Natubhai V. Patel College of Pure & Applied Sciences

T. Y. B.Sc. (Industrial chemistry)

IC – 302: Unit Process, Synthetic dyes and Pharmaceuticals

UNIT – 6

Syllabus

Vitamins, Hormones, Antibiotics, Antituberculor, Antifungal and Antiinflammatory drugs

6.0 INTRODUCTION

Besides proteins, carbohydrates, fats, minerals and water, living organism also need some additional naturally occurring organic compounds in their diet, to maintain normal growth and health. "Such essential dietary factors are required by an organism in very small amounts. Their absence results in a deficiency disease (avitaminosis). Such compounds are called "**vitamins**" They **supply very little energy** but **play** an **important role** in **energy transformation reactions** (e.g., oxidation-reduction reactions) and also act as coenzymes in biochemical reactions.

Hormones, also referred as **chemical messengers**, are **produced by** the **ductless glands** (endocrine organs) and discharged directly into the blood stream to be carried to a remote tissue to exert characteristic physiological effect. Like vitamins, they are also effective in small quantities but differ from the former in that they are produced inside the body (e.g., insulin from pancreas, thyroxine from thyroid, adrenaline from adrenal body, etc.) and need not require to be supplemented in food.

6.1 VITAMINS

Eijkmann, a Dutch physician (1897), observed that a disease beri-beri in men and polyneuritis in chick and pigeons occurred when fed on polished rice. The disease can be alleviated in men by supplementing milk and vegetables in their diet. Funk (1911) was able to isolate a crystalline compound from rice polishing, which could cure beri-beri in men and polyneuritis in pigeons. It was chemically an amine and hence called it as vitamine. (vita= necessary for life + amine). But later on it was found that only a few of them are amines. However, the term 'Vitamin' is retained by removing the terminal 'e' from its spelling. Initially, they were given; hames according to alphabets as vitamin, A, B, C, D, E, H and K etc

6.2 CLASSIFICATION OF VITAMINS

Broadly classified as

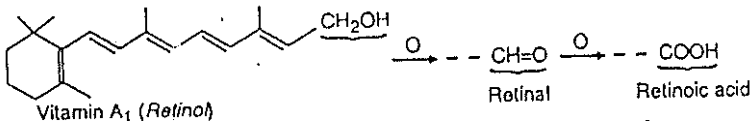
- Fat soluble (e.g. vitamin A, D, E and K) and
- Water soluble (e.g. vitamin B-complex and C).
- Vitamin H is placed in a separate group as is neither water soluble nor fat soluble.

6.3 FAT SOLUBLE VITAMINS

6.3.1 Vitamin A

6.3.1.1 Vitamin-'A' (or A_1) or Retinol or Axerophthol

It is a diterpenoid first recognized by Mc Collum and Davis as Vitamin A. It is now referred to as Vitamin A_1 or Retinol (IUPAC name). Its corresponding oxidation products are retinal (retenene$_1$) or retinoic acid.



A second form Vitamin A_2 found in fresh water fish has also been isolated.

1. Occurrence

It occurs in milk, milk products (butter, cheese, etc.), fats, cod liver oil (free or in ester form) and in vegetables like cabbage, carrots, potatoes, tomatoes, etc., in the form of its precursors (carotenoids) which are converted lo vitamin A_1 in the intestinal tract of animals.

2. Physical and Spectroscopic Characteristics

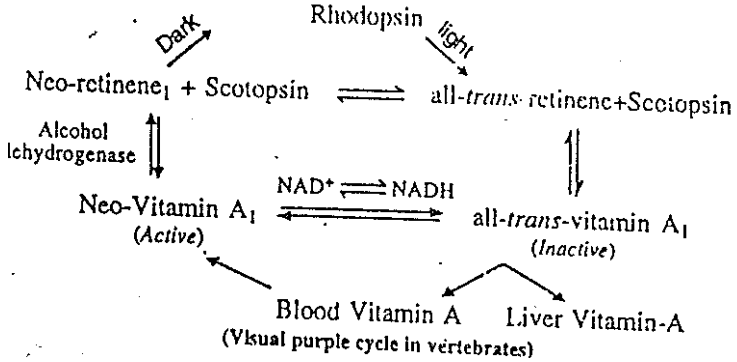
Originally, it was isolated as a yellow oil but later on Baxter et al. obtained it as a crystalline solid (m.p.63—64°C). It gives blue colour reaction with antimony chloride solution in chloroform (Carr-Price reaction). Because of the carbon-carbon double bonds, both forms (A_1 and A_2) exist in cis- and trans-isomers. It absorbs light having λ_{max} = 325 nm (ε 51,000). It is optically active and resistant to heal.

3. Function

Vitamin A_1 increases resistance to disease and influences the growth of animals. Its deficiency in human **cause's night blindness** (nyctalopia) and prolonged deficiency leads to **hardening of cornea** (xerophthalmia). The salivary gland also loses their ability to secrete saliva in its deficiency.

4. Vitamin A and Vision

During vision, **Vitamin A_1** (in the presence of catalyst NAD and alcohol dehydrogenase) is **converted to yellow pigment** (neo-retinene) in the retinal rods of the eye. The **neo-retinene** combines with a specific protein **scotopsin**, to form **rhodopsin**, a rose coloured pigment (visual purple). When light falls on the retinal rods, rhodopsin, splits to all-**trans retinene** and **scotopsin**. This chemical change causes a stimulus which is transmitted to optic nerve and results in vision. **To repeat the process** trans-retinene must be isomerised via vitamin A_1 to neo-retinene. However, this conversion is not cent percent and therefore vitamin A_1 must be freshly supplied to eye by blood stream. Since; adequate level of rhodopsin is the necessary requirement in dim light vision, vitamin A_1 deficiency (hence inadequate formation of rhodopsin) causes night blindness and eyes fail to adjust in dim light (see, visual-purple cycle given below)



5. Requirement

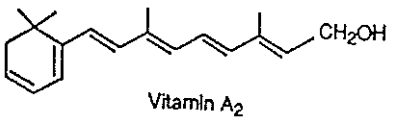
A human needs about 500 I.U. (International units) per day for normal growth. Infants need about 1500 I.U. per day and a pregnant woman needs about 7000 —8000 I.U. per day.

6. Effect of excess vitamin A_1

When taken in excess, it causes liver enlargement, nausea, weakness and fragility of bones.

6.3.1.2 Vitamin-A_2 (3, 4-dehydroretinol)

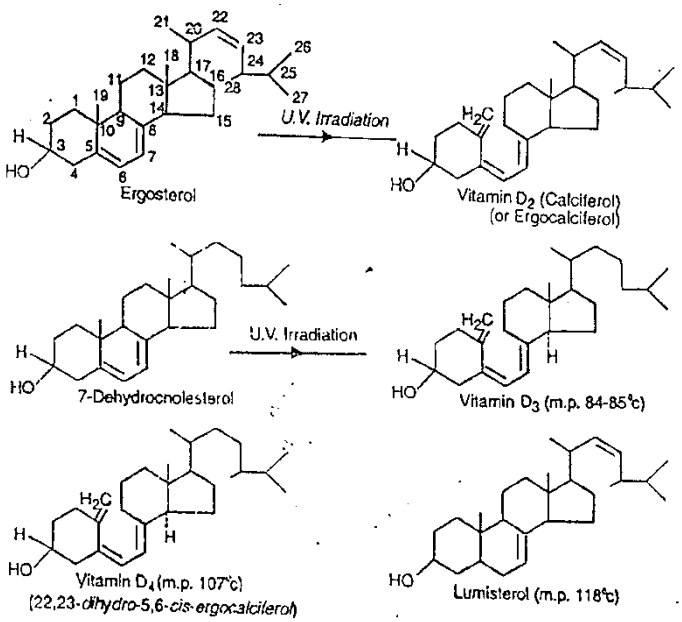
It is isolated from fresh water fish. It was synthesized by Jones et al. It is a dehydro - vitamin A_1. It is necessary for vision in fresh water fishes. Vitamin A_2 shows two absorption maxima: 287 (ε 22,000) and 351 (ε 41,000) nm in UV spectra. Its structure is as follows:



Vitamin A_2 (mp 63-65^{0}C) and its geometrical isomers have been synthesized by Isler et al. (1962)

6.3.2 Vitamin-D (Antirachitic factor)

It represents a group of closely related five fat soluble vitamins, namely D_1, D_2, D_3, D_4 and D_5; structurally related to sterols from which they can be prepared by irradiation with U.V. light. **E.g.,** vitamin D_3 (calciferol) from ergosterol (found in yeast and fungi), D_3 from 7-dehydrocholesterol (a lipid in the skin). D_4 from 22, 23-dihydroergosterol and D_3 from 7-dehydrositosterol. Vitamin D_1 is simply an equimolecular mixture of vitamin D_2 (calciferol) and lumisterol.



The formulae' for D_2, D_3 and D_4 show that these vitamins differ only in the side chain attached to C-17 of the ring.

1. Occurrence

It is produced in nature by the irradiation of certain sterols (found in lipid material in grains, nuts and body oils). Orally it can be taken in the form of its precursor (cod liver oil, hen's egg and milk).

2. Function and deficiency disease

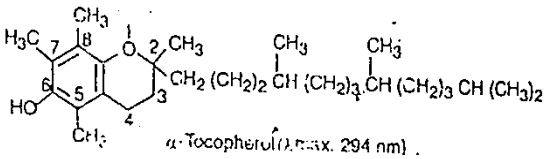
This vitamin is **essential** for **proper bone growth** and its **deficiency** causes a disease known as "**rickets**" in children, which is characterized by softening and bending of bones and poor teeth formation (due to drop in calcium and phosphorus level in blood). The administration of vitamin D_2 alleviates the symptoms of the disease in such patients and hence the name antirachitic factor.

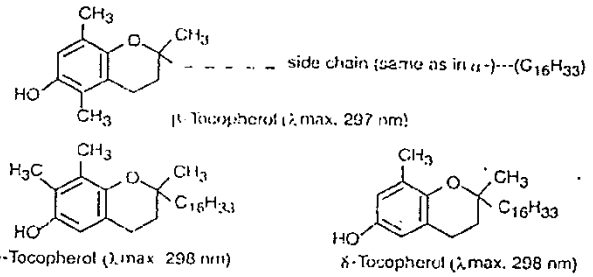
3. Requirement

Children need 400 I.U. per day of D_2 (or D_3) and chicks need 90 I.U. per pound of feed. Adults and pregnant women do not need additional vitamin D if they are exposed to sunlight.

6.3.3 Vitamin-E (or α, β, γ and σ-tocopherols) or Antisterility factor)

Vitamin E, necessary for **normal reproduction**, represents a group of four biologically active, structurally related compounds called tocopherols (α, β, γ and σ). The most active form is a -tocopherol. Mattil and Conklin (1920) first reported the interaction of this food factor with reproduction. The term tocopherol is derived from **normal child birth** *(*tokos - child birth; phero = to bear and ol = alcohol).





These structurally related phenolic compounds belong to class of organic compounds called "chroman derivatives"

1. Occurrence

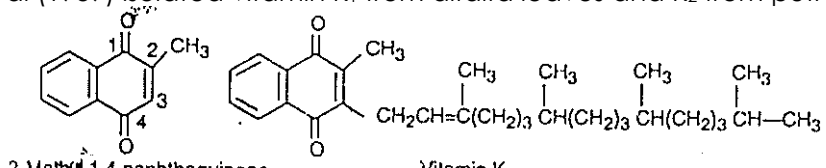
It occurs in wheat germ oil (a-and β-), cottonseed oil (γ-form) and Soyabean oil (σ-)

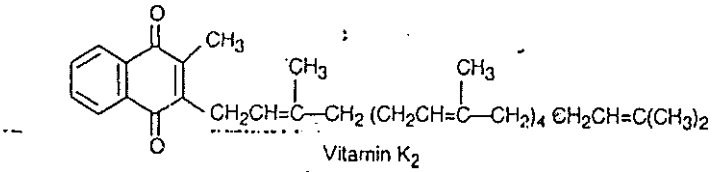
2. Functions and deficiency disease

These are **excellent antioxidants**; first recognized as antisterility vitamins. It is found that vitamin E deficient diet in **male rats** causes irreversible degeneration of sperm forming tissues. **Female rats** can conceive in vitamin E - free diet but the foetus dies about the twelfth day or gestation. Its deficiency also causes muscular dystrophy in rats, dogs, rabbits and guinea pigs. It also increases concentration of RNA and DNA in bone marrow.

6.3.4 Vitamin-K (Antihaemoirhagic factor)

Vitamin 'K' refers to a group of two structurally related compounds vitamin $K_1$and K_2. Doisy et al (1939) isolated vitamin K_1 from alfalfa leaves and K_2 from putrefied fish meal.





These are 2, 3-dtsubstituted naphthaquinones which differ from each other in the length and degree of unsaturation of isoprenoid side chain. It is noticed that the active part of vitamin 'K' activity is the 1, 4-naphthaqitinone nucleus, since the first commercially available product. 2-Methyl-1, 4-naphthoquinone (Menadione) has activity equal to that of naturally occurring forms, except as an antidote for dicoumarol poisoning.

1. Occurrence

Vitamin K_1 occurs in cabbage, alfalfa, spinach and carrot tops; vitamin K_2 is mainly found in bacteria and putrefied fish meal.

2. Physical and Spectroscopic Characteristics

Vitamin K_1 is a yellow oil and K_2 is a yellow crystalline solid (m.p. 54^0C). Both vitamin K_1 and K_2 show absorption maxima in U.V. region at 243, 249, 260, 270 nm (ε 20000) and 325 nm (ε=3000) due to common chromophore.

3. Function and deficiency disease

It is referred to as "**antihermorrhiagic**" vitamin, because of its important role in blood coagulation. The normal level of vitamin K must be present in the liver of animals and men to synthesize prothrombin (necessary for blood coagulation). Vitamin K_1 and its closely related derivatives (i.e. oxide) serves as an antidote in warfarin poisoning or in the case of over - dosage with dicoumarol in thrombosis therapy.

Pregnant women are given vitamin K to control undue hemorrhage in both mother and child.

6.4 WATER SOLUBLE VITAMINS

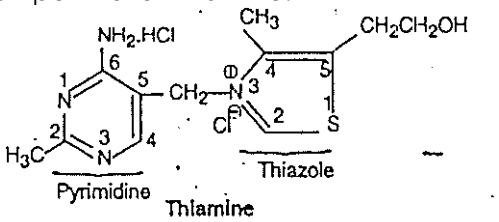
The water soluble vitamins include vitamin B-complex and vitamin C.

6.4.1 Vitamin-B complex

Initially anti beriberi factor present in rice polishing was recognized as water soluble vitamin B to distinguish from fat soluble vitamin A. But later on it is found that it is housing a group of vitamins found in yeast, liver, milk and rice polishing. This group includes mainly (1) Thiamine-B_1 (2) Riboflavm-B_2 (3) Pantothenic acid B_3 (4) Folic acid (5) Pyridoxine-B_6 (6) Niacin and (7) Cyanocobalamine-B_{12}.

6.4.1.1 Vitamin B_1, thiamine (Aneurin) or antiberiberi factor

Thiamine is a pyrimidine hydrochloride linked with a sulphur containing heterocyclic, thiazole. It can be crystallized as a white crystalline solid having one molecule of water of crystallization per mol of thiamine.



2-Methyl-*5-(4-methyl-5-hydroxyethyl-thiazolium chloride)* methyl-6-amino-pyrimidine hydrochloride.

1. Occurrence

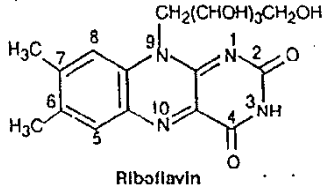
It occurs in yeast, milk, ground nut, eggs and outer seed coals of grains like rice, wheal etc.

2. Functions and deficiency diseases

It acts as a coenzyme, corarboxylase (a part of carboxylase and pyruvic acid oxidase) which functions in the **breakdown** of the **pyruvic acid** formed in carbohydrate metabolism. In **thiamine deficiency pyruvic acid accumulates in blood**, **lymph** and **body tissues** of animals. In humans, thiamine deficiency produces a disease called beri-beri. Two types of this disease are recognized (1) **dry beriberi**, which causes muscular disorders and loss of weight and (2) **wet beriberi**, which causes swelling of extremities, accumulation of fluid in body cavities, liver congestion and dilation of heart.

6.4.1.2 Vitamln B_2 (Riboflavin or lactoflavin):

It is structurally related to yellow water soluble pigments known as flavins. It was named according to source, as lactoflavin (from milk), heptoflavin (from liver) and ovoflavin (from eggs yolk). Warburg (1932) isolated it as yellow Warburg's enzyme (a respiratory pigment) from yeast. It is an orange yellow crystalline solid containing chromogenic flavin (isoalloxazine) nucleus linked to D-ribose-sugar at N-9 position. Its aqueous solution shows yellowish green fluorescence (having λ_{max}= 565 nm).



Riboflavin
(6,7-Dimethyl-9(D-ribityl)-isoalloxazine)

1. Occurrence

Milk, liver, egg yolk and germinating seeds

2. Functions and deficiency diseases

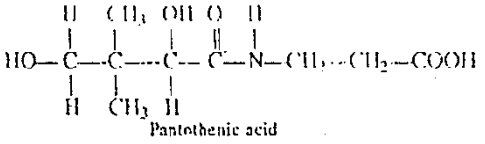
Riboflavin **acts as a coenzyme** in a series of enzymatic reactions (referred to as yellow enzymes) vital for life, such as xanthine oxidase, D- and L-amino acid oxidases, aldehyde oxidase, succinic dehydrogenase, cylochrome-C reductase etc. They catalyze the removal of hydrogen (e.g., FAD $\longrightarrow$ $FADH_2$) from metabolites and pass the hydrogen to an acceptor (e.g., cytochrome C or molecular oxygen).

Its **deficiency** in human causes ariboflavinosis or cheilosis (cracks on the lips and at the corners of the mouth), glossitis (inflammation of tongue) and eye disorders. Its deficiency is also responsible for Pellagra in humans and curled toe paralysis in chicks.

6.4.1.3 Vitamln-B3 *(*Pantothenic acid) *or* chick antidermatitis factor:

The word '**pantothenic**' is derived from Greek word that means '**everywhere**'. This factor is required for the growth of yeast and microorganisms and to cure chick dermatitis.

It is α, γ -dihydroxy- β, β-dimethyl-butyryl- β-alanine (i.e. it contains a peptide linkage which unites a β-alanine moiety and a dihydroxycaproic acid molecule). Due to one asymmetric carbon, it exists as d or (+) and l or (-) form. Only dextra form is biologically active. It is a pale yellow, oily liquid soluble in water. It is usually stored in the form of white crystalline calcium salt (i.e. calcium pantothenate)



Pantothenic acid

(α, γ-dihydroxy isocaproyl β-alanine)

1. Occurrence

It occurs in milk, honey, sweet potatoes, vegetables and in all common sources of vitamin B-complex.

2. Function and deficiency diseases

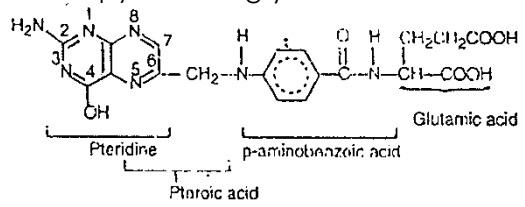
Pantothenic acid plays an important role with coenzyme A, in citric acid cycle, sterol formation, acetyl choline formation and in fatly acid metabolism.

Its **deficiency** causes **dermatitis in pigs**. Due to its wide-spread availability, its deficiency in humans is not clearly understood but is believed that its lack is responsible for bunting sensation, abdominal disorder, depression and muscular weakness.

6.4.1.4 Folic acid (B_4)

The **term** folic acid is **derived from** its wide occurrence in green leafy vegetables (Latin, folium-leaf). Folic acid is a growth factor for certain microorganisms and chick.

Several forms of this vitamin have been recognized as they contain one, three and seven molecules of glutamic acid respectively. They all consist one structure in common that is of glutamic acid, p-aminobenzoic acid (PABA) and a fused hetero-cycle pteridine (fused pyrimidine ami pyrazine rings).



Pteridine

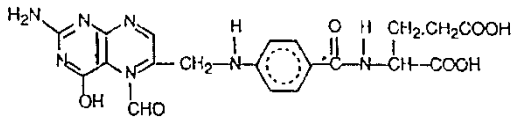
p-aminobenzoic acid

Glutamic acid

Pteroic acid

Folic acid or Pteroylglutamic acid

Its formyl derivative called folinic acid is equal or even superior in activity than other forms



Folinic acid

1. Occurrence

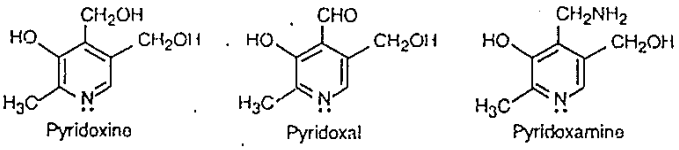
Green leafy vegetables are common sources of vitamin B-complex.

2. Functions and deficiency diseases

It supplies the carbon for the conversion of glycine to serine. Folic acid **deficiency** causes **anemia, Icucopenia** (reduction in while blood cell), **mouth lesions** and **diarrhoea**.

6.4.1.5 Pyridoxine (B_6) or Antidermatitic factor

Vitamin B_6 actually refers to a group of three vitamins, pyridoxine, pyridoxal and pyridoxamine. Structurally they are related to pyridine derivative nicotinic acid. These are all optically active, white crystalline solids.



1. Occurrence

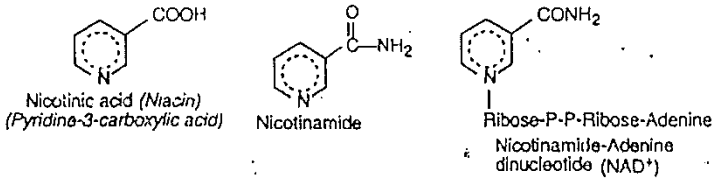
Cereal grains, milk, leafy vegetables, dried brewer's yeast and meat are chief sources of this vitamin.

2. Functions and deficiency diseases

Pyridoxal and pyridoxamine are coenzymes for decarboxylases, transaminases and pyridoxal phosphate involved in tryptophan (amino acid) synthesis in Neurosporu crassa. Pyridoxine **deficiency** causes **dermatitis** in rats. Administration of pyridoxine relieves the abdominal pain, weakness and nervousness of the patient suffering from pellagra.

6.4.1.6 Niacin (Nicotinic acid), Antipellagra factor

Niacin is a simple 3-carboxyl derivative of pyridine (nicotinic acid). Its amide, niacinamide and sodium salt arc also biologically active

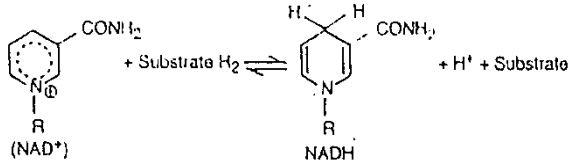


1. Occurrence

It occurs widely in plant and animal tissues like yeast, grain cereals, coffee, ground nut and meat products (liver and kidney).

2. Functions and deficiency diseases

It is a component of two important coenzymes, NAD^+ (Nicotinamide adenine dinucleotide and NADP (Nicotinamide adenine dinucleotide phosphate). These coenzymes with suitable apoenzymes, participate in hydrogen transfer reactions (e.g., NAD participates in reactions involving enzyme alcohol dehydrogenase, phosphoglyceraldehyde dehydrogenase, lactic acid dehydrogenase and malic dehydrogenase)



Its deficiency causes black tongue in dogs and pellagra in humans (hence the name pellagra preventive factor P.P.F.). The major symptoms of pellagra are stomatitis (inflammation of stomach), glossitis and skin lesions (patches on exposed skin).

6.4.1.7 Vitamin-B_{12}, Cobalamine or Anti-pernicious anemia factor:

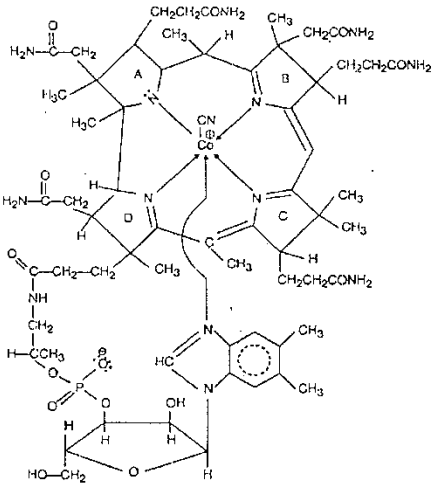
This is the first natural product containing cobalt atom centered in a porphyrin nucleus to which are attached ribose phosphate and benzimadazole. The cyanide group attached to cobalt atom can be replaced by SCN, OH, SO_4, Cl and other groups to prepare analogs of vitamin B_{12}.

1. Occurrence

It occurs as a byproduct in the production of antibiotics, in fermentation residue, dried sewage sludge and in animal tissues (liver of ox, sheep, fish, pig etc.). It is synthesized by certain microorganisms (e.g. penicillium molds, streptomyces bacteria etc.).

2. Functions and deficiency diseases

The antipenicious anemia factor functions in animals as a growth factor and is therefore, originally called animal protein factor (APF) It acts as a coenzyme in amino acid metabolism (e.g., in inter conversion of glutamate and β-methylasparate in bacteria). Its deficiency in humans causes pernicious anemia lowering of red blood cells). Injection of 1 meg daily of crystalline cyanocobalamine to a patient of pernicious anemia restores the normal level of red blood cells and alleviate the symptoms of the disease.



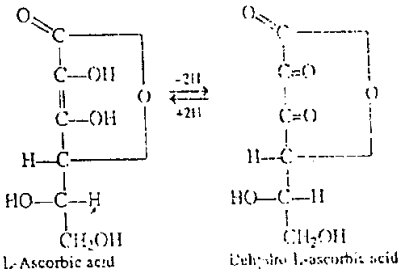
Structure of Cyanocobalamine (Vit.B_{12}).

3. Requirement

About 1 mg per day is adequate in adult humans and 5-10 mg per day is required in growing children.

6.4.2 Vitamin-C or Ascorbic acid (Antiscorburic factor)

It is structurally related to hexoses and may be considered as a derivative of L-gulose. The reduced form of L-ascorbic acid obtained on oxidation is a diketone lactone (dehydroascorbic acid). Both these forms are biologically active and form biochemical redox system involving oxidation-reduction reactions of the cell. It is a white crystalline solid acidic in taste.



L-Ascorbic acid

1. Occurrence

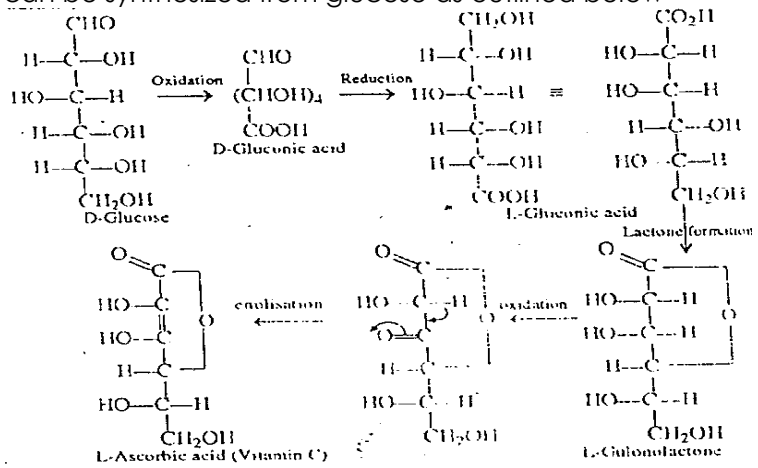
It occurs mainly in citrus fruits (like lemons and oranges), berries and melons. It is also found in green vegetables like cabbage, tomatoes, beans and potatoes.

Functions and deficiency diseases: It involves in tyrosine metabolism, controls cholesterol metabolism and helps in absorption and utilization of iron.

Deficiency of this vitamin causes a disease called scurvy (one of the oldest disease known to humans). The symptoms of scurvy in humans are weight loss, weakness, heart palpitations redness and swelling of the gums, loosening of teeth.

2. Synthesis

It can be synthesized from glucose as outlined below

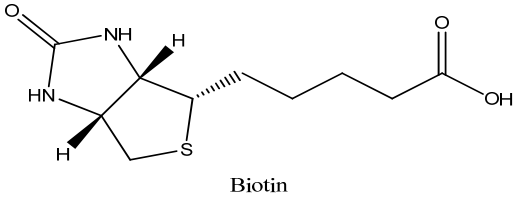


3. Requirement

For humans 75-150 mg daily, depending on physiological demand

6.5 BIOTIN (VITAMIN H) OR ANTI-EGG WHITE INJURY FACTOR

It consists of fused imidazole and thiophene rings with a fatly acid side chain. Two forms of biotin (α-, and β-) exist in nature, one obtained from egg yolk as a-biotin whereas the other obtained from liver as β-biotin. Both forms have same molecular formula and probably identical. Biotin isolated from animal liver is a while crystalline solid having following structural formula.



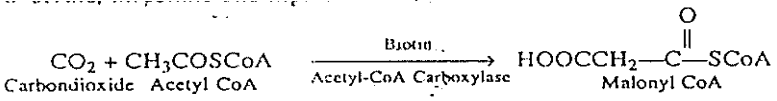
Biotin

1. Occurrence

It occurs in both animal and plant tissues. Egg yolk, liver, yeast, kidney, pancreas and milk are rich sources of biotin. Fruits and vegetables contain fair amounts of biotin.

2. Functions and deficiency diseases

It acts as a **catalyst** in addition of carbon dioxide to acetyl CoA in the formation of malonyl CoA required in fatty acid synthesis. In bacteria and yeast, biotin is needed for deamination of serine, threonine and aspartic acid.



Various names are given to this vitamin, e.g., **'coenzymes-R'** (because, it is a **growth factor** for nitrogen fixing bacteria Rhizobium),'anti-white injury factor' (because it protects animals against the toxic effect of excess raw egg white in diet).

6.6 HORMONES

A hormone is defined as a **chemical compound produced** in certain specialized cells, usually in a **ductless gland**, called **endocrine gland**, which is delivered directly to the **blood stream** in **minute amounts** and which **exerts** a **physiological effect** at **a site of action** remote from its origin. It is required in small quantities and is specific in its functions. The deficiency of a hormone leads to a particular disease which can be cured by the administration of that hormone.

The exact mechanisms by which hormones exert their effect are not known for any of the hormones. However, there is definite evidence that some hormones exert their control by acting either directly or more likely, indirectly on the DNA of the genes.

There are **eight glands** which are regarded as ductless glands in mammals. These are

Gland	**Type of Hormone Secreted**
Pituitary	Protein hormone
Thyroid	Thyroxine (amino-acid)
Parathyroid	Parathormone (Protein)
Adrenal	Adrenaline, steroid (Cortex)
Pancreas	Insulin (Protein)
Duodenal	Secretin, cholecystokinin, enterogastrone
Ovaries	Oestrogens, Progesterone
Testes	Testosterone

6.6.1 Functions of hormones

- **An integrative function**

It forms the interrelationship between hormones and the nervous system, blood circulation, the blood pressure etc.

- **A morphogenetic function**

It controls the type and rate of Growth of various tissues.

- **A regulatory function**

It maintains a constant internal environment with respect to intra-and extra-cellular fluids.

The hormones have specific actions in the body. Therefore, any deficiency in them leads to a disease which would be cured by the intake of that particular hormone only.

6.6.2 Differences between Hormones and Vitamins

- Hormones are produced in the animal body while vitamins are synthesized in the animal body.
- For hormones, animals are independent in producing in the body whereas for vitamins, the animals depend upon the plants.

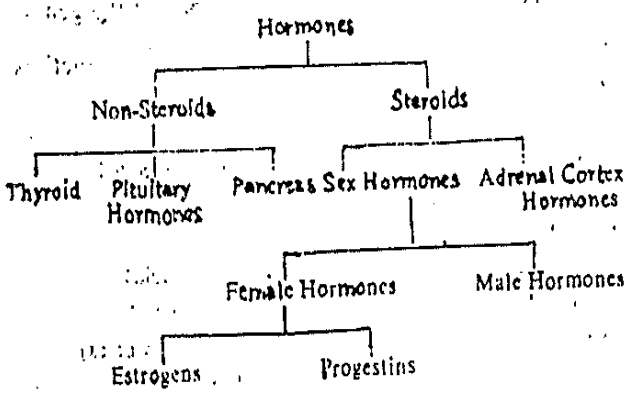
6.6.3 Classification

More than 80 hormones are known. Out of these more than 50 per cent are steroids whereas the remaining hormones ore non-steroidal in nature.

Steroid hormones have been divided into two main types

- Sex hormones (Female and male)
- Adrenal cortical hormones

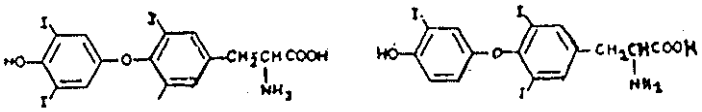
Further female sex hormones are of two types called the oestrogens-and gestogens.



6.7 THE NON-STEROID HORMONES

6.7.1 Thyroid hormones and antithyroid hormones

Thyroid glands secrete **two important hormones** called **thyroxine** (3, 5, 3', 5'-tetraiodothyronine, T_4) and **triiodothyronine** (3, 5, 3'-triiodothyropine, T_3). T_4 was first obtained in crystalline form in 1916 and was synthesized by Harington and Barger (1927). Later on the existence of the more potent hormone T_3 was established. It is probably the storage form while triiodothyronine is the circulatory form. Another view is that T_4 is more firmly bound to the globulin fraction as compared to T_3 which can enter the tissue of cells.



thyroxine (T_4) 3,5,3'-triiodothyronine (T_3)

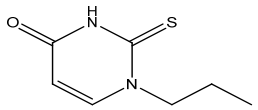
Thyroid hormones **control** the rate of **oxygen consumption** and **metabolism of carbohydrates**, **lipids** and **proteins**. They also exert specific actions on growth and metamorphic and embryonic developments. They lower the cholesterol level in serum, and increase coenzyme and vitamin requirements; they also facilitate maturation of central nervous system.

The **deficiency** of thyroid hormones may cause **disturbances in metabolism** of carbohydrates, lipids, proteins, electrolytes, etc. and also juvenile myxedema in childhood. The overproduction of thyroxine causes the rapid heart and nervous irritability.

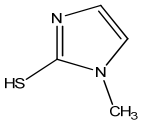
6.7.1.1 Anti-thyroid drugs

Sometimes **thyroid glands** become **overactive** and produce excess of thyroid glands, giving rise to a condition known as **hyperthryoidism** (or thyroiditis). This results in the enlargement of the thyroid gland, prolusion of the eyeballs; rapid heartbeats or pulse, tremors and nervousness. The **drugs** used in the treatment of these conditions are known as **anti-thyroid drug**.

Thiourea and related compounds exhibit anti-thyroid activity. However, these are too toxic for clinical use. The more useful drugs have been found to be derivatives of 2-thiouracil and 2-thioimidazole. Propylthiouracil (6-propyl-2-thiouracil) and methimazole (1-methylimidazole-2-thiol) are known to be important anti-thyroid drugs.



Propylthiouracil



Methimazole

Methimazole has been found to be more potent than propylthiouracil. These drugs have no action on thyroid hormone already stored in the gland and hence there occurs a delay in the appearance of their effects.

Sulphonamides, p-aminosalicylic acid and resorcinol are also known to exert varying degree of thyroid inhibition.

6.8 ADRENAL CORTEX HORMONE

The **adrenal glands** of mammals are **located near** each **kidney** and **consist of** two distinct parts: the **medulla** and the **cortex**. The **medulla** produces and stores catecholamines, i.e., **(—)-adrenaline** while the **cortex synthesizes** a **number of steroid hormones**. The production of these adrenocortical hormones or corticoids has been controlled by the hormone ACTH (adrenocorticotrophic hormone) which is produced in the anterior lobe of the pituitary.

6.8.1 Biological action

The corticoids have many physiological functions but their main functions are:

- Control of carbohydrate and protein metabolism
- Control of balance of water and electrolytes

A lack of the corticoid hormones leads to multiple symptoms, e.g., muscular weakness, changes in carbohydrate and protein metabolism, disturbances of electrolyte balance, etc., and eventually death.

The steroid hormones probably exert their effect by increasing cellular RNA (ribonucleic acid) synthesis, thus inducing the synthesis of specific tissue enzymes.

However two most important steroid hormones secreted by the adrenal cortex are:

6.8.2 Aldosterone

It is the **mineralocorticoid** which was first isolated in a crystalline form by Mason et al in1953.They got only 45 mg of this hormone from 939 kg of the gland.

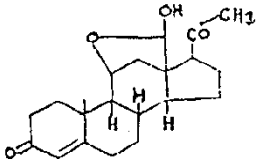
As soon as it was isolated, it was **named** as **electrocortin** but this name was later on **changed to aldosterone** because of its **aldehydic** and **ketonic** groups.

Aldosessterone forms colourless crystals; m.p. 112°C. It recrystallizes to melt at 164°C. Aldosterone in solution exists as an equilibrium mixture of the I8-aldehyde and 11, 18-hemiacetal forms. Synthetic dl-aldosterone consists of aldosterone and 17-isoaldosterone; the latter is devoid of biological action. Aldosteron 21-acctate melts at 198°C ; $[x]_D$== + 123° (alcohol).

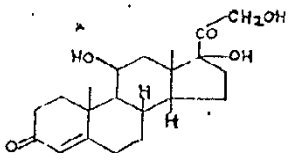
Aldosterone plays an important role in the electrolyte metabolism by promoting the retention of sodium and the excretion of potassium. A deficiency of this hormone leads to diseases such as hyperkalemia, dehydration, hypotension and sometimes circulatory in efficiency.

6.8.3 Hydrocortisone

It is the primary glucocorticoid in human beings which has an effect on intermediate metabolism, hyponatremia. It is used in inflamed condition of the skin, eye and ears and very often used along with an antibiotic. It is also **used for** arthritis and bursitis, in addisonian crisis and in hay fever.



aldosterone



hydrocortisone

6.9 SEX HORMONES

These are of two types, **male and female sex hormones**. Though **testosterone** is known as the **male hormone** while **estrogens** and **progesterone** as **female sex hormones**. However, all these harm ones are synthesized in both males and females; testosterone is produced in larger quantities in the males while estrogens and progesterone in females. In general, these hormones play vital role in reproduction in the menstrual cycle and give man and women their characteristic male and female characteristics.

6.9.1 Male Sex Hormones

Testosterone and dihydrotestosterone are two important male sex hormones.

6.9.1.1 Testosterone

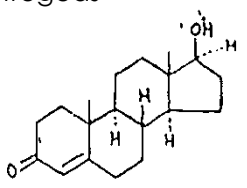
There are at least **5 steroidal hormones** which exhibit a typical androgenic activity. All are derivatives of androstane. However, the most potent so far is testosterone. Of the other compounds which approach the activity of testosterone, androsterone is the most potent, having approximately 1/7 th of the activity of testosterone.

It melts at 155°C. It is optically active; $[a]_D$=+109°. Its λ_{max} is 240 nm.

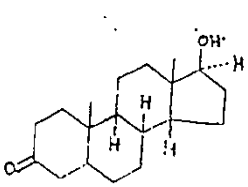
Testosterone appears to be the real male sex hormone; others are metabolic products of it.

6.9.1.2 Functions of testosterone

- Stimulates the development of the secondary male sex characteristics.
- Assists in bringing about the descent of the testis in cryptorchidism.
- Inhibits the secretion of the anterior pituitary gonadotropins (Moore, 1935).
- Testosterone and its derivatives have been found useful in the treatment of advanced metastatic carcinoma of the breast
- Occasionally, testosterone may produce jaundice.
- Testosterone is used in the treatment of the menopausal syndrome, combined with estrogeds



testosterone



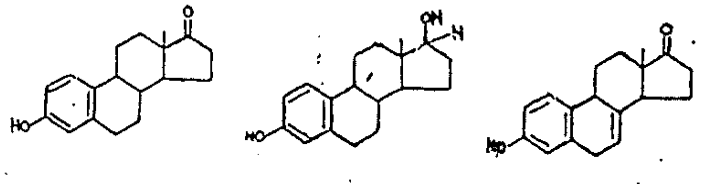
5α-dihydrotestosterone

6.9.2 Female Sex Hormones

Estrogens and progesterone are female sex hormones which, are secreted under the influence of pituitary gland, mostly by the ovaries.

6.9.2.1 Estrogen

The naturally occurring estrogens include 17- β-estradiol, estriol, equilin and equilinin

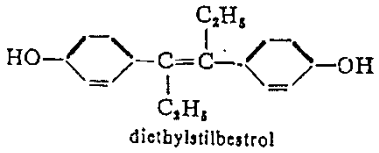


1. Function of estrogen

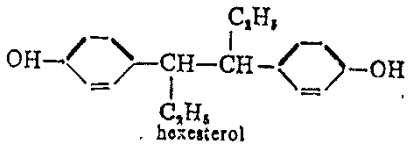
- Estrogen is known to induce an estrus cycle (a period of reproductive activity) in the female species of an animal.
- Stimulate the development of secondary sex characteristics in females.
- They directly stimulate the growth and development of vagina, uterus and fallopian tube. Pigmentation of the nipples and genital tissues and stimulation of the growth of pubic and under arm hair is also due to estrogens.
- Induce almost full and complete mammary development.
- They are also useful in the prevention of abortion and uterus bleeding.
- Due to the deficiency of this hormone, the skin loses some of its suppleness and heart and gout become health problems.

6.9.2.2 Diethylstilbestrol and hexesterol

A number of synthetic compounds having estrogenic activity but do not have steroid structure have been synthesized. Two of these are diethylstilbestrol and hexesterol.



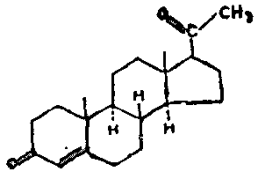
diethylstilbestrol



hexesterol

6.9.2.3 Progesterone

It is another important female hormone. Progesterone, is found to prepare the uterus by thickening its lining (a process called endometrium) so that it can readily receive the fertilized ovum.



progesterone

Estrogens or progestins or better a combination of the two are useful as oral contraceptives

6.10 ANTIBIOTICS

The term antibiotic has been **derived from** the word "**antibiosis**" which according to the biology concept means **survival of fittest** i.e., a process in which one organism may destroy another to preserve itself. The term "antibiotic" was first of all introduced by Vuillemin in 1889. The term antibiotic was first defined by Waksman (1944) and which was later on modified a little by Benedict and Langlykke (1947).

However, the **modern definition** of antibiotic is

"It is a chemical substance produced by or derived from living cells which is capable, in small concentrations, of inhibiting the life processes or even destroying the micro-organisms."

As very low concentrations of antibiotics are essential to bring about their antibiotic action, they are also **classified as chemotherapeutic agents**. Further, the **action of antibiotic** is **very specific**, i.e., a given antibiotic has been found to be effective against certain types of micro-organisms only.

All chemical substances produced by or derived from living cells cannot be antibiotics. However, they **have to satisfy certain conditions** which are summarized as follows

- Originally antibiotic must have been a product of metabolism although it might have been synthesized.
- If the antibiotic is a synthetic product, then it should be a structural analogue of naturally occurring antibiotic.
- The antibiotic must be effective at low concentrations.
- The antibiotic must antagonize the growth and/or survival of one/or more species of the micro-organisms.

In order for a **particular antibiotic to act as therapeutic agent**, it has **to satisfy following conditions**

- It must be effective against a pathogen
- It must not cause significant toxic side-effects
- Its stability must be appreciably high so that it can be isolated, and processed into suitable forms of dosages which are readily absorbed.
- It could be stored for a long time period without appreciable loss of its activity.
- The rate of detoxification and elimination from the body must be such that there exists sufficient time interval between two successive dosages and during that period a proper concentration level has to be maintained.
- The antibiotic should be completely eliminated from the system soon after its administration has been stopped.

6.11 CLASSIFICATION OF ANTIBIOTICS

The antibiotics have been classified in a number of different ways

6.11.1 First Classification

The broad based classification of antibiotics divides them into the following two types:

6.11.1.1 Broad spectrum antibiotics

These include such antibiotics which may be used **as curative agents** against several ailments. There is a considerable overlapping amongst them but each is usually superior to others against some specific disease. Examples of broad spectrum antibiotics are penicillin, chloramphenicol, tetracyclines etc.

6.11.1.2 Narrow spectrum antibiotics

These include such antibiotics which are **highly specific in their action**. Examples are bacitracin, nystatin etc.

6.11.2 Second Classification

Another classification of antibiotics is available which **depends upon** the **type of bacteria** (Gram positive or Gram-negative) the antibiotic can destroy. This classification was originally worked out by Christian Gram and is called Gram-staining method.

In the Gram-staining method, the fixed bacterial smear is made to treat with a solution of crystal violet (a dye) followed by the treatment with iodine solution. The smear is then washed with alcohol. The bacteria which retain the colour of the crystal violet and appear deep violet in colour are known as Gram positive bacteria. On the other hand, bacteria which lose the violet colour and get counter stained by safranin and appear red in colour are called Gram-negative bacteria.

6.11.3 Third Classification

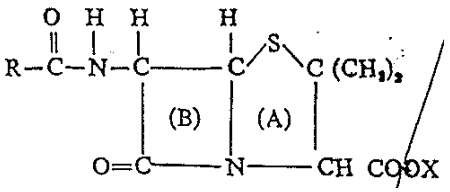
This classification of antibiotics is **based on their chemical structures**. Although there exists great variation in their chemistries, yet there are certain similarities in their structures and it has been suggested that such antibiotics are produced due to similar mechanisms in different organisms and exert their therapeutic actions also in a similar manner. The different classes are:

- **Penicillins:** These are derived from amino acids, e.g. penicillins, cephalosporins

- **Aminoglycosides:** These contain a sugar molecule in form of D-ribose or D-glucosamine) glycosidically linked to an amino compound. Examples are streptomycin, neomycin C
- **Chloramphenicol** and synthetic analogues.
- **Tetracyclines:** These have four six-member fused ring systems. Examples are tetracycline (achromycin), aureomycin, terramycin
- **Macrolides:** These contain a large lactone ring. Examples are erythromycin, oleandomycin
- **Ancomyctns:** These are sulphur containing antibiotics in which sulphur atom is not present in a ring. Examples are lincomycin, clindamycin
- **Polypeptides:** These are having a polypeptide chain. These include some of the most powerful bactericidal antibiotics. Examples are bacitracin, tyrothyricin
- **Polyenes:** These have a conjugated polyene system, e.g., mystatin, amphotericin,
- **Antitubercular antibiotics:** These include such antibiotics which have antitubercular action. Examples are cycloserine, Viomyein sulphate
- **Antineoplastic antibiotics:** These include such antibiotics which are used for control of cancer. Examples are dactinomycin, mitomycin
- **Unclassified antibiotics:** These include a number of antibiotics which are not related to any one of the classes described above. Some of these are highly specific against particular microorganisms. Examples of these are griseofulvin (fulvicin), vancomycin hydrochloride (vancocin)

6.12 PENICILLINS

Penicillin is the name given to the mixture of natural compounds which have molecular formula $C_9H_{11}N_2O_4SR$ and differ only in the nature of R. The general structure of penicillins is



The **thiazolidine ring nucleus** (A) is **fused to β-lactam ring**(B) which is **attached to** a **side chain** (R-CO-). Any chemical modification of β-lactam or thiazolidine rings destroys the anti-bacterial activity of the molecule, e.g., penicillinase breaks the β-lactam ring.

In the above structure of penicillin, X is sodium, potassium, aluminium, procaine, benzathine or free acid.

6.12.1Properties of Penicillin

- The purified penicillin are white or slightly yellowish white crystalline powders, some of which have unpleasant tastes
- All the natural penicillin are dextro-rotatory.
- The penicillin are only sparingly soluble in water. However, their sodium and potassium salts are soluble in water. Some of these salts are hygroscopic and hence they have to be stored in sealed containers.
- It is soluble in most organic solvents
- It is fairly strong monocarboxyl acids with a pH valve of 2.8.
- It is in the form of free acid has not been obtained crystalline and they undergo rapid decomposition in the presence of moisture.
- It undergoes hydrolysis readily and the nature of the product formed depends on the nature of the hydrolyzing agent. For example, If the hydrolysis of penicillin is carried out in alkaline medium, it yields penicilloic acid which loses carbon dioxide to form penilloic acid.

If the **hydrolysis of penicillin** is carried out in **acidic medium**, the **amide side chain** is involved with the **opening of** the **β -lactam ring**. This causes loss of its activity. Due to this reason, **natural penicillins** are **not very effective** when **given orally**. However, this defect has

been partially overcome by introducing an electron-attracting group, particularly in the alpha position in the amide side-chain as in penicillin (V) which is more acid resisting. Further, the stomach juices contain the enzymes penicillinases. These enzymes also cause hydrolysis of penicillin as resulting in the opening of the lactam ring followed by the loss of activity. When these enzymes are present insignificant amounts, a resistance to penicillin is produced.

6.12.2 Activity of Penicillin

Penicillins are found to be active against Gram positive stains. However, these are ineffective against Gram negative organisms. Organisms sometimes develop resistance to penicillin.

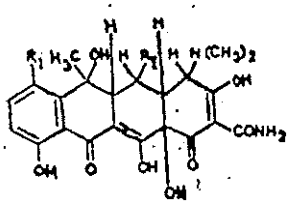
6.12.3 Toxicity (Side-reactions)

Penicillins generally have **low toxicity** in comparison to the sulpha drugs used earlier. However in some cases diarrhea and allergic reactions may result in. Penicillin is hence injected after a test prick is given.

6.13 TETRACYCLINE

In **1947** in study of thousands of **microscopic fungi** among the **actinomycete**s, **Duggar** discovered a soil organism for which the name **streptomyces aureofaciens** was proposed. When grown in culture broth a golden yellow antibiotic was elaborated that was **named Aureomycin**. In **1950 Finlay** and his associates **isolated** a new **actinomycete, Streptomyces rimosus**, from a soil sample that produced in antibiotic named **terramycin**. In **1952**, the **unique chemical structures** of these **two antibiotics** were determined and a third compound was prepared that possessed antibacterial properties. As a class, these antibiotics are called the tetracyclines, and one member of this class is named tetracycline. Many derivatives of the tetracyclines have been made synthetically.

The tetracycline antibiotics contain hydronaphthacene skeleton as a characteristic structural unit. The structures of the tetracycline antibiotics are given as follows.



Chlortetracycline $R_1 = Cl; R_2 = H$

Oxytetracycline $R_1 = H; R_2 = OH$

Tetracycline $R_1 = R_2 = H;$

All of the tetracyclines used as antibiotics in man have various substituent groups on carbon atoms 4, 5, 6 or 7.

Aureomycin was isolated from cultures of Streptomyces aureofaciens. Terramycin was isolated from cultures of Streptomyces rimosus. **Tetracycline** is prepared by dechlorinating chlortetracycline by catalytic dehydrogenation with palladium. It can also be made by fermentation. The stereochemistry of aureomycin had been partly established from the chemical work but it was completely determined by the X-ray analysis of its hydrochloride. Shemyakin et al. have established the absolute configuration of the tetracyclines by means of optical rotatory dispersion studies.

6.13.1 Oxytetracycline (terramycin)

This was the first member of the tetracycline group of antibiotics whose constitution established (Woodward et al. 1953).

Oxytertracycline is a **yellow, odourless, crystalline amphoteric substance**. One gram of this dissolves in about 2000 ml of water. One gram of hydrochloride is soluble in 2 ml of water. Solutions of the base and hydrochloride are not stable at pH below 2 and are rapidly destroyed by alkali hydroxide solutions.

6.13.2 Clinical Property

The tetracyclines are **active against** the **majority of gram positive organisms**, some gram negative bacteria, spirochaetes, rickettsial infections (such as typhus sad Q fever). Mycoplasma and against the lymphogranulomaprittacosis group of virus infections. By and large, they have no action against the viruses.

The tetracyclines are **drugs of choice** for treating **brucellosis, whooping coughs, typhus, Q fever, psifttacosis** and **lymphogranuloma venereum**. The tetracyclines are also

useful for treating **respiratory tract bacterial infections** and particularly exacerbations of **chronic bronchitis**. For **urinary tract infections**, tetracyclines are moderately useful but the organisms acquire resistance rapidly.

The tetracycline antibiotics are poorly absorbed from intramuscular injection sites. Chlortetracycline is not absorbed after intramuscular injection and it is not administered by this route.

6.14 ANTITUBERCULAR DRUGS

Tuberculosis is as old as mankind. It is a systemic infectious disease which is caused in man by organisms such as **Mycobacterium tuberculosis** and **Mycobacterium bovis**. About 1-2 million peoples die every year due to this disease.

Tubercle bacilli have been found **to affect any organ** or **tissue** in the body but the **most common** is tuberculosis of the **lungs**. The disease may vary in intensity from the "**latent tuberculosis**" which does not show any change over a prolonged period of time, but is incompletely healed and potentially active, to the acute generalized tuberculosis, in which the bacteria are widely distributed in large numbers throughout the body and which without treatment is rapidly fatal.

According to R.H. Ebert (1955), an **Ideal Chemotherapeutic agent** in **Tuberculosis** should have the following properties.

- It must be bactericidal or bacteriostatic in relatively low concentrations. It must always be able to accomplish this without the development of bacterial resistance.
- It must be highly diffusible and be able to reach all tissues including the meninges and brain. It should be able to penetrate vascular necrotic in sufficiently high concentrations to have an effect on the tubercle bacillus.
- As tubercle bacilli may survive and multiply within mononuclear cells, it must be able to penetrate the cell membrane.
- Mere availability of the drug is not enough, however, because it must be effective in a variety of biochemical environments, especially that which prevails within the caseous or nerotic lesion.
- It must also be effective against organisms which exist in a variety of metabolic states ranging from organisms actively dividing to those which appear dormant.
- It must be relatively non-toxic in therapeutic doses and toxicity must remain low even when the drug is given for protracted period.
- Finally, it must be relatively stable for reasonable lengths of time and not excerted too rapidly or altered so quietly by the host that it is impossible to obtain therapeutic levels.

No drug, so far known, satisfies the above requisites completely.

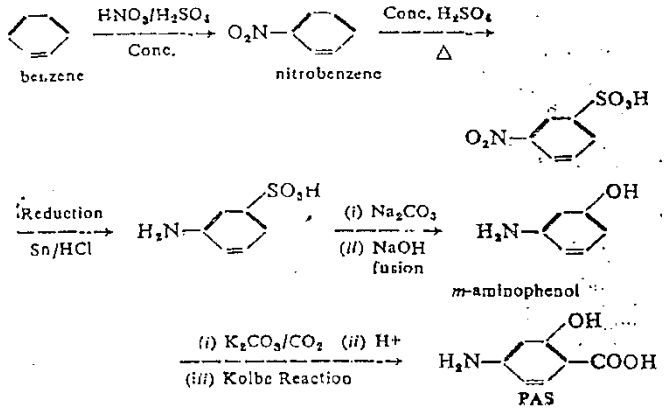
The different chemotherapeutic agents used for the treatment of tuberculosis are as follows:

6.14.1 p-Aminosalicylic acid (PAS)

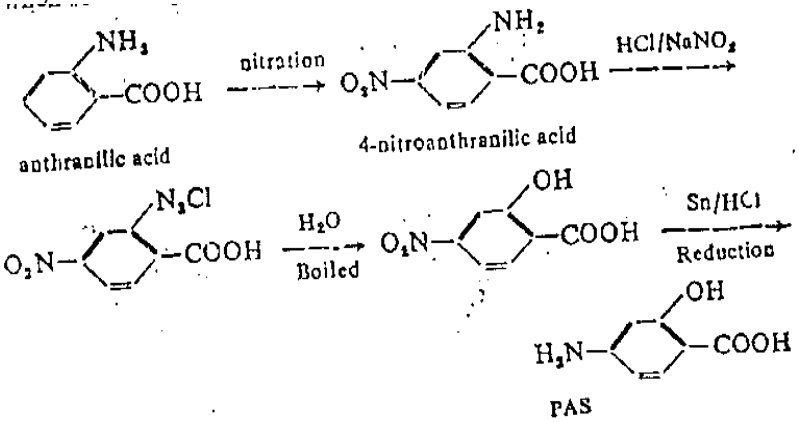
This compound was first proposed by **Lehmann in 1964** for the treatment of tuberculosis. After this it was widely used **both alone** and **with antibiotics** in the treatment of disease. Many attempts were made to modify this compound but all these attempts proved futile because the majority of new compounds are inactive. Therefore, this compound is still very important in the treatment of tuberculosis.

6.14.1.1 Manufacture

When benzene is nitrated, it gives nitrobenzene. The latter compound on sulfonation gives m-nitrobenzenesulphonic acid. The sodium salt of this sulphonic acid when fused with caustic soda yields m-aminophenol. This compound when treated with potassium carbonate, followed by treatment with CO_2 (Kolbe reaction) under pressure and between 120—140°C, followed by careful acidification yields p-aminosalicylic acid.



In another synthesis, anthranilic acid is first nitrated to give a 4-nitro-derivative. This compound is diazotized and boiled with water when -NH_2 group is replaced by -OH group to form 4-nitrosalicylic acid (2-hydroxy-4-nitrobenzoic acid). This acid when reduced gives p-aminosalicylic acid.



6.14.1.2Properties

It is bacteriostatic and stops the growth of actively multiplying tubercular bacilli both in vivo and vitro. It is readily absorbed on oral administration. A solution of sodium salt is being used for intravenous infusion. Treatment has to be continued for 3 to 6 months.

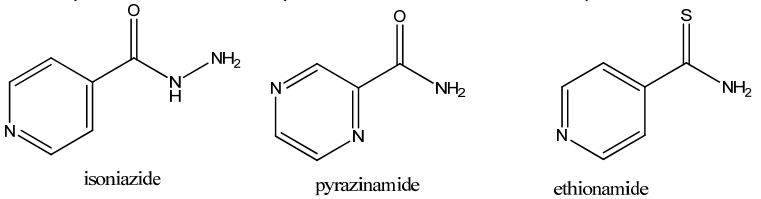
The main use of PAS is that it delays development of resistance to tuberculotic drugs. The probable mechanism of the action of this drug is that it interferes with the utilization of p-amino-benzoic acid (vitamin of B group) by tubercular bacilli.

The toxic effects of PAS is that it tends to cause gastrointestinal disturbances with occasional skin rashes.

6.14.2 Isoniazide (Rimifon)

The antitubercular effect of iso-niazide was **discovered accidentally** during the routine screening of chemical intermediates in the synthesis of thiosemicarbazones. It inhibits the growth of tubercle bacillus in vitro in concentrations less than 1µg/ml. It can be given orally and is absorbed rapidly from gastrointestinal tracts. It presumably acts both as bacteriostatic and bactericide by interference with essential enzyme metabolism. It should always be included in the therapy of the more dangerous forms of tuberculosis such as miliary, meningeal and acute extensive pneumonic pulmonary tuberclosis. Its side effects are headaches, vertigo and peripheral neuropathy. Sometimes depression in bone marrow and damage to liver have also been observed.

Resistance to isoniazide develops fairly rapidly and hence it is usually given along with p-aminosalicylic acid to delay the unwanted development.



6.14.3 Pyrazinamide

It is a secondary drug which is used only when PAS and isoniazide fail. It has to be administered under strict medical supervision.

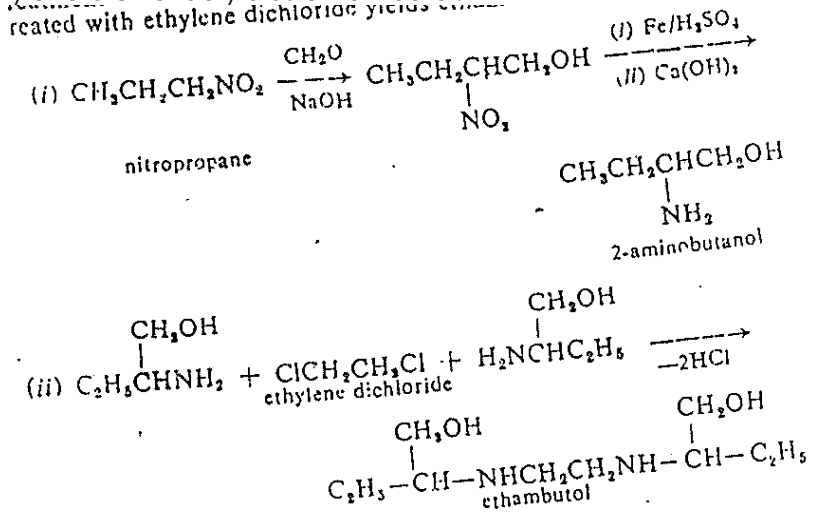
6.14.4 Ethionamide

It is also a secondary drug which is especially useful for the treatment of pulmonary tuberculosis.

6.14.5 Ethambutol

It is prepared as follows:

When nitropropane is treated with formaldehyde in the presence of sodium hydroxide, 2-nitrobutanol is formed. This compound when reduced with iron and sulphuric acid, followed by treatment with $Ca(OH)_2$ forms 2-aminobutanol. This alcohol when treated with ethylene dichloride yields ethambutol.



It is usually used as dihydrochloride and given orally, it is generally given along with ether antitubercular drug for the treatment of pulmonary tuberculosis.

6.14.6 Cycloserine

(+)-Cycloserine is **prepared** from (+)-serine. The latter compound is first converted into its methyl ester by Fischer esterification method. The ester when treated with ethyl iminobenzoate, $C_6H_5C(=NH)OC_2H_5$, forms 2-phenyl-4-carbomethoxy-2-oxazoline. This compound on treatment with hydroxylamine in the presence of ethanol, followed by acidification yields 2-phenyl-4-carbohydroxamide-2-oxazole. The treatment of this compound with HCl in dry dioxane gives a-benzamido-β-chloropropiohydroxamic acid which on treatment with 1N alkali undergoes cyclization to form benzamido-3-isoxazolidone. This compound when treated with concentrated solution of methanol saturated with hydrogen chloride gives β-aminoxylalnnine methyl ester dihydrochloride which when treated with potassium hydroxide yields (+) - 4-amino-3-isoxazolidone, i.e., (+)-cycloserine

6.14.7 Viomycin

It is another antibiotic which is used in the treatment of tuberculosis. However it causes renal and ordinary damages and hence not used.

6.14.8 Rifamipin (Rifadin)

It is a semi-synthetic antibiotic which is obtained from rifamiacins which represent a group of chemically related antibiotics obtained from **streptomyces mediterrani**. It has been found to be highly effective against mycobacterium tuberculosis and is of great value in patients with drug resistance infection. It is generally used alone and hardly any side effects have been reported.

6.15 ANTIFUNGAL AGENTS

Previously fungal infection was regarded as an uncommon disease. Now in recent years fungal infections are worldwide in nature and are systemic as well as local among individuals of all ages. Many remedies have been used against fungus infections, and research still continues which would lead one to conclude that the ideal topical anti-fungal

agent has not yet been found. However, now practically the whole spectrum of fungus diseases can be successful treated

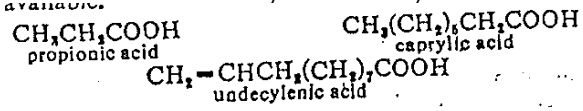
The **antifungal agents** used now-a-days have been **divided into** the following **two groups**:

- Those used for local infections
- Those used for systemic infections

Each group in turn is divided in those, obtained chemical synthesis and antibiotics.

6.15.1 Acids and their Salts

Previously it was postulated that it was the **pH of perspiration** which was responsible for its **fungicidal** and **fungistatic effect**. However, Peck in 1939 showed that the **presence** of **fatty acids** and **their salts** was responsible for this property of perspiration. Chemical analysis of sweat reveals that it possesses about 0.0081 per cent of propionic acid. Later on, it was found that the propionic acid and its sodium, ammonium, calcium, zinc, and potassium salts are active fungicides. Further the salts have been found to be active as the free acid. Other acids like caprylic and undecylenic acids also exhibit similar fungicidal propertics. Many other fatty acids are known which also possess antifungal properties. However, the above acids are used because they are readily available.



Of these undecylenic acid is best fatty acid which is used as topical fungicidal agent.

Benzoic acid and **salicylic acid** have also antifungal properties. Salicylic acid is a comparatively mild antifungal agent but possesses kerotolytic properties.

6.15.2 Other topical agents

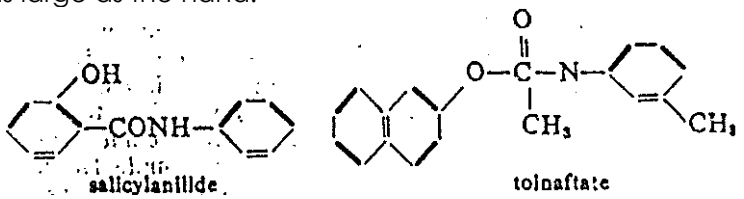
These are as follows

1. Salicylanilide (Salinidol)

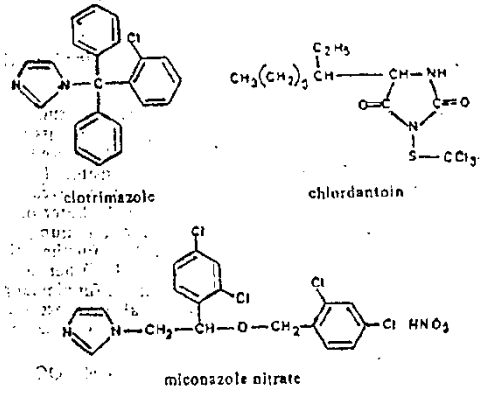
It is the anilide of salicylic acid. It is an antifungal agent useful in the treatment of tinea capitis. Due to its irritant action on the skin, the concentration used should be 5 per cent or less.

2. Tolnaftate

This compound, which is essentially an ester of β-naphthol; is a potent antifungal agent. Only one or two drops of 1percent solution in a polyethylene glycol is adequate for areas as large as the hand.



Some other topical fungicidal agents such as **chlordantoin** (Sporostacin), **clotrimazole** (Lobrim and BAYL 5097) and **miconazole nitrate** (Monistat) are also known.



Chlordaotoin has been found to be a non-staining fungicide which does not cause skin irritation or sensitization. Clotrimazol has been found to be effective against tinea infection and for candidiasis.

Many polyene antibiotics having a conjugated system of double bonds show similar antifungal activity. They are macrocyclic lactones but are different from the macrolide antibiotics of the erythromycin type having a larger lactone ring in which conjugated polyene system is present.

Three important macrocyclic antibiotics which are used as antifungal agents are **Nystain** (Mycostanin), **Amphotericin B** (Fungizone) and **Candicidin** (Candeptin)

6.16 ANTI – INFLAMMATORY DRUGS

Inflammation may be defined as **series of changes** that take place in the **living tissues following injury**. This injury may be **caused by** variety of conditions like physical agents the mechanical, trauma, ultraviolet or ionizing radiation, chemical agents like organic or inorganic compounds, the toxins of various bacteria, intracellular replication of viruses, hyper-sensitivity reactions like reaction due lo sensitized bacteria etc. Inflammation however is a normal, essential, protective response to any noxious stimulus that may threaten the host and may vary from localized reaction to a complex response involving the whole organism.

Rheumatic diseases are considered to be the most important inflammatory conditions that affect more people and cause more crippling than any other chronic illness. Rheumatic diseases can be classified as **connective tissue diseases**. They belong to complex group of auto immune condition. They include rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, rheumatic fever, psoriasis etc.

These have been chronic, disabling inflammatory conditions which may affect single or multiple organ systems of the body.

Anti-inflammatory drugs are said **to modify the inflammatory response** to diseases but are **not curative** and **do no remove** the **underlying cause** of the **diseases**. An ideal anti-inflammatory drug should affect only aberrant, uncontrolled inflammation and not interfere with the normal inflammatory response, which forms a part of the body's vital defense mechanism.

Earlier, **steroids**, namely, prednisolone, dexamethasone, betamethasone and hydrocortisone were regarded to be the drug of choice as anti-inflammatory drugs. But due to their **several adverse effects**, they have been more or less replaced by much safer and better tolerated non-steroidal anti-Inflammatory drugs (NSAID).

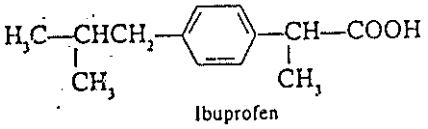
On the basis of their basic chemical structure **anti-inflammatory drugs** could be **classified** into following classes:

- Salicylic acid derivatives
- N-aryl anthranilic acid derivatives
- Aryl acetic acid derivatives
- Aryl propionic acid derivatives.
- Naphthalene acetic acid derivatives
- Gold Compounds
- Pyrazolones and pyrazolodiones
- Miscellaneous anti-inflammatory drugs

Among the anti-inflammatory drugs aryl acetic acid derivatives, N-aryl anthranilic acid derivatives and naphthalene acetic acid derivatives are important. They are described as follows:

6.16.1 Aryl acetic-acid derivatives

A few potent drugs belonging to this class of compounds include ibuprofen, ibufenac and diclofenac sodium.



Ibuprofen

[2- (p-isobutylphenyl) propionic acid]

Ibuprofen

It is also known as brufen.

It is an **anti-inflammatory drug** which is having **antipyretic** as well as **analgesic properties**. It is indicated for the treatment of rheumatoid arthritis and osteoarthritis. It has been also recommended to arrest acute flares and in the long term management of these diseases.

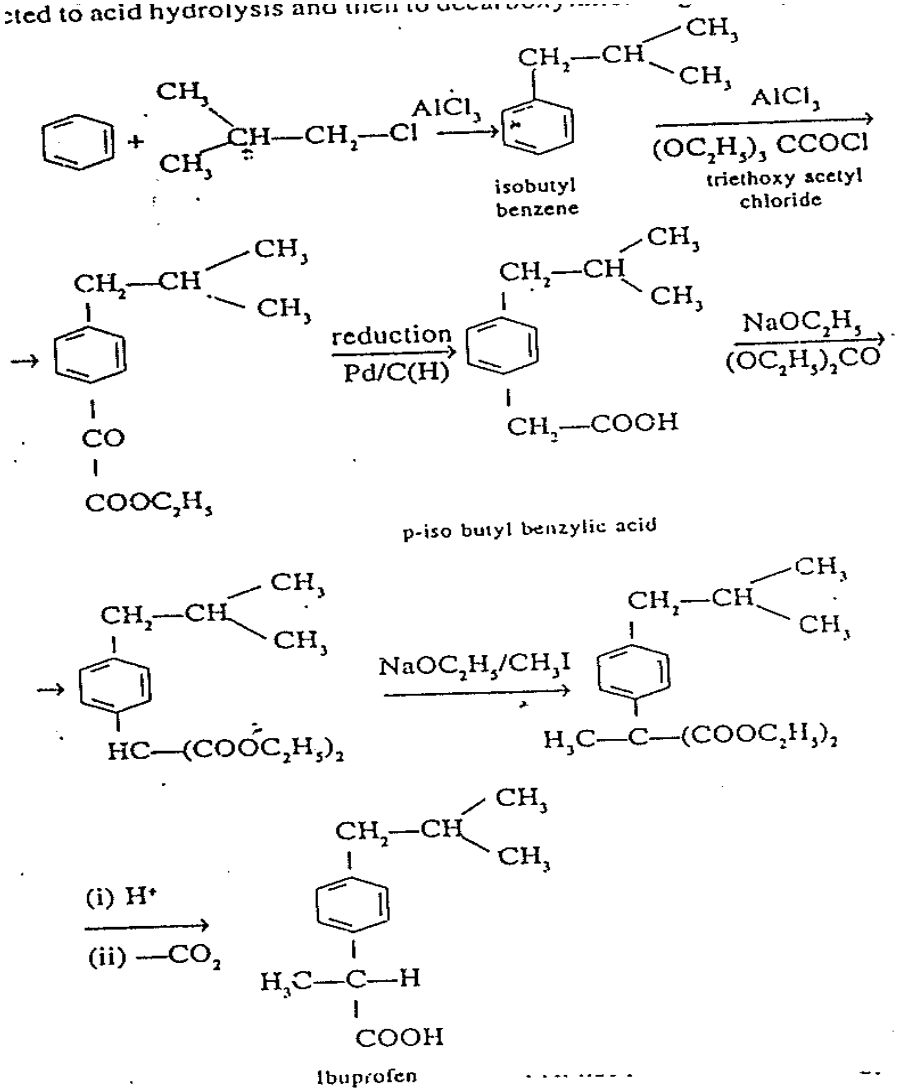
Manufacture

Benzene on treatment with isobutyl chloride in presence of anhydrous aluminum chloride or aluminum shavings gives isobutyl benzene, which is further trented with triethoxy acetyl chloride. Product obtained is reduced to give p-isobutyl benylic acid. It is treated with sodium ethoxide. Sodium derivative obtained is heated with diethyl carbonate. Product is again converted into sodium derivative with sodium ethoxide and then treated with methyl iodide. Methyl derivative thus formed is subjected to acid hydrolysis and then to decarboxylation to give Ibuprofen.

It is used as an analgesic, anti-inflammatory drug.

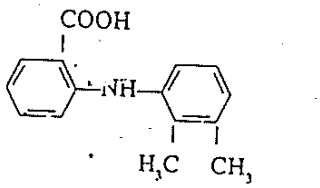
Dose

For analgesia (dysmenorrhea) 200-400 mgs, 4-6 times per day— orally. For rheumatic arthritis and osteoarthritis 300-400 mgs, 3-4 times per day orally.



6.16.2 N-aryl anthranilic acid derivatives

The structural analogues of N-aryl anthranilic acid is having analgesic, anti-pyretic and anti-inflammatory properties. The few potent drugs belonging to this class of compounds include mefenamic acid, flufenamic acid and meclofenamic acid.



Mefenamic acid

N-(2, 3- Xylyl) anthranilic acid

It is having analgesic, antipyretic and anti-inflammatory properties; it is normally used in the treatment of rheumatic or mauculoskeletal disorders, rheumatoid arthritis, dysmenorrhea and acute gout. Its sodium salt finds use as an analgesic for many varieties of painful conditions.

Dose

For rheumatic arthritis—250 to 375 mg as initial dose 2 times per day. In acute gout, 750 mg as loading dose followed by 250 mg 3 times a day until relieved.

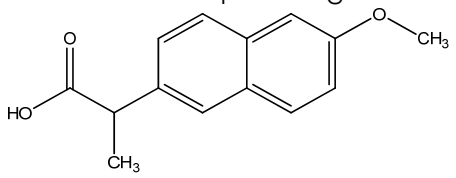
It has been a potent analgesic and an anti-inflammatory agent. It has been 5 times more effective than codeine and 3 times more effective than aspirin in relieving chronic pain. It is usually indicated for the relief of mild to moderate pain especially that following dental extraction. It also finds use in the treatment of primary dysmenorrhea. 500 mg followed by 250 mg 4 times daily —orally. (It must not be used for more than 7—days).

Side effects

Side effects are diarrhea, nausea, gastrointestinal ulceration, headache and drowsiness.

6.16.3 Naphthalene acetic acid derivatives

Naphthalene acetic acid compounds are considered to be the leading compounds of an extensive series of promising clinical agents, for example, Naproxen.



Naproxen

N.B.: Topics in the given study material may be in brief. Some prior introduction and more details may not be covered so, for detail study of Unit 5 and Unit 6 pls. refer following book: **Synthetic drugs by Gurdeep R. Chatwal.**

5.10 EXERCISE

1.	Define term hormones. Write down different functions of hormones.	04
2.	Give classification of vitamins and discuss occurrence, properties and deficiency diseases of vitamin A and vitamin B_{12}	05
3.	Write a notes on 1. adrenal cortex hormones 2. vitamin B_{12}	04
4.	Notes on Anti-fungal agent	03
5.	Write synthesis of vitamin C with medicinal uses	03
6.	Write a notes on 1. sex hormones 2. ibuprofen 3. ethambutol 4. classification of antibiotics 5. anti – inflammatory drugs	Each carry 3 marks

6. anti- tubercular drugs
7. analgin

7. Define the term antibiotics. State the condition that an antibiotic has to satisfy to act as an therapeutic agents 05
8. Give the classification of hormones and discuss the sex hormones 04
9. Give the classification of vitamin and discuss about vitamin A and K 05

5.11 FURTHER READING

Synthetic drugs by Gurdeep R. Chatwal