UNIT – I

Chemistry of Biomolecules

Two Marks

1. What are the electrolytes used in therapy
2. Define biomolecules
3. What are the disorders in metabolism of biomolecules
4. Write the composition of foods
5. What is bioenergetics
6. What is antioxidants
7. What are nutrition
8. What are ointment base
9. Define emulsifying agent
10. What is balanced diet

Five Marks

1. Write a note on Extracellular Electrolytes
2. Explain the metabolism in biomolecules
3. Explain about the biological oxidation
4. Explain about the ointment base

Ten Marks

1. Explain briefly about the electrolytes used in replacement therapy
2. Write in detailed about the Physiological Acid-base balance
3. Explain briefly about organic pharmacential aids

Metabolism of Biomelecules

Metabolism is the set of life-sustaining chemical reactions in organisms. The three main purposes of metabolism are: the conversion of food to energy to run cellular processes; the conversion of food/fuel to building blocks for proteins, lipids, nucleic acids, and some carbohydrates; and the elimination of metabolic wastes. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. (The word metabolism can also refer to the sum of all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the above described set of reactions within the cells is called intermediary metabolism or intermediate metabolism).

Metabolic reactions may be categorized as *catabolic* – the *breaking down* of compounds (for example, the breaking down of glucose to pyruvate by cellular respiration); or *anabolic* – the *building up* (synthesis) of compounds (such as proteins, carbohydrates, lipids, and nucleic acids). Usually, catabolism releases energy, and anabolism consumes energy.

The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, each step being facilitated by a specific enzyme. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that require energy that will not occur by themselves, by coupling them to spontaneous reactions that release energy. Enzymes act as catalysts – they allow a reaction to proceed more rapidly – and they also allow the regulation of the rate of a metabolic reaction, for example in response to changes in the cell's environment or to signals from other cells.

The metabolic system of a particular organism determines which substances it will find nutritious and which poisonous. For example, some prokaryotes use hydrogen sulfide as a nutrient, yet this gas is poisonous to animals. The basal metabolic rate of an organism is the measure of the amount of energy consumed by all of these chemical reactions.

A striking feature of metabolism is the similarity of the basic metabolic pathways among vastly different species. For example, the set of carboxylic acids that are best known as the intermediates in the citric acid cycle are present in all known organisms, being found in species as diverse as the unicellular bacterium *Escherichia coli* and huge multicellular organisms like elephants. These similarities in metabolic pathways are likely due to their early appearance in evolutionary history, and their retention because of their efficacy. The metabolism of cancer cells is also different from the metabolism of normal cells and these differences can be used to find targets for therapeutic intervention in cancer.

Metabolic disorders

Metabolic disorders are characterized by the inability to properly utilize and/or store energy, with the most prominent metabolic disorder being diabetes. Metabolic disorders have been associated with cognitive decline including decreased mental flexibility and memory deficits. Elderly patients with impaired glucose tolerance have greater impaired cognitive functions including verbal and visual-spatial memory relative to healthy groups.Current research suggests that probiotics may be able to ameliorate cognitive decline associated with metabolic disorders. In the streptozocin-induced rat model of type I diabetes, diabetic male Wistar rats exhibited spatial memory impairments relative to control rats. However, *L. acidophilus* ATCC 4356, *B. lactis* DSM 10,140, and *L. fermentum* ATCC 9338 restored cognitive function in diabetic rats (Davari et al., 2013). Moreover, diabetic rats showed impaired long-term potentiation (LTP) and excitatory postsynaptic potentials (EPSPs) in the CA1 region at baseline (Davari et al., 2013). LTP and the measured EPSPs in the CA1 region are implicated in learning and memory. However, LTP and EPSPs were restored in diabetic animals administered probiotics. In rats with hyperammonemia (HA), 5-HT metabolism was found to be increased in the cerebellum, hippocampus, and prefrontal cortex; however, rats that were given *L. helveticus* NS8 showed a reduced metabolism of 5-HT. High levels of 5-HT are associated with increased anxiety-like behavior in rat models. Mice with HA were observed to display cognitive defects and anxiety-like behavior; administration of *L. helveticus* NS8 effectively prevented these behavioral deficits.In addition, levels of 5-HT

and 5-hydroxyindoleacetic acid were also found to be reduced in HA rats administered probiotics. The results of both of these recent studies demonstrate that probiotic administration causes changes in brain activity and cognition in rodents with metabolic syndromes.

MAJOR INTRA AND EXTRA CELLULAR ELECTROLYTES

Electrolytes are substances that dissociate in solution and have the ability to conduct an electrical current. These substances are located in the extracellular and intracellular fluid. Within the extracellular fluid, the major cation is sodium and the major anion is chloride. The major cation in the intracellular fluid is potassium. These electrolytes play an important role in maintaining homeostasis. In this article, the etiology, signs, symptoms, and treatments for imbalances of these three electrolytes.

An electrolyte is any substance that dissociates into ions in aqueous solution. Ions can be positively charged (cations) or negatively charged (anions). Sodium (Na^+), Chloride (Cl^-) Potassium (K^+), Phosphate ($HPO4^{--}$) Calcium (Ca^{++}) Sulfate ($SO4^{--}$) Magnesium (Mg^{++}) Bicarbonate ($HCO3^-$) The major electrolytes found in the human body are: Interstitial fluid and blood plasma are similar in their electrolyte make up. Na^+ and Cl^- being the major electrolytes. In the intracellular fluid, K^+ and $HPO4^-$ are the major electrolytes. Physiological role of Sodium.This plays a crucial role in the excitability of muscles and neurones. It is also of crucial importance in regulating fluid balance in the body. Sodium levels are extremely closely regulated by kidney function. Sodium is easily filtered in the glomerular portion of the kidneys and most of it is reabsorbed in the kidney tubules. Major factors that control the GFR include the blood pressure at the glomerulus and the stimulation of renal arteriole by the sympathetic nervous system. The amount of sodium reabsorbed in the proximal convoluted tubule remains almost constantly at around 67%. It is also a stimulator for aldosterone release from the adrenal glands. Because water has a close chemical affinity for sodium, it will follow that more water is reabsorbed in the kidney as well and this will put up the BP to a normal level. An increase in the arterial BP will result in the release of atrial natriuretic factor (ANF) from the left and right atria of the heart. This hormone actually inhibits renin and aldosterone release. By so doing the loss of sodium by the kidneys is enhanced by the decrease of aldosterone stimulated reabsorption. As we have already seen that water will follow sodium, it follows that water is lost from the body allowing the BP to drop to a normal level. Physiological role of Potassium Potassium is the major cation of intracellular fluid. Concentration within the cells is 28x that of the extra cellular fluids. As with sodium it is extremely important in the correct functioning of excitable cells such as muscles, neurones, sensory receptors

etc. It is also importantly involved in the regulation of fluid levels within the cell and in maintaining the correct pH balance within the body. Potassium output is usually equal to potassium input. Sodium reabsorption by aldosterone is usually in exchange for either hydrogen ions or potassium ions. Therefore if sodium ions are reabsorbed more potassium is lost and vice versa. Thus, high levels of potassium in the interstitial fluid stimulate aldosterone response. Diseases such as Cushing's disease (over production of ACTH) and hyperaldosteronism (overproduction of aldosterone) can lead to a condition known as hypokalaemia (symptoms caused by low potassium levels) which manifests in muscle weakness, flaccid paralysis, cardiac arrhythmia and alkalosis. The pH balance of the body also affects potassium levels. In acidosis potassium excretion is decreased (leads to hyperkalaemia higher than normal levels of potassium) whereas the opposite occurs in alkalosis. Physiological role of Calcium is found mainly in the extracellular fluids whilst phosphorous is found mostly in the intracellular fluids. Both are important in the maintenance of healthy bone and teeth.Calcium is also important in the transmission of nerve impulses across synapses, the clotting of blood and the contraction of muscles. If the levels of calcium fall below normal level both muscles and nerves become more excitable. Physiological role of Phosphate Phosphate is required in the synthesis of nucleic acids and high-energy compounds such as ATP. It is also important in the maintenance of pH balance. Physiological role of Magnesium Most magnesium is found in the intracellular fluid and in bone. Within cells, magnesium functions in the sodium-potassium pump and as an aid to the action of enzymes. It plays a role in muscle contraction, action potential conduction, and bone and teeth production. Aldosterone controls magnesium concentrations in the extracellular fluid. Low Mg^{++} levels result in an increased aldosterone secretion, and the aldosterone increases Mg^{++} reabsorption by the kidneys. Chloride (Cl^{-}) is the most plentiful extracellular anion with an extracellular concentration 26 times that of its intracellular concentration.Chloride ions are able to diffuse easily across plasma membranes and their transport is closely linked to sodium movement, which also explains the indirect role of aldosterone in chlorine regulation.When sodium is reabsorbed, chlorine follows passively. It helps to regulate osmotic pressure differences between fluid compartments and is essential in pH balance.The chloride shift within the blood helps to move bicarbonate ions out of the red blood cells and into the plasma for transport. In the gastric mucosa, chlorine and hydrogen combine to form hydrochloric acid. Physiological role of Chloride Physiological role of Bicarbonate Bicarbonate is alkaline, and a vital component of the pH buffering system of the human body (maintaining acid-base homeostasis).70 to 75 percent of CO2 in the body is converted into carbonic acid (H2CO3), which can quickly turn into bicarbonate (HCO3−). With carbonic acid as the central intermediate species,

bicarbonate – in conjunction with water, hydrogen ions, and carbon dioxide – forms this buffering system, which is maintained at the volatile equilibrium required to provide prompt resistance to drastic pH changes in both the acidic and basic directions. This is especially important for protecting tissues of the central nervous system, where pH changes too far outside of the normal range in either direction could prove disastrous. Bicarbonate also acts to regulate pH in the small intestine. It is released from the pancreas in response to the hormone secretin to neutralize the acidic chyme entering the duodenum from the stomach.

Replacement therapy

Replacement Therapy The basic objective of replacement therapy is to restore the volume and composition of the body fluids to normal one. Volume contraction is a life threatening condition because it impairs the circulation. Blood volume decreases, cardiac output falls and the integrity of microcirculation is compromised. In volume depletion of sufficient magnitude to threaten life, a prompt infusion of isotonic sodium chloride solution is indicated. In an extreme case, intravenous therapy at the rate of 100 ml per minute for the first 1000ml has been considered necessary for the successful treatment of cholera. A general rule is to replace one half of the estimated volume loss in the first 12-24 hours of treatment. Sodium Replacement Sodium Chloride: NaCl (MW 58.44) I.P. Limit. Sodium chloride contains not less than 99.5 % and not more than 100.5 % calculated with reference to dried substance. It contains no added substances.It occurs as colorless cubic crystals or as white crystalline powder having saline taste. It is freely soluble in water, and slightly more soluble in boiling water, soluble in glycerin and slightly soluble in alcohol. Test for identification: For Sodium: To sample solution add 15 % w/v potassium carbonate heat, no precipitate. Add potassium antimonite solution, heat to boiling, cool and if necessary scratch the inside of test tube with a glass rod, a dense white precipitate is produced. For Chloride: Dissolve sample in water, acidify with dilute nitric acid and add silver nitrate solution shake, and allow to stand, a curdy white precipitate is formed which is insoluble in nitric acid but, soluble after being well washed with water, in dilute ammonium hydroxide solution from which it is reprecipitated by the addition of dilute nitric acid. Preparation: On commercial scale it is prepared by evaporation of sea water in shallow pans. It contains impurities of sodium carbonate, sodium sulphate, magnesium chloride, magnesium sulphate, calcium chloride etc. these impurities are removed by dissolving the salt in water in a cemented tank; some alum and lime are added. The suspended impurities are allowed to settle down. The clear solution is decanted into iron pans and concentrated. The crystals of sodium chloride settle down which are then collected and dried. Assay: The assay of sodium chloride is dependent on

the modified Volhard's method in which indirect volumetric precipitation titration is involved. An acidified solution of sodium chloride with nitric acid is treated with a measured excess amount of standard solution of silver nitrate in the presence of nitrobenzene. Some of the silver nitrate is consumed in the reaction with sodium chloride. The remaining unreacted AgNO3 is determined by titration with standard solution of ammonium thiocyanate using ferric alum (ferric ammonium sulphate) as indicator. The end point is obtained as a permanent brick red color due to formation of ferric thiocyanate. Procedure: Accurately weigh the substance (0.1 gm) and dissolve in 50 ml water. Add 50 ml of 0.1N AgNO3, 3 ml HNO3, 5 ml nitro benzene, 2 ml ferric ammonium sulphate and mix thoroughly. The solution is titrated with ammonium thiocyanate until the color becomes brick red. 1ml of 0.1N AgNO3 ≡ 0.005844 gm NaCl Use: Used as fluid and electrolyte replenisher, manufacture of isotonic solution, flavor enhancer. ¾ Isotonic solutions are used in wet dressings, for irrigating body cavities or tissues ¾ Hypotonic solutions are administered for maintenance therapy when patients are unable to take fluids and nutrients orally for one to three days. ¾ Hypertonic solution/injection are used when there is loss of sodium in excess. ¾ Official preparations of Sodium chloride Sodium Chloride Injection I.P. Sodium chloride injection is a sterile isotonic solution of sodium chloride in water for injection. It contains not less than 0.85 % and not more than 0.95 % w/v of sodium chloride. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 4.5-7.0. Sodium Chloride Hypertonic Injection I.P. (Hypertonic saline) It is a sterile solution of sodium chloride in water for injection. It contains not less than 1.52 % and not more than 1.68 % w/v of sodium chloride. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 5-7.5. It complies with the test for pyrogens. Compound Sodium Chloride Injection I.P. (Ringer injection) It contains not less than 0.82 % and not more than 0.9 % w/v of sodium chloride, not less than 0.0285 %, not more than 0.0315 % w/v of potassium chloride and not less than 0.03 % and not more than 0.036% w/v of calcium chloride in water for injection. It contains no antimicrobial agents. It is a clear, colorless solution with pH between 5-7.5. Sodium Chloride and Dextrose Injection It is a sterile solution of sodium chloride and dextrose in water for injection. It contains not less than 95% and not more than 105 % w/v of the stated amount of sodium chloride and dextrose as given below: Combinations of Sodium Chloride and Dextrose %of Sodium Chloride %of Dextrose %of Sodium Chloride %of Dextrose 0.11 5 0.45 5 0.18 5 0.45 10 0.20 5 0.90 2.5 0.225 5 0.90 5 0.3 5 0.90 10 0.33 5 0.90 25 0.45 2.5 It is clear colorless or faintly straw colored solution with pH between 3.5-6.5. Potassium Replacement Potassium Chloride: KCl (MW 74.56) I.P. Limit. Potassium chloride contains not less than 99 % calculated with reference to dried substance. It occurs as sylvine (KCl) and Carnallite

(KCl, MgCl2)6H2O contaminated with magnesium sulphate and chlorides. It occurs as white crystalline solid, cubic crystals. It is less soluble in water than sodium chloride, and slightly more soluble in boiling water, soluble in glycerin and insoluble in alcohol. Test for Identification: For potassium: To 1ml of solution add 1ml dilute acetic acid and 1ml of 10 % w/v sodium cobalt nitrite, a yellow color is produced. For Chloride: Substance in water is added with dilute solution of silver nitrate, shake the solution and allow to stand , on standing white precipitate is obtained which is insoluble in nitric acid but soluble after being washed with water; in dilute ammonium hydroxide, from which it is reprecipitated by the addition of dilute nitric acid. Preparation: 1. It is prepared by fusing carnallite whereby liquefied magnesium chloride hexahydrate is separated from the solid potassium chloride. 2. The crushed carnallite is dissolved by boiling with liquor leaving other impurities undissolved. These are filtered off and the filtrate is crystallizes to get cubic crystals of potassium chloride. 3. It is also prepared in laboratory by reacting HCl with potassium carbonate or bicarbonate K2CO3 + 2HCl KCl + H2O +CO2 KHCO3 + HCl KCl + H2O +CO2 Assay: The assay is based on Mohr's method of direct volumetric precipitation titration. An aqueous solution of the substance is titrated against a standard solution of silver nitrate using solution of potassium chromate as indicator. KCl + AgNO3 AgCl + KNO3 When whole of potassium chloride has been precipitated as AgCl, further addition of silver nitrate solution gives brick red color with the indicator. The end point is change of color from yellow to red. Procedure: Accurately weigh the specified (0.25g) amount of potassium chloride and dissolve in 50 ml of water. Titrate the solution with 0.1N silver nitrate solution using potassium chromate solution as indicator. 2AgNO3 + K2CrO4 Ag2CrO4 + 2KNO3 1ml of 0.1N silver nitrate ≡ 0.007455g of KCl Use: Electrolyte replenisher in potassium deficiency, familial periodic paralysis, Meniere's syndrome (disease of inner ear), antidote in digitalis intoxication, myasthenia gravis. Contraindication: renal impairment with oligouria, acute dehydration. Potassium Chloride injection: Ringer injection Calcium Replacement Calcium Lactate: C6H10CaO6 xH2O MW 308.30 (Pentahydrate) I.P. Limit. Potassium chloride contains not less than 97% and not less than 103% of Calcium Chloride dihydrate. It occurs as white odorless powder. The pentahydrate effloresces and becomes anhydrous at 120°. Aqueous solutions are prone to become moldy. It is soluble in water, practically insoluble in alcohol. Test for Identification: For Calcium: Dissolve substance in 5 M acetic acid and add 0.5 ml of potassium ferrocyanide solution. The solution remains clear. Add ammonium chloride white crystalline precipitate is formed. For Lactate: To sample solution add bromine water, 1 M H2SO4 and heat on water bath stirring occasionally until the color is discharged. Add ammonium sulphate mixture of 10% solution of sodium nitroprusside in

ammonia solution. Allow to stand for 10 mins, a dark ring appears at the interface of two liquids. Preparation:

1. It is obtained by neutralizing a hot solution of lactic acid with calcium carbonate in slight excess. The hot liquid is filtered and filtrate is evaporated to crystalline product.

2. It is also obtained by fermenting hydrolyzed starch with a suitable mold in the presence of calcium carbonate

3. Or by fermentation of mother liquor resulting from the production of milk sugar and chalk. The mixture is digested for a week at about 30°. The product is purified by crystallization. Assay: The assay is based on complexometric method of titration wherein disodium EDTA as titrant and calcon mixture as indication. The end point is change of color from pink to blue. Procedure: Accurately weigh specified amount of sample and dissolve in water (50 ml), titrate the solution with 0.05 M disodium EDTA to within few ml of the expected end point. Add sodium hydroxide solution and calcon mixture and continue titration till end point is observed. The color of solution changes from pink to blue. 1ml of 0.05 M disodium EDTA ≡ 0.005004 gm of calcium Use: An excellent source of calcium in oral treatment of calcium deficiency.

Physiological Acid Base Balance

Abnormalities of the pH of body are frequently encounter and are of major clinical importance. Acedemia and alkalemia refer respectively to an abnormal decrease or increase in the pH of the blood. Acidosis and alkalosis refer respectively to clinical state that can lead to either acedemia or alkalemia. However in each condition the extent to which there is an actual change in pH depends in part on the degree of compensation which varies in most clinical disturbances. It is most convenient to evaluate clinical disturbances of pH by reference to HCO3 – – H2CO3 System Because it is in buffer system of extracellular fluid, this results from a number of factors: 1. There is considerably more bicarbonate present in extracellular fluid than any other buffer component. 2. There is a limitless supply of carbon dioxide 3. Physiological mechanisms operate to maintain the extracellular pH function by controlling fluid 4. The bicarbonate – carbonic acid buffer system operates in conjunction with haemoglobin. Acids are constantly being produced during metabolism. Most metabolic reactions occur only within narrow pH range of 7.38-7.42. Therefore the body utilizes several buffer systems, two of them are bicarbonate and carbonic acid (HCO3 – : H2CO3) present in plasma and kidney and monohydrogen phosphate/dihydrogen phosphate (HPO4 2- : H2PO4 -) found in cells and kidney. RBC’s have hemoglobin buffer system which is most effective single

buffer system for buffering the carbonic acid produced during metabolic process. For each millimole of oxygen that dissociates from hemoglobin (Hb) 0.7 millimole of H+ are removed. Carbon dioxide, the acid anhydride of carbonic acid is continuously produced in the cells. It diffuses into the plasma and reacts with water to form carbonic acid. The increased carbonic acid is buffered by plasma proteins. Most CO2 enters the erythrocytes where it either rapidly forms H2CO3by the action of carbonic anhydrase or combines with Hb. The tendency to lower the pH of the erythrocytes due to increased concentration of H2CO3 is compensated by Hb. Carbonic anhydrase CO2 + H2O H2CO3 The bicarbonate anion then diffuses out of erythrocytes and chloride anion diffuses in. This has been named as chloride shift. Te bicarbonate in plasma, along with the plasma carbonic acid now acts as efficient buffer system H2CO3 + K+ +HbO2 - K+ + HCO3 - + HHb + O2 The normal HCO3 - / H2CO3 ratio is 27/1.35 meq/lt (20:1) corresponding to pH 7.4. In lungs there is reversal of the above process due to the large amount of O2 present. Oxygen combines with the protonated deoxyhemoglobin releasing proton. These combine with HCO3 - forming H2CO3 which then dissociates to CO2 and water. The carbon dioxide is exhaled by the lungs. Thus by regulating breathing it is possible for the body to exert a partial control on the HCO3 - /H2CO3 ratio.

The phosphate buffer system is also effective in maintaining physiological pH. At pH 7.4 the HPO4-2/H2PO4 - ratio is approximately 4:1. In kidney, the pH of urine can drop to 4.5-4.8 corresponding to HPO4-2/H2PO4 - ratio of 1:99- 1:100. The acid is excreted from kidney as follows: 1. sodium salt of mineral or organic acids are removed from the plasma by glomerular filtration 2. Sodium is preferentially removed from the renal filtrate or tubular fluid in the tubular cells. The process known as sodium hydrogen exchange. 3. The sodium bicarbonate returns to plasma (eventually being removed in the lungs as CO2) and protons enter tubular fluid, forming acids of the anions that originally were sodium salts.

Water Metabolism

Metabolic water refers to water created inside a living organism through their metabolism, by oxidizing energy-containing substances in their food. Animal metabolism produces about 110 grams of water per 100 grams of fat,[1] 42 grams of water per 100 g of protein and 60 grams of water per 100 g of carbohydrate.[1][2][3]

Some organisms, especially xerocoles, animals living in the desert, rely exclusively on metabolic water. Migratory birds must rely exclusively on metabolic water production while making non-stop flights.[4][5] Humans, by contrast, obtain only about 8-10% of their water needs through metabolic water production.[6]

In mammals, the water produced from metabolism of protein roughly equals the amount needed to excrete the urea which is a byproduct of the metabolism of protein.[6] Birds, however, excrete uric acid and can have a net gain of water from the metabolism of protein.

Sodium

Sodium is a chemical element with the symbol **Na** and atomic number 11. It is a soft, silvery-white, highly reactive metal. Sodium is an alkali metal, being in group 1 of the periodic table. Its only stable isotope is ^{23}Na. The free metal does not occur in nature, and must be prepared from compounds. Sodium is the sixth most abundant element in the Earth's crust and exists in numerous minerals such as feldspars, sodalite, and rock salt (NaCl). Many salts of sodium are highly water-soluble: sodium ions have been leached by the action of water from the Earth's minerals over eons, and thus sodium and chlorine are the most common dissolved elements by weight in the oceans.

Sodium was first isolated by Humphry Davy in 1807 by the electrolysis of sodium hydroxide. Among many other useful sodium compounds, sodium hydroxide (lye) is used in soap manufacture, and sodium chloride (edible salt) is a de-icing agent and a nutrient for animals including humans.

Sodium is an essential element for all animals and some plants. Sodium ions are the major cation in the extracellular fluid (ECF) and as such are the major contributor to the ECF osmotic pressure and ECF compartment volume.[*citation needed*] Loss of water from the ECF compartment increases the sodium concentration, a condition called hypernatremia. Isotonic loss of water and sodium from the ECF compartment decreases the size of that compartment in a condition called ECF hypovolemia.

By means of the sodium-potassium pump, living human cells pump three sodium ions out of the cell in exchange for two potassium ions pumped in; comparing ion concentrations across the cell membrane, inside to outside, potassium measures about 40:1, and sodium, about 1:10. In nerve cells, the electrical charge across the cell membrane enables transmission of the nerve impulse—an action potential—when the charge is dissipated; sodium plays a key role in that activity.

Potassium

Potassium is the main intracellular ion for all types of cells, while having a major role in maintenance of fluid and electrolyte balance.[1][2] Potassium is necessary for the function of all living cells, and is thus present in all plant and animal tissues. It is found in especially high concentrations within plant cells, and in a mixed diet, it is most highly concentrated in fruits. The high concentration of potassium in plants, associated with comparatively very low amounts of sodium there, historically resulted in potassium first being isolated from the ashes of plants (potash), which in turn gave the element its modern name. The high concentration of potassium in plants means that heavy crop production rapidly depletes soils of potassium, and agricultural fertilizers consume 93% of the potassium chemical production of the modern world economy.

The functions of potassium and sodium in living organisms are quite different. Animals, in particular, employ sodium and potassium differentially to generate electrical potentials in animal cells, especially in nervous tissue. Potassium depletion in animals, including humans, results in various neurological dysfunctions. Characteristic concentrations of potassium in model organisms are: 30-300mM in *E. coli*, 300mM in budding yeast, 100mM in mammalian cell and 4mM in blood plasma.

Composition of foods

Food composition data (**FCD**) are detailed sets of information on the nutritionally important components of foods and provide values for energy and nutrients including protein, carbohydrates, fat, vitamins and minerals and for other important food components such as fibre. The data are presented in food composition databases (FCDBs).

In the UK, FCD is listed in tables known as The Chemical Composition of Foods, McCance and Widdowson (1940)[1] and in the first edition the authors stated that:

'A knowledge of the chemical composition of foods is the first essential in the dietary treatment of disease or in any quantitative study of human nutrition'.

This demonstrates the main reason for establishing FCD at that time. To this day, food composition studies remain central to nutrition research into the role of food components and their interactions in health and disease. However, due to increasing levels of sophistication and complexity in nutrition science, there is a greater demand for complete, current and reliable FCD, together with information on a wider range of food components, including bioactive compounds.[2]

FCD are important in many fields including clinical practice, research, nutrition policy, public health and education, and the food manufacturing industry and is used in a variety of ways including: national programmes for the assessment of diet and nutritional status at a population level (e.g. epidemiological researchers assessing diets at a population level); development of therapeutic diets (e.g. to treat obesity, diabetes, nutritional deficiencies, food allergy and intolerance) and institutional diets (e.g. schools, hospitals, prisons, day-care centres) and nutrition labelling of processed foods.[2]

The earliest food composition tables were based solely on chemical analyses of food samples, which were mostly undertaken specifically for the tables. However, as the food supply has evolved, and with the increasing demand for nutritional and related components, it has become more difficult for compilers to rely only on chemical analysis when compiling FCDBs. For example, in the UK the third edition of The Composition of Foods[3] presented data on vitamin content of foods. However, due to the amount of information already available and in order to avoid the need to analyse every food for every vitamin, values from the scientific literature were included, although the tables are still predominately based on analytical data.

Balanced diet

A balanced diet is a diet that contains differing kinds of foods in certain quantities and proportions so that the requirement for calories, proteins, minerals, vitamins and alternative nutrients is adequate and a small provision is reserved for additional nutrients to endure the short length of leanness. In addition, a balanced diet ought to offer bioactive phytochemicals like dietary fiber, antioxidants and nutraceuticals that have positive health advantages. A balanced diet should offer around 60-70% of total calories from carbohydrates, 10-12% from proteins and 20-25% of total calories from fat.

HEALTH BENEFITS OF A BALANCED DIET

- Healthy eating increases energy, improves the way your body functions, strengthens your immune system and prevents weight gain. The other major benefits are:
- Meets your nutritional need. A varied, balanced diet provides the nutrients you need to avoid nutritional deficiencies.
- Prevent and treat certain diseases. Healthful eating can prevent the risk of developing certain diseases such as diabetes, cancer and heart disease. It is also helpful in treating diabetes and high blood pressure.
- Following a special diet can reduce symptoms, and may help you better manage an illness or condition.
- Feel energetic and manage your weight. A healthy diet will assist you to feel higher, provide you with more energy, and help you fight stress.
- Food is the mainstay of many social and cultural events. Apart from nutrition properties, it helps facilitate connections between individuals.

Biological Oxidation

A **biological oxidizer** is a device that uses micro-organisms to treat wastewater and the volatile organic compounds produced by commercial and industrial operations. Biological oxidation devices convert biodegradable organic compounds into carbon dioxide and water. This is a natural occurring process which differs from traditional chemical and thermal oxidizing agents and methods. Some of the more commonly used micro-organisms are heterotrophic bacteria, which play an important role in biological degradation processes. Generally, these micro-organisms are rod shaped and facultative. Biological oxidizers provide a stable environment which allows bacteria to naturally oxidize and stabilize a large number of organics in a more efficient manner. Some of the emissions that may be treated biologically include:

- heterocyclic compounds (such as quinoline or pyridine);
- polyaromatic hydrocarbons (PAHs);
- pharmaceutical substances;
- polychlorinated biphenyls;
- hydrocarbons (oil);
- benzene, toluene, ethylbenzene, and xylene (BETEX);
- methyl ethyl ketone (MEK);

- some metals.

The prompt removal of a wide range of wastes and pollutants from the environment is the foremost requisite leading to minimal negative environmental impact and sustainability. Microorganisms offer excellent anabolic and catabolic adaptability to degrade and produce stabilized organic matters from contaminants. Microbiology is providing significant views of regulatory metabolic pathways as well as effectiveness to adaption and biological degradation in our changing environment.

Bioenergetics

Bioenergetics is the part of biochemistry concerned with the energy involved in making and breaking of chemical bonds in the molecules found in biological organisms.[5] It can also be defined as the study of energy relationships and energy transformations and transductions in living organisms.[6] The ability to harness energy from a variety of metabolic pathways is a property of all living organisms that contains earth science. Growth, development, anabolism and catabolism are some of the central processes in the study of biological organisms, because the role of energy is fundamental to such biological processes.[7] Life is dependent on energy transformations; living organisms survive because of exchange of energy between living tissues/ cells and the outside environment. Some organisms, such as autotrophs, can acquire energy from sunlight (through photosynthesis) without needing to consume nutrients and break them down.[8] Other organisms, like heterotrophs, must intake nutrients from food to be able to sustain energy by breaking down chemical bonds in nutrients during metabolic processes such as glycolysis and the citric acid cycle. Importantly, as a direct consequence of the first law of thermodynamics, autotrophs and heterotrophs participate in a universal metabolic network—by eating autotrophs (plants), heterotrophs harness energy that was initially transformed by the plants during photosynthesis.[9]

In a living organism, chemical bonds are broken and made as part of the exchange and transformation of energy. Energy is available for work (such as mechanical work) or for other processes (such as chemical synthesis and anabolic processes in growth), when weak bonds are broken and stronger bonds are made. The production of stronger bonds allows release of usable energy.

Adenosine triphosphate (ATP) is the main "energy currency" for organisms; the goal of metabolic and catabolic processes are to synthesize ATP from available starting materials (from the environment), and to break- down ATP (into adenosine diphosphate (ADP) and inorganic phosphate) by utilizing it in biological processes.[4] In a cell, the ratio of ATP to ADP concentrations is known as the "energy charge" of the cell. A cell can use this energy charge to relay information about cellular needs; if there is more ATP than ADP available, the cell can use ATP to do work, but if there is more ADP than ATP available, the cell must synthesize ATP via oxidative phosphorylation.[5]

Living organisms produce ATP from energy sources, mostly sunlight or O_2,[10] mainly via oxidative phosphorylation. The terminal phosphate bonds of ATP are relatively weak

compared with the stronger bonds formed when ATP is hydrolyzed (broken down by water) to adenosine diphosphate and inorganic phosphate. Here it is the thermodynamically favorable free energy of hydrolysis that results in energy release; the phosphoanhydride bond between the terminal phosphate group and the rest of the ATP molecule does not itself contain this energy.[11] An organism's stockpile of ATP is used as a battery to store energy in cells.[12] Utilization of chemical energy from such molecular bond rearrangement powers biological processes in every biological organism.

Living organisms obtain energy from organic and inorganic materials; i.e. ATP can be synthesized from a variety of biochemical precursors. For example, lithotrophs can oxidize minerals such as nitrites or forms of sulfur, such as elemental sulfur, sulfites, and hydrogen sulfide to produce ATP. In photosynthesis, autotrophs produce ATP using light energy, whereas heterotrophs must consume organic compounds, mostly including carbohydrates, fats, and proteins. The amount of energy actually obtained by the organism is lower than the amount released in combustion of the food; there are losses in digestion, metabolism, and thermogenesis.[13]

Environmental materials that an organism intakes are generally combined with oxygen to release energy, although some can also be oxidized anaerobically by various organisms. The bonds holding the molecules of nutrients together and in particular the bonds holding molecules of free oxygen together are relatively weak compared with the chemical bonds holding carbon dioxide and water together.[14] The utilization of these materials is a form of slow combustion because the nutrients are reacted with oxygen (the materials are oxidized slowly enough that the organisms do not actually produce fire). The oxidation releases energy because stronger bonds (bonds within water and carbon dioxide) have been formed. This net energy may evolve as heat, which may be used by the organism for other purposes, such as breaking other bonds to do chemistry required for survival.

Organic Pharmacential aids

A **preservative** is a substance or a chemical that is added to products such as food products, beverages, pharmaceutical drugs, paints, biological samples, cosmetics, wood, and many other products to prevent decomposition by microbial growth or by undesirable chemical changes. In general, preservation is implemented in two modes, chemical and physical. Chemical preservation entails adding chemical compounds to the product. Physical preservation entails processes such as refrigeration or drying.[1] Preservative food additives reduce the risk of foodborne infections, decrease microbial spoilage, and preserve fresh attributes and nutritional quality. Some physical techniques for food preservation include dehydration, UV-C radiation, freeze-drying, and refrigeration. Chemical preservation and physical preservation techniques are sometimes combined.

Antimicrobial preservatives prevent degradation by bacteria. This method is the most traditional and ancient type of preserving—ancient methods such as pickling and adding honey prevent microorganism growth by modifying the pH level. The most commonly used antimicrobial preservative is lactic acid. Common antimicrobial preservatives are

presented in the table.[2][3][4] Nitrates and nitrites are also antimicrobial.[5][6] The detailed mechanism of these chemical compounds range from inhibiting growth of the bacteria to the inhibition of specific enzymes. Water-based home and personal care products use broad-spectrum preservatives, such as isothiazolinones and formaldehyde releasers, which may cause sensitization, allergic skin reactions, and toxicity to aquatic life.

Antioxidants

The oxidation process spoils most food, especially those with a high fat content. Fats quickly turn rancid when exposed to oxygen. Antioxidants prevent or inhibit the oxidation process. The most common antioxidant additives are ascorbic acid (vitamin C) and ascorbates.[9] Thus, antioxidants are commonly added to oils, cheese, and chips.[2] Other antioxidants include the phenol derivatives BHA, BHT, TBHQ and propyl gallate. These agents suppress the formation of hydroperoxides.[3] Other preservatives include ethanol and methylchloroisothiazolinone.

A variety of agents are added to sequester (deactivate) metal ions that otherwise catalyze the oxidation of fats. Common sequestering agents are disodium EDTA, citric acid (and citrates), tartaric acid, and lecithin.

Colouring Agent

Food colourants have been much important in food product manufacturing. Food and color additives are strictly studied, regulated and monitored. Federal regulations require evidence that each substance is safe at its intended level of use before it may be added to foods. Furthermore, all additives are subject to ongoing safety review as scientific understanding and methods of testing continue to improve. A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. FDA is responsible for regulating all color additives to ensure that foods containing color additives are safe to eat, contain only approved ingredients and are accurately labeled. Certified colors are synthetically produced (or human made) and used widely because they impart an intense, uniform color, are less expensive, and blend more easily to create a variety of hues. Color is added to food for one or more of the following reasons:
(1) to replace color lost during processing,
(2) to enhance color already present,
(3) to minimize batch-tobatch variations, and
(4) to color otherwise uncolored food.

Flavouring Agent

Flavour or **taste** is the perceptual impression of food or other substances, and is determined primarily by the chemical senses of the gustatory and olfactory system. The "trigeminal senses", which detect chemical irritants in the mouth and throat, as well as temperature and texture, are also important to the overall gestalt of flavor perception. The

flavor of the food, as such, can be altered with natural or artificial flavorants which affect these senses.

Flavourings are products not intended to be consumed as such, which are added to food in order to impart or modify odour and/or taste.

A "flavorant" is defined as a substance that gives another substance flavor, altering the characteristics of the solute, causing it to become sweet, sour, tangy, etc. A flavor is a quality of something that affects the sense of taste.

Of the three chemical senses, smell is the main determinant of a food item's flavor. Five basic tastes – sweet, sour, bitter, salty and umami (savory) are universally recognized,although some cultures also include pungency and oleogustus ("fattiness").The number of food smells is unbounded; a food's flavor, therefore, can be easily altered by changing its smell while keeping its taste similar. This is exemplified in artificially flavored jellies, soft drinks and candies, which, while made of bases with a similar taste, have dramatically different flavors due to the use of different scents or fragrances. The flavorings of commercially produced food products are typically created by flavorists.

Although the terms flavoring and flavorant in common language denote the combined chemical sensations of taste and smell, the same terms are used in the fragrance and flavors industry to refer to edible chemicals and extracts that alter the flavor of food and food products through the sense of smell. Due to the high cost or unavailability of natural flavor extracts, most commercial flavorants are "nature-identical", which means that they are the chemical equivalent of natural flavors, but chemically synthesized rather than being extracted from source materials. Identification of components of natural foods, for example a raspberry, may be done using technology such as headspace techniques, so the flavorist can imitate the flavor by using a few of the same chemicals present. In the EU law, the term natural-identical flavouring does not exist.

Sweetening Agents.

A **sugar substitute** is a food additive that provides a sweet taste like that of sugar while containing significantly less food energy than sugar-based sweeteners, making it a **zero-calorie** (non-nutritive)[1] or **low-calorie sweetener**. **Artificial sweeteners** may be derived through manufacturing of plant extracts or processed by chemical synthesis. Sugar alcohols such as erythritol, xylitol, and sorbitol are derived from sugars. In 2017, sucralose was the most common sugar substitute used in the manufacture of foods and beverages; it had 30% of the global market, which was projected to be valued at $2.8 billion by 2021.[2]

In 1969, cyclamate was banned for sale in the US by the Food and Drug Administration. As of 2018, there is no strong evidence that non-sugar sweeteners are either unsafe or result in improved health outcomes.[3]

When these sweeteners are provided for restaurant customers to add to beverages such as tea and coffee, they are provided in small colored paper packets (see image); in North

America, the colors are typically *blue* for aspartame, *pink* for saccharin (US)[note 1] or cyclamate (Canada), *yellow* for sucralose, *orange* for monk fruit extract, and *green* for stevia.[4] These sweeteners are also a fundamental ingredient in diet drinks to sweeten them without adding calories.

Emulsifying Agents

An **emulsifier** (also known as an "emulgent") is a substance that stabilizes an emulsion by increasing its kinetic stability. One class of emulsifiers is known as "surface active agents", or surfactants. Emulsifiers are compounds that typically have a polar or hydrophilic (i.e. water-soluble) part and a non-polar (i.e. hydrophobic or lipophilic) part. Because of this, emulsifiers tend to have more or less solubility either in water or in oil.[*citation needed*] Emulsifiers that are more soluble in water (and conversely, less soluble in oil) will generally form oil-in-water emulsions, while emulsifiers that are more soluble in oil will form water-in-oil emulsions. [18]

Examples of food emulsifiers are:

- Egg yolk – in which the main emulsifying and thickening agent is lecithin. In fact, *lecithos* is the Greek word for egg yolk.
- Mustard[19] – where a variety of chemicals in the mucilage surrounding the seed hull act as emulsifiers
- Soy lecithin is another emulsifier and thickener
- Pickering stabilization – uses particles under certain circumstances
- Sodium phosphates
- Mono- and diglycerides - a common emulsifier found in many food products (coffee creamers, ice-creams, spreads, breads, cakes)
- Sodium stearoyl lactylate
- DATEM (diacetyl tartaric acid esters of mono- and diglycerides) – an emulsifier used primarily in baking
- Simple cellulose – a particulate emulsifier derived from plant material using only water

Detergents are another class of surfactant, and will interact physically with both oil and water, thus stabilizing the interface between the oil and water droplets in suspension. This principle is exploited in soap, to remove grease for the purpose of cleaning. Many different emulsifiers are used in pharmacy to prepare emulsions such as creams and lotions. Common examples include emulsifying wax, polysorbate 20, and ceteareth 20.[20]

Sometimes the inner phase itself can act as an emulsifier, and the result is a nanoemulsion, where the inner state disperses into "nano-size" droplets within the outer phase. A well-known example of this phenomenon, the "ouzo effect", happens when water is poured into a strong alcoholic anise-based beverage, such as ouzo, pastis, absinthe, arak, or raki. The anisolic compounds, which are soluble

in ethanol, then form nano-size droplets and emulsify within the water. The resulting color of the drink is opaque and milky white.

Suspending agents

A suspension is a heterogeneous mixture in which the solute particles do not dissolve, but get suspended throughout the bulk of the solvent, left floating around freely in the medium.[1] The internal phase (solid) is dispersed throughout the external phase (fluid) through mechanical agitation, with the use of certain excipients or suspending agents.

An example of a suspension would be sand in water. The suspended particles are visible under a microscope and will settle over time if left undisturbed. This distinguishes a suspension from a colloid, in which the suspended particles are smaller and do not settle.[2] Colloids and suspensions are different from solution, in which the dissolved substance (solute) does not exist as a solid, and solvent and solute are homogeneously mixed.

A suspension of liquid droplets or fine solid particles in a gas is called an aerosol. In the atmosphere, the suspended particles are called particulates and consist of fine dust and soot particles, sea salt, biogenic and volcanogenic sulfates, nitrates, and cloud droplets.

Suspensions are classified on the basis of the dispersed phase and the dispersion medium, where the former is essentially solid while the latter may either be a solid, a liquid, or a gas.

In modern chemical process industries, high-shear mixing technology has been used to create many novel suspensions.

Ointment Base

An **ointment** is a homogeneous, viscous, semi-solid preparation, most commonly a greasy, thick oil (oil 80% - water 20%) with a high viscosity, that is intended for external application to the skin or mucous membranes. Ointments have a water number that defines the maximum amount of water that they can contain. They are used as emollients or for the application of active ingredients to the skin for protective, therapeutic, or prophylactic purposes and where a degree of occlusion is desired.

Ointments are used topically on a variety of body surfaces. These include the skin and the mucous membranes of the eye (an *eye ointment*), chest, vulva, anus, and nose. An ointment may or may not be medicated.

Ointments are usually very moisturizing, and good for dry skin. They have a low risk of sensitization due to having few ingredients beyond the base oil or fat, and low irritation risk. There is typically little variability between brands of drugs. They are often disliked by patients due to greasiness.[7]

The vehicle of an ointment is known as the *ointment base*. The choice of a base depends upon the clinical indication for the ointment. The different types of ointment bases are:

- Absorption bases, e.g., beeswax and wool fat
- Emulsifying bases, e.g., cetrimide and emulsifying wax
- Hydrocarbon bases, e.g., ceresine, microcrystalline wax, hard paraffin, and soft paraffin
- Vegetable oil bases, e.g., almond oil, coconut oil, olive oil, peanut oil, and sesame oil
- Water-soluble bases, e.g., macrogols 200, 300, 400

The medicaments are dispersed in the base and are divided after penetrating the living cells of the skin.

The water number of an ointment is the maximum quantity of water that 100g of a base can contain at 20 °C.

Ointments are formulated using hydrophobic, hydrophilic, or water-emulsifying bases to provide preparations that are immiscible, miscible, or emulsifiable with skin secretions. They can also be derived from hydrocarbon (fatty), absorption, water-removable, or water-soluble bases.

Suspensions are unstable from a thermodynamic point of view but can be kinetically stable over a longer period of time, which in turn can determine a suspension's shelf life. This time span needs to be measured in order to provide accurate information to the consumer and ensure the best product quality.

"Dispersion stability refers to the ability of a dispersion to resist change in its properties over time.

UNIT – III

Bioactivity

Two Marks

1. What is bioactivity
2. Define Induced fit theory
3. What are enzymes
4. What are enzyme inhibition
5. Write about enzyme stimulation
6. What are active drugs
7. What is Xenobiotics
8. What is sulphonamide
9. Define membrane
10. What are biotransformation
11. What are Pharmacodynamics

Five Marks

1. What are the factors affecting bioactivity
2. Write a note on elementary treatment of enzyme stimulation
3. Write a short note on membrane active drugs

Ten Marks

1. Explain briefly about QSAR
2. Explain in detail about Biotransformation

Biological activity or **pharmacological activity** describes the beneficial or adverse effects of a drug on living matter. When a drug is a complex chemical mixture, this activity is exerted by the substance's active ingredient or pharmacophore but can be modified by the other constituents. Among the various properties of chemical compounds, pharmacological/biological activity plays a crucial role since it suggests uses of the compounds in the medical applications. However, chemical compounds may show some adverse and toxic effects which may prevent their use in medical practice.

Activity is generally dosage-dependent. Further, it is common to have effects ranging from beneficial to adverse for one substance when going from low to high doses. Activity depends critically on fulfillment of the ADME criteria. To be an effective drug, a compound not only must be active against a target, but also possess the appropriate ADME (Absorption, Distribution, Metabolism, and Excretion) properties necessary to make it suitable for use as a drug.[3]

Bioactivity is a key property that promotes osseointegration for bonding and better stability of dental implants. [4] Bioglass coatings represent high surface area and reactivity leading to an effective interaction of the coating material and surrounding bone tissues. In the biological environment, the formation of a layer of carbonated hydroxyapatite (CHA) initiates bonding to the bone tissues. The bioglass surface coating undergoes leaching/exchange of ions, dissolution of glass, and formation of the HA layer that promotes cellular response of tissues. [5]The high specific surface area of bioactive glasses is likely to induce quicker solubility of the material, availability of ions in the surrounding area, and enhanced protein adsorption ability. These factors altogether contribute toward the bioactivity of bioglass coatings. In addition, tissue mineralization (bone, teeth) is promoted while tissue forming cells are in direct contact with bioglass materials.

Whereas a material is considered bioactive if it has interaction with or effect on any cell tissue in the human body, pharmacological activity is usually taken to describe beneficial effects, i.e. the effects of drug candidates as well as a substance's toxicity.

In the study of biomineralisation, bioactivity is often meant to mean the formation of calcium phosphate deposits on the surface of objects placed in simulated body fluid, a buffer solution with ion content similar to blood.

Factors affecting drugs :

(a) Ability of the Chemist : Knowledge about biology of the diseased state of which therapies are being considered. Ability of organize and plan the research project to get maximum success.

(b) Screening Facility Drugs : Capacity of the screening to evaluate a large number of compounds. The test system which is able to detect potentially and clinically useful drugs.

(c) Development facility : To develop a new drug, there should be a healthy environment with all physico-chemical facilities, including electron microscope etc. To investigate the modes of action of bioactive compounds.

(d) Cost of drug development : If the compound is prepared by an expensive process then the cost of manufacturing may also increase dramatically, hence the cost of drug into market may rise. The number of compounds synthesized in 1958 were 14600, out of them 94 compounds found their way into the market (I in 332 compounds). Similarly in 1964 1,50,000 compounds were synthesized as new drugs, but only 17 could be marketed.

Occupancy theory of drug-receptor interaction

Quoting from Kenakian (2008), *"receptor occupancy theory describes the quantitative relationships between drug concentrations and the responses that result from the interaction of those drugs with receptors".* This theory also describes the behaviour of agonists and antagonist.

For instance, observe the interaction of agonist A with receptor R, to create the drug/receptor complex AR:

$$A + R \underset{}{\overset{k_a}{\leftrightarrow}} R \qquad k_a = \frac{[AR]}{[A] \times [R]}$$

The equilibrium association constant k_a is the ratio of occupied receptor concentration to the product of agonist concentration and unoccupied receptor concentration. It is the **as**sociation constant, not to be confused with the **dis**sociation constant k_A.

Let us assume that only occupied receptors produce a response. Then, the magnitude of the response can be expressed as a fraction of occupied receptors. Occupy 50% of the receptors, get 50% of the response. Thus:

$$Response = \overbrace{\underbrace{\frac{[AR]}{[R] + [AR]}}_{\text{Total number of receptors (occupied + unoccupied)}} = \frac{[AR]}{[R_t]}}^{\text{Occupied receptors}}$$

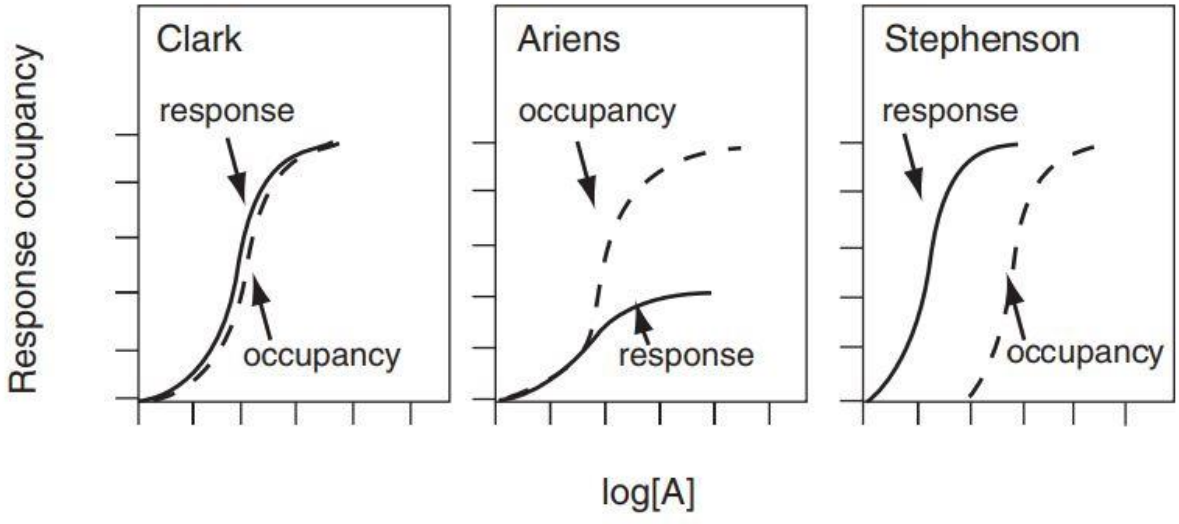
So, if the concentration of unoccupied receptors can be expressed as $[R] = [AR]/([A] \times k_a)$, the above equation can be rewritten as

$$Response = \frac{[A]}{[A] + 1/k_a} = \frac{[A]}{[A] + k_A}$$

To substitute k_A for k_a is useful because it has units of concentration: it is also the concentration of agonist that occupies half of the available receptor population.

Evolution of occupancy theory

There were several distinct evolutionary steps in the development of occupancy theory, each of which modified the concept to explain the differences between the model and the observed results of experiments. To borrow a graph from Kenakin (2008):



Clark's occupancy theory (1934) described the relationship between dose and response as a linear relationship, making the assumption that the maximal response to the drug is equal to the maximal tissue response. This theory is most suited to describe the behaviour of full agonists.

Ariens modification of the occupancy theory (1954) describes a situation where the maximal drug response is *not* equal to the maximal tissue response (i.e. it permits the existence of partial agonist drugs). This was done by using the modifier α, "intrinsic activity". A full agonist has an α-value of 1.0; if a drug only produces 50% of the maximal tissue response it is a partial agonist with an α-value of 0.5.

Stephensen's modification of the occupancy theory (1956) added the concepts of *stimulus* and *efficacy*. The agonist drug stimulates the system and produces a response; and there may be a non-linear relationship between the two. The tissue response to receptor activation could therefore be dissociated completely from the binding of agonist to receptor. This concept of *intrinsic efficacy* (ε) was defined as the unit stimulus per occupied receptor. Total efficacy (*e*) is therefore defined as $\varepsilon \times [R_t]$. This is discussed in greater detail in the chapter on potency and efficacy.

Induced fit theory

The classic model for the enzyme-substrate interaction is the induced fit model. This model proposes that the initial interaction between enzyme and substrate is relatively weak, but that these weak interactions rapidly induce conformational changes in the enzyme that strengthen binding.

The advantages of the induced fit mechanism arise due to the stabilizing effect of strong enzyme binding. There are two different mechanisms of substrate binding: uniform binding, which has strong substrate binding, and differential binding, which has strong transition state binding. The stabilizing effect of uniform binding increases both substrate and transition state binding affinity, while differential binding increases only transition state binding affinity. Both are used by enzymes and have been evolutionarily chosen to minimize the activation energy of the reaction. Enzymes that are saturated, that is, have a high affinity substrate binding, require differential binding to reduce the energy of activation, whereas small substrate unbound enzymes may use either differential or uniform binding.

These effects have led to most proteins using the differential binding mechanism to reduce the energy of activation, so most substrates have high affinity for the enzyme while in the transition state. Differential binding is carried out by the induced fit mechanism - the substrate first binds weakly, then the enzyme changes conformation increasing the affinity to the transition state and stabilizing it, so reducing the activation energy to reach it.

It is important to clarify, however, that the induced fit concept cannot be used to rationalize catalysis. That is, the chemical catalysis is defined as the reduction of $E_a^{\ddagger}$ (when the system is already in the $ES^{\ddagger}$) relative to $E_a^{\ddagger}$ in the uncatalyzed reaction in water (without the enzyme). The induced fit only suggests that the barrier is lower in the closed form of the enzyme but does not tell us what the reason for the barrier reduction is.

Induced fit may be beneficial to the fidelity of molecular recognition in the presence of competition and noise via the conformational proofreading mechanism.

QSAR

Quantitative structure–activity relationship models (**QSAR** models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable.

In QSAR modeling, the predictors consist of physico-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. Second, QSAR models predict the activities of new chemicals.

Related terms include *quantitative structure–property relationships* (*QSPR*) when a chemical property is modeled as the response variable. "Different properties or behaviors of chemical molecules have been investigated in the field of QSPR. Some examples are quantitative structure–reactivity relationships (QSRRs), quantitative structure–chromatography relationships (QSCRs) and, quantitative structure–toxicity relationships (QSTRs), quantitative structure–electrochemistry relationships (QSERs), and quantitative structure–biodegradability relationships (QSBRs)."

As an example, biological activity can be expressed quantitatively as the concentration of a substance required to give a certain biological response. Additionally, when physicochemical properties or structures are expressed by numbers, one can find a mathematical relationship, or quantitative structure-activity relationship, between the two. The mathematical expression, if carefully validated can then be used to predict the modeled response of other chemical structures.

A QSAR has the form of a mathematical model:

- Activity = *f*(physiochemical properties and/or structural properties) + error

The error includes model error (bias) and observational variability, that is, the variability in observations even on a correct model.

Pharmacodynamics

Pharmacodynamics (**PD**) is the study of the biochemical and physiologic effects of drugs (especially pharmaceutical drugs). The effects can include those manifested within animals (including humans), microorganisms, or combinations of organisms (for example, infection).

Pharmacodynamics and pharmacokinetics are the main branches of pharmacology, being itself a topic of biology interested in the study of the interactions between both endogenous and exogenous chemical substances with living organisms.

In particular, pharmacodynamics is the study of how a drug affects an organism, whereas pharmacokinetics is the study of how the organism affects the drug. Both together influence dosing, benefit, and adverse effects. Pharmacodynamics is sometimes abbreviated as PD and pharmacokinetics as PK, especially in combined reference (for example, when speaking of PK/PD models).

Pharmacodynamics places particular emphasis on dose–response relationships, that is, the relationships between drug concentration and effect.

Enzyme Stimulation

Enzymes are proteins that act as biological catalysts (biocatalysts). Catalysts accelerate chemical reactions. The molecules upon which enzymes may act are called substrates, and the enzyme converts the substrates into different molecules known as products. Almost all metabolic processes in the cell need enzyme catalysis in order to

occur at rates fast enough to sustain life. Metabolic pathways depend upon enzymes to catalyze individual steps. The study of enzymes is called *enzymology* and a new field of pseudoenzyme analysis has recently grown up, recognising that during evolution, some enzymes have lost the ability to carry out biological catalysis, which is often reflected in their amino acid sequences and unusual 'pseudocatalytic' properties.

Enzymes are known to catalyze more than 5,000 biochemical reaction types. Other biocatalysts are catalytic RNA molecules, called ribozymes. Enzymes' specificity comes from their unique three-dimensional structures.

Like all catalysts, enzymes increase the reaction rate by lowering its activation energy. Some enzymes can make their conversion of substrate to product occur many millions of times faster. An extreme example is orotidine 5'-phosphate decarboxylase, which allows a reaction that would otherwise take millions of years to occur in milliseconds.[5][6] Chemically, enzymes are like any catalyst and are not consumed in chemical reactions, nor do they alter the equilibrium of a reaction. Enzymes differ from most other catalysts by being much more specific. Enzyme activity can be affected by other molecules: inhibitors are molecules that decrease enzyme activity, and activators are molecules that increase activity. Many therapeutic drugs and poisons are enzyme inhibitors. An enzyme's activity decreases markedly outside its optimal temperature and pH, and many enzymes are (permanently) denatured when exposed to excessive heat, losing their structure and catalytic properties.

Some enzymes are used commercially, for example, in the synthesis of antibiotics. Some household products use enzymes to speed up chemical reactions: enzymes in biological washing powders break down protein, starch or fat stains on clothes, and enzymes in meat tenderizer break down proteins into smaller molecules, making the meat easier to chew.

Enzyme Inhibitor

An **enzyme inhibitor** is a molecule that binds to an enzyme and decreases its activity. By binding to enzymes' active sites, inhibitors reduce the compatibility of substrate and enzyme and this leads to the inhibition of Enzyme-Substrate complexes' formation, preventing the catalyzation of reactions and decreasing (at times to zero) the amount of product produced by a reaction. It can be said that as the concentration of enzyme inhibitors increases, the rate of enzyme activity decreases, and thus, the amount of product produced is inversely proportional to the concentration of inhibitor molecules. Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance, many drugs are enzyme inhibitors. They are also used in pesticides. Not all molecules that bind to enzymes are inhibitors; *enzyme activators* bind to enzymes and increase their enzymatic activity, while enzyme substrates bind and are converted to products in the normal catalytic cycle of the enzyme.

The binding of an inhibitor can stop a substrate from entering the enzyme's active site and/or hinder the enzyme from catalyzing its reaction. Inhibitor binding is either reversible or irreversible. Irreversible inhibitors usually react with the enzyme and change it chemically (e.g. via covalent bond formation). These inhibitors modify key amino acid residues needed for enzymatic activity. In contrast, reversible inhibitors bind non-covalently and different types of inhibition are produced depending on whether these inhibitors bind to the enzyme, the enzyme-substrate complex, or both.

Many drug molecules are enzyme inhibitors, so their discovery and improvement is an active area of research in biochemistry and pharmacology.[1] A medicinal enzyme inhibitor is often judged by its specificity (its lack of binding to other proteins) and its potency (its dissociation constant, which indicates the concentration needed to inhibit the enzyme). A high specificity and potency ensure that a drug will have few side effects and thus low toxicity.

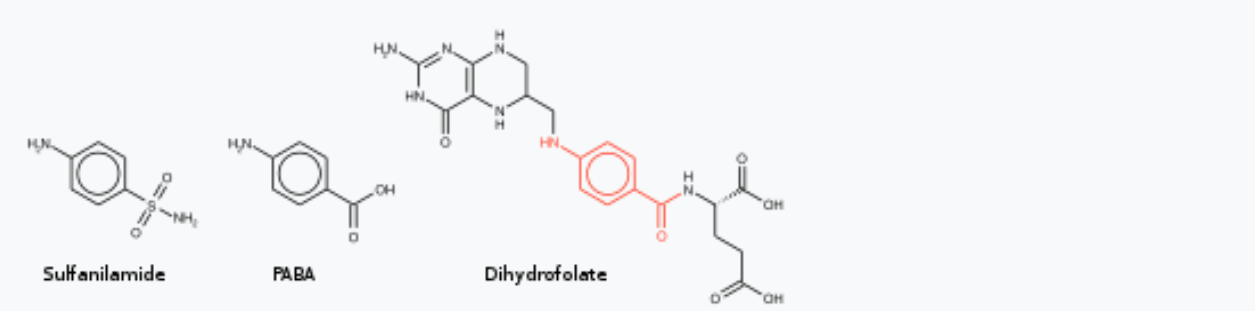
Enzyme inhibitors also occur naturally and are involved in the regulation of metabolism. For example, enzymes in a metabolic pathway can be inhibited by downstream products. This type of negative feedback slows the production line when products begin to build up and is an important way to maintain homeostasis in a cell. Other cellular enzyme inhibitors are proteins that specifically bind to and inhibit an enzyme target. This can help control enzymes that may be damaging to a cell, like proteases or nucleases. A well-characterised example of this is the ribonuclease inhibitor, which binds to ribonucleases in one of the tightest known protein–protein interactions.[2] Natural enzyme inhibitors can also be poisons and are used as defenses against predators or as ways of killing prey.

Sulfonamide

Sulfonamide is a functional group (a part of a molecule) that is the basis of several groups of drugs, which are called **sulphonamides**, **sulfa drugs** or **sulpha drugs**. The original antibacterial sulfonamides are synthetic (nonantibiotic) antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame. The sulfonylureas and thiazide diuretics are newer drug groups based upon the antibacterial sulfonamides.[1][2]

Allergies to sulfonamides are common. The overall incidence of adverse drug reactions to sulfa antibiotics is approximately 3%, close to penicillin;[3] hence medications containing sulfonamides are prescribed carefully.

In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthase (DHPS), an enzyme involved in folate synthesis. Sulfonamides are therefore bacteriostatic and inhibit growth and multiplication of bacteria, but do not kill them. Humans, in contrast to bacteria, acquire folate (vitamin B_9) through the diet.[4]



Structural similarity between sulfonilamide (left) and PABA (center) is the basis for the inhibitory activity of sulfa drugs on tetrahydrofolate (right) biosynthesis.

Sulfonamides are used to treat allergies and cough, as well as antifungal and antimalarial functions. The moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and indapamide, among others), loop diuretics (including furosemide, bumetanide, and torsemide), acetazolamide, sulfonylureas (including glipizide, glyburide, among others), and some COX-2 inhibitors (e.g., celecoxib).

Sulfasalazine, in addition to its use as an antibiotic, is also used in the treatment of inflammatory bowel disease.

xenobiotic

A **xenobiotic** is a chemical substance found within an organism that is not naturally produced or expected to be present within the organism. It can also cover substances that are present in much higher concentrations than are usual. Natural compounds can also become xenobiotics if they are taken up by another organism, such as the uptake of natural human hormones by fish found downstream of sewage treatment plant outfalls, or the chemical defenses produced by some organisms as protection against predators.

The body removes xenobiotics by xenobiotic metabolism. This consists of the deactivation and the excretion of xenobiotics, and happens mostly in the liver. Excretion routes are urine, feces, breath, and sweat. Hepatic enzymes are responsible for the metabolism of xenobiotics by first activating them (oxidation, reduction, hydrolysis and/or hydration of the xenobiotic), and then conjugating the active secondary metabolite with glucuronic acid, sulfuric acid, or glutathione, followed by excretion in bile or urine. An example of a group of enzymes involved in xenobiotic metabolism is hepatic microsomal cytochrome P450. These enzymes that metabolize xenobiotics are very important for the pharmaceutical industry, because they are responsible for the breakdown of medications. A species with this unique cytochrome P450 system is Drosophila mettleri, which uses xenobiotic resistance to exploit a wider nesting range including both soil moistened with necrotic exudates and necrotic plots themselves.

Although the body is able to remove xenobiotics by reducing it to a less toxic form through xenobiotic metabolism then excreting it, it is also possible for it to be converted into a more toxic form in some cases. This process is referred to as bioactivation and can

result in structural and functional changes to the microbiota. Exposure to xenobiotics can disrupt the microbiome community structure, either by increasing or decreasing the size of certain bacterial populations depending on the substance. Functional changes that result vary depending on the substance and can include increased expression in genes involved in stress response and antibiotic resistance, changes in the levels of metabolites produced, etc.

Organisms can also evolve to tolerate xenobiotics. An example is the co-evolution of the production of tetrodotoxin in the rough-skinned newt and the evolution of tetrodotoxin resistance in its predator, the Common Garter Snake. In this predator–prey pair, an evolutionary arms race has produced high levels of toxin in the newt and correspondingly high levels of resistance in the snake. This evolutionary response is based on the snake evolving modified forms of the ion channels that the toxin acts upon, so becoming resistant to its effects.[5] Another example of a xenobiotic tolerance mechanism is the use of ATP-binding cassette (ABC) transporters, which is largely exhibited in insects. Such transporters contribute to resistance by enabling the transport of toxins across the cell membrane, thus preventing accumulation of these substances within cells.

Biotransformation

Biotransformation is the chemical modification (or modifications) made by an organism on a chemical compound. If this modification ends in mineral compounds like CO_2, NH_4^+, or H_2O, the biotransformation is called mineralisation.

Biotransformation means chemical alteration of chemicals such as nutrients, amino acids, toxins, and drugs in the body. It is also needed to render non-polar compounds polar so

that they are not reabsorbed in renal tubules and are excreted. Biotransformation of xenobiotics can dominate toxicokinetics and the metabolites may reach higher concentrations in organisms than their parent compounds. Recently its application is seen as an efficient, cost effective, and easily applicable approach for the valorization of agricultural wastes with potentials of enhancing existing bioactive components and synthesis of new compounds.

Biotransformation of various pollutants is a sustainable way to clean up contaminated environments. These bioremediation and biotransformation methods harness the naturally occurring, microbial catabolic diversity to degrade, transform or accumulate a huge range of compounds including hydrocarbons (e.g. oil), polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), pharmaceutical substances, radionuclides and metals. Major methodological breakthroughs in recent years have enabled detailed genomic, metagenomic, proteomic, bioinformatic and other high-throughput analyses of environmentally relevant microorganisms providing unprecedented insights into biotransformation and biodegradative pathways and the ability of organisms to adapt to changing environmental conditions.

Biological processes play a major role in the removal of contaminants and pollutants from the environment. Some microorganisms possess an astonishing catabolic versatility to degrade or transform such compounds. New methodological breakthroughs in sequencing, genomics, proteomics, bioinformatics and imaging are producing vast amounts of information. In the field of Environmental Microbiology, genome-based global studies open a new era providing unprecedented *in silico* views of metabolic and regulatory networks, as well as clues to the evolution of biochemical pathways relevant to biotransformation and to the molecular adaptation strategies to changing environmental conditions. Functional genomic and metagenomic approaches are increasing our understanding of the relative importance of different pathways and regulatory networks to carbon flux in particular environments and for particular compounds and they are accelerating the development of bioremediation technologies and biotransformation processes. Also there is other approach of biotransformation called enzymatic biotransformation

UNIT – IV

Antineoplastic agent

Two Marks

1. What are antineoplastic agent
2. Write about isotopes used in chemotheraphy
3. What are the role of alkylating agents
4. Write the synthesis of amylnitrate
5. What are cardiovascular diseases
6. Write about Quinidine
7. What are analgesics
8. Write tha total synthetic analgesics
9. Write about indolyl derivatives
10. Write about p-amino phenol derivatives

Five Marks

1. Explain about the cancer chemotheraphy in detailed
2. Explain about the antimetabolites in treatment of cancer
3. Explain about the cardio diseases in detailed
4. Explain about Salicylic acid derivatives

Ten Marks

1. Explain briefly about recent development in chemotheraphy radio isotopes
2. Explain briefly about the cardiovascular drugs in detailed
3. Explain about the Morphine and its derivatives

An **alkylating antineoplastic agent** is an alkylating agent used in cancer treatment that attaches an alkyl group (C_nH_{2n+1}) to DNA.

The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring.

Since cancer cells, in general, proliferate faster and with less error-correcting than healthy cells, cancer cells are more sensitive to DNA damage—such as being alkylated. Alkylating agents are used to treat several cancers. However, they are also toxic to normal cells (cytotoxic), particularly cells that divide frequently, such as those in the gastrointestinal tract, bone marrow, testicles and ovaries, which can cause loss of fertility. Most of the alkylating agents are also carcinogenic. Hyperthermia therapy is especially effective at enhancing the effects of alkylating agents.

Cancer **Chemotherapy**

Chemotherapy (often abbreviated to **chemo** and sometimes **CTX** or **CTx**) is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardized chemotherapy regimen. Chemotherapy may be given with a curative intent (which almost always involves combinations of drugs), or it may aim to prolong life or to reduce symptoms (palliative chemotherapy). Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called *medical oncology*. The term *chemotherapy* has come to connote non-specific usage of intracellular poisons to inhibit mitosis (cell division) or induce DNA damage, which is why inhibition of DNA repair can augment chemotherapy. The connotation of the word chemotherapy excludes more selective agents that block extracellular signals (signal transduction). The development of therapies with specific molecular or genetic targets, which inhibit growth-promoting signals from classic endocrine hormones (primarily estrogens for breast cancer and androgens for prostate cancer) are now called hormonal therapies. By contrast, other inhibitions of growth-signals like those associated with receptor tyrosine kinases are referred to as targeted therapy.

Importantly, the use of drugs (whether chemotherapy, hormonal therapy or targeted therapy) constitutes *systemic therapy* for cancer in that they are introduced into the blood stream and are therefore in principle able to address cancer at any anatomic location in the body. Systemic therapy is often used in conjunction with other modalities that constitute *local therapy* (i.e. treatments whose efficacy is confined to the anatomic area where they are applied) for cancer such as radiation therapy, surgery or hyperthermia therapy.

Traditional chemotherapeutic agents are cytotoxic by means of interfering with cell division (mitosis) but cancer cells vary widely in their susceptibility to these agents. To a large extent, chemotherapy can be thought of as a way to damage or stress cells, which may then lead to cell death if apoptosis is initiated. Many of the side effects of chemotherapy can be traced to damage to normal cells that divide rapidly and are thus sensitive to anti-mitotic drugs: cells in the bone marrow, digestive tract and hair follicles. This results in the most common side-effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss). Because of the effect on immune cells (especially lymphocytes), chemotherapy drugs often find use in a host of diseases that result from harmful overactivity of the immune system against self (so-called autoimmunity). These include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, vasculitis and many others.

Role of alkylating agents

alkylating agents were better known for their use as sulfur mustard, ("mustard gas") and related chemical weapons in World War I. The nitrogen mustards were the first alkylating

agents used medically, as well as the first modern cancer chemotherapies. Goodman, Gilman, and others began studying nitrogen mustards at Yale in 1942, and, following the sometimes dramatic but highly variable responses of experimental tumors in mice to treatment, these agents were first tested in humans late that year. Use of methyl bis (B-chloroethyl)emine hydrochloride (mechlorethamine, mustine) and tris (B-chloroethy) amine hydrochloride for Hodgkin's disease lymphosarcoma, leukemia, and other malignancies resulted in striking but temporary dissolution of tumor masses. Because of secrecy surrounding the war gas program, these results were not published until 1946. These publications spurred rapid advancement in the previously non-existent field of cancer chemotherapy, and a wealth of new alkylating agents with therapeutic effect were discovered over the following two decades.

A common myth holds that Goodman and Gilman were prompted to study nitrogen mustards as a potential treatment for cancer following a 1943 incident in Bari, Italy, where survivors exposed to mustard gas became leukopenic. In fact, animal and human trials had begun the previous year, Gilman makes no mention of such an episode in his recounting of the early trials of nitrogen mustards, and the marrow-suppressing effects of mustard gas had been known since the close of World War.

Antimetabolites

Antimetabolites can be used in cancer treatment, as they interfere with DNA production and therefore cell division and tumor growth. Because cancer cells spend more time dividing than other cells, inhibiting cell division harms tumor cells more than other cells. Antimetabolite drugs are commonly used to treat leukemia, cancers of the breast, ovary, and the gastrointestinal tract, as well as other types of cancers. In the Anatomical Therapeutic Chemical Classification System antimetabolite cancer drugs are classified under L01B.

Antimetabolites generally impair DNA replication machinery, either by incorporation of chemically altered nucleotides or by depleting the supply of deoxynucleotides needed for DNA replication and cell proliferation.

Anti-metabolites masquerade as a purine (azathioprine, mercaptopurine) or a pyrimidine, chemicals that become the building-blocks of DNA. They prevent these substances from becoming incorporated into DNA during the S phase (of the cell cycle), stopping normal development and cell division. Anti-metabolites also affect RNA synthesis. However, because thymidine is used in DNA but not in RNA (where uracil is used instead), inhibition of thymidine synthesis via thymidylate synthase selectively inhibits DNA synthesis over RNA synthesis.

Due to their efficiency, these drugs are the most widely used cytostatics. Competition for the binding sites of enzymes that participate in essential biosynthetic processes and subsequent incorporation of these biomolecules into nucleic acids, inhibits their normal tumor cell function and triggers apoptosis, the cell death process. Because of this mode of

action, most antimetabolites have high cell cycle specificity and can target arrest of cancer cell DNA replication.

Antimetabolite

An **antimetabolite** is a chemical that inhibits the use of a metabolite, which is another chemical that is part of normal metabolism. Such substances are often similar in structure to the metabolite that they interfere with, such as the antifolates that interfere with the use of folic acid; thus, competitive inhibition can occur, and the presence of antimetabolites can have toxic effects on cells, such as halting cell growth and cell division, so these compounds are used as chemotherapy for cancer.

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Cardiovascular diseases

Cardiovascular disease (**CVD**) is a class of diseases that involve the heart or blood vessels. CVD includes coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack). Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, abnormal heart rhythms, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis.

The underlying mechanisms vary depending on the disease. Coronary artery disease, stroke, and peripheral artery disease involve atherosclerosis. This may be caused by high blood pressure, smoking, diabetes mellitus, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol consumption, among others. High blood pressure is estimated to account for approximately 13% of CVD deaths, while tobacco accounts for 9%, diabetes 6%, lack of exercise 6% and obesity 5%.Rheumatic heart disease may follow untreated strep throat. It is estimated that up to 90% of CVD may be preventable. Prevention of CVD involves improving risk factors through: healthy eating, exercise, avoidance of tobacco smoke and limiting alcohol intake. Treating risk factors, such as high blood pressure, blood lipids and diabetes is also beneficial. Treating people who have strep throat with antibiotics can decrease the risk of rheumatic heart disease. The use of aspirin in people, who are otherwise healthy, is of unclear benefit.

Cardiovascular diseases are the leading cause of death worldwide except Africa. Together CVD resulted in 17.9 million deaths (32.1%) in 2015, up from 12.3 million (25.8%) in 1990. Deaths, at a given age, from CVD are more common and have been increasing in much of the developing world, while rates have declined in most of the developed world since the 1970s. Coronary artery disease and stroke account for 80% of CVD

deaths in males and 75% of CVD deaths in females.[2] Most cardiovascular disease affects older adults. In the United States 11% of people between 20 and 40 have CVD, while 37% between 40 and 60, 71% of people between 60 and 80, and 85% of people over 80 have CVD. The average age of death from coronary artery disease in the developed world is around 80 while it is around 68 in the developing world. Diagnosis of disease typically occurs seven to ten years earlier in men as compared to women.

Cardiovascular drugs

Synthesis of amyl nitrate

Alkyl nitrites are prepared by the reaction of alcohols with nitrous acid

$$ROH + HONO \rightarrow RONO + H_2O, \text{ where R = alkyl group}$$

The reaction is called esterification. Synthesis of alkyl nitrites is, in general, straightforward and can be accomplished in home laboratories. A common procedure includes the dropwise addition of concentrated sulfuric acid to a cooled mixture of an aqueous sodium nitrite solution and an alcohol. The intermediately-formed stoichiometric mixture of nitrogen dioxide and nitric oxide then converts the alcohol to the alkyl nitrite, which, due to its low density, will form an upper layer that can be easily decanted from the reaction mixture.

Isoamyl nitrite decomposes in the presence of base to give nitrite salts and the isoamyl alcohol:

$$C_5H_{11}ONO + NaOH \rightarrow C_5H_{11}OH + NaNO_2$$

Amyl nitrite, like other alkyl nitrites, reacts with carbanions to give oximes.

Amyl nitrites are also useful as reagents in a modification of the Sandmeyer reaction. The reaction of the alkyl nitrite with an aromatic amine in a halogenated solvent produces a radical aromatic species, this then frees a halogen atom from the solvent. For the synthesis of aryl iodides diiodomethane is used, whereas bromoform is the solvent of choice for the synthesis of aryl bromides.

Sorbitrate

This medication is used before physical activities (such as exercise, sexual activity) to prevent chest pain (angina) in people with a certain heart condition (coronary artery disease). It may also be used to relieve chest pain in these people once it occurs.Isosorbide dinitrate belongs to a class of drugs known as nitrates. Angina occurs when the heart muscle is not getting enough blood. This drug works by relaxing and widening blood vessels so blood can flow more easily to the heart.

Quinidine

Quinidine is occasionally used as a class I antiarrhythmic agent to prevent ventricular arrhythmias, particularly in Brugada Syndrome, although its safety in this indication is uncertain.

It reduces the recurrence of atrial fibrillation after patients undergo cardioversion, but it has proarrhythmic effects and trials suggest that it may lead to an overall increased mortality in these patients.

Quinidine is also used to treat short QT syndrome.

Eli Lilly has discontinued manufacture of parenteral quinidine gluconate in the US, and its future availability in many countries is uncertain.

Quinidine is also an inhibitor of the cytochrome P450 enzyme 2D6, and can lead to increased blood levels of lidocaine, beta blockers, opioids, and some antidepressants. Quinidine also inhibits the transport protein P-glycoprotein and so can cause some peripherally acting drugs such as loperamide to have central nervous system side effects, such as respiratory depression, if the two drugs are coadministered.

Quinidine can cause thrombocytopenia, granulomatous hepatitis, myasthenia gravis, and *torsades de pointes* (dangerous heart rhythm), so is not used much today. *Torsades* can occur after the first dose. Quinidine-induced thrombocytopenia (low platelet count) is mediated by the immune system, and may lead to thrombocytic purpura.

Quinidine intoxication can lead to a collection of symptoms collectively known as cinchonism, with tinnitus (ringing in the ears) being among the most characteristic and common symptoms of this toxicity syndrome.

Atenolol

Atenolol (Tenormin) is a beta-blocker that affects the heart and circulation (blood flow through arteries and veins).Atenolol is used to treat **angina** (chest pain) and **hypertension** (high blood pressure).Atenolol is also used to lower the risk of death after a heart attack.

Oxprenolol

Oxprenolol (brand names **Trasacor**, **Trasicor**, **Coretal**, **Laracor**, **Slow-Pren**, **Captol**, **Corbeton**, **Slow-Trasicor**, **Tevacor**, **Trasitensin**, **Trasidex**) is a non-selective beta blocker with some intrinsic sympathomimetic activity. It is used for the treatment of angina pectoris, abnormal heart rhythms and high blood pressure.

Oxprenolol is a lipophilic beta blocker which passes the blood–brain barrier more easily than water-soluble beta blockers. As such, it is associated with a higher incidence of CNS-related side effects than beta blockers with more hydrophilic molecules such as atenolol, sotalol and nadolol.

Oxprenolol is a potent beta blocker and should not be administered to asthmatics under any circumstances due to their low beta levels as a result of depletion due to other asthma medication, and because it can cause irreversible, often fatal, airway failure and inflammation.

Analgesic

An **analgesic** or **painkiller** is any member of the group of drugs used to achieve analgesia, relief from pain.

Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which temporarily affect, and in some instances completely eliminate, sensation. Analgesics include paracetamol (known in North America as acetaminophen or simply APAP), the nonsteroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and oxycodone.

When choosing analgesics, the severity and response to other medication determine the choice of agent; the World Health Organization (WHO) pain ladder[1] specifies mild analgesics as its first step.

Analgesic choice is also determined by the type of pain: For neuropathic pain, traditional analgesics are less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as tricyclic antidepressants and anticonvulsants.

Morphine

Morphine is a pain medication of the opiate family that is found naturally in a number of plants and animals, including humans. It acts directly on the central nervous system (CNS) to decrease the feeling of pain. It can be taken for both acute pain and chronic pain and is frequently used for pain from myocardial infarction and during labor. Morphine can be administered by mouth, by injection into a muscle, by injection under the skin, intravenously, injection into the space around the spinal cord, or rectally. Its maximum effect is reached after about 20 minutes when administered intravenously and 60 minutes when administered by mouth, while the duration of its effect is 3–7 hours. Long-acting formulations of morphine also exist.

Potentially serious side effects of morphine include decreased respiratory effort and low blood pressure. Morphine is addictive and prone to abuse. If one's dose is reduced after long-term use, opioid withdrawal symptoms may occur. Common side effects of morphine include drowsiness, vomiting, and constipation. Caution is advised for use of morphine during pregnancy or breast feeding, as it may affect the health of the baby.

Morphine was first isolated between 1803 and 1805 by German pharmacist Friedrich Sertürner. This is generally believed to be the first isolation of an active ingredient from a plant. Merck began marketing it commercially in 1827. Morphine was more widely used after the invention of the hypodermic syringe in 1853–1855. Sertürner originally named the substance *morphium*, after the Greek god of dreams, Morpheus, as it has a tendency to cause sleep.

The primary source of morphine is isolation from poppy straw of the opium poppy. In 2013, approximately 523 tons of morphine were produced. Approximately 45 tons were used directly for pain, a four-fold increase over the last twenty years. Most use for this purpose was in the developed world. About 70 percent of morphine is used to make

other opioids such as hydromorphone, oxymorphone, and heroin. It is a Schedule II drug in the United States, Class A in the United Kingdom and Schedule I in Canada. It is also on the World Health Organization's List of Essential Medicines. Morphine is sold under many trade names. In 2017, it was the 155th-most commonly prescribed medication in the United States, with more than four million prescriptions.

Salicylic acid derivatives

Salicylic acid is a lipophilic monohydroxybenzoic acid, a type of phenolic acid, and a beta hydroxy acid (BHA). It has the formula $C_7H_6O_3$. This colorless crystalline organic acid is widely used in organic synthesis and functions as a plant hormone. It is derived from the metabolism of salicin.

In addition to serving as an important active metabolite of aspirin (*acetylsalicylic acid*), which acts in part as a prodrug to salicylic acid, it is probably best known for its use as a key ingredient in topical anti-acne products. The salts and esters of salicylic acid are known as salicylates.

Salicylic acid as a medication is used most commonly to help remove the outer layer of the skin. As such, it is used to treat warts, psoriasis, acne, ringworm, dandruff, and ichthyosis.

Similar to other hydroxy acids, salicylic acid is a key ingredient in many skincare products for the treatment of seborrhoeic dermatitis, acne, psoriasis, calluses, corns, keratosis pilaris, acanthosis nigricans, ichthyosis and warts.

Salicylic acid is used in the production of other pharmaceuticals, including 4-aminosalicylic acid, sandulpiride, and landetimide (via Salethamide).

Salicylic acid was one of the original starting materials for making acetylsalicylic acid (aspirin) in 1897.

Bismuth subsalicylate, a salt of bismuth and salicylic acid, is the active ingredient in stomach relief aids such as Pepto-Bismol, is the main ingredient of Kaopectate and "displays anti-inflammatory action (due to salicylic acid) and also acts as an antacid and mild antibiotic".

Other derivatives include methyl salicylate used as a liniment to soothe joint and muscle pain and choline salicylate used topically to relieve the pain of mouth ulcers.

Indolyl derivatives

Indole is a solid at room temperature. It occurs naturally in human feces and has an intense fecal odor. At very low concentrations, however, it has a flowery smell, and is a constituent of many perfumes. It also occurs in coal tar.

The corresponding substituent is called **indolyl**.

Indole undergoes electrophilic substitution, mainly at position 3 (see diagram in right margin). Substituted indoles are structural elements of (and for some compounds, the synthetic precursors for) the tryptophan-derived tryptamine alkaloids, which includes

the neurotransmitters serotonin and melatonin, as well as the naturally occurring psychedelic drugs dimethyltryptamine and psilocybin. Other indolic compounds include the plant hormone auxin (indolyl-3-acetic acid, IAA), tryptophol, the anti-inflammatory drug indomethacin, and the betablocker pindolol.

P-Aminophenol

4-Aminophenol (or ***para*-aminophenol** or ***p*-aminophenol**) is the organic compound with the formula $H_2NC_6H_4OH$. Typically available as a white powder,[3] it was commonly used as a developer for black-and-white film, marketed under the name Rodinal.

Reflecting its slightly hydrophilic character, the white powder is moderately soluble in alcohols and can be recrystallized from hot water. In the presence of a base, it oxidizes readily.The methylated derivatives *N*-methylaminophenol and *N*,*N*-dimethylaminophenol are of commercial value.