MARUDHAR KESARI JAIN COLLEGE FOR WOMEN, VANIYAMBADI

PG & RESEARCH DEPARTMENT OF BIOCHEMISTRY

CLASS : II M.SC BIOCHEMISTRY
SUBJECT CODE : GBC42
SUBJECT NAME : ADVANCED CLINICAL BIOCHEMISTRY

UNIT-V: FREE RADICALS, CANCER AND DISORDERS OF NUCLEIC ACID METABOLISM

Free radicals in health and disease - Endogenous and exogenous free radicals. Oxidative damages to lipids, proteins and DNA. Role of enzymatic and non-enzymatic antioxidants. Cancer: Morphological and metabolic changes in tumor cells. Tumor markers - AFP, CEA, hCG. Carcinogenic agents.

Inborn errors of nucleic acid metabolism - Lesch Nyhan syndrome, immunodeficiency diseases associated with defects in purine nucleotide metabolism, gout, oratic aciduria, xanthinuria. Serology: C-reactive protein.

Free radicals in health and disease

Antioxidants are structurally diverse group of small organic molecules and large enzymes that comprise complex systems of overlapping activities working synergistically to enhance cellular defense and to combat oxidative stress resulting from various reactive oxygen species (ROS) and reactive nitrogen species (RNS). The former substances are byproducts of metabolism and are ironically produced from oxygen, an indispensable element for life. Many of these reactive species are free radicals possessing one or more unpaired electrons and as such rendered highly reactive. The reactive species generated in cells include hydrogen peroxide (H_2O_2), hypochlorous acid (HClO), the hydroxyl radical (·OH), the superoxide anion radical (O_2^-), the nitric oxide radical (NO·), and the lipid peroxyl radical (LOO·). The term antioxidants may refer to either industrial chemicals that may be added to products to combat oxidation or to natural products that are found in foods and tissue. While the former act as preservatives for cosmetics, pharmaceuticals, and food products, the latter play an important role in human health as well. There are many reactive oxygen species conducting unwanted oxidation reactions in a variety of cell and tissue sites.

Antioxidants reduce reactive oxygen species which otherwise participate in oxidation reactions that can generate free radicals and cause damage to cellular components such as DNA, proteins, carbohydrates, and lipids. It is noted, however, that reactive oxygen species mediate certain cellular functions like redox signaling and gene expression as well as defend against pathogens. Thus, the role of antioxidant systems is not to eliminate oxidants completely, but instead maintain them at an optimum level. Despite the presence of the antioxidant defense mechanism to counteract oxidative stress, damage due to oxidation has a cumulative effect and has been implicated in several chronic conditions and disease states such as cancer, cardiovascular disease, and neurodegenerative disorders. Antioxidant compounds and antioxidant enzyme systems display synergistic and interdependent effects on one another.

Antioxidants found in nature can be classified in a number of ways. Based on their activity, they can be classified as enzymatic and nonenzymatic antioxidants (phytochemicals and vitamins). While antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GSR), peroxiredoxin I-IV and catalases (CAT) are macromolecules, the vast majority of the remaining natural antioxidants classified as phytochemicals and vitamins are relatively smaller organic molecules with low molecular weights. Antioxidants have also been categorized as water-soluble or fat-soluble molecules.

Enzymatic versus nonenzymatic antioxidants

Based on their activity, antioxidants are classified as enzymatic and nonenzymatic antioxidants. While enzymatic antioxidants function by converting oxidized metabolic products in a multi-step process to hydrogen peroxide (H_2O_2) and then to water using cofactors such as iron, zinc, copper, and manganese, nonenzymatic antioxidants intercept and terminate free radical chain reactions. Examples of natural nonenzymatic antioxidants are vitamin E, A, C, flavonoids, carotenoids, glutathione, plant polyphenols, uric acid, theaflavin,

allyl sulfides, curcumin, melatonin, bilirubin, and polyamines. Some of these antioxidants are water-soluble and predominantly found in the cytosol or cytoplasmic matrix, while others are liposoluble and are present in cell membranes. The enzymatic antioxidants and their mechanism of action have been discussed extensively in several review articles. The scope of this chapter will be limited to nonenzymatic exogenous and endogenous antioxidants.

Generation of free radicals in living organisms

The production of ROS in biological systems occurs during oxygen metabolism and plays an important role in homeostasis and cell signaling. However, under conditions of environmental stress, the concentration of ROS can increase significantly and inflict damage on cell structures. The generation of ROS begins with the reduction of molecular oxygen with NADPH to produce the superoxide anion radical ($O_2^{\cdot -}$), a precursor to most remaining reactive oxygen and nitrogen species (Figure 1). Subsequent dismutation of two molecules of the superoxide anion catalyzed by the enzyme superoxide dismutase (SOD) generates oxygen and hydrogen peroxide. The latter in turn may undergo partial reduction to hydroxyl radical through the Fenton reaction or alternatively *via* the Haber-Weiss process. While hydrogen peroxide is more damaging to DNA, the hydroxyl radical is highly reactive and turns biomolecules into free radicals, thus perpetuating a free radical chain reaction. Hydrogen peroxide may also be converted to the potent oxidant hypochlorous acid in the presence of the chloride ion, an omnipresent species. This transformation is catalyzed by the enzyme myeloperoxidase (MPO). Reaction of HOCl with H_2O_2 regenerates chloride ion and produces singlet oxygen as yet another ROS. On the other hand, RNS such as nitric oxide ($NO^{\cdot}$) are produced by the enzyme nitric oxide synthase (NOS) starting from the precursor L-arginine. Nitric oxide functions as a superoxide quencher forming peroxynitrite ($ONOO^-$), a strong oxidant that reacts indiscriminately with biological targets. Further, it may disintegrate into a pair of hydroxyl and nitric dioxide radicals and cause damage through such species(Figure 1).

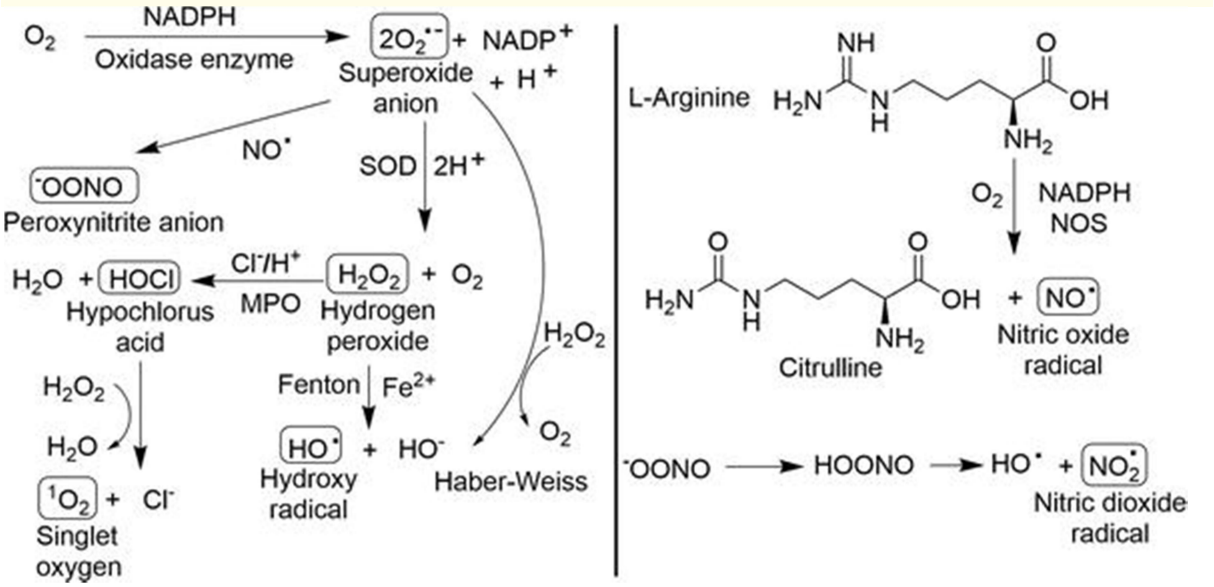

Figure 1. Generation of ROS and RNS in living species.

Regulation of free radicals with nonenzymatic exogenous antioxidants

Vitamins: Vitamin E

Vitamin E is a collection of optically active methylated phenolic compounds comprising four tocopherols and four tocotrienols where α-tocopherol is the most common and biologically active species. The structures feature two primary parts: a densely substituted polar chromanol aromatic ring and a lipophilic long polyprenyl side chain. The main chemical structural difference between different forms of Vitamin E is that tocotrienols feature unsaturated isoprenoid hydrocarbon side chains with three carbon-carbon double bonds versus saturated isoprenoid side chains for tocopherols. Within each group, the vitamers are differentiated by the number and positions of the methyls in the chromate ring. The polyprenyl precursor for the biosynthesis of tocopherols and tocotrienols is phytyl pyrophosphate (PPP) and geranylgeranyl pyrophosphate (GGPP), respectively. Vitamin E is biosynthesized though the shikimate pathway, and while α-tocopherol and α-tocotrienol are considered structurally unique, the remaining compounds in each class are constitutional isomers. The presence of three stereogenic centers (position C_2 of the chromate ring, position C_4 and C_8 of the phytyl side chain) produces 8 different stereoisomers (four pairs of enantiomers) depending on the position and orientation of the groups in each of the chiral centers. Since the discovery of vitamin E in 1920, it has been shown to be the most powerful membrane-bound antioxidant utilized by cells to scavenge reactive nitrogen and oxygen species with consequent disruption of oxidative damage to cell membrane phospholipids during cellular lipid peroxidation of the polyunsaturated fatty acids (PFA) and low-density lipoprotein (LDL). The antioxidant is liposoluble and localized to cell membranes. Vitamin E functions by reducing lipid peroxyl radicals ($LOO^{\cdot}$) by transferring the phenolic hydrogen atom of the chroman ring, resulting in a relatively stable and unreactive resonance-stabilized tocopheroxyl radical which is unable to trigger further lipid peroxidation itself. The α-tocopherol radical can be reduced back to the original active α-tocopherol form by ascorbic acid or coenzyme Q10. Alternatively, it may quench a second peroxyl radical where the resulting tocopheryl peroxide eliminates a peroxide leaving group, forms a hemiketal after reacting with water, and lastly hydrolyses to the tocopherolquinone. This is an essential foundation and benchmark of a good antioxidant. The synergistic antioxidation interactions between vitamin E and the ascorbate ion of vitamin C position the former at the forefront of the anti-radical defense system. Vitamin E is exogenous and hence is essential and must be obtained through diet in small amounts since the organism cannot synthesize it. Its biosynthesis is restricted to plants, photosynthetic algae, and certain cyanobacteria. Although vitamin A deficiency is rare, the most frequent manifestations of its lack comprise a number of disorders and disease states which include encephalomalacia, exudative diathesis, muscular dystrophy, and ceroid pigmentation. α-Tocopherol exhibits the highest bioactivity (100%), with the relative activities of β-, γ-, and δ-tocopherols being 50, 10, and 3%, respectively.

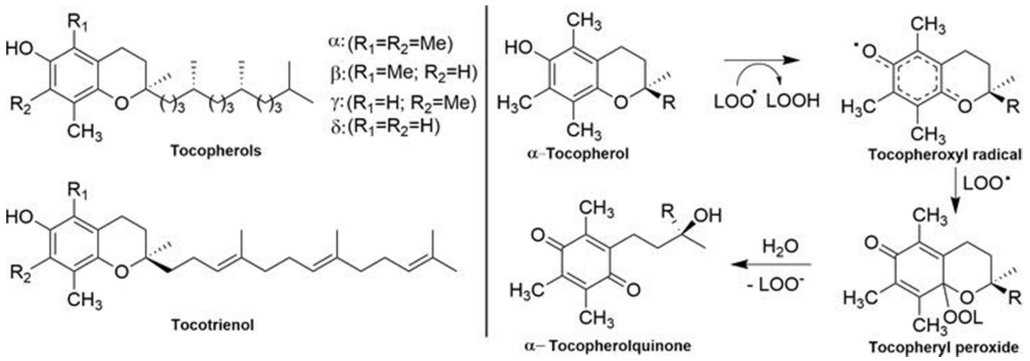

Figure 2. Chemical structures of the tocopherols and tocotrienols that comprise vitamin E and Ntermination of lipid peroxidation with α-tocopherol.

Vitamin A

Vitamin A, just like vitamin E, is a term that designates a family of unsaturated liposoluble organic compounds that include retinol, retinal, retinoic acid, and retinyl palmitate, and many provitamin A carotenoids such as beta-carotene. All forms share a beta-ionone ring to which an isoprenoid tether known as retinyl group is attached. It is noteworthy that both features are essential for vitamin A activity. The common chemical structure is a diterpene ($C_{20}H_{32}$) where the various molecular forms differ by the terminal side chain functional group. Thus, retinol contains a hydroxyl group, retinal contains an aldehyde function, retinoic acid has a terminal carboxylic acid group, and retinyl palmitate bears an ester moiety. The discovery of the antioxidant activity of vitamin A dates back to 1932 when Schmitt and Monaghan reported that vitamin A prevents lipid rancidity. Several reviews outlining the antioxidant role and metabolic functions of vitamin A have appeared in the literature. Besides eliminating free radicals, it plays a major role in maintaining good vision. The aldehyde form of vitamin E is required by the retina to form the light-absorbing molecule rhodopsin necessary for both color and scotopic vision. On the other hand, the fully irreversibly oxidized form of retinol functions in a very different way as a growth factor for epithelial and other types of cells. As an antioxidant, vitamin A scavenges lipid peroxyl radicals ($LOO^{\cdot}$). Thus, by trapping the peroxyl radical through an addition reaction to the beta-ionone ring of retinol, the resultant tertiary and highly conjugated trans-retinol carbon radical intermediate is relatively stable and under normal conditions is not reactive enough to induce further lipid peroxidation itself. However, the intermediate may continue reacting with lipid peroxyl radicals or molecular oxygen to produce a bis-peroxyl adduct or retinol-derived peroxyl radical, respectively. Alternatively, it may eliminate LO radical and oxidizes to 5,6-retinol epoxide.

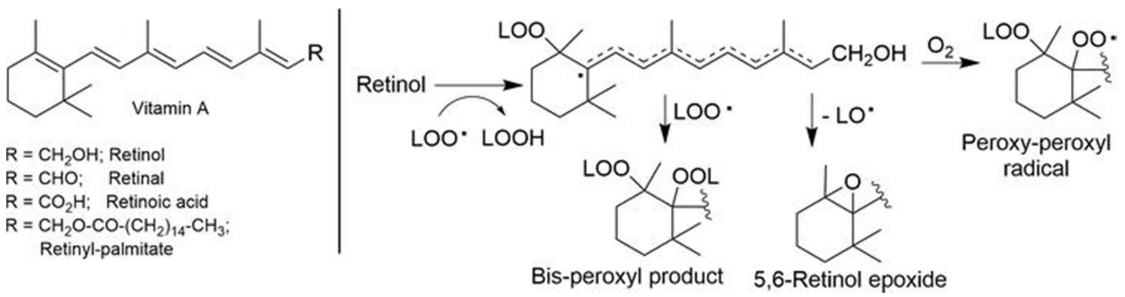

Figure 3. Chemical structure of vitamin A and termination of lipid peroxidation with retinol.

CANCER

Tumor markers

Tumour "markers" are defined as a biochemical substance (e.g. hormone, enzymes, orproteins) synthesized
and released by cancer cells or produced by the host in response to cancerous substance and are used to monitor or identify the presence of a cancerous growth.

Sites: Tumour markers may be present in

- Blood circulation
- Body cavity fluids
- Cell membranes
- Cell cytoplasm

Tumour markers are different from substances produced by normal cells, in quantity and quality.

Methods for Detection:

1. Immunohistological and immunocytological tests are used to detect those tumour markers which are
present only on cell-membranes and cytoplasm of cells and not in blood circulation.

Examples

- Immunofluorescence
- Immunoperoxidase
- Monoclonal antibody technology

2. Biochemical methods are used for measuring tumour markers found in the blood circulation.

Examples

- Radioimmunoassay (RIA)
- Enzyme-immune assay
- Immunochemical reactions

TYPES OF TUMOUR MARKERS

Two types of tumour antigens have been described:

1. Tumour-specific antigens
2. Tumour-associated antigens

1. Tumour-Specific Antigens

• These are a direct product of oncogenesis induced by an oncogene (viral), radiation, chemical carcinogen or an unknown risk factor.

• Oncogenesis causes abnormalities of genetic information available to the cancer cells, which then subsequently synthesises neoantigens specific to cancer cells.

• They play an important role in clinical oncology.

2. Tumour-Associated Antigens

• Also called as oncofoetal proteins/antigens.

• Shown to exist in both in embryo-foetal tissues and cancer cells.

• These are produced in large quantities in foetal life and released in foetal circulation. After birth, these oncofoetal antigens disappear from blood circulation and may be present in trace amounts in normal healthy adults.

• With the onset of malignancy in adult life, the synthesis of oncofoetal antigens in foetal life which was suppressed in adult life, is again reactivated with malignant transformation of cells and reappears in cancer cells and in blood circulation (retrogenetic expression theory).

Examples of such oncofoetal antigens are:

• CEA (carcinoembryonic antigen)

• AFP (Alpha-fetoprotein)

A. Carcinoembryonic Antigen (CEA)

CEA is one of the oncofoetal antigens used most frequently and widely as a tumour marker in clinical oncology. It was originally described by Gold and Freedman as a tumour specific antigen present only in cancer cells, in the circulation of patients with gastrointestinal malignancy and in the normalepithelial cells of foetal GI tract, hence it was named as CEA because of its presence in both carcinoma and embryonic tissue. It was discovered in 1965 by raising antiserum against a colon cancer.

Properties of CEA and Chemical Composition

• It is a glycoprotein.

• Molecular weight varies from 150,000 to 300,000 (average 185,000).

• Protein Part

– A single polypeptide chain (monomeric unit) consisting of 30 aa. with lysine at N-terminus.

– By EM, it appears as a twisted rod.

– Protein content is 46 to 75 per cent .

• Carbohydrate Component

• Carbohydrates surround the protein and constitutes 45 to 57 per cent . On analysis of carbohydrates, it is found to contain fucose, mannose and galactose.

• N-acetyl galactosamine is low whereas large amount of N-acetyl glucosamine is present.

• Sialic acid varies significantly.

Physiology and Metabolism

1. Sites: CEA is chiefly present in:

• Endodermally derived tissues, viz. GI mucosa, lungs and pancreas.

• Also may be in non endodermally derived tissues, conclusive evidences lacking.

It has been detected in GI tract of foetuses as early as three months of gestation. Also found in embryonic liver,pancreas and lungs. CEA has been detected in free brush border of normal mucosal cells and also in cytoplasm of colonic carcinoma cells.

2. Metabolism: Not known exactly. CEA is probably broken down in liver. It disappears from circulation in 3 to 4 weeks after removal of CEA-producing tumour.

Clinical Uses and Remarks

1. CEA has been reported to be most useful as tumour marker in colorectal Cancer.
2. It is elevated also in other malignancies. Found to be useful in:
• Breast cancer
• Bronchogenic carcinoma of lung specially small cell carcinoma of lungs (SCCL)
• Other malignancies where the value is raised are:
– Pancreatic carcinoma
– Gastric carcinoma
– Cancer of urinary bladder
– Prostatic cancer, neuroblastomas, ovarian cancer and carcinoma of thyroids.

B. Human Chorionic Gonadotropin (β-HCG)

HCG is a placental hormone. It is synthesised by the syncytiotrophoblastic cells of placental villi.

Normally

• It is present in the serum of nonpregnant women in very trace amounts or not at all.
• But it is markedly elevated in pregnancy.

Maximum peak level is reached by 12 weeks of pregnancy, then it declines slowly, reaching $1/5^{th}$ of peak by the end of 20th week and then continues at a very low level for a few days even after parturition.

• Measurement of elevated HCG in serum and urine has been used to diagnose pregnancy.

Chemistry

• It is a glycoprotein. Molecular weight averages 45,000.
• Protein is present as a central core with branched carbohydrate side chains, which terminate with sialic acid.
• It is dimer and has two dissimilar subunits:
– α-subunit and
– β-subunit

α-subunit:

• Molecular wt 15,000 to 20,000
• Consists of 92 amino acids

• Is identical with α-subunit of FSH, LH and TSH

β-subunit

• Molecular wt 25,000 to 30,000

• β-subunit or c-terminal part of the β-subunit isspecific immunologically.

Clinical uses and remarks for B-Hcg

1. The β-subunit of HCG is typically measured because of its increased specificity and because some tumours secrete only β-subunit.
2. β-HCG is an ideal tumour marker for diagnosing and monitoring gestational trophoblastic tumours and germ cell tumours of testes and ovary.
3. Frequency of elevated β-HCG has been observed to be as follows:
    - Seminomas 15%
    - Embryonal carcinomas 50%
    - Teratocarcinoma 42%
    - Choriocarcinoma 100%

Specificity increases when AFP and LDH isoenzymes are done simultaneously. Both LDH and LDH-1 isoenzyme show increased levels in 50 to 80 per cent of patients of testicular cancers.

4. β-HCG in CS fluid: Recently, measurement of β-HCG in cerebrospinal fluid (CSF) has aided in diagnosis of brain metastases. A serum/CS fluid ratio of less than 60:1 points to central nervous system (CNS) metastasis. The response of therapy in patients with CNS metastases can be monitored using HCG levels.

C. Alpha-Fetoprotein (AFP)

Like CEA, α-Fetoprotein (AFP) is another oncofoetal antigen. AFP is synthesised in the liver, yolk sac and GI tract in foetal life and is released into the serum of foetus. It is a normal component of serum protein in human foetus. The concentration is highest during embryonic and foetal life. At birth, the serum AFP declines to 1/ 100th of AFP value at the highest foetal concentration. At one year of life, the value decreases further and in normal adults it is negligible, less than 20 ng/ml.

Chemistry

• It is a glycoprotein**.** Protein constitutes 95 per cent and carbohydrate moiety 5 per cent. Having molecular weight 61,000 to 70,000.

• Physically and chemically it is related to albumin, pI is similar to albumin (4.8).

• It is a single polypeptide chain (monomeric unit) with regions in the interior being similar to human serum albumin.

Clinical uses and remarks

1. AFP is the most specific and ideal tumour marker for primary carcinoma of the liver (hepatocellular carcinoma). Serum level of AFP level is elevated markedly. Hepatoma cells are analogous to foetal hepatocytes and are capable of synthesising AFP.

2. AFP assay has been used in case of hepatic mass:

• In suspected hepatoma.

• In patients with cirrhosis liver suspected to have superimposed hepatoma.

• Also serial assay in established case of hepatoma to follow the effect of therapy.

3. AFP as tumour marker has been found to be also most useful in germ cell tumours of the testes and ovary.
Serum AFP and β-HCG are the best available tumour markers for germ cell type of tumours.

Carcinogenic Agents (Agents Causing Cancer):

Carcinogens that cause cancer can be divided into three main broad groups:

1. Physical: Radiant energy

2. Chemicals: Variety of chemical compounds can cause cancer. Some of these can act directly and others can act as procarcinogens

3. Biological: Oncogenic viruses.

I. Radiant energy (radiations): Mechanism of carcinogenesis

Radiations can cause cancer mainly in two ways:

1. Direct Effect

By producing damage to DNA, which appears to be the basic mechanism but the details are not clear. Radiations like X-rays, γ-rays or UV rays are harmful to DNA of cells and they can be mutagenic and carcinogenic.

Damages to DNA brought about by radiations may be as follows:

• Single or double strand breaks.

• Elimination of purine/pyrimidine bases.

• Cross-linking of strands.

• Formation of pyrimidine dimers.

2. Indirect Effects

In addition to direct effects on DNA as stated above, radiations like γ-rays and X-rays produce free radicals, viz. OH–, superoxide and others which may interact subsequently with DNA and other macromolecules leading to molecular damage. UV rays: Natural UV rays from sun can cause skin cancer. Fair-skinned people living in places where sunshine is plenty are at greatest risk. Carcinomas and melanomas of exposed skin are particularly common in Australia and New Zealand.

UV rays produce:

• Damage to DNA by formation of pyrimidinedimers.

• Secondly by immunosuppression.

Ionising Radiations

The ability of ionising radiations to cause cancer lies in their ability to produce mutations (mechanisms discussed above). Particulate radiations such as α-particles and neutrons are more carcinogenic than electromagnetic radiations like X-rays and γ-rays.

Evidences in favour of carcinogenicity of ionising radiations:

• Incidence of leukaemias increased in Japan after atom bomb explosion.
• Development of thyroid cancer in later life in children exposed to therapeutic radiation in neck.
• Lung cancer is more in miners who work in radioactive ores.

II. Chemicals as carcinogens

A large number of chemicals have been incriminated as carcinogenic. Some of these are direct reacting and majority occur as procarcinogens which are converted in the body to ultimate carcinogenic chemicals. Many of the chemicals have been tested on animals (experimental carcinogenesis).

Class	**Nature of Chemicals Compound**
1. Polycyclic aromatic Hydrocarbons	• Benzpyrene • Dimethyl-benzanthracene

Aromatic hydrocarbons are present in cigarette smoke and they are thus relevant in pathogenesis of lung cancer.

2. Azo dyes (Aromatic amines)	• β-Naphthylamine • N-methyl-4-aminoazobenzene • 2-acetylaminofluorine

β-naphthylamine, an aniline azo dye used in the rubber industries has been held responsible for bladder cancers in exposed workers.

3. Nitrosamines and amides	• Dimethylnitrosamine • Diethylnitrosamine

Nitrosamines and amides can be synthesised in GI tract from ingested nitrites or derived from digested proteins and may contribute to induction of gastric cancer.

4. Naturally occurring compounds	• Aflatoxin B1 produced by the fungus, Aspergillus flavus.

The fungus grows on groundnuts, peanuts and other grains in congenial environmental conditions. It produces "aflatoxin B1" which is a potent hepatocarcinogen**.** This is believed to be responsible for high incidence of liver cell carcinoma in Africa, where the contaminated foods are eaten.

5. Various Drugs	• Alkylating and acylating agents, e.g. cyclophosphamide and busulfan.

The drugs are used in cancer treatment and also as immunosuppressants. Patients receiving such therapy are at a higher risk for developing cancer.

• Diethylstilbestrol, oestrogen.
• Nitrogen mustard.
• β-propiolactone

6. Miscellaneous agents:

- Beryllium, cadmium, nickel, chromium, arsenic
- Asbestos
- Vinyl chloride
- Saccharin and cyclamates

Lesch-Nyhan syndrome

Lesch-Nyhan syndrome is an extremely rare metabolic disorder that occurs before birth, mostly in boys. It causes brain and behavior problems, including severe arthritis, poor muscle control and mental disability. A key symptom is uncontrollable self-injury. The prognosis is poor, but early detection and treatment can improve quality of life.

Lesch-Nyhan syndrome (LNS) is a rare congenital (at birth) disorder that affects a child's brain and behavior. A key symptom is engaging in uncontrollable self-injury, including lip and finger biting or head banging.

The disease causes a buildup of a natural waste product called uric acid in the body. Researchers suspect LNS may also affect dopamine levels. Dopamine is a chemical messenger important for healthy brain function.

Classic Lesch-Nyhan syndrome is severe, involving physical, mental and behavioral symptoms. Children with other types (variants) of the disease tend to experience milder symptoms. They are often less likely to injure themselves or develop movement problems.

These types include:

- HPRT1-related neurologic function (HND).
- HPRT1-related hyperuricemia (Kelley–Seegmiller syndrome), the mildest type.

Causes

The cause of Lesch-Nyhan syndrome is a change (mutation) in a specific gene (*HPRT1* gene). This gene makes an important enzyme known as HPRT. Enzymes are proteins that help you function by speeding up chemical reactions in the body (metabolism).

When you have Lesch-Nyhan syndrome, your body has difficulty processing chemicals called purines. When purines are not used properly, they turn into uric acid, a waste product found in blood.

Most uric acid passes through the kidneys and leaves the body in urine. But in Lesch-Nyhan syndrome, the body collects too much uric acid (hyperuricemia).

The acid clumps into tiny stones or crystals (urate) in the skin, hands and feet. These crystals may irritate the joints and cause a type of arthritis known as gout.

Tiny stones may also form in your kidneys or bladder, where they can block the flow of urine and cause pain. In severe cases, both kidneys may stop working (renal failure).

Symptoms

Symptoms of Lesch-Nyhan syndrome in children affect mental ability, movement and behavior. Poor muscle control and developmental delays are common early signs of the disorder.

Babies may have orange-colored crystals in their diapers if they have too much uric acid. But most children with the disease do not show symptoms until they are about 4 months old.

There is a wide range of symptoms parents and providers may notice, including:

Injuring self and others

Compulsive (uncontrollable) self-injury is a noticeable symptom of Lesch-Nyhan syndrome after a child's teeth come in. This behavior usually involves:

- Banging the head or limbs.
- Biting lips, fingers and cheeks.
- Poking the eyes.

In some cases, children with the disorder may try to hurt others. They may use verbal abuse or grab, hit, pinch or spit.

Muscle and movement problems

Other common symptoms include muscle control problems such as:

- Constant repetitive movement of the arms or legs (ballismus).
- Difficulty crawling, walking or feeding with hands.
- Difficulty swallowing (dysphagia).
- Exaggerated reflexes (hyperreflexia).
- Arched back due to muscle spasms (opisthotonos).
- Involuntary movements (dystonia) or facial expressions.
- Involuntary twitching, wiggling or writhing (choreoathetosis).
- Jerking movements (chorea).
- Muscles that stiffen or tighten, preventing movement (spasticity).
- Slurred or slow speech (dysarthria).

Health problems

Children with Lesch-Nyhan syndrome may develop certain health issues due to a buildup of uric acid in the body. These include:

- Bladder stones.
- Kidney failure.
- Kidney stones.
- Gout.
- Megaloblastic anemia due to a lack of vitamin B12.
- Repeated vomiting.

Treatment

Treatment for Lesch-Nyhan syndrome depends on your child's symptoms and their severity.

Newborns and infants with Lesch-Nyhan syndrome may need extra monitoring and feeding support.

Your healthcare provider may recommend:

- Medications to treat excess uric acid or ease behavioral problems.
- Feeding or swallowing support.
- Supportive equipment like a wheelchair to aid mobility.
- Physical and occupational therapy.
- Protective devices such as a splint or mouthguard to prevent involuntary movements such as finger biting.
- Procedures such as shockwave or laser lithotripsy to break up kidney or bladder stones.

Immunodeficiency diseases

Immunodeficiency disorders prevent your body from fighting infections and diseases. This type of disorder makes it easier for you to catch viruses and bacterial infections. Immunodeficiency disorders are either congenital or acquired. A congenital, or primary, disorder is one you were born with. An acquired, or secondary, disorder is one you get later in life. Acquired disorders are more common than congenital disorders.

Immune system includes the following organs:

- spleen

- tonsils
- bone marrow
- lymph nodes

These organs process and release lymphocytes. These are white blood cells classified as B cells and T cells. B and T cells fight invaders called antigens. B cells release antibodies specific to the disease your body detects. Certain T cells destroy foreign or atypical cells.

Examples of antigens that your B and T cells might need to fight off include:

- bacteria
- viruses
- cancer cells
- parasites

An immunodeficiency disorder disrupts your body's ability to defend itself against these antigens.

Signs of an immunodeficiency disorder

There are hundreds of forms of immunodeficiency disorders. Each disorder has unique symptoms that can be frequent or chronic. However, there are a few warning signs that something may be going on with your immune system.

Individuals with immunodeficiency disorders tend to have frequent infections — one round after another — of certain conditions, such as:

- pink eye
- sinus infections
- thrush
- colds
- chronic gum disease (gingivitis)
- pneumonia
- yeast infections

Individuals with immunodeficiency disorders may also develop chronic abdominal pain, and they may even lose weight over time.

Types of immunodeficiency disorders

An immune deficiency disease or disorder occurs when the immune system is not working as expected. If you're born with a deficiency from a genetic cause, it's called primary immunodeficiency disease. There are more than 200 primary immunodeficiency disorders.

Examples of primary immunodeficiency disorders include:

- common variable immunodeficiency (CVID)
- severe combined immunodeficiency (SCID), which is also known as alymphocytosis
- chronic granulomatous disease (CGD)

Secondary immunodeficiency disorders happen when an outside source like a chemical or infection weakens your body. The following can cause a secondary immunodeficiency disorder:

- severe burns
- chemotherapy
- radiation
- diabetes mellitus
- malnutrition

Examples of secondary immunodeficiency disorders include:

- AIDS
- cancers of the immune system, like leukemia
- immune-complex diseases, like viral hepatitis
- multiple myeloma (cancer of the plasma cells, which produce antibodies)

Gout

Gout is painful arthritis formed on the joints of the big toe. It is usually caused by the presence of high level of uric acid in the blood, which crystallizes and settles in the body. The uric acid in the body is formed due to the breakdown of the waste products in the bloodstream, mainly those containing the purines or alkalis. Purines are the organic compound which is produced naturally by the body. Also, they can be ingested from high-alkaline foods such as meat or by being over-weighted. Purines are the organic compounds produced naturally within the body.

When the body is affected by these uric acid crystals, it causes an inflammation and a kind of redness, swelling in the joint tissues of the big toe, which is the result of gout. This condition is commonly found in men under the age of 30 and rarely seen in women.

Symptoms of Gout

The severe or painful symptoms of gout usually resolve within a week, later they altogether disappear for months or over years of time. Some of the symptoms of this disease are given below:

- The joints such as the knees, heels, and sometimes wrist are also infected.
- More often the joint of the big toe is inflamed, which is seen in the form of reddish swollen like.
- Gout also causes severe bursitis: An inflammation caused by the fluid-filled sac of the joints.
- There is also a risk of kidney related diseases like kidney stones which are developed from the Gout.
- The occurrence of fatigue and also a high fever from this arthritis.

Pseudogout

Pseudogout, a kind of inflammatory gouty arthritis that causes stiffness, pain, redness, and swelling in the joints of the body. It can affect one or several joints at once. The knee is the part of the body that is majorly affected. Some of the other parts include the hips, elbows, shoulders, joints of the fingers, toes, and ankles.

Treatments and Prevention of Gout

The precautionary measures and remedies given below can help to prevent the gout attack:

- Add some of the nutritional supplements in your diets such as vitamin that improves and maintains health benefits.
- Focus on maintaining the normal uric acid levels, repairing tissue damages, and also promoting the healing of tissues.
- Several shreds of evidence show that regular application of ice cubes for about 20 minutes a day reduces swelling and the pain.
- Intake of protein supplements should be limited to under a 0.8g/kg of body weight per day.
- During a severe attack, a proper diagnosis and medication should be followed and a continuous focus on relieving inflammation and the pain.

Orotic Aciduria

Hereditary orotic aciduria is an extremely rare genetic disorder. When untreated, affected infants can develop a blood (hematologic) disorder called megaloblastic anemia as well as failure to thrive, susceptibility to infection, and orotic acid crystals in the urine (crystalluria)

resulting from excretion of orotic acid in the urine. Impaired neurological development has been observed, but invariably, especially since a treatment has become available.

Because so few individuals have been identified with this disorder, much about hereditary orotic aciduria is not fully understood. The disorder is caused by variations in the *UMPS* gene. In 2015, the U.S. Food and Drug Administration (FDA) approved a treatment called uridine triacetate (Xuriden) for this disorder.

Signs & Symptoms

Some affected infants develop megaloblastic anemia, a condition in which the bone marrow produces unusually large, structurally-abnormal, immature red blood cells (megaloblasts). Megaloblastic anemia usually becomes apparent within the first few months of life.

Some infants and children may have neurological problems including delays in reaching developmental milestones (developmental delays). There may also be delays or issues with intellectual development including mild intellectual disability. Seizures (epilepsy) have been reported in some individuals. Some infants fail to gain weight and grow as they normally would for their age and gender (failure to thrive), but others are normal. As all children grow older, height and weight appear to fall in the normal range.

Sometimes, the urine of people with hereditary orotic aciduria is cloudy because of the presence of orotic acid crystals (crystalluria). These crystals may also play a role in episodes of obstructive uropathy that have can also occur. Obstructive uropathy is a condition in which there is some type of obstruction of the urinary tract, which can cause urine to back up, lead to blood to appear in the urine (hematuria), and other complications.

Other symptoms have been reported in one or two individuals, but researchers are not sure if they are features of the disorder, or if they occurred for other reasons or were coincidental findings. These symptoms include diarrhea, congenital malformations, inflammation of the mouth and lips (stomatitis), and misalignment of the eyes (strabismus). Some affected infants had congenital heart disease, including septal defects. Septal defects are abnormalities in the walls (septum) that separate the lower chambers of the heart (ventricles), or the upper chambers of the heart (atria).

CAUSES

Hereditary orotic aciduria is caused by variations in the uridine monophosphate synthetase (*UMPS*) gene. Genes provide instructions for creating proteins that play a critical role in many functions of the body. When a mutation of a gene occurs, the protein product may be faulty, inefficient, absent, or overproduced. Depending upon the functions of the particular protein, this can affect many organ systems of the body, including the brain.

Xanthinuria

Hereditary xanthinuria is a condition that most often affects the kidneys. It is characterized by high levels of a compound called xanthine and very low levels of another compound called uric acid in the blood and urine. The excess xanthine can accumulate in the kidneys and other tissues. In the kidneys, xanthine forms tiny crystals that occasionally build up to create kidney stones. These stones can impair kidney function and ultimately cause kidney failure. Related signs and symptoms can include abdominal pain, recurrent urinary tract infections, and blood in the urine (hematuria). Less commonly, xanthine crystals build up in the muscles, causing pain and cramping. In some people with hereditary xanthinuria, the condition does not cause any health problems.

Causes

Hereditary xanthinuria type I is caused by mutations in the XDH gene. This gene provides instructions for making an enzyme called xanthine dehydrogenase. This enzyme is involved in the normal breakdown of purines, which are building blocks of DNA and its chemical cousin, RNA. Specifically, xanthine dehydrogenase carries out the final two steps in the process, including the conversion of xanthine to uric acid (which is excreted in urine and feces). Mutations in the XDH gene reduce or eliminate the activity of xanthine dehydrogenase. As a result, the enzyme is not available to help carry out the last two steps of purine breakdown. Because xanthine is not converted to uric acid, affected individuals have high levels of xanthine and very low levels of uric acid in their blood and urine. The excess xanthine can cause damage to the kidneys and other tissues.

Hereditary xanthinuria type II results from mutations in the MOCOS gene. This gene provides instructions for making an enzyme called molybdenum cofactor sulfurase. This enzyme is necessary for the normal function of xanthine dehydrogenase, described above, and another enzyme called aldehyde oxidase. Mutations in the MOCOS gene prevent xanthine dehydrogenase and aldehyde oxidase from being turned on (activated) . The loss of xanthine dehydrogenase activity prevents the conversion of xanthine to uric acid, leading to an accumulation of xanthine in the kidneys and other tissues. The loss of aldehyde oxidase activity does not appear to cause any health problems.

Serology: C-reactive protein

A C-reactive protein (CRP) test measures the level of C-reactive protein in your blood. Your liver releases CRP into your bloodstream in response to inflammation. Healthcare providers use this test to help diagnose and monitor several different causes of inflammation, such as infections and certain autoimmune conditions.

A C-reactive protein (CRP) test measures the level of C-reactive protein — a protein made by your liver — in your blood. Your liver releases CRP into your bloodstream in response to inflammation.

When the body encounters an offending agent (like viruses, bacteria or toxic chemicals) or an injury, it activates your immune system. The immune system sends out its first responders: inflammatory cells and cytokines.

These cells begin an inflammatory response to trap bacteria and other offending agents or start healing injured tissue. The result can be pain, swelling, bruising or redness. But inflammation also affects body systems you can't see, such as your joints.

Low levels of CRP in your blood. Moderately to severely elevated levels may be a sign of a serious infection or other inflammatory condition.

A C-reactive protein (CRP) test to help diagnose or rule out certain conditions, including:

- Severe bacterial infections, such as sepsis.
- Fungal infections.
- Osteomyelitis (infection of your bone).
- Inflammatory bowel disease (IBD).
- Some forms of arthritis.
- Autoimmune diseases, such as rheumatoid arthritis or lupus (systemic lupus erythematosus).
- Pelvic inflammatory disease (PID).

Providers also use CRP tests to monitor people after surgery or other invasive procedures to check for infection during their recovery period.

A CRP test alone can't diagnose a condition or where the inflammation is in your body. Because of this, providers generally order additional tests if the CRP results show that you have inflammation.

A CRP test is needed if you have symptoms of a serious bacterial infection, including:

- Fever.
- Chills.
- Rapid breathing (tachypnea).
- Rapid heart rate (tachycardia).
- Nausea and vomiting.