KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed University Established Under Section 3 of UGC Act 1956)
Coimbatore - 641021.
(For the candidates admitted from 2017 onwards)

DEPARTMENT OF BIOCHEMISTRY

STAFF NAME: Ms.P.LOGANAYAKI
SUBJECT : MOLECULAR BASIS OF NON- INFECTIOUS HUMAN DISEASE

SEMESTER : III
SUBJECT CODE : 18**BCU504-A** **CLASS : II B.Sc.(BC)**

SCOPE:
To equip the students to understand, critically evaluate, analyze and interpret the basics of non infectious diseases

OBJECTIVE:
Summarize the expected laboratory findings in regard to non infectious diseases such as diabetes mellitus and to develop skills in the interpretation of biochemical data used in the investigation and diagnosis of non-infectious disease

Unit 1
Nutritional disorders
Overview of major and minor nutrient components in the diet. Balanced diet and the concept of RDA. Nutrient deficiencies; Kwashiorkor and Marasmus, Scurvy, beri beri, pellagra and B12 deficiency, Xerophthalmia and Night blindness, Vitamin D deficiency, Vitamin K deficiency. Discuss with relation to biochemical basis for symptoms. Obesity and eating disorders like Anorexia nervosa and Bullemia.

Unit 2
Metabolic and Lifestyle disorders
Diabetes mellitus A metabolic syndrome and the relationship with hypertension, obesity, hypothyroidism and stress. Cardio vascular disorders and Atherosclerosis-defining the broad spectrum of ailments that fall in this category, understanding the factors that contribute to the syndrome, stages of disorder and the management of the condition. Irritable bowel syndrome-biochemistry behind the disorder and the influence of diet, stress and environment on the condition.

Unit 3
Cancer: Initiation and stages of progression
Cancer: characteristics of a transformed cell, causes and stages of Cancer, molecular basis for neoplastic growth and metastasis, Proto-oncogenes and tumor suppressor genes; Cancer causing mutations; Tumor viruses; Biochemical analysis of cancer; Molecular approaches to cancer treatment.

Unit 4

Diseases due associated with misfolded proteins and multifactorial complex disorders

Introduction to protein folding and proteosome removal of misfolded proteins; etiology and molecular basis for Alzheimer's, Prion diseases, Huntington's Chorea, sickle cell anemia, Thalassemia. Understanding the definition of multifactorial diseases. Polygenic diseases and the relationship of environmental factors and genetic makeup in the onset of diseases.

Disorders of mood : Schizophrenia, dementia and anxiety disorders. Polycystic ovarian syndrome, Parkinson's disease, ALS

Unit 5

Monogenic diseases

In born errors in metabolism: PKU, Alkaptonuria, Maple syrup urine disease; Receptor and transport defects: Cystic fibrosis, Long QT syndrome, familial hypercholesterolemia, Achondroplasia. Hemoglobinopathies and clotting disorders.

REFERENCES

Willey, J.M., Sherwood, L.M., Woolverton, C.J. (2008). Prescott, Harley, Klein's Microbiology, 7th Ed., Mc Graw Hill International Edition (New York) ISBN: 978-007-126727.

Mandell, Douglas and Bennett. S., (2008). Principles and practices of Infectious diseases, 7th edition, Volume, 2. Churchill Livingstone Elsevier.

Kenneth, J.R., Ray, C.G., (2010). Sherris Medical Microbiology: An Introduction to Infectious Diseases by Publisher: McGraw-Hill.

Patrick, R., Murray, K.S., Michael A.R., and Pfaller, (2011). Medical Microbiology, Elsevier Health Sciences

KARPAGAM ACADEMY OF HIGHER EDUCATION

(Deemed to be University Established Under Section 3 of UGC Act 1956)

Coimbatore – 641 021.

LECTURE PLAN
DEPARTMENT OF BIOCHEMISTRY

STAFF NAME: Ms.P.LOGANAYAKI
SUBJECT NAME: MOLECULAR BASIS OF NON-INFECTIOUS HUMAN DISEASES

SUB.CODE: 18BCU504-A

SEMESTER:III **CLASS: III B.Sc (BC)**

S. No	Duration of period	Topics covered	Books referred	Page No	Web page referred
1	**1**	Overview of major and minor nutrient components in the diet	R1	1087-1134	
2	**1**	Balanced diet and the concept of RDA	R1, T1	1108-1109, 688-689	
3	**1**	Kwashiorkor and Marasmus	T1	689-691	
4	**1**	Scurvy, beri beri, pellagra	T1	156-165	
5	**1**	Vitamin D deficiency, Vitamin K deficiency and B12 deficiency	T1	149-152, 178-182	
6	**1**	Xerophthalmia and Night blindness	J1		
7	**1**	Obesity	T1	691-694	
8	**1**	Eating disorders like Anorexia nervosa and Bullemia.	T1		W1
9	**1**	Revision and Question paper Discussion			
Total no of hours planned for unit I: 9					
Unit II: Metabolic and Lifestyle disorders					
1	**1**	Diabetes mellitus A metabolic syndrome	R2	972-976	
2	**1**	Diabetes mellitus A metabolic syndrome relationship with hypertension, obesity, hypothyroidism and stress	R2	974-975	
3	**1**	Cardio vascular disorders	R2	271-276, 258-264	
4	**1**	Atherosclerosis-defining the broad spectrum of ailments that fall in this category,	R2	849-852	
5	**1**	Understanding the factors that contribute to the syndrome	R2, T1	850, 389-392	
6	**1**	Stages of disorder and the management of the	R2	849	

		condition			
7	**1**	Irritable bowel syndrome	J2		
8	**1**	Biochemistry behind the disorder and the influence of diet, stress and environment on the condition.	T1	704-710, 688-689	
9	**1**	Revision and Question paper Discussion			
Total no of hours planned for unit II: 9					
		Unit III: Cancer: Initiation and stages of progression			
1	**1**	Cancer: Characteristics of a transformed cell	T1	714-715	
2	**1**	Causes and stages of Cancer	T1	715-719	
3	**1**	Molecular basis for neoplastic growth	T1	721	
4	**1**	Metastasis	T1	728-729	
5	**1**	Proto-oncogenes and tumor suppressor genes	T1	720-721	
6	**1**	Tumor viruses	T1	717-719	
7	**1**	Biochemical analysis of cancer	T1	730-736	
8	**1**	Molecular approaches to cancer treatment.	R4	487-502	
9	**1**	Revision and Question paper Discussion			
Total no of hours planned for unit III: 9					
		Unit IV: Diseases due associated with misfolded proteins and multifactorial complex disorders			
1	**1**	Introduction to protein folding and proteosome removal of misfolded proteins	R3	140-148	
2	**1**	Etiology and molecular basis for Alzheimer's, Prion diseases, Huntington's Chorea	R2	746, 711-712	
3	**1**	Sickle cell anemia, Thalassemia	T1	89-95	
4	**1**	Understanding the definition of multifactorial diseases	J5		
5	**1**	Polygenic diseases and the relationship of environmental factors and genetic makeup in the onset of diseases.	J5		
6	**1**	Disorders of mood : Schizophrenia, dementia and anxiety disorders	R2	745-747	
7	**1**	Polycystic ovarian syndrome	R2	974	
8	**1**	Parkinson's disease, ALS	T2	822-883	
9	**1**	Revision and Question paper Discussion			
Total no of hours planned for unit IV: 9					
		Unit V: Monogenic diseases			

1	**1**	In born errors in metabolism: PKU, Alkaptonuria	T1	432-434	
2	**1**	Maple syrup urine disease	T1	456-457	
3	**1**	Receptor and transport defects: Cystic fibrosis	T1	19	
4	**1**	Long QT syndrome	J3		
5	**1**	Familial hypercholesterolemia	T1	377	
6	**1**	Achondroplasia	J4		
7	**1**	Hemoglobinopathies	T1	140-143	
8	**1**	Clotting disorders.	T2	137-138	
9	**1**	Revision and Question paper Discussion			
Total no of hours planned for unit V: 9					
		Previous year ESE question paper discussion			
1	1	Previous year question paper discussion			
2	1	Previous year question paper discussion			
3	1	Previous year question paper discussion			
Total no of hours required to complete the course: 48					

REFERNCE BOOKS:

R1- Textbook of Biochemistry with clinical correlations, Thomas M. Delvin, Fourth Edition, A John Wiley and Sons, Inc., Publications.

R2– Textbook of Medical Physiology, Guyton and Hall, Eleventh Edition, Elsevier Saunders.

R3– Lehninger Principles of Biochemistry, David L.Nelson and Micael M.Cox, Fifth Edition, W. H. Freeman and Company.

R4- Cancer biology, Raymond W.Ruddon, 2007, Oxford University press.

TEXT BOOKS:

T1 - Textbook of Medical Biochemistry, MN Chatterjea, Eight Edition, Jaypee Brothers Medical Publishers (P) LTD, New Delhi.

T2 – Essentials of Medical Physiology, K Sembulingam and Prema Sembulingam, Sixth Edition, Jaypee Brothers Medical Publishers (P) LTD, New Delhi.

JOURNAL REFERENCE

J1- WHO- VMNIS, Xerophthalmia and Night blindness, 2014.

J2 - William D. Chey, MD; Jacob Kurlander, MD; Shanti Eswaran, MD, Clinical Review& Education JAMA March 3, 2015 Volume 313, Number 9.

J3- K.E. Waddell-Smith, J.R. Skinner, Update on the Diagnosis and Management of Familial Long QT Syndrome Heart, Lung and Circulation (2016) 25, 769–776.

J4- Wright MJ, Irving MD. Clinical management of achondroplasia, *Arch Dis Child* (2011). doi:10.1136/adc.2010.189092

J5- Saba Sheikh, Safia, Journal of Neurodegenerative Diseases,Volume 2013, Article ID 563481, 8 pages.

WEB PAGE REFERANCE:

W1 - https://www.researchgate.net/publication/19636541 The Pathophysiology of Anorexia Nervosa and Bulimia Nervosa

UNIT-I-SYLLABUS

Nutritional disorders
Overview of major and minor nutrient components in the diet. Balanced diet and the concept of RDA. Nutrient deficiencies; Kwashiorkor and Marasmus, Scurvy, beri beri, pellagra and B12 deficiency, Xerophthalmia and Night blindness, Vitamin D deficiency, Vitamin K deficiency. Discuss with relation to biochemical basis for symptoms. Obesity and eating disorders like Anorexia nervosa and Bullemia.

Nutrition:

Nutrition is best defined as the composition and quantity of food intake and the utilization of the food intake by living organisms. Study of human nutrition can be divided into three areas:

- Under nutrition
- Over nutrition
- Ideal nutrition

Energy Metabolism:

Much of the food we eat is converted to ATP and other high-energy compounds, which are utilized to drive biosynthetic pathways, generate nerve impulses, and power muscle contraction. Energy content of foods is generally described in terms of calories. Technically speaking, this refers to kilocalories of heat energy released by combustion of that food in the body. Energy Expenditure is influenced by Four Factors:

- **surface area (Height and Weight)**
  The effects of surface area are thought to be simply related to the rare of heat loss by the body-the greater the surface area, the greater the rate of heat loss. While it may seem surprising, a lean individual actually has a greater surface area, and thus a greater energy requirement, than an obese individual of the same weight.

- **Age**
  Age may reflect two factors: growth and lean muscle mass in infants and children more energy expenditure is required for rapid growth, which is reflected in a higher basal metabolic rate (rate of energy utilization in resting state). In adults muscle tissue is

gradually replaced by fat and water during the aging process, resulting in a 2% decrease in basal metabolic rate (BMR) per decade of adult life.

- **Sex**
  Women tend to have a lower BMR than men due [o a smaller percentage of lean muscle mass and the effects of female hormones on metabolism.

- **Physical Activity**
  The effect of activity levels on energy requirements is obvious. The effect of a regular exercise program on energy expenditure can be quite beneficial Regular exercise increases basal metabolic rate, allowing calories to burn up more rapidly 24 hours a day.

- Hormone levels are important also, since thyroxin, sex hormones, growth hormone, and, to a lesser extent, epinephrine and cortisol increase BMR. The effects of epinephrine and cortisol in severe stress and major trauma significantly increase energy requirements.

Overview of major nutrient components in the diet:

Protein:

- Protein carries a certain mystique as a "body-building" food. While protein is an essential structural component of all cells, it is equally important for maintaining essential functions in our body.
- Excess protein is treated as a source of energy, with the glucogenic amino acids being converted to glucose and the ketogenic amino acids to fatty acids and keto acids. Both kinds of amino acids are eventually converted to triacylglycerol in adipose tissue if fat and carbohydrate supplies are already adequate to meet energy requirements.
- One is the complement of essential amino acids present in the diet. Essential amino acids are amino acids that cannot be synthesized by the body.
- Most animal proteins generally contain all essential amino acids in about the quantities needed by the human body Vegetable proteins, often lack one or more essential amino acids, in some cases, be more difficult to digest.
- Even so, vegetarian diets can provide adequate protein provided enough extra protein is consumed to provide sufficient quantities of the essential amino acids and/or two or more different proteins are consumed together, which complement each other in amino acid content.

- Assuming adequate calorie intake and a 75ok efficiency of utilization, which is typical if mixed protein in the average American diet, the recommended protein intake is 0.8 /kg body wt day-1. This amounts to about 58 g protein day-1 for a 72-kg (I60Jb) man and about 44 g dry-t for a 55-kg (120-1b) woman.
- The most common form of malnutrition in the world is protein-energy malnutrition (PEM). In developing countries inadequate intake of protein and energy is all too common, especially in infants and young children.
- Marasmus is defined as inadequate intake of both protein and energy Kwashiorkor is defined as inadequate intake of protein with adequate energy intake.

Nitrogen balance:

- Nitrogen balance is the relationship between intake of nitrogen and excretion of nitrogen. A normal adult is in nitrogen equilibrium, with losses just balanced by intake.
- Negative nitrogen balance results from inadequate dietary intake of protein, since amino acids utilized for energy and biosynthetic reactions are not replaced.
- Positive nitrogen balance occurs when there is a net increase in body protein stores, such as in growing children, pregnant women, or convalescing adults.

Carbohydrates:

- Glucose, fructose, galactose and to a minor degree, mannose, as well as those carbohydrates that yield them on digestion, are available to the body as energy producers. Ribose, deoxy ribose required for nucleic acid synthesis, is obtained from HMP-shunt. Dietary polysaccharides or disaccharides cannot be utilized until digested to the monosaccharide stage. When introduced directly into blood stream, they act as foreign bodies and are excreted, chiefly by the kidneys.
- *Requirement of carbohydrates in diet:* Normally 55 to 65 per cent of the total food calories should come from carbohydrates. A moderately active man requiring 3000 C/day, should take about 450 gm carbohydrates daily. But in India, poorer sections of the population derive more than 85 per cent of the food calories from carbohydrates.
- Dietary protein must be used for energy generation and becomes unavailable for building and replacing tissue. Thus, as energy (calorie) content of the diet from carbohydrate and fat increases, the need for protein decreases. This is referred to as protein sparing.
- *Action of carbohydrates on plasma lipids:* Replacement of a ‘low’ or moderate carbohydrate diet by a high carbohydrate diet may produce temporary rise in plasma TG and VLDL and temporary reduction in blood cholesterol. Substitution of starch by

fructose or sucrose in the diet may also increase plasma TG by increasing lipogenesis from fructose.

- *Relation with B-vitamins:* With diets rich in carbohydrates, the requirements for B-vitamins, particularly thiamine (vit B1) increases because of the essential role of these in carbohydrate metabolism.
- *Role of cellulose:* Celluloses are polysaccharides found in plants. They are indigestible by human beings as there is no enzyme in our GI tract which can split β-1 →4 linkage. But, celluloses in diet, contribute bulk to the intestinal contents, and therefore, in normal amounts promote intestinal motility, i.e. increases peristalsis and remove constipation.
- *Excessive Intake of Carbohydrates in Diet:* The most common form of carbohydrate intolerance is diabetes mellitus, caused either by subnormal insulin production or lack of insulin receptors. Lactase insufficiency is also a common disorder of carbohydrate [e metabolism. Without the enzyme lactase, dietary Lactose is not significantly hydrolyzed or absorbed.

Glycaemic Index (GI):

- The glycaemic index or GI is a measure of effects of carbohydrates on blood sugar levels. The glycaemic index (GI) of a food is defined as the area under the two hour blood glucose response
- curve (AUC) following the ingestion of a fixed portion of carbohydrates (usually 50 gm)

$$GI = \frac{\text{AUC of the test food}}{\text{AUC of the standard}} \times 100$$

- Carbohydrates that break down quickly during digestion releasing glucose *rapidly* into the circulation have a *high GI.*
- Carbohydrates that break down more *slowly*, releasing glucose more gradually into the bloodstream have a ***low GI***.

Lipids:

- A wide variety of lipids is provided in a balanced diet. All components of biologically significant lipids, with the exception of essential fatty acids, can be synthesized in the body from non-lipid precursors. The main function of dietary lipids, like that of

carbohydrates, is ***to provide energy,*** largely through oxidation of their constituent free fatty acids.

- The dietary lipids serve another indirect function, serving ***as "carriers" of certain fat soluble vitamins*** (vit A, D, E and K) and pro vitamins like carotenes, which because of their solubility in fats, occur in nature mainly in association with these substances.
- Lipids may also exert a relatively ***minor "proteins paring effect"***, apart from their calorie contribution.
- ***Requirement:*** Neutral fats (TG), comprising the largest fraction of food lipids are quantitatively the most important of these substances. Under usual conditions, fats provide 20 to 35% of the calories of the diet, i.e. 1 to 2 gm/kg of body weight in the average moderately active adult.
- Dietary fat has a ***high "satiety value",*** i.e. the ability to satisfy hunger.
- ***Supply of polyunsaturated FA:*** Food fats should contain adequate amounts of polyunsaturated FA to supply at least 1 per cent of total calories in adult man and 4 per cent of same in children. The nutritional significance of the polyunsaturated "EFA" have already been discussed. They are provided in ample amounts by a balanced diet that contains an adequate quantity of naturally occurring lipids (Linoleic acid mainly in plant and seed oils and arachidonic acid of animal origin). Not all vegetable fats are rich in linoleic acid (low content in coconut oil), nor are all animal fats deficient in this substance (high content in chicken fat). It is generally agreed that in man elevated plasma cholesterol levels of certain types may be lowered by:
    - Restriction of fat intake and
    - Substitution of polyunsaturated FA for saturated FA.
- ***Quality of fat:*** Chain length and saturation of FA and MP of TG influence the nutritive quality of food fats. TG of short chain, medium chain, or polyunsaturated FA are more easily digested by *Lipases* in the intestine. While the TG of caprylic acid (C8) has a digestibility of more than 97 per cent, that of palmitic acid (C16) has a digestibility of about 70per cent only. Unsaturated TG are also more readily absorbed than saturated ones. Oils of vegetable and seeds (e.g. sunflower oil, groundnut oil, soyabean oil, mustard oil) contain mainly unsaturated FA and are preferable.
- Medium chain TG has been used in treatment of chyluria and chylothorax as they are absorbed directly in portal blood.
- ***Excess of fats in diet:*** An excessive high fat intake inhibits gastric secretion and motility, producing anorexia and gastric discomfort. Intestinal irritation and diarrhoea may result

from excessive amounts of FA in the intestine. Excess of fats, particularly saturated fats, in the diet may reduce the gastric digestion of proteins, because fat digestion starts mainly in the intestine, thus preventing exposure of food proteins to pepsins. Excess fat intake can cause excessive production of ketone bodies, due to high FA oxidation and also can lead to Type 1 fatty liver.

- Delay or failure of fat absorption may also reduce Ca++ absorption as calcium forms insoluble soaps with higher FA in intestine.

Fibers:

- Dietary fiber comprises those components of food that cannot be broken down by human digestive enzymes and sometimes can be broken down partially.
- Cellulose and most hemicelluloses increase stool bulk and decrease transit time and are associated with the effects of fiber on regularity.
- Lignins adsorb organic substances such as cholesterol so as to lower plasma cholesterol concentration.
- Mucilaginous fibers, such as pectin and gums, tend to form viscous gels in the stomach and intestine and slow [he rate of gastric emptying, thus slowing the rate of absorption of many nutrients.

Overview of Minor nutrient components in the diet:

Vitamins:

- Vitamins are organic nutrients that are essential for life. Our bodies need vitamins to function properly. We cannot produce most vitamins ourselves, at least not in sufficient quantities to meet our needs. Therefore, they have to be obtained through the food we eat.
- The vitamins are mainly classified into two:
  - **Fat-soluble vitamins**
    1. Vitamin A
    2. Vitamin D
    3. Vitamin E
    4. Vitamin K
  - **Water Soluble vitamins**
    1. Vitamin C (ascorbic acid),
    2. Vitamin B complex group includes:
       a. Vitamin B1 (thiamine)
       b. Vitamin B2 (riboflavin)

c. Vitamin B6 (pyridoxine)
d. Vitamin B12
e. Niacin
f. Biotin
g. Pantothenic acid
h. Choline

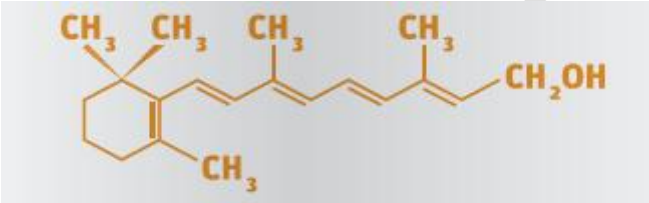
- While plants and micro-organisms can themselves produce the vitamins necessary for the metabolism, humans and animals lost this ability during the course of evolution. Because they lack the enzymes necessary to make vitamins in the body, humans and animals have to ingest them via the diet (with the exception of vitamin D, which is synthesized via the action of sunlight). Choline is the most recent addition to the group of essential nutrients.

- **Vitamin A -Eyes, immune system, skin, genes, growth**
- **Vitamin D -Skin (formed in), intestines, kidneys, bones**
- **Vitamin E -Antioxidant, blood cells, stored in liver**
- **Vitamin K -Blood (clotting)**
- **Vitamin B1 -Energy metabolism, nerve and muscle activity**
- **Vitamin B2- Energy metabolism, growth and reproduction, vision**
- **Vitamin B3 -Energy metabolism, neurological processes**
- **Vitamin B5-Skin and hair, wound healing, blood lipid profile**
- **Vitamin B6-Nerve activity, blood formation, DNA**
- **Vitamin B7 -Hair, nails, skin Vitamin B9 DNA synthesis**
- **Vitamin B12 -Nerve activity, neurotransmitters**
- **Vitamin C -Antioxidant, iron absorption, immune system**
- **Choline -Nerve activity, gene expression**

Vitamin A -Retinol | Carotenoids:

- Vitamin A plays a central role in our vision, skin, genes, growth, and immune system. It is especially important during the early stages of pregnancy in supporting the developing embryo. Infections and fevers increase the requirement for vitamin A.
- Three different forms of vitamin A are active in the body: retinol, retinal, and retinoic acid. These are known as retinoids. The cells of the body can convert retinol and retinal to the other active forms of vitamin A as needed.

- Each form of vitamin A performs specific tasks. Retinol supports reproduction and is the major transport form of the vitamin. Retinal is active in vision and is also an intermediate in the conversion of retinol to retinoic acid. Retinoic acid acts like a hormone, regulating cell differentiation, growth, and embryonic development. Foods derived from animals provide retinol in a form that is easily digested and absorbed.



The primary sources of vitamin A:

- Retinol is found in liver, egg yolk, butter, whole milk, and cheese. Carotenoids are found in orange-flesh sweet potatoes, orange-flesh fruits (i.e., melon, mangoes, and persimmons), green leafy vegetables (i.e., spinach, broccoli), carrots, pumpkins, and red palm oil.

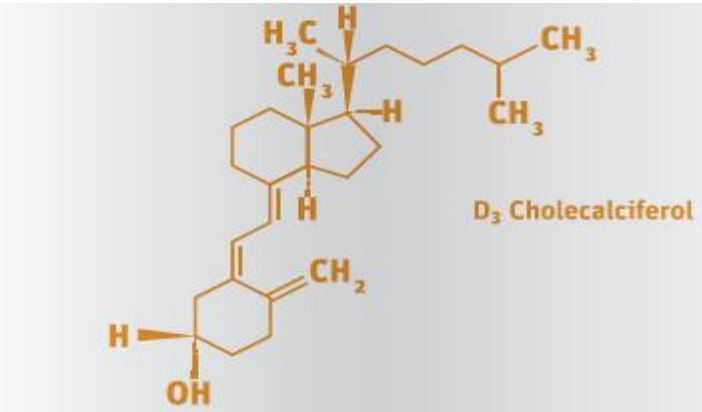
Risks related to inadequate or excess intake of vitamin A :

- About 90% of vitamin A is stored in the liver. Vegetarians can meet their vitamin A requirements with sufficient intakes of deeply colored fruits and vegetables, with fortified foods, or both.
- Vitamin A deficiency is a major problem when diets consist of starchy staples, which are not good sources of retinol or β-carotene, and when the consumption of deeply colored fruits and vegetables, animal-source foods, or fortified foods is low.
- Vitamin A plays a role in mobilizing iron from liver stores, so vitamin A deficiency may also compromise iron status. Excessive intakes of pre-formed vitamin A can result in high levels of the vitamin in the liver – a condition known as hypervitaminosis A.

Vitamin D- Calciferol:

- With the help of sunlight, vitamin D is synthesized by the body from a precursor derived from cholesterol. The active from of vitamin D is actually a hormone that targets organs – most notably the intestines, kidneys, and bones.

- In the intestine, vitamin D is involved in the absorption of calcium and phosphorus. In the bone, it assists in the absorption of calcium and phosphorus, helping bones grow denser and stronger as they absorb and deposit these minerals.



The primary sources of vitamin D:

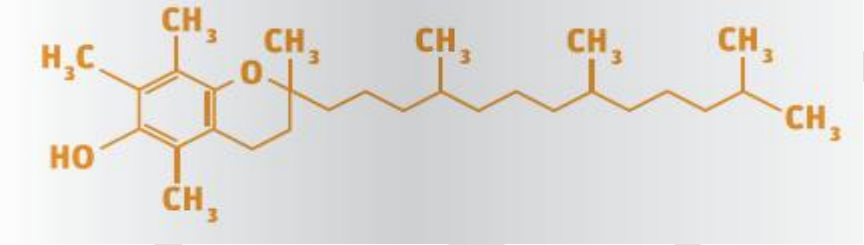
- Sunlight – exposure to ultraviolet B (UVB) rays is necessary for the body to synthesize vitamin D from the precursor in the skin.
- There are a few foods that are natural sources of vitamin D. These sources are oily fish, egg yolk, veal, beef, and mushrooms.

Risks related to inadequate or excess intake of vitamin D:

- Inadequate exposure to sunlight is the primary risk factor for poor vitamin D status. The use of sunscreen, higher levels of melanin in skin (i.e., dark skin), skin coverings (clothes, veils), and time of day are factors that decrease exposure to UVB rays.
- Breast milk is poor sources of vitamin D. Children who are exclusively breastfed and have no or little sun exposure require vitamin D supplements to meet their vitamin D requirements.
- One of the main roles of vitamin D is to facilitate the absorption of calcium and phosphorus. Consequently, a vitamin D deficiency creates a calcium deficiency, with significant consequences to bone health.
- Among children and adolescents, it may cause rickets and adversely affect peak bone mass. In adults, vitamin D deficiency increases the risk of osteomalacia and osteoporosis.

Vitamin E- α-Tocopherol:

- The most active form of vitamin E is α-tocopherol, which acts as an antioxidant. Vitamin E protects cell membranes, proteins, and DNA from oxidation and thereby contributes to cellular health. It prevents oxidation of the polyunsaturated fatty acids and lipids in the cells.
- Vitamin E is stored in the liver and is safe even at high intakes.



The primary sources of vitamin E:

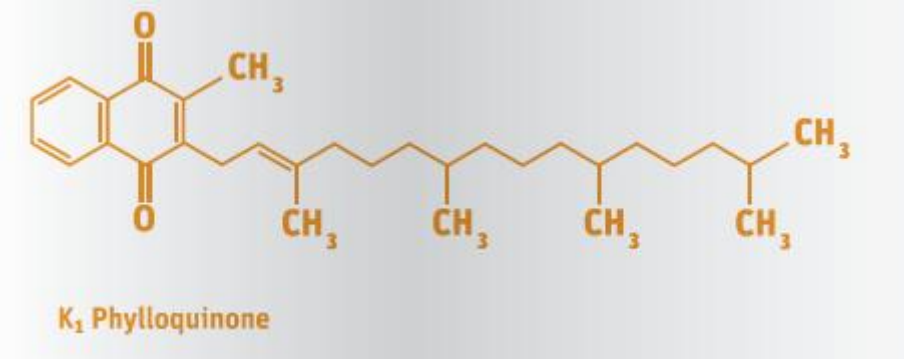
- Vitamin E in the α-tocopherol form is found in edible vegetable oils, especially wheat germ, and sunflower and rapeseed oil. Other good sources of vitamin E are leafy green vegetables (i.e., spinach, chard), nuts (almonds, peanuts) and nut spreads, avocados, sunflower seeds, mango and kiwifruit.

Risks related to inadequate or excess intake of vitamin E:

- Individuals whose diets consist mostly of starchy staples – with inconsistent intake of edible oils or other vegetable sources of vitamin E – are at a higher risk of inadequate vitamin E intake.
- Vitamin E deficiency leads to red blood cell breakage and nerve damage. Recent studies from Bangladesh link low vitamin E blood levels to an increased risk of miscarriage.
- In other studies vitamin E supplementation has been successfully used for the treatment of non-alcoholic fatty liver disease, a condition widespread in overweight and obese people. Excessive intake of vitamin E from food is very rare.

Vitamin K -Phylloquinone | Menaquinones:

- Vitamin K acts primarily in blood clotting, where its presence can make the difference between life and death. More than a dozen different proteins and the mineral calcium are involved in making a blood clot.
- Vitamin K is essential for the activation of several of these proteins. When any of the blood clotting factors is lacking, hemorrhagic disease (uncontrolled bleeding) results.
- Vitamin K also participates in the metabolism of bone proteins, most notably osteocalcin. Without vitamin K, osteocalcin cannot bind to the minerals that normally form bones, resulting in poor bone mineralization. Vitamin K is stored in the liver.



The primary sources of vitamin K:

- Vitamin K is found in plant foods as phylloquinone (K1). Bacteria in the lower intestine can synthesize vitamin K as menaquinone (K2), which is absorbed by the body. Sources of phylloquinone are green leafy vegetables (i.e., parsley, spinach, collard greens, and salad greens), cabbage, and vegetables oils (soybean, canola, olive).
- Menaquinones are also found in fermented foods such as fermented cheese, curds, and natto (fermented soybeans).

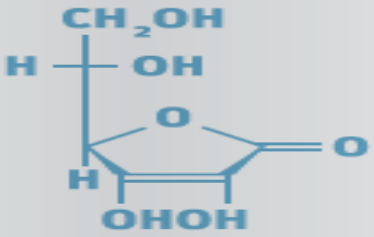
Risks related to inadequate or excess intake of vitamin K:

- Vitamin K is poorly transferred via the placenta and is not found in significant quantities in breast milk, so newborn infants are especially at risk for bleeding.

- This innate vitamin K deficiency is treated with intramuscular injection or oral administration of phylloquinone.
- Supplementation with vitamin K has been found to be beneficial for improving bone density among adults with osteoporosis because it drives synthesis of a special protein called matrix Gla protein.

Vitamin C -Ascorbic Acid:

- Vitamin C parts company with the B-vitamins in its mode of action. It acts as an antioxidant or as a cofactor, helping a specific enzyme perform its job. High levels of vitamin C are found in pituitary and adrenal glands, eyes, white blood cells, and the brain.
- Vitamin C has multiple roles - in the synthesis of collagen, absorption of iron, free radical scavenging, and defense against infections and inflammation.



The primary sources of vitamin C:

- Fruits (especially citrus fruits), cabbage-type vegetables, green leafy vegetables, lettuce, tomatoes, potatoes, and liver (ox /calf).

Bioavailability of vitamin C:

- Levels of vitamin C in foods depend on the growing conditions, season, stage of maturity, cooking practices, and storage time prior to consumption. Vitamin C is easily destroyed by heat and oxygen. Absorption levels depend on the amounts consumed.
- About 70–90% of vitamin C is absorbed. If intakes exceed 1000 mg/day, absorption levels drop to 50%.

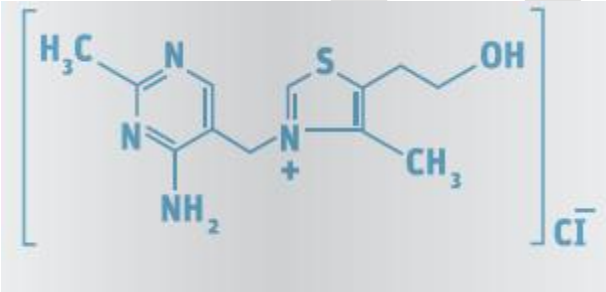
Risks related to inadequate intake of vitamin C:

- Individuals who do not consume sufficient quantities of fruits and vegetables are at risk for inadequate intakes of vitamin C. Because smoking generates free radicals, individuals who smoke have elevated requirements for vitamin C.

- Vitamin C deficiency can cause scurvy; signs of scurvy are bleeding gums, small hemorrhages below the skin, fatigue, loss of appetite and weight, and lowered resistance to infections.

Vitamin B1- Thiamin:

- Thiamin is a sulfur-containing vitamin that participates in energy metabolism, converting carbohydrates, lipids and proteins into energy. Thiamin also plays a key role in nerve and muscle activity.



The primary sources of vitamin B1:

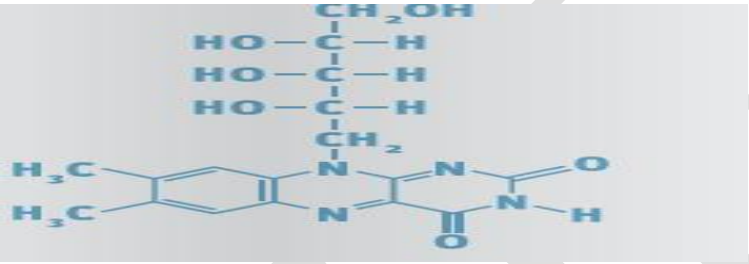
- Offal (liver, kidneys, heart), fish, meat (pork), whole grain cereals, leafy green vegetables, asparagus, eggplant, fruits , legumes (beans and lentils), nuts, soymilk, squash, brewer's yeast.

Risks related to inadequate or excess intake of vitamin B:

- People who consume diets consisting of primarily refined grains (mostly milled flours and polished rice) are at risk for thiamin deficiency. The risk of inadequacy is less when food manufacturers fortify refined grains with vitamin B1.
- Clinical vitamin B1 deficiency is called beriberi, a condition which still occurs in South-East Asia. In beriberi, there is damage to the nervous system characterized by muscle weakness in the arms and legs, or damage to the cardiovascular system which is characterized by dilated blood vessels, causing the heart to work harder and the kidneys to retain salt and water, resulting in edema. No adverse effects have been associated with excessive thiamin intakes.

Vitamin B2- Riboflavin:

- Vitamin B2 participates in oxidation-reduction reactions, by accepting and then donating two hydrogen molecules, which are necessary for releasing energy from carbohydrates, fats and proteins.
- Vitamin B2 stimulates growth and reproduction, plays a role in vision, and in the conversion of vitamins B6, folic acid, and niacin into their active coenzyme forms.



The primary sources of vitamin B2:

- Vitamin B2 is found in offal (liver, kidneys, heart), eggs, meat, milk, yogurt, cheeses, whole grain cereals, dark green leafy vegetables, and brewer's yeast.

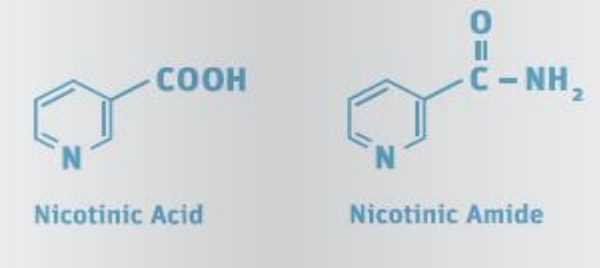
Risks related to inadequate intake of vitamin B2:

- Individuals whose food intake relies primarily on refined cereals, the elderly, chronic dieters, and individuals who exclude milk products from their diet are at risk for inadequate intakes.
- Vitamin B2 requirements are increased during periods of strong growth, such as in pregnancy and lactation. Vitamin B2 deficiency co-occurs with other nutrient deficiencies and it may precipitate deficiencies in vitamin B6 and niacin.
- People with cardiovascular disease, diabetes or cancer are at risk for vitamin B2 deficiency.

Vitamin B3- Niacin:

- Niacin acts as coenzyme in energy-transfer reactions, especially the metabolism of glucose, fat, and alcohol. Niacin is similar to the riboflavin coenzymes in that it carries hydrogen molecules during metabolic reactions.

- It also protects against neurological degeneration. Niacin is unique in that it can also be synthesized from the amino acid tryptophan. It occurs in two forms: niacinamide and nicotinic acid.



The primary sources of vitamin B3:

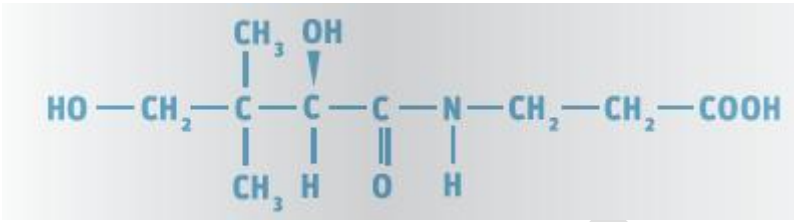
- Primary sources are offal (liver), fish, meat, milk, eggs, whole grain cereals, legumes, fruit (avocados, figs, dates, prunes), and nuts. Other: Synthesized from tryptophan.

Risks related to inadequate or excess intake of vitamin B3:

- Severe niacin deficiency results in a disease called pellagra and its symptoms are dermatitis, diarrhea, dementia and eventually death. Risk of excessive intake is unlikely if niacin is consumed from food sources.
- However consumption of niacin in the form of nicotinic acid from multiple sources at high levels, including dietary supplements, pharmaceutical doses, and fortified foods, may result in adverse effects such as flushing, nausea and vomiting, liver toxicity, blurred vision and impaired glucose tolerance.

Vitamin B5- Pantothenic Acid:

- Vitamin B5 is part of the structure of coenzyme A, the “crossroads” compound in several metabolic pathways, and is involved in more than 100 different steps in the synthesis of lipids, neurotransmitters, steroid hormones, and hemoglobin.
- Vitamin B5 is important for maintenance and repair of tissues and cells of the skin and hair, helps in healing of wounds and lesions, and pantethine, which is a form of vitamin B5, normalizes blood lipid profiles.



The primary sources of vitamin B5:

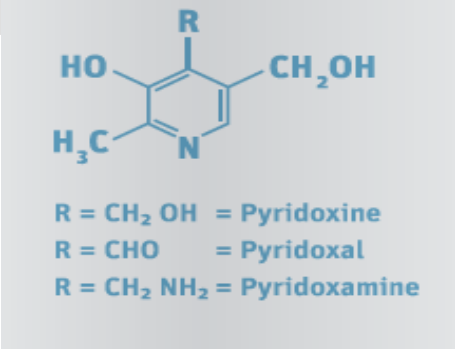
- Vitamin B5 is found in offal (liver, kidneys), meat (chicken, beef), egg yolk, milk, fish, whole grain cereals, potatoes, tomatoes, broccoli, mushrooms. Other: synthesized by intestinal microorganisms but the contribution of this to nutrient status is unknown.

Risks related to inadequate or excess intake of vitamin B5:

- Vitamin B5 deficiency is very rare and symptoms involve a general failure of all the body's systems. Symptoms include fatigue, nausea, vomiting, headaches, tingling sensations ("burning feet" syndrome). No adverse effects have been reported with high intakes of vitamin B5.

Vitamin B6- Pyridoxine:

- Vitamin B6 is required for the majority of biological reactions (i.e., amino acid metabolism, neurotransmitter synthesis, red blood cell formation).
- It occurs in three forms: pyridoxal, pyridoxine, and pyridoxamine. All can be converted to the coenzyme PLP (pyridoxal phosphate), that transfers amino groups from an amino acid to make nonessential amino acids, an action that is valuable in protein and urea metabolism. Vitamin B6 is stored in muscle tissue.



The primary sources of vitamin B6:

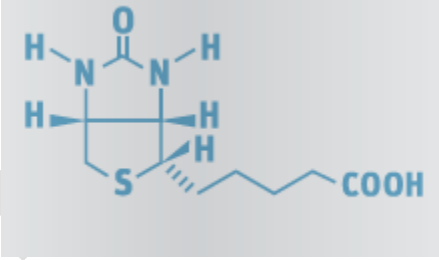
- There are many good sources of vitamin B6, including chicken, liver (cattle, pig), fish (salmon, tuna). Nuts (walnut, peanut), chickpeas, maize and whole grain cereals, and vegetables (especially green leafy vegetables), bananas, potatoes and other starchy vegetables are also good sources.

Risks related to inadequate or excess intake of vitamin B6:

- Deficiency of vitamin B6 alone is uncommon; usually it occurs in combination with a deficit in other B-vitamins. Individuals at risk for poor intakes are alcoholics and those taking tuberculosis medication.
- Signs of vitamin B6 deficiency include microcytic anemia due to inadequate synthesis of hemoglobin, depression, nerve problems, and irritability.

Vitamin B7- Biotin | Vitamin H:

- Biotin plays an important role in metabolism as a coenzyme that transfers carbon dioxide. This role is critical in the breakdown of food (carbohydrates, fats and proteins) into energy.
- Biotin is involved in many cellular reactions, particularly in fat and protein metabolism of hair roots, finger nails, and skin.



The primary sources of vitamin B7:

- Eggs, milk, vegetables, cereals, nuts (almonds, walnuts, peanuts), liver, kidney, yeast, soybeans. Other: synthesized by intestinal bacteria.

Risks related to inadequate or excess intake of vitamin B7:

- Experts have yet to quantify the amount of biotin in natural foods. Deficiency due to lack of dietary intake is rare in healthy populations.
- Symptoms of deficiency include general fatigue, nausea, neurological problems, poor skin and hair quality.

Vitamin B9 Folate:

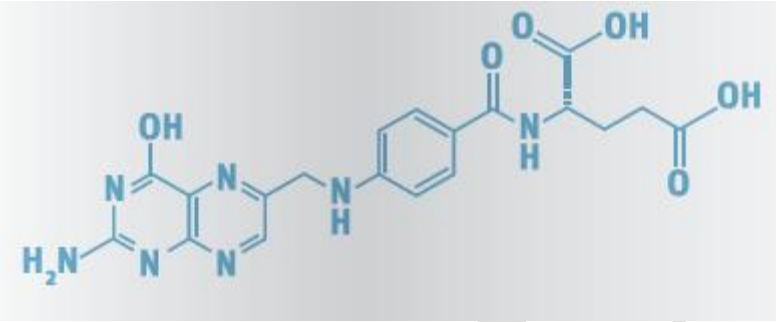
- Folate refers to the naturally occurring forms (pteroylglutamic acid) as well as the forms found in fortified foods and supplements (folic acid). Folic acid is the most stable form of folate. The primary function of folate is as a coenzyme, THF (tetrahydrofolate), that transfers single-carbon compounds for DNA synthesis and repair and in energy and amino acid metabolism.
- Without vitamin B12, folate in its methyl form becomes trapped inside cells, unavailable to support cell growth. Folate is essential for brain development and function.

The primary sources of folate:

- Dark green leafy vegetables, beans, lentils, asparagus, wheat germ, yeast, peanuts, oranges, strawberries.

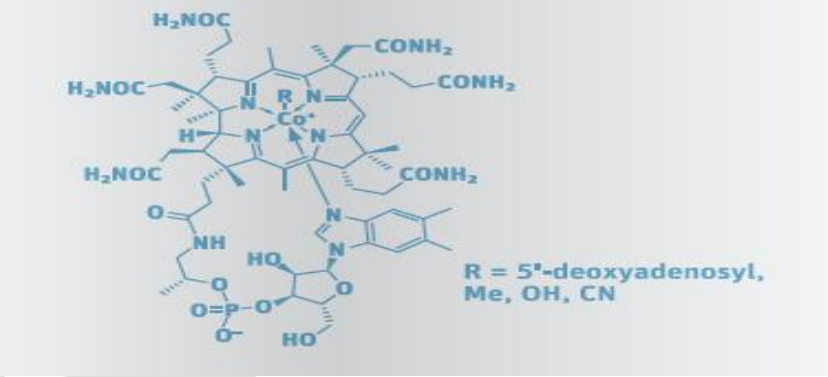
Risks related to inadequate intake of folate:

- Folate requirements are increased during pregnancy, especially in the first couple of weeks of gestation. Folate deficiency is highly associated with the risk for neural tube defects in the growing fetus.
- Thus, women of child-bearing age and pregnant women are advised to meet folate requirements using a combination of natural foods (folate forms) and fortified foods or supplements (folic acid.
- vitamin B12 deficiency will provoke a folate deficiency because it means vitamin B12 is not available to donate its methyl group to convert folate into its active form.



Vitamin B12- Cobalamin:

- Vitamin B12 functions as a coenzyme in the conversion of homocysteine to methionine, in the metabolism of fatty acids and amino acids, and in the production of neurotransmitters.
- It also maintains a special lining that surrounds and protects nerve fibers, and bone cell activity depends on vitamin B12.
- Folate and vitamin B12 are closely related. When folate gives up its methyl group to B12, it activates this vitamin.



The primary sources of vitamin B12:

- Vitamin B12 is found only in foods of animal origin, except where plant-based foods have been fortified. Rich sources of vitamin B12 include shellfish, liver, game meat (venison and rabbit), some fish (herring, sardines, salmon, trout), milk and milk products.

Risks related to inadequate or excess intake of vitamin B12:

- About 10–30% of older adults are estimated to have chronic inflammation of the stomach, a condition that impairs the absorption of vitamin B12. It is advised that older adults consume fortified foods or supplements to meet their vitamin B12 requirements.
- Vitamin B12 requirements are increased for individuals who are HIV-positive with chronic diarrhea.
- Symptoms of vitamin B12 deficiency include anemia, general fatigue, loss of appetite, gastric atrophy, neuromuscular pain, neurological problems (gait, memory loss).

Choline:

- Strictly speaking, choline is not a vitamin, but an essential nutrient that is often grouped under the B-vitamins. Although the body can make choline, dietary intake of choline is necessary to meet the body's needs for this nutrient.
- Choline also acts as a methyl donor. Choline has several functions, including fat and cholesterol metabolism, cell structure and cell integrity, cellular signaling, neurotransmission, and gene expression.
- In pregnancy, choline is important for brain development of the growing fetus.

The primary sources of choline:

- Choline can be found in many foods, mainly in milk, eggs and peanuts.

Risks related to inadequate or excess intake of choline:

- Inadequate intake of choline can lead to liver dysfunction and muscle damage. During pregnancy choline is especially important as it is involved in fetal brain development.
- Choline biosynthesis declines in women during the menopause.
- Excess intake of choline is rare but can result in a fishy body odor, vomiting, salivation, hypotension and liver toxicity.

Minerals:

- A mineral is an element that originates in the Earth and always retains its chemical identity. Minerals occur as inorganic crystalline salts. Once minerals enter the body, they remain there until excreted.
- They cannot be changed into anything else. Minerals cannot be destroyed by heat, air, acid, or mixing.
- Compared to other nutrients such as protein, carbohydrates and fat, vitamins and minerals are present in food in tiny quantities. This is why vitamins and minerals are called micronutrients, because we consume them only in small amounts.

Mineral	What it does	Good food sources	Effects of deficiency
Calcium	Builds and protects bones and teeth. Helps with muscle contractions and relaxation, blood clotting, and nerve impulse transmission. Plays a role in hormone secretion and enzyme activation. Helps maintain healthy blood pressure	Yogurt, cheese, milk, tofu, sardines, salmon, fortified juices, leafy green vegetables, such as broccoli and kale (but not spinach or Swiss chard, which have binders that lessen absorption)	Muscle cramps, brain function, rickets in children; (soft bones) and osteoporosis in adults.
Chromium	Enhances the activity of insulin, helps maintain normal blood glucose levels, and is needed to free energy from glucose	Meat, poultry, fish, some cereals, nuts, cheese	Can affect the potency of insulin in regulating sugar balance.

Copper	Plays an important role in iron metabolism. Helps make red blood cells	Liver, shellfish, nuts, seeds, whole-grain products, beans, prunes	Anemia, hair problems, dry skin, vitamin C deficiency
Fluoride (Fluorine)	Encourages strong bone formation. Keeps dental cavities from starting or worsening	Water that is fluoridated, toothpaste with fluoride, marine fish, teas	Weak teeth and bones.
Iodine	Part of thyroid hormone, which helps set body temperature and influences nerve and muscle function, reproduction, and growth. Prevents goiter and a congenital thyroid disorder	Seafood, seaweed, dairy, products, iodized, salt	Enlargement of the thyroid gland.
Iron	Helps the blood and muscles carry oxygen to the body.	Liver, red meat, egg yolk, legumes, whole / enriched grains, dark green vegetables	Tiredness and lethargy, feelings of weakness, insomnia, palpitations, headaches, shortness of breath, difficulty concentrating, brittle nails, cracked lips
Magnesium	Helps muscles work, aids metabolism and aids bone growth.	Green vegetables such as spinach and broccoli, legumes, cashews, sunflower seeds and other seeds, halibut, whole-wheat bread, milk	Fatigue, numbness, poor memory, muscle twitching and irritability, tingling, rapid heartbeat.

Manganese	Helps bone growth and cell production. Helps metabolize amino acids, cholesterol, and carbohydrates	Nuts, legumes, whole grains, tea	Deficiency is rare but could include dermatitis, problems metabolizing carbohydrates, poor memory, nervous irritability, fatigue, blood sugar problems, heavy menstrual periods, fragile bones
Phosphorus	With calcium builds bones and teeth. Needed for metabolism, body chemistry, nerve and muscle function	Chicken Breast, Milk, Lentils, Egg Yolks, Nuts, Cheese	Deficiency is rare but could include weakness; bone pain; anorexia
Potassium	Balances fluids in the body. Helps maintain steady heartbeat and	Peanuts, Bananas, Orange Juice, Green Beans, Mushrooms,	Nausea, anorexia, muscle weakness, irritability, depression,

	send nerve impulses. Needed for muscle contractions. A diet rich in potassium seems to lower blood pressure. Getting enough potassium from your diet may benefit bones	Oranges, Broccoli, Sunflower Seeds.	fatigue, hypertension, decreased heart rate.
Sodium	Balances fluids in the body. Helps send nerve impulses. Needed for muscle contractions. Impacts blood pressure; even modest reductions in salt consumption can lower blood pressure	Salt, soy sauce, processed foods,	Fatigue, apathy, and nausea as well as cramps in the muscles of the extremities
Zinc	Helps wounds to heal and aids taste and smell sensory.	Red meat, poultry, oysters and some other seafood, fortified cereals, beans, nuts	Slow healing of wounds; loss of taste; retarded growth and delayed sexual development in children.

Obesity

- Obesity is that physical state in which the amount of fat stored in the body is excessive or Obesity is due to excess of adipose tissue and is defined as that body weight over 20 per cent above mean ideal body weight.

Importance of obesity

Obese persons are more prone than the average populations to certain disease processes. They are:

- **Diabetes mellitus** type II (maturity-onset).
- **Cardiovascular disorders:** Hypertension, angina of efforts, widespread atherosclerosis, varicose veins and thromboembolism.
- **Liver diseases:** Prone to develop fatty liver, cholelithiasis and cholecystitis.
- **Physical consequences of too much fat:**
  - Bronchitis

– Alveolar hypoventilation associated with massive besity eventually leading to CO_2 retention

– Backache, arthritis of hips and knee joints, flat feet

– Hernias, ventral and diaphragmatic.

- **Metabolic diseases:** Like gout (hyperuricaemia).
- **Skin disorders:** Intertriginous dermatitis. Intertrigo is quite common in the folds below the breasts and in the inguinal regions.
- **Gynaecological disorders:**
  – Amenorrhoea, oligomenorrhoea

  – Toxaemia of pregnancy; and

  – Endometrial carcinoma.

- **Surgical postoperative complication:**
  Surgical "risks" in general is greater in obesity.

- **Industrial, household and street accidents:** Obese persons are susceptible to these accidents.

TYPES OF OBESITY

Immediate cause of obesity is always a positive energy balance, but there are many ways in which the balance may be tilted towards the positive side. Thus obesity is often divided into 2 types:

a. Exogenous obesity.

b. Endogenous obesity.

a. Exogenous Obesity

Overfeeding and gluttony with less physical activity. Many people overeat than the calorie requirements either because they are too fond of their foods which is a pleasure, or quite often because they are unhappy, foods give them solace.

b. Endogenous Obesity

There may be one or more endogenous factors: endocrinal, metabolic, hypothalamic lesion.

a. Hyperplastic type.

b. Hypertrophic type.

a. Hyperplastic type:

This type is a life long obesity characterized by an increase in adipose cell number as well as increase in adipose cell size. Fat distribution is usually peripheral as well as central. Long-term response to treatment is not good. After weight reduction, adipose cell size may shrink but the increased numbers of cells persist.

b. Hypertrophic type:

It is seen in adults after twenty years of age (adult onset type). It is characterized by hypertrophy of adipose tissue cells without increase in adipose cells number. There is increase in cell size only. Fat distribution is usually central. The energy requirements of the body diminish with the advancing age and if there is no corresponding reduction in eating habits, a middle-aged spread is the natural result.

CAUSES

Obesity can be encountered with other diseases, viz. certain metabolic disorders, and endocrine disorders. Thus, the causes of obesity as listed below, though may not be all complete, but encompasses the more common and certain uncommon syndromes which have been reported.

a. Genetic influences.

- There is strong evidence to suggest that obesity has genetic basis. Thus, a child born to two obese people has about 25% chances of being obese. One gene namely ob gene, expressed in adipocytes (of white adipose tissue) producing a protein called is closely associated with obesity.
- Leptin is regarded as a body weight regulatory hormone. lt binds to a specific receptor in the brain and functions as a lipostat. When the fat stores in the adipose tissue are adequate, leptin levels are high.

- This signals to restrict the feeding behavior and limit fat deposition. Further, leptin stimulates lipolysis and inhibits lipogenesis. Any genetic defect in leptin or its receptor will lead to extreme overeating and massive obesity.
- During starvation, leptin levels fall which promote feeding, and fat production and its deposition.

b. Physiological:

- Overeating than caloric requirement.
- Pregnancy.
- Postmenopausal women.
- Use of oral contraceptives for prolonged periods.

c. Metabolic:

- Diabetes mellitus maturity onset (Type II).
- Hyperlipidaemic states specially, type IV and type V.

d. Hypothalamic injuries or abnormalities (e.g. Prader- Willi syndrome).

e. Miscellaneous and endocrine disorders:

- Hypothyroidism, Cushing's disease and Cushing's syndrome, pseudo hypoparathyroidism, islet cell tumour (insulinoma), polycystic ovary syndrome, Laurence-Moon-Biedl syndrome, Fröhlich syndrome, Acromegaly.

- The only effective treatment of obesity is reduction in the ingestion or increase in the use of calories Practically speaking, this means dieting, since even vigorous exercise such as running only consumes 10 kcal/min of exercise Thus an hour long run (perhaps 5-6 miles) uses the energy present in about two candy bars However, exercise programs can be useful to help motivate individuals to remain on their diets.
- Unfortunately the body compensates for decreased energy intake with reduced formation of triiodothyronine and a corresponding decrease in the basal metabolic rate. Thus there is a biochemical basis for the universal complaint that it is far easier to gain than to lose weight. Furthermore, about 95olo of people who are able to lose a significant amount of weight regain it within one year.

Scurvy

- Scurvy is a condition characterised by general weakness, anaemia, gingivitis (gum disease), and skin haemorrhages caused by a prolonged deficiency of vitamin C (ascorbic acid) in the diet.
- Vitamin C plays a crucial role in the formation of collagen, a major component of connective tissue. Connective tissue has structural and supportive functions which are indispensable to blood vesselsand all tissues within the body.
- Vitamin C is also important in the proper functioning of the immune system, iron absorption, cholesterol metabolism and other biological activities. Thus scurvy has widespread effects.
- Scurvy was often seen in sailors on long ocean voyages described from the 15th century onwards. Many men died from the disease until it was discovered that scurvy could be effectively cured and prevented by consuming vitamin C through lemons, oranges and limes.
- It is thought that scurvy occurs very rarely in modern societies of today as most people have access to year-round fresh fruits and vegetables which are rich sources of vitamin C. However, several groups of people are at risk. These include:
- People with chronic malnutrition or those that eat less than 2 servings of fruits/vegetables per day
    - Alcoholics
    - Elderly
    - Men who live alone (bachelor or widower scurvy)
    - Children
    - People on peculiar diets or food fads
    - Psychiatric disease (delusions or fear of food, suicide attempt by self-starvation, eating disorders)
- People with other medical conditions that may prevent the intake and/or absorption of vitamin C
    - Dialysis patients
    - Inflammatory bowel disease (Crohns Disease)
    - Malabsorption disorders
    - Severe dyspepsia
- Under-developed third world countries where general malnutrition exists. Also, in populations that subsist mainly on cereal grains and without access to fresh fruit or vegetables.

Signs and Symptoms of Scurvy:

- The diagnosis of scurvy is primarily a clinical one, based on a dietary history of inadequate vitamin C intake and the signs and symptoms described below.
- Symptoms of scurvy generally develop after at least 3 months of severe or total vitamin C deficiency. Patients initially complain of weakness, fatigue, listlessness and aching limbs, especially in the legs. If left untreated, scurvy can progress to the following more severe problems.
- Skin problems – one of the first signs of scurvy is the development of perifollicular hyperkeratotic papules, often on the shins. These appear as reddish/bluish bruise-like spots surrounding hair follicles.
- The central hairs are twisted like corkscrews that may break easily. The papules may join together to form large areas of palpable purpura or ecchymoses (bruises).
- Oral problems – gums may swell and become red, soft and spongy. Any slight friction may cause the gums to bleed. Often this results in poor oral hygiene and dental diseases.
- Musculoskeletal problems – bleeding in the joints causes extreme discomfort and pain. Joints may be swollen and tender and the pain can be so severe that patients cannot walk.
- Eye problems – patients may complain of dryness, irritation, light intolerance, transient visual blurring and stickiness. Haemorrhaging (bleeding) beneath the conjunctiva and within the optic nerve sheath may also occur.
- Anaemia – this develops in 75% of patients as a result of blood loss into tissue, altered absorptions and metabolism of iron and folate, gastrointestinal bleeding and intravascular haemolysis.
- Heart and lung problems – shortness of breath, low blood pressure, and chest pain leading to shock and death.

Diagnosis:

- Scurvy is diagnosed in someone with typical signs and symptoms, after taking a dietary history in which a low intake of fresh fruit and vegetables is identified.
- It is confirmed by a blood test for ascorbic acid showing levels < 11 µmol/L, and response of symptoms to treatment with vitamin C supplements and/or fresh fruit and vegetables.

Treatment and prevention with vitamin C:

- Treatment of scurvy is simply with vitamin C supplements taken orally. The adult dosage is 800–1000 mg/day for at least one week, then 400 mg/day until complete recovery.
- Children should be given 150–300 mg/day for one month. Some improvement of symptoms is usually noticed within 24 hours. Except for the loss of teeth through dental disease, permanent damage from scurvy does not usually occur.
- Prevention of scurvy is easily achieved by take the recommended daily intake (RDI) of vitamin C. This is between 30-60 mg/day. By following the "5 servings of fruit and vegetables per day" rule, you will be getting the RDI and maintaining sufficient body stores of vitamin C.

Beri-Beri

- Beriberi is a disease caused by a vitamin B-1 deficiency, also known as thiamine deficiency. There are two types of the disease: wet beriberi and dry beriberi. Wet beriberi affects the heart and circulatory system.

- In extreme cases, wet beriberi can cause heart failure. Dry beriberi damages the nerves and can lead to decreased muscle strength and eventually, muscle paralysis. Beriberi can be life-threatening if it isn't treated.

- If you have access to foods rich in thiamine, your chances of developing beriberi are low. Today, beriberi mostly occurs in people with an alcohol use disorder.

- Beriberi from other causes are rare in the United States. Still, the disease can be seen in women who have extreme nausea and vomiting in pregnancy (hyperemesis gravidarum), in people with AIDS, and after bariatric surgery.

Symptoms of beriberi:

The symptoms of beriberi vary depending on the type.

Wet beriberi symptoms include:

- shortness of breath during physical activity
- waking up short of breath
- rapid heart rate
- swollen lower legs

Dry beriberi symptoms include:

- decreased muscle function, particularly in the lower legs
- tingling or loss of feeling in the feet and hands
- pain
- mental confusion
- difficulty speaking
- vomiting
- involuntary eye movement
- paralysis

In extreme cases, beriberi is associated with Wernicke-Korsakoff syndrome. Wernicke encephalopathy and Korsakoff syndrome are two forms of brain damage caused by thiamine deficiency.

Wernicke encephalopathy damages regions of the brain called the thalamus and hypothalamus. This condition can cause:

- confusion
- memory loss

- loss of muscle coordination
- visual problems such as rapid eye movement and double vision.

Causes beriberi:

- The main cause of beriberi is a diet low in thiamine. The disease is very rare in regions with access to vitamin-enriched foods, such as certain breakfast cereals and breads.
- Beriberi is most common in regions of the world where the diet includes un enriched, processed white rice, which only has a tenth of the amount of thiamine as brown rice.

Treatment:

- Beriberi is easily treated with thiamine supplements. Your doctor may prescribe a thiamine shot or pill. For severe cases, a healthcare professional will administer intravenous thiamine.

Pellagra

- Pellagra is a disease characterized by diarrhea, dermatitis and dementia. If left untreated, death is the usual outcome. It occurs as a result of niacin (vitamin B-3) deficiency.
- Niacin is required for most cellular processes. Since tryptophan in the diet can be converted to niacin in the body, both of these need to be deficient for pellagra to develop.

Causes of pellagra:

- Pellagra is caused by a deficiency in niacin. This can occur in 2 ways:
- Primary pellagra results from inadequate niacin and/or tryptophan in the diet (mainly in developing countries or poverty stricken areas)
- Secondary pellagra occurs when there is enough niacin in the diet but something prevents its absorption and processing. Causes of secondary pellagra include:

- Chronic alcoholism
- Prolonged diarrhoea
- Gastrointestinal diseases such as ulcerative colitis
- Liver cirrhosis
- Carcinoid tumours
- Hartnup disease (tryptophan metabolism disorder)
- Drugs e.g. isoniazid, azathioprine

Signs and symptoms of pellagra:

Site	Clinical features
Skin	• The first sign is reddened skin with superficial scaling in areas exposed to sunlight, heat and friction. This may resemble severe sunburn then gradually subsides leaving a dusky brown-red colouration • The rash is usually symmetrical with a clear edge between affected and unaffected skin • There may be itching or a burning sensation • In time the skin becomes thick, hard, scaly and cracked. Bleeding may result in blackened crusts • Lesions may occur anywhere on the body especially the hands, arms, lower legs, feet, face, and neck (known as Casal's necklace) • Lips, tongue and gums may be sore and peeling
Gastrointestinal	• Diarrhoea occurs in 50% of cases • Poor appetite, abdominal pain, nausea and vomiting are common • It may be difficult to eat and drink, leading to further malnutrition
Neurological	• Initially symptoms of apathy and slight depression may go unnoticed • Other symptoms include headache, confusion, irritability, restlessness, anxiety, tremor, delusions, disorientation and psychosis • Patients eventually become stuporous, comatose and may die

Treatment:

- Pellagra can be effectively cured with intravenous or oral niacin or nicotinamide. Adequate doses to treat secondary pellagra are quite hard to get hold of in New Zealand!

- An improvement in primary pellagra should be seen within two days of commencing treatment. A high protein diet supplemented with B-group vitamins is needed for complete recovery. Secondary pellagra may be harder to treat in view of its possible causes.
- Skin lesions may be treated with topical emollients. Sun protection is important during the recovery phase. Cover up and apply a broad spectrum sunscreen to all exposed areas daily.

Vitamin B-12 Deficiency

Vitamins are essential organic compounds required for normal maintenance of our body. We all require vitamins for proper growth and development as they play a vital role in strengthening and boosting our metabolism. Vitamin B12 is water-soluble vitamins which are required for proper functioning of cells, tissues and other organs system of a human body.

They are also responsible for:

- Blood clotting.
- Synthesizing hormones.
- During digestion for the breakdown of food molecules.
- The formation of bones, blood cells, muscles, nerves and genetic materials.

Symptoms:

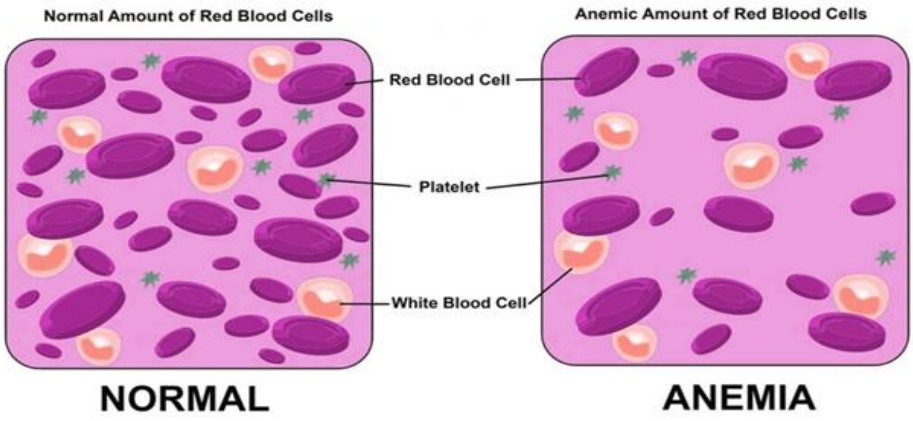
- Feeling tired or lack of energy.
- Anemia along with bone marrow happens due to the inhibition of DNA synthesis.
- Gastrointestinal symptoms include alteration in bowel motility such as constipation, mild diarrhea, and loss of bladder which is caused mainly because of defective in DNA synthesis by inhibiting replication along with a huge number of cells and also by the autoimmune attack on the parietal cells of the stomach during the pernicious anemia.
- Neurological symptoms comprise of sensory or motor deficiencies, subacute mixes degeneration of spinal cord, and some other symptoms of psychiatric.
- Depression and dementia belong to the deficiency from the underproduction of methionine because of the inability of converting homocysteine into the product.
- The neurological complex is also named as myelosis funicularis which consists of the following:
  - Pathological reflexes.
  - Ataxia of dorsal chord type.
  - Loss of deep muscle-tendon.

– Impaired perception, loss of sense of touch, pressure, vibration, and persistent paresthesias.

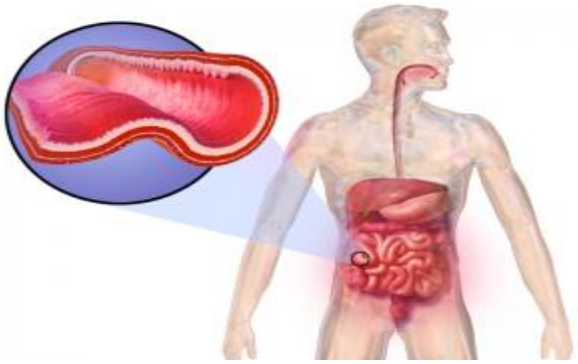
Causes of B12 Deficiency:

- The Vitamin B12 deficiency results in not having enough of vitamins in the daily diet. It is important to have B12 in the diet as it helps in forming red blood cells which carry oxygen across the body.
- Improper B12 will not permit red blood cells to perform their function and results in tired and weakness. This deficiency can even affect the nerves and power of a brain.

Pernicious Anemia – In these conditions, the body starts destroying the stomach cells which is associated with the absorption vitamin B12.



Crohn Disease – It includes several problems during food digesting such as the growth of the bacteria in the small intestine. It is the inflammatory bowel disease that affects the lining of the digestive tract. Treatment includes the surgery to remove part of the small intestine.



Vitamin D Deficiency

- Vitamin D is a fat-soluble vitamin that is made when the skin is exposed to sunlight. It is present in only a small number of foods, including fortified products, such as milk. Vitamin D is best known for supporting calcium metabolism.

- It helps the body absorb calcium from food and supplements to support the maintenance of healthy bones cells. But working with calcium to protect the bones is far from the only function of vitamin D in the body.

Vitamin D also:

- supports muscle health
- plays a role in the immune system
- aids cell growth
- reduces inflammation, which can lead to illness such as rheumatoid arthritis and cancer
- regulates blood pressure and supports cardiovascular health

- Vitamin D intake is not the best measure of the vitamin's status in the body, as many factors can affect its uptake. For example, the health of the stomach can interfere with how much vitamin D a person absorbs from the food they eat.

Symptoms:

- Many people with a vitamin D deficiency may have no symptoms or may go many years without experiencing symptoms.

- The symptoms of vitamin D deficiency can be vague, may change over time, and are similar to symptoms of a wide range of ailments. Hence, it is dangerous to self-diagnose a vitamin D deficiency.

- People who experience symptoms of vitamin D deficiency, or who have unexplained illnesses or nutritional deficiencies, should request a test for vitamin D deficiency. Some symptoms of a deficit in vitamin D include:

  - thinning or brittle bones, osteoporosis, or frequent bone fractures
  - muscle weakness, particularly if there is an unexplained change in muscle strength
  - changes in mood, with people who have low vitamin D experiencing anxiety or depression
  - chronic pain, as vitamin D plays a key role in supporting bone, muscle, and cell health
  - high or rising blood pressure
  - exhaustion, even with enough sleep
  - decreased endurance
  - unexplained infertility.

Treatment

- There is disagreement about the right amount of vitamin D for good health. Ideal vitamin D intake varies with different factors, such as age, activity level, and metabolic health. People should talk to a doctor about vitamin D intake goals.

- It is a good idea to keep a log of symptoms when treatment begins. This is a simple way to track progress, and to assess whether it is necessary to increase vitamin D intake.

There are three strategies for increasing vitamin D levels:

- **Take a vitamin D supplement**: These are readily available over the counter. A doctor may also prescribe a supplement or multivitamin. For most adults, the recommended dietary allowance (RDA) is 600 IU. For adults over 70, the RDA is 800 IU. For children under 12 months, it is 400 IU.
- **Eat foods rich in vitamin D**: Fatty fish such as tuna, salmon, and mackerel, as well as fish liver oils, are excellent natural sources. Beef liver, cheese, and egg yolks contain small quantities of vitamin D. Milk is fortified with vitamin D, as are many cereals.
- **Increase exposure to natural sunlight**: The risks of sun exposure might be greater than the risks of vitamin D deficiency for people vulnerable to sunburn, with a history of skin cancer, or with very pale skin. They should talk to a doctor about whether spending more time in natural light is a good idea or not.

Vitamin K Deficiency

- There are two main kinds of vitamin K. Vitamin K1 (phylloquinone) comes from plants, especially leafy green vegetables like spinach and kale. Vitamin K2 (menaquinone) is naturally created in the intestinal tract and works similarly to K1.
- Vitamin K plays an important role in coagulation, better known as blood clotting. Clotting is a process that helps prevent excessive bleeding both inside and outside the body.
- Your body needs vitamin K in order to produce the proteins that go to work during the clotting process. If you're vitamin K deficient, your body doesn't have enough of these proteins. The telltale sign of vitamin K deficiency is bleeding too much.
- Vitamin K deficiency is rare in adults because many of the foods we eat contain adequate amounts of K1, and because the body makes K2 on its own. Plus, the body is good at recycling its existing supply of vitamin K. However, certain conditions and some drugs can interfere with vitamin K absorption and creation, making it possible to become deficient.

Vitamin K deficiency symptoms

The main symptom of vitamin K deficiency is excessive bleeding. Keep in mind that bleeding may happen in areas other than at a cut or wound site. The bleeding may also be apparent if someone:

- bruises easily
- gets small blood clots underneath their nails
- bleeds in mucous membranes that line areas inside the body
- produces stool that looks dark black (almost like tar) and contains some blood

In infants, doctors may observe vitamin K deficiency if there is:

- bleeding from the area where the umbilical cord is removed
- bleeding in the skin, nose, the gastrointestinal tract, or other areas
- bleeding at the penis if the baby has been circumcised
- sudden bleeding in the brain, which is extremely dangerous and life-threatening.

Causes:

- take coumarin anticoagulants such as warfarin, which thins the blood
- are taking antibiotics
- have a condition that causes the body to not absorb fat properly (fat malabsorption)
- have a diet that is extremely lacking in vitamin K.

- Coumarin anticoagulants interfere with the production of the proteins involved in blood clotting.

- Some antibiotics cause the body to produce less of its own vitamin K. Other antibiotics may cause vitamin K to become less effective in the body.

- Fat malabsorption leading to vitamin K deficiency may occur in people with:
  - celiac disease
  - cystic fibrosis
  - a disorder in the intestines or biliary tract (liver, gallbladder, and bile ducts) part of their intestine removed.

Vitamin K deficiency treatment:

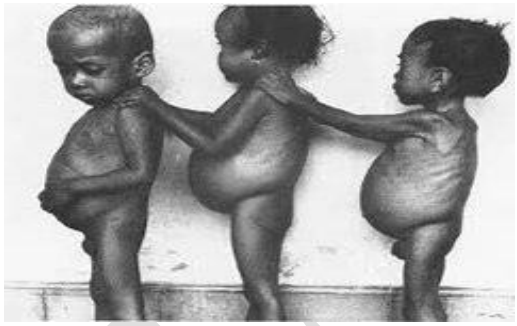
- The treatment for vitamin K is the drug phytonadione, which is vitamin K1. Most of the time doctors prescribe it as an oral medication. A doctor or nurse might also inject it under the skin (as opposed to into a vein or muscle). The dosage for adults ranges from 1 to 25 milligrams (mg).
- Doctors will prescribe a smaller phytonadione dose for someone who is taking an anticoagulant. Typically this dosage is about 1 to 10 mg. This is to avoid a complication due to anticoagulants interfering with the body's vitamin K production.

Long-term outlook for vitamin K deficiency:

- If left untreated in adults, vitamin K deficiency can result in excessive bleeding and become dangerous. But in almost all cases, vitamin K deficiency is treatable.
- In infants where VKDB is identified and treated quickly, the outlook is good. However, if the bleeding, known as an intracranial hemorrhage, lasts too long or goes untreated, brain damage or death can occur.

Kwashiorkor and Marasmus

- Kwashiorkor and Marasmus both fall in category of malnutrition. Malnutrition is a serious condition occurred due to insufficient intake of nutrients in the diet.



Kwashiorkor:

- Kwashiorkor is a kind of malnutrition that is most often found in children. It is primarily caused due to insufficient intake of proteins.
- However, it do not have any relation with the amount of calories intake i.e. may be a person is having a high calorie food but specifically less proteins then in that case the person is prone to Kwashiorkor.
- This kind of malnutrition is primarily found in developing countries. Due to poverty, children are deprived of the necessary proteins in diet and therefore suffer from malnutrition like kwashiorkor.
- It stunts growth and children tend to have bloated bellies and thin arms and legs. Kwashiorkor is also known by names like protein malnutrition, protein-calorie malnutrition or malignant malnutrition.
- It is very rare in children of developed countries like the United States of America.

Marasmus:

- Marasmus is also a kind of malnutrition that occurs due to deficiency of proteins, carbohydrates and fats in the diet.
- In marasmus the child consumes little or no food leading to minimal caloric intake and also a total lack of nutrients.
- It is also caused due to metabolic and genetic problems which make the body incapable of absorbing the necessary nutrients.
- Due to lack of nutrients, the body starts consuming own tissues, fats and muscle. Breast feeding helps in preventing the disease. It mainly affects children who are weaned away from mother's milk.

Difference between Kwashiorkor and Marasmus:

- They are both types of malnutrition but the main difference is that kwashiorkor is caused by deficiency of proteins and the marasmus is caused by deficiency of proteins, fats and carbohydrates.
- Sometimes the symptoms of kwashiorkor are so mild that it is difficult to recognize the patient of this malnutrition, but on the other hand a marasmus patient can be easily identified at a glance.
- Both types of malnutrition are very dangerous and can cause severe effects. Thus, timely treatment should be provided and special attention should be given to the diet of the children.
- Another kind of malnutrition that is related to kwashiorkor and marasmus is known as Marasmic kwashiorkor.
- Marasmic kwashiorkor is a form of malnutrition that lies in between kwashiorkor and marasmus, as is clear by its name. Kwashiorkor and marasmus can be differentiated primarily on the basis of symptoms, causes and treatment.

Kwashiorkor	Marasmus	
Definition	Kwashiorkor is a kind of malnutrition. It is primarily caused due to insufficient intake of proteins.	Marasmus is a kind of malnutrition that occurs due to deficiency of proteins, carbohydrates and fats in the diet.
Symptoms	Large belly sticking out, diarrhea, change in skin pigment, decreased muscle mass, diarrhea, failure to gain weight and grow, fatigue, hair changes, etc.	Peeling and alternately pigmented skin, hair loss, edema or swelling, skin folds are formed, etc.

Affecting	Generally children of age 1-5 years	Generally children under the age 1
Main causes	Weaned from mother's milk to a diet low in protein	Failed breastfeeding, feeding inadequate infant formula or suffering from some disease like diarrhea
Wasting of muscles	Not evident	Quite evident
Bloated belly	Yes, due to retention of fluids	No
Treatment	Providing carbohydrates followed by high protein foods. Dried milk specially.	Providing a nutritious, well-balanced diet with lots of fresh fruits and vegetables, grains, and protein. Especially adding Vitamin B to the diet.

Xerophthalmia and night blindness

Xerophthalmia:

- The term "xerophthalmia" refers to the spectrum of ocular manifestations due to vitamin A deficiency.
- Such signs include those involving impaired sensitivity of the retina to light (night blindness), and (in order of their appearance and severity) epithelial disruptions of the cornea and conjunctiva, such as conjunctival xerosis, Bitot spots, corneal xerosis and keratomalacia .

- These ocular symptoms are related to vitamin A deficiency and vary according to the severity of the deficiency, and age.
- Xerophthalmia can occur in any age group and especially in preschool-age children, adolescents and pregnant women.
- However, children are at higher risk of vitamin A deficiency and xerophthalmia, owing to their greater vitamin A requirements for growth.
- Children are also at higher risk of intestinal infestations and infections, which may impair the absorption of vitamin A and increase its loss.
- A peak in the incidence of night blindness is generally observed between 3 and 6 years of age. However, as it is difficult to assess night blindness in infants and young children who have not yet begun to crawl or walk, its presence may not always be recognized, and therefore it may be erroneously perceived that night blindness is not a problem. Affected children often exhibit limited.

Classification of xerophthalmia by ocular signs:

- Night blindness (XN)
- Conjunctival xerosis (X1A)
- Bitot spots (X1B)
- Corneal xerosis (X2)
- Corneal ulceration/keratomalacia <⅓ corneal surface (X3A)
- Corneal ulceration/keratomalacia ≥⅓ corneal surface (X3B)
- Corneal scar (XS)
- Xerophthalmic fundus (XF)

Night blindness:

- Night blindness, a condition in which a person cannot see in dim light, is generally the earliest clinical manifestation of vitamin A deficiency and is both a sensitive and a specific indicator for low serum retinol levels.
- Within the eye, vitamin A, in the form of retinal, combines with opsin to produce rhodopsin, the photosensitive visual pigment of rods.
- Vitamin A deficiency leads to a decline in rhodopsin levels and impaired rod function, manifested as night blindness.

- In mild cases, night blindness is often only first noticeable following photopic stress from sudden exposure to bright light, and results in an increased turnover of rhodopsin.
- Historically, the most characteristic sign of ocular problems related to vitamin A deficiency has been Bitot spots – opaque whitish deposits on the scleral conjunctiva.
- At this point, conjunctival xerosis is already present, with the conjunctiva appearing dry and dull. Spots of keratinized epithelial cells with the appearance of foam are also present.
- If vitamin A deficiency continues, corneal xerosis may set in, with the appearance of a hazy cornea, followed by keratomalacia where there is liquefaction of part or all of the cornea.
- Corneal scars are not considered to be part of active vitamin A deficiency, but are considered a result of a previous bout of the deficiency.
- With prolonged vitamin A deficiency, there is an increase in morbidity and mortality from common infections, and blindness can occur.

Anorexia nervosa and bulimia

- Anorexia nervosa and bulimia are common syndromes characterized by bizarre eating patterns which become the central focus of the patient's life.
- Occurring primarily in young women, they represent life-disrupting illnesses for the afflicted and their families and lead to death in a small but significant number of cases.
- Although the clinical manifestations and outcome of the two syndromes are distinctive, overlap features suggest that the root disorder is the same: an obsessive fear of being fat.
- In anorexic patients the primary reactive mechanism is the rigid restriction of food intake; with bulimia, loss of control in the drive to eat is compensated for by induced vomiting and laxative use.

Anorexia nervosa:

- Patients are not free of hunger; rather, they are obsessed with the fear of being fat such that hunger sensations are ignored or denied. An intense preoccupation with food is usually discernible.
- Although anorexic patients drastically restrict their own food intake, it is not unusual for them to enjoy preparing elaborate meals for others, collect recipes and hoard food in the home.
- Most subjects appear knowledgeable on nutritional matters, particularly the caloric content of food, although up to 25% may show lesser insight than matched controls.

- It is usually stated that carbohydrates are avoided preferentially, but carbohydrate intake was found to be normal.
- Fat intake was decreased and protein content was high. In order to assist weight loss it is common for patients to exercise excessively, often in ritualistic fashion.
- A significant percentage induces vomiting and use laxatives. or diuretics. Periodic gorging of the type seen in the bulimic variant/phase of the disease may also occur in classic anorexia nervosa.

Symptoms:

- Amenorrhea, primary or secondary, in almost 100% of patients
- Constipation often with complaints of abdominal pain
- Cold intolerance
- Agitation or lethargy
- Emesis

Physical findings:

- Cachexia
- Skin abnormalities ; increased lanugo-like body hair
- Bradycardia
- Hypotension
- Hypercarotenemic skin
- Peripheral edema
- Hypothermia

Laboratory findings:

- Decreased thyroid function test values
- Abnormalities in cortisol and growth hormone secretion
- Decreased gonadotropins
- Hypercarotenemia
- Other evidence of hypothalamic dysfunction
- Elevation of blood urea nitrogen.

Bulimia:

- The term bulimia literally means "ox-hunger" or a voracious appetite. It has come to stand for a syndrome of astonishing food intake over short periods of time in young women who usually have a previous or present picture of anorexia nervosa.
- The gorging is then followed by induced vomiting and often by the use of laxatives in large amounts.
- Two fundamental features characterize the syndrome:

  (1) an irresistible urge to overeat

  (2) a marked fear of becoming fat.

- The former predominates in this form of the illness but there are other features than distinguish it from classic anorexia nervosa.
- In simple terms patients with non-bulimic anorexia nervosa deal with the fear of being fat by restricting food intake ("restrictors").
- Their phobia of being fat appears to be so powerful that control over eating is not lost. Bulimic patients, on the other hand, lose control and thus become "gorgers," controlling weight gain only by vomiting and use of laxatives.

Symptoms:

- In contrast to classic anorexia nervosa amenorrhea was present in only 11 of 28 subjects when cessation of menses was not used as part of the selection criteria.
- This is likely due to the fact that weight loss was less severe in the bulimic group.
- The other major complaint, often spontaneously voiced, is of depression.
- In view of the recurrent vomiting with hypokalemia one would expect complaints of weakness to be frequent, but this was not obvious in the cited series.
- Convulsions and tetany have been reported but are rare.

Treatment and outcome:

- There is no specific treatment for anorexia although multiple approaches have been tried, many of them controversial.
- A partial list includes: insulin, thyroid hormone, gonadotropins, antidepressants, antipsychotics, tranquilizers, electroconvulsive therapy, appetite stimulants and leucotomy. From a psychologic and psychiatric standpoint, behavior modificati on, individual psychotherapy and relationship therapy have been tried, singly and in combination.

- However, certain general principles can be developed
    a. It is generally preferable to hospitalize the patient for initial treatment; the usual period is 6-8 weeks.
    b. The immediate aim is to induce weight gain; psychotherapy is of little benefit until after nutritional status has improved.
    c. The patient should never eat alone; either the patient must eat in the company of a nurse or combined patients and staff should eat together.
    d. It is preferable to have a single staff person ("special") carry out primary interactions with the patient.
    e. While the support staff should be friendly and reassuring about the "safety" of eating, lengthy intellectualizing about food and weight should be avoided.
    f. Parenteral or enteral nutrition should be prescribed only as a life-saving measure; hyperalimentation is never indicated as a primary treatment .
    g. Caloric intake should be increased gradually over 7 to 10 days from 1000 calories to a level twice that of a normal adult (3000 to 5000 calories depending on size).
    h. Psychoactive drugs should be used if needed for depression or anxiety.
    i. As nutritional status improves social therapy should be initiated (arts, crafts, games, etc.).
    j. Parental involvement should be started early either as family therapy or with a parental group.
    k. Following discharge the patient should be seen at least biweekly for support and guidance.

POSSIBLE QUESTIONS

2 marks

1. Write a note on Nutrition.
2. What is Balanced Diet? Give the importance.

3. Give the importance Macronutrients.
4. Write about RDA.
5. What is meant by Protein Malnutrition?
6. Write note on Night Blindness?
7. Give a note on Micronutrients?

6 marks

1. Discuss in detail about Balanced diet.
2. Give an account on importance of macronutrients.
3. Explain the following,
   i) Kwashiokor
   ii) Marasmus
4. Explain about Vitamin deficiencies and their types in detail.
5. Detailed note on Obesity
6. Describe about Xerophthalmia and Night blindness
7. Discuss about eating disorders?

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III- B.Sc., BIOCHEMISTRY
MOLECULAR BASIS OF NON-INFECTIOUS HUMAN DISEASES 18BCU504-A
MULTIPLE CHOICE QUESTIONS

UNIT V

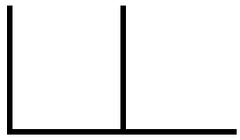
S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Oxidation of which substance in the body yields the most calories per gram?	Glucose	Glycogen	Animal protein	Lipids	Lipids
2	Milk is notoriously deficient of which vitamin?	Vitamin B1	Vitamin C	Vitamin A	Pantothenic acid	Vitamin C
3	Cellulose cannot be digested by the humans because of the inability to hydrolyse:	α-Glycosidic bonds	α-Amyloses	Pectins	α-Amyloses	α-Amyloses
4	Milk is notoriously deficient in which of the minerals?	Calcium	Iron	Phousphors	sodium	Iron
5	The biological activity of vit E has been attributed, in part, to its action as:	A carrier in electron transport chain	An antidote for selenium poisoning	An anti-coagulant	An anti-oxidant	An anti-oxidant
6	Dietary fibre:	Includes limit dextrins	Affects digestion of other dietary components	Is defined as nondigestible and water insoluble polysaccharides	Is composed of undigested proteins	Is defined as nondigestible and water insoluble polysaccharides
7	Which of the following essential dietary factors is a precursor for a compound that can act as carrier of “one carbon” fragments at different levels of oxidation?	Methionine	Folic acid	Biotin	Pyridoxine	Folic acid
8	A cup of strong coffee would be expected to:	Decrease the effects of glucagons	Enhance the effects of epinephrine	Provide the vitamin nicotinic acid	Interfere with the synthesis of prostaglandins	Enhance the effects of epinephrine

9	Humans most easily tolerate a lack of which of the following nutrients?	Protein	Lipids	Carbohydrates	Calcium	Carbohydrates
10	An important etiological factor in kwashiorkor is:	Excess dietary ethionine	Steatorrhoea	Dietary protein deficiency	Anaemia	Dietary protein
11	Oxidation of which substance yields the most calories pergram:	Glucose	Vitamins	Lipids	Animal proteins	Lipids
12	Whole wheat is an excellent source of:	Vitamin A	Vitamin D	Ascorbic acid	Thiamine	Thiamine
13	A substance needed by the body for growth, energy, repair and maintenance iscalled a	nutrient	carbohydrate	calorie	fatty acid	nutrient
14	A diet high in saturated fats can be linked to which of the following?	Includes limit dextrins	bulimia	anorxia	cardiovascular disease	cardiovascular disease
15	Amylases in saliva begin the breakdown of carbohydrates into	fatty acids	polypeptides	aminoacids	simple sugars	simple sugars
16	Your body needs vitamins and minerals because	they give the body energy	they help carry out metabolic reactions	they insulate the body's organs	they withdraw heat from the body	they help carry out metabolic reactions
17	Food passes through the stomach directly by	the large intestine	the small intestine	the heart	the pancreas	the small intestine
18	About half of your diet should be made up of _	grains and vegetables	fruit and milk	milk and cheese	fats and sugars	grains and vegetables
19	The bread, cereal, rice and pasta group is a good source of _____?	carbohydrate	vitamin C	Vitamin A	calcium	carbohydrate
20	Citrus fruits are an excellent source of _____?	vitamin C	Vitamin A	calcium	carbohydrate	vitamin C
21	Which of the following nutrients is known as the sunshine vitamin?	Vitamin D	Vitamin A	vitamin C	vitamin K	Vitamin D
22	This nutrient is needed for a healthy immune system and strong connectivetissue	vitamin C	vitamin K	Vitamin D	fiber	vitamin C
23	This mineral is essential for healthy red blood cells and a deficiency might causeanemia	Iron	Magnesium	Iodide	Chromium	Iron
24	This nutrient is needed for making hormones, healthier skin, and to make cellmembranes	Fat	Carbohydrates	Fiber	Vitamin B12	Fat
25	This nutrient is most important for healthy vision	Vitamin A	Vitamin D	Iodide	carbohydrate	Vitamin A

26	oncerning the major dietary constituents:	The body cannot store glucose	All essential amino acids are found in mea	Plant oils mainly consist of saturated fats	The body cannot store fats	All essential amino acids are found in mea
27	Which of the following is the main nitrogenous compound in urine?	Uric acid	Ammonia	Urea	Creatinine	Urea
28	What is the worldwide prevalence of obesity?	1%	13%	15%	39%	13%
29	What is the definition of overweight?	BMI > 25 kg/m2	BMI = 25 kg/m2	BMI 25-29.9 kg/m2	BMI 25-30 kg/m2	BMI 25-29.9 kg/m2
30	Why were low-carbohydrate diets not recommended previously?	*Due to less weight loss efficacy*	Due to low adherence to the diet	*Due to the high protein content of the diet*	*Due to possible cardiovascular side-effects*	*Due to possible cardiovascular side-effects*
31	The following is a deficiency disease.	Jaundice	Scurvy	Cancer	Asthma	Scurvy
32	The toxicity of ____ leads to liver cirrhosis.	Iron	Mercury	Copper	Lead	Copper
33	The deficiency of which of the following Vitamin leads to bent limb bone in children.	A	B1	C	D	D
34	Patients suffering from ____ are recommended Oral Rehydration Therapy.	Cholera	Tetanus	Typhoid	Tuberculosis	Cholera
35	Low vision in the evening and nights results from the deficiency of	Vitamin A	Vitamin B	**Vitamin c**	Vitamin D	Vitamin A
36	Which one of the following is not an insect borne disease?	Malaria	Beriberi	Yellow fever	Dengue fever	Beriberi
37	Deficiency of Vitamin B6 in man causes	Night blindness	Goitre	Anaemia	Rickets	Anaemia
38	A man having colour blindness will see red as	Pink	Green	Blue	Purple	Green
40	Dental caries are due to the deficiency of	Iron	Copper	Zinc	Fluorine	Fluorine
41	Which of the following is a diagnostic criterion for anorexia nervosa in DSM-IV-TR?	A refusal to maintain a minimal body weight	A pathological fear of gaining weight	A distorted body image in which, even when clearly emaciated, sufferers continue to insist they are overweight	All of the above	All of the above
42	In Restricted Type anorexia nervosa, self-starvation is NOT associated with which of the following?	Concurrent purging	Socialising	Body dysmorphic issues	Eating only certain food types	Concurrent purging

43	In Binge-Eating/Purging Type anorexia nervosa, self-starvation is associated with:	Not eating to help control weight gain	Not being bothered about weight gain	Regularly engaging in purging activities to help control weight gain	Eating only certain food types	Regularly engaging in purging activities to help control weight gain
44	High rates of comorbidity exist between anorexia and other Axis I and Axis II disorders. What percentage of anorexia sufferers who also have a lifelong diagnosis of major depression?	50-68%	30-40%	20-30%	70-80%	50-68%
45	In Bulimia Nervosa, the purging sub-type, vomiting is the most common form of purging. What percentage of sufferers present with this type of purging?	50-60%	80-90%	15-25%	50-60%	80-90%
47	In Bulimia nervosa, the nonpurging sub-type, a behaviour which is used to compensate for binging is	Exercise	Controlling intake of certain food types	Withdrawing from social interaction	Controlling carbohydrate intake	Exercise
48	Individuals with bulimia have a perceived lack of control over their eating behaviour, and often report which of the following?	High levels of self-disgust	Low self-esteem	High levels of depression	All of the above	All of the above
49	Which of the following is a laboratory procedure developed to provide an objective behavioural measure of the tendency to binge eat?	Palatability test	Food pre-load test	Full capacity test	Fully loaded test	Food pre-load test
50	Selective serotonin-reuptake inhibitors (specifically fluoxetine) are used to treat bulimia due to their:	Acceptability	Tolerability	Reduction of symptoms	All of the above	All of the above
51	One of the most common treatments for eating disorders is:	Electro-convulsive therapy	Electro-convulsive therapy	Family therapy	Aversion therapy	Family therapy
52	Which of the following is a common treatment for bulimia?	Family therapy	Cognitive Behaviour Therapy	Psychodynamic therapy	Humanistic therapy	Cognitive Behaviour Therapy

53	Anorexia and bulimia are frequently comorbid with major depression, thus eating disorders have tended to be treated pharmacologically with which of the following?	Antipsychotics	Antibiotics	Antihistamine	Antidepressants	Antidepressants
54	Which of the following characteristics has regularly been implicated in the aetiology of eating disorders?	Perfectionism	Narcissism	Extraversion	Introversion	Perfectionism
55	Which of the following is a prominent characteristic of individuals with eating disorders?	High self esteem	Low self esteem	High levels of responsibility	Narcissism	Narcissism
56	Body dissatisfaction is associated with triggering bouts of:	Purging	Binging	Dieting	Shopping	Dieting
57	Body dissatisfaction is defined by Polivy & Herman (2002) as:	The gap between one's actual weight and that of your best friend	The gap between one's actual and ideal weight and shape	The gap between one's actual weight and childhood weight	The number of things you would like to change about your body	The gap between one's actual and ideal weight and shape
58	Research of bulimia nervosa has found low levels of:	Alpha-dopamine	Beta-serotonin	Beta-endorphin	Alpha-amphetamine	Beta-endorphin
59	Biological accounts of anorexia and bulimia suggest that maintaining a low body weight and self-starvation may be reinforced by:	Endogenous opioids	Serotonin	Endorphins	Dopamine	Endogenous opioids
60	In animal research, lesions to which part of the brain have been shown to cause appetite loss, resulting in a self-starvation syndrome?	Lateral hypothalamus	Cerebellum	Amygdala	Basal ganglia	Lateral hypothalamus



UNIT-II-SYLLABUS

Metabolic and Lifestyle disorders

Diabetes mellitus A metabolic syndrome and the relationship with hypertension, obesity, hypothyroidism and stress. Cardio vascular disorders and Atherosclerosis-defining the broad spectrum of ailments that fall in this category, understanding the factors that contribute to the syndrome, stages of disorder and the management of the condition. Irritable bowel syndrome-biochemistry behind the disorder and the influence of diet, stress and environment on the condition.

Diabetes Mellitus

A chronic disease due primarily to a disorder of carbohydrate metabolism, **cause of which is deficiency or diminished effectiveness of insulin,** resulting in hyperglycaemia and glycosuria. Secondary changes may occur in the metabolism of proteins, fats, water and electrolytes and in tissues/organs sometimes with grave consequences.

CLINICAL TYPES AND CAUSES

These are **two main groups:**

(a) Primary (Idiopathic): constitute major group. Exact cause is not known; metabolic defect is insufficient insulin which may be absolute or relative.

Two clinical types:

- **"Juvenile"-onset diabetes:** Now called as **Type-I-** (Insulin dependent)—**IDDM.**
- **"Maturity" onset diabetes: Type-II NIDDM**— (Non- Insulin Dependent).

Differences between the two clinical types are listed in a box in next page.

(b) Secondary: constitute minor group where it can be secondary to some disease process.

Other Factors

1. Heredity: In both types, familial tendency noted. Genetic factors more important in those who develop after 40. In younger, "Juvenile" type, susceptibility is associated with particular HLA phenotype. RISK is two to three times more in those who are HLA phenotype B8 or BW15.

2. Autoimmunity: Insulin-dependent juvenile type may be an autoimmune disorder and has been found to co-exist with other autoimmune disorders. Evidences in favour of autoimmunity:

- Lymphocytic and plasma cells infiltrations in pancreas
- Detection of autoantibodies by immunofluorescence.

3. Infections: Certain viral infections may precipitate Juvenile type. Experimentally it has been shown that certain viruses can induce diabetes. Incidence is high after mumps. Antibodies to coxsackie B4 virus have been found in young Juvenile type.

4. Obesity: Majority of middle aged maturity-onset diabetics are obese, "stress" like pregnancy may precipitate.

5. Diet: Over-eating and **under activity** are also predisposing factors in elderly middle aged maturity onset diabetes.

6. Insulin antagonism: In "maturity onset" diabetes, the deficiency of insulin is relative and glucose induced insulin secretion may be greater and more prolonged than normal. This relative deficiency may be due to insulin antagonism, exact cause for the same is not known but various factors have been incriminated from time to time. They are:

- Synalbumin of Vallence-Owen in plasma, dialyzable, thermostable substance.
- β1-lipoprotein factor: Another similar factor found in β1-lipoprotein fraction of plasma in diabetics.
- Insulin "antibodies".
- Secretion of abnormal and less active insulin or 'altered' insulin.
- A "tissue barrier" to the transport of insulin to the cells, probably "receptor" deficiency.
- Lack of cellular response to insulin.

(b) Secondary: This forms a minor group. Diabetes is secondary to some other diseases.

***1.* Pancreatic diabetes:**

- Pancreatitis
- Haemochromatosis
- Malignancy of Pancreas.

2. Abnormal concentrations of antagonistic hormones:

- Hyperthyroidism
- Hypercorticism: like Cushing's disease and syndrome.
- Hyperpituitarism: Like acromegaly
- Increased glucagon activity.

3. Iatrogenic: In genetically susceptibles, may be precipitated By herapy like corticosteroids, thiazide diuretics.

Presentation Diabetes Mellitus

The disease has a varied presentation.

- Glycosuria may be detected during routine examination of urine like annual check-up or when doing routine examination due to some other diseases. There may not be any symptoms/signs.
- Some may present with all classical symptoms like thirst, polydypsia, Polyuria, Polyphagia, loss of weight etc ("Overt" diabetics).
- Some women present during pregnancy (stress)
- A few specially Type-1 cases may present as fulminant ketoacidosis and a few with complications.

CLINICAL FEATURES AND BIOCHEMICAL CORRELATIONS

- Large amounts of glucose may be excreted in urine (may be 90 to 100 G/day in some cases). Loss of solute produces osmotic diuresis thus large volume of urine ***(polyuria).***
- Loss of fluid leads to thirst and ***polydypsia.***
- ***Polyphagia:*** Eats more frequently. More fond of sweets. The above symptoms may persist for many months in maturity-onset diabetes. In juvenile onset type-1, further symptoms develop if treatment is not started.
- Tissues including muscles received liberal supply of glucose but cannot use glucose due to absolute or relative deficiency of insulin/ or transport defect to cells. This causes ***weakness and tiredness.***
- As glucose cannot be used for fuel, fat is mobilized leading to increase FFA- in blood and liver.
- Increased acetyl-CoA is diverted for cholesterol synthesis— ***Hypercholesterolaemia*** and ***atherosclerosis.*** Xanthomas may develop.
- Increased ketone bodies leads to acidosis, which leads to hyperventilation ("air-hunger").
- If ketosis is severe, acetone will be breathed out, giving characteristic "fruity" smell in breath (due to acetone).
- Along with above, there may be excessive breakdown of tissue proteins. Deaminated amino acids are catabolised to provide energy, which accounts for Loss of weight.
- Due to ketosis, develops anorexia, nausea, and vomiting. Continued loss of water and electrolytes increases dehydration.
- Ketoacidosis produces increasing drowsiness, leading to diabetic coma in untreated cases.

1. Hyperglycaemia:

- Decreased and impaired transport and uptake of glucose into muscles and adipose tissues.
- Repression of key glycolytic enzymes like Glucokinase, phosphofructokinase and pyruvate kinase takes place.
- Derepression of key gluconeogenic enzymes like Pyruvate carboxylase, phosphoenol pyruvate carboxykinase, fructose biphosphatase and glucose-6-phosphatase occur, promoting gluconeogenesis in Liver. This further contributes to hyperglycaemia.
- Elevated amino acid level in the blood particularly alanine provides fuel for gluconeogenesis in Liver.

2. Amino Acids Level

- Transport and uptake of amino acids in peripheral tissues is also depressed causing an elevated circulating level of amino acids, particularly alanine. Glucocorticoid activity predominate having catabolic action on peripheral tissue proteins, releasing more amino acids in blood.
- Amino acids breakdown in Liver results in increased production of urea N.

3. Protein synthesis:

Protein synthesis is decreased in all tissues due to:

- Decreased production of ATP□
- Absolute or relative deficiency of Insulin.

4. Fat Metabolism

- Decrease extramitochondrial *de Novo* synthesis of FA and also TG synthesis due to decrease in acetyl- CoA from carbohydrates, ATP, NADPH and ⟨- glycero-(p) in all tissues.
- Stored lipids are hydrolysed by increased Lipolysis liberating free fatty acids (FFA)□.
- Increased FFA interferes at several steps of carbohydrate phosphorylation in muscles, further contributing to hyperglycaemia.

Effects of Increased FFA Level

- FFA reaching the Liver in high concentration inhibits further FA synthesis by a feedback inhibition at the *acetyl-CoA carboxylase* step.
- Fats are mobilised for energy; increased fatty acid oxidation increases acetyl-CoA level, which in turn activates *Pyruvate carboxylase*, stimulating the gluconeogenic pathway required for conversion of amino acids C-skeletons to glucose.

- FA also stimulates gluconeogenesis by entering TCA cycle and increasing production of citrates. Citrate in turn inhibits glycolysis at *phosphofructokinase* level.
- Eventually FA inhibits TCA cycle at the level of *citrate synthase* and possibly pyruvate dehydrogenase complex and Isocitrate dehydrogenase level.

5. Effect on glycogen synthesis:

Glycogen synthesis is depressed as a result of:

- Decreased glycogen synthase activity due to deficiency of insulin.
- By activation of phosphorylase producing glycogenolysis through the action of epinephrine and/or glucagon (antagonistic) hormones.
- By increased ADP: ATP ratio.

6. Other Effects of Hyperglycaemia

(a) Glycosylation of Hb and formation of glycosylated Hb (HbA1C):

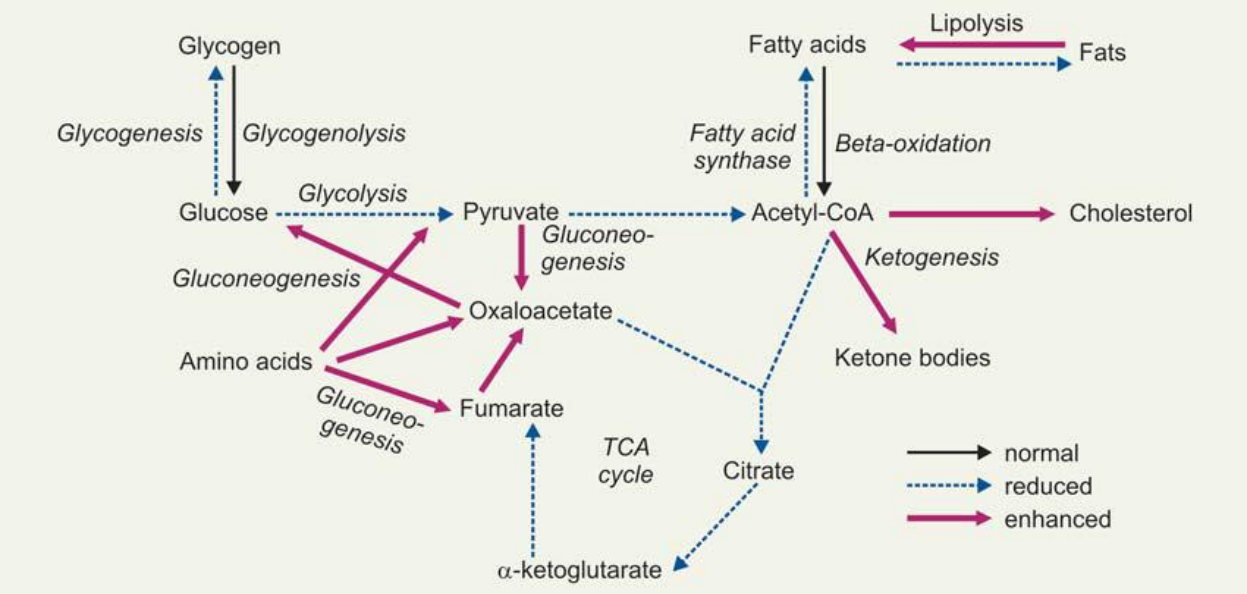
- Glycosylated haemoglobins particularly HbA1C rises in prolonged and uncontrolled diabetes 3 to 4 times than the normal level.

(b) Non-enzymatic glycosylation of other proteins as plasma albumin, collagenous tissues and the lens protein α-crystallin:

- Such glycosylations of colla-genous tissues bring about thickening and morphological changes of vessel walls and also glomerular basement membrane thickening. Glycosylation of lens protein may also account for diabetic cataract.

Diabetic cataract biochemically may be due to:

i. Glycosylation of Lens Proteins, i.e. α-crystallin.
ii. Accumulation of 'sorbitol' which produces osmotic damage.



COMPLICATIONS OF DIABETES MELLITUS

I. Immediate: Diabetic ketoacidosis and coma is one of the most important and dreaded complication specially in Type-I.

II. Late complications: Other complications are late to appear and are due to changes in blood vessels. These are **two types:**

- Involvement of large vessels
- Involvement of small vessels.

(a) Large vessels involvement: Atherosclerosis and its effects:

- Involvement of coronary vessels can produce myocardial infarction.
- Involvement of cerebral vessels can produce "stroke".

(b) Small vessels changes involve:

- Thickening of basement membrane
- Microvascular changes.

1. ***Diabetic retinopathy (70%):***
   - Tiny haemorrhages, punctate or flame-shaped, exudates. Haemorrhage in vitreous humour can cause sudden blindness.
2. ***Diabetic cataract:***
   - Non-enzymatic glycosylation of lens protein, α-crystallin;
   - Osmotic damage to lens protein due to accumulation of sorbitol.

3. *Diabetic nephropathy (50% cases):*

- Characterised by (a) Proteinuria, (b) Hypertension and (c) Oedema. The triad is called as *Kimmelsteil-Wilson syndrome.* Microscopic lesions are called as *'Kimmelsteil-Wilson lesions/disease'.* Lesions are often present when syndrome is not developed. Sometimes kidney lesions may be shown as:
- Papillary necrosis: A dangerous complication.
- Pyelonephritis: When secondary infections occur.

4. *Peripheral neuritis (neuropathy):*

- Manifestated by loss of sensation and tingling. Biochemically probably the cause is myoinositol deficiency. Sometimes there may be associated myopathies, weakness of muscles.

5. *Diabetic gangrene:*

- Cause is due to diminished blood supply due to atherosclerotic changes in blood vessels. Also associated tissue hypoxia due to formation of HbA1C (glycosylated Hb), less oxygen carrying capacity.

6. *Skin lesions:*

- Prone to infections: boils/ulcers and carbuncles. There may be necrosis of skin, ***Necrobiosis diabeticorum.***
- May be punctate depigmented atrophy
- Wound healing is delayed.

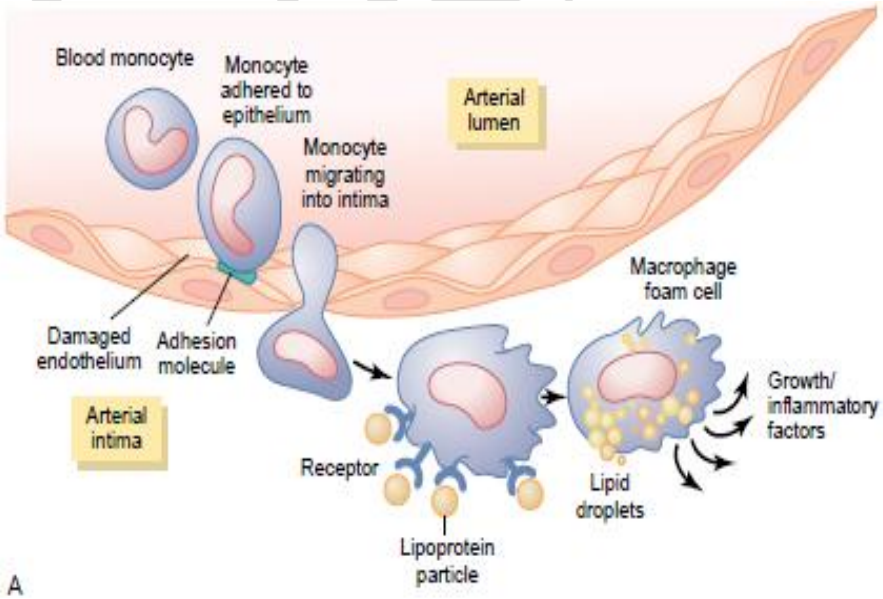
7. *Pulmonary tuberculosis:*

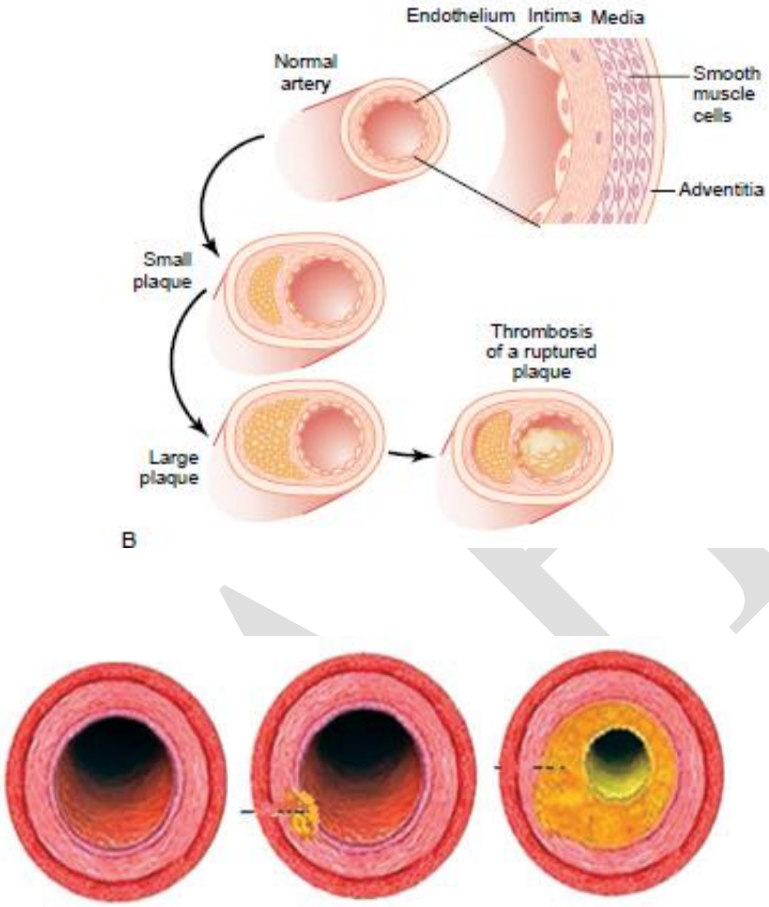
- Susceptible to pulmonary tuberculosis.

Atherosclerosis

- Atherosclerosis is a disease of the large and intermediate- sized arteries in which fatty lesions called atheromatous plaques develop on the inside surfaces of the arterial walls. Arteriosclerosis, in contrast, is a general term that refers to thickened and stiffened blood vessels of all sizes.
- One abnormality that can be measured very early in blood vessels that later become atherosclerotic is damage to the vascular endothelium. This, in turn, increases the expression of adhesion molecules on endothelial cells and decreases their ability to release nitric oxide and other substances that help prevent adhesion of macromolecules, platelets, and monocytes to the endothelium.

- After damage to the vascular endothelium occurs, circulating monocytes and lipids (mostly low-density lipoproteins) begin to accumulate at the site of injury.
- The monocytes cross the endothelium, enter the intima of the vessel wall, and differentiate to become macrophages, which then ingest and oxidize the accumulated lipoproteins, giving the macrophages a foam like appearance.
- These macrophage foam cells then aggregate on the blood vessel and form a visible fatty streak. With time, the fatty streaks grow larger and coalesce,and the surrounding fibrous and smooth muscle tissues proliferate to form larger and larger plaques.
- Also, the macrophages release substances that cause inflammation and further proliferation of smooth muscle and fibrous tissue on the inside surfaces of the arterial wall.
- The lipid deposits plus the cellular proliferation can become so large that the plaque bulges into the lumen of the artery and greatly reduces blood flow, sometimes completely occluding the vessel.
- Even without occlusion, the fibroblasts of the plaque eventually deposit extensive amounts of dense connective tissue; sclerosis (fibrosis) becomes so great that the arteries become stiff and unyielding.
- Still later, calcium salts often precipitate with the cholesterol and other lipids of the plaques, leading to bony-hard calcifications that can make the arteries rigid tubes. Both of these later stages of the disease are called “hardening of the arteries.”





Basic Causes of Atherosclerosis:

Increased Low-Density Lipoproteins.:

- An important factor in causing atherosclerosis is a high blood plasma concentration of cholesterol in the form of low-density lipoproteins.
- The plasma concentration of these high cholesterol low-density lipoproteins is increased by several factors, including eating highly saturated fat in the daily diet, obesity, and physical inactivity.
- To a lesser extent, eating excess cholesterol may also raise plasma levels of low-density lipoproteins.
-

Familial Hypercholesterolemia*:*

- This is a disease in which the person inherits defective genes for the formation of low-density lipoprotein receptors on the membrane surfaces of the body's cells.
- In the absence of these receptors, the liver cannot absorb either intermediate-density or low-density lipoproteins.
- Without this absorption, the cholesterol machinery of the liver cells goes on arampage, producing new cholesterol; it is no longer responsive to the feedback inhibition of too much plasma cholesterol.
- As a result, the number of very low density lipoproteins released by the liver into the plasma increases immensely.

Other Major Risk Factors for Atherosclerosis:

- In some people with perfectly normal levels of cholesterol and lipoproteins, atherosclerosis still develops.

- Some of the factors that are known to predispose to atherosclerosis are (1) *physical inactivity* and *obesity,* (2) *diabetes mellitus,* (3) *hypertension,* (4) *hyperlipidemia,* and (5) *cigarette smoking.*
- **Hypertension**, for example, increases the risk for atherosclerotic coronary artery disease by at least twofold.
- Likewise, a person with diabetes mellitus has, on average, more than a twofold increased risk of developing coronary artery disease. When hypertension and diabetes mellitus occur together, the risk for coronary artery disease is increased by more than eightfold.
- when hypertension, diabetes mellitus, and hyperlipemia are all present, the risk for atherosclerotic coronary artery disease is increased almost 20-fold.

Prevention of Atherosclerosis:

- The most important measures to protect against the development of atherosclerosis and its progression to serious vascular disease are
  1. Maintaining a healthy weight, being physically active, and eating a diet that contains mainly unsaturated fat with a low cholesterol content;
  2. Preventing hypertension by maintaining a healthy diet and being physically active, or effectively controlling blood pressure with antihypertensive drugs if hypertension does develop; (3) effectively controlling blood glucose with insulin treatment or other drugs if
  3. Diabetes develops;
  4. Avoiding cigarette smoking.

Cardio Vascular Diseases

Heart Failure:

- Heart failure or **cardiac failure** is the condition in which the heart looses the ability to pump sufficient amount of blood to all parts of the body.
- Heart failure may involve left ventricle or right ventricle or both. It may be acute or chronic.

Acute Heart Failure

- Acute heart failure refers to sudden and rapid onset of signs and symptoms of abnormal heart functions. Its symptoms are severe initially.
- However, the symptoms last for a very short time and the condition improves rapidly. Usually it requires treatment.

Chronic Heart Failure

- Chronic heart failure is the heart failure that is characterized by the symptoms that appear slowly over a period of time and become worst gradually.

Congestive Heart Failure

- Congestive heart failure is a general term used to describe the heart failure resulting in accumulation of fluid in lungs and other tissues.
- When heart is not able to pump blood through aorta, the blood remains in heart. It results in dilatation of the chambers and accumulation of blood in veins (vascular congestion). Fluid retention and pulmonary edema also occur in this condition.

Causes of heart failure

Common causes of heart failure are:

1. Coronary artery disease
2. Defective heart valves
3. Arrhythmia
4. Cardiac muscle disease such as cardiomyopathy
5. Hypertension
6. Congenital heart disease
7. Diabetes
8. Hyperthyroidism
9. Anemia
10. Lung disorders

11. Inflammation of cardiac muscle **(myocarditis)** due to viral infection, drugs, alcohol, etc.

Signs and symptoms of heart failure:

Signs and Symptoms of Chronic Heart Failure

1. Fatigue and
2. Rapid and irregular heartbeat
3. Shortness of breathing
4. Fluid retention and weight gain
5. Loss of appetite
6. Nausea and vomiting
7. Cough
8. Chest pain, if developed by myocardial infarction.

Signs and Symptoms of Acute Heart Failure:

- Signs and symptoms of acute heart failure may be same as chronic heart failure. But the signs and symptoms appear suddenly and severely.
- When heart starts to fail suddenly, the fluid accumulates in lungs causing pulmonary edema. It results in sudden and severe shortness of breath, cough with pink, foamy mucus and heart palpitations.
- It may lead to sudden death, if not attended immediately.

Types of heart failure:

1. Systolic Heart Failure

- Systolic heart failure is the heart failure due to the decreased ability of heart to contract. It may involve right heart or left heart or both. It is caused either by muscular weakness or valvular defect.
- Ventricles may be filled with blood but cannot pump it out with sufficient force. Ejection fraction decreases to about 20%. So the amount of blood pumped to the body and to the lungs is decreased.
- As a result, more amount of blood remains in ventricle. Later the blood starts accumulating in lungs or systemic veins or both. Usually the ventricle enlarges in systolic heart failure.

2. Diastolic Heart Failure

- Diastolic heart failure is the heart failure that occurs when the ventricles cannot relax properly due to the stiffening of cardiac muscle. So, there is reduction in ventricular filling and cardiac output.

3. Right Sided Heart Failure

- Right sided heart failure occurs due to loss of pumping action of the right side of the heart. Because of loss of pumping action of right ventricle, blood accumulates in right atrium and blood vessels.
- It causes edema in the feet, ankles, legs and abdomen.

4. Left Sided Heart Failure

- Left sided heart failure is due to the loss of pumping action of the left side of the heart. It causes congestion of lungs.

Aortic Stenosis and Aortic Regurgitation:

- In aortic stenosis, the contracting left ventricle fails to empty adequately, whereas in aortic regurgitation, blood flows backward into the ventricle from the aorta after the ventricle has just pumped the blood into the aorta.
- Therefore, in either case, the net stroke volume output of the heart is reduced.

Hypertrophy of the Left Ventricle:

- In both aortic stenosis and aortic regurgitation, the left ventricular musculature hypertrophies because of the increased ventricular workload.
- In *regurgitation,* the left ventricular chamber also enlarges to hold all the regurgitant blood from the aorta. Sometimes the left ventricular muscle mass increases fourfold to fivefold, creating a tremendously large left side of the heart.
- When the aortic valve is seriously *stenosed,* the hypertrophied muscle allows the left ventricle to develop as much as 400 mm Hg intraventricular pressure at systolic peak.
- In severe aortic regurgitation, sometimes the hypertrophied muscle allows the left ventricle to pump a stroke volume output as great as 250 milliliters, although as much as three fourths of this blood returns to the ventricle during diastole, and only one fourth flows through the aorta to the body.

Pulmonary Edema in Mitral Valvular Disease:

- The buildup of blood in the left atrium causes progressive increase in left atrial pressure, and this eventually results in development of serious pulmonary edema.
- Ordinarily, lethal edema does not occur until the mean left atrial pressure rises above 25 mm Hg and sometimes as high as 40 mm Hg, because the lung lymphatic vasculature enlarges many fold and can carry fluid away from the lung tissues extremely rapidly.

Enlarged Left Atrium and Atrial Fibrillation:

- The high left atrial pressure in mitral valvular disease also causes progressive enlargement of the left atrium, which increases the distance that the cardiac electrical excitatory impulse must travel in the atrial wall.
- Therefore, in late stages of mitral valvular disease, especially in mitral stenosis, atrial fibrillation usually occurs. This further reduces the pumping effectiveness of the heart and causes further cardiac debility.

Arrhythmia:

- Arrhythmia refers to **irregular heartbeat** or disturbance in the rhythm of heart. In arrhythmia, heartbeat may be fast or slow or there may be an extra beat or a missed beat. It occurs in physiological and pathological conditions.

Classification:

- In arrhythmia, SA node may or may not be the pacemaker. If SA node is not the pacemaker, any other part of the heart such as atrial muscle, AV node and ventricular muscle becomes the pacemaker. Accordingly, arrhythmia is classified into two types:
  A. Normotopic arrhythmia
  B. Ectopic arrhythmia.

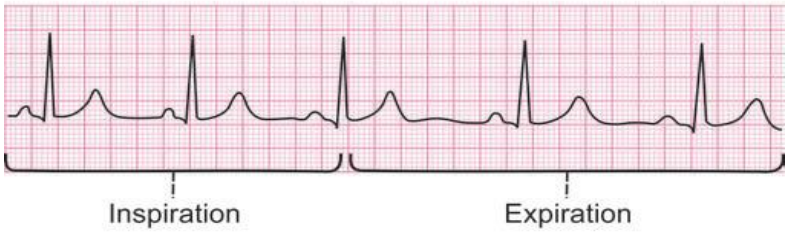
Normotopic arrhythmia:

- Normotopic arrhythmia is the irregular heartbeat, in which SA node is the pacemaker. Normotopic arrhythmia is of three types:
  1. Sinus arrhythmia
  2. Sinus tachycardia
  3. Sinus bradycardia.

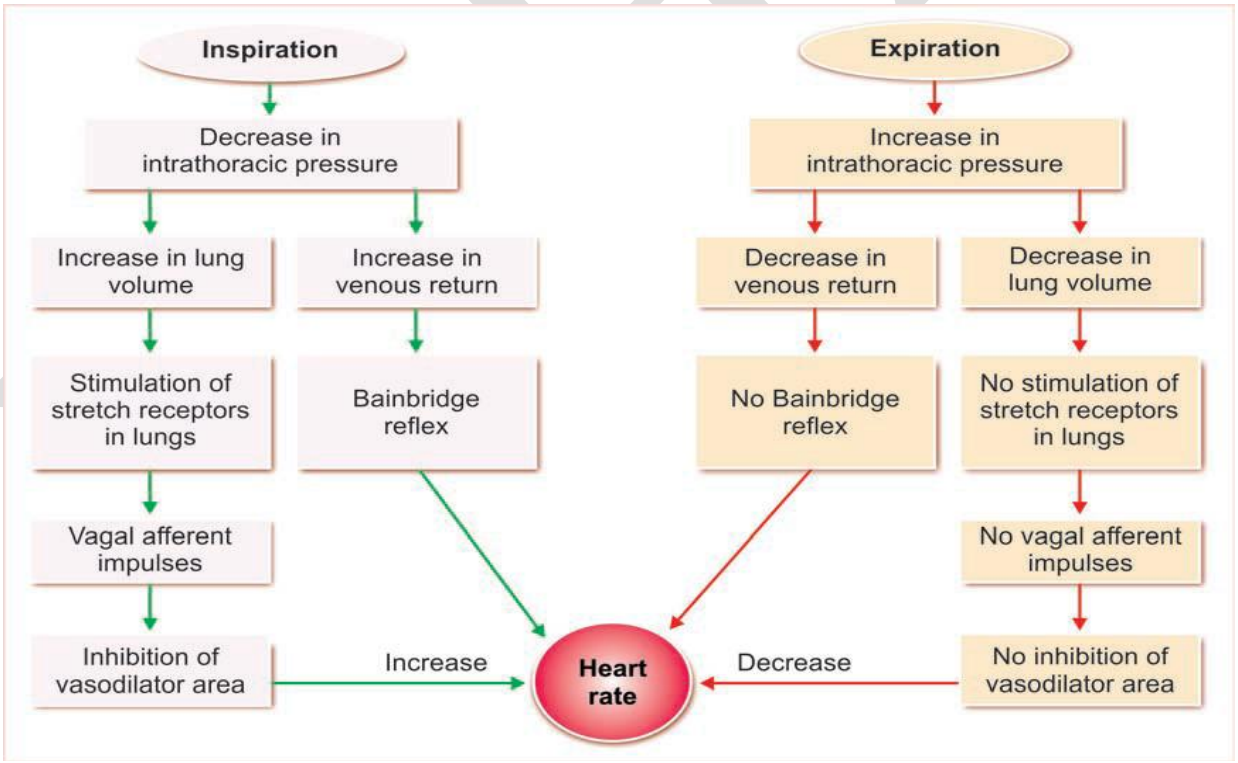
„ 1.Sinus arrhythmia:

- Sinus arrhythmia is a normal rhythmical increase and decrease in heart rate, in relation to respiration. It is also called **respiratory sinus arrhythmia** (RSA).
- Normal sinus rhythm means the normal heartbeat with SA node as the pacemaker. Normal heart rate is 72 per minute.
- However, under physiological conditions, in a normal healthy person, heart rate varies according to the phases of respiratory cycle. Heart rate increases during inspiration and decreases during expiration.

ECG Changes



- ECG is normal during sinus arrhythmia. Only the duration of R-R interval varies rhythmically according to phases of respiration. It is shortened during inspiration and prolonged during expiration.



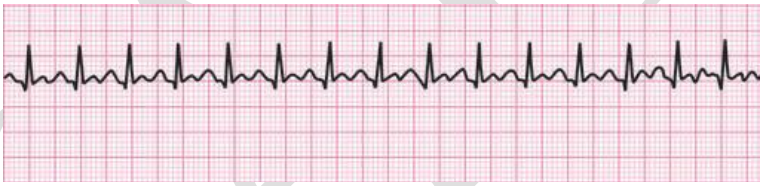
Causes:

- Sinus arrhythmia is due to fluctuation in the discharge of impulses from SA node. During inspiration, the lungs are inflated and the intrathoracic pressure decreases.
- This increases the venous return. Inflation of lungs stimulates the stretch receptors of lungs, which send impulses to vasodilator area (cardioinhibitory center) through afferent fibers of vagus.
- It leads to reflex inhibition of vasodilator area and reduction in vagal tone. Because of these two factors, heart rate increases. Simultaneously, increased venous return initiates **Bainbridge reflex** that causes increase in heart rate.

Sinus tachycardia:

- Sinus tachycardia is the increase in discharge of impulses from SA node, resulting in increase in heart rate. Discharge of impulses from SA node is very rapid and the heart rate increases up to 100/minute and sometimes up to 150/minute.

ECG Changes:



- ECG is normal in sinus tachycardia, except for short R-R intervals because of increased heart rate.

Conditions when Sinus Tachycardia Occurs

- Sinus tachycardia occurs in physiological as well as pathological conditions.
  Physiological conditions when tachycardia occurs
  1. Exercise
  2. Emotion
  3. High altitude
  4. Pregnancy.

  Pathological conditions when tachycardia occurs
  1. Fever
  2. Anemia
  3. Hyperthyroidism
  4. Hypersecretion of catecholamines

5. Cardiomyopathy
6. Valvular heart disease
7. Hemorrhagic shock.

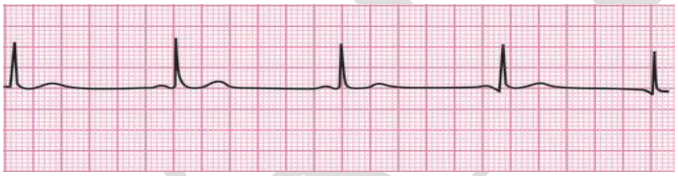
Features of Sinus Tachycardia

1. Palpitations (sensation of feeling the heartbeat)
2. Dizziness
3. Fainting
4. Shortness of breath
5. Chest discomfort (angina).

Sinus bradycardia:

- Sinus bradycardia is the reduction in discharge of impulses from SA node resulting in decrease in heart rate. Heart rate is less than 60/minute.

ECG Changes:



- ECG shows prolonged waves and prolonged R-R interval.

Conditions when Sinus Bradycardia Occurs:

- Sinus bradycardia occurs in both physiological and pathological conditions. It occurs during sleep.
- It is common in athletes due to the cardiovascular reflexes, in response to increased force of contraction of heart. Physiological conditions when sinus bradycardia occurs
  1. Sleep
  2. Athletic heart.

Pathological conditions when sinus bradycardia occurs

1. Disease of SA node
2. Hypothermia
3. Hypothyroidism
4. Heart attack
5. Congenital heart disease
6. Degenerative process of aging

7. Obstructive jaundice
8. Increased intracranial pressure
9. Use of certain drugs like beta blockers, channel blockers, digitalis and other **antiarrhythmic drugs**
10. Atherosclerosis. Bradycardia due to **atherosclerosis** of carotid artery, at the region of carotid sinus is called **carotid sinus syndrome.**

Features of Sinus Bradycardia:

1. Sick sinus syndrome
2. Fatigue
3. Weakness
4. Shortness of breath
5. Lack of concentration
6. Difficulty in exercising.

Irritable Bowel Syndrome

- Irritable bowel syndrome (IBS) is the most commonly diagnosed gastrointestinal condition. It is a symptom-based condition defined by the presence of abdominal pain or discomfort, with altered bowel habits, in the absence of any other disease to cause these sorts of symptoms.
- Women more commonly report abdominal pain and constipation, whereas men more commonly report diarrhea.2 It appears that IBS prevalence decreases with age.

Pathophysiology of Irritable Bowel Syndrome (IBS)

Environmental Contributors to IBS Symptoms

- Early life stressors (abuse, psychosocial stressors)
- Food intolerance
- Antibiotics
- Enteric infection

Host Factors Contributing to IBS Symptoms

- Altered pain perception
- Altered brain-gut interaction
- Dysbiosis
- Increased intestinal permeability
- Increased gut mucosal immune activation
- Visceral hypersensitivity

- IBS symptoms that arise after acute gastroenteritis or so called post infectious IBS present an interesting developmental model.
- Host factors such as genetics, immune function, microbiome, and psychological status, as well as environmental factors such as stress, severity of infection, or treatment with antibiotics, could predispose to the development of chronic IBS symptoms.
- It is important to identify patients with post infectious IBS because, unlike typical IBS, which tends to be a chronic relapsing condition, it spontaneously resolves in roughly half of patients within 6 to 8 years of the index infection.

Features of Irritable Bowel Syndrome:

Typical Features

- Loose/frequent stools
- Constipation
- Bloating
- Abdominal cramping, discomfort, or pain
- Symptom brought on by food intake/specific food sensitivities Symptoms dynami cover time

Concerning Features for Organic Disease

- Symptom onset after age 50 y
- Severe or progressively worsening symptoms
- Unexplained weight loss
- Nocturnal diarrhea
- Family history of organic gastroenterological diseases, including colon
- cancer, celiac disease, or inflammatory bowel disease
- Rectal bleeding or melena
- Unexplained iron-deficiency anemia

Treatment:

Treatment	Quality of Evidence	Treatment Benefits	Most Common Adverse Events
Over-the-Counter			
Fiber: psyllium	Moderate	Best suited for IBS-C	Bloating, gas
Laxatives: polyethylene glycol	Very low	Beneficial for constipation but not global symptoms or pain in IBS-C	Bloating, cramping, diarrhea
Antidiarrheals: loperamide	Very low	Beneficial for diarrhea but not global symptoms or pain in IBS-D	Constipation
Probiotics	Low	Possible benefits for global symptoms, bloating, and gas as a class but unable to recommend specific probiotics	Similar to placebo
Antispasmodics: peppermint oil	Moderate	Benefits for global symptoms and cramping	GERD, constipation
Prescription			
Antidepressants: TCAs, SSRIs, SNRIs	High	TCAs and SSRIs improve global symptoms and pain; leverage adverse effects to choose TCAs for IBS-D patients and SSRIs for IBS-C patients	Dry eyes/mouth, sedation, constipation, or diarrhea
Antispasmodics	Low	Some drugs offer benefits for global symptoms and pain	Dry eyes/mouth, sedation, constipation
Prosecretory agents			
Linaclotide	High	Improves global, abdominal, and constipation symptoms in IBS-C	Diarrhea
Lubiprostone	Moderate	Improves global, abdominal, and constipation symptoms in IBS-C	Nausea, diarrhea
Antibiotics: rifaximin	Moderate	Improves global symptoms, pain, and bloating in nonconstipated IBS patients	Similar to placebo
5-HT_3 receptor antagonists: alosetron	Moderate	Improves global, abdominal, and diarrhea symptoms in women with severe IBS-D	Constipation, rare ischemic colitis
Other Therapies			
Psychological/behavioral therapy	Very low	Benefits for global IBS symptoms in all subgroups	Similar to placebo

POSSIBLE QUESTIONS

2 marks

1. Write a note on Diabetes Mellitus.
2. What is Insulin? Give the importance.
3. What are all the causes of diabetes mellitus?
4. What is Atherosclerosis?
5. What is meant by Valve Regurgitation?
6. Write note on Irritable Bowel syndrome?

6 marks

1. Discuss in detail about Diabetes Mellitus?.
2. Give an account on how Hyperthyroidism, Obesity, Hypertension related to diabetes mellitus?
3. Explain the following,
   i) Hypertrophy
   ii) Tachycardia
4. Explain about Irritable Bowel syndrome in detail?

.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III- B.Sc., BIOCHEMISTRY
MOLECULAR BASIS OF NON-INFECTIOUS HUMAN DISEAS 18BCU504-A
MULTIPLE CHOICE QUESTIONS

Unit II

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Which of the following confirmed values meet the diagnostic threshold for diabetes?	fasting blood glucose ≥ 140 mg/dl	random glucose > 160 mg/dl	2 hour post prandial glucose ≥ to 126 mg/dl	fasting blood glucose ≥ 126 mg/dl	fasting blood glucose ≥ 126 mg/dl
2	Which of the following statements is correct?	Insulin suppresses the activity of glycogen synthase	Insulin mediates glucose uptake in the brain	"Prediabetes" is a condition characterized by an increased risk for the future development of type 2 diabetes	The rise in insulin concentration after meal ingestion is reduced in type 1 but not in type 2 diabetes	"Prediabetes" is a condition characterized by an increased risk for the future development of type 2 diabetes
3	Insulin deficiency is associated with	Reduced lipolysis	Increased ketogenesis	Reduced gluconeogenesis	Reduced proteolysis	Increased ketogenesis
4	The risk factors for type 2 diabetes mellitus include:	family history	being overweight	high intake of dietary fat	All of the options listed are correct	
5	The pathogenesis of hyperglycemia in type 2 diabetes includes all the following mechanisms except for:	Increased glucose production by the liver	Impaired insulin secretion	Decreased glucose uptake from the skeletal muscle	All of the options given are correct	All of the options given are correct

6	The test for checking mean plasma glucose concentration over the previous 8-10 weeks is:	Hemoglobin A1c	Oral glucose tolerance test (OGTT)	Fructosamine test	Fasting plasma glucose concentration	Hemoglobin A1c
7	Which statement best describes the differences between the characteristics of type 1 and type 2 diabetes:	persons with type 2 diabetes usually require lower doses of insulin than person with type 1 diabetes because they have a milder form of diabetes	persons with type 1 diabetes rapidly develop chronic complications	autoimmune factors are involved in the pathogenesis of type 1 but not type 2 diabetes	persons with type 1 diabetes can increase endogenous insulin production by taking oral hypoglycemic agents	autoimmune factors are involved in the pathogenesis of type 1 but not type 2 diabetes
8	Which of the following is not a beneficial effect of exercise in people with diabetes	Reduction of triglycerides	Hypoglycaemia	increase of insulin sensitivity	help controlling hypertension	Hypoglycaemia
9	According to trials on diabetes prevention, high-risk individuals can reduce their risk to develop diabetes by doing the following	Eating a very low carbohydrate diet	Consuming a diet high in monounsaturated fats	Losing 5-7% of body weight through a hypocaloric low fat diet and 30 minutes of daily activity	Initiating metformin 850 mg BID and practicing daily vigorous exercise	Losing 5-7% of body weight through a hypocaloric low fat diet and 30 minutes of daily activity
10	Which of the following are the recommended blood pressure and lipid goals for the prevention of cardiovascular disease in adults with diabetes?	BP < 140/90, Trig <150, LDL < 100	BP < 130/85, Trig < 300, LDL < 100	P < 135/80, Trig < 200, LDL < 130	BP < 130/80, Trig <150, LDL < 100	P < 135/80, Trig < 200, LDL < 130
11	What is the first-line drug for patients with type 2 diabetes and obesity?	Acarbose	Metformin	Sulphonylureas	Insulin	Metformin
12	According to the recommendations for the nutritional management of patients with diabetes, the consumption of saturated fat should be	<10% of total daily ene	<12%	<15%	<16%	<10% of total daily energy
13	All of the following are risk factors for atherosclerosis except:	Increased waist hip ratio	Hyperhomocysteinemia	Decreased fibrinogen levels	Decreased HDL levels	Decreased fibrinogen levels

14	Hard yellow plaque of lipoid which is found in inner most layer of arteries is called	carcinomas	pace maker	atheroma	atherosclerosis	atheroma
15	All veins in body carry deoxygenated blood except	A. aorta	inferior venacava	superior venacava	A. pulmonary vein	A. pulmonary vein
16	Constriction and hardening of arteries occur in a condition known as	A. Arteriosclerosis	Atherosclerosis	both of them	Venusclerosis	A. Arteriosclerosis
17	Back flow of blood in veins is controlled by	bicuspid valves	tricuspid valves	semi valves	A. semi lunar valves	A. semi lunar valves
18	Veins collects blood from body and send it to	A. liver	lungs	heart	A. arteries	heart
19	Dyspnea, fatigue, increased pulmonary artery pressure, and decreased cardiac output are indicitive of.	MI	Right sided valve damage	Left sided valve damage	JVD	Left sided valve damage
20	Atrial fibrillation is a common symptom that only occurs with	Mitral stenosis	Mitral regurgitation	Aortic stenosis	Aortic regurgitation	Mitral regurgitation
21	A client with mitral stenosis is scheduled for mitral valve replacement. Which condition may arise as a complication of mitral stenosis?	Pulmonary hypertension	Left-sided heart failure	MI	Left ventricular hypertrophy	Left ventricular hypertrophy
22	One of the most common causes of valvular heart disease is…	HTN	Tobacco smoking	Diabetes	Alcoholism	HTN
23	The medical term for chest pain is _____.	Angina	Flutter	Hypertropy	Arrhythmia	Angina
24	In the heart, a clogged artery causes a heart attack. In the brain it causes a _____.	migraine	mental illness	Stroke	Seizure	Stroke
25	What is a myocardial infarction?	Heart failure	Heart Attack	Cardiac arrest	All the above	Heart Attack
26	The lipid abnormalities commonly associated with diabetes mellitus are:	Decreased Apo-b liprotein.	) Decreased VLDL.	Increased HDL.	Increased LDL.	Increased LDL.
27	Metabolic syndrome consists of :	Hyperlipidaemia	Insulin resistance.	Hypertension.	All of the above	All of the above

28	Which of the following is the most common symptom of myocardial infarction?	Chest pain	Dyspnea	Edema	Palpitations	Chest pain
29	When do coronary arteries primarily receive blood flow?	During inspiration	During diastole	During expiration	During systole	During diastole
30	Which of the following conditions most commonly results in CAD?	Atherosclerosis	DM	MI	Renal failure	Atherosclerosis
31	Atherosclerosis impedes coronary blood flow by which of the following mechanisms?	Plaques obstruct the vein	Plaques obstruct the artery	Blood clots form outside the vessel	Hardened vessels dilate to allow the	Plaques obstruct the artery
32	Which of the following risk factors for coronary artery disease cannot be corrected?	Cigarette smoking	DM	Heredity	HPN	Heredity
33	Exceeding which of the following serum cholesterol levels significantly increases the risk of coronary artery disease?	100 mg/dl	150 mg/dl	175 mg/dl	200 mg/dl	200 mg/dl
34	Medical treatment of coronary artery disease includes which of the following procedures?	Cardiac catheterization	Coronary artery bypass surgery	Oral medication administration	Percutaneous transluminal coronary angioplasty	Oral medication administration
35	Which of the following blood tests is most indicative of cardiac damage?	Lactate dehydrogenase	Complete blood count	Troponin I	Creatine kinase	Troponin I
37	Which of the followng conditions is most commonly responsible for myocardial infarction?	Aneurysm	Heart failure	Coronary artery thrombosis	Renal failure	Coronary artery thrombosis
38	Which of the following complications is indicated by a third heart sound (S3)	Ventricular dilation	Systemic hypertension	Aortic valve malfunction	Increased atrial contractions	Ventricular dilation
39	. After an anterior wall myocardial infarction, which of the following problems is indicated by auscultation of crackles in the lungs?	Left-sided heart failure	Pulmonic valve malfunction	Right-sided heart failure	Tricuspid valve malfunction	Left-sided heart failure
40	Which of the following diagnostic tools is most commonly used to determine the location of myocardial damage?	Cardiac catheterization	Cardiac enzymes	Echocardiogram	Electrocardiogram	Electrocardiogram

41	Which of the following classes of drugs is most widely used in the treatment of cardiomyopathy?	Antihypertensive	Beta-adrenergic blockers	Calcium channel blockers	Nitrates	Beta-adrenergic blockers
43	Which of the following cardiac conditions does a fourth heart sound (S4) indicate?	Dilated aorta	Normally functioning heart	Decreased myocardial contractility	Failure of the ventricle to eject all the blood during systole	Failure of the ventricle to eject all the blood during systole
44	What is the term used to describe an enlargement of the heart muscle?	Cardiomegaly	Cardiomyopathy	Myocarditis	Pericarditis	Cardiomegaly
45	Which of the following types of cardiomyopathy can be associated with childbirth?	Dilated	Hypertrophic	Myocarditis	Restrictive	Dilated
46	Stimulation of the sympathetic nervous system produces which of the following responses?	Bradycardia	Tachycardia	Hypotension	Decreased myocardial contractility	Tachycardia
47	In which of the following areas is an abdominal aortic aneurysm most commonly located?	Distal to the iliac arteries	Distal to the renal arteries	Adjacent to the aortic branch	Proximal to the renal arteries	Distal to the renal arteries
48	A pulsating abdominal mass usually indicates which of the following conditions?	Abdominal aortic aneurysm	Enlarged spleen	Gastic distention	Gastritis	Abdominal aortic aneurysm
49	What is the definitive test used to diagnose an abdominal aortic aneurysm?	Abdominal X-ray	Arteriogram	CT scan	Ultrasound	Arteriogram
50	Which of the following groups of symptoms indicated a ruptured abdominal aneurysm?	Lower back pain, increased BP, decreased RBC, increased WBC	Severe lower back pain, decreased BP, decreased RBC, increased WBC	Severe lower back pain, decreased BP, decreased RBC, decreased WBC	ntermittent lower back pain, decreased BP, decreased RBC, increased WBC	Severe lower back pain, decreased BP, decreased RBC, increased WBC
51	Which of the following complications of an abdominal aortic repair is indicated by detection of a hematoma in the perineal area?	Hernia	Stage 1 pressure ulcer	Retroperitoneal rupture at the repair site	Rapid expansion of the aneurysm	Retroperitoneal rupture at the repair site
52	Which hereditary disease is most closely linked to aneurysm?	Cystic fibrosis	Lupus erythematosus	Marfan’s syndrome	Myocardial infarction	Marfan’s syndrome

53	Which ofthe following symptoms is most commonly associated with left-sided heart failure?	Crackles	Arrhythmias	Hepatic engorgement	Hypotension	Crackles
54	In which of the following disorders would the nurse expect to assess sacral eddema in bedridden client?	DM	Pulmonary emboli	Renal failure	Right-sided heart failure	Right-sided heart failure
55	Which of the following blood vessel layers may be damaged in a client with an aneurysm?	Externa	Interna	Media	Interna and Media	Media
56	Which of the following illnesses is the leading cause of death in the US?	Cancer	Coronary artery disease	Liver failure	Renal failure	Coronary artery disease
57	Risk factors associated with colorectal cancer include which one of the following?	Irritable bowel syndrome	Low intake of dietary fibre	Low intake of red meat	Chronic aspirin therapy	Low intake of dietary fibre
58	Acute bowel obstruction in advanced colorectal cancer:	is usually managed by surgery.	is usually caused by obstruction at a single site in the bowel.	should be treated with regular oral anti-emetics, analgesics and anti-spasmodics.	should be treated with using a syringe driver containing a mixture of anti-emetics, analgesics and anti-spasmodics.	should be treated with using a syringe driver containing a mixture of anti-emetics, analgesics and anti-spasmodics.
59	Characteristic presenting features of left sided colorectal tumours include:	acute large bowel obstruction.	iron deficiency anaemia.	painless abdominal mass.	foul smelling stools which are difficult to flush.	acute large bowel obstruction.
60	Features associated with poor prognosis in colorectal cancer include:	adenocarcinoma cell type.	rectal bleeding at presentation.	presence of involved lymph nodes.	lymphocytic response to tumour.	presence of involved lymph nodes.

UNIT-III-SYLLABUS

Cancer: Initiation and stages of progression

Cancer: characteristics of a transformed cell, causes and stages of Cancer, molecular basis for neoplastic growth and metastasis, Proto-oncogenes and tumor suppressor genes; Cancer causing mutations; Tumor viruses; Biochemical analysis of cancer; Molecular approaches to cancer treatment.

Cancer

- Cancer is a cellular tumour that, unlike benign tumour cells, can metastasize and invade the surrounding and distant tissues.
- Cancer has been a major cause of death in the USA for the past few decades, being second only to cardiac diseases. Approximately 20 per cent of all deaths in America are due to cancer. There are at least fifty different types of malignant tumours being identified. More than 50 per cent of the newly diagnosed cancers occur in five major organs:

  (i) lungs, (ii) colon/rectum, (iii) breast, (iv) prostate and(v) uterus.
- Cancers of the lungs, colon/rectum and prostate are the principal leading causes of deaths in males and in females, breast, colorectal and uterine cancers are the most common. Environmental factors play a very important part.
- Increased risk of certain cancers with occupational exposures to asbestos, naphthylamine, etc.
- Association of cancers of oropharynx, larynx, oesophagus and lungs with tobacco chewing and cigarette smoking.

Properties of cancer cells:

Cancer cells are characterized by three important properties:

1. Diminished or unrestricted control of growth.
2. Capability of invasion of local tissues, and
3. Capable of spreading to distant parts of body by metastasis.

General and morphological changes:

- Shape of cells: The tumor cells are much rounder in shape compared to normal cells.
- Alterations in cell structures: The cytoskeletal structure of the tumor cells with regard to actin filaments is different.

- Loss of contact inhibition: The normal cells are characterized by contact inhibition i .e. they form monolayers .Further, they cannot move away from each other. The cancer cells form multilayer's due to loss of contact inhibition. As a result, the cancer cells freely move and get deposited in any part of the body, a property referred to as metastasis.
- Loss of anchorage dependence: The cancer cells can grow without attachment to the surface. This is in contrast to the normal cells which firmly adhere to the surface.
- Alteration in permeability properties: The tumor cells have altered permeability and transport.

Biochemical changes:

- Increased replication and transcription: The synthesis of DNA and RNA is increased in cancer cells.
- Increased glycolysis: The fast growing tumor cells are characterized by elevation in aerobic and anaerobic glycolysis due to increased energy demands of multiplying cells.
- Reduced requirement of growth factors: The tumor cells require much less quantities of growth factors. Despite this fact, there is an increased production of growth factors by these cells.
- Synthesis of fetal proteins: During fetal life, certain genes are active, leading to the synthesis of specific proteins. These genes are suppressed in adult cells. However, the tumor cells synthesize the fetal proteins e.g. carcino embryonic antigen, alfa fetoprotein.
- Alterations in the structure of molecules: Changes in the structure of glycol proteins and glycol lipids are observed.

Etiology of cancer (Carcinogenesis):

1. Age: Cancer can develop in any age, though it is most common in those over 55 years of age. Certain cancers are particularly common in children below 15 years of age, viz.

- Retinoblastomas
- Neuroblastomas
- Wilms' tumours
- Certain tumours of haemopoietic tissues as lymphomas and leukaemias.
- Sarcomas of bones and skeletal muscles.

2. Heredity: Heredity plays an important role in carcinogenesis. Certain precancerous conditions are inherited. Examples are:

- Susceptibility to childhood retinoblastomas is inherited as an autosomal dominant trait and approximately 40 per cent of retinoblastomas are familial.
- Susceptibility to multiple colonic polyposis is inherited as autosomal dominant trait and almost all cases develop into adenocarcinomas in later life.
- Chromosomal DNA instability may be inherited as an autosomal recessive trait. Conditions are characterised by some defect in DNA repair.
- In xeroderma pigmentosa, a skin condition, the affected individuals develop carcinomas of skin in areas exposed to UV rays of sunlight.

3. Environmental factors: Statistically it has been shown that 80 per cent of human cancers are caused by environmental factors, principally chemicals, viz.

• Lifestyle: Cigarette smoking, tobacco chewing.

• Dietary: Groundnuts and other foodstuffs infected with fungus like Aspergillus produce aflatoxin B1 which is carcinogenic.

• Occupational: Asbestos, benzene, naphthylamines, beryllium, etc.

• Iatrogenic: Certain therapeutic drugs may be carcinogenic.

4. Acquired precancerous disorders: Certain clinical conditions are associated with increased risk of developing cancers. *Examples are:*

• ***Leukoplakia*** of oral mucosa and genital mucosa developing into squamous cell carcinomas.

• ***Cirrhosis of liver:*** A few cases can develop hepatoma (hepatocellular carcinoma).

• ***Ulcerative colitis:*** Can produce adeno carcinoma of colon.

• ***Carcinoma in situ of cervix:*** Can produce squamous cell carcinoma of cervix.

(b) 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.

Radiant energy (radiations):

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 pyrimidine dimers.
- Secondly by immunosuppression.

Chemicals as carcinogens:

A list of carcinogenic chemicals is given below

Class	*Nature of Chemicals Compound*
1. *Polycyclic aromatic hydrocarbons*	• Benzpyrene • Dimethyl-benzanthracene
Note: 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-amino-azobenzene • 2-acetylaminofluorine
Note: 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

Note: 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 B_1 produced by the fungus, *Aspergillus flavus.*

Note: The fungus grows on groundnuts, peanuts and other grains in congenial environmental conditions. It ***produces "aflatoxin B_1" 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.

Note: 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

Mechanisms of Chemical Carcinogenesis:

As discussed above, chemical carcinogens may be:

- Direct acting
- Procarcinogens

(a) Direct Acting

A few chemical carcinogens like alkylating agents, e.g. cyclophosphamide, busulfan, etc. can interact directly with target molecules.

(b) Procarcinogens

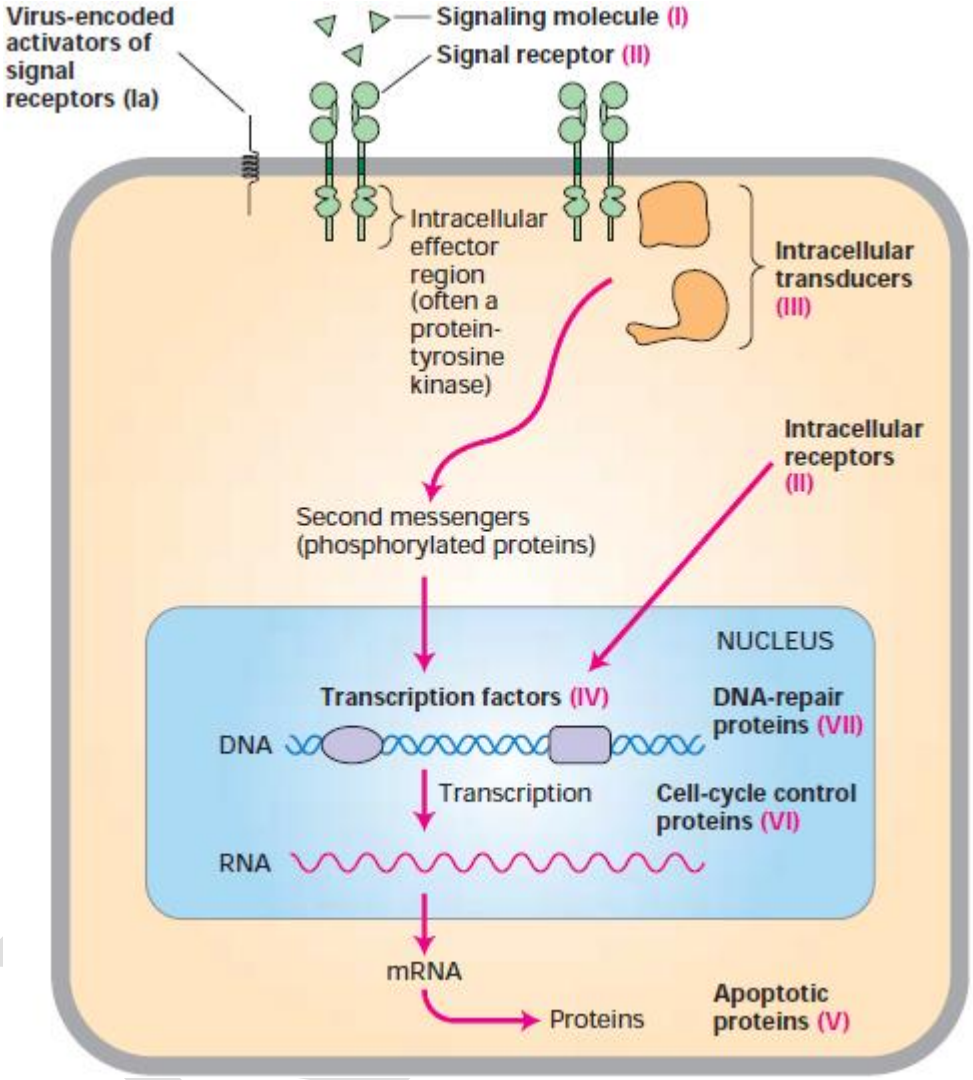
Vast majority of the chemicals act as **procarcinogens.** Procarcinogens are not chemically reactive. In the body, after metabolism they are converted to **"ultimate carcinogens"** which are highly carcinogenic.

Procarcinogen → Proximate Carcinogen → Ultimate Carcinogen (highly carcinogenic)

- Most of the ultimate carcinogens are *"electrophiles"*, i.e. the molecules are deficient in electrons and thus they can readily react with "nucleophilic electron rich" groups in DNA, RNA and various proteins.
  - Metabolic activation: The process by which a procarcinogen is converted in the body to highly active ultimate carcinogen by one or more enzyme catalysed reactions is called as metabolic activation.
  - Enzymes involved: The enzyme systems involved in metabolic activation are cytochrome P450 species present in the endoplasmic reticulum of cells. Recently a particular mono-oxygenase species cytochrome P498 (AHH-Aromatic hydrocarbon hydroxylase) has been incriminated in the metabolism of polycyclic aromatic hydrocarbons.
  - Molecular Targets of Chemical Carcinogens: DNA is the primary and most important target of chemical carcinogens. Hence chemical carcinogens are mutagens.
    1. Binding covalently with DNA, (also to RNA and proteins).
    2. Interaction with the purine, pyrimidine and phosphor diester groups of DNA.
    3. Most common site of attack is guanine and addition of various carcinogens to the N2, N3, N7, O6 and O8 atoms of this base has been observed.

The Genetic Basis of Cancer:

- Mutations in two broad classes of genes— proto-oncogenes (e.g., *ras*) and tumor-suppressor genes (e.g., *APC*)—play key roles in cancer induction. These genes encode many kinds of proteins that help control cell growth and proliferation.
- Virtually all human tumors have inactivating mutations in genes that normally act at various cell-cycle **checkpoints** to stop a cell's progress through the cell cycle if a previous step has occurred incorrectly or if DNA has been damaged.
- For example, most cancers have inactivating mutations in the genes coding for one or more proteins that normally restrict progression through the G1 stage of the cell cycle. Likewise, a constitutively active Ras or other activated signal-transduction protein is found in several kinds of human tumor that have different origins.
- Thus malignancy and the intricate processes for controlling the cell cycle are two faces of the same coin. In the series of events leading to growth of a tumor, oncogenes combine with tumorsuppressor mutations to give rise to the full spectrum of tumor cell properties.



- Seven types of proteins that participate in controlling cell growth and proliferation. Cancer can result from expression of mutant forms of these proteins.
- Mutations changing the structure or expression of proteins that normally promote cell growth generally give rise to dominantly active oncogenes.
- Many, but not all, extracellular signaling molecules (I), signal receptors (II), signal-transduction proteins (III), and transcription factors (IV) are in this category. Cell Cycle

control proteins (VI) that function to restrain cell proliferation and DNA-repair proteins (VII) areencoded by tumor-suppressor genes.

- Mutations in these genes act recessively, greatly increasing the probability that the mutant cells will become tumor cells or that mutations will occur in other classes.
- Apoptotic proteins (V) include tumor suppressors that promote apoptosis and oncoproteins that promote cell survival. Virus encoded proteins that activate signal receptors (Ia) also can induce cancer.

Molecular Basis of Cancer:

- Cancer is caused by a genetic change in a single cell resulting in its uncontrolled Multiplication. Those tumors are monoclonal.
- Two types of regulatory genes-oncogenes and anti oncogenes are involved in the development of cancer (carcinogenesis). Recent years, a third category of genes that control the cell death or apoptosis are also believed to be involved in carcinogenesis.

0ncogenes:

- The genes capable of causing cancer are known as oncogenes (G reek: oncos-tumor or mass). Oncogenes were originally discovered in tumor causing viruses. These viral oncogenes were found to be closely similar to certain genes present in the normal host cells which are referred to as proto-oncogene.
- Now, about 40 viral and cellular proto oncogenes have been identified. Proto oncogenes encode for growth regulating proteins. The activation of proto oncogene to oncogenesis an important step in the causation of cancer.

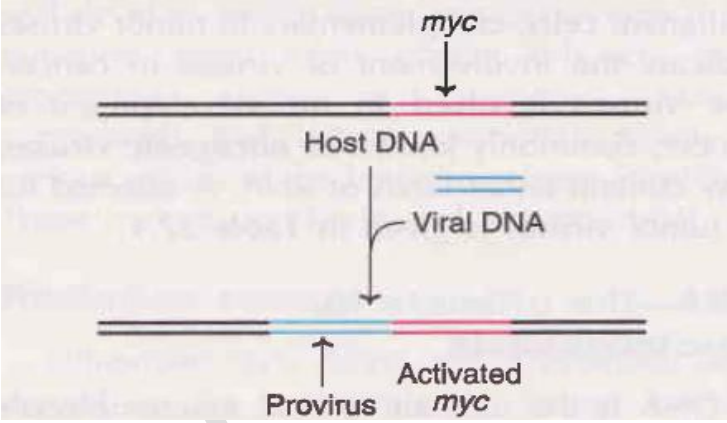
Oncoproteins	*Protooncogene*	*Associated human cancer(s)*
Growth factors		
Platelet derived growth factor (PDGF)	*sis*	Osteosarcoma
Epidermal growth factor (EGF)	*hst*-1	Cancers of stomach, breast and bladder
Growth factor receptors	*erb*–B_1	Lung cancer
	erb–B_2	Stomach cancer
	erb–B_3	Breast cancer
Signal—transducing proteins		
GTP— binding proteins	*ras*	Leukemias, cancers of lung, pancreas and colon
Non-receptor tyrosine kinase	*abl*	Leukemia

Activation of proto-oncogene to oncogenes:

There are several mechanisms for converting the proto oncogenes to oncogenes.

1. **Viral insertion n to chromosome:**

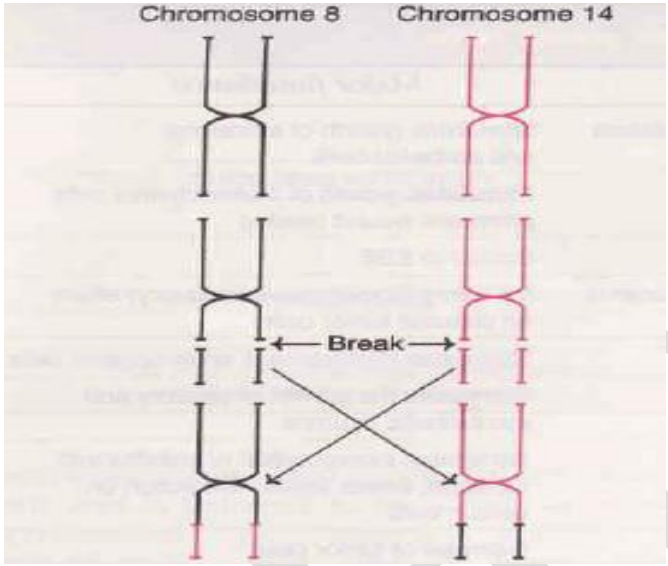
When certain retroviruses (genetic material RNA) infect cells, a complementary DNA (cDNA) is made from their RNA by the enzyme reverse transcriptase. The cDNA so produced gets inserted into the host genome. The integrated double-stranded cDNA is referred to as provirus. This pro-viral DNA takes over the control of the transcription of cellular chromosomal DNA and transforms the cells. Activation of proto oncogenes myc to oncogenes by viral insertion ultimately causing carcinogenesis is well known (e.g. Avian leukemia). Some DNA viruses also get inserted in to the host chromosome and activate the proto oncogenes.



2. **Chromosomal translocation:**

Some of the tumors exhibit chromosomal abnormalities. This is due to the rearrangement of genetic material (DNA) by chromosomal translocation i.e. splitting off a small fragment of chromosome which is joined to another chromosome. Chromosomal translocation usually results in over expression of proto oncogenes.

- Burkitt's lymphoma, a cancer of human B-lymphocytes, is a good example of chromosomal translocation in this case, a fragment from chromosome B is split off and Joined to chromosome 14 containing myc gene. This results in the activation of inactive myc gene leading to the increased synthesis of certain proteins which make the cell malignant.



3. Gene amplification:

Several fold amplifications of certain DNA sequences are observed in some cancers. Administration of anticancer drugs methotrexate associated with gene amplification. The drug becomes in active due to gene amplification are resulting in a several fold increase in the activity of dihydrofolate reductase.

4. Point mutation:

The ras proto oncogenes the best example of activation by point mutation (change in a single base in the DNA). The mutated ras oncogene produces a protein (CTPase) which differs in structure by a single amino acid. This alteration diminishes the activity of CTPase a, key enzyme involved in the control of cell growth. The presence of ras mutations is detected in Several human tumors-90%" of pancreatic, 50% of colon and 30% of lung. However, ras mutations have not been detected in the breast cancer.

Mechanism of action of oncogenes:

Oncogenes encode for certain proteins, namely oncoproteins. These proteins are the altered versions of their normal counterparts and are involved in the transformation and multiplication of cells.

- **Growth factors :** Several growth factors stimulating t e proliferation of normal cells are known. They regulate cell division by transmitting the message cross the plasma membrane to the interior of the cell (transmembrane signal transduction). It is believed that growth factors

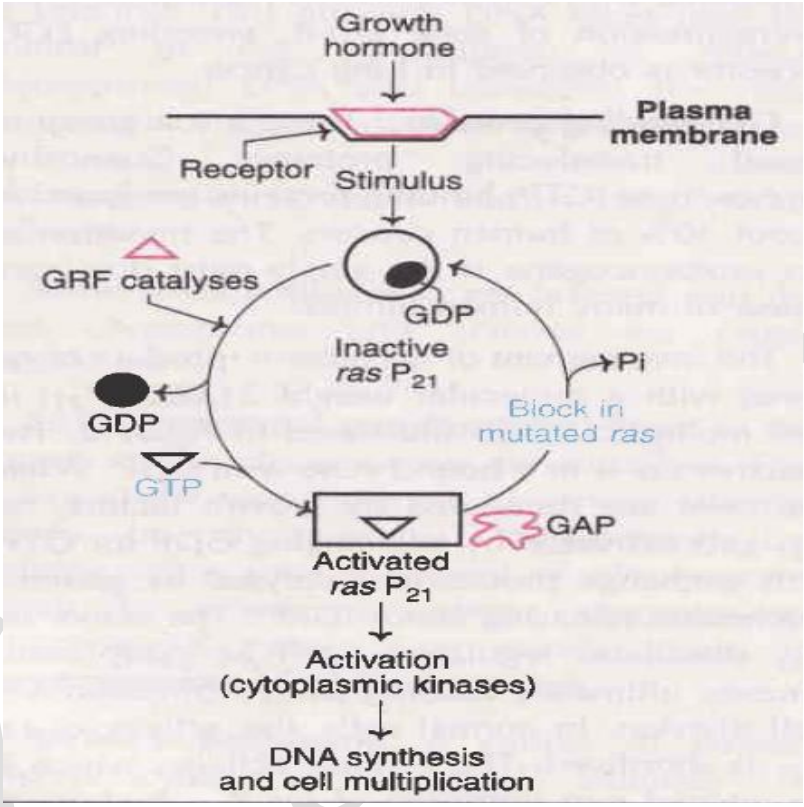
play a key role in carcinogenesis.

- The cell proliferation is stimulated by growth factors. In general, a growth factor binds to a protein receptor on the plasma membrane. This binding activates cytoplasmic protein kinasesleading to the phosphorylation of intracellular target proteins.
- The phosphorylated proteins, in turn, act as intracellular messengers to stimulate cell division, the mechanism of which is not clearly known.
- Transforming growth factor (TCF-d) is a protein synthesized and required for the growth of epithelial cells. TCF-a is produced in high concentration in individuals suffering from psoriasis, a disease characterized by excessive proliferation of epidermal cells.

Growth factor	*Source(s)*	*Major function(s)*
Epidermal growth factor (EGF)	Salivary gland, fibroblasts	Stimulates growth of epidermal and epithelial cells
Platelet derived growth factor (PDGF)	Platelets	Stimulates growth of mesenchymal cells, promotes wound healing
Transforming growth factor-α (TGF-α)	Epithelial cell	Similar to EGF
Transforming growth factor-β (TGF-β)	Platelets, kidney, placenta	Inhibitory (sometimes stimulatory) effect on cultured tumor cells
Erythropoietin	Kidney	Stimulates development erythropoietic cells
Nerve growth factor (NGF)	Salivary gland	Stimulates the growth of sensory and sympathetic neurons
Insulin like growth factors (IGF-I and IGF-II, respectively known as somatomedins C and A)	Serum	Stimulates incorporation of sulfates into cartilage; exerts insulin-like action on certain cells
Tumor necrosis factor (TNF-α)	Monocytes	Necrosis of tumor cells
Interleukin-1 (IL-1)	Monocytes, leukocytes	Stimulates synthesis of IL-2.
Interleukin-2 (IL-2)	Lymphocytes (mainly T-helper cells).	Stimulates growth and maturation of T-cells

- **Growth factor receptors :** Some oncogenes encoding growth factor receptors have been identified. Over expression and/or structural alterations in growth factor receptors are associatedw ith carcinogenesis. For instance, the over expression of gene erb-9, encoding ECFreceptor is observed in lung cancer.

- **GTP-binding proteins :** These are a group of signal transducing proteins. Guanosine triphosphate (GTP)-binding proteins are found in about 30%" of human cancers. The mutation of ras proto oncogene is the single-most dominant cause of many human tumors.



The inactive ras is in a bound state with GDP. When the cells are stimulated by growth factors, ras P21 gets activated by exchanging GDP for GTP. This exchange process is catalysed by guanine nucleotide releasing factor (GRF).The active ras P21 stimulates regulators such as cytoplasmic kinases, ultimately c ausing DNA replication and cell division. In normal cells, the activity of ras P21 is short lived. The GTPase activity, which is an integral part (intrinsic) of ras P21, hydrolyses GTP to GDP, reverting ras 21 to the original state, There are certain proteins, namely GTPase activating proteins (GAP), which accelerate the hydrolysis of GTP of ras 21. Thus, in normal cells, the activity ol ras P21 is well regulated. Point mutations in ras gene result

in the production of altered ras P21, lacking GTPase activity. This leads to the occurrence of ras P21 in a permanently activated state, causing un controlled multiplication of cells.

Tumor-suppressor genes:

Tumor-suppressor genes generally encode proteins that in one way or another inhibit cell proliferation. Loss-of function mutations in one or more of these "brakes" contribute to the development of many cancers. Five broad classes of proteins are generally recognized as being encoded by tumor-suppressor genes:

- Intracellular proteins that regulate or inhibit progression through a specific stage of the cell cycle (e.g., p16 and Rb)
- Receptors or signal transducers for secreted hormones or developmental signals that inhibit cell proliferation (e.g., TGF_, the hedgehog receptor patched).
- Checkpoint-control proteins that arrest the cell cycle if DNA is damaged or chromosomes are abnormal (e.g., p53)
- Proteins that promote apoptosis
- Enzymes that participate in DNA repair.

- Although DNA-repair enzymes do not directly inhibit cell proliferation, cells that have lost the ability to repair errors, gaps, or broken ends in DNA accumulate mutations in many genes, including those that are critical in controlling cell growth and proliferation. Thus loss-of-function mutations in the genes encoding DNA-repair enzymes prevent cells from correcting mutations that inactivate tumor suppressor genes or activate oncogenes.
- Since generally one copy of a tumor-suppressor gene suffices to control cell proliferation, both alleles of a tumor suppressor gene must be lost or inactivated in order to promote tumor development. Thus oncogenic loss-of-function mutations in tumor-suppressor genes are genetically **recessive.**
- In many cancers, tumor-suppressor genes have deletions or point mutations that prevent production of any protein or lead to production of a nonfunctional protein. Another mechanismfor inactivating tumor-suppressor genes is methylation of cytosine residues in the promoter or other control elements. Such methylation is commonly found in non transcribed regions of DNA.

Example:

An important model for understanding is the tumor known as retinoblastoma which occurs in children. Retinoblasts are precursor cells of cones, the photoreceptor cells in retina. 40 per cent of retinoblastomas are familial; and the remaining are sporadic. Rb gene is located on

chromosome 13q14 which is the cancer suppressor gene and exerts an inhibitory effect. Hence both copies of normal Rb gene has to be inactivated for the tumour to develop.

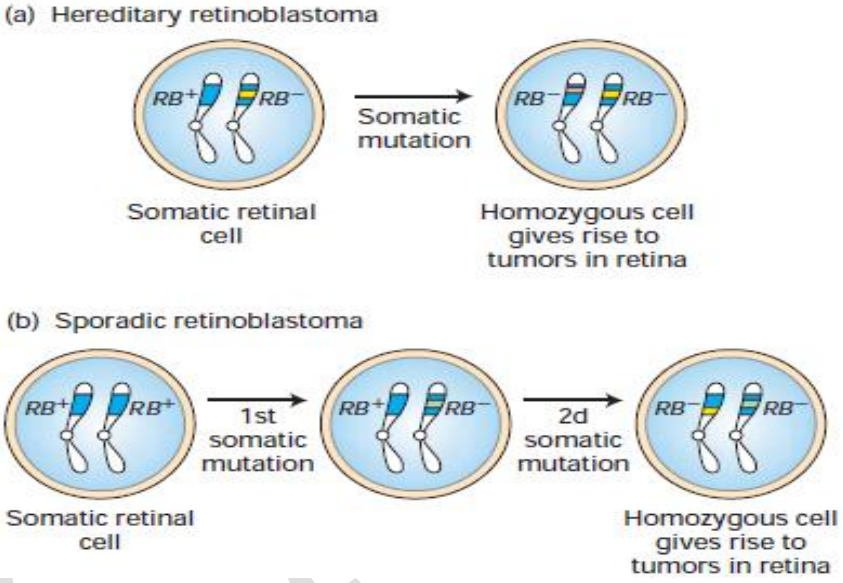
Two-hit hypothesis has been proposed as follows:

• Both normal alleles of the Rb locus must be inactivated (two hits) for the development of retinoblastoma.

• In "familial" cases, the children inherit one defective Rb gene and the other is normal. Retinoblastoma

develops only when the normal Rb gene is lost in the retinoblasts as a result of mutation.

• In sporadic cases, both normal Rb alleles are lost by somatic mutation.



Biochemistry of Metastasis:

Metastasis is the spread of cancer cells from the primary site of origin to other tissues, both neighbouring and istant, where they grow as the secondary tumours.

- Benign tumours can grow very rapidly and attain big sizes and may be sometimes life-threatening but they do not metastasize.
- It is the malignant tumours, cancerous ones, invade surrounding tissues and send out cells to begin new tumours at distant sites. The spread may be bloodborne/ or through lymphatics.

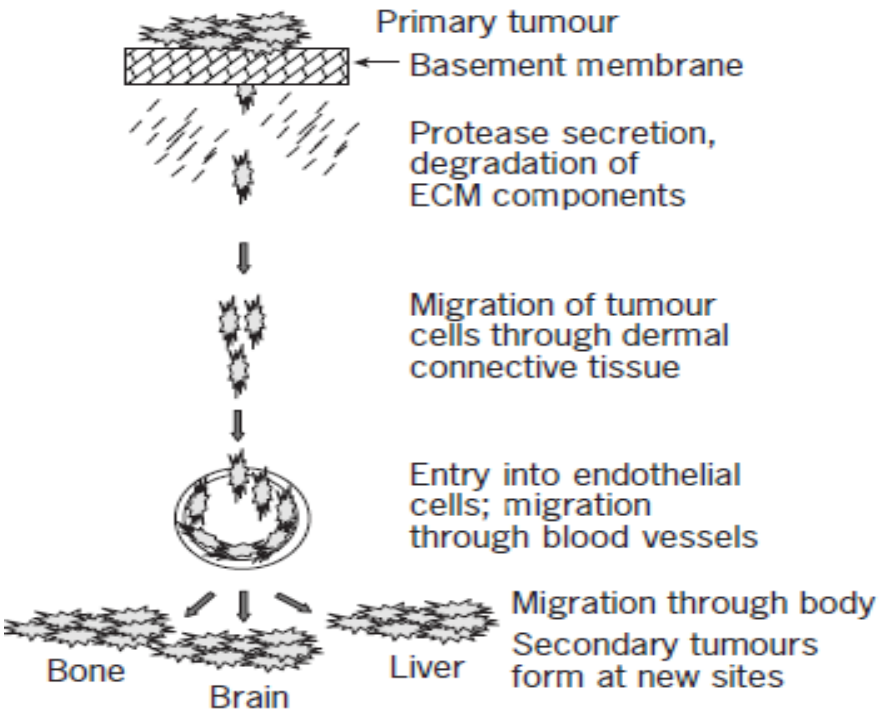
- This *colonisation at distant sites is metastasis* and is the major cause of death from human malignancies.
- Tumour cells must attach to degrade and penetrate the "extracellular matrix" (ECM) at several steps of metastasis. Thus metastasis biochemically is a multistep process.
- Approximately 50 per cent of patients who develop malignant tumours can be cured with various therapies, viz. surgical removal, radiation therapy and chemotherapy. Of the remaining 50 per cent , majority die because of metastasis. Hence, in a real sense, if metastasis could be controlled, cancer could be controlled and for the most part, cured.

Metastasis has been shown to require:

- Specific surface receptors
- Requires enzymes
- The process uses energy
- Requires protein synthesis.

Metastasis is not a passive phenomenon. ***It is an active process.*** The phenomenon of metastasis involves:

- A metastatic cell has to penetrate the extracellular matrix (ECM) that surrounds the tumour.
- Travels through the tissue till it reaches a blood vessel/or a lymphatic.
- In case of blood borne metastasis, the tumour cell then attaches to the blood vessel wall, dissolves a portion of the wall and propels itself through into the circulating blood.
- Metastatic cells often travel in the circulation as small clumps of cells, called ***emboli.***
- At a distant site, the tumour cell again re-attaches to the blood vessel wall and repeats the process, travelling as much as two or three cell diameters into the invaded tissue before it settles down and begins to form a new tumour.



Interaction of invading cancer cell with extracellular matrix:

Composition of Extracellular Matrix:

Extracellular matrix (ECM) can be divided into **two major categories:**

- *Basement membrane (BM)*
- *Interstitial connective tissue (ICT)*

Important Constituents of ECM:

- ***Collagen:*** Basement membrane contains type IV collagen and interstitial connective tissues type I and type III collagen.
- ***Adhesion-promoting proteins***: Basement membrane contains laminin and interstitial connective tissue fibronectin.
  - Both laminin and fibronectin are large multifunctional molecules that can bind to other ECM components such as collagen, proteoglycans and to cells.
  - Attachment of cells to laminin and fibronectin is brought about by distinct and specific cell surface receptors.

Interaction with basement membrane:

Basement membrane (BM) is the first tough elastic barrier that surrounds both tissues and blood vessels. Hence, an invading cancer cell must pass this barrier several times, in order to establish metastatic colonies in distant tissues.

Stages

The above interaction of cancer cell with BM can be considered arbitrarily under **three steps.**

- ***Step 1:*** Attachment of the invading metastatic cell to basement membrane (BM).
- ***Step 2:*** Dissolution of the basement membrane (BM), so that the cell can pass through it.
- ***Step 3:*** Migration of tumour cells. It has been shown that specific biochemicals are required for the tumour cell to complete the process.

Step 1:

Benign tumours are always surrounded by an intact BM whereas in invading malignant tumours, the membrane becomes thin and broken and often entirely lacking.

- The tumour cell binds to one of the membrane's glycoproteins, a cross-shaped molecule called as laminin
- Binding sites for laminin on the surfaces of certain types of cancer cells have been demonstrated.
- Laminin appears to serve as a bridge between receptors on the surface of the invading cancer cell and the BM itself.

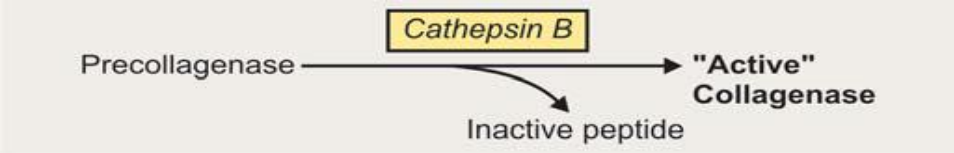
II. Step 2

Once the tumour cell is attached to laminin, the invasive tumour cell secretes certain proteolytic enzymes that degrade the BM. Several such proteolytic enzymes have been incriminated:

1. Collagenases: A collagen degrading enzyme that acts specifically on type IV collagen, the principal structural component of membrane has been isolated from highly metastatic cells.

Properties

- It is a *metalloenzyme,*
- Secreted as zymogen latent form and is clipped to form the "active" enzyme by a second enzyme *cathepsin B.*
- Active enzyme has a molecular wt of 60,000.



2.Heparanase:

Many metastatic cells also produce an enzyme called "heparanase" that degrades heparan SO4, the predominant proteoglycan of the basement membrane. Many other components of the membrane attach to heparan SO4, including laminin and fibronectin.

- The enzyme produced by tumour cells appears to clip the heparan SO4 chain at a slightly different position and produce different fragments than the enzyme produced by non-malignant cells.

3. Cathepsin B: A *lysosomal protease.*

- ***Cathepsin B activates "Latent" collagenases.*** It clips type IV collagenase to its 60,000 molecular weight 'active' form.
- This enzyme has been found in metastatic cancer cells in high concentration.

4. Plasmin:

Degrades several non-collagenous extracellular matrix proteins.

III. Step 3

Factors that favour migration of tumour cells in the passage created by the degradation of EC matrix including BM are not well understood.

Implicated in this process are:

• Autocrine motility factors called as migration factors.

• Tumour cells induced degradation of the interstitial matrix produces fragments of ECM that are attractive to the tumour cells and cause it to move forward.

Tumor Viruses:

Tumor viruses may be either DNA viruses or RNA viruses. A variety of them are now known to cause cancer in animals and some have been implicated in human cancer.

- **DNA Viruses:**

Many of the DNA viruses cause tumors in animals. Three DNA viruses have been established as causing human cancers, viz. EBV, HBV and HPV.

1. Epstein-Barr Virus (EBV)

(a) Burkitt's Lymphoma

- Belongs to herpes family and produces Burkitt's lymphoma.
- It is a tumor of B lymphocytes that is consistently associated with a [t 8:14] translocation.
- It is endemic in Africa and patient's tumor cells carry EBV genome.
- EBV alone cannot cause the tumor. In patients with subtle or overt immune dys regulation, EBV causes sustained B-cells proliferation; they acquire additional mutations and sometimes translocation [t 8:14] and becomes tumourogenic.

(b) Nasopharyngeal Carcinoma

- Is endemic in southern China.
- EBV genome is found in all such tumor cells.

2. Hepatitis B Virus (HBV):

Hepatitis B virus infection is found to be closely associated with formation of liver cancer.

3. Human Papillomavirus (HPV):

(a) Multiple Warts

- Give rise to multiple warts (benign squamous papillomas).
- In 30 per cent cases, some of the warts undergo malignant transformation.
- Usually associated with depressed cell-mediated immunity.
- Several types of HPV identified but types 1, 2, 4 and 7 are important.

(b) Cervical Cancer:

- Carcinoma *in situ* (precancerous condition) and squamous cell carcinoma of cervix have been found to be associated in HPV specially types 16 and 18 (in more than 90% cases).

Mechanism of Action of DNA Viruses

- DNA viruses form stable associations with host cell genome.
- Integrated virus is not able to complete its replicative cycle.
- Early genes, i.e. those viral genes that are transcribed early in viral lifecycle are important for transformation.

- Early genes produce specific proteins which can act on nucleus and derange normal growth regulation.

- **RNA Viruses:**
  - All oncogenic RNA viruses are retroviruses
  - They are of two types as given below

(a) Acute Transforming Retroviruses

These include type C viruses and cause rapid induction of tumors in animals. Transforming sequences of these viruses are 'Viral Oncogenes' (V-oncs).

(b) *Slow Transforming Retroviruses*

- These do not contain V-oncs and are replication competent and cause transformation of the cells slowly.
- Mechanism of transformation is insertional mutagenesis.

Human T-Cell Leukaemia Virus (HTLV):

- HTLV-1, found associated with human leukaemia/ lymphoma.
- It is endemic in parts of Japan. Sporadic cases seen in other parts.
- Mechanism of HTLV-1 induced transformation is not clear. It neither has V-oncs, nor is it found integrated near a proto-oncogene.
- HTLV-1 contains a segment in its genome called "tat". The proteins encoded by 'tat' gene are believed to be responsible for transformation. They affect the transcription of certain growth factors and receptors like IL-2 and IL-2R.

Rous sarcoma Virus:

- Genome of this retrovirus contains 4 genes.

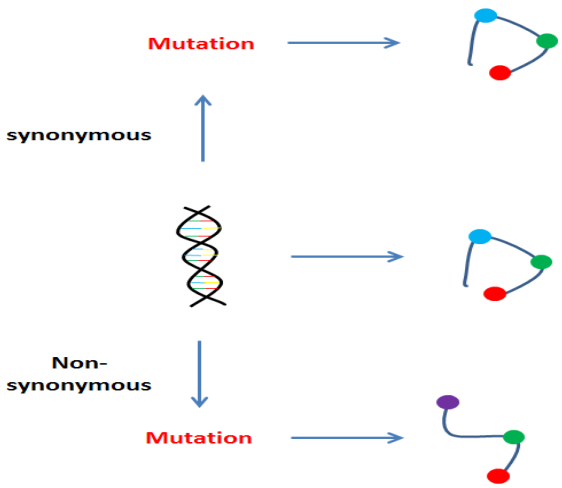
genes	functions
Gag :	Codes for group specific antigens of the virus
Pol :	Codes for reverse transcriptase
Env :	Codes for certain glycoproteins for viral envelope
Src :	Sarcoma causing gene

- The product of 'src' gene is a "protein tyrosine kinase", which has been found to be responsible for the cell transformation. The protein is produced in cytoplasm by inner cell

membrane and called PP60 src. The specific biochemical mechanism involved is abnormal phosphorylations of a number of proteins.\

Cancer causing Mutations:

- Mutations are a change in an organisms DNA, some of which (described below) can lead to a change in amino acid composition and protein structure.
- Mutations that lead to a change in amino acid composition are called non-synonymous mutations, whereas those which do not change the amino acid composition are called synonymous mutations.

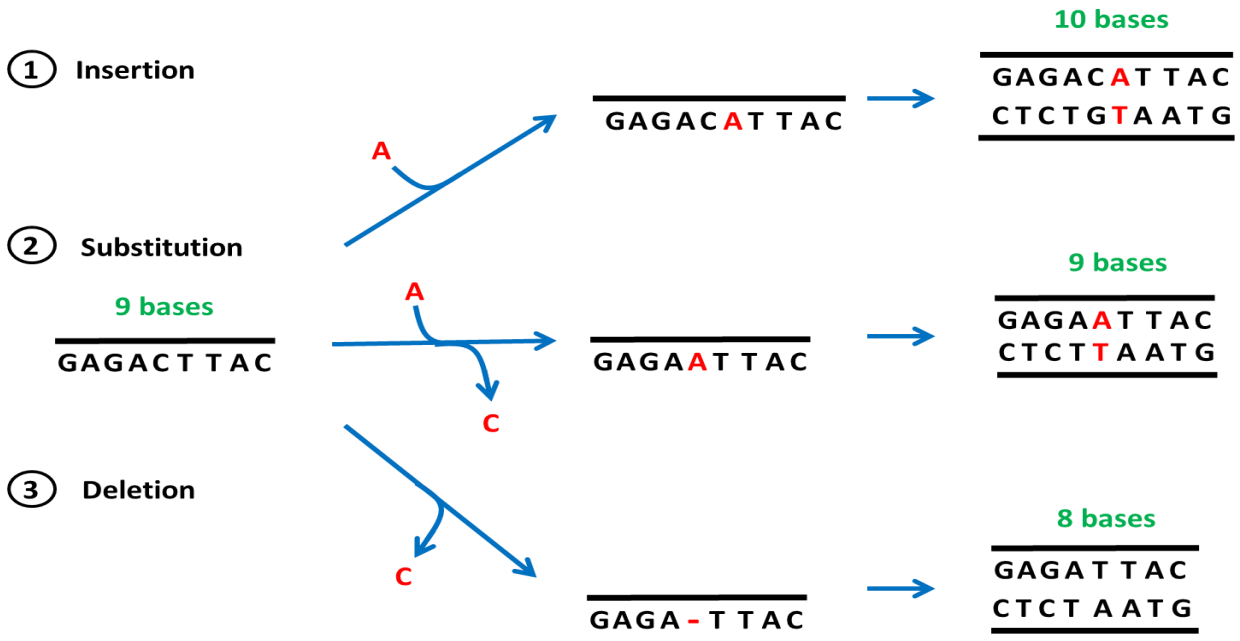


- *One amino acid can be coded for by multiple codons. It is therefore possible that a mutation may change a codon, but still code for the same amino acid. These mutations do not affect protein structure, and are 'synonymous'.*
- *Some mutations however (often in the third nucleotide of a codon) will alter the amino acid and protein structure. These mutations are 'non-synonymous'.*

Types of mutation:

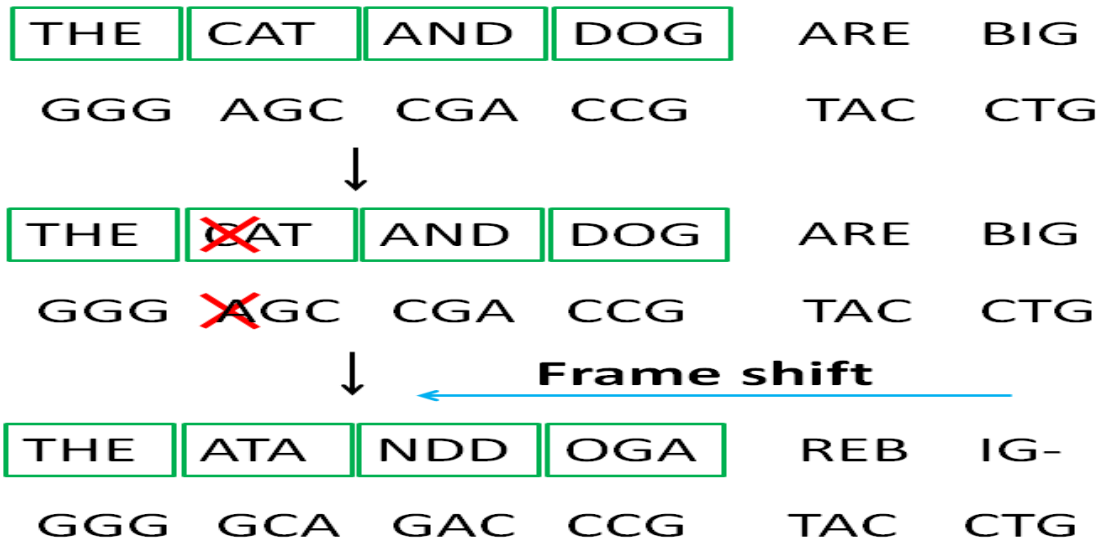
Insertions, deletions and substitutions:

- Insertion mutations occur when an additional base is added into the DNA sequence. If a single nucleotide is inserted (not a pair), the molecule is unstable as it doesn't have a partner base on the opposite strand.
- When DNA is copied by semi-conservative replication, one strand will incorporate the insertion mutation by synthesizing a complementary nucleotide.
- When the cell divides, the result is two daughter cells, one with the wild type DNA, and one carrying the insertion mutation.
- It is also possible that both nucleotides forming a complementary base pair may be inserted as well. In this case both daughter cells will carry the mutation.
- The same principle applies for deletions and substitutions. If a base is accidentally deleted or swapped, when the strand replicates, the deletion/substitution will be introduced into the newly synthesized DNA molecule and passed down to the daughter cells.



Frame shift mutations:

- DNA is read in sets of 3 based called codons. These consecutive, non-overlapping codons form what is known as the **reading frame.** Reading frames are recognised by ribosomes and used to built up complex protein molecules.
- DNA deletions and insertions cause shifts in the reading frame of a piece of DNA. Both introducing an additional nucleotide and deleting one will cause each set of three down stream of the mutation to be read differently.
- Ribosomes will not read a codon with 2 bases (deletion) or 4 bases (insertion) instead they will read a **frame shifted** piece of DNA.



Biochemical analysis of cancer

- Tumour "markers" are defined as a biochemical substance (e.g. hormone, enzymes, or proteins) 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

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 synthesizes **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:

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 normal epithelial 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).

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)
3. 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.
4. ***Value in Colorectal Cancer***
    - Most valuable, has been used as an aid in diagnosis. Value of CEA as a tumour marker is greatest in colorectal cancer.
    - Has been useful in staging. Found to be elevated in 28 per cent of patients with stage A colorectal cancer and in 45 per cent of patients with stage B colorectal cancer.
    - Most important use of CEA has been monitoring the response of colorectal cancer to treatment.
    - Patients with colorectal cancer who initially had elevated CEA show return of CEA values to normal after complete and successful surgical removal.

B. Human Chorionic Gonadotropin (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.
- The β-subunit of HCG is typically measured because of its increased specificity and because some tumors secrete only β-subunit.
- HCG is an ideal tumor marker for diagnosing and monitoring gestational trophoblastic tumors and germ cell tumors of testes and ovary.
- 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.
- 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 metastasescan 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.
- 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.

- 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.
- 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**.**

POSSIBLE QUESTIONS

2 marks

1. Write a note on Cancer
2. Difference between Benign and Malignant?
3. Give the importance of Tumor suppressor genes?
4. Write about Metastasis?
5. What is meant by Proto- oncogenes?
6. Write note on Tumor markers.

6 marks

1. Discuss in detail about Cancer and types?
2. Differnce of normal and cancer cells?
3. Explain about metastasis?
4. Explain about biochemical analysis of cancer?
5. Detailed note on Molecular approaches and diagnostics of cancer?
6. Describe about Cancer Mutation?
7. Etiology of cancer?

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III- B.Sc., BIOCHEMISTRY
MOLECULAR BASIS OF NON-INFECTIOUS HUMAN DISEASES 18BCU504-A
MULTIPLE CHOICE QUESTIONS

Unit III

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Which of the following is believed to be a key cause of immortalization of cancer cells in many tumours?	Complete loss of telomeres.	Inactivation of the telomerase enzyme.	Reactivation of the telomerase enzyme.	Shortening of telomeres.	Reactivation of the telomerase enzyme.
2	Which of the following best defines an oncogene?	An oncogene codes for a cell cycle control protein.	An oncogene codes for a mutated form of a protein that forms part of a signal transduction pathway.	An oncogene codes for a protein that prevents the cell from undergoing apoptosis.	An oncogene is a dominantly expressed mutated gene that gives a cell a growth or survival advantage.	An oncogene is a dominantly expressed mutated gene that gives a cell a growth or survival advantage.
3	Which of the following types of protein could be coded by a tumour-suppressor gene?	A protein that forms part of a growth factor signalling pathway.	A protein that codes for a DNA repair enzyme.	A protein that helps prevent apoptosis.	A protein that controls progression through the cell cycle.	A protein that controls progression through the cell cycle.
4	In what way does the ras oncogene contribute to cancers?	Ras codes for an anti-apoptotic protein, which is produced in abnormally large amounts.	Ras codes for a GTPase switch protein, which in its mutated form cannot be switched off.	Ras codes for a transcription factor, which is produced in abnormally large amounts	Ras codes for a truncated form of a growth factor receptor, which is continually active.	Ras codes for a GTPase switch protein, which in its mutated form cannot be switched off.

5	Which property of p53 enables it to prevent the development of cancer?	p53 is a transcription factor that causes production of proteins that stimulate the cell cycle.	p53 prevents the replication of cells with damaged DNA.	p53 prevents cells from triggering apoptosis.	p53 stimulates synthesis of DNA repair enzymes that replace telomere sequence lost during cell division.	p53 prevents the replication of cells with damaged DNA.
6	Which of the following is a characteristic of a cancer cell? Please select all that apply.	Replicates an unlimited number of times.	Grows and divides without stimulation by a growth factor.	DNA damage does not halt cell division or stimulate apoptosis	Releases factors which cause nearby cells to become cancerous.	All of them
7	Which of the following is characteristic of a malignant rather than a benign tumour?	Undergoes metastasis.	Develops a blood supply.	Cells divide an unlimited number of times.	Grows without needing a growth signal.	Undergoes metastasis.
8	Which of the following can cause mutations which contribute to development of cancers? Please select all that apply.	Chemicals in food	UV and ionising radiation.	Reactive oxygen species.	HIV virus.	All of them
9	The term cancer means	cell division.	out of control.	crab.	lobster.	out of control.
10	Cancer is often the result of activation of ____ to	oncogenes, tumor-	proto-oncogenes,	oncogenes, proto-	proto-suppressor genes,	proto-oncogenes,
11	About 50% of all human cancers may involve an abnormal or missing	oncogene.	proto-oncogene.	p53 gene.	BRCA-1 gene.	p53 gene.
12	Inherited retinoblastoma requires ____ mutation(s) or deletion(s).	one	two	three	four	two
13	In which of the human cells listed below is telomerase active?	blood	bone	muscle	sperm	sperm
14	The Philadelphia chromosome is associated with which type of cancer?	breast	thyroid	nerve	leukemia	leukemia
15	BRCA-1 is associated with which cancer?	breast	thyroid	nerve	leukemia	breast

16	Which of the following statements about telomerase is incorrect?	It is an enzyme that adds DNA to telomeres.	It serves as the template for telomeres lengthening.	It is not activated in cancer cells.	Its activity continually resets the cellular clock.	It is not activated in cancer cells.
17	Familial cancer is caused by	a mutation in somatic cells only.	a mutation in germline cells only.	a germline mutation plus a somatic mutation in affected tissue.	two germline mutations.	a germline mutation plus a somatic mutation in affected tissue.
18	Which type of cancer in humans is directly caused by a viral infection?	acute T cell leukemia	Wilms' tumor	Burkitt's lymphoma	Rous sarcoma	acute T cell leukemia
19	An oncogene transcribed and translated with another gene produces a	transcribed protein.	fusion protein.	fusion cell.	cancer protein.	fusion protein.
20	The P53 protein normally promotes	DNA repair.	tumor formation.	cell division.	apoptosis.	apoptosis.
21	The P53 gene is especially prone to	point mutation.	chromosomal rearrangement.	loss.	none of the above.	point mutation.
22	FAP colon cancer results from ____ mutation(s).	one	two	three	four or more	four or more
23	Which type of study compares the incidence of a type of cancer among very different groups of people?	population	case-control	prospective	empiric	population
24	Which of the following cancers develops from loss of tumor suppression?	cute T cell leukemia	Wilms' tumor	Burkitt's lymphoma	Rous sarcoma	Rous sarcoma
25	Why is genetic counseling for familial breast cancer difficult?	BRCA1 and BRCA2 are incompletely penetrant.	Breast cancer can occur in other ways.	Not all mutations are associated with disease.	all of the above	all of the above
26	A mutation in which gene makes nearby DNA more susceptible to replication errors?	APC	BRCA1	P53	RB	APC

33	Which of the following may contribute to causing cancer?	a mutation in a gene that slows the cell cycle	faulty DNA repair	loss of control over telomere length	all of the above	all of the above
34	Which of the following is believed to be a key cause of immortalization of cancer cells in many tumours?	Complete loss of telomeres.	Inactivation of the telomerase enzyme.	Reactivation of the telomerase enzyme.	Shortening of telomeres.	Reactivation of the telomerase enzyme.
36	Which of the following types of protein could be coded by a tumour-suppressor gene?	A protein that forms part of a growth factor signalling pathway.	A protein that codes for a DNA repair enzyme.	A protein that helps prevent apoptosis.	A protein that controls progression through the cell cycle.	A protein that controls progression through the cell cycle.
37	A _____ gene codes for a repressor protein.	promoter	operator	structural	regulator	regulator
39	The promoter is _____.	a short sequence of DNA where the repressor binds, preventing RNA polymerase from attaching to the promoter	a short sequence of DNA where RNA polymerase first attaches when a gene is to be transcribed	one to several genes of a metabolic pathway that are transcribed as a unit	a gene that codes for a repressor protein	a short sequence of DNA where RNA polymerase first attaches when a gene is to be transcribed
40	Ordinarily, cells with damaged DNA undergo _____ or programmed cell death.	apoptosis	tumor-suppression	differentiation	angiogenesis	apoptosis
41	_____ are cancer-causing genes	Mutagens	Carcinogens	Oncogenes	Homozygous recessive genes	Oncogenes
42	A cell contains many _____ where one mutation can cause them to become oncogenes.	metastases	tumor-suppressor	benign tumors	proto-oncogenes	proto-oncogenes
43	Proto-oncogenes promote the cell cycle and _____ genes inhibit the cell cycle.	recessive	tumor-suppressor	benign	proto-oncogenes	tumor-suppressor
44	A _____ is an environmental agent that can contribute to the development of cancer.	mutagen	fibrinogen	carcinogen	factor	mutagen

45	The pap smear is a test for _____ cancer.	colon	cervical	breast	ovarian	cervical
46	he standard methods of treatment for cancer are _____.	surgery	radiation	chemotherapy	All of the above	All of the above
47	Most chemotherapy drugs kill cells by damaging _____.	DNA	protein	nearby blood vessels	the cell membrane	DNA
48	Indicate method of diagnostic “cancer in situ”	Histology	Cytology	Ultrasonography	X-Ray	Histology
49	Which cancer can be completaly erradicated by radiation therapy?	Cancer of stomash	Lung cancer	Cancer of skin	Rectal cancer	Cancer of skin
50	What is the meaning of remission of malignant tumor?	Return of symptoms of disease	Lessening of symptoms of disease	Disappear of symptoms of disease	Stabilization of symptoms of disease	Disappear of symptoms of disease
51	Which sort of treatment patient with cancer is the best for convalescence?	Surgical treatment	Chemotherapy	Hormonotherapy	Immunotherapy	Surgical treatment
52	What kind of diagnostic methods of malignant tumors is the best?	Clinical	Cytology	Endoscopy	Gystology	Gystology
53	Which of the following chemotherapy drug is likely to be toxic to gonads?	Procarbazine	Adriamycin	Vinblastine	Paclitaxe	Procarbazine
54	Which of the following is least to occur as Gallbladder primary?	Adenocarcinoma	Squamous cell carcinoma	Lymphoma	. Carcinoid tumour	Lymphoma
55	Which of the following is less likely to be associated with Gallbladder cancer?	Obesity	Use of tobacco and alcohol	Aflotoxins	Past history of enteric fever	Aflotoxins
56	For children with β-thalassemia, the transplant outcome is likely to be best in which subgroup?	Hepatomegaly	Liver fibrosis	Inadequate iron chelation	Absence of above factors	Absence of above factors
57	For allogenic hemopoietic stem cell transplantation in children with hemoglobinopathies. Presently best source of stem cells is	Bone marrow	umbilical cord	peripheral blood	umbilical cord	Bone marrow
58	Involvement of which of the following organ is likely to be associated with poor outcome in primary amyloidosis	cardiac	renal	skin	liver	cardiac

59	Which one of the following cancers is usually associated with a moderate to high uptake of 18F-fluorodeoxyglucose (18 FFDG)?	Bladder	Colorectal	Thyroid	Testicular	Colorectal
60	On immunohistochemistry, classical Hodgkin's lymphoma Reed sternberg cells are likely to be	CD15(-), CD 30(+),CD45(-)	CD15(+), CD 30(+),CD45(+)	CD15(+), CD 30(+),CD45(-)	CD15(-), CD 30(+),CD45(+)	CD15(+), CD 30(+),CD45(-)

UNIT-IV-SYLLABUS

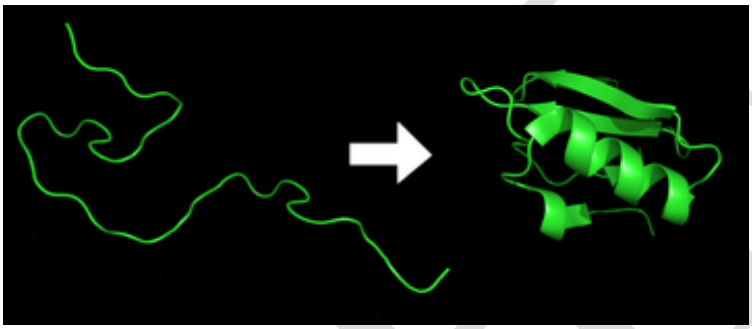
Diseases due associated with misfolded proteins and multifactorial complex disorders:
Introduction to protein folding and proteosome removal of misfolded proteins; etiology and molecular basis for Alzheimer's, Prion diseases, Huntington's Chorea, sickle cell anemia, Thalassemia. Understanding the definition of multifactorial diseases. Polygenic diseases and the relationship of environmental factors and genetic makeup in the onset of diseases.
Disorders of mood : Schizophrenia, dementia and anxiety disorders. Polycystic ovarian syndrome, Parkinson's disease, ALS

Introduction to protein folding and proteosome removal of misfolded proteins:

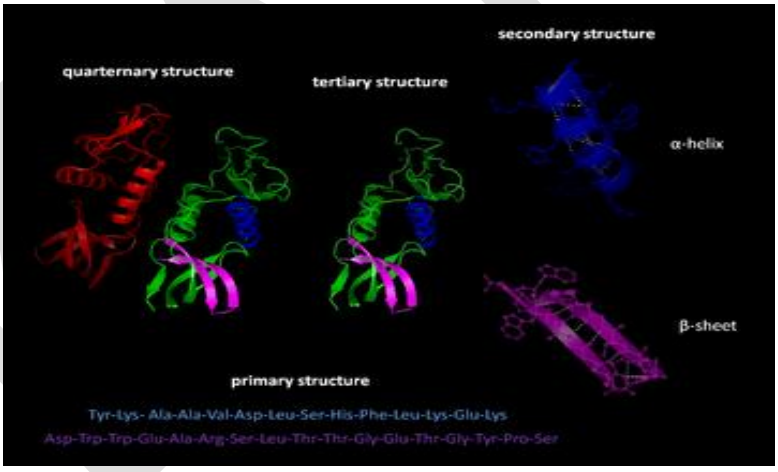
Protein folding:

- Protein folding is the physical process by which a protein chain acquires its native 3-dimensional structure, a conformation that is usually biologically functional, in an expeditious and reproducible manner.
- It is the physical process by which a polypeptide folds into its characteristic and functional three-dimensional structure from random coil
- Each protein exists as an unfolded polypeptide or random coil when translated from a sequence of mRNA to a linear chain of amino acids. This polypeptide lacks any stable (long-lasting) three-dimensional structure (the left hand side of the first figure).
- As the polypeptide chain is being synthesized by a ribosome, the linear chain begins to fold into its three dimensional structure. Folding begins to occur even during translation of the polypeptide chain.
- Amino acids interact with each other to produce a well-defined three-dimensional structure, the folded protein (the right hand side of the figure), known as the native state. The resulting three-dimensional structure is determined by the amino acid sequence or primary structure (Anfinsen's dogma).
- The energy landscape describes the folding pathways in which the unfolded protein is able to assume its native state.
- The correct three-dimensional structure is essential to function, although some parts of functional proteins may remain unfolded, so that protein dynamics is important.

- Failure to fold into native structure generally produces inactive proteins, but in some instances misfolded proteins have modified or toxic functionality.
  Several neurodegenerative and other diseases are believed to result from the accumulation of amyloid fibrils formed by misfolded proteins.
- Many allergies are caused by incorrect folding of some proteins, because the immune system does not produce antibodiesfor certain protein structures.



Protein before and after folding

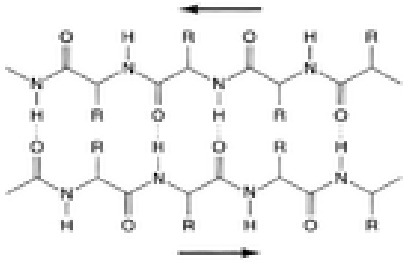


Primary structure:

- The primary structure of a protein, its linear amino-acid sequence, determines its native conformation.

- The specific amino acid residues and their position in the polypeptide chain are the determining factors for which portions of the protein fold closely together and form its three dimensional conformation.
- The amino acid composition is not as important as the sequence. The essential fact of folding, however, remains that the amino acid sequence of each protein contains the information that specifies both the native structure and the pathway to attain that state.
- This is not to say that nearly identical amino acid sequences always fold similarly. Conformations differ based on environmental factors as well; similar proteins fold differently based on where they are found.

Secondary structure:

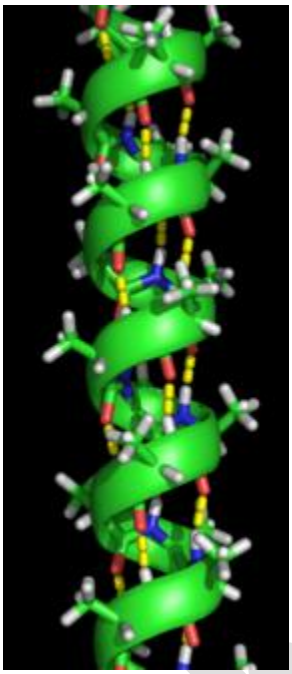


An anti-parallel beta pleated sheet displaying hydrogen bonding within the backbone.

- Formation of a secondary structure is the first step in the folding process that a protein takes to assume its native structure.
- Characteristic of secondary structure are the structures known as alpha helices and beta sheets that fold rapidly because they are stabilized by intra molecular hydrogen bonds, as was first characterized by Linus Pauling.
- Formation of intramolecular hydrogen bonds provides another important contribution to protein stability. α-helices are formed by hydrogen bonding of the backbone to form a spiral shape.
- The β pleated sheet is a structure that forms with the backbone bending over itself to form the hydrogen bonds.

- The hydrogen bonds are between the amide hydrogen and carbonyl oxygen of the peptide bond.
- There exists anti-parallel β pleated sheets and parallel β pleated sheets where the stability of the hydrogen bonds is stronger in the anti-parallel β sheet as it hydrogen bonds with the ideal 180 degree angle compared to the slanted hydrogen bonds formed by parallel sheets.

Tertiary structure:



- The alpha helices and beta pleated sheets can be amphipathic in nature, or contain a hydrophilic portion and a hydrophobic portion.
- This property of secondary structures aids in the tertiary structure of a protein in which the folding occurs so that the hydrophilic sides are facing the aqueous environment surrounding the protein and the hydrophobic sides are facing the hydrophobic core of the protein.
- Secondary structure hierarchically gives way to tertiary structure formation. Once the protein's tertiary structure is formed and stabilized by the hydrophobic interactions, there may also be covalent bonding in the form of disulfide bridges formed between two cysteine residues.
- Tertiary structure of a protein involves a single polypeptide chain; however, additional interactions of folded polypeptide chains give rise to quaternary structure formation

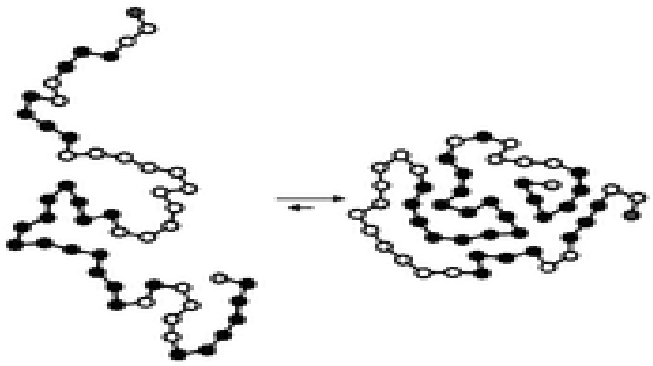
Quaternary structure

- Tertiary structure may give way to the formation of quaternary structure in some proteins, which usually involves the "assembly" or "coassembly" of subunits that have already

folded; in other words, multiple polypeptide chains could interact to form a fully functional quaternary protein

Driving forces of protein folding:

- Folding is a spontaneous process that is mainly guided by hydrophobic interactions, formation of intramolecular hydrogen bonds, van der Waals forces, and it is opposed by conformational entropy.
- The process of folding often begins co-translationally, so that the N-terminus of the protein begins to fold while the C-terminal portion of the protein is still being synthesized by the ribosome; however, a protein molecule may fold spontaneously during or after biosynthesis.
- While these macromolecules may be regarded as "folding themselves", the process also depends on the solvent (water or lipid bilayer), the concentration of salts, the pH, the temperature, the possible presence of cofactors and of molecular chaperones.
- Proteins will have limitations on their folding abilities by the restricted bending angles or conformations that are possible.
- These allowable angles of protein folding are described with a two-dimensional plot known as the Ramachandran plot, depicted with psi and phi angles of allowable rotation.

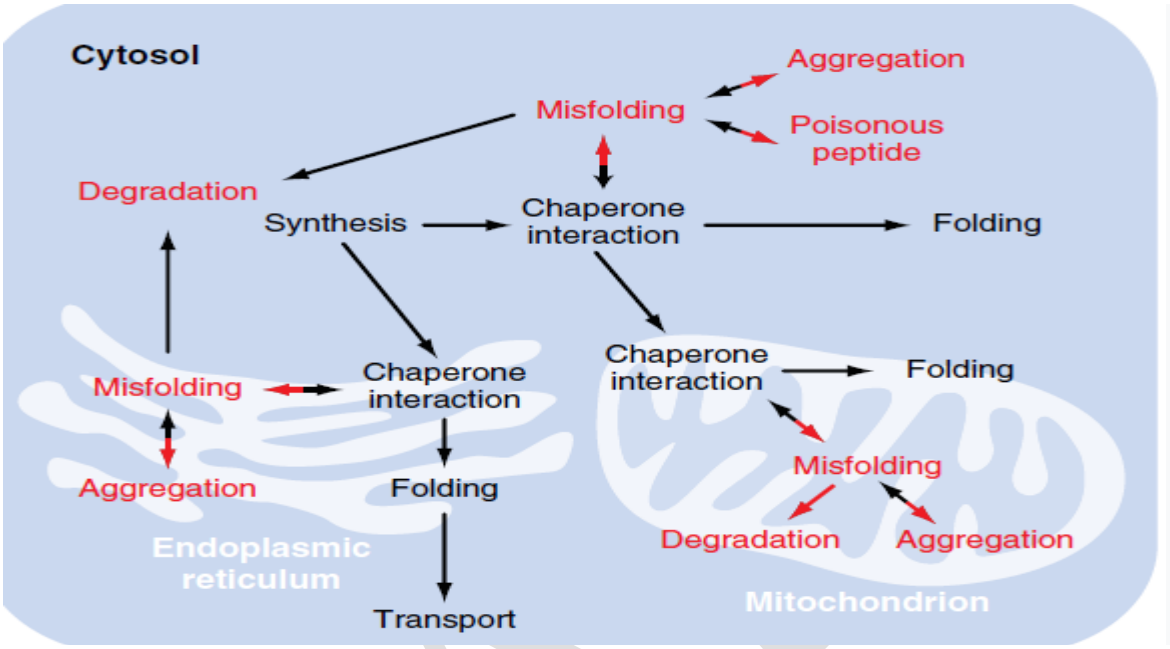


Hydrophobic collapse. In the compact fold (to the right), the hydrophobic amino acids (shown as black spheres) collapse toward the center to become shielded from aqueous environment.

Chaperones:

- Molecular chaperones are a class of proteins that aid in the correct folding of other proteins in vivo.
- Chaperones exist in all cellular compartments and interact with the polypeptide chain in order to allow the native three-dimensional conformation of the protein to form; however, chaperones themselves are not included in the final structure of the protein they are assisting in.
- Chaperones may assist in folding even when the nascent polypeptide is being synthesized by the ribosome.Molecular chaperones operate by binding to stabilize an otherwise unstable structure of a protein in its folding pathway, but chaperones do not contain the necessary information to know the correct native structure of the protein they are aiding; rather, chaperones work by preventing incorrect folding conformations.
- In this way, chaperones do not actually increase the rate of individual steps involved in the folding pathway toward the native structure; instead, they work by reducing possible unwanted aggregations of the polypeptide chain that might otherwise slow down the search for the proper intermediate and they provide a more efficient pathway for the polypeptide chain to assume the correct conformations.
- Chaperones are not to be confused with folding catalysts, which actually do catalyze the otherwise slow steps in the folding pathway.
- xamples of folding catalysts are protein disulfide isomerases and peptidyl-prolyl isomerases that may be involved in formation of disulfide bonds or interconversion between cis and trans stereoisomers, respectively.
- Chaperones are shown to be critical in the process of protein folding in vivo because they provide the protein with the aid needed to assume its proper alignments and conformations efficiently enough to become "biologically relevant".
- This means that the polypeptide chain could theoretically fold into its native structure without the aid of chaperones, as demonstrated by protein folding experiments conducted in vitro; however, this process proves to be too inefficient or too slow to exist in biological systems; therefore, chaperones are necessary for protein folding in vivo.
- Along with its role in aiding native structure formation, chaperones are shown to be involved in various roles such as protein transport, degradation, and even allow denatured

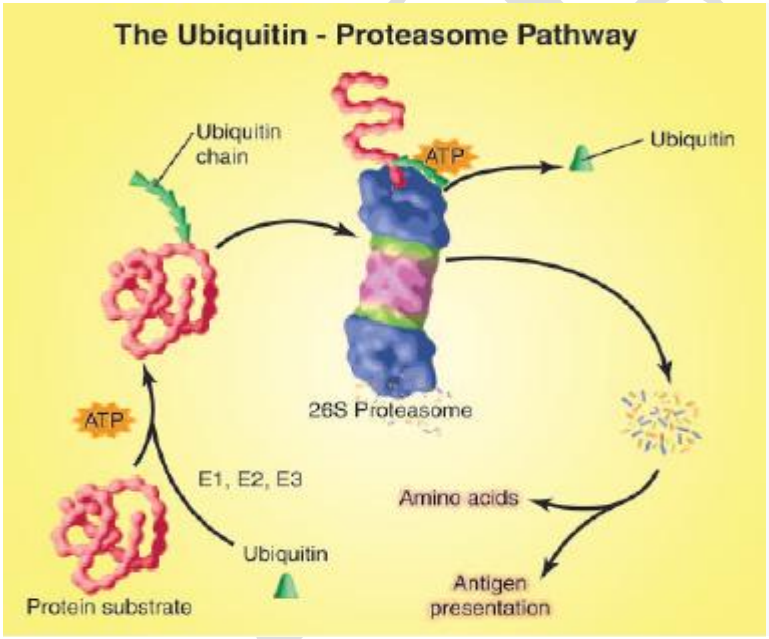
proteins exposed to certain external denaturant factors an opportunity to refold into their correct native structures.



Proteosome removal of misfolded proteins:

- Ubiquitin Proteasome Pathway During the past two decades, the UPP has taken center stage in our understanding of the control of protein turnover.
- The UPP consists of concerted actions of enzymes that link chains of the polypeptide co-factor, Ub, onto proteins to mark them for degradation.
- This tagging process leads to their recognition by the 26S proteasome, a very large multicatalytic protease complex that degrades ubiquitinated proteins to small peptides.
- Three enzymatic components are required to link chains of Ub onto proteins that are destined for degradation. E1 (Ub-activating enzyme) and E2s (Ub-carrier or conjugating proteins) prepare Ub for conjugation, but the key enzyme in the process is the E3 (Ub-protein ligase), because it recognizes a specific protein substrate and catalyzes the transfer of activated Ub to it.
- The discovery of Ub and the biochemistry of its conjugation to substrate proteins culminated in the awarding of the Nobel Prize in Chemistry in 2004 to Avram Hershko, Aaron Ciechanover, and Irwin Rose.

- Since the initial description of the UPP as a protein tagging and destruction mechanism, knowledge in this area has exploded, with thousands of proteins shown to be degraded by the system and additional novel functions for Ub conjugation being uncovered.
- The major functions of the pathway are described next. Rapid Removal of Proteins Unlike most regulatory mechanisms, protein degradation is inherently irreversible.
- Destruction of a protein can lead to a complete, rapid, and sustained termination of the process involving the protein as well as a change in cell composition. The rapid degradation of specific proteins permits adaptation to new physiologic conditions.



- The ubiquitin (Ub)-proteasome pathway (UPP) of protein degradation. Ub is conjugated to proteins that are destined for degradation by an ATP-dependent process that involves three enzymes.
- A chain of five Ub molecules attached to the protein substrate is sufficient for the complex to be recognized by the 26S proteasome. In addition to ATP-dependent reactions, Ub is removed and the protein is linearized and injected into the central core of the proteasome, where it is digested to peptides.
- The peptides are degraded to amino acids by peptidases in the cytoplasm or used in antigen presentation.

Defects in Protein Folding May Be the Molecular Basis for a Wide Range of Human Genetic Disorders:

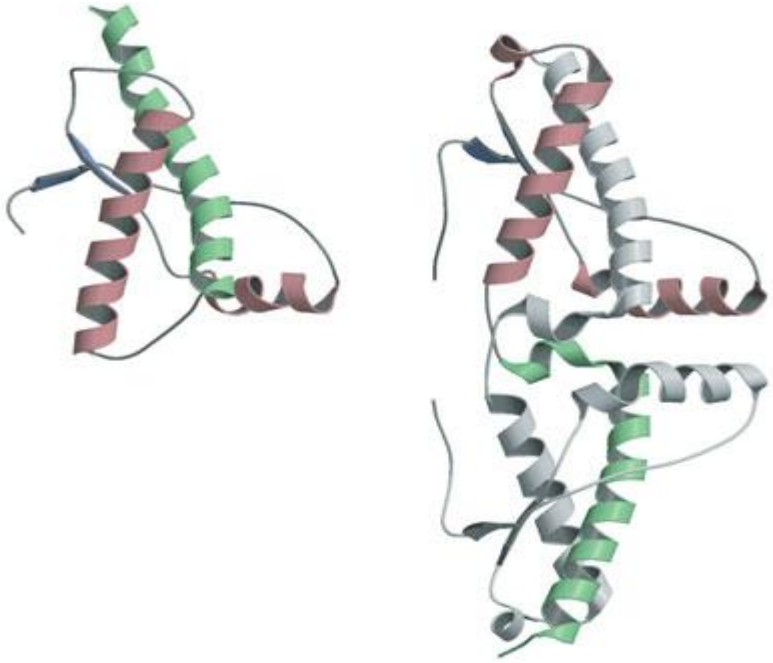
- Despite the many processes that assist in protein folding, misfolding does occur. In fact, protein misfolding is a substantial problem in all cells, and a quarter or more of all polypeptides synthesized may be destroyed because they do not fold correctly.
- In some cases, the misfolding causes or contributes to the development of serious disease. Many conditions, including type 2 diabetes, Alzheimer's disease, Huntington's disease, and Parkinson's disease, arise from a common misfolding mechanism.
- In most cases, a soluble protein that is normally secreted from the cell is secreted in a misfolded state and converted into an insoluble extracellular **amyloid** fiber.
- The diseases are collectively referred to as **amyloidoses**. The fibers are highly ordered and unbranched, with a diameter of 7 to 10 nm and a high degree of _-sheet structure.
- The strands are oriented perpendicular to the axis of the fiber.
- Protein misfolding need not lead to amyloid formation to cause serious disease. For example, cystic fibrosis is caused by defects in a membrane-bound protein called *c*ystic *f*ibrosis *t*ransmembrane conductance *r*egulator (CFTR), which acts as a channel for chloride ions.
- The most common cystic fibrosis–causing mutation is the deletion of a Phe residue at position 508 in CFTR, which causes improper protein folding. Most of this protein is then degraded and its normal function is lost. Many of the disease-related mutations in collagen also cause defective folding.

Prion diseases

- A misfolded brain protein seems to be the causative agent of several rare degenerative brain diseases in mammals. Perhaps the best known of these is bovine spongiform encephalopathy (BSE; also known as mad cow disease).
- Related diseases include kuru and Creutzfeldt-Jakob disease in humans, scrapie in sheep, and chronic wasting disease in deer and elk.

- These diseases are also referred to as spongiform encephalopathies, because the diseased
- brain frequently becomes riddled with holes.

- Progressive deterioration of the brain leads to a spectrum of neurological symptoms, including weight loss, erratic behavior, problems with posture, balance, and coordination, and loss of cognitive function.
- The diseases are fatal. In the 1960s, investigators found that preparations of the disease-causing agents seemed to lack nucleic acids.
- All disease-causing agents known up to that Time viruses, bacteria, fungi, and so on contained nucleic acids, and their virulence was related to genetic reproduction and propagation.
- However, four decades of investigations, pursued most notably by Stanley Prusiner, have provided evidence that spongiform encephalopathies are different.
- The infectious agent has been traced to a single protein (*M*r 28,000), which Prusiner dubbed **prion** (*pr*oteinaceous *i*nfectious *onl*y) protein (PrP).
- Prion protein is a normal constituent of brain tissue in all mammals. Its role is not known in detail, but it may have a molecular signaling function. Strains of mice lacking the gene for PrP (and thus the protein itself) suffer no obvious ill effects.
- Illness occurs only when the normal cellular PrP, or PrPC, occurs in an altered conformation called PrPSc (Sc denotes scrapie).
- The interaction of PrPSc with PrPC converts the latter to PrPSc, initiating a domino effect in which more and more of the brain protein converts to the diseasecausing form.
- The mechanism by which the presence of PrPSc leads to spongiform encephalopathy is not understood.
- In inherited forms of prion diseases, a mutation in the gene encoding PrP produces a change in one amino acid residue that is believed to make the conversion of PrPC to PrPSc more likely.
- A complete understanding of prion diseases awaits new information on how prion protein affects brain function. Structural information about PrP is beginning to provide insights into the molecular process that allows the prion proteins to interact so as to alter their conformation.



Structure of the globular domain of human PrP in monomeric (left) and dimeric (right) forms.

Alzheimer's Disease

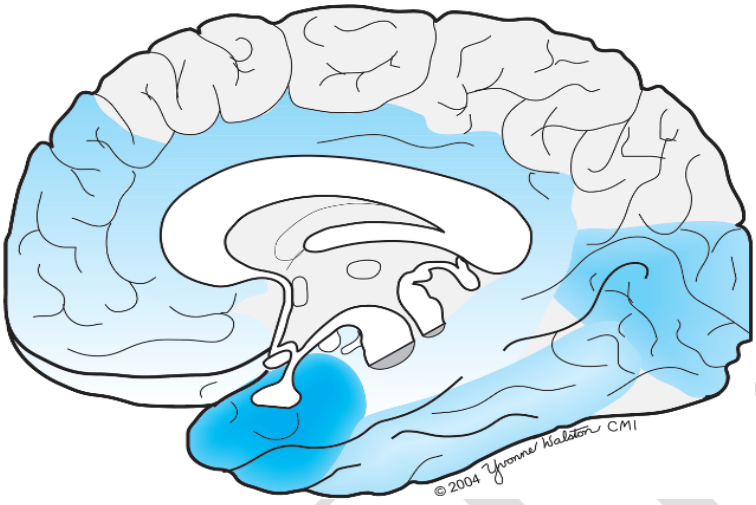
- Alzheimer's disease (AD) accounts for 60% of dementia in the elderly. Of the elderly, 4 million currently suffer from this disease, and the prevalence is expected to climb to 14 million by 2050.
- About 1,000 elderly adults are diagnosed daily with AD. The prevalence rate is 1% for individuals ages 60 to 64 years and doubles every 5 years to reach 40% by the age of 85 years.

Pathophysiology:

- The hallmark pathology of AD is an excess of neuritic plaques and neurofibrillary tangles in the cerebral cortex compared with healthy agematched controls.
- Neuritic plaques consist of a central core of β-amyloid protein surrounded by a ring of astrocytes, microglia, and dystrophic neurites.
- The dystrophic neurites often contain abnormal paired helical filaments. Neurofibrillary tangles are abnormal accumulations in the neuronal cell body and dendrites of paired

helical filaments of abnormally hyperphosphorylated tau proteins that can be seen by electron microscopy or by light microscopy after silver staining.

- Neuritic plaques and neurofibrillary tangles are maximally seen in the hippocampus, limbic system, and frontal lobes.
- Additional histological features of AD include the loss of cortical neurons, producing cerebral atrophy with enlarged ventricles (hydrocephalus ex vacuo), marked reductions in the density of cortical synapses, and granulovascular degeneration in hippocampal neurons.
- Neuronal loss in the nucleus basalis accounts for the loss of cholinergic neurons and their cortical axons.
- The pathogenic mechanisms that produce these histologic changes are incompletely understood.
- Current evidence points to the accumulation of an abnormal amyloid protein as being central to the cerebral damage. The β-amyloid gene encodes a large protein, amyloid precursor protein, which is normally inserted into neuronal membranes with a β-amyloid fragment of 40 to 42 amino acids located outside the cell.
- In AD the β-amyloid fragment is abnormally cleaved, producing a β-amyloid peptide that is poorly catabolized, accumulates locally, and is toxic to neurons.
- The most potent risk factor for developing AD is the presence of the apolipoprotein (apo) E4 allele.
- Of the three forms, E2, E3, and E4, only E4 increases the likelihood of AD. The lifetime risk for individuals carrying an E4 allele is 29% compared with 9% for individuals carrying the other alleles.
- How the E4 protein increases the risk is unclear. Other risk factors for developing AD are increasing age, head trauma, low folate and vitamin B12 levels, and elevated homocysteine levels.
- Some risk factors such as fewer years of formal education, low income, and lower occupational status appear to work by decreasing the amount of "cognitive reserve" the patient can lose before dementia becomes evident.



Major Clinical Features:

- Nearly 10% of AD occurs in association with vascular dementia.Vascular dementia is characterized pathologically by widespread white matter changes presumably from ischemic brain injury, and multiple infarcts.
- Clinically, vascular dementia is identified by a tendency for a stepwise progression of dementia.
- The clinical or presumptive diagnosis of AD is based on an insidiously progressive decline in intellect, especially recent memory and executive functioning, beginning after age 50 years.
- This progresses over several years to a global dementia,including loss of insight and judgment as well as behavioral changes. No other medical causes of dementia should be present.

Early Disease	Later Disease
Progressive decline in recent memory	Loss of insight
Progressive decline in executive functioning	Loss of judgment
Normal speech and gait	Behavioral changes with marked mood swings and depression
Mild to moderate frontal-temporal brain atrophy on neuroimaging	Global dementia including apraxias and severe memory loss
Normal Cerebrospinal fluid	Terminal apathy and withdrawal from social situations, leading to virtual mutism Marked brain atrophy on neuroimaging with hydrocephalus ex vacuo

Major Laboratory Findings

- No laboratory test establishes the diagnosis of AD. A definite diagnosis is based on characteristic neuritic plaques and neurofibrillary tangles seen on brain biopsy or autopsy. Routine blood and CSF tests are normal.
- Neuroimaging usually demon- strates symmetrical brain atrophy that is out of proportion for age, with an accompanying hydrocephalous ex vacuo of the third and lateral ventricles.
- An EEG shows a diffuse slowing of background activity that is nonspecific. PET/SPECT scans demonstrate hypometabolism and reduced blood flow to the temporal and parietal lobes.

Principles of Management and Prognosis

- There is no method to stop or reverse the progression of AD. However, cholinesterase inhibitors produce modest transient improvements in memory and cognition and may reduce behavioral outbursts.
- Low doses of psychoactive medications may be required to treat patients who have frequent outbursts of anger or agitation.

- Studies are underway to determine if reducing amyloid production and aggregation or enhancing amyloid removal may offer clinical benefit.
- The duration of AD, once diagnosed, is about 3 to 5 years and death usually comes from pneumonia and other systemic illnesses.

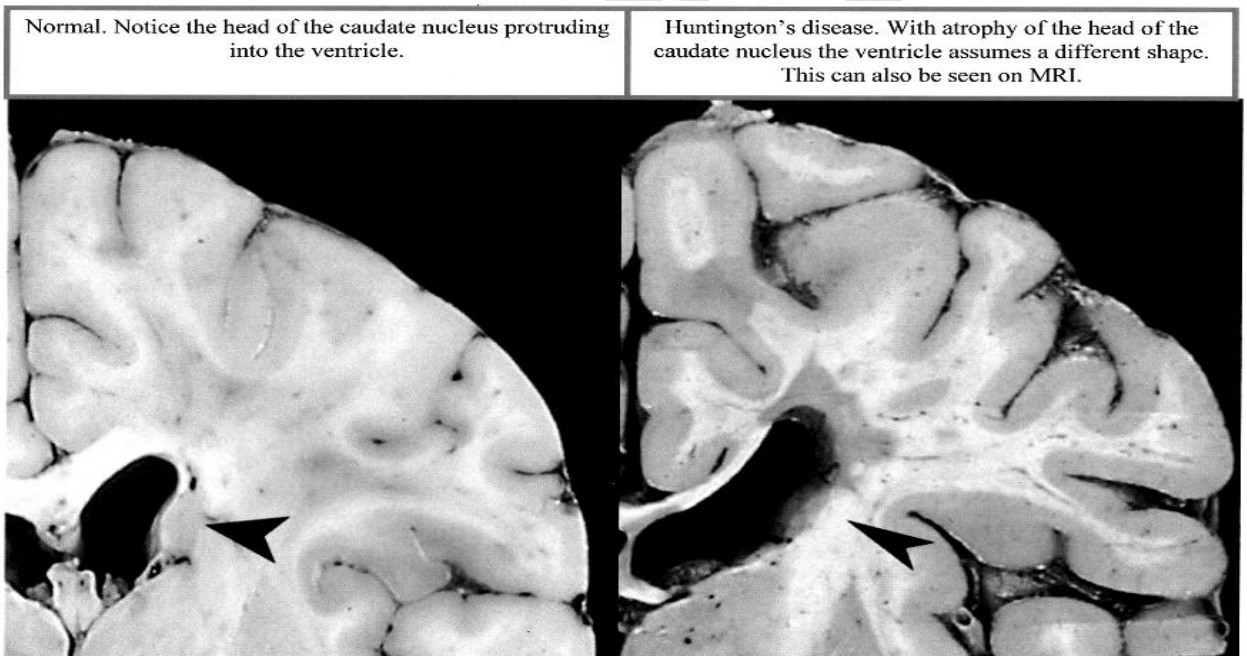
Huntington's Disease

- Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by progressive chorea, cognitive decline, and behavioral disturbances that usually begin in mid-life.
- The original description came from Dr. George Huntington, a family physician, who in 1872 accurately described the clinical and genetic features of HD from his observations of three generations of illness in a family living on Long Island, New York.
- HD is found around the world, with the highest prevalence (5/100,000) in populations of western European ancestry. In the United States, about 25,000 individuals have HD and another 60,000 carry the abnormal gene but are too young to express the disease.
- As an autosomal-dominant disorder, men and women are equally affected, and there is a high degree of penetrance in individuals who live to middle age.
- Women who carry the abnormal gene may give birth to affected offspring before manifesting any signs of the disease.

Pathophysiology:

- All cases of HD develop from an abnormal extended length of CAG triplet repeats in the *HD*gene.
- The normal length of the trinucleotide repeats is polymorphic and ranges from 10 to 26 units, producing a string of 10 to 26 polyglutamine amino acids in the normal Huntingtin protein.
- The length of the CAG trinucleotide repeats is not constant, and healthy offspring normally gain or lose up to 6 repeats. However, CAG repeat lengths longer than 39 units give rise to HD.
- There is an inverse correlation between the length of the CAG repeats and the age of disease onset. Individuals with repeat lengths of greater than 50 to 60 units develop juvenile HD with onset before age 20 years.
- Men with HD often have sperm containing an *HD* gene with many more CAG repeats than in their own somatic cell *HD* gene.

- Thus the next generation displays the phenomenon of increasing trinucleotide repeat length and gives rise to *anticipation*, where the disease develops at an earlier age.
- Huntingtin protein is a large protein (>3,000 amino acids) that is expressed widely in neural and nonneural tissues and whose normal function is currently unknown.
- The amino acid sequence is not related to other proteins, but shows a high degree of evolutionary conservation.
- Studies in animals and man show the gene is essential in fetal development as loss of both gene copies leads to fetal death.
- However, fetuses containing HD protein molecules with abnormal polyglutamine length have normal fetal and childhood development. Thus current evidence suggests the pathogenesis of HD is mediated by a "gain of function" of the Huntingtin protein.
- In this construct, the normal Huntingtin protein functions remain intact, but a new function is detrimental to the neuron. In the end, the abnormal Huntingtin protein somehow causes premature death of selected neuronal populations.



Major Clinical Features

- The mean age of onset of HD is 40 years but some patients do not develop signs until past age 60 years.

- The clinical features are progressive disorders of movement, cognition, and behavior. Sudden nonrepetitive, nonperiodic, involuntary jerking movements involving random shifting muscles or muscle groups characterize chorea, the principle movement disorder.
- Chorea soon becomes very frequent during waking hours, involving the arms, hands, legs, tongue, or trunk.
- These movements can be voluntarily suppressed only briefly and are made worse by stress. Early in the disease, patients frequently appear fidgety and mask the involuntary limb movement by incorporating the involuntary jerk into a semi purposeful movement.
- Voluntary rapid eye movements from one target to another (saccadic eye movements) become slowed and uncoordinated.
- The inability to sustain a constant voluntary muscle contraction manifests as trouble extending their tongues for any period of time and maintaining a tight handshake (milkmaid's grip).
- In the early stage of the disease, patients often have normal activities of daily living and may continue to be employed.
- As the disease worsens, dystonia and parkinsonism appears. Dysarthria develops, with hypophonic irregular speech that becomes unintelligible.
- At this stage the patient depends on others for help. Dysphagia appears late and often contributes to the death of the patient.

Major Laboratory Findings:

- Routine blood and CSF tests are unremarkable. Neuroimaging studies demonstrate atrophy of the caudate and may show atrophy of the putamen.
- The progressive caudate atrophy parallels loss of cognitive function and putaminal atrophy with motor decline. Neuropsychiatric tests demonstrate many abnormalities, but none are diagnostic.
- The clinical diagnosis is usually made based on
  (1) onset in mid-life with typical chorea, cognitive loss, and behavioral changes,
  (2) positive family history, and
  (3) neuroimaging demonstrating caudate atrophy.
- The definite diagnosis is made by demonstrating abnormally long CAG trinucleotide repeat lengths (>40) in the *HD* gene (chromosomal locus 4p16) on genetic testing.

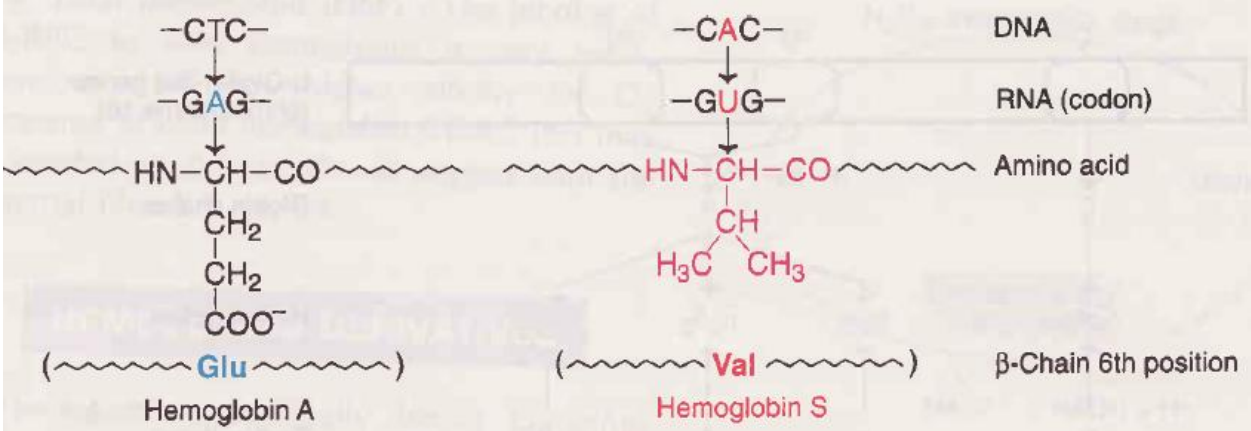
  - This commercial test is useful in establishing the diagnosis in atypical cases, ymptomatic individuals without a positive family history, individuals at risk for the illness, and prenatal screening.

- For predictive testing to be performed, there should be
  (1) multidisciplinary supportive counseling before and after testing,
  (2) clear informed consent, and
  (3) confidential reporting.

- In general, predictive tests should not be done on minors. Although the number of CAG repeats is correlated with age of disease onset, the range of onset for each CAG length is so broad as not to be useful for individual tests and hence the length is seldom reported to the patient.

Sickle-cell anemia

- Sickle-cell anemia (HbS) is the most common form of abnormal hemoglobins. lt is so named because the erythrocytes of these patients adopt a sickle shape (crescent like) at low oxygen concentration.



- Sickle-cell anemia is largely confined to tropical areas of the world. lt primarily occurs in place of CAG) which leads to the incorporation of valine instead of glutamate at the sixth position in β-chain.

Homozygous and heterozygous HbS :

- Sickle cell anemia is said to be homozygous, if caused by inheritance of two mutant genes (one from each parent) that code for p-chains.

- In case of heterozygous HbS, only one gene is affected while the other is normal. The erythrocytes of heterozygotes contain both HbS and HbA and the disease is referred to as sickle cell trait which is more common in blacks.
- The individuals of sickle-cell trait lead a normal life, and do not usually show clinical symptoms. This is in contrast to homozygous sickle-cell anemia.

Abnormalities associated with HbS:

Sickle-cell anemia is characterized bv the following abnormalities

1. Life-long hemolytic anemia : The sickle erythrocytes are fragile and their continuous breakdown leads to life-long anemia.
2. Tissue damage and pain : The sickle cells block the capillaries resulting in poor blood Supply to tissues. This leads to extensive damage and inflammation of certain tissues causing pain.
3. Increased susceptibility to infection: Hemolysis and tissue damage are accompanied by increased susceptibility to infection and diseases.
4. Premature death : Homozygous in individuals of sickle-cell anemia die before they reach adulthood (< 20 years).

Mechanism of sickle-cell anemia:

Glutamate is a polar amino acid and it is replaced by a non-polar valine in sickle-cell hemoglobin. This causes a marked decrease in the solubility of HbS in deoxygenated form (Tform). However, solubility of oxygenated HbS is unaffected.

Diagnosis of sickfe.cell anemia:

1 . **Sickling test** : This is a simple microscopic examination of blood smear prepared by adding reducing agents such as sodium dithionite. Sickled erythrocytes can be detected under the mrcroscope.

2. **Electrophoresis** : When subjected to electrophoresis in alkaline medium (pH 8.6) , sickle-cell hemoglobin (HbS) moves slowly towards anode (positive electrode) than does adult hemoglobin (HbA).

- The slow mobility of HbS is due to less negative charge, caused by the absence of glutamate residues that carry negative charge. In case of sickle-cell trait, the fast moving HbA and slow moving HbS are observed.
- The electrophoresis of hemoglobin obtained from lysed erythrocytes can be routinelyu sedf or the diagnosiso f sicklecell anemia and sickle-cell trait.

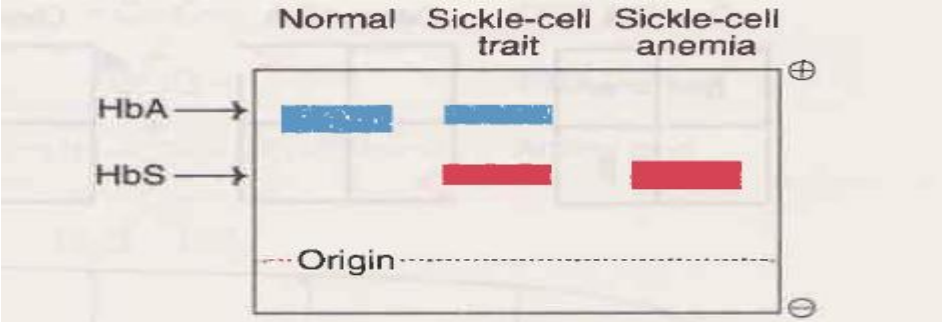


Fig. 10.16 : *Electrophoresis of hemoglobins at pH 8.6 (HbA–Normal adult hemoglobin; HbS–Sickle cell hemoglobin).*

Management of sickle cell disease:

- Administration ol sodium cyanate inhibits sickling of erythrocyte Cyanate increases the affinity of 02 to HbS and lowers the formation of deoxy HbS.
- However, it causes certain side effects like peripheral nerve damage. In patients with severe anemia, repeated blood transfusion is required. This may resulting iron overload and cirrhosis of liver.
- Replacement of HbS with other forms of hemoglobins has been tried. Fetal hemoglobin (HbF)r educes sickling.

THALASSAEMIAS

Impairment of synthesis of a single kind of Hb-chain result in ***thalassaemias,*** so called because the conditions are more common in Mediterranean countries. They occur due to ***mutation of*** Regulator gene.

1. α-chain Thalassaemias

Synthesis of α-chains are repressed and there occurs a compensatory increase in synthesis of other chains of which the cell is capable either β-chains or γ-chains.

(a) Hb-H (β4):

- In this there is inhibition of α-chain synthesis and rate of β-chain production increases. The excess of β-chains form a large intracellular pool and presumably aggregate to form β4 molecules (tetramer) and called Hb-H.

HB-H disease is characterised by

- Moderate degree of ***haemolytic anaemia***
- Red cell morphological appearance of thalassaemia
- Variable amount of Hb-H (usually 10–20%).

Inclusion bodies:

- After incubation of blood sample with brilliant cresyl blue and then drawing a smear on the slide, when seen under microscope, numerous ***inclusion bodies*** can be seen which represent denatured Hb-H.

(b) Hb-Barts (γ4):

In this the gross defect is in repression of α-chain synthesis resulting in great excess of γ-chains, which aggregate to γ4 molecules (tetramer).

β-chain Thalassaemia (Thalassaemia Major)

When the thalassaemia gene represses β-chain synthesis, an excess of α-chains occur which can combine with δ-chains producing an increase in Hb- A2 or with γ-chains producing an increase in Hb-F. This is the group of thalassaemias associated with severe anaemias of infancy or early childhood which was first described by Cooley, called Cooley's anaemia. Infants suffering from this disease have Mongoloid features and have stunted growth. They suffer from severe haemolytic anaemia.

On examination:

Marked pallor is seen; icterus is variable; enlargement of spleen (splenomegaly) is found.

Blood:

Hb very low may be 3 to 5 Gm%; hypochromic microcytic anaemia; osmotic fragility increased.

Blood smear:

Shows hypochromasia, polychromasia, basophilic stippling, Target cells ++, nucleated cells +.

Radiological examination:

A lateral view of bones of skull shows hair-on-end appearance, a characteristic radiological finding.

Biochemically:

Serum Fe level is normal. Rise in Hb-F- 5 to 80 per cent. Hb-A2 is significantly increased.

Disorders of mood: Schizophrenia

- Schizophrenia comes in many varieties. One of the most common types is seen in the person who hears voices and has delusions of grandeur, intense fear, or other types of feelings that are unreal. Many schizophrenics

(1) are highly paranoid, with a sense of persecution from outside sources;

(2) may develop incoherent speech, dissociation of ideas, and abnormal sequences of thought;

(3) are often withdrawn, sometimes with abnormal posture and even rigidity.

There are reasons to believe that schizophrenia results from one or more of three possibilities:

(1) multiple areas in the cerebral cortex *prefrontal lobes* in which neural signals have become blocked or where processing of the signals becomes dysfunctional because many synapses normally excited by the neurotransmitter *glutamate* lose their responsiveness to this transmitter;

(2) excessive excitement of a group of neurons that secrete *dopamine* in the behavioral centers of the brain, including in the frontal lobes; and/or

(3) abnormal function of a crucial part of the brain's *limbic behavioral control system centered around the hippocampus.* The reason for believing that the prefrontal lobes are involved in schizophrenia is that a schizophrenic-like pattern of mental activity can be induced in monkeys by making multiple minute lesions in widespread areas of the prefrontal lobes.

- Dopamine has been implicated as a possible cause of schizophrenia because many patients with Parkinson's disease develop schizophrenic-like symptoms when they are treated with the drug called L-dopa.
- This drug releases dopamine in the brain, which is advantageous for treating Parkinson's disease, but at the same time it depresses various portions of the prefrontal lobes and other related areas.
- It has been suggested that in schizophrenia excess dopamine is secreted by a group of dopamine-secreting neurons whose cell bodies lie in the ventral tegmentum of the mesencephalon, medial and superior to the substantia nigra.
- These neurons give rise to the so-called *mesolimbic dopaminergic system* that projects nerve fibers and dopamine secretion into the medial and anterior portions of the limbic system, especially into the hippocampus, amygdala, anterior caudate nucleus, and portions of the prefrontal lobes.

- All of these are powerful behavioral control centers. An even more compelling reason for believing that schizophrenia might be caused by excess production of dopamine is that many drugs that are effective in treating schizophrenia—such as chlorpromazine, haloperidol, and thiothixene—-all either decrease secretion of dopamine at dopaminergic nerve endings or decrease the effect of dopamine on subsequent neurons.
- Finally, possible involvement of the hippocampus in schizophrenia was discovered recently when it was learned that *in schizophrenia, the hippocampus is often reduced in size*, especially in the dominant hemisphere.

Dementia

- Dementia is the progressive deterioration of intellect, emotional control, social behavior and motivation associated with loss of memory.
- It is an age-related disorder. Usually, it occurs above the age of 65 years. When it occurs under the age of 65, it is called **presenile dementia.**

Causes:

- Dementia occurs due to many reasons.
- Most common cause of dementia is Alzheimer disease. In about75% of cases, dementia is due to this disease
- Other common causes of dementia are hydrocephalus, Huntington chorea, Parkinson disease, viral encephalitis, HIV infection, hypothyroidism, hypoparathyroidism, Cushing syndrome, alcoholic intoxication, poisoning by high dose of barbiturate, carbon monoxide, heavy metals, etc.

Clinical features

- Common features are loss of recent memory, lack of thinking and judgment and personality changes.
- As the disease progresses, psychiatric features begin to appear. Motor functions are also affected. Finally, the patient has to lead a vegetative life without any thinking power.
- The person is speechless and is unable to understand anything.
- There is no effective treatment for this disorder. Physostigmine, which inhibits cholinesterase causes moderate improvement.

Parkinson Disease

- Parkinson disease is a slowly progressive degenerative disease of nervous system associated with destruction of brain cells, which produce dopamine.

- It is named after the discoverer James Parkinson. It is also called parkinsonism or paralysis agitans.

Causes of Parkinson Disease:

- Parkinson disease occurs due to lack of dopamine caused by damage of basal ganglia. It is mostly due to the destruction of substantia nigra and the nigrostriatal pathway, which has dopaminergic fibers. Damage of basal ganglia usually occurs because of the following causes:

  i. Viral infection of brain like encephalitis
  ii. Cerebral arteriosclerosis
  iii. Injury to basal ganglia
  iv. Destruction or removal of dopamine in basal ganglia. It occurs mostly due to longterm treatment with antihypertensive drugs like reserpine. Parkinsonism due to the drugs is known as drug-induced parkinsonism.
  v. Unknown causes: Parkinsonism can occur because of the destruction of basal ganglia due to some unknown causes. This type of parkinsonism is called idiopathic parkinsonism.

Signs and Symptoms of Parkinson Disease:

- Parkinson disease develops very slowly and the early signs and symptoms may be unnoticed for months or even for years. Often the symptoms start with a mild noticeable tremor in just one hand.
- When the tremor becomes remarkable the disease causes slowing or freezing of movements followed by rigidity. Following are the common signs and symptoms of Parkinson disease:

i. *Tremor:*

- Refer Chapter 147 for details of tremor. In Parkinson disease, the tremor occurs during rest. But it disappears while doing any work.
- So, it is called static tremor or resting tremor. It is also called drum-beating tremor, as the movements are similar to beating a drum.
- Thumb moves rhythmically over the index and middle fingers. These movements are called pill-rolling movements.

ii. *Slowness of movements:*

- Over the time, movements start slowing down (bradykinesia) and it takes a long time even to perform a simple task.

- Gradually the patient becomes unable to initiate the voluntary activity (akinesia) or the voluntary movements are reduced (hypokinesia). It is because of hypertonicity of the muscles.

iii. *Poverty of movements:*

- Poverty of movements is the loss of all automatic associated movements. Because of absence of the automatic associate movements, the body becomes statue-like. The face becomes mask-like, due to absence of appropriate expressions like blinking and smiling.

iv. *Rigidity*

- Stiffness of muscles occurs in limbs resulting in rigidity of limbs. The muscular stiffness occurs because of increased muscle tone which is due to the removal of inhibitory influence on gamma motor neurons.
- It affects both flexor and extensor muscles equally. So, the limbs become more rigid like pillars. The condition is called lead-pipe rigidity. In later stages the rigidity extends to neck and trunk.

v. *Gait*

- Gait refers to manner of walking. The patient looses the normal gait. Gait in Parkinson disease is called festinant gait.
- The patient walks quickly in short steps by bending forward as if he is going to catch up the center of gravity.

vi. *Speech problems*

- Many patients develop speech problems. They may speak very softly or sometimes rapidly. The words are repeated many times.
- Finally, the speech becomes slurred and they hesitate to speak.

vii. *Emotional changes*

- The persons affected by Parkinson disease are often upset emotionally.

viii. *Dementia*

- In later stages, some patients develop dementia.

Treatment for Parkinson Disease:

- As Parkinson disease is due to lack of dopamine caused by damage of dopaminergic fibers, it is treated by dopamine injection. Dopamine does not cross the blood brain barrier.
- So, another substance called levodopa (Ldopa) which crosses the blood brain barrier is injected. Ldopa moves into the brain and there it is converted into dopamine.
- Since, Ldopa can be converted into dopamine in liver, some side effects occur due to excess dopamine content in liver and blood.
- So, along with Ldopa, another substance called carbidopa is administered. Carbidopa prevents the conversion of Ldopa into dopamine and carbidopa cannot pass through bloodbrain barrier.

- Thus, Ldopa moves into the brain tissues and is converted into dopamine. Some of the symptoms of Parkinson disease such as tremor are abolished by surgical destruction of basal ganglia or thalamic nuclei.

POSSIBLE QUESTIONS

2 marks

1. Write a note on Protein folding?
2. Which enzyme removes misfolded proteins? Give the importance.
3. What is Alzheimer's disease?
4. Write about Prion and Huntington's diseases?
5. What is meant by Polycystic ovarian syndrome?
6. Write note on Multifactorial disease?
7. What is Dementia?

6 marks

1. Discuss in detail about Portein folding and Misfolding?
2. Give an account on diseases caused by misfolded Proteins? .
3. Explain the following,

    i) Sickle cell anemia

    ii) Thalasemia

4. Explain about Parkinson's disease in detail.
5. Detailed note on mood disorders?
6. Describe about Polygenic diseases?.
7. Discuss about cell surface carbohydrates.

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III- B.Sc., BIOCHEMISTRY
MOLECULAR BASIS OF NON-INFECTIOUS HUMAN DISEASES 18BCU504-A
MULTIPLE CHOICE QUESTIONS

Enable | Enlighten | Enrich
KARPAGAM
ACADEMY OF HIGHER EDUCATION
(Deemed to be University)
(Established Under Section 3 of UGC Act, 1956)

Unit IV

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Which of the following forces is favorable for protein folding?	Hydrophobic interactions	Hydrogen bonding	Vander Waals forces	Ionic bonding	Hydrophobic interactions
2	A process by which a protein structure assumes its functional shape or conformation is	Denaturing	Folding	Synthesis	Hydrolysis	Folding
3	Process of folding does not depend on	Concentration of salts	pH	Solute	Solvent	Solute
4	Which of the following cannot denature a protein?	Iodoacetic acid	SDS detergent	Urea	Heating to 90°C	Iodoacetic acid
5	. Which of the following is a function of chaperone protein?	It degrades proteins that have folded improperly	It provide a template for how the proteins should fold	It rescues proteins that have folded improperly and allows them to refold properly	It degrades proteins that have folded properly	It rescues proteins that have folded improperly and allows them to refold properly
6	As folding progresses which of the following does not take place?	Entropy decreases	Amount of protein in native state increases	Free energy increases	Amount of protein in native state decreases	Amount of protein in native state decreases
7	Which of the following are chaperons in E.coli?	Hsp70	Hsp40	DnaA	DnaK and DnaJ	DnaK and DnaJ
8	Which of the following about spontaneous folding is false?	It involves initial formation of highly compact structure	It involves initial formation of a local secondary structure	It is essentially a random process	It may be defective in some human diseases	It is essentially a random process

9	Protein A will fold into its native state only when protein B is also present in the solution. However protein B can fold itself into native confirmation without the presence of protein A. Which of the following is true?	Protein B serves as precursor for protein A	Protein B serves as molecular chaperon for protein A	Protein B serves as ligand for protein A	Protein B serves as structural motif for protein A	Protein B serves as molecular chaperon for protein A
10	Which of the following is true about ribonucease?	Native state which is	Unfolded state is	Renatured ribonuclease is	Renaturation involves	Native state which is
11	In SDS electrophoresis, the proteins are separated on the basis of	charge	mass	both A and B	structure	mass
12	The interactions which holds and stabilizes the sub units in 4° structure of proteins are	hydrophilic interactions	hydrogen bonding	hydrophobic interactions	Ionic bonding	hydrophobic interactions
13	The process of folding depends upon the	solvent	the concentration of salts	pH	all of above	all of above
14	A technique which separates charged particles using electric field is	Hydrolysis	electrophoresis	protein synthesis	protein denaturing	electrophoresis
15	If proteins are separated according to their electrophoretic mobility than the type of electrophoresis is	A. SDS page	free flow electrophoresis	electro focusing	affinity electrophoresis	A. SDS page
16	Proteins that do not function but recover their activity upon folding are	denatured	folded	synthesized	hydrolyzed	denatured
17	In the peptide chain the alpha helix is secured In the peptide chain the alpha helix is secured by	sulfur linkage	amide group	carboxyl group	hydrogen bonding	hydrogen bonding
18	The coiling and folding of polypeptide chain gives us	1° structure	2° structure	3° structure	4° structure	2° structure
19	2° structure of proteins is of	only one type	three types	two types	four types	two types
20	Interactions between multiple polypeptide chains forms	1° structure	2° structure	3° structure	4° structure	4° structure
21	Within mood disorders, two key symptoms of a major depressive episode are:	Lack of interest in usual activities and recurrent thoughts of death	Very low mood and agoraphobia.	Diminished need for sleep and loss of energy.	Problems in concentration and compulsive behaviours.	Lack of interest in usual activities and recurrent thoughts of death

22	Within mood disorders, two key symptoms of a manic episode are:	Delusional thinking and intense fear of weight gain	Distractibility and social phobia.	Hallucinations and flight of ideas.	Extremely elevated mood and grandiose ideas.	Extremely elevated mood and grandiose ideas.
23	Bipolar disorder used to be known as:Bipolar disorder used to be known as:	Antisocial personality disorder.	Manic-depression.	Munchausen syndrome.	Messiah complex.	Manic-depression.
24	Bipolar disorder 1 differs from bipolar disorder 2because:	Hypomanic symptoms are present and there are recurrent thoughts of death.	Manic symptoms are less severe and obsessional thoughts are common.	Manic symptoms are more severe and sexual dysfunction is present.	Manic symptoms are more severe and there may be the presence of psychosis.	Manic symptoms are more severe and there may be the presence of psychosis.
25	Which of the following is not an explanation of the causes of depression:	Insufficient availability of the neurotransmitters serotonin and norepinephrine.	Being born into a large family.	Genetic abnormalities.	Faulty cognition.	Being born into a large family.
26	In the pharmacological treatment of depression, antidepressants known as SSRIs are often used. SSRI stands for:	Standard serotonin restoration intake.	Serotonin safely restoring imbibings.	Selective serotonin reuptake inhibitors.	Selective serotonin restoring injections.	Selective serotonin reuptake inhibitors.
33	Behavioural explanations for mania suggest that:	Individuals with mania get more pleasure from a positive event than those without mania	Individuals with mania copy the behaviour of their parents.	Individuals with mania feel less embarrassment than those without mania.	Classical conditioning is the primary cause of mania.	Individuals with mania get more pleasure from a positive event than those without mania
34	The main mood-stabilising medication used in bipolar disorder is:	Lorazepam	Fluoxetine	Lithium	Risperidone.	Lithium
36	Parkinson disease is marked by a lack of which chemical in the brain?	Serotonin	GABA	Dopamine	Norepinephrine	Dopamine
37	What is the average age when Parkinson disease first appears?	25	50	60	75	60
39	What is often the first symptom of Parkinson disease?	Headache	Nausea	Shaking of a hand or foot	Turning of the head	Shaking of a hand or foot

40	How is Parkinson disease diagnosed?	With a blood test	With a neurological exam	With an X-ray	All of the above	With a neurological exam
41	How is Parkinson disease treated?	Medicine	Surgery	Radiation	A and B	A and B
42	Effective drug for treatment of parkinson's disease is	l-dopa	m-dopa	t-dopa	k-dopa	l-dopa
43	Alzheimer's is the most common form of which of these?	Malnutrition	Dementia	Fatigue	Psychosis	Dementia
44	How is Alzheimer's diagnosed?	Mental-status tests	Blood tests	Neurological tests	All of the above	All of the above
45	Physiologically, what happens to the brain as Alzheimer's progresses?	Tissue swells	Fluid collects	Many cells die	Brain-stem atrophies	Many cells die
46	Which of these is the strongest risk factor for developing the disease?	Heredity	Age	Exposure to toxins	None of the above	Age
47	Occasionally, other medical conditions may mimic this disease. What are they?	Side effects to medication	Dehydration	Poor nutrition	All of the above	All of the above
48	Signs of Alzheimer's include which of these symptoms?	Loss of memory	Increase in irritability	Restlessness	All of the above	All of the above
49	Which age group has the highest rate of Alzheimer's cases reported?	85 and older	74 to 84	65 to 74	55 to 65	85 and older
50	Because no drugs cure this condition, emphasis is put on delaying the onset of severe symptoms. Which of these strategies helps?	Exercise	Hobbies	Good nutrition	All of the above	All of the above
53	The average time from the onset of symptoms to death is how long?	20 years	8 years	6 years	4 years	8 years
54	If you care for a relative with Alzheimer's, which of these measures will help stabilize the patient mentally?	Move to a small apartment	Correct "bad" behavior gently	Establish a regular routine	Repaint or buy new furniture	Establish a regular routine
55	ovary features in PCOD include all except	estrogen withdrawal bleeding	estrogen breakthrough bleeding	progesterone breakthrough bleeding	none of the above	estrogen breakthrough bleeding
56	ovary features in PCOD include all except	presence of corpora albicans	hyperplastic theca and stroma	multiple follicular cysts	sclerotic ovary	presence of corpora albicans
57	symptoms of PCOS usually begins around	menarche	first sexual contact	first child birth	following OCP intake	menarche

58	hyperandrogenemia in PCOS leads to cutaneous manifestation which includes all except	acne	acanthosis nigricans	androgenic alopecia	hirsuitism	acanthosis nigricans
59	polymenorrhea refers to regular mensturation occurring more frequently than	21 days	23 days	25 days	27 days	21 days
60	features of PCOS includes all except	anovulation/oligoovulation	reduced level of LH	hyerandrgenemia	hyperandrogenism	reduced level of LH

UNIT-V-SYLLABUS

Monogenic diseases
In born errors in metabolism: PKU, Alkaptonuria, Maple syrup urine disease; Receptor and transport defects: Cystic fibrosis, Long QT syndrome, familial hypercholesterolemia, Achondroplasia. Hemoglobinopathies and clotting disorders.

Unit-V – Monogenic Diseases

Inborn errors of metabolism:

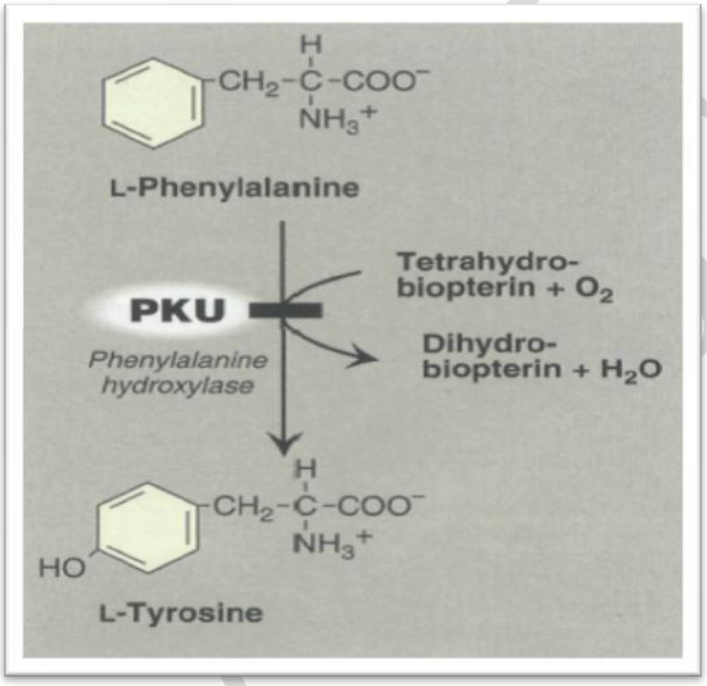
- Inborn errors of metabolism are commonly caused by mutant genes that generally result in abnormal proteins, most often enzymes.
- The inherited defects may be expressed as a total loss of enzyme activity or, more frequently, as a partial deficiency in catalytic activity. Without treatment, the inherited defects of amino acid metabolism almost invariably result in mental retardation or other developmental abnormalities as a result of harmful accumulation of metabolites.
- Although more than fifty of these disorders have been described, many are rare, occurring less than 1 per 250,000 in most populations. Collectively, however, they constitute a very significant portion of pediatric genetic diseases.

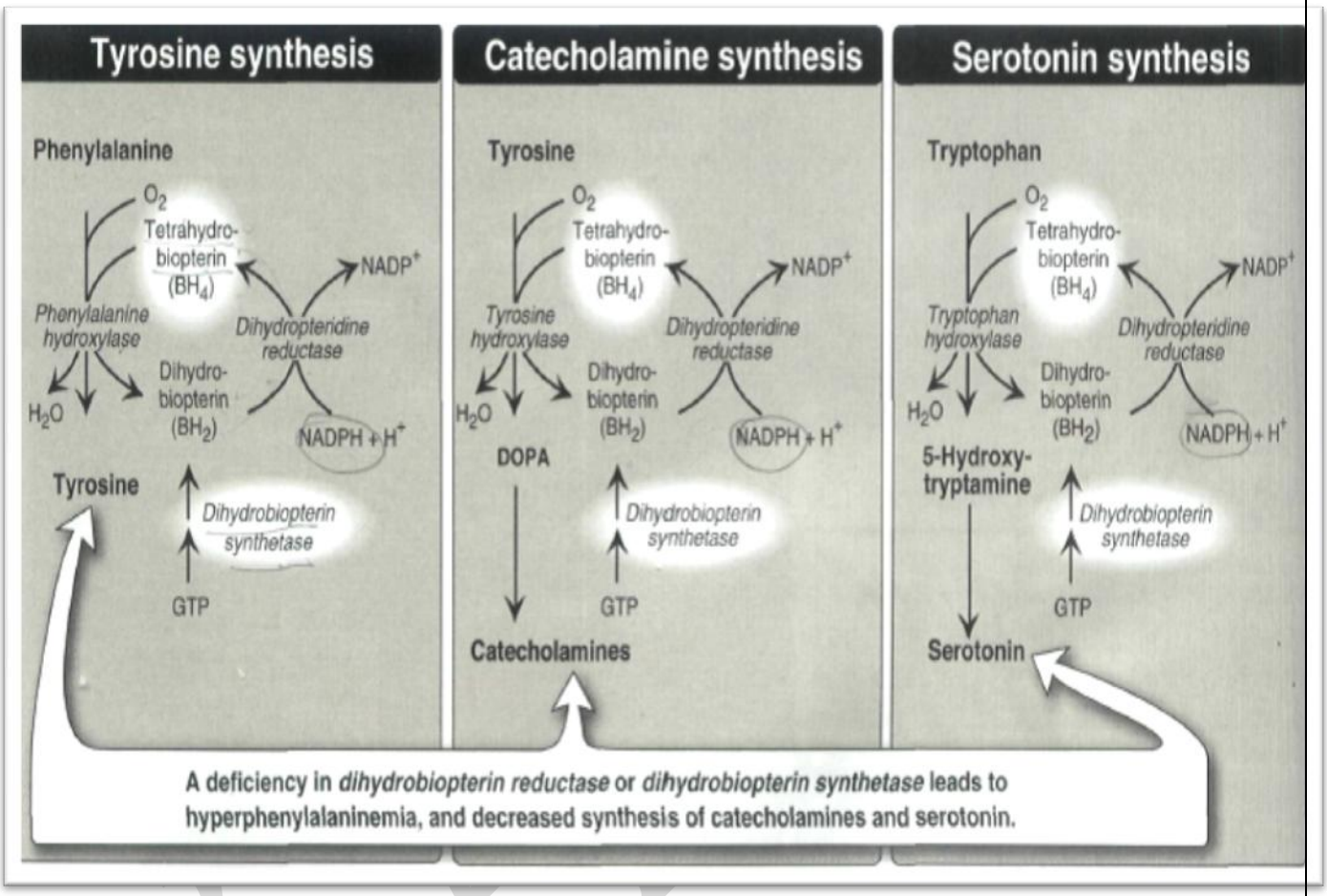
Phenylketonuria:

- Phenylketonuria (PKU), caused by a deficiency of phenylalanine hydroxylase (Figure 20.15), is the most common clinically encountered inborn error of amino acid metabolism (prevalence 1:11,000).
- Hyperphenylalaninemia may also be caused by deficiencies in the enzymes that synthesize or reduce the coenzyme tetrahydro- biopterin (BH4). It is frequently important to distinguish among the various forms of hyperphenylalaninemia, because their clinical management is different.
- For example, a small fraction of PKU is a result of a deficiency in either dihydropteridine (BH2) reductase or BH2 synthetase .
- These mutations prevent synthesis of BH4, and indirectly raise phenylalanine concentrations, because phenylalanine hydroxylase requires BH4 as a coenzyme. BH4 is also required for tyrosine hydroxylase and tryptophan hydroxylase, which catalyze

reactions leading to the synthesis of neurotransmitters, such as serotonin and catecholamines.

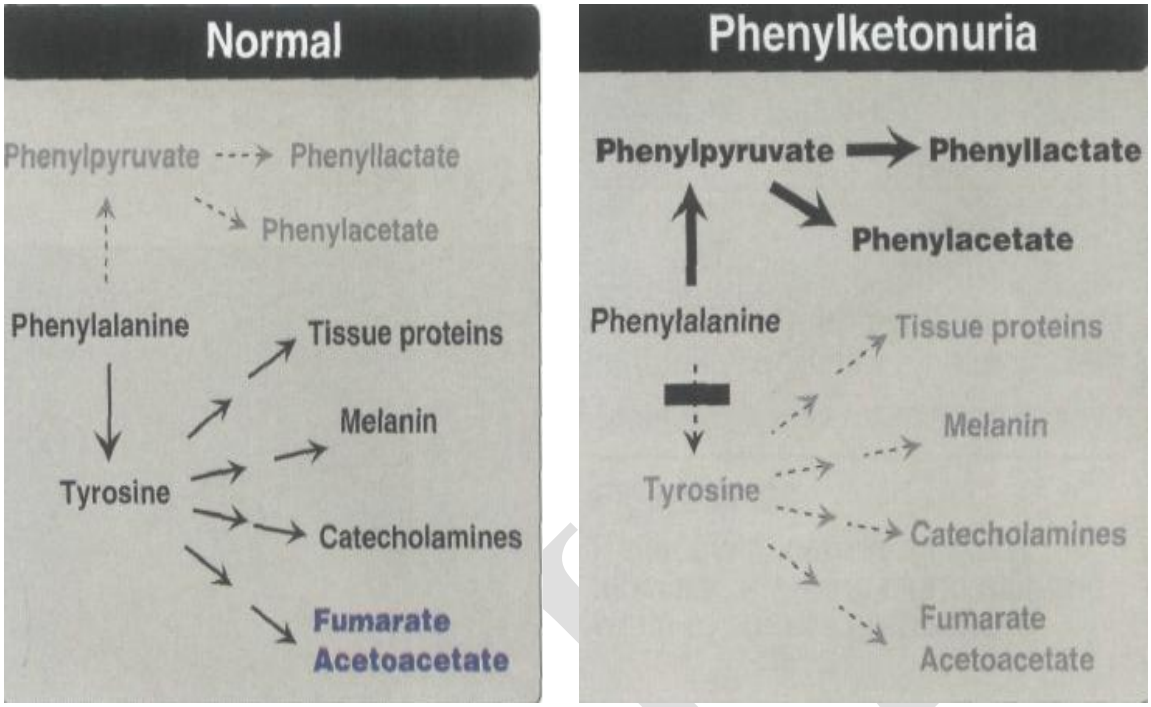
– Simply restricting dietary phenylalanine does not reverse the central nervous system (CNS) effects due to deficiencies in neurotransmitters. Replacement therapy with BH4 or 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan improves the clinical outcome in these variant forms of hyperphenylalaninemia, although the response of these patients is unpredictable and often disappointing.





Characteristics of PKU:

a. Elevated phenylalanine: Phenylalanine is present in elevated concentrations in tissues, plasma, and urine. Phenyl lactate, phenyl acetate, and phenyl pyruvate, which are not normally produced in significant amounts in the presence of functional *phenylalanine hydroxylase*, are also elevated in PKU. These metabolites give urine a characteristic musty ("mousey") odor.



b. CNS symptoms:

- Mental retardation, failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure togrow are characteristic findings in PKU. The patient with untreated PKU typically shows symptoms of mental retardation by the age of one year.

c. Hypopigmentation:

- Patients with phenyl ketonuria often show a deficiency of pigmentation (fair hair, light skin color, and blue eyes). The hydroxylation of tyrosine by *tyrosinase,* which is the first step in the formation of the pigment **melanin,** is competitively inhibited by the high levels of phenylalanine present in PKU.

Neonatal diagnosis of PKU:

- Early diagnosis of phenylketonuria is important because the disease is treatable by dietary means. Because of the lack of neonatal symptoms, laboratory testing for elevated blood levels of phenylalanine is mandatory for detection.
- However, the infant with PKU frequently has normal blood levels of phenylalanine at birth because the mother clears increased blood phenylalanine in her affected fetus

through the placenta. Thus, tests performed at birth may show false negative results. Normal levels of phenylalanine may persist until the newborn is exposed to at least 24 hours of protein feeding.

- Blood levels of phenylalanine should be determined on a second blood sampleobtained after the infant has ingested protein. Normally, feeding breast milk or formula for 48 hours is sufficient to raise the baby's blood phenylalanine to levels that can be used for diagnosis.

Treatment of PKU:

- Most natural protein contains phenylalanine,and it is impossible to satisfy the body's protein requirement when ingesting a normal diet without exceeding the phenylalanine limit.
- Therefore, in PKU, blood phenylalanine is maintained in the normal range by feeding synthetic amino acid preparations low in phenylalanine, supplemented with some natural foods (such as fruits, vegetables, and certain cereals) selected for their low phenylalanine content.
- The amount is adjusted according to the tolerance of the individual as measured by blood phenylalanine levels. The earlier treatment is started, the more completely neurologic damage can be prevented.
- Because phenylalanine is an essential amino acid, overzealous treatment that results in blood phenylalanine levels below normal should be avoided because this can lead to poor growth and neurologic symptoms.
- patients with PKU, tyrosine cannot be synthesized from phenylalanine and, therefore, it becomes an essential amino acid that must be supplied in the diet. Discontinuance of the phenyalanine-restricted diet before eight years of age is associated with poor performance on IQ tests. Adult PKU patients show deterioration of IQ scores after discontinuation of the diet.
- Life-long restriction of dietary phenylalanine is, therefore, recommended.

Maternal PKU:

- When women with PKU who are not on a low phenylalanine diet become pregnant, the offspring are affected with "maternal PKU syndrome." High blood phenylalanine levels in the mother cause microcephaly, mental retardation, and congenital heart abnormalities in the fetus.

- Some of these developmental responses to high phenylalanine occur during the first months of pregnancy. Thus, dietary control of blood phenylalanine must begin prior to conception, and must be maintained throughout the pregnancy.
- Children borne to mothers with PKU in metabolic control often show some residual developmental or behavioral effects, such as hyperactivity.

Maple Syrup Urine Disease

- Maple syrup urine disease (MSUD) is a recessive disorder in which there is a partial or complete deficiency in branced chain *α-ketoacid dehydrogenase*, an enzyme that decarboxylates leucine, isoleucine, and valine.
- These amino acids and their corresponding α-keto acids accumulate in the blood, causing a toxic effect that interferes with brain functions. The disease is characterized by feeding problems, vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.
- If untreated, the disease leads to mental retardation, physical disabilities, and death.

Classification: The term maple syrup urine disease includes a classic type and several variant forms of the disorder.

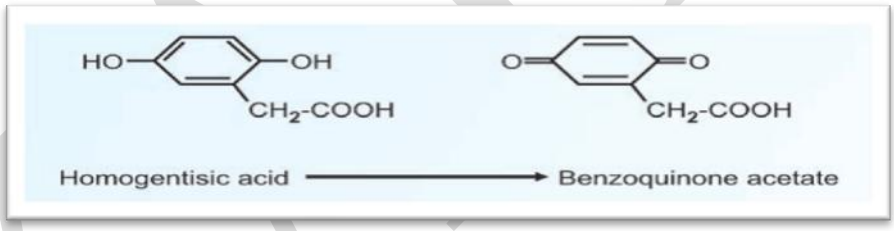
- **Classic type:** This is the most common type of MSUD. Leukocytes or cultured skin fibroblasts from these patients show little or no *branched-chain* α-keto acids *dehydrogenase* activity. Infants with classic MSUD show symptoms within the first several days of life.
- **Intermediate and intermittent forms:** These patients have ahigher level of enzyme activity (approximately three to fifteenpercent of normal). The symptoms are milder and show anonset from infancy to adulthood.
- **Thiamin-responsive form:** Large doses of thiamin can helppatients with this rare variant of achieve increased MSUD *branched-chain α-ketoacid dehydrogenase* activity.

Treatment:

- The disease is treated with a synthetic formula that contains limited amounts of leucine, isoleucine, and valine sufficient to provide the branched-chain amino acids necessary fornormal growth and development without producing toxic levels.
- Infants suspected of having any form of MSUD should be tested within 24 hours of birth. Early diagnosis and treatment is essential if the child with MSUD is to develop normally.

Alkaptonuria

- The term alkaptonuria arises from the Arabic word alkapton for ‘alkali' and Greek word ‘to suck up oxygen greedily in alkali'.
- This is based on the observation that the **urine becomes black** on standing when it becomes alkaline.
- Sir Archibald Garrod in 1902 reported that patients complain that their underwears are getting blackened. Garrod concluded that the disease is inherited and it is due to the deficiency of the enzyme required for further metabolism of homogentisic acid.



Biochemical Defect:

- Alkaptonuria is an autosomal recessive condition with an incidence of 1 in 250,000 births. The metabolic defect is the deficiency of homogentisate oxidase. This results in excretion of homogentisic acid in urine.
- It is compatible with fairly normal life. The only abnormality is the blackening of urine on standing. The homogentisic acid is oxidized by polyphenol oxidase to benzoquinone acetate.
- It is then polymerized to black colored alkaptone bodies. By the 3rd or 4th decade of life, patient may develop ochronosis (deposition of alkaptone bodies in intervertebral discs, cartilages of nose, pinna of ear). Black pigments are deposited over the connective tissues including joint cavities to produce arthritis.

- No specific treatment is required. But minimal protein intake with phenylalanine less than 500 mg/day is recommended.

Diagnosis of Alkaptonuria

1. **Urine becomes black on standing** when it becomes alkaline. Blackening is accelerated on exposure to sunlight and oxygen. The urine when kept in a test tube will start to blacken from the top layer.
2. **Ferric chloride test** will be positive for urine.
3. **Benedict's test** is strongly positive. Therefore, alkaptonuria comes under the differential diagnosis of reducing substances in urine.

Familial Hypercholesterolaemia (FHC)

A common disorder which has been extensively investigated. The disease is characterized by:

- Hyper β-lipoproteinaemia (LDL ↑)
- Associated with increased total cholesterol ↑
- VLDL may be raised, hence total TG may be high.

But plasma usually remains clear.

Inheritance: Autosomal dominant; Frequency—0.2 per cent

Enzyme deficiency (metabolic defect): There is no enzyme deficiency. Metabolic defects are:

• An increased synthesis of apo-B ↑

• Defective catabolism of LDL. Deficiency of LDL receptors in fibroblasts demonstrated.

Clinical features:

(a) Xanthomas of tendinous and tuberous type have been described, (b) Corneal arcus, (c) Occasionally xanthelesma. Clinically most important is the increased incidence of atherosclerosis and premature cardiovascular diseases.

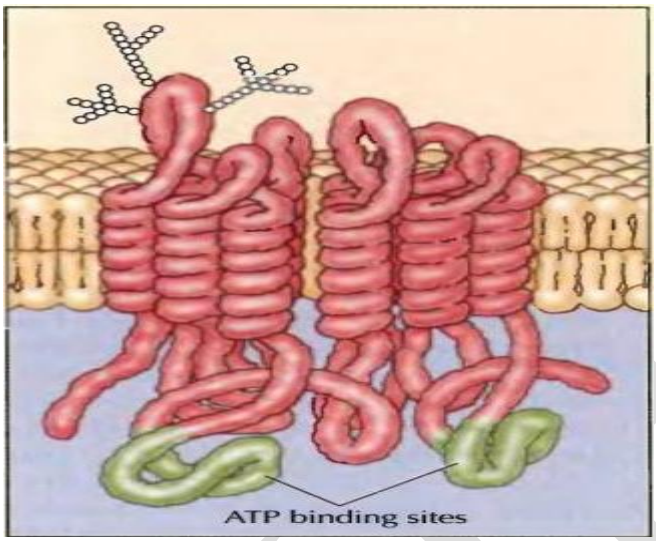
Cystic Fibrosis

- Cystic Fibrosis is a recessive genetic disease affecting children and young adults. It is most common lethal inherited disease of Caucasians, with approximately one in 2500 newborns affected, although it is rare in other races.

- The characteristic dysfunction in cystic fibrosis is the production of abnormally thick sticky mucus by several types of epithelial cells, including the cells lining the respiratory and gastrointestinal tracts.
- The primary clinical manifestation is respiratory disease resulting from obstruction of the pulmonary airways by thick plugs of mucus, followed by the development of recurrent bacterial infections.
- In most patients, the pancreas is also involved because the pancreatic ducts are blocked by mucus. Sweat glands also function abnormally, and the presence of excessive salt in sweat is diagnostic of cystic fibrosis.
- Current management of the disease of the disease includes physical therapy to promote bronchial drainage, antibiotic administration, and pancreatic enzyme replacement.
- Although such treatment has extended the survival of affected individuals to about 30 years of age, cystic fibrosis is ultimately fatal, with lung disease being responsible for 95% of mortality.

Molecular and Cellular Basis:

- The hallmark of cystic fibrosis is defective Cl^- transport in affected epithelia, including sweat ducts and the cells lining the respiratory tract.
- In 1984 it was demonstrated that Cl^- channels fail to function normally in epithelial cells from cystic fibrosis patients. The molecular basis of the disease was then elucidated in 1989 with the isolation of the cystic fibrosis gene as a molecular clone.
- The sequence of the gene revealed that it encodes a protein (called CFTR for cystic fibrosis trans membrane conductance regulator) belonging to the ABC transporter family.
- A variety of subsequent studies then demonstrated that CFTR functions as a Cl^- channel and that the inherited mutations responsible for cystic fibrosis result directly in defective Cl^- transport.
- More than 70% of these are a single point mutation at phenylalanine 508 that disrupts folding or assembly of the protein.



Model of Cystic fibrosis trans membrane conductance regulator (CFTR)

Prevention and Treatment:

- As with other inherited diseases, isolation of the cystic fibrosis gene opens the possibility of genetic screening to identify individuals carrying mutant alleles.
- In some populations, the frequency of heterozygote carriers of mutant genes is as high as one in 25 individuals, suggesting the possibility of general population screening to identify couples at risk and provide genetic counseling.
- In addition, understanding the function of CFTR as a Cl^- channel has suggested new approaches to treatment. One possibility is the use of drugs that stimulate the opening of other Cl^- channels in affected epithelia.
- Alternatively, gene therapy provides the potentials of replacing normal CFTR genes in the respiratory epithelium of cystic fibrosis patients.
- The potential of gene therapy has been supported by experiments demonstrating that introduction of a normal CFTR gene into cultured cells of cystic fibrosis patients is sufficient to restore Cl^- channel function.
- The possible application of gene therapy to cystic fibrosis is also enhanced by the accessibility of the epithelial cells lining the airway to aerosol delivery systems.
- Studies with experimental animals have demonstrated that viral vectors can transmit CFTR cDNA to the respiratory epithelium, and the first human trial of gene therapy for cystic fibrosis was initiated in 1993.

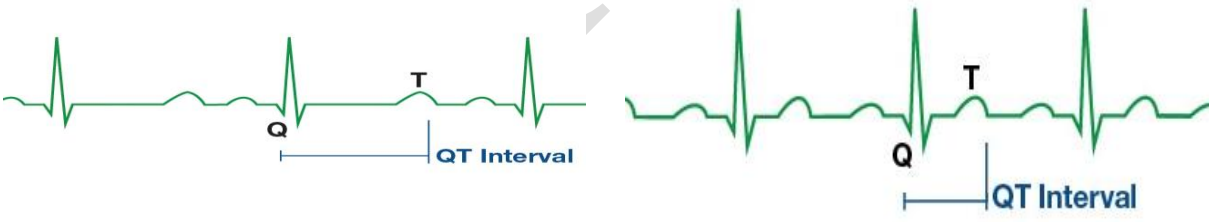
- Trials to date have demonstrated that the CFTR can be safely delivered to and expressed in the bronchial epithelial cells cystic fibrosis patients. So far, however, the efficiency of gene transfer has been low and expression of the transferred CFTR cDNA has persisted for less than a month.
- Thus the principle of successful gene transfer has been established, but significantly obstacles in developing an effective gene therapy protocol remain to be overcome.

Long QT syndrome (LQTS)

- Long QT syndrome (LQTS) is a heart rhythm condition that can potentially cause fast, chaotic heartbeats. These rapid heartbeats might trigger a sudden fainting spell or seizure.

- Genetic mutation that puts you at risk of being born with congenital long QT syndrome. In addition, certain medications, imbalances of the body's salts and minerals (electrolyte abnormalities), and medical conditions might cause acquired long QT syndrome.

- Long QT syndrome is treatable. Need to take medications to prevent an erratic heart rhythm. In some cases, treatment for long QT syndrome involves surgery or an implantable device.



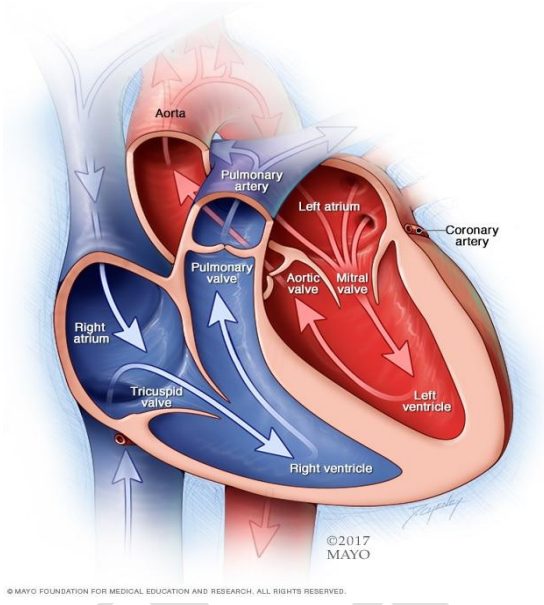
Symptoms:

Many people who have long QT syndrome don't have any signs or symptoms.

- **Fainting.** This is the most common sign of long QT syndrome. Long QT syndrome-triggered fainting spells (syncope) are caused by the heart temporarily beating in an erratic way. These fainting spells might happen when you're excited, angry, scared or during exercise.
- **Seizures.** If the heart continues to beat erratically, the brain will eventually not get enough oxygen, which can cause seizures.
- **Sudden death.** Generally, the heart returns to its normal rhythm. If this doesn't happen by itself, or if an external defibrillator isn't used in time to convert the rhythm back to normal, sudden death will occur.
  - Signs and symptoms of inherited or congenital long QT syndrome might start as a fetus, during the first weeks to months after birth, as late as older age, or never at all.
  - Most people who experience signs or symptoms from long QT syndrome have their first episode by age 40.
  - Signs and symptoms of long QT syndrome might occur during sleep or arousal from sleep.

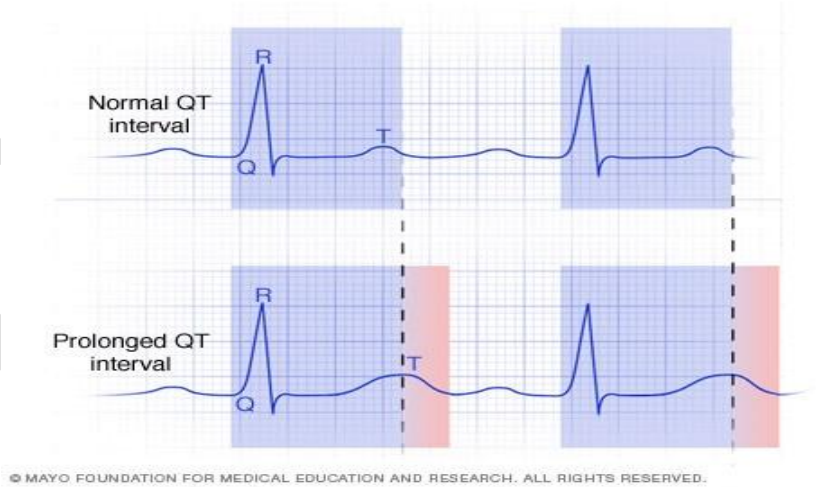
Causes:

- Long QT syndrome is a heart rhythm disorder that can cause serious irregular heart rhythms (arrhythmias).Normally heart circulates blood throughout your body during each heartbeat. Your heart's chambers contract and relax to pump blood.
- These actions are controlled by electrical impulses that travel through your heart and cause it to beat. After each heartbeat, your heart's electrical system recharges itself in preparation for the next heartbeat.
- In long QT syndrome, your heart muscle takes longer than normal to recharge between beats. This electrical disturbance, which often can be seen on an electrocardiogram (ECG), is called a prolonged QT interval.



Chambers and valves of the heart

Prolonged Q-T interval:



- An electrocardiogram (ECG) measures electrical impulses as they travel through heart. Patches with wires attached to your skin measure these impulses, which are displayed on a monitor or printed on paper as waves of electrical activity.

- An ECG measures electrical impulses as five distinct waves. Doctors label these five waves using the letters P, Q, R, S and T. The waves labeled Q through T show electrical activity in heart's lower chambers (ventricles).

- The space between the start of the Q wave and the end of the T wave (QT interval) corresponds to the time it takes for your heart to contract and then refill with blood before beginning the next contraction.

- Long QT syndrome results from abnormalities in the heart's electrical recharging system. However, the heart's structure is normal. Abnormalities in your heart's electrical system might be inherited. Or, they may be acquired due to an underlying medical condition or a medication.

Inherited long QT syndrome

- At least 17 genes associated with long QT syndrome have been found so far, and hundreds of mutations within these genes have been identified. Mutations in three of these genes account for about 75 percent of long QT syndrome cases, while mutations in the other minor genes contribute a small percent of long QT syndrome cases.

- About 20 percent of people who definitely have congenital long QT syndrome have a negative genetic test result. On the other hand, among families with genetically established long QT syndrome, between 10 percent and 37 percent of the relatives with a positive long QT syndrome genetic test have a normal QT interval.

Doctors have described two forms of inherited long QT syndrome:

- **Romano-Ward syndrome.** This more common form occurs in people who inherit only a single genetic variant from one parent.
- **Jervell and Lange-Nielsen syndrome.** This rare form usually occurs earlier and is more severe. In this syndrome, children inherit genetic variants from both parents. They have long QT syndrome and also are born deaf.

Acquired long QT syndrome

- Acquired long QT syndrome can be caused by certain medications, electrolyte abnormalities such as low body potassium (hypokalemia) or medical conditions.

- More than 100 medications many of them common can lengthen the QT interval in otherwise healthy people and cause a form of acquired long QT syndrome known as drug-induced long QT syndrome.

Medications that can lengthen the QT interval and upset heart rhythm include:

- Certain antibiotics
- Certain antidepressant and antipsychotic medications
- Some antihistamines
- Diuretics
- Medications used to maintain normal heart rhythms (antiarrhythmic medications)
- Some anti-nausea medications

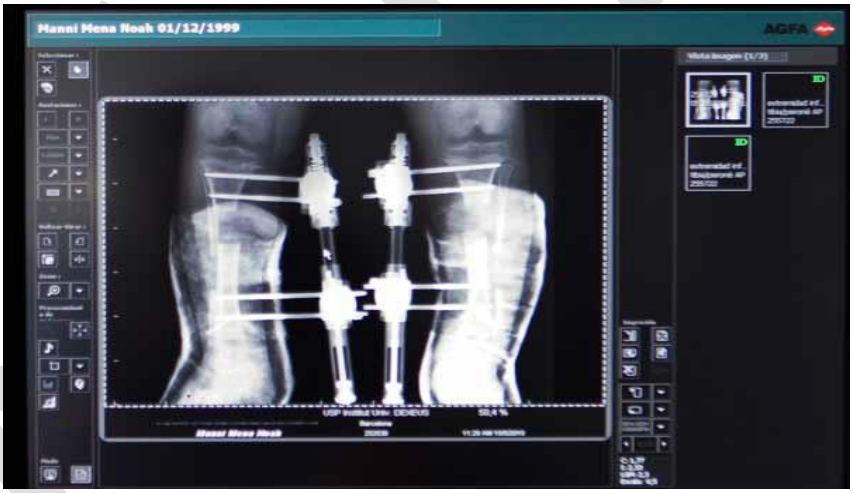
Diagnosis:

- **Electrocardiogram (ECG).** During an ECG, doctors attach sensors to your chest (electrodes) that can detect the electrical activity of your heart. An ECG measures the timing and duration of each electrical phase in your heartbeat.
- **Holter monitor.** This portable ECG device can be worn for a day or more to record your heart's activity as you go about your routine.
- **Event monitor.** This portable ECG device is attached to your body to monitor your heart activity over a few weeks to a few months. When you have symptoms, you press a button. This allows your doctor to check your heart rhythm at the time of your symptoms.
- **Genetic testing.** A genetic test for long QT syndrome is available and may be covered by some private and governmental insurance plans. Genetic tests for long QT syndrome can

generally find the genetic cause for about 3 out of every 4 cases of inherited long QT syndrome. However, genetic tests can't detect all cases of long QT syndrome.

Achondroplasia

- Achondroplasia is the most common form of disproportionate short stature and one of the skeletal dysplasias, a heterogeneous group of several hundred conditions.
- With a prevalence in newborn infants of 1 in 10 000–30 000, many pediatricians can expect to encounter affected children at some point.
- Although most will be healthy without ongoing health concerns, routine surveillance to detect the significant complications that occur in approximately 10% of these children is required, with appropriate onward referral for specialist intervention.
- As such, detailed knowledge of the possible complications and a sound approach to anticipatory management can significantly reduce the associated morbidity and even mortality.
- Here we provide an overview of the clinical aspects of achondroplasia and suggest a system based approach to monitor the development of complications.



Etiology:

- Achondroplasia is caused in over 95% of cases by one of two recurrent mutations in the gene
- encoding fibroblast growth factor receptor type 3 (*FGFR3*), both resulting in the same amino acid substitution (G380R).

- These activating mutations have a detrimental effect on longitudinal growth through increased signal transduction in the cartilage growth plate. *FGFR3* is also important in craniofacial, vertebral and neurological development such that this mutation has multiple effects in an affected individual.
- Achondroplasia is a dominantly inherited condition with a high new mutation rate, such that 80% of children with achondroplasia have parents of average stature. Of note, there is a strong association between achondroplasia and increasing paternal age.
- This is thought to be due to a selective growth advantage in sperm containing the *FGFR3* mutations associated with achondroplasia.

Presentation:

- In the homozygous form the condition is severe and lethal.
- At birth or within the first year of life, with disparity between large skull, normal length trunk and short arms and legs.
- The chest is usually very narrow.
- Fingertips may only come down to the iliac crest.
- Shortness is particularly evident in the proximal segments of limbs.
- Limbs appear very broad with deep creases and trident-like hands with short fingers.
- There is often increased joint laxity.
- Skull shows a bulging vault, small face and a flat nasal bridge or 'scooped out' glabella.
- Spine shows marked lumbar lordosis.
- Frontal bossing, depressed nasal bridge.

Diagnosis:

- The diagnosis is based on the typical clinical and X-ray features.

- Prenatal diagnosis is by ultrasound. However, prenatal sonographic diagnosis often fails as limb length is preserved until around 22 weeks of gestation, after the time of the routine fetal anomaly scan.
- Prenatal diagnosis of homozygous achondroplasia is also available in families at risk and in which the parents are heterozygous for either the 1138A or 1138C allele.

- Plasma can be analysed for the FGFR3 mutation in the mother when a short-limb skeletal dysplasia is diagnosed prenatally on ultrasound.
- A full skeletal survey should be undertaken if there is clinical suspicion of skeletal dysplasia, such as disproportionate short stature, limb malalignment or specific dysmorphic features.
- Confirmatory molecular analysis to detect the recurrent G380R FGFR3 mutations may be helpful where there is residual doubt about the diagnosis.
- X-rays show meta physeal irregularity, flaring in the long bones, and late-appearing irregular epiphyses. The pelvis is narrow in anteroposterior diameter with deep sacroiliac notches and short iliac wings. The spine shows progressive narrowing of the interpedicular distance from top to bottom (reverse of normal).

- Investigation of possible cranial abnormalities and hydrocephalus includes ultrasound, and CT and MRI scans. Detailed imaging of the craniocervical junction is particularly important in infants in order to rule out spinal cord compression.

- However, one recent study has shown that cervical cord lesions are observed in around 40% of people with achondroplasia and this are actually not associated with any clinical symptoms.
- Molecular genetic testing is the gold standard. Whilst clinical and X-ray features will identify the majority of patients, this is the only means of differentiating achondroplasia from the other forms of skeletal dysplasias. It is also a helpful investigation prior to considering therapeutic options and genetic counselling.

Management

- Management of frequent middle ear infections. Treatment of obstructive sleep apnoea - eg, adenotonsill ectomy, weight loss and continuous positive airway pressure.

- As excess weight gain is often a significant issue for many affected children, regular height and weight measurement later in childhood and an emphasis on maintaining weight gain within acceptable limits from an early age are very important.
- Growth hormone therapy is not routinely given as there is no evidence of significant increases in final adult stature following the administration of growth hormone.
- Anti-inflammatory drugs may be helpful in patients with degenerative joint disease.
- Surgical intervention includes enlargement of the foramen magnum in cases of severe stenosis, lengthening of the limb bones, tibial osteotomy or epiphysiodesis of the fibular growth plate to correct bowing of the legs, and lumbar laminectomy for spinal stenosis (typically presents in early adulthood).

Complications

The degree of complications and disability is variable:

- Gross motor skills in particular develop later in the child with achondroplasia; approximately 50% of children will sit alone by 9 months and just over 50% will walk alone by 18 months.
- Short arms, limited elbow and hip extension, and knee and leg deformities can cause disabilities in arm function and locomotion.
- A progressive, unresolving thoracolumbar kyphosis can occur.
- Hydrocephalus, a narrow foramen magnum, spinal deformity, and spinal canal stenosis can cause neurological problems (eg, progressive quadriparesis, pain, ataxia, incontinence) leading to disabilities in locomotion, communication, and learning.
- Skeletal disproportion can lead to early osteoarthritis, problems with childbirth in women, hydrocephalus and paraplegia.
- Narrowing of the spinal canal causes symptoms of spinal stenosis.
- Obesity is common; once the child has reached 75 cm there tends to be a disproportionate increase in weight compared with height.
- Ear, nose and throat abnormalities such as recurrent otitis media, upper respiratory tract obstruction, deafness, speech delay, and jaw malocclusion can also lead to disabilities in communication and learning.

- Respiratory complications may include apnoea (including obstructive sleep apnoea) and abnormalities of gas exchange.[12]Children with respiratory dysfunction may be associated with cognitive deficit.
- The most severe complication results from craniocervical stenosis and medullary and upper spinal cord compression, which can have devastating and even lethal sequelae during early childhood.

Hemoglobinopathies

A genetic defect that results in abnormal structure of one of the globin chains of the hemoglobin molecule. Abnormal hemoglobins appear in one of three basic circumstances:

1. **Structural defects in the hemoglobin molecule:** Alterations in the gene for one of the two hemoglobin subunit chains, alpha (α) or beta (β), are called mutations. Often, mutations change a single amino acid building block in the subunit. Occasionally, alteration of a single amino acid dramatically disturbs the behavior of the hemoglobin molecule and produces a disease state.
2. **Diminished production of one of the two subunits of the hemoglobin molecule:** Mutations that produce this condition are termed "thalassemias." Equal numbers of hemoglobin alpha and beta chains are necessary for normal function. Hemoglobin chain imbalance damages and destroys red cells thereby producing anemia. Although there is a dearth of the affected hemoglobin subunit, with most thalassemias the few subunits synthesized are structurally normal.
3. **Abnormal associations of otherwise normal subunits:** A single subunit of the alpha chain (from the α-globin locus) and a single subunit from the β-globin locus combine to produce a normal hemoglobin dimer. With severe α-thalassemia, the β-globin subunits begin to associate into groups of four (tetramers) due to the paucity of potential α-chain partners. These tetramers of β-globin subunits are functionally inactive and do not transport oxygen. No comparable tetramers of alpha globin subunits form with severe beta-thalassemia. Alpha subunits are rapidly degraded in the absence of a partner from the beta-globin gene cluster (gamma, delta, beta globin subunits).

Types of hemoglobins:

There are hundreds of hemoglobin variants that involve involve genes both from the alpha and beta gene clusters. The list below touches on some of the more common and important hemoglobin variants.

Normal Hemoglobins

- Hemoglobin A. This is the designation for the normal hemoglobin that exists after birth. Hemoglobin A is a tetramer with two alpha chains and two beta chains (a_2b_2).
- Hemoglobin A2. This is a minor component of the hemoglobin found in red cells after birth and consists of two alpha chains and two delta chains (a_2d_2). Hemoglobin A2 generally comprises less than 3% of the total red cell hemoglobin.
- Hemoglobin F. Hemoglobin F is the predominant hemoglobin during fetal development. The molecule is a tetramer of two alpha chains and two gamma chains (a_2g_2).

The genes for hemoglobin F and hemoglobin A are closely related, existing in the same gene cluster on chromosome. Hemoglobin F production falls dramatically after birth, although some people continue to produce small amounts of hemoglobin F for their entire lives.

Clinically Significant Variant Hemoglobins:

- **Hemoglobin S -** This predominant hemoglobin in people with sickle cell disease. The alpha chain is normal. The disease-producing mutation exists in the beta chain, giving the molecule the structure, $a_2b^S_2$. People who have one sickle mutant gene and one normal beta gene have sickle cell trait which is benign.
- **Hemoglobin C-** Hemoglobin C results from a mutation in the beta globin gene and is the predominant hemoglobin found in people with hemoglobin C disease ($a_2b^C_2$). Hemoglobin C disease is relatively benign, producing a mild hemolytic anemia and splenomegaly. Hemoglobin C trait is benign.
- **Hemoglobin E-** This variant results from a mutation in the hemoglobin beta chain. People with hemoglobin E disease have a mild hemolytic anemia and mild splenomegaly. Hemoglobin E trait is benign. Hemoglobin E is extremely common in S.E. Asia and in some areas equals hemoglobin A in frequency.
- **Hemoglobin Constant Spring-** Hemoglobin Constant Spring is a variant in which a mutation in the alpha globin gene produces an alpha globin chain that is abnormally long. The quantity of hemoglobin in the cells is low for two reasons. First, the messenger RNA for hemoglobin Constant Spring is unstable.
- **Hemoglobin Barts-** Hemoglobin Barts develops in fetuses with four-gene deletion alpha thalassemia. During normal embryonic development, the episilon_gene of the alpha globin gene locus combines with genes from the beta globin locus to form functional hemoglobin molecules. The episolon gene turns off at about 12 weeks, and normally the alpha gene takes over. With four-gene deletion alpha thalassemia no alpha chain is produced. The gamma

chains produced during fetal development combine to form gamma chain tetramers. These molecules transport oxygen poorly.

Compound Heterozygous Conditions:

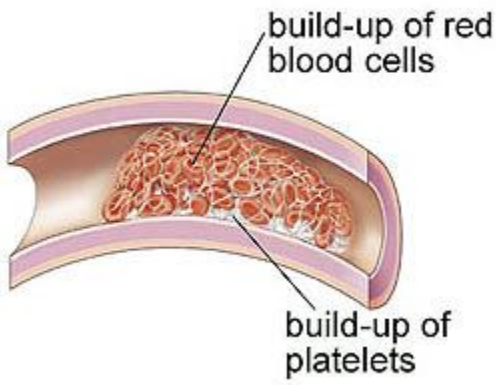
Hemoglobin is made of two subunits derived from genes in the alpha gene cluster on chromosome 16 and two subunits derived from genes in the beta gene cluster on chromosome 11. Occasionally someone inherits two different variant genes from the alpha globin gene cluster or two different variant genes from the beta globin gene cluster. This condition is called "compound heterozygous". The nature of two genes inherited determines whether a clinically significant disease state develops. The compound heterozyous states tends to consist of common groupings (e.g., hemoglobin SC), due to the geographic clustering of hemoglobin variants around the world.

- **Hemoglobin SC disease-**Patients with hemoglobin SC disease inherit a gene for hemoglobin S from one parent, and a gene for hemoglobin C from the other. Hemoglobin C interacts with hemoglobin S to produce some of the abnormalities seen in patients with sickle cell disease. On average, patients with hemoglobin SC disease have milder symptoms than do those with sickle cell disease. This is only an average, however. Some people with hemoglobin SC disease have a condition equal in severity to that of any patient with sickle cell disease.
- **Sickle/beta-thalassemia-** In this condition, the patient has inherited a gene for hemoglobin S from one parent and a gene for beta-thalassemia from the other. The severity of the condition is determined to a large extent by the quantity of normal hemoglobin produced by the beta-thalassemia gene. Beta-thalassemia is quite common in this region, and the sickle cell gene occurs in some sections of these countries.
- **Hemoglobin E/beta-thalassemia-** The combination of hemoglobin E and beta-thalassemia produces a condition more severe than is seen with either hemoglobin E trait or beta-thalassemia trait. The disorder manifests as a moderately severe thalassemia that falls into the category of thalassemia intermedia.
- **Alpha thalassemia/Hemoglobin Constant Spring-** This syndrome is a compound heterozygous state of the alpha globin gene cluster. The alpha globin gene cluster on one of the two chromosomes 16 has both alpha globin genes deleted. On the other chromosome 16, the alpha1 gene has the Constant Spring mutation. The compound heterozygous condition produces a severe shortage of alpha globin chains. The excess beta chains associate into tetramers to form hemoglobin H.

Clotting Disorders

Blood Clot Formation:

- When you cut or injure yourself, your body stops the bleeding by forming a blood clot. Proteins and particles in your blood, called platelets, stick together to form the blood clot. The process of forming a clot is called coagulation.
- Normal coagulation is important during an injury, as it helps stop a cut from bleeding and starts the healing process.
- However, the blood shouldn't clot when it's just moving through the body. If blood tends to clot too much, it is referred to as a hypercoagulable state or thrombophilia.



Hypercoagulable states dangerous:

- Hypercoagulable states can be dangerous, especially when these conditions are not properly identified and treated. People with hypercoagulable states have an increased risk for blood clots developing in the arteries and veins .A clot inside a blood vessel is also called a thrombus or an embolus.
- Blood clots in the veins or venous system can travel through the bloodstream and cause deep vein thrombosis or a pulmonary embolus.
- Blood clots in the arteries can increase the risk for stroke, heart attack, severe leg pain, difficulty walking, or even the loss of a limb.

Causes:

Hypercoagulable states are usually genetic (inherited) or acquired conditions. The genetic form of this disorder means a person is born with the tendency to form blood clots. Acquired conditions are usually a result of surgery, trauma, medications or a medical condition that increases the risk of hypercoagulable states.

***Inherited* hypercoagulable conditions include:**

- Factor V Leiden (the most common)
- Prothrombin gene mutation
- Deficiencies of natural proteins that prevent clotting (such as antithrombin, protein C and protein S)
- Elevated levels of homocysteine
- Elevated levels of fibrinogen or dysfunctional fibrinogen (dysfibrinogenemia)
- Elevated levels of factor VIII (still being investigated as an inherited condition) and other factors including factor IX and XI
- Abnormal fibrinolytic system, including hypoplasminogenemia, dysplasminogenemia and elevation in levels of plasminogen activator inhibitor (PAI-1).

Clotting Disorders:

There are 2 types of clotting disorders. The first is a hereditary disorder that is inherited from one or both parents. The second is an acquired disorder, which a person is not born with, but that develops later in life.

Hereditary Clotting Disorders:

The hereditary clotting disorders come in 2 groups:

Group 1: A lack of anti-clotting factors in the blood

Group 2: An increased amount of pro-clotting factors in the blood

Lack of anti-clotting factors in the blood :

Antithrombin Deficiency:

- Antithrombin is a natural blood thinner found in the body. It works to reduce clot formation. Over 100 gene mutations have been found that can lead to antithrombin deficiency.
- This disorder is inherited as an autosomal dominant trait, which means that if a person gets an abnormal gene from one parent and a normal gene from the other parent, they will have the disease.
- Patients with antithrombin deficiency are resistant to heparin therapy because heparin requires the presence of antithrombin to work. Heparin is a commonly used. intravenous blood thinner.
- Patients with antithrombin deficiency who need blood thinners should get another type of blood thinner that does not need antithrombin to work. Antithrombin itself can be given if necessary. After a VTE has occurred, lifelong oral anticoagulation is generally recommended.

Protein C Deficiency:

- Protein C is a natural anticoagulant that is made primarily in the liver. During the clotting process, protein C is activated, and along with protein S acts as a blood thinner to keep the clotting process in check.
- Deficiency in protein C results in decreased ability to keep the clotting process in check, leading to abnormal clot formation.
- If a person has protein C deficiency, and they have never had a VTE, then no medication is required. They need to have blood thinners given to prevent VTE prior to surgery or during other situations where they would be at increased risk of VTE.

Protein S Deficiency:

- Protein S acts with protein C to keep the body's natural clotting process controlled. A low protein S level has similar effects as a low level of protein C.

An increased amount of pro-clotting factors in the blood:

Activated Protein C Resistance/Factor V Leiden Mutation:

- Activated Protein C (APC) resistance refers to the resistance of Factor V to the activated protein C in the clotting reaction. Since activated protein C works on Factor V to slow down the clotting reaction, resistance to this causes increased risk of clotting.
- The majority of APC resistance is due to the Factor V Leiden mutation, which is a mutation in the gene that codes for Factor V.

Prothrombin Gene 20210A Mutation:

- The prothrombin G20210A mutation is an inherited defect of the gene for prothrombin. Prothrombin is a protein in the blood that helps clot to form. A person with this condition has high levels of prothrombin, which increases the risk of abnormal clot formation.

Hyperhomocysteinemia:

- Hyperhomocysteinemia refers to an acquired or inherited elevation of the level of the amino acid homocysteine. Amino acids are the building blocks that make up proteins in the body.
- Homocysteine is one of several types of amino acids. Acquired hyperhomocysteinemia can occur with certain medical conditions, such as kidney failure, hypothyroidism, folate deficiency or Vitamin B6 or B12 deficiency.
- Inherited hyperhomocysteinemia results from mutations in the genes coding for enzymes that break down homocysteine. These enzymes are methylene-tetrahydrofolate reductase (MTHFR), cystathione B sytnthase (CBS), or methionine synthase. Defects in these enzymes may or may not lead to hyperhomocysteinemia, depending on their severity. Hyperhomocysteinemia is associated with both artery and vein clotting problems.

POSSIBLE QUESTIONS

2 marks

1. Write a note on Amino acid metabolism?
2. What is Phenylalanine? Give the importance.
3. Give a note on PKU.
4. Write about ECG?
5. What is the representation of QT interval in ECG?
6. Write note on Blood clotting?
7. Importance of Hemoglobin?

6 marks

1. Discuss in detail about PKU?
2. Give an account on Cystic Fibrosis?
3. Explain the following,
    i) Alkaptonuria
    ii) Maple syrup urine disease
4. Explain about Long QT syndrome in detail.
5. Detailed note on hypercholesterolemia?
6. Describe about Achondroplasia?
7. Discuss about Hemoglobinopathies?

KARPAGAM ACADEMY OF HIGHER EDUCATION
DEPARTMENT OF BIOCHEMISTRY
III- B.Sc., BIOCHEMISTRY
MOLECULAR BASIS OF NON-INFECTIOUS HUMAN DISEASES 18BCU504-A
MULTIPLE CHOICE QUESTIONS

Enable | Enlighten | Enrich
KARPAGAM
ACADEMY OF HIGHER EDUCATION
(Deemed to be University)
(Established Under Section 3 of UGC Act, 1956)

Unit V

S.No	Questions	Option A	Option B	Option C	Option D	Answer
1	Histidine is degraded to α-ketoglutarate and is described as a	gluco amino acid	glucogenic amino acid	ketogenic amino acid	keto-gluco amino acid	glucogenic amino acid
2	Which of the following amino acids is considered as both ketogenic and glucogenic?	Valine	Tryptophan	Lysine	None of these	Tryptophan
3	A glucogenic amino acid is one which is degraded to	keto-sugars	either acetyl CoA or acetoacetyl CoA	pyruvate or citric acid cycle intermediates	none of the above	pyruvate or citric acid cycle intermediates
4	Which of the following is the best described glucogenic amino acid?	Lysine	Tryptophan	Valine	None of these	Valine
5	A person with phenylketonuria cannot convert	phenylalanine to tyrosine	phenylalanine to isoleucine	phenol into ketones	phenylalanine to lysine	phenylalanine to tyrosine
6	Oxidative deamination is the conversion of an amino	group from an amino acid to a keto acid	acid to a carboxylic acid plus ammonia	acid to a keto acid plus ammonia	group from an amino acid to a carboxylic acid	acid to a keto acid plus ammonia
7	An example of a transamination process is	glutamate = hexanoic acid + NH3	aspartate + hexanoic acid = glutamate + oxaloacetate	aspartate + α ketoglutarate = glutamate + oxaloacetate	glutamate = α-ketoglutarate + NH3	aspartate + α ketoglutarate = glutamate + oxaloacetate

8	Transamination is the process where	carboxyl group is transferred from amino acid		α-amino group is removed from the amino acid	polymerisation of amino acid takes place	α-amino group is removed from the amino acid
9	The most toxic compounds is	tyrosine	phenylpyruvate	lysine	phenylalanine	phenylpyruvate
10	A person with phenylketonuria is advised not to	Glycine containing	Fat containing food	Glucose	Aspartame	Aspartame
11	Tyrosine is degraded to acetoacetyl CoA and fumarate and is described as a	glucogenic amino acid	ketogenic amino acid	ketogenic and glucogenic amino acid	keto-gluco amino acid	ketogenic and glucogenic amino acid
12	Transaminase enzymes are present in	liver	pancreas	intestine	none of these	liver
13	A person with phenylketonuria will convert	phenylalanine to phenylpyruvate	phenylalanine to isoleucine	phenylpyruvate to phenylalanine		phenylalanine to phenylpyruvate
14	An example of the oxidative deamination is	glutamate = hexanoic acid + NH3	aspartate + α-ketoglutarate = glutamate + oxaloacetate	glutamate = α-ketoglutarate + NH3	aspartate + hexanoic acid = glutamate + Oxaloacetate	glutamate = α-ketoglutarate + NH3
15	In the normal breakdown of phenylalanine, it is initially degraded to	fumarate	tyrosine	lysine	phenylpuruvate	tyrosine
16	Transamination is the transfer of an amino	acid to a carboxylic acid plus ammonia	group from an amino acid to a keto acid	acid to a keto acid plus ammonia	group from an amino acid to a carboxylic acid	group from an amino acid to a keto acid
17	Lysine is degraded to acetoacetyl CoA and is described as a	ketogenic amino acid	glucogenic amino acid	keto-gluco amino acid	none of these	ketogenic amino acid
18	A ketogenic amino acid is one which degrades to	keto-sugars	either acetyl CoA or acetoacetyl CoA	pyruvate or citric acid cycle intermediates	multiple intermediates including pyruvate or citric acid cycle intermediates and acetyl CoA or acetoacetyl CoA	either acetyl CoA or acetoacetyl CoA
19	A person suffering from phenylketonuria on consumption food containing high phenylalanine may lead to the accumulation of	phenylalanine	phenylpyruvate	tyrosine	isoleucine	phenylpyruvate

20	The amino acid that undergoes oxidative deamination at a highest rate is-	Glutamine	Glutamate	Aspartate	Alanine	Glutamate
21	Hydroxylation of Phenyl Alanine to Tyrosine requires all except	Glutathione	Tetra hydrobiopterin	Molecular oxygen	NADPH	Glutathione
22	In mammalian tissue serine can be a biosynthetic precursor for which amino acid?	Methionine	Glycine	Arginine	**Lysine**	Glycine
23	Dopamine is synthesized from which of the following amino acids?	Tyrosine	Tryptophan	Histidine	Methionine	Tyrosine
24	A child was brought to paediatric OPD with complaint of passage of black colored urine. A disorder of Phenylalanine metabolism was diagnosed. A low phenylalanine diet and a supplementation of vitamin C were recommended. Which enzyme defect is expected in this child?	Phenyl alanine hydroxylase	Tyrosine transaminase	Homogentisic acid oxidase	Hydrolase	Homogentisic acid oxidase
25	Which out of the following statements about Glutamate dehydrogenase is correct?	Required for transamination reactions	Universally present in all the cells of the body	Can utilize either of NAD+/NADP+	Catalyzes conversion of glutamate to glutamine	Can utilize either of NAD+/NADP+
26	A child presented with increased frequency of urination, photophobia and impairment of vision. Which out of the following defects could be responsible for the said symptoms?	Tyrosinosis	Cystinosis	Alkaptonuria	Albinism	Cystinosis
33	The L-amino acids are absorbed from intestine by-	Active transport	Passive diffusion	Pinocytosis	Facilitated diffusion	Active transport
34	In a patient suffering from Cystinuria, which out of the following amino acids is not seen in urine of affected patients?	Arginine	**Methionine**	Lysine	Ornithine	**Methionine**
36	A child presented with increased frequency of urination, photophobia and impairment of vision. Which out of the following defects could be responsible for the said symptoms?	Tyrosinosis	Cystinosis	Alkaptonuria	Albinism	Cystinosis

37	A patient diagnosed with Homocystinuria should be supplemented with all of the following vitamins except-	Vitamin C	Folic acid	Vitamin B12	Pyridoxal- P	Vitamin C
39	The first line of defence in brain in conditions of hyperammonemia is-	Urea formation	Glutamine synthesis	Glutamate synthesis	Asparagine formation	Glutamine synthesis
40	The diet of a child suffering from Maple syrup urine disease (an amino acid disorder), should be low, in which out of the following amino acids content?	Branched chain amino acids	Phenylalanine Alanine	Methionine	Tryptophan	Branched chain amino acids
41	The synthesis of all of the following compounds except one is deficient in a patient suffering from Phenylketonuria-	Melanin	Melatonin	Catecholamines	Thyroid hormone	Melatonin
42	Which of the following statements about haemoglobin is correct?	2,3-Bisphosphoglycerate (BPG) increases the affinity of haemoglobin for oxygen.	Deoxygenated haemoglobin has a higher binding affinity for protons than has oxyhaemoglobin.	Haemoglobin has a higher affinity for oxygen than does myoglobin.	One molecule of haemoglobin binds sixteen molecules of oxygen - four per subunit	Deoxygenated haemoglobin has a higher binding affinity for protons than has oxyhaemoglobin.
43	Which of the following amino acids is mostly likely to disrupt an alpha helix?	Proline.	Leucine.	Glycine.	Valine.	Proline.
44	As haemoglobin binds oxygen molecules, its affinity for oxygen increases, driving the binding of further oxygen molecules. Which term best describes this phenomenon?	Catalysis.	Saturation.	Allostery.	Isomerism.	Allostery.
45	Which of the following statements correctly describes the behaviour of the haemoglobin protein in sickle-cell disease?	The haemoglobin protein dissociates into four subunits.	The haemoglobin protein lacks a haem group	Neighbouring haemoglobin proteins aggregate together.	The haemoglobin protein possesses an iron atom in the Fe (III) form rather than the normal Fe (II) form.	Neighbouring haemoglobin proteins aggregate together.

46	In the deoxygenated state, the mutation in sickle hemoglobin primarily affects which of the following interactions?	Hemoglobin tetramer to Hemoglobin tetramer	Heme ring to hemoglobin	E. Erythrocyte to erythrocyte	α globin to β globin	Hemoglobin tetramer to Hemoglobin tetramer
47	Hemoglobin E is best described as which of the following:	A. Thalassemia found in Southeast Asia	B. Thalassemia found in Mediterranean regions	E. Thalassemic hemoglobinopathy	D. Hemoglobinopathy found in Mediterranean regions	E. Thalassemic hemoglobinopathy
48	Compared to normal erythrocytes, spherocytes have:	Increased osmotic fragility at all saline concentrations	Increased osmotic fragility at 0.5% saline	Decreased osmotic fragility at 0.9% saline	Increased levels of 2,3 DPG	Increased osmotic fragility at 0.5% saline
49	9. Normal adult hemoglobin (□ 2 □ 2) has a decreased affinity for oxygen in which of the following settings?	Carbon monoxide intoxication	Exposure to sulfa drugs	Increased 2,3 DPG	Methemoglobinemia	Increased 2,3 DPG
50	hemoglobin oxygen dissociation curve is between percent saturation of Hb and	pH	tissue PO2	alveolar PO2	tissue CO2	tissue PO2
53	mutations altering the amino acid sequence of globin chain leads to which type of hemoglobinopathies	structural hemoglobinopathies	thallessemia syndromes	HPFH	acquired hemoglobinopathies	structural hemoglobinopathies
54	mutations impairing production or translation of globin mRNA leads to which type of hemoglobinopathies	structural hemoglobinopathies	thallessemia syndromes	HPFH	acquired hemoglobinopathies	thallessemia syndromes
55	useful in the treatment of sickle cell disease	angarlide	danazol	IFN-alpha	hydroxyurea	hydroxyurea
56	muddy appearance of freshly drawn blood is characteristic of	sickle cell anemia	methemoglobinemia	thalassemia	all of the above	methemoglobinemia
57	Which of the following statements about the ECG are true?	The P wave of the ECG reflects atrial contraction	The P-Q interval is normally about 0.1 s	The QRS complex reflects the start of ventricular depolarization.	The T-wave reflects the repolarization of the ventricular fibres.	B,C,D
58	Which of the following might be a reason for a patient to refuse an ECG?	Fear or concern about the procedure	The wires from the machine may shock the patient	Patients are fearful or feel they lack privacy	All of the above	All of the above

59	Which of the following best describes the ICS?	Center of the clavicle	The space between two ribs	Suprasternal notch	None of the above	The space between two ribs
60	ECG used to Diagnostic for?	Circulation	Structure	Conduction	respiration	Conduction

Reg. No. :

KARPAGAM ACADEMY OF HIGHER EDUCATION
COIMBATORE – 21
DEPARTMENT OF BIOCHEMISTRY
III B.Sc., BIOCHEMISTRY
Fifth Semester
I Internal test-Jul'2018
MOLECULAR BASIS OF NONINFECTIOUS DISEASE [16BCU504A]

Time: 2 hours **Maximum: 50 marks**
Date / Session:

PART-A
Multiple Choice Questions **20 x 1 = 20 marks**

1 Alexander Fleming discovered the _____ from *Penicillium notatum*
A. Lysozyme B. Phenol
C. Penicillin D. Protein

2. Who is the father of microbiology?
A. Robert Hooke B. Anton von Leeuwenhoek
C. Joseph Lister D. Robert Koch

3. Biogenesis means
A. Living things arise from water B. Living things arise from air
C. Living things arise from soil D. Living things arise from living matter

4. Fermentation is caused by
A. Insects B. Worms
C. Microbes D. Rats

5. Robert Hoch postulates "the pathogen can be isolated from a _____and grown in pure culture"
A. Diseased host B. Healthy host
C. Sterile nail D. Sterile hair

6. Pasteurization temperature of milk is
A. between 20 and 50 °C B. between 40 and 60 °C
C. between 100 and 110 °C D. between 60 and 100 °C

7. *Bacillus anthracis* causes
A. Cholera B. Anthrax
C. Diarrhoea D. Tuberculosis

8. Five kingdom classification was proposed by
A. Whittaker B. Louis Pasteur
C. Carl Woese D. Carl Linnaeus

9. A _____ is a unicellular organism that lacks a membrane-bound nucleus
A. Eukaryotic microbes B. Prokaryotic microbes
C. Plant D. Animal

10. Which is not included in binomial nomenclature?
A. Species B. Genus
C. Order D. Colonies

11. Germ theory of disease is proposed by
A. Robert Koch B. Louis Pasteur
C. Alexander Fleming D. Elie Metchnikoff

12. Autoclave is required for
A. Cleaning B. Inoculation of microbes
C. Incubation of microbes D. Sterilization

13. Immunology is a study of
A. Respiratory system B. Digestive system
C. Immune system D. Viruses

14. Edward Jenner discovered the vaccine for
A. Smallpox B. Cholera
C. Diarrhoea D. Anthrax

15. Microorganisms arise from lifeless matter such as beef broth is called
A. Biogenesis B. Spontaneous generation
C. Organogenesis D. Direct regeneration

16. _____ is a surface sterilization chemical
A. Hydrochloric acid B. Glutaraldehyde
C. Nitric acid D. 70% alcohol

17. Nutrient agar medium is favourable for
A. Algae B. Viruses
C. Bacteria D. Fungi

18. The smallest unit of binomial nomenclature is
A. Genus B. Family
C. Order D. Species

19. Paul Ehrlich contributed to
A. Plant pathology B. Immunology
C. Genetics D. Bacteriology

20. What is CFU
A. Count of Fungal Unit B. Culture Forming Unit
C. Colony Forming Unit D. Calculation of Fungal Unit

Part B
Answer all the questions **3x2 = 6 marks**

21. Add short note on Kwashiokar
22. Explain the basic defect in tetany
23. Explain the significance of balanced diet

Part C
Answer all the questions **3x8 = 24 marks**

24. a. Explain the Xerophthalmia and night blindness
Or
b. Give a detail note on vitamin defeciencies

25. a. Describe the basic defect and consequences of diabetes mellitus
Or
b. Explain the pathophysiology of hypothyroidism

26. a. What is RDA? Explain its significance in disease management
Or
b. Discuss in detail on eating disorders

****

Molecular Basis of Non- Infectious Diseases

III-rd Year Biochemistry- First Internal Examination

Part-A

Multiple Choice Questions (20×1= 20 marks)

1. Penicilin

2. Antonie Van Leeuwenhoek

3. Living things arise from living matter

4. Microbes

5. Diseased host

6. Between 60 and 100 ^{o} C

7. Anthrax

8. Whittaker

9. Prokaryotic microbes

10. Colonies

11. Louis pasture

12. Sterilization

13. Immune system

14. Small box

15. Spontaneous generation

16. b. Gluteraldehyde or d. 70% alcohol

17. Bacteria

18. Species

19. Immunology

20. Colony forming unit

Part- B

(20×1= 20 marks)

21. Add a short note on Kwashiorkor

- Kwashiorkor is a kind of malnutrition that is most often found in children. It is primarily caused due to insufficient intake of proteins.
- However, it do not have any relation with the amount of calories intake i.e. may be a person is having a high calorie food but specifically less proteins then in that case the person is prone to Kwashiorkor.
- It stunts growth and children tend to have bloated bellies and thin arms and legs. Kwashiorkor is also known by names like protein malnutrition, protein-calorie malnutrition or malignant malnutrition.

22. Explain the basic defect in tetany

- Tetany can be the result of an electrolyte imbalance. Most often, it's a dramatically low calciumlevel, also known as hypocalcemia.

- Tetany can also be caused by magnesium deficiency or too little potassium. Having too much acid (acidosis) or too much alkali (alkalosis) in the body can also result in tetany.

- Overly stimulated nerves cause involuntary muscle cramps and contractions, most often in the hands and feet. But these spasms can extend throughout the body, and even into the larynx, or voice box, causing breathing problems.

23. Explain the significance of balanced diet

- A balanced diet is one that gives your body the nutrients it needs to function correctly. To get the proper nutrition from your diet, you should consume the majority of your daily calories in: fresh fruits. fresh vegetables. whole grains.

Part- C

24.a). Explain the Xerophthalmia and night blindness

Xerophthalmia:

- The term "xerophthalmia" refers to the spectrum of ocular manifestations due to vitamin A deficiency.
- Such signs include those involving impaired sensitivity of the retina to light (night blindness), and (in order of their appearance and severity) epithelial disruptions of the cornea and conjunctiva, such as conjunctival xerosis, Bitot spots, corneal xerosis and keratomalacia .
- These ocular symptoms are related to vitamin A deficiency and vary according to the severity of the deficiency, and age.
- Xerophthalmia can occur in any age group and especially in preschool-age children, adolescents and pregnant women.
- However, children are at higher risk of vitamin A deficiency and xerophthalmia, owing to their greater vitamin A requirements for growth.
- Children are also at higher risk of intestinal infestations and infections, which may impair the absorption of vitamin A and increase its loss.
- A peak in the incidence of night blindness is generally observed between 3 and 6 years of age. However, as it is difficult to assess night blindness in infants and young children who have not yet begun to crawl or walk, its presence may not always be recognized, and therefore it may be erroneously perceived that night blindness is not a problem. Affected children often exhibit limited.

Classification of xerophthalmia by ocular signs:

- Night blindness (XN)
- Conjunctival xerosis (X1A)
- Bitot spots (X1B)
- Corneal xerosis (X2)
- Corneal ulceration/keratomalacia <⅓ corneal surface (X3A)
- Corneal ulceration/keratomalacia ≥⅓ corneal surface (X3B)
- Corneal scar (XS)
- Xerophthalmic fundus (XF)

Night blindness:

- Night blindness, a condition in which a person cannot see in dim light, is generally the earliest clinical manifestation of vitamin A deficiency and is both a sensitive and a specific indicator for low serum retinol levels.
- Within the eye, vitamin A, in the form of retinal, combines with opsin to produce rhodopsin, the photosensitive visual pigment of rods.
- Vitamin A deficiency leads to a decline in rhodopsin levels and impaired rod function, manifested as night blindness.

- In mild cases, night blindness is often only first noticeable following photopic stress from sudden exposure to bright light, and results in an increased turnover of rhodopsin.
- Historically, the most characteristic sign of ocular problems related to vitamin A deficiency has been Bitot spots – opaque whitish deposits on the scleral conjunctiva.
- At this point, conjunctival xerosis is already present, with the conjunctiva appearing dry and dull. Spots of keratinized epithelial cells with the appearance of foam are also present.
- If vitamin A deficiency continues, corneal xerosis may set in, with the appearance of a hazy cornea, followed by keratomalacia where there is liquefaction of part or all of the cornea.
- Corneal scars are not considered to be part of active vitamin A deficiency, but are considered a result of a previous bout of the deficiency.
- With prolonged vitamin A deficiency, there is an increase in morbidity and mortality from common infections, and blindness can occur.
-

24. b). Give a detail note on vitamin deficiencies

i).Scurvy

- Scurvy is a condition 4haracterized by general weakness, anaemia, gingivitis (gum disease), and skin haemorrhages caused by a prolonged deficiency of vitamin C (ascorbic acid) in the diet.
- Vitamin C plays a crucial role in the formation of collagen, a major component of connective tissue. Connective tissue has structural and supportive functions which are indispensable to blood vesselsand all tissues within the body.
- Vitamin C is also important in the proper functioning of the immune system, iron absorption, cholesterol metabolism and other biological activities. Thus scurvy has widespread effects.
- Scurvy was often seen in sailors on long ocean voyages described from the 15th century onwards. Many men died from the disease until it was discovered that scurvy could be effectively cured and prevented by consuming vitamin C through lemons, oranges and limes.
- It is thought that scurvy occurs very rarely in modern societies of today as most people have access to year-round fresh fruits and vegetables which are rich sources of vitamin C. However, several groups of people are at risk. These include:

ii). Beri-Beri

- Beriberi is a disease caused by a vitamin B-1 deficiency, also known as thiamine deficiency. There are two types of the disease: wet beriberi and dry beriberi. Wet beriberi affects the heart and circulatory system.

- In extreme cases, wet beriberi can cause heart failure. Dry beriberi damages the nerves and can lead to decreased muscle strength and eventually, muscle paralysis. Beriberi can be life-threatening if it isn't treated.

- In extreme cases, beriberi is associated with Wernicke-Korsakoff syndrome. Wernicke encephalopathy and Korsakoff syndrome are two forms of brain damage caused by thiamine deficiency.

iii). Pellagra

- Pellagra is a disease characterized by diarrhea, dermatitis and dementia. If left untreated, death is the usual outcome. It occurs as a result of niacin (vitamin B-3) deficiency.
- Niacin is required for most cellular processes. Since tryptophan in the diet can be converted to niacin in the body, both of these need to be deficient for pellagra to develop.

Causes of pellagra:

- Pellagra is caused by a deficiency in niacin. This can occur in 2 ways:
- Primary pellagra results from inadequate niacin and/or tryptophan in the diet (mainly in developing countries or poverty stricken areas)
- Secondary pellagra occurs when there is enough niacin in the diet but something prevents its absorption and processing.

iv). Vitamin B12 defeciency

- The Vitamin B12 deficiency results in not having enough of vitamins in the daily diet. It is important to have B12 in the diet as it helps in forming red blood cells which carry oxygen across the body.
- Improper B12 will not permit red blood cells to perform their function and results in tired and weakness. This deficiency can even affect the nerves and power of a brain.

Pernicious Anemia – In these conditions, the body starts destroying the stomach cells which is associated with the absorption vitamin B12.

25.a). Describe the basic defect and consequences of diabetes mellitus.

A chronic disease due primarily to a disorder of carbohydrate metabolism, **cause of which is deficiency or diminished effectiveness of insulin,** resulting in hyperglycaemia and glycosuria. Secondary changes may occur in the metabolism of proteins, fats, water and electrolytes and in tissues/organs sometimes with grave consequences.

CLINICAL TYPES AND CAUSES

These are **two main groups:**

(a) Primary (Idiopathic): constitute major group. Exact cause is not known; metabolic defect is insufficient insulin which may be absolute or relative. Two clinical types:

- **"Juvenile"-onset diabetes:** Now called as **Type-I-** (Insulin dependent)— **IDDM.**
- **"Maturity" onset diabetes: Type-II NIDDM**— (Non- Insulin Dependent). Differences between the two clinical types are listed in a box in next page.

(b) Secondary: constitute minor group where it can be secondary to some disease process.

Other Factors

1. Heredity: In both types, familial tendency noted. Genetic factors more important in those who develop after 40. In younger, "Juvenile" type, susceptibility is associated with particular HLA phenotype. RISK is two to three times more in those who are HLA phenotype B8 or BW15.

2. Autoimmunity: Insulin-dependent juvenile type may be an autoimmune disorder and has been found to co-exist with other autoimmune disorders. Evidences in favour of autoimmunity:

- Lymphocytic and plasma cells infiltrations in pancreas
- Detection of autoantibodies by immunofluorescence.

3. Infections: Certain viral infections may precipitate Juvenile type. Experimentally it has been shown that certain viruses can induce diabetes. Incidence is high after mumps. Antibodies to coxsackie B4 virus have been found in young Juvenile type.

4. Obesity: Majority of middle aged maturity-onset diabetics are obese, "stress" like pregnancy may precipitate.

5. Diet: Over-eating and **under activity** are also predisposing factors in elderly middle aged maturity onset diabetes.

6. Insulin antagonism: In "maturity onset" diabetes, the deficiency of insulin is relative and glucose induced insulin secretion may be greater and more prolonged than normal. This relative deficiency may be due to insulin antagonism, exact cause for the same is not known but various factors have been incriminated from time to time. They are:

- Synalbumin of Vallence-Owen in plasma, dialyzable, thermostable substance.
- β1-lipoprotein factor: Another similar factor found in β1-lipoprotein fraction of plasma in diabetics.
- Insulin "antibodies".
- Secretion of abnormal and less active insulin or 'altered' insulin.
- A "tissue barrier" to the transport of insulin to the cells, probably "receptor" deficiency.
- Lack of cellular response to insulin.

(b) Secondary: This forms a minor group. Diabetes is secondary to some other diseases.

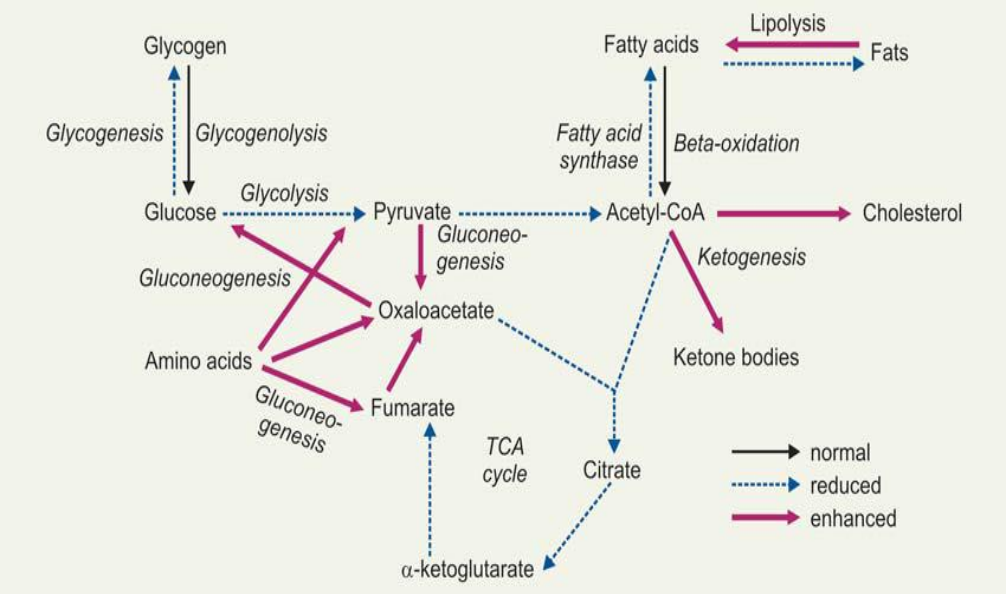
1. **Pancreatic diabetes:**

- Pancreatitis
- Haemochromatosis
- Malignancy of Pancreas.

2. Abnormal concentrations of antagonistic hormones:

- Hyperthyroidism
- Hypercorticism: like Cushing's disease and syndrome.
- Hyperpituitarism: Like acromegaly
- Increased glucagon activity.

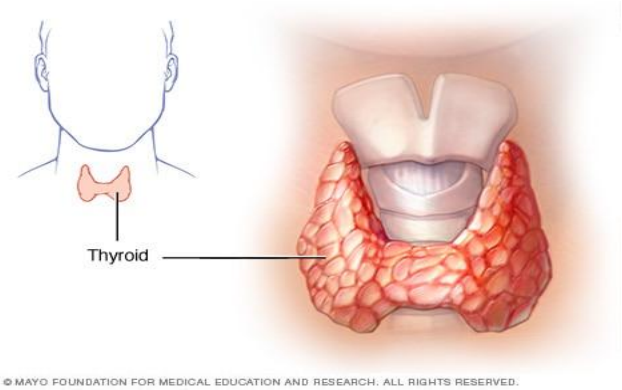
3. Iatrogenic: In genetically susceptibles, may be precipitated By herapy like corticosteroids, thiazide diuretics.



25.b). Explain the pathophysiology of hypothyroidism

Hypothyroidism (underactive thyroid) is a condition in which your thyroid gland doesn't produce enough of certain important hormones.

Women, especially those older than age 60, are more likely to have hypothyroidism. Hypothyroidism upsets the normal balance of chemical reactions in your body. It seldom causes symptoms in the early stages, but over time, untreated hypothyroidism can cause a number of health problems, such as obesity, joint pain, infertility and heart disease.



Symptoms

The signs and symptoms of hypothyroidism vary, depending on the severity of the hormone deficiency. But in general, any problems you have tend to develop slowly, often over a number of years.

At first, you may barely notice the symptoms of hypothyroidism, such as fatigue and weight gain, or you may simply attribute them to getting older. But as your metabolism continues to

slow, you may develop more-obvious signs and symptoms. Hypothyroidism signs and symptoms may include:

- Fatigue
- Increased sensitivity to cold
- Constipation
- Dry skin
- Weight gain
- Muscle weakness
- Elevated blood cholesterol level
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Heavier than normal or irregular menstrual periods

When hypothyroidism isn't treated, signs and symptoms can gradually become more severe. Constant stimulation of your thyroid gland to release more hormones may lead to an enlarged thyroid (goiter). In addition, you may become more forgetful, your thought processes may slow, or you may feel depressed.

Advanced hypothyroidism, known as myxedema, is rare, but when it occurs it can be life-threatening. Signs and symptoms include low blood pressure, decreased breathing, decreased body temperature, unresponsiveness and even coma. In extreme cases, myxedema can be fatal.

Hypothyroidism in children and teens

In general, children and teens who develop hypothyroidism have the same signs and symptoms as adults do, but they may also experience:

- Poor growth, resulting in short stature
- Delayed development of permanent teeth
- Delayed puberty
- Poor mental development

Hypothyroidism results when the thyroid gland fails to produce enough hormones. Hypothyroidism may be due to a number of factors, including:

- **Autoimmune disease.** People who develop a particular inflammatory disorder known as Hashimoto's thyroiditis have the most common cause of hypothyroidism. Autoimmune disorders occur when your immune system produces antibodies that attack your own tissues.

Sometimes this process involves your thyroid gland. Scientists aren't sure why the body produces antibodies against itself. Some think a virus or bacterium might trigger the response, while others believe a genetic flaw may be involved. Most likely, autoimmune diseases result from more than one factor. But however it happens, these antibodies affect the thyroid's ability to produce hormones.

- **Treatment for hyperthyroidism.** People who produce too much thyroid hormone (hyperthyroidism) are often treated with radioactive iodine or anti-thyroid medications to reduce and normalize their thyroid function. However, in some cases, treatment of hyperthyroidism can result in permanent hypothyroidism.
- **Thyroid surgery.** Removing all or a large portion of your thyroid gland can diminish or halt hormone production. In that case, you'll need to take thyroid hormone for life.
- **Radiation therapy.** Radiation used to treat cancers of the head and neck can affect your thyroid gland and may lead to hypothyroidism.

26.a). What is RDA? Explain its significance in disease management

- The Recommended Dietary Allowances (RDAs) are quantities of nutrients in the diet that are required to maintain goodhealth in people.
- RDAs are established by the Food and Nutrition Board of the National Academy of Scien ces, and maybe revised every few years.
- A separate RDA value exists for each nutrient. The RDA values refer to the amount ofnut rient expected to maintain good health in people. The actual amounts of each nutrient req uired to maintain good healthin specific individuals differ from person to person.

The "recommended daily allowance" (RDA) value for proteins is given below

Category	*Age in years*	*Protein in gm*
• Men	18–35	70
	35–55	70
	55–75	70
• Women	18–35	58
	35–55	58
	55–75	58
• Pregnancy (2nd and 3rd trimesters)	—	+ 20
• Lactation	—	+ 40
• Infants	—	kg × 2.5 ± 0.5
• Children	1 to 3	32
	3 to 6	40
	6 to 9	52
• Boys	9 to 12	60
	12 to 15	75
	15 to 18	85
• Girls	9 to 12	55
	12 to 15	62
	15 to 18	58

26.a). Discuss in detail on eating disorders

- Anorexia nervosa and bulimia are common syndromes characterized by bizarre eating patterns which become the central focus of the patient's life.
- Occurring primarily in young women, they represent life-disrupting illnesses for the afflicted and their families and lead to death in a small but significant number of cases.
- Although the clinical manifestations and outcome of the two syndromes are distinctive, overlap features suggest that the root disorder is the same: an obsessive fear of being fat.
- In anorexic patients the primary reactive mechanism is the rigid restriction of food intake; with bulimia, loss of control in the drive to eat is compensated for by induced vomiting and laxative use.

Anorexia nervosa:

- Patients are not free of hunger; rather, they are obsessed with the fear of being fat such that hunger sensations are ignored or denied. An intense preoccupation with food is usually discernible.
- Although anorexic patients drastically restrict their own food intake, it is not unusual for them to enjoy preparing elaborate meals for others, collect recipes and hoard food in the home.
- Most subjects appear knowledgeable on nutritional matters, particularly the caloric content of food, although up to 25% may show lesser insight than matched controls.
- It is usually stated that carbohydrates are avoided preferentially, but carbohydrate intake was found to be normal.
- Fat intake was decreased and protein content was high. In order to assist weight loss it is common for patients to exercise excessively, often in ritualistic fashion.
- A significant percentage induces vomiting and use laxatives. or diuretics. Periodic gorging of the type seen in the bulimic variant/phase of the disease may also occur in classic anorexia nervosa.

Symptoms:

- Amenorrhea, primary or secondary, in almost 100% of patients
- Constipation often with complaints of abdominal pain
- Cold intolerance
- Agitation or lethargy
- Emesis

Bulimia:

- The term bulimia literally means "ox-hunger" or a voracious appetite. It has come to stand for a syndrome of astonishing food intake over short periods of time in young women who usually have a previous or present picture of anorexia nervosa.
- The gorging is then followed by induced vomiting and often by the use of laxatives in large amounts.
- Two fundamental features characterize the syndrome:

  (1) an irresistible urge to overeat

  (2) a marked fear of becoming fat.

- The former predominates in this form of the illness but there are other features than distinguish it from classic anorexia nervosa.
- In simple terms patients with non-bulimic anorexia nervosa deal with the fear of being fat by restricting food intake ("restrictors").
- Their phobia of being fat appears to be so powerful that control over eating is not lost. Bulimic patients, on the other hand, lose control and thus become "gorgers," controlling weight gain only by vomiting and use of laxatives.

Symptoms:

- In contrast to classic anorexia nervosa amenorrhea was present in only 11 of 28 subjects when cessation of menses was not used as part of the selection criteria.
- This is likely due to the fact that weight loss was less severe in the bulimic group.
- The other major complaint, often spontaneously voiced, is of depression.
- In view of the recurrent vomiting with hypokalemia one would expect complaints of weakness to be frequent, but this was not obvious in the cited series.
- Convulsions and tetany have been reported but are rare.

Treatment and outcome:

- There is no specific treatment for anorexia although multiple approaches have been tried, many of them controversial.
- A partial list includes: insulin, thyroid hormone, gonadotropins, antidepressants, antipsychotics, tranquilizers, electroconvulsive therapy, appetite stimulants and leucotomy. From a psychologic and psychiatric standpoint, behavior modificati on, individual psychotherapy and relationship therapy have been tried, singly and in combination.

Reg. No. _____

KARPAGAM ACADEMY OF HIGHER EDUCATION

DEEMED UNIVERSITY

COIMBATORE – 21

DEPARTMENT OF BIOCHEMISTRY

III B.Sc., BIOCHEMISTRY

Fifth Semester

Second Internal Examination –September 2018

MOLECULAR BASIS OF NON- INFECTIOUS HUMAN DISEASE (16BCU504-A)

Date : 11.09.2018 [AN]

Time: 2 hours Maximum: 50 marks

PART A (20x1=20 marks)

Answer ALL the questions

1. The medical term for chest pain is _____.
   a) Angina b) Flutter c) Hypertropy d) Arrhythmia
2. What is a myocardial infarction?
   a) Heart failure b) Heart Attack c) Stroke d) All the above
3. When do coronary arteries primarily receive blood flow?
   a) During inspiration b) During diastole c) During expiration d) During systole
4. What is the term used to describe an enlargement of the heart muscle?
   a) Cardiomegaly b) Cardiomyopathy c) Myocarditis d) Pericarditis
5. All veins in body carry deoxygenated blood except
   a) aorta b) inferior venacava c) superior venacava d) pulmonary vein
6. In the heart, a clogged artery causes a heart attack. In the brain it causes a
   a) migraine b) mental illness c) Stroke d) Seizure
7. Which of the following conditions most commonly results in CAD?
   a) Atherosclerosis b) DM
   c) Myocardial infection d) Renal failure
8. A condition called irritable bowel syndrome occurs in
   a) Rectum b) colon c) Small intestin d) stomach
9. Which property of p53 enables it to prevent the development of cancer?
   a) p53 is a transcription factor that causes production of proteins that stimulate the cell cycle.
   b) p53 prevents the replication of cells with damaged DNA.
   c) p53 prevents cells from triggering apoptosis.
   d) p53 stimulates synthesis of DNA repair enzymes that replace telomere sequence lost during cell division.
10. Ordinarily, cells with damaged DNA undergo _____ or programmed cell death.
    a) apoptosis b) tumor-suppression
    c) differentiation d) angiogenesis
11. The genes capable of causing cancer are known as
    a) Tumor-suppressor genes b) Oncogenes
    c) Proto- oncogenes d) Carcinogen
12. Cancer arises from epithelial cells known as
    a) Blastoma b) Sarcoma c) Carcinoma d) Melanoma
13. Example of intercalating agent is
    a) Aflotoxin b) Benzene c) EtBr d) Azo dyes
14. Malignant cells have specific property rather than benign cells
    a)Spreading b) Round shape c) abnormal cell division d) loss of apoptosis
15. CDK and Cyclins involve in the process called
    a) Necrosis b) Apoptosis c) Call cycle d) Translation
16. Spread of cancer cells from the primary site of origin to other tissues is known as
    a) Apoptosis b) Metastasis c) Cytokinesis d) Angiogenesis
17. A single nucleotide inserted into the DNA sequence is known as
    a) Insertion Mutation b) Deletion Mutation
    c) Frame shift Mutation d) Nonsense Mutation
18. Apoptosis process induced by
    a) P ten b) RAS c) p 53 d) Tyrosine kinase
19. Cancer cells produce growth factors that stimulate their own proliferation is called
    a) Paracrine b) Autocrine c) Tumor progression d) Contact inhibition
20. Cecum is a part which is present in
    a) Rectum b) colon c) lungs d)Small intestine

PART B **(3x2=6 marks)**

Answer ALL the questions

21. Explain the following, i) Heart Attack ii) Heart Failure

22. Difference between Benign and Malignant

23. Write note on p 53 gene.

PART C **(3x8=24 marks)**

Answer ALL the questions

24. a) Give an account on Coronary Artery Disease.

or

b) Explain the mechanism of heart failure occurs in both sides of heart.

25. a)Discuss about Irritable Bowel syndrome.

or

b) Describe about etiology of cancer?

26. a) Explain in detail about Oncogenes and proto- oncogenes.

or

b) Detailed note on tumor suppressor gene and its importance.

****

Class : III . B.Sc. Biochemistry

Sub : Molecular Basis of Infec-
human Disease

Sub Code : 16BCU504-A

No. of. copies : (60)