1. i. The generalised concept of isosters which has evolved that there are groups of atoms that impart similar physical or chemical properties to a molecule, because of similarity in size, electro negativity or stereochemistry. Example: the substitution of sulphur atom in the phenothiazone ring system of neuroleptic agents with the vinylene group (-CH=CH-) to develop dibenzazepine class of antidepressant drugs serves as a classical example of isosterism.

ii. Chlorpromazine, perphenazine.

iii. Imipramine

iv. Ibuprofen

v. Chlorambucil

vi. Nortryptyline

vii. Lithium carbonate

viii. Classification based on chemical structure as follows:
(a) Nucleoside Analogs- acyclovir, didanosine, AZT
(b) Adamantane Amine derivatives- amantadine
(c) Interferons
(d) Phosphorus derivatives- Foscarnet

ix. Vander Wal force

x. Ibuprofen, phenylbutazone

xi. Propionic acid

xii. Dactinomycin
2. The term isosterism was introduced by I. Langmuir in 1919 who defined isosters as compounds or groups of atoms having the same number and arrangements of electrons. Accordingly, those entities which had the same total charge as well as the same number of electrons (isoelectric) would possess similar physical properties. Thus the molecules of nitrogen and carbon monoxide show similar physical properties as both possess 14 total electrons and both are unchanged. Pairs of CO₂ and N₂O and N₃- and NCO- are other examples. Langmuir had introduced this concept to explain similarities in physical properties for nonisomeric molecules.

Bioisosterism can be classified into two classes: (a) Classical bioisosterism (b) Non-classical bioisosterism. Classical bioisosterism may be applied for “like for like” atoms. It relates the electronic configuration, valence electrons, shape, size, polarizability without changing the therapeutic activity. Classical bioisosterism are of following types: (a) Replacement of Univalent (-F (Cl), -CH₃, NH₂, -SH and -OH); Divalent (-CH₂, -OH, -NH-, -S-); trivalent (=CH-, -N=, =S-); tetravalent, ring equivalent. Non classical bioisosterism do not obey the steric and electronic definition of classical isosters. Also they do not have the same number of atoms as a replacement. Non Classical isosteric modification are those that substituted in a certain molecule, give origin to a component where steric arrangement and electronic configuration are similar to those of the parent compound; examples of pairs of these isosters are H and F, CO and SO₂, SO₂NH₂ and –PO(OH)NH₂. It includes in the isosterism of carbonyl group, carboxylic acid, carbonyl amide, carboxylic ester, hydroxyl group, etc. Non Classical isosteric modification discuss the (a) reversal of groups (b) ring opening and closure (c) groups with similar polar effects (d) amide group bioisoteres (e) thiourea bioisosteres (vi) halogen bioisoteres.

Since its introduction the concept of isosterism has changed significantly. A more generalised concept of isosters which has evolved is that these are groups of atoms that impart similar physical and chemical properties to a molecule, because of similarity in size, electronegativity or stereochemistry. Considering the observation that benzene and thiophene showed similarity in many of their properties, the vinylene group (-CH=CH-) and divalent sulphur (-S-) were termed as ring equivalents. The substitution of sulphur atom in the phenothiazine ring system of neuroleptic agents with the vinylene group (-CH=CH-) to develop dibenzapine class of antidepressant drugs serves as a classical example of isosterism. Other isosteric pairs which possess similar steric and electronic configurations are: carboxylate (-COO⁻) and sulphanamido (-SO₂NR) groups; chloro(-Cl) and trifluoromethyl (-CF₃) groups. Interchanging of either (O-) , sulphide(-S-) amine (-NH⁻) and methylene (-CH₂-) groups, although dissimilar electronically, is a common feature one encounters in medicinal chemistry.

Analogue designed through isosteric replacement may be agonists in relation to the parent molecule or antagonists. Antineoplastic drug mercaptopurine is an analogue of adenine, one of the base component of nucleic acids, designed by isosteric replacement of amino group in adenine by sulphhydryl group. Mercaptopurine acts as an antimetabolite and interferes with nucleic acid synthesis. A similar example is of thioguanine, an analogue of naturally occurring purine guanine. Methotrexate is another drug developed through isosteric replacement of hydroxyl group of folic acid by amino group.

3. Non steroidal anti-inflammatory drugs (NSAIDS) exhibit a variety of structures and it is usual to classify these drugs by their structural groups:

**Nonselective Cox Inhibitors**

Salicylic acids: Aspirin, benorylate, choline, magnesium trisalicylate, diffunisal, salsalate.

Acetic acids: acemetacin, diclofenac, indomethacin, ketorolac, sulindac, tiaprofenic acid, tolmetin.

Propionic acid: ibuprofen, ketoprofen, naproxen, tiaprofenic acid, fenbute, fenoprofen, flurbiprofen.

Fenamic acids: mefenamic acid

Enolic acids: Piroxicam, tenoxicam, azapropazone, oxyphenbutazone, phenylbutazone.
Nonacidic drug: nabumetone

Selective Cox-2 Inhibitors: celecoxib, etodolac, rofecoxib, nimesulide
Non-arcotic Analgesics – para  ] paracetamol
Aminophenol

Indomethacin:
Structure:

\[
\text{Indomethacin}
\]

It is 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid.
It is among the earliest non-salicylate compounds to be discovered and developed for use as an anti-inflammatory agent. It can be synthesised from a 1,1 disubstituted hydrazine and levulinic acid.

SAR (i) Substituents R1 useful for increasing anti-inflammatory activity are ranked as R'C6H4CH2>alkyl>H (ii) R2 substituents for improved activity are ranked CH3 >H. (iii) X substituents are ranked 5-OCH3>(CH3)2N >CH3>H. The carboxyl group is necessary for anti-inflammatory activity. A para halogen for halogen equivalent, such as CF3 or SCH3, substituted in the 1-benzoyl group provides the greatest activity. At position 2, a methyl group is better than an aryl group. At the alpha position of the side chain, hydrogen and a methyl group is better than an aryl group. At the alpha position of the side chain, a hydrogen and a methyl group are roughly equivalent. At positions 5 of the ring methoxy, allyloxy, dimethylamino, acetyl, methyl and fluoro functions are superior to hydrogen or chlorine. The 3-acetic acid side chain is free to rotate to assume different conformations. In a methyl analog, anti-inflammatory activity was displayed only by the dextrorotatory enantiomorphs with similar absolute configuration. It has 25 times the activity of phenylbutazone.

Properties and uses:
Pale yellow, crystalline powder without any taste, practically insoluble in water, melting range 158-162\(^\circ\)C.
It benefits 25% of rheumatoid arthritis patients by relieving pain, reducing swelling and tenderness of the joints. A typical dosage schedule is 25 mg twice daily.
Side effects: headache, nausea, and diarrhoea. Peptic and jejuna ulcers have been reported.
Preparations: Indomethacin in capsules I.P. 25 mg.
Dose: 75-100 mg daily, in divided doses.

4. The term “receptor” was first introduced in 1907 by Paul Ehrich, who said compounds do not act unless bound. Receptors can be regarded as the sensing elements in the system of chemical communications that coordinate the functions of all the different cells in the body, the chemical messengers being hormone or transmitter substances.
There are four main types of receptors classified according to the nature of the receptor effectors linkage.
The four main types of receptor:
Type 1: Direct ligand-gated channel type: Receptors for fast neurotransmitters, occupied directly to an ion channel, e.g., the nicotinic acetylcholine receptor (nAChR), the GABA_A receptor, the glutamate receptor.

Type 2: G-protein-coupled type: Receptors for many hormones and slow transmitters, coupled to effector system via a G –protein, e.g., the muscarinic acetyl-choline receptor (m AChR), adrenergic receptors.

Type 3: Tyrosine –Kinase-Linked type: Receptors for insulin and various growth factors, which are directly linked to tyrosine kinase.

Type 4: Intracellular Steroid/ Thyroid type: steroid receptor.

Table: The four typed of receptor

<table>
<thead>
<tr>
<th>Type 1</th>
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<td>Examples</td>
<td>nAChR</td>
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<td>Insulin</td>
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A: A Direct ligand-gated Ion channel. Nicotinic AChR Structure

The molecular structure

The nicotinic acetylcholine receptor is typical and by far the best studied ligandgated ion channels (LGIC). The electric organ of the Californian ray, Torpedo California, is an exceedingly rich source of receptors. By utilizing alpha-bungarotoxins (a compound of Cobra snake venom with extremely high affinity for the nicotinic AChR) it was possible to isolate and characterise this receptor. The receptor consists of four different types of subunits, termed alpha, beta, gamma, delta in a stoichiometry $\alpha_2\beta\gamma\delta$ arranged in a pseudosymmetrical fashion around a central ion channel pore. Each subunit is thought to cross the cell membrane four times giving four transmembrane (TM) domains which are numbered from the aminoterminus of the proteins. Since, five subunits make up each receptor; there are 20 transmembrane domains for receptors. The amino acid residues in TM2 of each subunit line the central ion channel and determine its conductance properties.

The $\alpha$-subunit was found to be unique in having two cysteine residues in amino acid positions 192 and 193. These cysteine residues are located before the first transmembrane domain in the extracellular part of the protein and the agonist-binding site is thought to be close by, perhaps in a shallow cleft between the $\alpha$- and adjacent subunits.

A role for the hydrophobic M1 segment of amino acid in gating nicotinic ion channels has been proposed. M1 is highly conserved with a central proline being found in all ligand gated ion channels. This proline produces a kink in the $\alpha$-helix structure with proximal apolar residues producing nondirectional hydrophobic bonds that confer flexibility to the regions. The structure of M1, its location close to pore and the likelihood that it is the first transmembrane region after the Ach binding site, all suggest that M1 is involved in gating the channel.

B. G-Protein Coupled Receptors (GPCR)

The G-protein (guanine-nucleotide binding proteins)–coupled receptor family comprises most of the receptors that are familiar to medicinal chemists, such as muscarinic acetyl choline, adrenergic and dopamine receptor. A distinction has been made between GPCRs on the basis of the chemical nature of their ligands.

(i) Non-peptide ligands: $\alpha$-and $\beta$- adrenergic, adenosine A1 and A2, cAMP, dopamine, histamine, serotonin, tyramine, cannabinoid and muscarinic rhodopsin.


Table: Some examples of ion channel and G-protein –coupled receptors
G-Protein coupling and Transduction Triggering

It has long been speculated that a receptor conformational change, triggered by agonist binding, would be responsible for initiating the resulting transduction mechanism. As active proline is involved toward this effect. In one study, two amphiphilic helical segments predicted in the third intracellular loop have been shown to align parallel to each other, in close proximity to the helical bundles 5 and 6. It is suggested that a conformational change in the helical bundles could alter the orientation of these cytoplasmic helices leading to the interaction with the Gs (G-protein stimulating) coupling.

G-protein consist of three subunits, α, β, γ. Guanine nucleotides bind to the α subunit, which has enzyme activity. Catalysing the conversion of GTP to GDP. The β and γ subunits are very hydrophobic and remain associated as a βγ complex with the cytoplasmic surface of the membrane. In the resting stage, the G-protein exists as an unattached α, β, γ trimer with GDP occupying the site on the α subunit. When a receptor is occupied by an agonist molecule, a conformational change occurs, presumably involving the cytoplasmic domain of the receptor causing it to acquire high affinity for α, β, γ. Association of α, β, γ with the receptor causes the bound GDP which further dissociates from the effector (adenyl cyclase) and reassociates with β, γ subunit completing the cycle.

C. Tyrosine kinase–linked receptors

Tyrosine kinase linked receptors mediate the action of a variety of growth factors such as epidermal growth factor (EGF), IGF-I, platelet–derived growth factor (PDGF). The large family of tyrosine protein kinase also includes several retrovirus-encoded proteins that cause cellular transformation. Insulin receptors are tyrosine-kinase-linked.

The basic structure of these receptors has very large extracellular and intracellular domains, with about 400-700 residues in each. The insulin receptor is a large transmembrane glycoprotein composed of two 135-kDa α subunits (719 or 731 amino acids); the subunits are linked by disulfides bonds to form a β –α –α –β-heterotetramer. Both subunits are derived from a single chain precursor molecule that contains the entire sequence of the– and β- subunits, separated by a processing site consisting of four basic amino acid residues. These two subunits are specialised to perform the two functions of the receptor. The α-subunits are entirely extracellular and contain the insulin-binding domain, while the β-subunits are transmembrane protein that possesses tyrosine protein kinase activity. The binding of insulin to the α- subunits of the insulin receptor induces conformational changes that are transduced to the β-subunits, promoting a rapid dephosphorylation of a specific tyrosine residue of each β-subunit. The activated tyrosine kinase phosphorylates a peptide, called insulin receptor substrate-1 (IRS-1). IRS-1 serves as docking protein for other proteins and activates other kinases eg, phosphoinositide (PI) 3-kinase, mitogen-activated protein (MAP) kinases.

D. Intracellular steroid /thyroid receptors: gene Regulation:
The receptor-mediated regulation of DNA transcription is characteristic of steroid and thyroid hormones. These hormones stimulate transition of selected genes, leading to the synthesis of particular proteins and the production of cellular effects. These receptors possess large monomeric protein of 400-1000 residues, containing a highly conserved region of about 60 residues in the middle of the molecule, which is believed to constitute the DNA-binding domain of the receptor. It contains two loops of about 15 residues each, of which the knot consists of a cluster of four cysteine residues surrounding a zinc atom; these structures occur in many proteins that regulate DNA transcription and the loops are believed to wrap around the DNA helix. The hormone-binding domain lies down stream of this central region.

Each steroid hormone crosses the cell membrane readily, being highly lipid soluble and binds to a specific cytosolic or nuclear receptor. This receptor on binding of steroid unfolds, thus exposing the normally buried DNA binding domain. Translocation of the receptor from the cytosol to the nucleus may occur. The receptor binds to certain well defined regions of the nuclear DNA known as hormone responsive elements, which lie about 200 base pairs upstream from the genes that are regulated. An increase in DNA polymerase activity and the production of specific mRNA occur. In this a few minutes of adding the steroid, the physiological response may take hours or days to develop. For example, in mammals the uterine wall is prepared for implantation of the embryo by estrogens.

5. Antimetabolites in anticancer therapy prevent the biosynthesis or utilization of normal cellular metabolites. They usually are closely related in structure to the metabolite that is antagonised. Sometimes the antimetabolites must be transformed biosynthetically into the active inhibitor.

**Folic acid antagonists:** example: methotrexate, aminopterin
**Purine antagonists:** azathioprine, mercaptopurine, thioguanine.

**Methotrexate:**
**Structure**

![Methotrexate molecular structure](image)

**Name:** L-(+) N- [p- [2,4-diamio-6-pteridinyl ] methyl ] methylamino] benzoyl] glutamic acid. It is prepared by combining 2,4,5,6-tetraminopyrimidine, 2,3–dibromopropionaldehyde, disodium p-(methylamino) benzoyl-L-glutamate, iodine and KI, followed by heating with lime water. It is isolated as the monohydrate, a yellow solid.

**Synthesis:**
It is supplied as 25 mg tablets and in vials containing either 5 mg or 50 mg of methotrexate solution in 2 ml of solution. Methotrexate can be given by any route, directly into spinal canal.

They are designed on the basis of differences between the folate influx system in certain tumours and that in normal tissues, bone marrow. Methotrexate was the first drug to produce substantial remissions in leukemia. It afforded a cure against choriocarcinoma in women. Because it has some ability to enter the CNS, it is used in the treatment and prophylaxis of meningeal leukemia. Methotrexate is used in combination chemotherapy for palliative management of breast cancer, epidermoid cancers
of the head and mouth and lung cancer. Vincristine increases the cellular uptake of methotrexate and this effect has been used in the treatment of osteosarcoma.

**Mechanism of action:** Methotrexate acts as an antifolate by binding almost irreversibly to the enzyme dihydrofolate reductase and preventing the formation of the coenzyme tetrahydrofolic acid, essential for DNA synthesis and for replication of animal cells. The basis of this binding strength is in the diaminopyrimidine ring, which is protonated at physiological pH.

It suggests that the blockade of purine biosynthesis might have greater effects on tumor cells than normal cells. Consequently, the administration of thymidine protect the normal cells relative to the tumor cells.

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**6-Mercaptopurine:**

**Structure**

![6-MERCAPTOPURINE](image)

6-MERCAPTOPURINE

It is prepared by treating hypoxanthine with phosphorous pentasulphide and is obtained as odourless yellow crystalline powder.

Scored 50 mg tablets are supplied. It is effective in acute lymphoblastic and stem cell leukaemia of children (2.5 mg/kg). Allopurinol potentiates the effect of MP by inhibiting its metabolism. It also increases toxicity. The chief toxic effects are leukopenia, bone marrow depression and bleeding.

**Synthesis:**

6-MP is an antagonist to purines, which are essential constituents of DNA. It serves as a specific replacement for hypoxanthine. It acts as a substrate for a methyl transferase, requiring 5-adenosyl methionine, that converts it into 6-methylthioinosinate.

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**6-Thioguanine**

**Structure**

![6-THIOGUANINE](image)

6-THIOGUANINE

Its sole use in the treatment of acute myelocytic leukemia in combination with cytarabine. The usual initial dose is 2 mg per kg daily by the oral route, scored 40 mg tablets are supplied. Toxic effects are like 6-MP.

**Synthesis**

TG is converted into its ribonucleotide which inhibits the enzymes into synthesis of purines. TG is incorporated into RNA and its 2’-deoxy metabolite is incorporated into DNA.

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**Azathioprine**
AZATHIOPURINE

Name: 6-[(1-methyl-4-nitroimidazole-5-yl)thio] purine
It is prepared from 6-MP and 5-chloro-1-methyl-4-nitromidazole. It is promercaptopurine. It is supplied as 50 mg scored tablets. The injectable sodium salt is available in 20 ml vials containing 100 mg of azathioprine. It is extensively converted to 6-MP. The main indication for azathioprine is as an adjuvant to prevent the rejection of renal homotransplants. Immunosuppressants: Dose: 3-5 mg/day single dose by oral or IV; for transplantation: 3-5 mg/day.

6. Antiviral agents are substances used in the treatment and prophylaxis of diseases caused by viruses. Antiviral drugs are broadly classified on the basis of their specific mode of action as stated below:
   (a) Substances that inhibit early stages of viral replication.
   (b) Substances that interfere with viral nucleic acid replication
   (c) Substances that affect translation on cell ribosomes

   Again, antiviral agents may be divided into the following classes based on their chemical structure.
   (e) Nucleoside Analogs- Acyclovir, Didanosine, AZT
   (f) Adamantane Amine derivatives- Amantadine
   (g) Interferons
   (h) Phosphorus derivatives- Foscarnet

   Antiviral drugs according to treatment protocol:
   I. Treatment of respiratory virus infection
      a. Amantane derivatives- Amantadine, Rimantadine
   II. Treatment of Herpes and cytomegalovirus infections
      a. Purine nucleotides- Acyclovir, Ganciclovir, Vidarabine
      b. Pyrimidine nucleosides- Trifluridine, Idoxuridine
      c. Phosphorus derivatives- Foscarnet
   III. Treatment of HIV infections
      a. Reverse Transcriptase Inhibition
         (i) Purine derivatives- Didanosine
         (ii) Pyrimidine derivatives- Zidovudine (AZT), stavudine
         (iii) Non-nucleosides- Nevirapine, Delavirdine
      b. Protease inhibition
         Saquinavir, indinavir, Ritonavir
      c. Integrase Inhibition – Zintevir
   (IV) Treatment for acquired Immuno Deficiency Syndrome (AIDS)
      Reverse Transcriptase Inhibitors

   Zidovudine (Azidothymidine; AZT, Retrovir)
   Structure
Zidovudine has become the most important agent available for the palliation of AIDS and inhibits the HIV-1 with an absolute helper inducer (CD₄⁺, T₄⁺) T cell count of less than 200/mm³ (adult or children). It reduces the incidence of opportunistic infections e.g. pneumonia and other AIDS related complexes. It is in effect a prodrug. The active triphosphate metabolite inhibits viral RNA-dependent DNA polymerase (reverse transcriptase, RT). This enzyme is essential for the life cycle of the retrovirus. The oral bioavailability of zidovudin is 60-65%. Serious side effects include granulocytopenia and anaemia, severe headache, nausea, insomnia and myalgias.

Dose: The usual dose is 200 mg every 4 hours continuously.

**Acyclovir Sodium**

Name: (9-[2-hydroxyethyl]-methyl guanine; 2-amino-1,9 dihydro -9-[(2-hydroxyethoxy)-methyl]-6H-purine-6-one.

It is a drug of choice in both prophylaxis and treatment of herpes simplex virus, particularly type 1 including chronic and recurrent mucocutaneous herpes in the immunologically impaired host, primary and secondary genital herpws and herpes simples encephalitis. Cells infected with herpes simplex phosphorylate the drug to yield a cycloguanosine triphosphate, which preferentially inhibits viral DNA polymerase. Adverse responses included irritation and pain at the injection site, rash, nausea and headache.

Dose: 200 mg orally every 4 hours for 10 days; Ointment 3 hours, six times daily for 7 days; intravenous, 5 mg/kg every 8 hours for 5 to 7 days; for encephalitis, 10 mg/kg every 8 hours.

Dosage: capsules: 200 mg, ointment (5%) in polyethyleneglycol base; powder for I.V. use.

**Vidarabine**
Name: 9-beta-D-arabinofuranosyl-9H-purine-6-amine monohydrate.
Vidarabine is used in the treatment of serious herpes simplex infections, including encephalitis, keratoconjunctivitis and neonatal infections. It is phosphorylated within the cell to the corresponding triphosphate, which in turn inhibits viral DNA polymerase. It is metabolised to hypoxanthine arabinoside, which acts synergistically and enhances the antiviral activity of vidarbine. It is infused over 12 to 24 hours at a daily dosage of 15 mg/kg for treatment of encephalitis. Herpes simplex keratoconjunctivitis is treated with a 3% ophthalmic ointment administered topically every 3 hours.
Side effects: GI disturbances, CNS toxicity, nausea, diarrhoea.

Idoxuridine

Name: 5-iodo-2’-deoxyuridine
It is a white, crystalline powder, slightly soluble in water. It is available only for herpes simplex virus peratitis and labial herpes and approved as ophthalmic ointment or solution. It is phosphorylated within cells to triphosphate, which is incorporated into both viral and mammalian DNA, producing DNA that is more susceptible to breakage and ultimately causing production of altered proteins.
Side effects: Hematologic toxicity for systemic use. It may cause ocular itching and photophobia.
Dosage: ointment (0.5%), solution (0.1%), one drop of 0.1% solution every two hours during the day and every 4 hours at night for 3 to 5 days.

Amantadine hydrochloride I.P.
Structure:

1-amantadine hydrochloride
It is a white, odourless, crystalline powder with a bitter taste, freely soluble in water. Amantadine is effective in the prophylaxis and therapy of infection caused by influenza A and is active against a number of DNA and RNA viruses in vitro. It may
block either the assembly of influenza virus or the release of viral nucleic acid in the host cell.

Adverse effects: confusion, hallucinations, seizures and coma. Neurotoxicity is enhanced by concomitant antihistamine and caffeine ingestion.

Dose: Capsules 100 mg, syrup 50 mg/5ml; Adults 200 mg/day, 100 mg twice daily. Children, 150 mg twice daily. For prophylaxis 100 mg twice daily.

SAR:
1. N-alkyl and N, N-dialkyl derivatives of amantadine exhibit antiviral activity similar to that of amantadine HCL.
2. N-acyl derivatives show reduced antiviral activity except clycyl derivatives and tromantadine possesses efficacy against clinical herpes labialis and herpes genitalis.
3. Replacement of the amino group with a OH, SH, CN or halogen produced inactive compounds.

**Interferon**

Interferons were first discovered by Isaacs and Linderman in 1957. It was produced by the viral infected cells which protected the cells from further infection. At present the interferons are synthesised by recombinant DNA technology. They are glycoproteins that exist in multiple molecular forms in different cells. There are three major types of human interferon: alpha, beta and gamma. Interferon alpha has been applied topically in herpes kerato-conjunctivitis in combination with acyclovir and trifluridine, shown some promise in chronic hepatitis B infections and in prophylaxis of the common cold. It is marked for the genital warts, AIDS related kaposi sarcoma. Adverse Effects: fever, headache and myalgia. Interferon in high doses acts as an abortifacient in primates. Administration is by IM, SC route or intralesionally into genital warts.

Dose: For herpes virus- 36 X 10⁶ IV per day for 5 to 7 days. For hepatitis 3 to 20 X 10⁶ IV per day thrice per week. For intralesional 1 X 10⁶ IV per lesion thrice weekly for 3 weeks.

(7) All organonitrates have a common mechanism of action. The nitrates are denitrated in vivo to form nitric oxide (NO), which is also an endothelial -derived relaxin factor (EDRF) endogenously generated by the oxidation of L-arginine. In turn, NO reacts with sulfhydryl compounds in blood vessels to form adducts which stimulate guanylate cyclase, thus causing smooth muscle relaxation. Sustained use of organic nitrates depletes tissue sulfhydryl and tolerance to the nitrates can ensue. Therefore, many experts now recommend pulse or intermittent dosing rather than continuous nitrate administration in order to reduce the likelihood of tolerance during chronic therapy. Sustained exposure to high doses of nitrates can result in a physical dependence which, upon abrupt discontinuation of drug, can be manifested as severe angina attacks and/or myocardial infarction and sudden death.

Organonitrates are relaxant of all smooth muscle and may be employed as spasmolytics in certain instances, eg, in biliary and ureteral spasms. Since their actions are directly on the smooth muscle, they are independent of the type of innervations and cannot be prevented by any known agent.

Organonitrates are eratic in vasospastic (variant) angina. Their effect is to decrease venous return and cardiac afterload which ultimately decreases pulmonary venous pressure. The result is a decrease in pulmonary congestion and edema in left heart failure and after myocardial infarction; hence, organonitrates can be used to relieve orthopnea and paroxysmal nocturnal dyspnea. In the recumbent position, the effect to decrease venous return is less marked than in the upright position and the effect to decrease cardiac afterload also is greater, so that cardiac output is maintained in recumbency.

**Isosorbide dinitrate**
Isosorbide dinitrate (C_6H_8N_2O_8, D-Glucitol, 1, 4:3, 6-dianhydro, dinitrate) is ivory–white, odourless powder (in diluted with mannitol, lactose or other inert ingredients) and white, crystalline rosettes (in undiluted condition).

Preparation: An aqueous syrup of 1, 4:3, 6–dianhydro-o-glucitol is added slowly to a cooled mixture of HNO_3 and H_2SO_4. After standing a few minutes the mixture is poured into cold water and the precipitated product is collected and recrystallized from ethanol.

Solubility: undiluted: very slightly soluble in water; very soluble in acetone, freely soluble in chloroform, sparingly soluble in alcohol.

Uses: It is a long-acting organonitrate of choice. With sublingual and chewable tablet forms, the onset of effect is 2 to 5 min; with oral forms, the onset is about 30 min and offset 4 to 6 hr; with sustained release forms the offset is 8 to 12 hr. Isosorbide dinitrate is indicated only for the prophylaxis of attacks of angina in situations in which attacks can be anticipated. The sustained release forms have not been proved to be as effective as oral tablets for acute prophylaxis.

Side effects: The most frequent complaint by users is headache. In some persons there is also a paradoxical increase in angina pain. Mild gastrointestinal disturbances, as well as vertigo and other signs of orthostatic hypotension may occur. It should be given cautiously in patients with glaucoma.

Dose: Oral (capsule or tablets), adult, chronic prophylaxis, initially 5 to 20 mg in conventional forms or 40 mg in SR forms followed by maintenance doses of 10 to 40 mg every 6 hr or 40 to 80 mg every 8 to 12 hr with SR forms. Oropharyngeal (chewable tablets), adults, chronic prophylaxis, initially 5 to 10 mg every 2 to 3 hr; In acute attack, initially 5 mg, to be adjusted upward at 5 min intervals until relief is obtained. Sublingual/buccal (sublingual tablets), adult acute prophylaxis 5 to 10 mg every 2 to 3 hr, in acute 2.5 to 5 mg initially to be adjusted upward at 5 min intervals until relief is obtained.

Dosage forms: capsules, 40 mg; SR capsules, 40 mg; tablets 5, 10, 20, 30 and 40 mg; Chewable Tablets: 5, 10 mg., Sublingual Tablets: 2.5, 5 and 10 mg.