures to enter the pulp cavity of the tooth.

***b .Salivary Glands***

Three pairs of salivary glands empty their secretions into the mouth.

- **Parotid glands;** The large parotid glands lie anterior to the ears and empty their secretions into the mouth.
- **Submandibular and sublingual glands;** The submandibular and sublingual glands empty their secretions into the floor of the mouth through tiny ducts.
- **Saliva;** The product of the salivary glands, saliva, is a mixture of mucus and serous fluids.
- **Salivary amylase;** The clear serous portion contains an enzyme, salivary amylase, in a bicarbonate-rich juice that begins the process of starch digestion in the mouth.

***c. Pancreas***

Only the pancreas produces enzymes that break down all categories of digestible foods.

- **Location;** The pancreas is a soft, pink triangular gland that extends across the abdomen from the spleen to the duodenum; but most of the pancreas lies posterior to the parietal peritoneum, hence its location is referred to as retroperitoneal.

- **Pancreatic enzymes;** The pancreatic enzymes are secreted into the duodenum in an alkaline fluid that neutralizes the acidic chyme coming in from the stomach.
- **Endocrine function;** The pancreas also has an endocrine function; it produces hormones insulin and glucagon.

***d. Liver***

The liver is the largest gland in the body.

- **Location;** Located under the diaphragm, more to the right side of the body, it overlies and almost completely covers the stomach.
- **Falciform ligament;** The liver has four lobes and is suspended from the diaphragm and abdominal wall by a delicate mesentery cord, the falciform ligament.
- **Function;** The liver's digestive function is to produce bile.
- **Bile;** Bile is a yellow-to-green, watery solution containing bile salts, bile pigments, cholesterol, phospholipids, and a variety of electrolytes.
- **Bile salts;** Bile does not contain enzymes but its bile salts emulsify fats by physically breaking large fat globules into smaller ones, thus providing more surface area for the fat-digesting enzymes to work on.

***e. Gallbladder***

While in the gallbladder, bile is concentrated by the removal of water.

- **Location;** The gallbladder is a small, thin-walled green sac that snuggles in a shallow fossa in the inferior surface of the liver.
- **Cystic duct;** When food digestion is not occurring, bile backs up the cystic duct and enters the gallbladder to be stored.

**1.2. Physiology of the Digestive System**

Specifically, the digestive system takes in food (ingests it), breaks it down physically and chemically into nutrient molecules (digests it), and absorbs the nutrients into the bloodstream, then, it rids the body of indigestible remains (defecates).

### 1.2.1 Activities Occurring in the Mouth, Pharynx, and Esophagus

The activities that occur in the mouth, pharynx, and esophagus are food ingestion, food breakdown, and food propulsion.

- **Food Ingestion and Breakdown**

Once food is placed in the mouth, both mechanical and chemical digestion begin.Physical breakdown. First, the food is physically broken down into smaller particles by chewing.

- **Chemical breakdown**

Then, as the food is mixed with saliva, salivary amylase begins the chemical digestion of starch, breaking it down into maltose.

- **Stimulation of saliva**

When food enters the mouth, much larger amounts of saliva pour out; however, the simple pressure of anything put into the mouth and chewed will also stimulate the release of saliva.

- **Passageways**

The pharynx and the esophagus have no digestive function; they simply provide passageways to carry food to the next processing site, the stomach.

- **Food Propulsion – Swallowing and Peristalsis**

For food to be sent on its way to the mouth, it must first be swallowed.

- **Deglutition**

Deglutition, or swallowing, is a complex process that involves the coordinated activity of several structures (tongue, soft palate, pharynx, and esophagus).

- **Buccal phase of deglutition**

The first phase, the voluntary buccal phase, occurs in the mouth; once the food has been chewed and well mixed with saliva, the bolus (food mass) is forced into the pharynx by the tongue.

- **Pharyngeal-esophageal phase**

The second phase, the involuntary pharyngeal-esophageal phase, transports food through the pharynx and esophagus; the parasympathetic division of the autonomic nervous system controls this phase and promotes the mobility of the digestive organs from this point on.

➢ **Food routes**

All routes that the food may take, except the desired route distal into the digestive tract, are blocked off; the tongue blocks off the mouth; the soft palate closes off the nasal passages; the larynx rises so that its opening is covered by the flaplike epiglottis.

➢ **Stomach entrance.**

Once food reaches the distal end of the esophagus, it presses against the cardioesophageal sphincter, causing it to open, and food enters the stomach.

### *1.2.2 Activities of the Stomach*

The activities of the stomach involve food breakdown and food propulsion.

➢ **Food Breakdown**

The sight, smell, and taste of food stimulate parasympathetic nervous system reflexes, which increase the secretion of gastric juice by the stomach glands

- **Gastric juice;** Secretion of gastric juice is regulated by both neural and hormonal factors.
- **Gastrin;** The presence of food and a rising pH in the stomach stimulate the stomach cells to release the hormone gastrin, which prods the stomach glands to produce still more of the protein-digesting enzymes (pepsinogen), mucus, and hydrochloric acid.
- **Pepsinogen**; The extremely acidic environment that hydrochloric acid provides is necessary, because it activates pepsinogen to pepsin, the active protein-digesting enzyme.
- **Rennin;** Rennin, the second protein-digesting enzyme produced by the stomach, works primarily on milk protein and converts it to a substance that looks like sour milk.
- **Food entry;** As food enters and fills the stomach, its wall begins to stretch (at the same time as the gastric juices are being secreted).
- **Stomach wall activation;** Then the three muscle layers of the stomach wall become active; they compress and pummel the

food, breaking it apart physically, all the while continuously mixing the food with the enzyme-containing gastric juice so that the semifluid chyme is formed.

➢ **Food Propulsion**

Peristalsis is responsible for the movement of food towards the digestive site until the intestines.

- **Peristalsis;** Once the food has been well mixed, a rippling peristalsis begins in the upper half of the stomach, and the contractions increase in force as the food approaches the pyloric valve.
- **Pyloric passage;** The pylorus of the stomach, which holds about 30 ml of chyme, acts like a meter that allows only liquids and very small particles to pass through the pyloric sphincter; and because the pyloric sphincter barely opens, each contraction of the stomach muscle squirts 3 ml or less of chyme into the small intestine.
- **Enterogastric reflex;** When the duodenum is filled with chyme and its wall is stretched, a nervous reflex, the enterogastric reflex, occurs; this reflex "puts the brakes on" gastric activity and slows the emptying of the stomach by inhibiting the vagus nerves and tightening the pyloric sphincter, thus allowing time for intestinal processing to catch up.

### *1.2.3 Activities of the Small Intestine*

The activities of the small intestine are food breakdown and absorption and food propulsion.

➢ **Food Breakdown and Absorption**

Food reaching the small intestine is only partially digested.

- **Digestion;** Food reaching the small intestine is only partially digested; carbohydrate and protein digestion has begun, but virtually no fats have been digested up to this point.
- **Brush border enzymes;** The microvilli of small intestine cells bear a few important enzymes, the so-called brush border enzymes, that break down double sugars into simple sugars and complete protein digestion.

- **Pancreatic juice;** Foods entering the small intestine are literally deluged with enzyme-rich pancreatic juice ducted in from the pancreas, as well as bile from the liver; pancreatic juice contains enzymes that, along with brush border enzymes, complete the digestion of starch, carry out about half of the protein digestion, and are totally responsible for fat digestion and digestion of nucleic acids.
- **Chyme stimulation;** When chyme enters the small intestine, it stimulates the mucosa cells to produce several hormones; two of these are secretin and cholecystokinin which influence the release of pancreatic juice and bile.
- **Absorption;** Absorption of water and of the end products of digestion occurs all along the length of the small intestine; most substances are absorbed through the intestinal cell plasma membranes by the process of active transport.
- **Diffusion;** Lipids or fats are absorbed passively by the process of diffusion.
- **Debris;** At the end of the ileum, all that remains are some water, indigestible food materials, and large amounts of bacteria; this debris enters the large intestine through the ileocecal valve.

➢ **Food Propulsion**

Peristalsis is the major means of propelling food through the digestive tract.

- **Peristalsis;** The net effect is that the food is moved through the small intestine in much the same way that toothpaste is squeezed from the tube.
- **Constrictions;** Rhythmic segmental movements produce local constrictions of the intestine that mix the chyme with the digestive juices, and help to propel food through the intestine.

### *1.2.4 Activities of the Large Intestine*

The activities of the large intestine are food breakdown and absorption and defecation.

➢ **Food Breakdown and Absorption**

What is finally delivered to the large intestine contains few nutrients, but that residue still has 12 to 24 hours more to spend there.

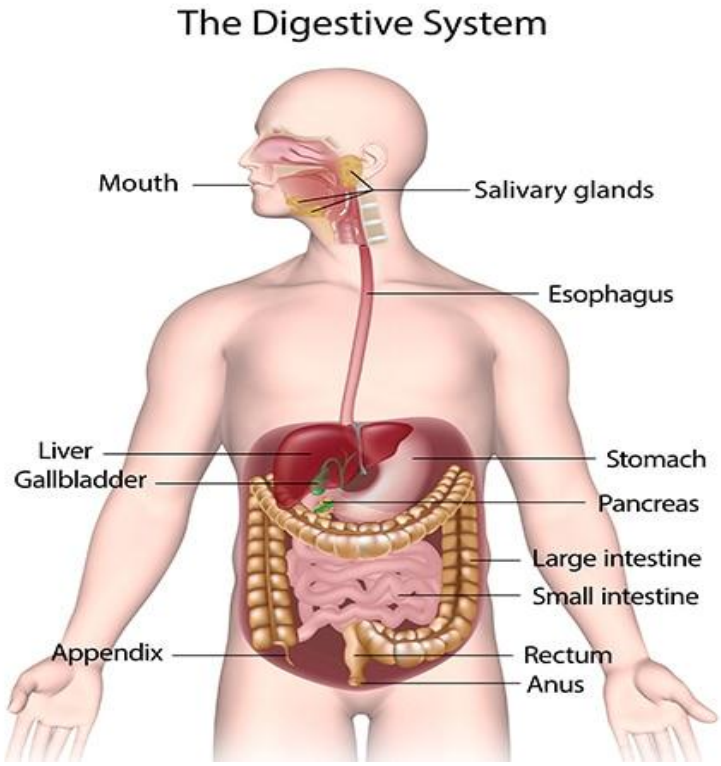
- **Metabolism;** The "resident" bacteria that live in its lumen metabolize some of the remaining nutrients, releasing gases (methane and hydrogen sulfide) that contribute to the odor of feces.
- **Flatus**; About 50 ml of gas (flatus) is produced each day, much more when certain carbohydrate-rich foods are eaten.
- **Absorption;** Absorption by the large intestine is limited to the absorption of vitamin K, some B vitamins, some ions, and most of the remaining water.
- **Feces;** Feces, the more or less solid product delivered to the rectum, contains undigested food residues, mucus, millions of bacteria, and just enough water to allow their smooth passage.

➢ **Propulsion of the Residue and Defecation**

When presented with residue, the colon becomes mobile, but its contractions are sluggish or short-lived.

- **Haustral contractions**; The movements most seen in the colon are haustral contractions, slow segmenting movements lasting about one minute that occur every 30 minutes or so.
- **Propulsion;** As the haustrum fills with food residue, the distension stimulates its muscle to contract, which propels the luminal contents into the next haustrum.
- **Mass movements;** Mass movements are long, slow-moving, but powerful contractile waves that move over large areas of the colon three or four times daily and force the contents toward the rectum.
- **Rectum;** The rectum is generally empty, but when feces are forced into it by mass movements and its wall is stretched, the defecation reflex is initiated.
- **Defecation reflex;** The defecation reflex is a spinal (sacral region) reflex that causes the walls of the sigmoid colon and the rectum to contract and anal sphincters to relax.

- **Impulses;** As the feces is forced into the anal canal, messages reach the brain giving us time to make a decision as to whether the external voluntary sphincter should remain open or be constricted to stop passage of feces.
- **Relaxation;** Within a few seconds, the reflex contractions end and rectal walls relax; with the next mass movement, the defecation reflex is initiated again.




The human digestive system

# CHAPTER TWELVE
# DRUGS USE FOR MANAGEMENT OF THE GIT

## 1. Laxative drugs

Laxatives are used to treat constipation (defined as passing hard stools less frequently than normal for the patient). The etiology of constipation is varied and can be a symptom of organic disease, or can be a side effect of certain drug treatments (e.g. opioid-induced constipation, OIC). Laxatives are of clinical value in the treatment of irritable bowel syndrome (IBS), OIC, as part of anthelmintic treatment or to clear the alimentary tract before surgery and radiological procedures. Abuse of laxatives may lead to hypokalaemia.

The mechanism of action of laxatives is varied, being physical or biochemical in nature:

Bulk-forming laxatives improve stool formation by adding bulk to the diet. This group includes wheat bran-based dietary supplements, methylcellulose, ispaghula husk and stercullia. Bulk-forming laxatives are useful in the management of IBS, chronic diarrhoea associated with diverticular disease, and in patients with colostomy, ileostomy, haemorrhoids and anal fissure. Can also be used as an adjunct in the treatment of ulcerative colitis.

Stimulant laxatives for example, bisacodyl, sodium picosulphate, anthroquinines such as senna, and parasympathomimetics such as bethanechol chloride (a muscarinic cholinergic receptor agonist), neostigmine and pyridostigmine bromide (both acetylcholinesterase inhibitors) increase intestinal motility. Over use can cause diarrohea and hypokalaemia.

Faecal softeners ease the passage of stool in the gut. Bulk-forming laxatives, non-ionic surfactant agents, glycerol and arachis oil all have softening properties.

Osmotic laxatives commonly contain polyethylene glycol (PEG) or salts as the active ingredient. These agents increase water in the large

intestine to soften the stool and promote bowel movement. High-dose saline preparations are often used as bowel clearing agents prior to colonoscopy, colonic surgery or radiological examination.
Other laxative drugs include linactolide (an oral guanylate cyclase C receptor agonist, see Busby et al. (2010)), lubiprostone (a chloride channel activator) and prucalopride (a serotonin 5HT4 receptor agonist).

**2. Antisecretory drugs**
In the gastrointestinal system, anti-secretory drugs are used to decrease acid secretion in the stomach.
**Drug families include**:

- **Histamine H2 receptor antagonists** are used to treat functional dyspepsia and to promote healing of NSAID-associated ulcers e.g. ranitidine, cimetidine and famotidine.
- **Proton pump inhibitors (PPIs)** are used to treat gastric and duodenal ulcers, dyspepsia, gastro-oesophageal reflux disease (GERD) and NSAID-associated ulcers. Combined with antibacterials, PPIs are used to eradicate Helicobacter pylori infection. Can also be used to reduce the degradation of pancreatic enzyme supplements in cystic fibrosis patients, and to control excessive gastric acid production in Zollinger–Ellison syndrome. Examples are omeprazole and its single active enantiomer esomeprazole, lansoprazole, rabeprazole and pantoprazole. Infrequently, patients taking PPIs have been reported to be suffering from drug-induced subacute cutaneous lupus erythematosus (SCLE), so prescribers should be aware of this rare side-effect and consider discontinuing PPI treatment if feasible.
- **The Prostaglandin analogue misoprostol** is approved for treatment of gastric and duodenal ulceration and NSAID-associated ulceration and prophylaxis of NSAID-induced gastric and duodenal ulcers.
- **Antimuscarinic drugs** such as the muscarinic M1 receptor antagonist pirenzepine were used to treat peptic ulcer, but are no longer widely used.

- **Mucosal protectants** such as sucralfate may be used to manage benign gastric and duodenal ulceration and chronic gastritis, and as a prophylactic for stress-induced ulcers. Sucralfate aids healing by forming a viscous, protective layer on the ulcer's surface, but does not prevent new ulcer formation.

**3. Antidiarrhoeal drugs**

Antidiarrhoeal drugs are classified according to their mechanism of action:

- **Oral rehydration agents** are used to re-balance fluid and electrolytes lost during a diarrhoeal episode. These contain defined quantities of salts and sugars to be taken with clean water.
- **Antibacterial agents** can be used to treat diarrhea with a confirmed bacterial cause.
- **Antimotility agents, or antipropulsives**, are used to slow intestinal transit. For example, the opioid analogue loperamide (sold as Imodium®) slows peristalsis and reduces overall stool mass (often combined with the anti-foaming agent simeticone in the brand Imodium Plus®). Diphenoxylate is another opioid analgesic used with atropine (Lomotil®) as an antimotility agent.

**4. Antispasmodic drugs**

Antispasmodic agents are used to reduce the pain and cramping that can accompany diarrhea. For example, mebeverine, sold as Colofac® in the UK.

- **Antacids**

  Antacids are used to relieve symptoms in dyspepsia and in gastro-oesophageal reflux disease and usually contain aluminum or magnesium compounds. They should be given when symptoms occur or are expected, usually between meals and at bedtime. They may have to be given several times each day. Although they may help with ulcer-healing, their impact is much less than for antisecretory drugs. Liquid preparations are usually more effective than tablet preparations.
- **Aluminium- and magnesium-containing antacids**

Aluminium- and magnesium-containing antacids (e.g. aluminium hydroxide, and magnesium carbonate, hydroxide and trisilicate), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable for most antacid purposes. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium accumulation does not appear to be a risk if renal function is normal.

- **Sodium bicarbonate**
  Sodium bicarbonate should no longer be prescribed alone for the relief of dyspepsia but it is present as an ingredient in many indigestion remedies. It is still used to treat urinary-tract disorders and acidosis. Sodium bicarbonate contains a significant salt load and should be avoided in patients who may retain this.
- **Bismuth**
  Bismuth containing antacids are not recommended because absorbed bismuth can be neurotoxic and lead to encephalopathy.
- **Calcium**
  Calcium containing antacids can induce rebound acid secretion: with modest doses the clinical significance is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis, and can precipitate the milk-alkali syndrome.
- **Simeticone**
  Simeticone (activated dimeticone) is added to an antacid as an antifoaming agent to relieve flatulence. These preparations may be useful for the relief of hiccup in palliative care.
  Alginates, added as protectants, may be useful in gastro-oesophageal reflux disease. The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.
- **Antispasmodic**
  Antispasmodic drugs are used to reduce the pain and cramping that can accompany conditions such as irritable bowel syndrome (IBS)

and diverticular disease. For example, mebeverine, sold as Colofac® in the UK, and scopolamine butylbromide (a.k.a. hyoscine butylbromide or butylscopolamine) sold under the trade name Buscopan.

**V.5 Probiotics**

Probiotics are defined by the World Health Organization as living microorganisms that have health benefits when ingested in adequate amounts. The most widely studied probiotics for gastrointestinal conditions are from the Lactobacillus and Bifidobacterium genus.

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