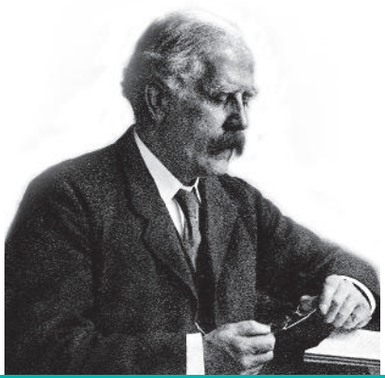
UNIT 7

INBORN ERRORS OF METABOLISM



Sir Archibald Garrod

Sir Archibald Garrod, an English physician, introduced the term "Inborn Errors of Metabolism" in 1908. He postulated that inherited disorders result from reduced activity or complete absence of an enzymes involved in biochemical pathways, causing a block in the metabolic pathway. His study of alkaptonuria led to the finding that a mutation in a gene resulted in the accumulation of homogentisic acid and the presence of black urine on exposure to air. Following this, in 1941, George Beadle and Edward Tatum, using the bread mould *Neurospora,* confirmed Garrod's hypothesis and proposed the 'One gene one enzyme' theory. This hypothesis was further modified in 1957 by Vernom Ingram, as 'One gene one polypeptide' since many proteins are made up of more than one polypeptide chain.

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Learning Objectives

After studying this unit you will be able to understand the following:

- Biochemical basis of Inborn errors of metabolism
- Types of inborn errors of metabolism
- Causes and symptoms of Galactosemia
- Causative factors of Von Gierke disease
- Various types of haemophilia and clotting factors
- Ocular and oculo-cutaneous albinism
- Causes and symptoms of Alkaptonuria
- Causative factors of Tay – Sachs disease.

INTRODUCTION

Inborn errors of metabolism (IEM) or inherited metabolic disorders are a group of disorders with specific enzyme defects that impede with normal metabolism of protein, fat or carbohydrate. As its name implies, inborn errors mean birthdefects in young infants which are inherited. IEM like galactosemia, phenylketonuria, alkaptonuria, albinism, Tay -Sachs disease and von Gierke disease, can appear atbirth or later in life .

A food product that is not broken down into energy can build up in the body and cause a wide range of symptoms. Several inborn errors of metabolism cause developmental delays or other medical problems if they are not controlled. The main indication of IEM is an excess storage or accumulation of specific metabolites in tissues, organs and blood which further manifest to health diseases. Most IEM are rare but some are life threatening.

The metabolism of our body comprises two major balanced activities: anabolism (synthesis) and catabolism (degradation). The absence or deficiency of an enzyme will cause an abnormal accumulation of the intermediate products of metabolism in the body and increased excretion in urine as such, or, as their degradation products. Some of the intermediates could even be toxic. For example, in the following reaction

$$R \xrightarrow{a} B \xrightarrow{b} C \xrightarrow{c} D \xrightarrow{d} P$$

- R is the reactant,
- B, C and D are intermediates, P is the product
- a, b, c and d are enzymes catalyzing the indicated steps of the reactions.
- In this pathway, if any enzyme is deficient or absent, the previous intermediate accumulates and produces toxicity. It also affects the amount of product (P) formed and thereby leads to a disease.

The classification of IEM is presented in the following table

A few important diseases associated with IEM are given below:

Disorders	Examples
Disorders of aminoacid metabolism	Phenylketonuria, Alkaptonuria, Albinism Homocysteinuria
Disorders of carbohydrate metabolism	Galactosemia, hereditary fructose intolerance, Glycogen storage disorders (Von Gierke disease)
Lysosomal storage disorders	Mucopolysaccharidosis, Tay-Sachs disease, Niemann-Pick disease, Gaucher's disease
Organic acidemia	Methyl malonic acidemia

Disorders of purine or pyrimidine metabolism	Lesch–Nyhan syndrome
Transport disorders	Cystinuria Hypercholesterolemia
Peroxisomal disorders	Adrenoleukodystrophy
Urea cycle disorders	Citrullinemia, Ornithine transcarbomylase deficiency
Metal metabolic disorders	Wilson's disease

7.1 GALACTOSEMIA

Galactosemia, first described in 1908 by Von Reuss, is a genetic disease, characterized by the inability to process galactose, which is found in many foods. galactosemia implies 'galactose in the blood'. Galactose, a sugar byproduct of lactose, is present in cow's milk, breast milk and dairy products. As a result, if not treated , it builds up in the tissues and blood causing life threatening problems. The incidence of this disease is about 1 in 18,000 livebirths.

7.1.1 Causes

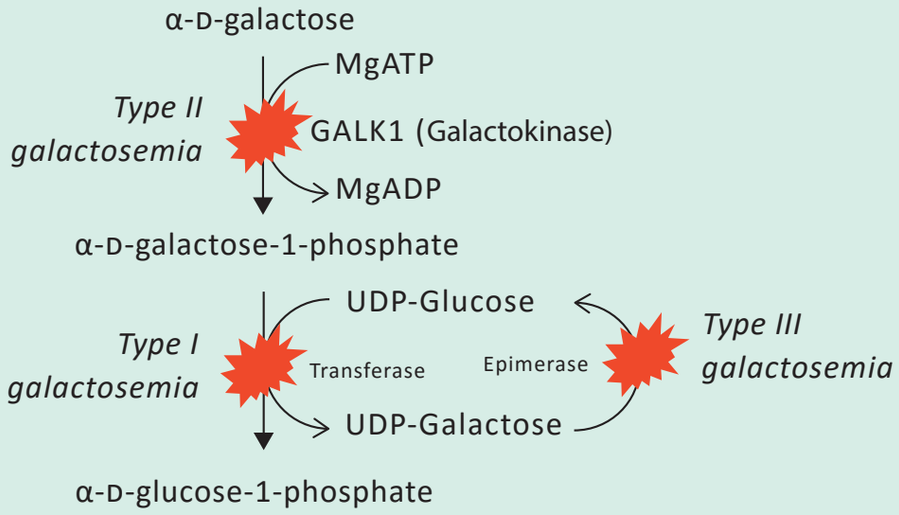

Figure 7.1 Pathways of Galactose metabolism

Galactosemia occurs when a specific enzyme known as galactose-1-phosphate uridyltransferase (GALT) is absent. This enzyme present in liver is responsible for breaking down galactose into glucose. In normal subjects, GALT binds to galactose, and converts it into glucose. However, in galasctosemia, due to the absence of GALT, galactose-1-

phosphate, is not converted to glucose 1 phosphate and accumulates in tissues and blood. The toxic galactose levels lead to enlarged liver, kidney failure and cataract.

The pathway of galactose metabolism is shown in figure 7.1.

Three types of galactosemia are known which are caused by mutations in GALT, GALK1 (galactokinase) and GALE (UDP-galactose 4′-epimerase) genes. However, GALT deficiency is the most severe and life threatening form of the disease (Figure.7.2).

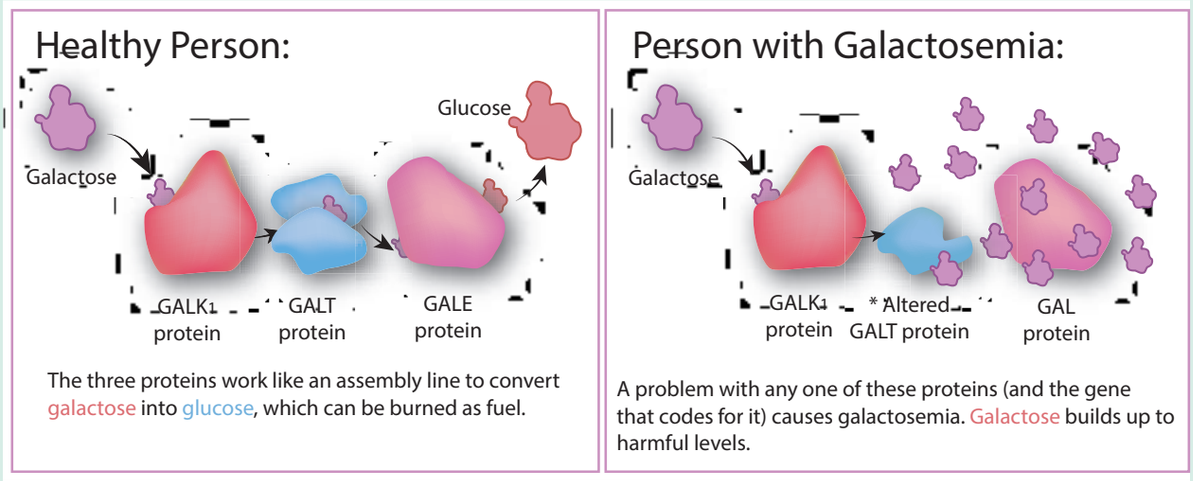

Figure.7.2 HealthyVs Galactosemia subjects

7.1.2 Symptoms

The deficiency of GALT is clinically important. Due to the enzyme defect, galactose accumulates in blood and is reduced by aldose reductase in the eye to the corresponding galactitol which causes cataract. The general condition is more severe, since, due to a deficiency in GALT, galactose 1- phosphate accumulates and injures the liver leading to its failure. Mental deterioration is caused due to accumulation of direct bilurubin, as it moves from blood to brain .

If an infant is breast feeding, but still experiences poor weight gain, it may due to galactosemia. Infants appear normal at birth but later they show failure to thrive and become lethargic. They have frequent vomiting and hypoglycemia. After 2 - 3 months of age, the liver may show fatty infiltration and lead to cirrhosis (nonfunctioning of liver cells). Galactosemia at this age is associated with mental retardation due to accumulation of galactose and galactose 1 - phosphate in cerebral cortex. Other symptoms include, jaundice, vomiting, hepatomegaly, *E.coli* sepsis and irritability.

7.2 VON GIERKE DISEASE

Glycogen storage diseases are a group of inherited disorders associated with glycogen metabolism. Von Gierke disease, also known as glycogen storage disease(GSD) type I, is one of the groups of rare genetic disorders due to the defect in one or more of the enzymes involved in glycogen metabolism leading to excessive accumulation of glycogen in the

tissue, especially in liver, muscle and heart. In 1929, Von Gierke identified the first patient with GSD type I and named it as hepatonephromegalia glycogenica.The enzymatic defect, namely glucose 6 phosphatase deficiency, that caused type I GSD was elucidated in 1952 byCarl and Gerty Cori. They found that glucose 6-phosphatase was missing from the liver of a patient with this disease. This was the first demonstration of an inherited deficiency of a liver enzyme. The liver glycogen is normal in structure but present in abnormally large amounts.

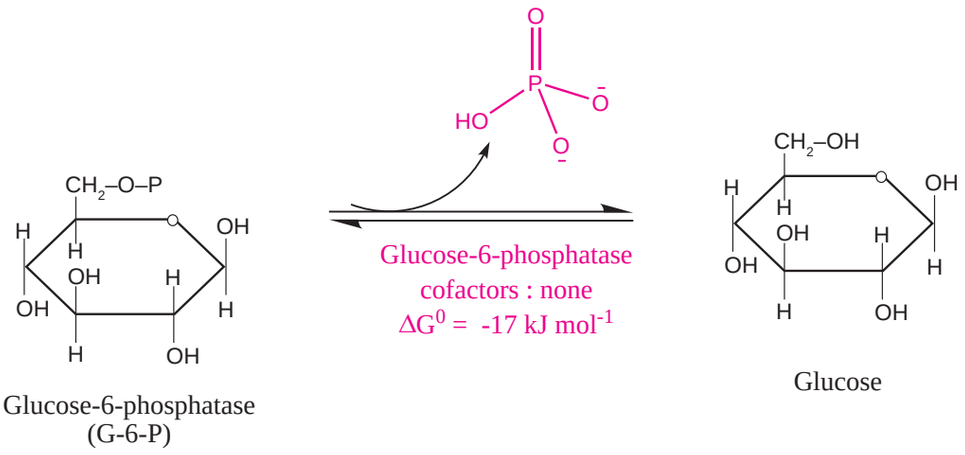

Figure.7.3 Action of glucose-6-phosphatase

Glucose -6-phophatase catalyzes the final step leading to the release of glucose in blood stream by the liver **(Figure.7.3)**. Deficiency of this enzyme results in an increase in intracellular glucose -6-phosphate. This phosphorylated sugar cannot leave the liver, because it cannot cross the plasma membrane, which leads to a large accumulation of glycogen in the liver and inability to increase blood glucose concentration in response to glucagon or epinephrine. Since glucose6- phosphate cannot leave liver cells, there is compensatory increase in glycolysis leading to increased levels of pyruvic acid and lactic acid.

Patients who have Von Gierke disease also have an increased dependence on fat metabolism. This disease can also be produced by a mutation in the gene that encodes the glucose 6-phosphate transporter.

7.2.1 Clinical manifestations

The clinical manifestations of Von Gierke disease, as shown in Figure.7.4, include hypoglycemia with lactic acidosis during fasting, enlarged liver, distended abdomen, cherubic or doll like face and seizures.

7.2.2 Symptoms

Signs and symptoms of this disease appear around 3-4 years of age. Affected infants may have hypoglycemia associated with seizures. High level of blood uric acid and hyperlipidemia are evident. Symptoms include low blood sugar, intolerance of fasting, frequent nose bleeds. Both liver cells and the cells of renal convoluted tubules are loaded with glycogen. Ketosis and hyperlipidemia are also present. Treatment includes intake of food high in starch

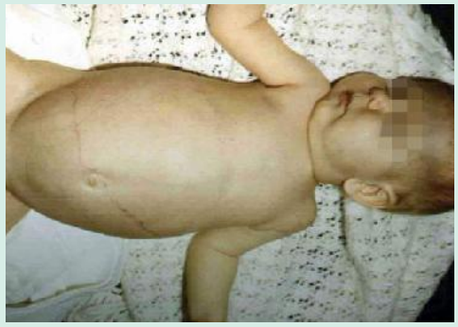

Figure.7.4 Von Gierke affected child

7.3 HEMOPHILIA

Clotting factors are a set of proteins that control bleeding. When a blood vessel is affected, the lining of the blood vessels contract to reduce the blood loss at the site of injury. Small blood cells called as platelets stick to the injured site and prevent blood loss. Inside the platelets, chemicals that attract other cells and make up a clump called as a platelet plug. At the site of injury, in the surface of platelets, clotting factors orchestrated by a set of proteins which form a coagulation cascade leading to the formation of fibrin clot. The fibrin clot acts as a mesh and stops bleeding.

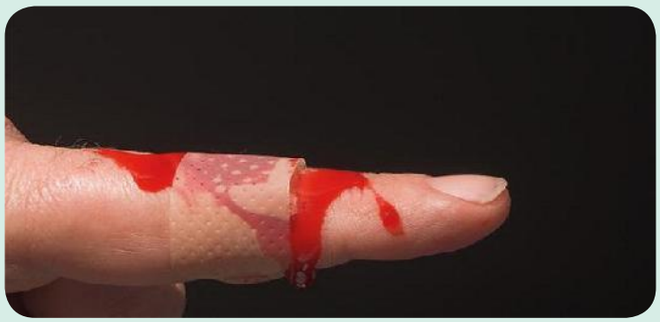

Figure 7.5 Hemophilia

The term Hemophilia was first coined by Dr. John Conrad Otto, in the early 19th century. Hemophilia is an inherited bleeding disorder in which a person lacks or has low levels of certain proteins called "clotting factors" and the blood does not clot properly. There are nearly 13 factors involved in the mechanism of blood clotting. If any one or more of these factors are not synthesized adequately that results in the defect in blood clotting and thereby haemorrhage. A number of inherited deficiencies of the blood clotting factors are found in human and are collectively called as hemophilias. The clotting factors are presented in Table 7.1.

Clotting factor	Factor name	Source
I	Fibrinogen	Liver
II	prothrombin	Liver

III	Tissue thromboplastin (Tissue factor)	Tissue cells
IV	Calcium ions	Plasma
V	Labile factor (pro-accelerin)	Liver, platelets
VII	Stable factor (pro-convertin)	Liver
VIII	Anti-hemophilic factor	Liver, lung capillaries
IX	Christmas factor Plasma thromboplastin component	Liver
X	Stuart-prower factor	Liver
XI	Plasma thromboplastin anticedent	Liver
XII	Hageman factor	Liver
XIII	Fibrin stabilizing factor	Liver, bone marrow

7.3.1 Causes

Hemophilia is an inherited disease, where clotting occurs at an abnormally slow rate due to the absence of one or more of the blood clotting factors. The sufferers are known as 'hemophiliacs' or 'bleeders'. It is peculiar that it mainly affects males, but in rare circumstances, females can also be affected. There are several types of hemophilia and most forms are inherited. Three major forms of hemophilia namely hemophilia A, B, and C are important.

(i) *Hemophilia A*: Classic hemophilia or Hemophilia A, is a sex linked recessive disorder characterized by a deficiency of factor VIII. About 1 in 10,000 males is born with a deficiency of factor VIII.

(ii) *Hemophilia B*: Hemophilia B is the second most common form of hemophilia. It is due to a dysfunction in factor IX, which is also called as Christmas disease

(iii) *Hemophilia C* : It is mild and is caused by a deficiency of factor XI.

7.3.2 Symptoms

People with hemophilia may lose large amounts of blood from even the smallest injury, and the blood takes a longer time to clot. They will experience spontaneous or internal bleeding and often have painful, swollen joints due to bleeding into the joints. Unusual bleeding after vaccination is also evident. This rare but serious condition can have life-threatening complications. Symptoms of hemophilia vary with the level of clotting factors. If blood clotting-factor level is not very low, bleeding will occur only after surgery or trauma. If blood clotting factor deficiency is severe, it causes spontaneous bleeding.

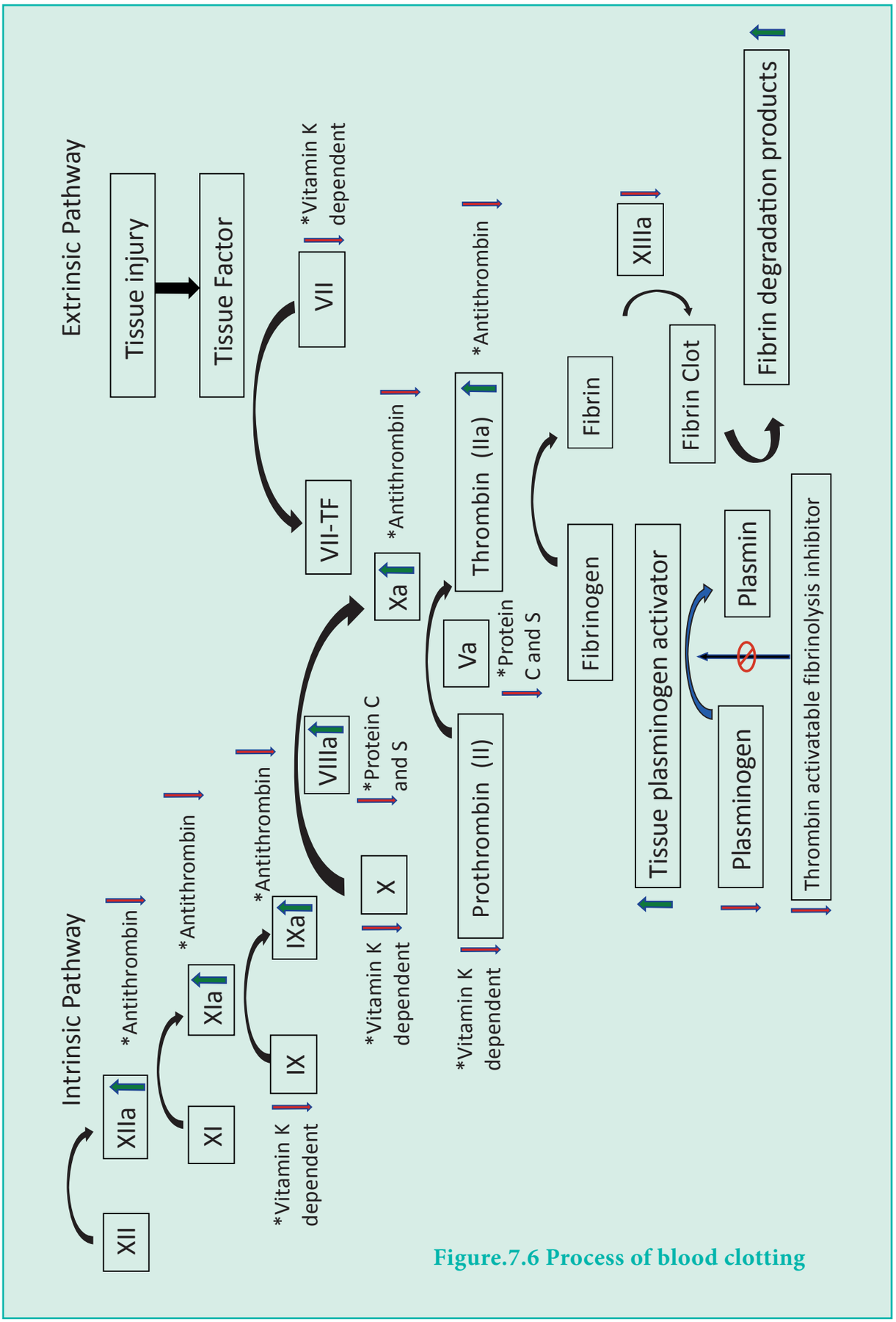

Figure.7.6 Process of blood clotting

In certain cases, the immune system gives a negative reaction, in response to the clotting factors when used as a treatment for bleeding. The immune system develops proteins (inhibitors) that inactivate the clotting factors, making treatment less effective.

7.4 ALBINISM

Albinism is a rare group of congenital disorders that cause the skin, hair, or eyes to have little or no colour. Melanin is the pigment responsible for the colour of the skin, hair, and eyes. The term albinism is from the Latin *albus*, means "white". Albinism is associated with a number of vision defects, such as photophobia (abnormal intolerance to visual perception of light), nystagmus(involuntary eye movement, acquired in infancy or later in life, that may result in reduced or limited vision) and amblyopia (disorder of eye sight due to the eye and brain not working well together). Lack of skin pigmentation makes the individual for more susceptibile to sunburn and skin cancers.

There are different types of albinism. Defects in different gene characterize its types.

OCA1 : Defect in tyrosinase and possesses two subtypes , OCA1a and OCA1b.

OCA1a: Subjects with OCA1a have a total absence of the pigment melanin. Therefore the affected individuals have white hair, very pale skin, and light coloured eyes.

OCA1b: Subjects with OCA1b make some melanin. They have light-colored skin, hair, and eyes.

OCA2: This type is common in African descendants and Native American populations. It is less severe than OCA1 and there is reduced melanin production. Individuals with OCA2 are born with light colored skin. Their hair may be yellow, blonde, or light brown.

OCA3: A defect in the TYRP1 gene. This type affects individual with dark skin especially, South African populations. It usually affects people with dark skin, particularly black South Africans. These individuals have reddish-brown skin, reddish hair, and brown eyes.

OCA4: It is due to a defect in the SLC45A2 protein. Like other types, it results in impeded melanin production and common in East Asian descendants.

7.4.1 Causes

A defect in one of several genes described above that produces melanin causes albinism. Melanin are natural pigments found in humans and animals. In the human eye, melanin is present in the uveal tract and the pigmented epithelial layer of the retina. It protects eyes by absorbing visible light that penetrate the lens through binding free radicals. The defective gene passes down from both parents to the child and leads to albininism.

The synthesis of melanin from tyrosine is as shown in the figure 7.7. The figure depicts that melanin is synthesized from tyrosine through DOPA. DOPA is the product of the enzyme, tyrosinase (diphenol oxidase). It is a copper containing enzyme and uses

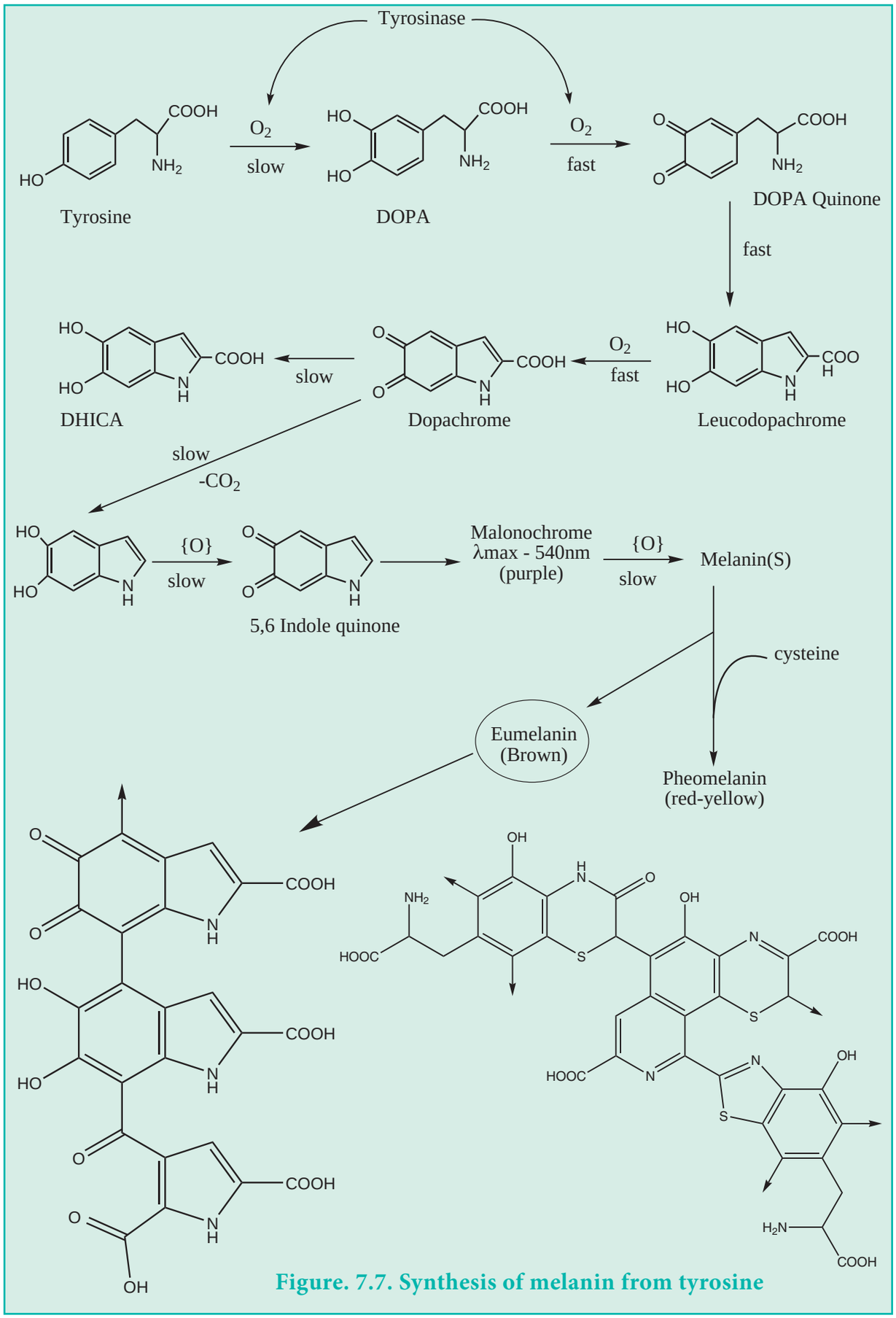

Figure. 7.7. Synthesis of melanin from tyrosine

oxygen directly to form DOPA. The synthesis of melanin occurs in the melanocyte, and the reactions starting with tyrosine are shown in **Figure.7.7**.

DOPA is converted to DOPA quinone. A number of intermediates are formed giving melanin. The more common product is eumelanin, brown in appearance. However, in the presence of cysteine, pheomelanin can be formed (red to yellow). Melanin is formed primarily in the melanocyte, located in the inner layers of the skin where melanin and carotene blend to produce the skin colour as well as the colour in the eyes and hair (Figure.7.8).

7.4.2 Symptoms

In Oculo-cutaneous albinism, there is decreased pigmentation of skin and eyes, whereas in Ocular albinism, there is decreased pigmentation of only eyes and not the skin. The common symptoms include the following

- Absence of colour in the skin or iris of the eye
- Patchy and missing skin colour
- Crossed eyes (Strabismus)
- Light sensitivity (photophobia)
- Rapid eye movements (Nystagmus)

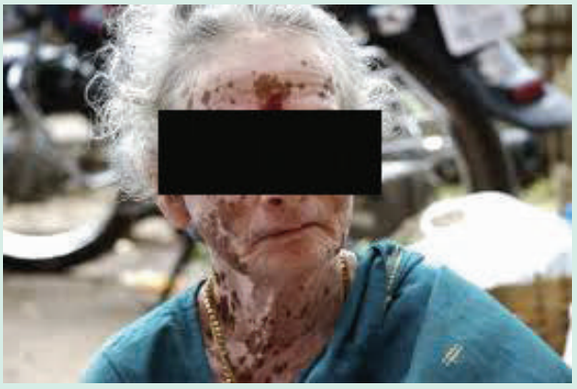

Figure 7.8. A woman affected with albinism

7.5 ALKAPTONURIA

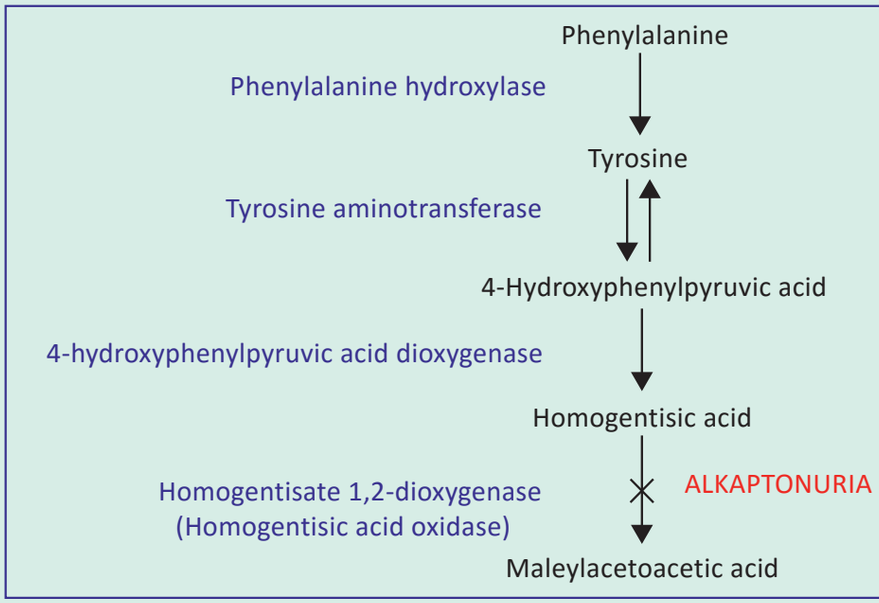

Figure 7.9 Metabolism of Phenyl alanine and Tyrosine

In 1584, Scribonius was the first to describe dark coloured urine, looking at the caseof a child, which excreted urine which turned "black as ink" on exposure to air. In 1859, Boedekerused, for the first time, the term alkaptonuria. It is a rare congenital metabolic abnormality where urine contains large quantities of homogentisic acid. Homogentisic acid (2,5, dihydroxyphenylacetic acid), is the key intermediate in the metabolism of phenyalanine and tyrosine.. A block in the conversion of homogentisic acid to maleyl aceto acetic acid is due to deficiency of the enzyme homogentisic oxidase. Consequently, homogentisic acid (called Alkapton) is excreted in the urine and the defect is called Alkaptonuria. The urine becomes dark brown or black on standing through oxidation by air.

7.5.1 Causes

Alkaptonuria is characterized by the deficiency of homogentisate 1, 2 dioxidasewhich catalyses the conversion of homogentisic acid to Maleylacetoacetic acid. Ochronosis,a dark pigment in connective tissue,is characteristic of this disorder. Ochronotic pigment may be sedimented in any of the outer structures of the eye: sclera, cornea, conjunctiva. The pigment can be seen in the nasal and temporal aspects of the sclera (Fig.7.8).

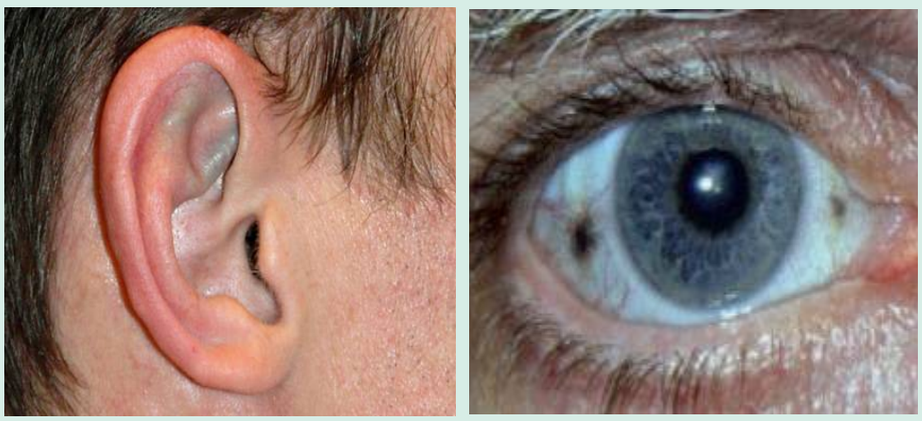

Figure. 7.10 Symptoms of alkaptonuria

Alkaptonuria does not show any ill effects in early life but it leads to degenerative arthritis in old age. This is because of the crystallization of the homogentisic acid derivatives in cartilages of ears and other exposed places. This results in generalized pigmentation of connective tissues and deposition in joints leading to arthritis.

7.5.2 Symptoms

It has a very low prevalence (1:100,000-250,000) in most ethnic groups. Two countries, Slovakia and Dominican republic, exhibit an increased incidence of this disorder. The first clinical sign is the appearance of dark spots in nappies of the affected children, due to darkening of urine owing to oxidation of the HGA. Till now no treatment modalities are known to treat this disease. The best way is to reduce the intake of tyrosine and

phenylalanine and intake of ascorbic acid. It must be noted that dietary restriction may be promising for children but not for adults.

7.6 TAY-SACHS DISEASE

Gangliosides are glycosphingolipids which are main components of cell membranes. Nervous tissues are particularly rich in gangliosides. They constitute a significant fraction (6%) of brain lipids. Other tissues also contain gangliosides but in lesser amounts. Their complex carbohydrate head groups, which extend beyond the surfaces of cell membrane, act as specific receptors for certain glycoprotein hormones. They act as receptors for some bacterial toxins. Gangliosides are also involved in cell – cell recognition. Generally, the carbohydrate segments of glycolipids are removed bylysosomal hydrolases in the early phases of the turnover of these compounds. Disorders of ganglioside break down are responsible for several hereditary sphingolipid storage diseases including Tay – Sachs disease.

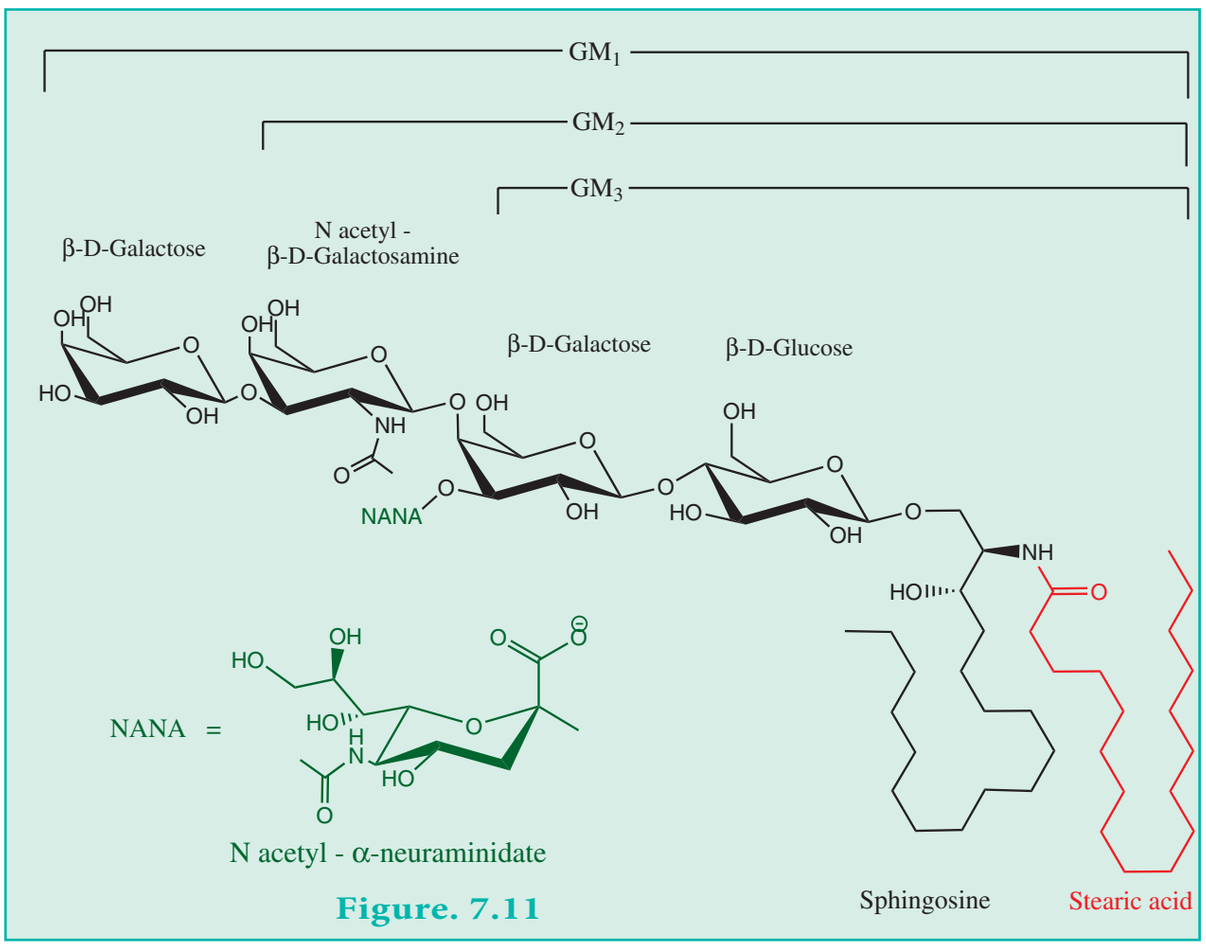

Figure. 7.11

β-galactosidase hexaminadase-A

GM1 → GM2 → GM3

Tay-Sachs Disease is an autosomal recessive neurodegenerative disorder. It is common in Jewish population which is fatal within the first three to four years of life. A British physician, Warren Tay, and an American physician, Bernard Sachs independently worked on this disease.

Tay noticed the characteristic red spot in the eye that is the earlier symptom of this disease due to degeneration in the central nervous system. Sach characterized this syndrome and identifying its familial characteristics, like mental disturbances, a deficiency in normal reflexes, progressive blindness and mortality, in Ashkenazi Jews (A Jewish ethnic group).

7.6.1 Causes

Tay-Sachs disease is classified as a lysosomal storage disease (Figure.7.9). In a healthy child, a lipid known as GM2 ganglioside, enter the nerve cell as a source of food. Among the components of the cell are lysosomal bags, which contain hexoaminidase A to digest this GM2 gangliosides. However, in Tay-Sachs disease, due to a failure in this degradation, levels of GM2-ganglioside increases in the lysosomes of neuronal tissue, thereby worsening the condition.

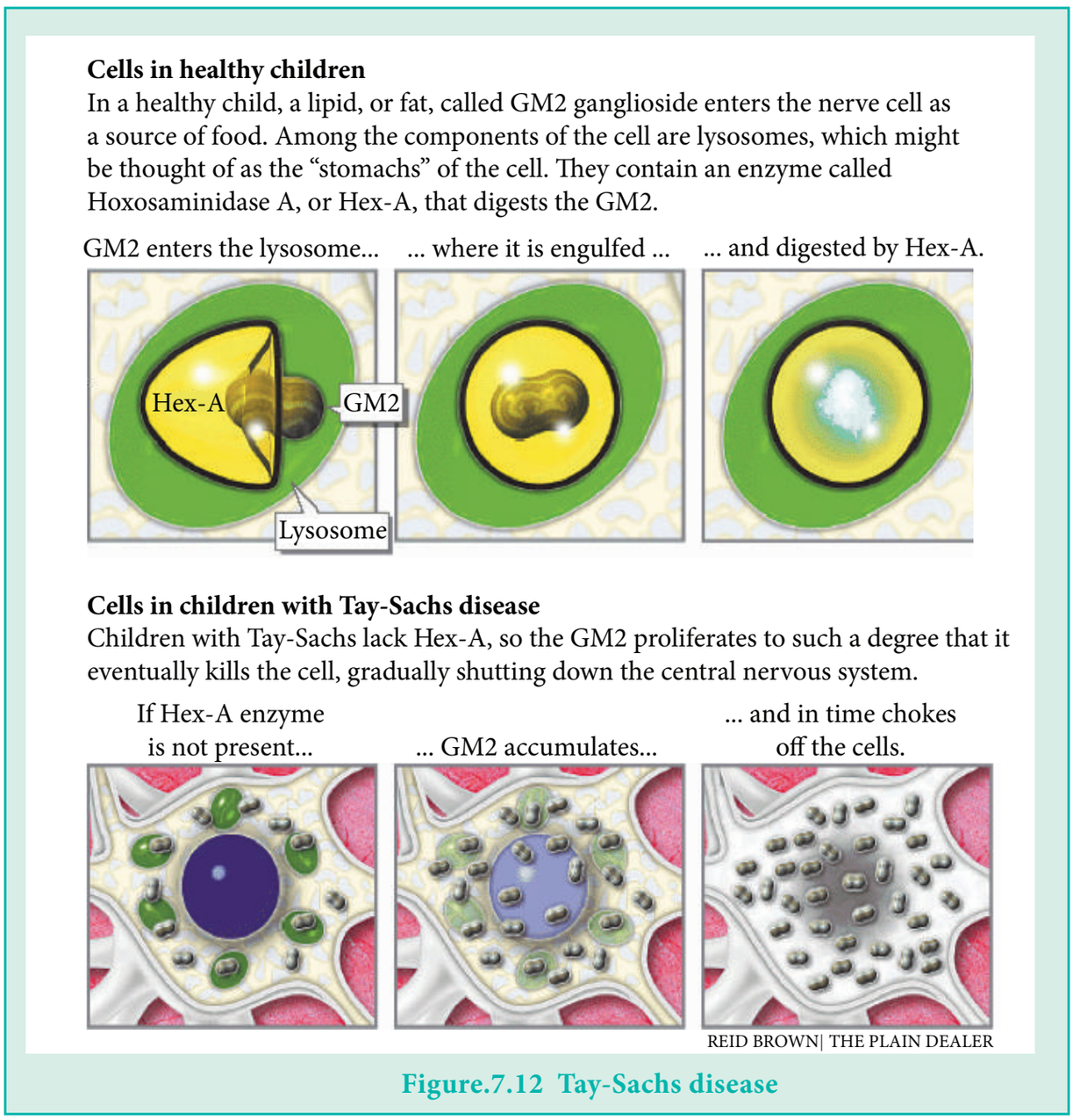

Figure.7.12 Tay-Sachs disease

7.6.2 Symptoms

Muscle weakness, progressive retardation in development and difficulty in eating are typical early symptoms. Mental retardation and blindness are the characteristic symptoms in this rare genetic disorder. Death between 3 -4 years is unavoidable. More than 90 % of the patients have a characteristic cherry red spot in the retina. Tay-Sachs disease can be diagnosed by taking amniotic fluid from the motherand assaying the hexosaminidase A activity. Bad memory, defective learning skills, poor decision making, eventually the child goes blind, deaf, paralyzed, and dies within 3 years.

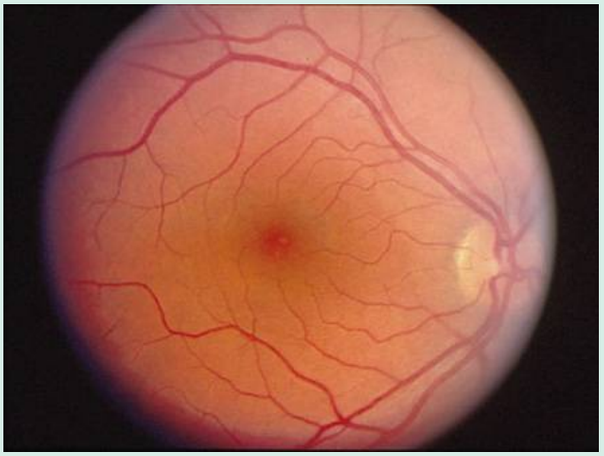

Figure 7.13 Cherry red spot in the retina

Till now, there is no cure for Tay-Sachs disease. Treatments include gene therapy or enzyme replacement therapy. They are not promising cure for the disease but could slow down disease progression.

SUMMARY

Metabolic processes, including transport of molecules across the membrane, are coordinated by a series of biochemical reactions and each reaction is controlled by an enzyme. One or both of a pair of genes involved in the production of a particular enzyme may be defective. The production of an enzyme, be it normal or low, depends on whether the gene is dominant or recessive, which is inherited from the parents. Inborn errors of metabolism, are fortunately, linked to recessive traits. Though, the consequences of this disease are extremely rare, they are collectively common and presented in new born infants or shortly thereafter.

The basis of IEM is the mutation in a gene that codes for a particular enzyme in a specific pathway, involving either the break-down or storage of carbohydrates, fats and proteins.

1. The term 'inborn errors of metabolism' was first proposed by Garrod followed by Beadle and Tatum
2. Common defects in biochemical pathways include, defects in the transport, excessive accumulation of substrate, deficiency of product and secondary inhibition.
3. Enzymes play a major role in performing the anabolism and catabolism of reactive pathways and serve as catalysts in the conversion of one compound to the other.
4. The major classification of inborn errors of metabolism includes protein, carbohydrate,

lipid disorders.

5. Galactosemia is an inherited disorder characterized by inability of the body to metabilize galactose. The major deficient enzyme is galactose 1 phosphate uridyl transferase (GALT).

6. Von Gierke disease is a type I glycogen storage disease characterized by deficiency of glucose 6 phosphatase, that hydrolyzes glucose 6 phosphate. This impairs the ability of the liver to produce glucose from glycogen.

7. A deficiency in clotting factors causes hemophilia, with several types described.

8. Alkaptonuria or black urine disease is a rare genetic inherited disorder, characterized by deficiency in homogetisate 1,2 dioxygenase, which takes part in the degradation of tyrosine.

9. Albinism is characterized by pigmentation of skin due to impairment in the melanin synthesis.

10. Tay-Sachs disease, a lysosomal disorder, is characterized by the inability of hexosaminidase A to degrade the GM2 gangliosides in brain. This causes neurotoxicity and death of child.

EVALUATION

I. Choose the correct answer

1. Which of the following enzyme deficiency causes galactosemia
   a. gluco kinase
   b. galacto kinase
   c. galactose 1 phosphate uridyl transferase
   d. phosphoglucomutase
2. Liver failure and mental retardation are symptoms of
   a. von-gierke diseases
   b. galactosemia
   c. albinism
   d. all of these
3. glucose 6-phosphatase deficiency causes
   a. galactosemia
   b. albinism

c. von-gierke diseases

d. hemophilia

4. The absence of glucose 6-phosphatase in liver causes

a. hypoglycemia

b. hyperglycemia

c. depletion of glycogen in liver

d. none of the above

5. Which of the following is not the symptoms of Von-Gierke diseases?

a. ketosis

b. Hyperlipidemia

c. Hypoglycemia

d. Hyperglycemia

6. How many factors are involved in blood clotting process?

a. 10

b. 8

c. 12

d. 13

7. Hemophilia A is caused by the following factor

a. Factor VIII

b. Factor VII

c. Factor VI

d. Factor V

8. Blood clotting factor IV is

a. Fibrinogen

b. Calcium ions

c. Christmas factor

d. Hageman factor

9. Albinism is due to deficiency of

a. Tyrosinase

b. Hexokinase

c. DOPA hydroxylase

d. All of these

10. The decreased pigmentation in eyes are called as

a. Ocular albinism

b. Oculo-cutaneous albinism

c. Alkaponuria

d. Hemophilia

11. _____ amino acids are involved in alkaptonuria

a. Glycine & alanine

b. Cysteine & methionine

c. Tryptophan & lysine

d. Phenyl alanine & tyrosine

12. Deficiency of hexaminIdase-A leads to accumulation of

a. GM3 b. GM2

c. GM1 d. GM1 and GM3

13. The first condition identified as an inborn error of metabolism was

a. Albinism b. Alkaptonuria

c. Phenylketonuria d. Hemophilia

14. Most IEMs have autosomal recessive modes of inheritance. It means _____?

a. Two copies of the defective gene must be passed on to the child for the disease to develop

b. The defective gene is passed down to the child from the mother.

c. The defective gene is passed down to the child from the father.

d. The defective gene is not present on the mother or father's chromosomes.

15. One gene one enzyme theory was proposed by

a. Beadle and Tatum

b. Garrod

c. Ingram

d. Von gierke

16. Deficiency in homogentisic acid oxidase causes

a. Phenylketonuria

b. Alkaptonuria

c. Tyrosinemia

d. Galactosemia

17. A child's diapers on exposure to air became dark coloured. What is your probable diagnosis?

a. Tay-Sachs disease

b. Glycogen storage disease

c. Lysosomal storage disease

d. Alkaptonuria

18. ---------- clot acts as a mesh and stops bleeding

a. fibrogen

b. prothrombin

c. christmas factor

d. fibrin

II. Answer the following:

1. Classify inborn errors of metabolism.
2. Give the metabolism of galactose.
3. Comment on the symptoms of Von Gierke disease.
4. Describe lysosomal storage disease.
5. Write a note on hemophilia.
6. Give an account on the deficient enzyme involved in alkaptonuria.
7. What are symptoms of galactosemia?
8. Describe the types of albinism.
9. Give an account on alkaptonuria.
10. How GM1 is converted into GM2?
11. Write the conversion reaction of glucose-6-phosphate to glucose.
12. Describe the causes and symptoms of Tay-Sachs disease.

References

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CONCEPT MAP

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