HEREDITARY FRUCTOSE INTOLERANCE
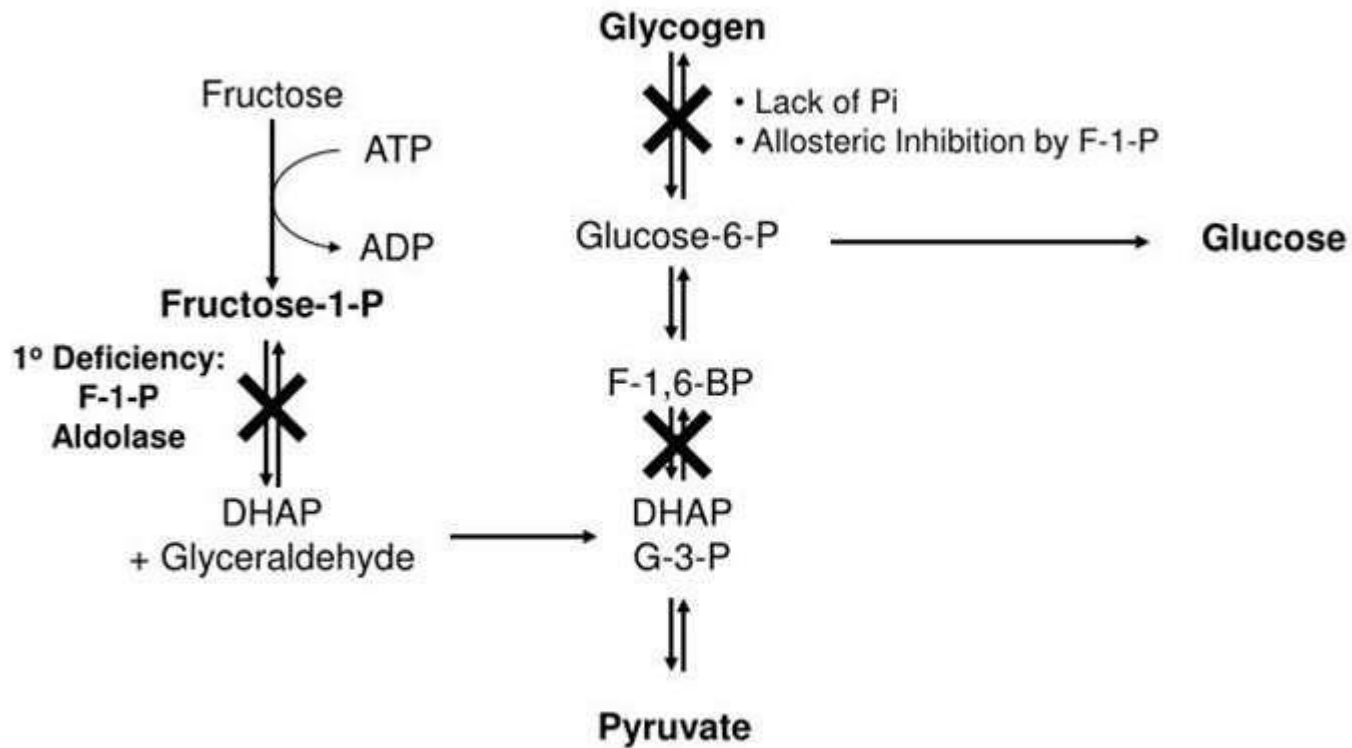
INTRODUCTION

O Fructose intolerance, occurs when cells on the surface of the intestines aren't able to break down fructose efficiently.

O Fructose is a simple sugar, known as a monosaccharide, that comes mostly from fruit and some vegetables.

O Fructose intolerance is a rare genetic condition occurs because the body doesn't make the enzyme needed to break down fructose.

O This can lead to serious health issues such as liver failure if a strict fructose-free diet isn't followed.

- **HFI is an autosomal recessive disorder of fructose metabolism due to a deficiency of fructose-1-phosphate aldolase (EC 2.1.2.13) activity, which results in an accumulation of fructose-1- phosphate in the liver, kidney, and small intestine.**

- **The accumulated fructose-1-phosphate inhibits glycogen breakdown and glucose synthesis, thereby causing severe hypoglycaemia following ingestion of fructose**

- **Prolonged fructose ingestion in infants leads ultimately to hepatic and/or renal failure and death.**

Fructose Intolerance

Fructose → (ATP → ADP) → **Fructose-1-P**

1° Deficiency:
F-1-P Aldolase

Fructose-1-P ⇵ DHAP + Glyceraldehyde

Glycogen ⇵ Glucose-6-P
• Lack of Pi
• Allosteric Inhibition by F-1-P

Glucose-6-P → **Glucose**

Glucose-6-P ⇵ F-1,6-BP

F-1,6-BP ⇵ DHAP / G-3-P

DHAP + Glyceraldehyde → DHAP / G-3-P

DHAP / G-3-P ⇵ **Pyruvate**

Genetic Condition of Fructose Intolerance

O Mutations in the **ALDOB gene** (generally found in liver) cause hereditary fructose intolerance. The ALDOB gene provides instructions for making the aldolase B enzyme. This enzyme is found primarily in the liver and is involved in the breakdown (metabolism) of fructose so this sugar can be used as energy.

Causes

Fructose intolerance is fairly common, affecting up to 1 in 3 people.

Fructose Intolerance can be due to many causes that include:

O imbalance of good and bad bacteria in the gut.

O high intake of refined and processed foods.

O preexisting gut issues such as irritable bowel syndrome (IBS).

O Stress.

Symptoms

Symptoms for fructose Intolerance include:

O Nausea.

O Bloating.

O Gas.

O Abdominal pain.

O Diarrhea.

O Vomiting.

Diagnosis

- The only definitive way to diagnose if one is suffering from HFI is to have one of two test.

- An enzymatic assay to determine aldolase activity.

  O - The aldolase is obtained from patient liver tissue in an invasive surgical procedure called **liver biopsy.**

- A **fructose tolerance test,** fructose is injected introvenously under controlled condition where acute glucose, fructose & phosphate levels are monitered.

O Hydrogen breathe test is a method currently used to diagnosis following ingestion of fructose, the hydrogen concentration of the patients breathe is measured at various time intervals. The normal range for hydrogen is 20ppm in 60 minutes.

Clinical Diagnosis

The aldolase test was used to look for liver or muscle damage. Doctors use more specific blood tests, including:

O creatine kinase (CK) [**normal range** is 22 to 198 U/L (units per liter)].

O alanine aminotransferase (ALT) [The **normal value for ALT** in blood ranges from 29 to 33 units per liter (IU/L) for males and 19 to 25 IU/L for females]

O aspartate aminotransferase (AST) [The normal range of values for AST is about 5 to 40 units per liter of serum.

Treatment

O Treatment of HFI is currently done through a **strict fructose free diet**.

O Read nutrition labels and ingredients lists carefully to determine what foods are safe and which ones you want to avoid.

Foods To Avoid :

Fruits

O Although you can safely consume fruit on a   low fructose diet, it is important to know which ones are high in fructose.

O High fructose fruits include watermelon, pineapple, oranges, apples, pears, peaches and   mangoes.

O However, some people can tolerate eating some   of these fruits in small amounts and in combination with other foods.

Sweeteners

O Sweet foods are likely to contain some form of fructose.

O High fructose corn syrup is one that you should limit or avoid if you are maintaining a low fructose diet.

O Soda, candy, yogurt, jam and some sports drinks contain this sweetener.

O Any food sweetened with sorbitol, fruit juice or honey should also be limited.

What to Eat

O There are plenty of foods you can eat on a low fructose diet so that you are covering your nutrient needs and staying healthy.

O Recommended diet are meat, dairy, eggs, beans and vegetables.

Meat :-

O Fresh meat contain no fructose. They are also high in protein and iron, and low in carbs. Chicken are lean and contain no fructose.

Vegetables :-

The majority of vegetables are low in fructose. Such as peppers, Cabbage ,Radishes etc.

Cont.

Dairy

O Dairy products, such as cheese, milk and buttermilk are low in fructose. These items are high in calcium, protein and fat.

Eggs

O Eggs contain no fructose, are low in carbs and are high in protein and fat.

Beans

Beans in their natural state are free of fructose. They are also high in fiber, protein and complex carbohydrates.

UNIT 12   INBORN ERRORS OF METABOLISM

Structure

12.1   INTRODUCTION

As you have completed the study of Units 1-11, you have virtually finished studying this Course of Nutritional Biochemistry. You saw that this course consisted basically of two parts – chemistry of physiologically important molecules and the metabolic pathways undergone by these molecules in our body. You may wonder then what is Unit 12 all about. If Units 1 to 11 are considered as 'Basic Knowledge', then Unit 12 may be looked upon as 'Applications'. Perhaps, more aptly it may be described as "Misapplications". Yes, as you would have guessed rightly, this unit will give you a brief insight into what would happen if normal metabolic steps (about which you learnt earlier) do not take place correctly.

When we fall ill, we ask ourselves why something went wrong in our body. But after learning about the myriad of metabolic reactions occurring in our body and the fine-tuning of homeostatic regulatory mechanisms which are in place, you must have realized how efficient nature really is in giving us good health.

In this unit we will consider specific inborn errors of metabolism. It is impossible to discuss all the known diseases. The diseases which will be discussed have been chosen for different reasons like:

- they are of some historical importance,

- they occur commonly in our country,

- they can be managed at least to some extent by nutritional intervention,

- mass screening programs have been conducted worldwide for early detection, and

- surprisingly, no clinical symptoms are encountered.

Objectives

After studying this unit, you should be able to:

- explain general concepts underlying inborn errors of metabolism,

- identify the specific biochemical defect in each disease,

- list the clinical symptoms occurring in each disease,

- compare the incidence/prevalence of different diseases,

- name the mode of inheritance, and

- formulate therapeutic diets wherever useful.

12.2 INBORN ERRORS OF METABOLISM – GENERAL CONCEPTS

Sir *Archibald Garrod* coined the term *'Inborn Errors of Metabolism'* in 1902. He said that there are a number of metabolic abnormalities that are congenital, present throughout life and hereditary. He suggested that metabolic blocks resulting from an abnormality of certain specific enzymes caused the hereditary diseases. This can be because the enzyme molecule is completely absent and hence unable to do its work. Or more likely, the protein molecule is present, but there is a genetically determined mutation at the reactive site. It may also be possible that the enzyme is present and structurally normal too, but unable to function properly because of alterations within the cell. A deficiency of cofactors or the presence of inhibitors could produce such an effect.

At the time when *Garrod* described inborn errors of metabolism, it was presumed that these errors were due to the deficiency of enzymes. However, now it has been realized that these could be due to deficient working of carrier transport molecules, receptor molecules, certain hormones and of course, enzymes. Do you remember what are carrier transport molecules and receptor molecules, about which you have read in Units 10 and 11, respectively? For example, blood is a vehicle for transporting various molecules from intestine, the site of absorption, to the liver. From there, these molecules are transported to all the tissues which need them, or if not needed at that time, to tissues which store them. It is now known that all molecules transported in blood are carried bound to different kinds of proteins called *carrier transport molecules*. Thus no molecule is really 'free' in blood. You have also read that only after a hormone binds to a protein molecule present in a cell can it exert its effect on the cell. This protein molecule is called a *receptor molecule*. Thus it helps the hormone to recognize the cell where it has to act.

Now to get back to our discussion on general concepts of inborn errors of metabolism, you will notice *that one common factor among inborn errors of metabolism is that these defects are concerned with protein molecules*. You have already learnt

that synthesis of proteins is genetically controlled. Hence, these diseases are manifested when genetic mutations occur and also become inherited. What do we mean by genetic mutation? A mutation occurs when a DNA gene is damaged or changed in such a way as to alter the *genetic* (inherited) message carried by that gene. What is a *'gene'?* You have already studied in Unit 8 under metabolism of nucleotides that gene is *a segment of the DNA (nucleic acid) chain that contains the instructions for a complete protein*. Hence, the gene is the fundamental unit of genetic information. These genes contain instructions that affect not only structure, size, colour and other physical attributes but also intelligence, susceptibility to disease, life span and even some aspects of behaviour.

All these characteristics are transferred from one generation to another. A lot of information is now available as to how various characteristics (e.g. colour of hair and eyes, height etc) are transferred from parents to the offspring. This is the science of genetics. It was *Mendel*, a monk, who carried out experiments on garden pea and formulated the principles of genetics. These are called *Mendelian Laws of Inheritance (Mendelian Genetics)*. To get a basic idea of this concept, we suggest you look up the NCERT Biology book for Class XI and XII or any other reference related to the topic.

Mendelian Laws of Inheritance holds good for animal species including human beings. In fact not only physical characteristics, but even diseases are inherited from parents, again according to these laws of inheritance. Thus it could be an autosomal (chromosomal) recessive characteristic or a dominant characteristic or could be a sex-linked (i.e. through X or Y sex chromosomes) inherited characteristic. As these names suggest, inheritance is in less number of offsprings in recessive inheritance. When it is dominant, many more offsprings will get the disease. In sex-linked diseases/ characteristics, the disease is inherited only from the father or the mother, as the case may be.

In most of the diseases, failure of a metabolic step leads to the excretion of intermediate products which cannot be carried further along the metabolic path. Very often accumulation of these intermediates leads to clinical symptoms. The identification of the intermediate metabolic products in urine aids in diagnosis of the disease. In many diseases, the clinical symptoms are variable and non-specific. Hence biochemical estimations in biological fluids such as blood, urine etc. is essential to confirm the existence of the particular disease.

Clinical symptoms could appear as early as in the first week of birth. Hence, timely diagnosis is of prime importance. Further, at the present time, no effective treatment is available for most of the diseases. Thus the inevitable end is death of the affected person, very often within 1-2 years of birth. Hence genetic counseling and prevention of such births is the only course open. Accordingly, prenatal diagnosis of many of the diseases is now regularly resorted to. For this, the amniotic fluid is analyzed and assayed for the enzyme in question, or for the metabolite that accumulates or for the defective product synthesized.

The estimated burden of inborn errors of metabolism (IEM) is 3-4 per 1000 live births. About 20% of acute illnesses in newborns in the developed countries are due to IEM. In India, there is a paucity of information regarding incidence/prevalence of IEM. This is because we have a poor system of record keeping. Further, the actual figures would be much higher than what is available, since deaths due to IEM would go unreported due to non-diagnosis of the disease. This would be particularly true in our villages where the primary health care services are non-existent or poorly availed of by the people. According to an ICMR multicentric study, about 5% of genetic causes of mental retardation are due to IEM. Other studies have quoted a figure of 0.5-2.5%.

Next, moving on to the treatment of IEM. Treatment, wherever possible, is still only symptomatic i.e. alleviating the pain etc. or preventing the disease from progressing to more severe consequences. Nutritional management has been useful in many instances. You will understand this better as you read about the disorders here and also in the Therapeutic Nutrition Course. However the ideal treatment would be adoption of devices which would enable the cell to start synthesizing the right kind of protein. This evidently would involve gene manipulation, which sounded far-fetched just a few years back. But enormous progress made recently in the field of molecular genetics has made gene therapy in humans a potential therapeutic approach in the near future. This is the advent of recombinant DNA technology or what is commonly referred to as *'genetic engineering'*.

What is genetic engineering? Look at Figure 12.1 which illustrates the genetic engineering process. This involves isolation and manipulation of DNA, wherein the defective portion of the DNA molecule (wrong base sequences) is removed. The right sequences are inserted at this point to produce the correct desired DNA molecule. Molecules containing both human and bacterial DNA sequences joined together have been produced. These are called *chimeric DNA*. The hybrid DNA molecule is then inserted into small circular duplex DNA molecules called *plasmids* which are present in bacteria. These are called *vectors*. When the plasmids replicate or duplicate, identical DNA molecules are produced in large numbers. This method of DNA amplification is called *cloning*. The correct DNA molecule is cleaved off from the plasmid. If this is inserted into cells where the DNA was originally defective, the cell will now also replicate the correct gene, which in turn can direct the synthesis of the right protein molecule.
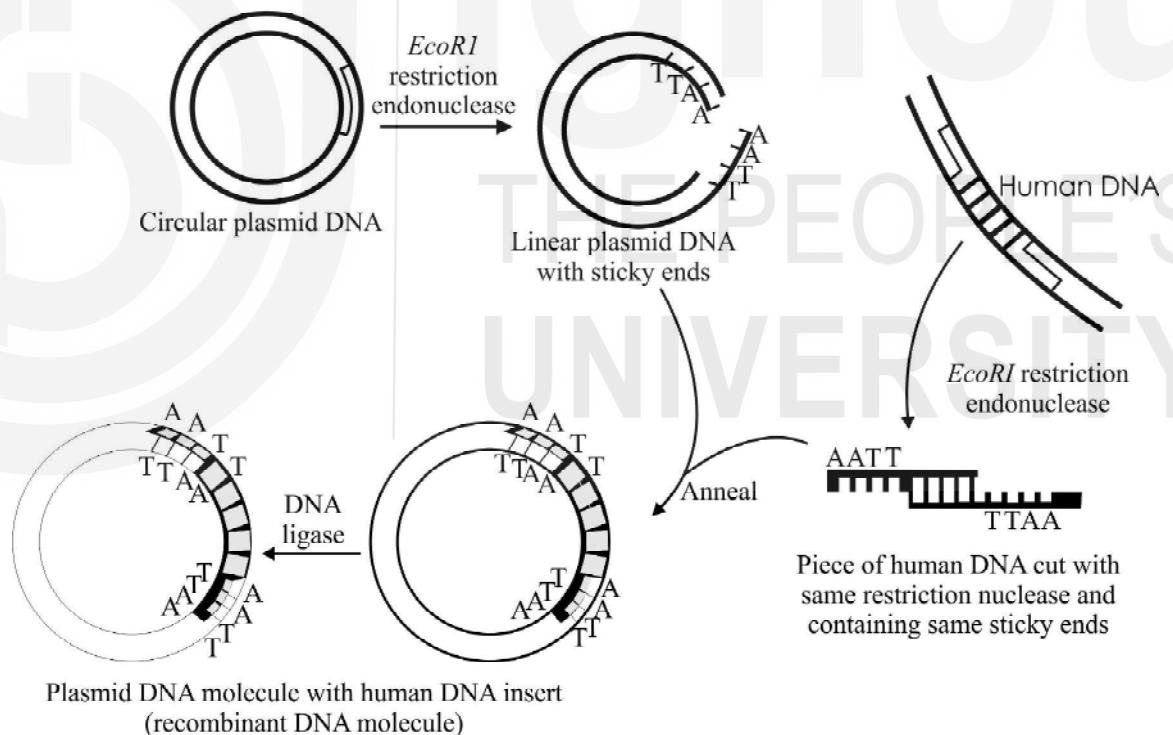
Figure 12.1: Genetic Engineering

Extensive research is needed before gene therapy can become a reality. The first step in this quest was to obtain complete information about the human gene. It is now suspected that virtually every disease, to some extent, has a genetic component. And hence a 'Gene Hunt' was launched. You should read Box 1 for more information on this very interesting subject.

We just discussed how DNA can be cloned. You must have read about 'Cloning' in the newspapers. Does DOLLY ring a bell? Yes, Dolly was the first clone. It was the first mammal, a sheep, which was cloned from cells of an adult animal in 1986 by scientists of Roslin Institute in Scotland. Then Polly was created, a lamb with a human gene in its genome. Italian researchers have made a strain of pigs that carry

human genes in their hearts, livers and kidneys. This gives rise to the possibility that genetic disorders may someday be treated with drugs supplied by sheep and other animals or provide organs for transplantation. Subsequently many animals are reported to have been cloned. These include pigs, goats, cats, rabbits, mice, mule and horse. So there is a large cloned animal farm. Wait, hold your breath – a cloned human child is expected to be born soon!

Before going through this unit, you must revise the earlier units to reinforce your knowledge regarding Metabolic Pathways. It will also be interesting for you to read Mendelian Laws of Genetics. You should also try to formulate therapeutic diets for diseases where such dietary regimen is beneficial. As you are specializing in dietetics, this will not only be a challenge to you, but at the same time, it will also be very interesting and possible for you.

With this knowledge, let us move on to learn about the inborn errors of metabolism. *As you read on, you will find that these inborn errors are specific to defects in the metabolism of carbohydrates, proteins, fats etc.* Let us learn about them. We will begin our discussion with disorders of protein metabolism.

Box 1 : The Gene Hunt

A Human Genome Advisory committee was formed in 1989. Its goal was to map (decipher) the human genome (all the genes present in the human body) and spell out for the world the entire message hidden in its chemical code. The committee consisted of biologists, industry scientists and engineers, computer experts and ethicists. This Human Genome Organization had 42 scientists representing 17 nations. Hence it was called 'The UN of gene mapping'.

The human genome has now been mapped to a large extent. In addition to the above group headed by *Francis Colins*, a second group (privately funded), Celera Genomics founded by biologist, *Craig Venter* has been working on gene mapping. Thus two almost identical findings of the human genome have been published.

The key findings are:
- There are approximately 30,000 genes in human beings (instead of 10,000 as was believed earlier).
- This is the same range as in mice, twice that of roundworms, three times as many as fruitflies and only five times more than bacteria.
- All human races are 99.99% alike. So racial differences are genetically insignificant. This could mean we all descended from the same original mother who was from Africa.
- Most genetic mutations occur in the male of the species. So men are the agents of change. They are also more likely to be responsible for genetic diseases.
- It is quite humbling because not only are the numbers similar, the genes themselves, barring a few, are alike in mice and men. Hence this is a pointer that 'science cannot tell man from mouse'.

Very soon people might have access to computer readout of their own genome with an interpretation of their genetic strengths and weaknesses. Hence *James Watson* (who elucidated the structure of DNA) has said– 'we used to think that our fate was in our stars. Now we know, in large measure, our fate is in our genes'.

Being able to read the entire genetic message and perhaps alter it, is also alarming. Such knowledge could create many moral and ethical problems. Some people feel genetic testing may constitute an invasion of privacy. It could lead to discrimination against the 'genetically unfit'. Another question raised is should someone destined to be stricken with a deadly genetic disease be told about ones fate, especially if no-cure is available? This would result in creating the so-called 'worried-well' people who are well now but have found out what might ail them in the future. Insurance companies may demand this information from clients before offering a policy. Hence, a word of caution is necessary. Will human genome mapping usher in an era of 'genetic apartheid'?

12.3 DISORDERS OF PROTEIN METABOLISM

We will first have a look at disorders of aromatic amino acids followed by other amino acids (non-aromatic). You have already learnt about the chemical structures of amino acids in Unit 2. Amino acids like phenylalanine, tyrosine, tryptophan have a phenyl (benzene) ring in their structure and hence are called *aromatic amino acids*. The rest of the amino acids which do not have a phenyl ring are called *non-aromatic* (or aliphatic) *amino acids*.

The diseases we will be considering here are Alcaptonuria, Phenylketonuria (PKU), Tyrosinemia– Types I, II and Neonatal Tyrosinemia and Albinism.

All the disorders included in this study have an autosomal recessive pattern of inheritance. Additionally, ocular albinism also has X-linked pattern of inheritance. Further occurrence of these diseases is rare. Wherever reported incidence is available, it has been given in Table 12.1.

Along with the discussion presented here for each disorder, other characteristics have been listed in Tables 12.1 and 12.2. Read these tables carefully. This will make it easy for you to recapitulate, as well as, follow the information presented in the text. The chemical reactions involved are given in Figure 12.2. In fact, Figure 12.2 gives all the chemical reactions along with the names of enzymes involved in the catabolism of the aromatic amino acids phenylalanine and tyrosine. For an easy understanding, defective step leading to diseases are coloured red, steps unaffected are coloured green and alternate pathways used to reduce accumulated metabolites (intermediates) are coloured blue. So let us get started.

12.3.1 Alcaptonuria

Alcaptonuria is a very rare hereditary disorder of *tyrosine* (an aromatic amino acid) *metabolism*. The disease is characterized by the excretion of urine, which upon standing, gradually becomes darker in colour and may finally turn black. There is a defect in the enzyme *homogentisate oxidase* (also called homogentisate dioxygenase). In a normal person, tyrosine is metabolized through steps to homogentisic acid and further to maleylacetoacetic acid as can be seen in Figure 12.2. Absence or deficiency of the enzyme homogentisate oxidase (homogentisate dioxygenase) causes a block in the metabolic pathway at homogentisic acid. Further metabolism of homogentisic acid is prevented. Hence this intermediate compound (homogentisic acid) accumulates in blood. In order to decrease the level in blood, homogentisic acid is therefore excreted in urine. The homogentisic acid in urine, on exposure to atmospheric oxygen (air), is oxidized to a coloured pigment. Urine also has strong reducing properties and gives a violet colour with ferric chloride. These characteristics can be used for diagnosis of this disorder.

This condition – Alcaptonuria – is compatible with long life since there are no clinical manifestations. Late in the disease, there is a generalized pigmentation of connective tissues called *ochronosis*. This is due to the oxidation of homogentisate by polyphenol oxidase, forming benzoquinone acetate, which polmerizes and binds to connective tissue macromolecules. This is also linked to high incidence of cardiovascular disease. Accumulation of homogentisic acid in cartilage causes arthritis in older patients.

Alcaptonuria enjoys the historic distinction of being the human disease that led to elucidation of the concept of inborn errors of metabolism by *Garrod*.

Figure 12.2 : Metabolism of phenylalanine and tyrosine

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12.3.2 Phenylketonuria (Phenylpyruvic Oligophrenia)

Phenylketonuria was discovered in 1933 and is commonly referred to as PKU. The disease is caused due to deficiency of the enzyme *phenylalanine hydroxylase* which is responsible for the breakdown of the essential amino acid 'phenylalanine' in the body. In most cases, less than 2% activity of normal phenylalanine hydroxylase is seen in PKU.

In normal people, the enzyme *phenylalanine hydroxylase* converts phenylalanine to tyrosine which is then utilized by the body. In PKU, since phenylalanine cannot be hydroxylated to tyrosine, it accumulates. In an attempt to lower the concentration, it goes through alternate pathways and is transaminated to phenylpyruvate, which in turn is reduced or oxidized to form phenyllactate and phenylacetate respectively as can be seen in Figure 12.2. Much of the phenylacetate is conjugated (combined) in the liver with glutamine and excreted in the urine as *phenylacetylglutamine*. The accumulated metabolites cause damage to the CNS (Central Nervous System) resulting in acute neurological symptoms. Hence such inborn errors of metabolism with neurological abnormalities are also called neuro-metabolic disorders. Accordingly half of phenylketonurics exhibit mild to marked *microcephaly* (small head). *Bioterin*, a protein molecule synthesized in the body, is an obligatory (binding) cofactor. Hence any metabolic condition which interferes with its production will lead to PKU symptoms.

Relief of symptoms in PKU can be achieved by nutritional management which involves use of phenylalanine restricted diets. Several low phenylalanine diets are available in the west. However the cost of importing is the limitation. These are mainly protein hydrolysates (natural protein subjected to controlled hydrolysis to remove phenylalanine and tyrosine molecules) derived from casein or ox serum protein. Special corn starch products have also been used successfully. Based on the phenylalanine content of various foods eaten in India, you can calculate the dietary exchanges and formulate a suitable diet.

The following information given in Box 2 will help you in formulating a dietary regimen for PKU.

Box 2 : Guidelines for dietary management in PKU

- The brain of a foetus with classic PKU develops normally in intrauterine stage.

- The critical period of human brain growth and development extends over the first 6 months of neonatal life requiring that dietary therapy be instituted right after birth.

- Myelination may not be completed until 5 or 6 years of age and hence dietary restriction must be rigidly followed.

- The proportion of dietary phenylalanine that is utilized for protein synthesis varies with age-50-60% during early growth and only about 10% for normal adult.

- Blood phenylalanine levels must be maintained between 3-15 mg/dl.

- For a phenylalanine restricted diet, 50-80% of the natural protein must be replaced by a protein preparation that contains little or no phenylalanine.

- Most natural proteins contain about 50 mg phenylalanine/g protein.

- The composition of the preparation should meet all nutritional requirements for all the nutrients.

- Tyrosine must be supplemented in the diet.

- Usually one-third to one-tenth of normal phenylalanine content is recommended.

- Infections in the infant should be avoided to prevent tissue catabolism and increased phenylalanine levels in blood.

- Higher dietary phenylalanine intakes may be allowed after 6-10 years of age along with frequent clinical and biochemical supervision.

- Strict dietary restrictions should be adhered to by phenylketonuric women during pregnancy to prevent damage to the fetus.

Screening of newborn infants for PKU is compulsory in the US.

12.3.3 Tyrosinemias

Tyrosinemias, as the name suggests, are due to *defects in tyrosine catabolism*. Depending on which enzyme is absent/defective, different kinds of symptoms appear. Accordingly, three distinct defects have been identified. These are:

- Tyrosinemia Type I

- Tyrosinemia Type II

- Neonatal Tyrosinemia

Let us get to know them one by one.

Tyrosinemia Type I (Tyrosinosis) (Hepatorenal Tyrosinemia)

Tyrosinemia Type I was originally called Tyrosinosis. Failure to properly break down tyrosine leads to an abnormal accumulation of tyrosine and its metabolites in the liver, resulting in severe liver disease. There is a progressive liver and kidney failure in this disease and hence is also called *hepatorenal tyrosinemia*.

What is the cause for this disorder? This occurs due to the deficiency of the enzyme *fumaryl acetoacetate hydrolase* (the terminal enzyme in the tyrosine pathway), which as shown in Figure 12.2, converts fumaryl acetoacetic acid to fumaric and acetoacetic acids. Deficiency of this enzyme allows the accumulation of fumaryl acetoacetate and its conversion to succinyl acetone.

Fumaryl acetoacetic acid is formed from maleylacetoacetic acid which, in turn, is the breakdown product formed from tyrosine through various steps. Maleyl acetoacetic acid can also be acted upon by the enzyme *maleyl acetoacetate hydrolase* to form maleic acid and acetoacetic acid. Very often in Tyrosinemia Type I, this enzyme is also defective leading to accumulation of maleylacetoacetate too. In this disease, there is a formation of an extremely toxic compound called *succinyl acetone*. This causes impairment in the movement of various molecules in and out of cells in the body. Many other enzymes in the liver do not function properly. There is also decreased synthesis of *heme*, which as you know, is a component of haemoglobin. Accumulation of fumaryl acetoacetate and maleyl acetoacetate leads to changes in chemical composition of DNA causing formation of tumor. Various symptoms observed in the acute form are listed in Table 12.2. Plasma tyrosine levels are elevated (6-12 mg/dl) as are those of methionine. In the acute form, without treatment, death from liver failure ensues in 6-8 months. There is also a chronic form in which similar but milder symptoms lead to mild mental retardation and death occurs by age 10. Diet low in tyrosine and phenylalanine and in some cases, low in methionine will provide relief. When the diet is low in methionine, cysteine supplementation must be recommended. Inclusion of *hematin* (hydroxide of heme with the iron in the ferric state) compensates reduced heme biosynthesis. Plasma phenylalanine levels should be maintained between 40-80 mol/L and plasma tyrosine levels between 50-150 mol/L. In this disease, prenatal diagnosis is possible, which involves measuring fumaryl acetoacetate hydrolase activity in cultured amniotic fluid cells.

Tyrosinemia Type II (Richner-Hanhart Syndrome) (Oculocutaneous Type)

This condition is caused by deficiency of hepatic *tyrosine aminotransferase* (also commonly called tyrosine transaminase). It catalyzes the first step in the catabolism of tyrosine forming the corresponding keto acid, p-hydroxy phenyl pyruvic acid as shown in Figure 12.2. Here too, plasma tyrosine levels are elevated (4-5 mg/dl) and tyrosine crystals deposit in cells causing inflammation. This is the more common type. There is moderate mental retardation. Tyrosine and phenylalanine restricted diet is essential.

Neonatal Tyrosinemia

In *neonatal tyrosinemia,* the defective enzyme is *p-hydroxy phenyl pyruvic hydroxylase* which normally converts p-hydroxy phenyl pyruvic acid to homogentisic acid. The condition is asymptomatic and is more common in premature infants.

12.3.4 Albinism

Albinism is another congenital defect of tyrosine metabolism in which there is a decrease or absence of *melanin* formation (hypomelanosis). Melanin, you may already know, is a pigment which gives colour to skin, hair and eyes. Melanins are the *polymers of tyrosine catabolites*. The defect is due to the deficiency of the enzyme *tyrosinase* (tyrosine hydroxylase), a copper-containing oxidase, which converts tyrosine to 3,4-dihydroxyphenylalanine (DOPA), as can be seen in Figure 12.2. Normally DOPA through a series of steps gets converted to melanin. The defect may involve the entire melanocyte system or only one locus of melanocyte. In addition to the actual synthesis of melanin, there are also processes involving the formation and transport of the melanin containing bodies (melanosomes). Defects could be present in any of the above mechanisms.

There are various types of hereditary albinism in which pigment is lacking only from certain parts of the body such as eyes, patches of skin and areas of hair. Ten forms of human oculocutaneous (defect in eye and skin) have been identified. All ten forms can be differentiated on the basis of their clinical, biochemical, ultrastructural (cell structure) and genetic characteristics. Most severe form is *tyrosinase-negative* (ty-neg) where there is a total absence of pigments. In tyrosinase-positive (ty-pos) patients, as they grow older, some pigmentation develops and visual activity increases. There is a universal, generalized or localized albinism. Differences between the various forms of hereditary albinism are given in Table 12.2.

Patients with universal albinism or generalized albinism have white or very pale yellow hair which is silky in texture. The pupils of the eye appear to be red and the iris is pink or bluish from reflected light. Patients are very sensitive to light (photophobia). Hence prevention of exposure to sunlight and proper protection of eyes by dark glasses is recommended. Patients are also susceptible to skin cancer since the light coloured skin permits UV rays of the sun to penetrate inside. Albinism is transmitted by autosomal recessive inheritance. Ocular albinism in addition to autosomal recessive inheritance also shows X-linked pattern of inheritance.

Table 12.1: Disorders of aromatic amino acid metabolism

Name of disease	Defective enzyme	Amino acid involved	Amino acid/metabolite accumulated	Reported incidence	Beneficial diet therapy
1) Alcaptonuria	Homogentisate oxidase	Phenylalanine Tyrosine	Homogentisate	2-5 per million live births	Phenlyalanine and tyrosine restriction Ascorbic acid supplementation
2) Phenylketonuria (PKU)	Phenylalanine hydroxylase	Phenylalanine	Phenylalanine, phenylpyruvate, phenyllactate, phenylacetate	1:10,000 white newborns 1:132,000 black newborns	Phenylalanine restricted diet Tyrosine supplementation
3) Tyrosinemia Type I (Tyrosinosis)	Fumaryl acetoacetate hydrolase and maleyl acetoacetate hydrolase	Tyrosine Phenylalanine ± Methionine	Tyrosine, phenylalanine, succinyl acetone, fumaryl acetoacetate, maleyl acetoacetate, δ-amino levulenate, ± methionine	–	Diet low in tyrosine, phenylalanine, ± methionine High carbohydrate feeds (65-75% of calories), hematin supplementation
4) Tyrosinemia Type II (Richner-Hanhart Syndrome)	Tyrosine transaminase	Tyrosine	Tyrosine, p-hydroxy phenylpyruvate, p-hydroxy phenyllactate, p-hydroxy phenylacetate, N-acetyl tyrosine, tyramine	–	Phenylalanine and tyrosine restriction required less severe than Type I Early but transient dietary protein restriction
5) Neonatal tyrosinemia	p-hydroxy phenyl pyruvate hydroxylase	Tyrosine	Tyrosine, phenylalanine, p-hydroxy phenyl acetate, N-acetyl tyrosine, tyramine	–	–
6) Albinism	Tyrosine hydroxylase (tyrosinase)		–	1:20,000	–

Table 12.2: Clinical symptoms of disorders of aromatic amino acid metabolism

Name of disease	Clinical symptoms
1) Alcaptonuria	In later life, ochronosis and deforming arthritis.
2) Phenylketonuria (PKU)	Mental retardation, unusual irritability, epileptic seizures, tremors, hand posturing, rhythmic rocking back and forth, severe temper tantrums, eczema, decreased pigmentation leading to blue eyes, blond hair and fair skin, 'mousey odour'.
3) Tyrosinemia Type I	Diarrhoea, vomiting, 'cabbage-like' odour, failure to thrive, renal tubular dysfunction, vitamin D-resistant rickets, acute intermittent porphyria-like symptoms (abdominal pain, neuropsychiatric findings and sensitive to light), hypertension, episodic behaviour (go into periodic confinements), being photosensitive favour nocturnal activities. Progressive liver and renal failure. Rapid treatment of infections to prevent 'catastrophic' catabolic state. Liver transplants may be required.
4) Tyrosinemia Type II	Persistent keratitis and hyperkeratosis occur on the fingers, palms of hands and soles of feet, moderate mental retardation.
5) Neonatal tyrosinemia	Generally asymptomatic, but long term effects may include mild mental retardation.
6) Albinism	Tyrosine hydroxylase positive (ty-pos)- presence of some visible pigment and white-yellow to light tan hair. Tyrosine hydroxylase negative (ty-neg)- absence of total visual pigment.

	Universal albinism-absence of melanin in hair bulb, skin and retinal pigment epithelium.
	Generalized albinism- absence of melanin in skin, hair, and retina, but presence in iris and occasionally skin.
	Localized albinism-absence of melanin only in eyes or hair or skin.

Check Your Progress Exercise 1

1) What do you understand by the term 'inborn errors of metabolism'? Discuss its etiology.

   ....

   ....

   ....

2) How can we detect genetic diseases? Briefly discuss how these can be treated?

   ....

   ....

   ....

3) List any three aromatic amino acids and their metabolic disorders. Also mention the defective enzymes involved.

   ....

   ....

   ....

4) Comment on the following statements:
   a) Tyrosine becomes an essential amino acid for PKU patients.

   ....

   ....

   b) In Alcaptonuria, urine upon standing becomes dark in colour.

   ....

   ....

   c) Inclusion of hematin is beneficial in Tyrosinemia I.

   ....

   ....

   d) PKU is a neuro-metabolic disorder.

   ....

   ....

   e) Patients with albinism suffer from photophobia.

   ....

   ....

5) Match the following:

A	B
a) Alcaptonuria	i) Increased visual activity
b) Tyrosinase	ii) Tyrosine supplementation
c) PKU	iii) Persistent keratitis
d) Tyrosinemia Type I	iv) Dark-coloured urine
e) Albinism	v) Hypomelanosis

We will next have a look at the diseases caused by disorders of non-aromatic amino acids. All these diseases have autosomal recessive inheritance. While you are reading the following text, also refer to the other details related to these disorders given in Tables 12.3 and 12.4.

12.3.5 Arginemia (Hyperargininemia)

Arginemia is a genetic defect caused due to the defective enzyme *arginase*. In this disease, one step in the synthesis of urea from ammonia is affected. You have already studied urea cycle. Look up Unit 8 for this reaction. As you know, urea synthesis involves five steps. In fact there are diseases associated with each of the five enzymes involved in urea synthesis. We will have a look at just one of them. Arginemia is the least common of the disorders of urea cycle. All disorders of urea synthesis ultimately cause accumulation of ammonia. Ammonia, you already know, is a neurotoxin. It affects the CNS finally leading to severe mental retardation and coma. Detailed symptoms of this disorder are given in Table 12.4.

So we have seen that the enzyme defective in case of this disorder is *arginase*, which in normal persons catalyzes the conversion of arginine to urea and ornithine. Hence there is also accumulation of arginine. The excess arginine competes with lysine and cystine for reabsorption in the renal tubules, which are then excreted in urine (lysine-cystinuria). Aim of dietary treatment should be to maintain blood NH_3 levels below 50 mmol/L. A low-protein diet lowers plasma ammonia levels and abolishes lysine-cystinuria.

12.3.6 Homocystinuria (Homocysteinemia)

Homocystinuria is a rare metabolic condition characterized by an excess of the compound homocystine in the urine. In this disease, metabolism of the sulfur containing essential amino acid, methionine is affected.

In most cases, homocystinuria is caused by reduced activity of an enzyme known as *cystathionine beta-synthase* (CBS). Hence as shown in Figure 12.3, the homocysteine formed from methionine cannot be further metabolized to cystathionine. Accordingly, homocysteine accumulates. Two molecules of homocysteine combine to form the disulfide, homocystine which is excreted in urine. Various types of homocystinurias are known. The most common (Type I) is discussed here. Upto 300 mg of homocystine is excreted daily in urine. Normally homocysteine is further catabolized via cystathionine to yield cysteine. Hence cysteine becomes an essential amino acid in this condition. Diet has to be complemented with special preparations low in or free of methionine. Additionally, choline should be present as a methyl donor along with cysteine. Such commercially produced formulae are not available and have to be imported at a high cost. Plasma levels of methionine must be maintained between 0.03-0.1 mmol/L and cystine levels between 0.037-0.085 mmol/L.
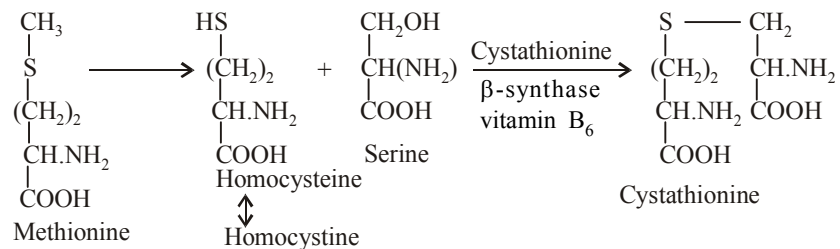
Figure12.3 : Metabolism of methionine

Increasingly homocystinuria is being linked as a high risk factor for *atherogenesis*. Excess homocysteine forms *homocysteine thiolactone*, a highly reactive intermediate that thiolates free amino groups in low density lipoproteins (LDL) and causes them to aggregate and be endocytosed by *macrophages* (phagocytic cells). The lipid deposits form atheromas (cysts). Homocysteine also causes lipid oxidation and platelet aggregation which in turn leads to fibrosis and calcification of atherosclerotic plaques.

Some dietary tips for management of this disorder have been highlighted here:

*   Foods to be excluded – Meat, chicken, fish, eggs, milk and dairy products, wheat flour, *bajra*, maize, rice, pulses, nuts and dried fruits, peas etc.

*   Foods to be consumed in moderate amounts – Most vegetables and fresh fruits.

*   Unrestricted foods – Sugars, fats and oils, tea, coffee, salt, spices, arrowroot, cornflour, sago.

You will realize how difficult it will be to formulate a satisfactory diet.

If there is some residual enzyme activity, the condition improves after treatment with large amounts (supraphysiologic) of pyridoxine. Hence both vitamin B_6-responsive and vitamin B_6-unresponsive forms are known (see Box 3). However excess vitamin B_6 for prolonged periods may cause peripheral neuropathy and liver injury. Consequently regular monitoring is needed.

12.3.7 Histidinemia

Histidinemia is a rare hereditary metabolic disorder characterized by a deficiency of the enzyme *histidase*, which is necessary for the metabolism of the amino acid histidine. It is a disorder of histidine metabolism due to inadequate activity of the hepatic enzyme *histidase* (also called histidine α-deaminase). This enzyme normally converts histidine to urocanic acid as can be seen in Figure 12.4. Due to the metabolic block, histidine levels increase in blood. The alternate route is transamination to form imidazole pyruvic acid, which now being in excess, is excreted in the urine. Imidazole lactic acid and imidazole acetic acid are formed by reduction and oxidation repectively of imidazole pyruvic acid and have also been detected in urine. Very often speech development is retarded. Some cases also show signs of mental retardation. Screening of over 20 million newborn infants has revealed a worldwide incidence of 1:10,000. Diagnosis can be done by assaying (estimating) for histidase. The assay for histidase uses skin which produces urocanate as a constituent of sweat.
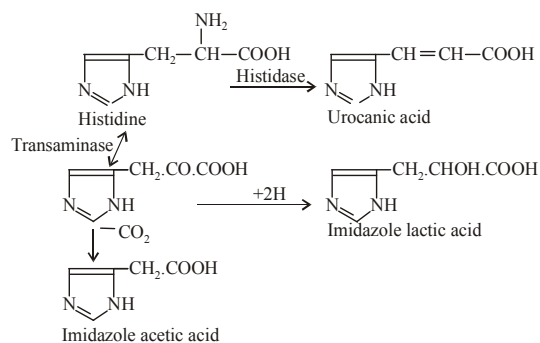
Figure 12.4 : Metabolism of histidine

12.3.8 Primary Hyperoxaluria

Primary hyperoxaluria is a rare metabolic disease characterized by high levels of oxalate in the blood and urine. The amount of oxalate excreted is unrelated to the dietary intake of oxalate. The excess oxalate arises from deamination of glycine forming glyoxylate which is not catabolized further and instead is oxidized to oxalate which is excreted in urine as shown in Figure 12.5. Oxalate cannot be further metabolized in the body. Normally glyoxylate and α-ketoglutaric acid undergo synergistic decarboxylation catalyzed by α-ketoglutarate:glyoxylate carboligase to form α-hydroxy β-keto adipate. In primary hyperoxaluria, there is a deficiency of this enzyme in liver, spleen and kidney. Solubility of oxalate is poor, hence excess of oxalate in urine leads to supersaturation. This results in precipitation of calcium oxalate leading to stone formation (oxalate calculi, *nephrolithiasis*). There is a recurrent infection of the urinary tract. In addition, there is a widespread deposit of oxalate crystals throughout the body called *oxalosis*. Death occurs in childhood or early adult life from renal failure or hypertension. Hence early diagnosis is essential.
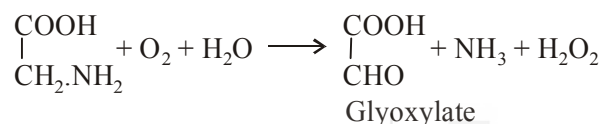
$$\begin{array}{c} COOH \\ | \\ CH_2.NH_2 \end{array} + O_2 + H_2O \longrightarrow \begin{array}{c} COOH \\ | \\ CHO \end{array} + NH_3 + H_2O_2$$
Glyoxylate

Figure 12.5: Metabolism of glycine

The major approaches to therapy have been directed either towards reduction of oxalate synthesis and excretion or towards prevention of calcium oxalate stone formation at a given level of urinary oxalate. Trapping of glycine as hippurate with benzoate administration has been attempted. Maintenance of a large urine volume is also recommended.

12.3.9 Cystinuria (Cystine-Lysinuria)

Cystinuria is an inherited metabolic disorder characterized by the abnormal movement (transport) in the intestines and kidneys, of certain amino acids. These include *cystine, lysine, arginine* and *ornithine*. Excessive amounts of undissolved cystine in the urine (cystinuria) cause the formation of stones (calculi) in the kidney, bladder and/ or ureter.

In this inborn error of metabolism, there is a defect in the renal reabsorptive mechanisms as a result of which four amino acids – cystine, lysine, arginine and ornithine are not reabsorbed in the kidney tubules. Hence they are found in excessive amounts in urine. Urinary excretion of cystine increases upto 30 times normal. Cystine is relatively insoluble leading to cystine calculi. Apart from this, cystinuria is benign (harmless).

12.3.10 Cystinosis

Cystinosis is a rare inherited disorder characterized by the impaired transport of cystine out of lysosomes. *Cystine*, as you know, is an amino acid found in many different proteins in the body. *Lysosomes*, on the other hand, are *membrane bound particles within cells, which aid in intracellular digestive function*. Cystinosis is characterized by the accumulation of cystine in tissues throughout the body, which can cause certain organs to malfunction.

Cystinosis, therefore, is a rare lysosomal disorder characterized by the excessive deposition of cystine crystals in various tissues of the body. Hence it is also called *cystine storage disease*. Normal transport of cystine brought about by carrier molecules is defective. Kidney is particularly affected and patients usually die young from acute renal failure. Prenatal diagnosis is an established procedure. Affected foetuses have 20 to 100 times the usual amount of free cystine in most internal organs.

12.3.11 Maple Syrup Urine Disease (MSUD)

MSUD is an inherited metabolic disease caused by the inability of the body to metabolize the branched-chain amino acids– *valine, leucine* and *isoleucine*. As you have already read in Unit 2, these 3 amino acids show a branch point in their structure and hence are commonly referred to as *branched-chain amino acids*. The disease is called MSUD because urine from affected people has a smell resembling maple sugar or burnt sugar. In the catabolism of these 3 amino acids, they first undergo transamination as shown in Figure 12.6. Transamination, you already know, is a process undergone by various amino acids during their breakdown (as you may recall reading in Unit 8). The enzyme catalyzing this reaction is *transaminase* (or also known as amino transferase). One transaminase can act on all these 3 amino acids. Here the branched-chain amino acid reacts with any α-keto acid (like α-keto glutaric acid) and gets converted to the corresponding branched-chain α-keto acid. In normal individuals, this branched-chain α-keto acid is acted upon by α-keto acid decarboxylase complex. This is an oxidative decarboxylation reaction similar to the reaction catalyzed by pyruvate dehydrogenase complex (following glycolysis) or α-ketoglutarate dehydrogenase complex (in citric acid cycle) (as you may recall studying in Unit 6). You will recollect that all such reactions require 5 cofactors-thiamin diphosphate (TDP), lipoic acid, coenzyme A, FAD and NAD^+. The end product is the corresponding branched-chain coenzyme derivative. However, in MSUD, this α-keto decarboxylase is defective. *Hence branched-chain α-keto acids accumulate in blood and are excreted in urine.* The keto acid of L-leucine called α-keto isocaproic acid is found in highest amounts. *Thus MSUD is also known as branched-chain ketonuria.* In addition, the branched-chain amino acids also accumulate in blood. As all the three branched chain amino acids are excreted, it suggests that one enzyme complex is involved in the decarboxylation step.
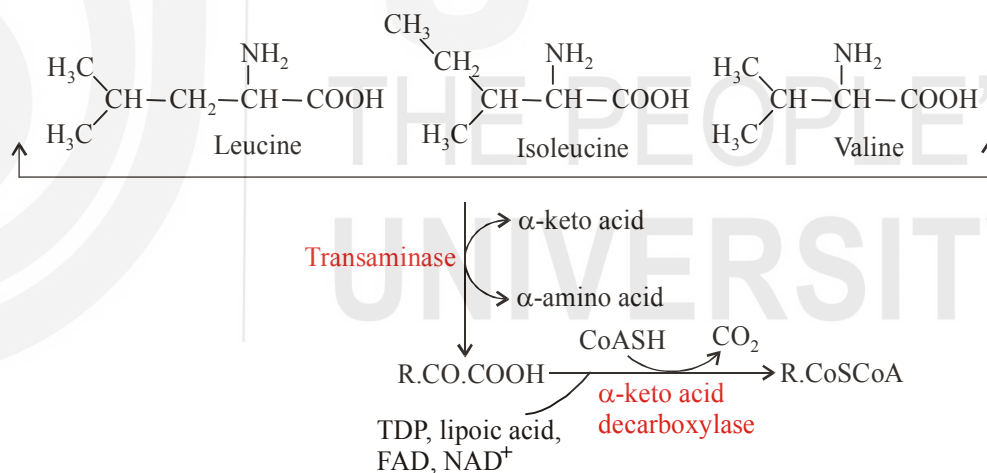
Figure 12.6 : Catabolism of branched chain amino acids

Affected infants begin to show clinical symptoms, as highlighted in Table 12.4, between the third and fifth days of life. Infants die within a few weeks or months. Hence early diagnosis, especially prior to 1 week is essential. This is done by measuring the level of the decarboxylase complex. Treatment has to be started immediately after birth. MSUD is much more difficult to treat as compared to PKU since three essential amino acids are involved. Intake of all the 3 branched-chain amino acids must be restricted. Hence very little of natural protein can be given. Appropriate IV therapy must be initiated to correct acidosis and electrolyte imbalances which may occur by the time diagnosis is made. Further, constant fluctuation in the tolerance for the amino acids involved, requires frequent monitoring of blood for the 3 branched-chain amino acids (plasma aminograms). The levels for leucine must be maintained between 100-700 µmol/L and between 100-400 µmol/L for valine and isoleucine. Even with strict dietary regimen, height and weight lie in the lower normal range with some mental retardation.

Administration of vitamin cofactors (cofactor therapy) is beneficial in many patients. The basis of use of cofactors in the diseases is given in Box 3.

Table 12.3: Disorders of non-aromatic amino acid metabolism

Name of disease	Defective enzyme	Amino acid involved	Amino acid/metabolite accumulated	Reported incidence	Beneficial diet therapy
1) Arginemia	Arginase (erythrocytes)	Arginine	Arginine, NH_3	–	Low protein diet, frequent small meals to avoid sudden increases in blood NH_3 levels
2) Homocysti-nuria	Cystathionine β-synthase	Methionine	Homocystine S-adenosyl methionine	1:160,000 live births	Low methionine, high cysteine diets, choline (or betaine) as a methyl donor, VitaminB$_6$ supplementation may be helpful
3) Histidinemia	Histidase	Histidine	Histidine imidazole pyruvate imidazole acetate imidazole lactate	1:10,000 new borns screened	Histidine free diet
4) Primary hyperoxaluria	Glycine oxidase	Glycine	Oxalate	–	Reducing availability of glycine by dietary protein restriction
5) Cystinuria	Renal reabsorptive mechanism	Cystine	–	–	–
6) Cystinosis	Cystine transporter of lysosomal membranes	Cystine	Cystine	1:100,000	Providing adequate fluid intake for increasing cystine solubility
7) MSUD	α-keto acid decarboxylase	Branched chain amino acids	Leucine Isoleucine valine	1:185,000	Restriction of intake of all 3 branched chain amino acids. High caloric intake to prevent breakdown of endogenous protein. Correction of metabolic acidosis and electrolyte imbalances through appropriate IV therapy

Table 12.4: Clinical symptoms of disorders of non-aromatic amino acid metabolism

Name of disease	Clinical symptoms
1) Arginemia	Vomiting in infancy, avoidance of high protein foods, intermittent ataxia, irritability, lethargy, mental retardation, respiratory distress, convulsions and coma.
2) Homocystinuria	Thrombosis, osteoporosis, dislocated lenses in the eyes, other ocular abnormalities and frequently mental retardation.
3) Histidinemia	Speech development often retarded. Some patients show signs of mental retardation.
4) Primary hyperoxaluria	Calcium oxalate urolithiasis, recurrent infection of the urinary tract, widespread deposits of oxalate crystals throughout the body called oxalosis.
5) Cystinuria	Cystine calculi
6) Cystinosis	Cystine crystals deposited in tissues and organs particularly reticuloendothelial system, various renal functions impaired.

7) MSUD	Difficulty in feeding, vomiting, failure to thrive, absence of Moro reflex, extensive brain damage, retarded physical and mental development.

Box 3 : Use of cofactors (cofactor therapy) in inborn errors of amino acid metabolism

Use of nutritional intervention (wherever possible) is the first form of therapy. A second mode of therapy, which works in some cases, is the use of vitamin cofactors. A number of enzymatic disturbances of amino acid metabolism have been identified, which respond to supraphysiologic (upto 100 times the physiologic dose) amounts of various water soluble vitamins including B_1, B_6, B_{12}, folic acid, biotin and niacinamide.

What is the biochemical basis for this?

This could be explained by 2 general classes of mutation:

- Those that involve vitamin metabolism *per se*. This could occur at various steps (in intestinal absorption, plasma transport, cellular entry, conversion of vitamin to active coenzyme form), with a different protein functioning at each step and hence subject to genetic mutation resulting in defective vitamin activity. Without the vitamin cofactor, the enzyme will not be able to work.

- Vitamin metabolism is normal but the defect involves a specific apoenzyme (protein part of the active enzyme) that needs a vitamin cofactor for normal activity.

If as a result of genetic mutation, there is loss of complete activity of any of these proteins, then the condition will not respond to vitamin therapy. But if the mutations involved are 'leaky', i.e. there is some residual activity, then administration of supraphysiologic amounts of vitamin may allow for enhanced residual activity according to mass action principles. The more residual enzyme (protein) activity present, the more dramatic the response to the vitamin therapy.

However, a word of caution must be introduced here. The side effects of these supraphysiologic doses of the vitamins have to be looked into. And this is as important as their therapeutic value.

Check Your Progress Exercise 2

1) Briefly justify the following statements:

a) High calorie intake is recommended in MSUD.

....

....

b) It is more difficult to treat nutritionally, MSUD as compared to PKU.

....

....

c) Cysteine must be included in the diet in homocystinuria.

....

....

d) Cystinosis causes malfunctioning of certain organs.

....

....

e) Homocystinuria is a high risk factor for atherogenesis.

....

....

2) Name the defective enzyme in the following diseases:

a) Homocystinuria

....

b) Arginemia

....

c) Histidinemia

....

d) MSUD

....

e) Primary Hyperoxaluria

....

3) Tick the correct answer:

a) Physical and mental retardation has been observed in cases of (MSUD/ histidinemia).

b) In MSUD oxidative decarboxylation is brought about by (one enzyme/ three different enzymes).

c) CNS symptoms are observed in arginemia due to neuro toxicity of (arginine/ ammonia).

d) Cystine is deposited in most internal organs in (cystinosis/cystinuria).

e) Primary hyperoxaluria leads to (nephrolithiasis/platelet aggregation).

The discussion above focussed on the disorders of protein metabolism. Next, we shall review the disorders of carbohydrate metabolism.

12.4 DISORDERS OF CARBOHYDRATE METABOLISM

Here in this section, we will have a look at the defects involving both pentose (5-carbon) and hexose (6-carbon) sugars. The diseases which we will study, however, occur rarely. They all have an autosomal recessive pattern of inheritance. Nutritional intervention is possible in many of these diseases. As you read the text given below, follow the other characteristics listed in Tables 12.5 and 12.6. Many of the chemical reactions affected in the following disorders have already been described in Unit 6. So you should have a look at them again.

We start with the disease pentosuria.

12.4.1 Pentosuria (Essential Pentosuria)

Pentosuria is *an inborn error of carbohydrate metabolism, characterized by the excessive urinary excretion of the sugar xylitol*. It is caused by a defect in the enzyme *xylitol dehydrogenase,* by which xylitol is normally metabolized. No disabilities are incurred, and no dietary or other measures are necessary.

Since in this condition the enzyme NADP-dependent xylitol dehydrogenase is defective, the conversion of L-xylulose (which is a pentose sugar with a ketonic group) to xylitol (the corresponding alcohol formed when ketone group is reduced to CHOH group) does not take place. Persons excrete as much as 4 g L-xylulose/day in urine. However, it is simply a harmless biochemical anomaly with luckily no clinical symptoms.

12.4.2 Fructosuria (Essential Fructosuria)

Fructosuria is a *genetic condition with inability to process fructose i.e. fruit sugar*. It is characterized by the excretion of fruit sugar (fructose) in the urine. Normally, no fructose is excreted in the urine. This condition is caused by a deficiency of the enzyme *fructokinase* in the liver.

The dietary fructose absorbed in the intestine is transported by portal vein to the liver. Here this enzyme fructokinase phosphorylates fructose to form fructose-1-phosphate (look up glycolysis in Unit 6 for details). Since fructokinase is defective, conversion of fructose to fructose-1-phosphate does not take place and fructose absorbed in the intestine accumulates and is excreted in urine. However, this condition too is completely harmless.

12.4.3 Hereditary Fructose Intolerance

Hereditary Fructose Intolerance (HFI) is an autosomal recessive disorder of fructose metabolism due to a deficiency of *fructose-1-phosphate aldolase* activity, which results in an accumulation of fructose-1-phosphate in the liver, kidney and small intestine.

The enzyme *fructose-1-phosphate aldolase* normally converts fructose-1-phosphate to *dihydroxyacetone phosphate* and *glyceraldehyde* as you have already learnt earlier in the glycolysis pathway in Unit 6. In the absence of the enzyme, fructose-1-phosphate accumulates. The accumulated fructose-1-phosphate inhibits glycogen breakdown and glucose synthesis, thereby causing severe hypoglycemia following ingestion of fructose. Clinical symptoms include severe abdominal pain, vomiting and hypoglycemia following ingestion of fructose or other sugars metabolized through fructose-1-phosphate.

Unlike fructosuria, in this condition severe symptoms are encountered since all the inorganic phosphate (Pi) is tied up as fructose-1-phosphate and thus is not available for phosphorylation of ADP to form ATP. Thus there is depletion of Pi (inorganic phosphate) and ATP. During breast feeding, no metabolic derangement occurs since breast milk does not contain fructose or sucrose (as you know sucrose is made up of glucose and fructose). But if the newborn infant receives a milk formula with fructose or sucrose, the infant develops various symptoms as highlighted in Table 12.6. But at weaning, with the intake of vegetables and fruits containing fructose, symptoms appear. There is *fructosemia* (high levels of fructose in blood), *fructosuria* (fructose in urine), *hypophosphatemia* (low phosphate level in blood) and *hypoglycemia* (low blood sugar) despite the presence of high glycogen reserves. This is because accumulation of fructose-1-phosphate inhibits the activity of liver phosphorylase (which breaksdown liver glycogen to glucose) by allosteric mechanisms (look up glycogen breakdown in Unit 6). Hence fructose/sucrose free diet should be initiated as soon as diagnosis is made. Adequate fructose restriction is reported to normalize liver and renal function. Foods of animal origin (meat and dairy products) are free of fructose unless they have been processed using fructose/sucrose. Older children have been reported to develop an aversion to sweets and fruits. The diet, free of fructose, obviously eliminates many pleasant tasting foods normally enjoyed by children.

12.4.4 Galactosemia

Galactosemia is an inherited disorder characterized by an inability of the body to utilize galactose. Galactosemia means "galactose in the blood".

In this hereditary disease, patients are not able to metabolize galactose. As a result, galactose accumulates leading to *galactosemia* (high levels of galactose in blood) which is accompanied by *galactosuria* (excretion of galactose in urine). This may be caused due to defect in any of the enzymes involved in metabolism of galactose. Look up galactose metabolism in Unit 6. The most common type of galactosemia is due to deficiency of the enzyme *galactose-1-phosphate uridyl transferase* which converts galactose-1-phosphate to glucose-1-phosphate. Hence galactose-1-phosphate and galactose accumulate in the body causing various symptoms. The galactose absorbed following intestinal digestion of milk lactose remains unutilized in the infant. Unavailability of sufficient carbohydrate as a source of energy leads to usage of tissue proteins and fats as sources of energy. This can lead to *amino aciduria* (high level of amino acids in urine) and *ketosuria* (presence of ketone bodies in urine). Excess galactose is reduced by aldose reductase in the eye to the corresponding alcohol (galactitol) which accumulates causing cataract. In untreated cases, symptoms as listed in Table 12.6 usually begin days to several weeks after birth. Some infants are even born with cataracts and cirrhosis due to maternal ingestion of galactose. Those who survive are usually malnourished and dwarfed at 2 or 3 months of age and are mentally retarded.

Treatment should begin as early as possible, in the first week of life since breast milk contains lactose (made up of glucose and galactose). Lactose free formulae are available in our country and hence it has been reported that this disorder can be managed with ease. However, even with excellent nutrition control, children may have a lower IQ, difficulty with language, abstract thinking and visual perception. Females may have ovarian failure. These may be related to intrauterine damage due to maternal blood galactose crossing the placenta into the vulnerable foetus. Restriction of pulses, beans and peas has been recommended due to presence of galactose containing oligosaccharides (cabohydrates containing 2-10 monosaccharide units). However since they are not digested in human GI tract, galactose may not be released for absorption. With increased intake of solid foods, dietary regimen becomes easier. However, total relaxation in diet restriction is not recommended even in adult life.

12.4.5 Hereditary Lactose Intolerance

Lactose intolerance is an inability to digest milk sugar due to a specific deficiency of the enzyme *lactase*, and not, as commonly believed, a "milk allergy."

Majority of Asians, Africans and American Blacks are affected by this hereditary condition. Lactose intolerance appears to develop in healthy young children at about 3 years of age in those population groups having a high prevalence rate. In others, it may not occur until 13 years of age. The condition is due to a gradual decline in activity of *lactase* enzyme owing to reduction in synthesis of the enzyme. Lactase is an intestinal enzyme which hydrolyzes dietary lactose to glucose and galactose during the process of digestion. The decrease in activity occurs probably because there is a failure in translation of lactase mRNA. Hence the enzyme is not synthesized and there is accumulation in the intestine of undigested lactose which is osmotically active, so that it holds water leading to diarrhoea. Additionally intestinal bacteria bring about fermentation of lactose with the formation of short-chain acids and gases like H_2 and CO_2. This causes flatulence. All foods containing lactose should be eliminated from the diet. This would include milk and milk products (ice creams, milk shakes).

12.4.6 Glycogen Storage Disease

In 1929, *Von Gierke* first described a glycogen storage disease in which as the name suggests, large amounts of glycogen were stored in the liver. *Glycogen storage disease (glycogenosis) is a generic term used to describe a group of inherited disorders in which either the synthesis or breakdown of glycogen is defective.* This results in deposition of an abnormal type or quantity of glycogen in the tissues. Accumulation of large amounts of glycogen disrupts the normal functions of the cell. As you already know, glycogen is a polymer of glucose units and thus is the storage form of glucose in the body. Whenever blood sugar level goes down, liver glycogen is broken down to glucose units which then enter the blood and raise the sugar level. Muscle glycogen is used to supply glucose units for muscular activity. Hence in glycogen storage diseases, several clinical symptoms occur due to defective glycogen metabolism. In some of the cases, nutritional intervention can reduce the severity of the symptoms. Eight different types have been described which differ with respect to the enzyme which is defective. Accordingly the symptoms and management also vary. For easy understanding of the symptoms (of the eight different types), the information has been tabulated in Table 12.7. Read it carefully and also at this point please revise synthesis and breakdown of glycogen done in Unit 6.

Table 12.5: Disorders of carbohydrate metabolism

Name of disease	Defective enzyme	Amino acid involved	Amino acid/metabolite accumulated	Reported incidence	Beneficial diet therapy
1) Pentosuria	NADP-dependent xylitol dehydrogenase	L-Xylulose	L-Xylulose	1:50,000	No treatment needed
2) Fructosuria	Hepatic fructokinase	Fructose	Fructose	1:130,000	No treatment needed
3) Hereditary fructose intolerance	Hepatic aldolase B	Fructose	Fructose-1-phosphate	1:40,000	Fructose/sucrose free diet. Exclusion of vegetables and fruits
4) Galactosemia	Galactose-1-phosphate uridyl transferase	Galactose	Galactose-1-phosphate Galactitol (eyes)	1:50,000-1:100,000	Dietary exclusion of galactose and lactose throughout childhood (galactose/lactose free milk substitutes to be used). Partial relaxation in adult life.
5) Hereditary lactose intolerance	Lactase	Lactose	Undigested lactose in intestine	–	Elimination of lactose from diet

Table 12.6: Clinical symptoms of disorders of carbohydrate metabolism

Name of disease	Clinical symptoms
1) Pentosuria	No Symptoms. Condition compatible with health and well being.
2) Fructosuria	No clinical symptoms reported. Only delayed fructose intolerance reported.
3) Hereditary fructose intolerance	Frequent vomiting, poor feeding, fever, poor growth, pallor, diarrhoea, lethargy, jaundice, hepatomegaly, oedema, ascites, coma, convulsions
4) Galactosemia	Vomiting, failure to thrive, fever, jaundice, hepatomegaly, liver cirrhosis, cataracts, mental retardation
5) Hereditary lactose intolerance	Abdominal cramps, diarrhoea, flatulence. Production of gases like H_2 and CO_2 and short chain acids, all of which serve as intestinal irritants.

Table 12.7: Glycogen storage diseases

Glycogenosis	Name	Defective enzyme	Prevalence	Characteristics
Type I	Von Gierke's disease	Glusose-6-phospatase	~1:100,000	Liver and renal tubule cells loaded with glycogen leading to organomegaly. Anorexia, weight loss, vomiting, hypoglycemia, convulsions and coma. Low response of blood glucose to injection of epinephrine. Hyperuricemia (high uric acid levels in blood) causing clinical gout. Death ensues within 2 years. Frequent feeding, high protein diet, nasogastric infusion of glucose, oral uncooked starch acting as slow release form of glucose beneficial.
Type II	Pompe's disease	Lysosomal α-1$\rightarrow$4 and α-1$\rightarrow$6 glucosi-dase (acid maltase)	~1:100,000	There is massive cardiomegaly and heart failure by 1 year of age. Prenatal diagnosis by enzyme assay offers the only form of management.
Type III	Limit dextrinosis, Forbe's or Cori's disease	Debrancher	~1:100,000	Glycogen with enormous branches and very short outer chains stored in liver and muscle. Symptoms milder than those seen in Type I. Similar dietary management indicated.
Type IV	Andersen's disease	Brancher	~1:500,000	Glycogen with few branch points accumulates leading to cirrhosis, hepatosplenomagaly with bleeding tendencies. Death due to cardiac or liver failure in first year of life.
Type V	McArdle's disease	Muscle phosphory-lase	~1:500,000	Muscles have abnormally high content of glycogen (2.5-4.0%). Little or no lactate in blood after exercise since muscle glycogen unavailable as fuel. Hence markedly diminished tolerance to exercise. Clinically patients are well developed, normal and no abnormalities at rest. Avoidance of extreme exercise advocated.
Type VI	Her's disease	Liver phosphorylase	~1:200,000	High glycogen content in liver with hepatomegaly. Tendency towards hypoglycemia.
Type VII	Taur's disease	Phosphofructokinase in muscle and erythrocytes	~1:500,000	Glycogen storage in muscle due to activation of glycogen synthase combined with inhibition of phosphorylase by accumulated glucose-6-phosphate. Also promotes PRPP synthesis leading to hyperuricemia and gout. Exercise intolerance and possibility of hemolytic anaemia.
Type VIII	–	Liver phosphorylase kinase	–	Due to kinase deficiency, liver phosphorylase cannot be activated leading to high glycogen content in liver.

Check Your Progress Exercise 3

1) Which sugars are involved in disorders of carbohydrate metabolism? List any three disorders.

   ....

   ....

   ....

2) Briefly justify the following statements:

   a) Extreme exercise should be avoided by patient's with McArdle's disease.

      ....

      ....

   b) Occurrence of cataracts is a common symptom in galactosemia.

      ....

      ....

   c) Unlike fructosuria, severe symptoms are encountered in hereditary fructose intolerance.

      ....

      ....

   d) Nutritional intervention should be started as early as possible in galactosemia.

      ....

      ....

   e) Glycogen with few branch points accumulates in Andersen's disease.

      ....

      ....

3. Name the defective enzyme in the following diseases:

   a) Von Gierke's disease

      ....

      ....

   b) Essential pentosuria

      ....

      ....

   c) Essential fructosuria

      ....

      ....

   d) Andersen's disease

      ....

      ....

   e) Galactosemia

      ....

      ....

4) Match the following:

A	B
i) Her's disease	a) Hepatomegaly
ii) Pompe's disease	b) Liver phosphorylase
iii) Galactosemia	c) Depletion of ATP
iv) Fructosuria	d) Xylitol dehydrogenase
v) Pentosuria	e) Cardiomegaly

12.5 DISORDERS OF LIPID METABOLISM

We will be discussing here three diseases involving lipid metabolism. In fact all the 3 conditions result in storage of lipid in the cell, i.e. *lipidosis*. Nutritional intervention is not possible in these three diseases. At the present time, no effective treatment is available. Administering the defective enzyme by a process called *enzyme replacement therapy* has been tried, but it has not been very successful. The difficulty is in obtaining a highly purified human enzyme along with administration [(has to be intravenous/intrathecal (injected into the fluid surrounding the spinal cord)]. Hence gene therapy of the future is the only hope. All these three diseases have recessive autosomal pattern of inheritance. Table 12.8 gives other details related to the diseases. Before going through the details it would be worthwhile to revise the structure of these molecules as given in Unit 2.

12.5.1 Gaucher's Disease (Glucosyl Ceramide Lipidosis)

Gaucher's Disease was observed by *Gaucher* in 1882 and is the most common inherited metabolic disorder of glycolipid (combination of carbohydrate and lipid) metabolism. In this disease, the defective enzyme is *glucocerebrosidase*. In normal individuals, this enzyme catabolizes glucocerebroside. Glucocerebroside or glucosyl ceramide is composed of equimolar portions of long-chain amino alcohol (alcohol containing amino group) called *sphingosine*, a long-chain fatty acid and glucose. The enzyme glucocerebrosidase breaks glucocerebroside into glucose and another compound containing sphingosine and long-chain fatty acid called *ceramide*. Hence, in Gaucher's disease, since this reaction cannot take place, glucocerebroside accumulates in the cells of the reticuloendothelial (blood forming) system. Thus these cells become enlarged. The cytoplasm of such cells is replaced entirely by the lipid and under the microscope the cells appear as large pale cells (cells do not take up the aqueous dye used for staining the cells). The cytoplasm of such cells when observed under the microscope looks like 'wrinkled tissue paper' or 'crumpled silk'. These cells are called *Gaucher's cells*.

The disorder has been detected in patients of all ages, symptoms may appear at any time. Accordingly, three different types have been described. At this point, see Table 12.8 for the clinical symptoms. As you would notice, Type 1 is the chronic type in which visceral organs like liver, spleen etc. are affected. But CNS is not involved. In Type 2, CNS is involved and hence it is an acute type with death occurring by 2 years of age. In Type 3 visceral organs and CNS are involved, but to a less severe extent. In Gaucher's disease since cells of the reticuloendothelial system are affected, blood abnormalities occur. Hence, surveillance by haematologists is necessary throughout life along with treatment for anaemia. When the spleen gets enlarged to a great extent, *splenectomy* (surgical removal of spleen) is necessary in many cases. Strong analgesics are needed for pain in bones and joints. The different types are genetically distinct. Type 1 is more common in Jews with a prevalence of 1:2500 births.

12.5.2 Niemann-Pick Disease (Sphingomyelin Lipidosis)

Niemann-Pick Disease, the hereditary metabolic disease, was first described by *Niemann* in 1914 and was later confirmed in 1927 by *Pick*. In this disease, there is an excessive storage of the lipid, *sphingomyelin*, which is a phospholipid. It is made up of the amino alcohol *sphingosine*, fatty acid, phosphoric acid and choline. The defective enzyme is *sphingomyelinase* which normally cleaves sphingomyelin forming phosphorylcholine and ceramide (sphingosine + long-chain fatty acid). Hence sphingomyelin accumulates in cytoplasm of cells of spleen, liver, bone marrow and lymph nodes. Here too because of excessive accumulation of lipid, the cells appear large and pale when seen under a microscope. They are called *Niemann-Pick cells*. Here too 3 clinically different types have been described. Type A develops in infancy with severe CNS damage. Type B is subacute and chronic with only visceral involvment. In Type C, both visceral organs and CNS are involved. Types D and E have also been described. At the present time, no treatment is available. Only prenatal diagnosis is possible by assaying (estimating) for sphingomyelinase activity in cultured amniotic cells. Therefore genetic counseling is important to prevent the birth of the affected baby. The disorder is panethnic (in people of different ethnic groups) in prevalence. Type A is found in people of Ashkenazic Jewish ancestry with a very high prevalence of 1:100.

12.5.3 Tay-Sach's Disease (TSD) (Ganglioside Lipidosis)

Tay-Sachs disease is an inherited disease caused by an abnormal gene. People with this abnormal gene lack an important enzyme called *hexosaminidase A (HEXA)* that helps to break down a fatty material called *ganglioside*. This material builds up in the brain, and eventually damages nerve cells and causes neurological problems.

In this disease, there is a severe deficiency of the enzyme Hexoaminidase A, which in normal persons catabolizes the lipid called *gangliosides*. Ganglioside is a *complex glycosphingolipid* (fatty acid+sphingosine+oligosaccharide chain). The oligosaccharide chain also contains sialic acid which is a 9-carbon sugar derivative. Gangliosides are present in high concentration in ganglion cells (neurons or nerve cells), hence the name. There are different types of gangliosides depending upon the number of sialic acid units and are accordingly called GM1, GM2, GM3. In Tay-Sachs disease, GM2 accumulates and hence is also referred to as GM2 ganglioside. Normally hexoaminidase A cleaves N-acetyl hexosamine from GM2. TSD is the most common ganglioside storage disease (gangliosidosis). Very severe symptoms are encountered in TSD. There is motor weakness and mental and motor deterioration progresses rapidly after 1 year of age, with death occurring by 3 years of age. For detailed symptoms of this disorder, look up Table 12.8. At present, no treatment is available and gene therapy is the only future hope.

Mass screening programs have been carried out in 73 cities in 13 different countries with over 312,000 individuals tested since 1970 for TSD. These community based voluntary screening programs have led to the identification of over 250 at risk carrier (having one defective gene) couples who have had no history of TSD in their families. Prenatal diagnosis in such couples has led to the identification of TSD in utero. Thus TSD is the first example of a genetic disease in which the birth of an affected child has been prevented by mass screening for heterozygotes (having one defective gene) in at risk populations.

For GM2 TSD, an extremely high frequency of 1:24 in Jewish individuals has been reported. Prenatal diagnosis can be done by estimating the enzyme Hexoaminidase A in amniotic fluid. Hence at the present time, proper recognition, early diagnosis and immediate genetic counseling followed by contraception is the simplest, most effective means available for preventing the conception and birth of children with ganglioside storage disease.

Table 12.8: Disorders of lipid metabolism

Name of disease	Defective enzyme	Type of lipid stored	Normal action of enzyme	Clinical Symptoms
1) Gaucher's disease	Glucocerebrosidase (β-Glucosidase)	Glucocerebroside	Cleaving ceramide and glucose	*Type 1*-Adult, chronic, non-neuronopathic form manifesting at any time from birth till old age. Organomegally, haemetologic abnormalities due to hyperspleenism and bone lesions. CNS not involved. *Type 2*-Acute, neuronopathic, infantile form. Usually apparent before 6 months of age, hepatosplenomegally, Gaucher's cells in bone marrow, CNS acutely involved, fatal by 2 years. *Type 3*-Subacute, neuronopathic, juvenile form. Visceral organs and CNS involved. Signs of neuorologic damage appear later than in Type 2 patients.
2) Niemann-Pick disease	Sphingomyelinase	Sphingomyelin	Cleaving ceramide and phosphoryl choline	*Type A*- Develops in infancy. Severe CNS damage. Feeding difficulties, emaciation with protuberant abdomen. Fatal by 3-4 years. *Type B*- Becomes apparent in infancy or childhood. Visceral involvement extensive but CNS normal, splenomegaly, respiratory involvement. Condition is subacute and chronic. *Type C*- Both CNS and visceral involvement, condition is subacute and chronic. Ataxia, loss of speech, seizures. Fatal before 20 years.
3) Tay-Sach's disease	Hexoaminidase A	GM2 Ganglioside	Cleaving N-acetyl hexosamine from ganglioside	Motor weakness manifesting between 3 and 6 months of age. Startle reaction is a characteristic early symptom. Infants cannot walk. Feeding difficulty, poor muscle tone, generalized paralysis, deafness, blindness, convulsions, spasticity appearing by about 18 months. Death occurs from bronchopneumonia by 3 years of age.

Check Your Progress Exercise 4

1) What do the disorders of lipid metabolism lead to? What is the pattern of inheritence of these and what is the possible treatment of the conditions?

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....

....

2) Briefly justify the following statements:

a) Large pale cells are seen in Gaucher's disease.

....

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....

b) There is an accumulation of sphingomyelin in cytoplasm of cells in Niemann-Pick disease.

  ....

  ....

c) Rapid progression in mental and motor deterioration is observed in Tay-Sach's disease.

  ....

  ....

3) Name the defective enzyme and any two characteristic symptoms associated with the following diseases.

  a) Gaucher's disease

  ....

  ....

  b) Niemann-Pick disease

  ....

  ....

  c) Tay-Sach's disease

  ....

  ....

Having learnt about some of the important inborn errors of metabolism, we shall end our study of this unit by presenting a brief discussion on haemoglobinopathies.

12.6 HAEMOGLOBINOPATHIES

Haemoglobinopathies are those *conditions where haemoglobin (Hb) is unable to perform its function*. The function of *haemoglobin*, as we all know, is the transport of oxygen from the lung to all the tissues of the body.

To understand these disorders better, we shall first look at the structure of haemoglobin. Haemoglobin consists of *heme,* a non-protein part and *globin,* which is a protein. The heme portion contains iron. The protein globin is made up of four polypeptide chains (polymer of amino acids joined together by peptide bonds). Each chain is designated by a Greek letter. The amino acid composition of 2 chains is identical and these 2 chains are called α-*chains*. The amino acid composition of the remaining 2 chains is different from α-chains, but identical to each other and is called β-*chains*. Hence normal adult Hb called HbA has $\alpha_2\beta_2$ structure (2 α-chains and 2 β-chains). Thus Hb has a tetramer structure. The tetramer structure is essential to the efficiency of this process. Hb in the foetus has a different structure. While it also contains 2 α-chains, the amino acid composition of the other 2 chains is different from that of β-chain and is called γ-chain. Therefore it is $\alpha_2\gamma_2$. At birth , foetal Hb (HbF) ($\alpha_2\gamma_2$) predominates and is rapidly replaced by HbA ($\alpha_2\beta_2$), which is the normal adult Hb, by about 6 months of age. There is also HbA$_2$ ($\alpha_2\delta_2$), a minor adult Hb, which constitutes about 2.5% of the total. HbA is a globular protein with a molecular weight of 68,000. Each α-chain has 141 amino acids while each β-chain has 146 residues. Several mutations (changes) in the structure of the gene coding for Hb are known,

each leading to a specific disease. We will have a look at these diseases now, basically sickle-cell anaemia and the thalassemias.

12.6.1 Sickle Cell Anaemia

Sickle cell anaemia is an inherited blood disease. As the name suggests, in this disease RBCs assume sickle or cresent shape. The sickling is dependent on the removal of oxygen and it is reversible. You may recall reading about this in the Applied Physiology Course in Unit 12.

Due to genetic mutation, in this disorder, the globin chain synthesis is not normal. In the β-chain at position 6, amino acid valine replaces glutamic acid. Sickle cell anaemia is thus the prime example of a 'molecular disease'. Is it not remarkable that a single amino acid substitution in the Hb molecule leads to severe disease in homozygous (having both defective genes) individuals?

The S (sickle-cell) gene occurs throughout tropical Africa, as well as, in blacks in the US and other countries to which Africans were exported during the slave trade. It is also found in the Middle East and may occur in Caucasians (light coloured racial groups). About 8% American blacks are carriers. It is also prevalent in various states in India, particularly among tribal groups.

A given cell can undergo reversible sickling several times but during each 'sickle-unsickle' cycle, it probably loses a small portion of membrane. This results in loss of cell water with an increase in intracellular Hb concentration and an increased tendency to sickle. Finally, it is no longer able to unsickle and becomes an irreversibly sickled cell. These have very short survival period and very low oxygen affinity. HbF (which does not contain β-chain) when present in the cells of persons carrying HbS is beneficial. Thus the newborn is not affected until HbF synthesis declines. An unusually high level (about 18%) of HbF found in the Middle East offers a protective effect.

Clinical symptoms include *vasooclusion* (blockage of blood flow in blood vessels), pain and tissue death. *Reticulocytosis* (synthesis of reticulocytes-immature erythrocytes), sickling and extensive haemolysis (destruction of red blood cells) are seen by 10-12 weeks of age. By 5-6 months, *splenomegaly* (enlargement of the spleen) is seen. There is a swelling of the dorsum (back) of the hands and feet (hand-foot syndrome). There is a relentless gnawing pain in the long bones and joints. Children are susceptible to various infections.

There is no effective treatment at present. Good nutrition and personal hygiene, early diagnosis and treatment of infections, prophylaxis (prevention) against malaria and folic acid administration are beneficial. Many antisickling agents are constantly being tested.

12.6.2 Thalassemias

Thalassemias are *a heterogenous group of hereditary diseases characterized by anaemia*. In thalassemias, due to genetic mutation, synthesis of the protein globin is affected. Normally α and β globin chain production is balanced to form globin tetramers (with 4 polypeptides) about which you learnt above. Adult HbA is $\alpha_2\beta_2$. In thalassemia, the impaired production of one or more of these globin components causes deficient Hb molecule. The unaffected chain continues to be produced in normal amounts and in the homozygous (having both defective genes) state excessive accumulation of the unaffected chain may disrupt erythroid (red) cell maturation and function causing premature destruction of the RBC.

Thalassemia occurs throughout the world and constitutes one of the most common hereditary disorders. It has an autosomal recessive inheritance.

When synthesis of α-globin chain is defective, the condition is called α-thalassemia, while in β-thalassemia, synthesis of β-globin chain is affected. Let us see the important features of both these conditions.

α-Thalassemia

The defect ranges from mild to complete suppression of α-chain synthesis. This is due to mutations in the genes which carry the information for the synthesis of α-globin chain. Four clinical syndromes of increasing severity are recognized. These are:

• *Silent carrier state* – here the person is a carrier having one defective gene. α-globin chain production is very mildly impaired. Even making a firm clinical diagnosis is often impossible. Red cell morphology is normal and anaemia is absent.

• *α-Thalassemia trait* – here the disease is present in a more severe form. Hb levels may be slightly below normal. However, the affected person is not usually anaemic. RBCs are characteristically microcytic (small in size).

• *Hb-H disease* – here distinctly there is mild to moderate degree of haemolytic anaemia which can become severe in young children, during pregnancy or whenever the person gets some infection. Hb levels average 10 g/dl. There is reticulocytosis of about 5%. This is a compensatory mechanism by the body in an effort to improve the anaemic condition. Spleen is often enlarged. Occasional bone abnormalities are present. RBCs are microcytic.

• *Hydrops faetalis* – this is the most severe form of α-thalassemia and the condition is invariably lethal. As the name suggests, the affected foetus dies during the third trimester of pregnancy or if born alive within hours or at most 1or 2 days after birth. At the present time, no treatment is available. Hence it is important to have a timely diagnosis along with genetic counseling for prevention/ termination of pregnancy which is doomed to fail.

α-thalassemia occurs predominantly in people of Mediterranean, African and Asian origin. Hydrops faetalis occurs exclusively in South-East Asia e.g. in Chinese, Thai, Vietnamese etc. It has rarely been found in people of Greek and Cypriot origin and also has never been detected in people of African descent. Hb-H disease however is common in Mediterranean area and in Asia but rare in Africa.

β-Thalassemia

This occurs due to a very wide variety of mutations in the β-globin gene affecting every aspect of its structure. There are 2 variations of the disease depending on whether the individual is heterozygous (one defective gene) or homozygous (both defective genes). The 2 variants are discussed below :

• *β-Thalassemia Trait (β-Thalassemia Minor)*: This is the carrier or heterozygous state, which is usually asymptomatic. Hb levels are normal or slightly decreased. In times of stress, precipitated by pregnancy or infection, the patient may become anaemic. In children, Hb levels may be below 10 g/dl. Occasionally, there is hepatosplenomegaly. There is elevated HbA_2 $(\alpha_2\delta_2)$ (minor adult Hb component) level which is protective since HbA_2 does not contain β-chain. Incidence of thalassemia trait is about 240 million around the world. In India it is about 30 million, being more common in North India (3-15%) as compared to South India (1-2%).

• *β-Thalassemia Major*: This is the homozygous state and is also known as *Cooley's Anaemia*. Every year about 8,000-10,000 children in India are born with this disease. It occurs widely in people of Mediterranean origin, Middle

East, the Indian subcontinent, South East Asia and Africa. In India, prevalence is high in the northern and eastern parts of the country. It is believed to have originated here following Alexander's invasion when there was intermingling of his soldiers with the local population. The Indian Council of Medical Research (ICMR) has conducted a study to determine the incidence of the disease in India. It afflicts communities like Sindhis, Punjabis and Gujaratis. The study has also carried out a religion-wise and a caste-wise breakup of the subjects.

The affected child is not anaemic at birth due to the high levels of foetal haemoglobin HbF ($\alpha_2\gamma_2$) which does not contain β-chain. However as γ-globin chain synthesis gradually diminishes after a few months to be replaced by β-chain synthesis, anaemia becomes increasingly evident. Symptoms include pallor, listlessness and failure to thrive. Hb levels fall to 3-5 g/dl. RBC is severely hypochromic (less coloured) and varies greatly in size and shape. There is hepatosplenomagaly. Bone marrow proliferation causes deformities in bone structure (e.g. there is typical mongoloid face) and fractures occur. Lymph nodes get hypertrophied (excessive activity) due to erythropoiesis (synthesis of RBCs). Physical and sexual development is retarded. Female patients often have delayed onset of menarche or some do not menstruate at all. Infection is the common cause of childhood mortality.

β-thalassemia has been traditionally treated by giving the affected person blood transfusion as and when required, depending upon the severity of the disease. In very severe cases, this could be once in 3-4 weeks. The cost of this is very high. Further with continous blood transfusions, there is accumulation of iron in the body tissues. This is called *hemosiderosis*. Hence to prevent hemosiderosis (accumulation of iron in tissues), thalassemics have to take expensive iron-chelation drugs (desferal or kelfer) to drain the excess iron out of the system. These drugs combine (chelate) readily with iron and the complex is excreted. These drugs are called *iron-chelating drugs*. The cost of medication could exceed Rs.2.5 lakhs per annum. However a bone marrow or cord blood stem cell transplant confers permanent cure and eliminates all necessity of blood transfusion. This is now performed in various major hospitals in the country and the one- time estimated cost of the one-time treatment is Rs.10-12 lakhs. Blood transfusion also poses the additional danger of contacting infections like hepatitis and HIV. Hence it must be ensured that blood transfusion is safe. *Thalassemics India*, which is a registered body regularly, organizes camps to create public awareness and initiate detection and prevention program.

Some of the steps that would go a long way in the prevention of this disease are listed in Box 4. Read them for better understanding of the topic.

Box 4: Steps in prevention of Thalassemia

- Awareness about the disease should be created in high risk populations.
- High risk communities and affected families should undergo blood tests.
- Ideally marriage should be avoided between two known thalassemia carriers.
- In case both partners are carriers, prenatal test must be undergone by the pregnant woman at each pregnancy.
- All married women must be screened for thalassemia carrier status before planning their family.
- All patients/parents should be educated about all aspects of blood transfusion.

Check Your Progress Exercise 5

1) What are haemoglobinopathies? Name the two disorders caused due to it.

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   ....

2) Briefly justify the following statements:

   a) Clinical symptoms do not appear in the newborn in sickle-cell anaemia.

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      ....

   b) Synthesis of protein globin is affected in Thalassemia.

      ....

      ....

   c) Iron chelation therapy is necessary in thalassemic patients.

      ....

      ....

3) State whether the following statements are true or false. Also correct the false statements.

   a) Sickling-unsickling is a irreversible process.

      ....

      ....

   b) Elevated HbA_2 levels are seen in case of α-Thalassemia disease.

      ....

   c) HbF is made up of globin chains.

      ....

      ....

   d) Hydrops faetalis is invariably fatal.

      ....

      ....

   e) Hepatosplenomegaly is observed in sickle cell anaemia.

      ....

      ....

12.7   LET US SUM UP

In this unit we learnt about the various inborn errors of metabolism. The discussion was presented under the three headings – disorders of protein metabolism, carbohydrate metabolism and lipid metabolism. Some of the common specific biochemical defects

in each of these disorders along with their symptoms were highlighted. The last part of the unit focussed on haemoglobinopathies within which sickle cell anaemia and thalassaemias were discussed.

The unit presented an interesting discussion (of course not interesting to be suffering from!) on inborn errors of metabolism. The salient features are summarized herewith:

- These diseases are congenital, present throughout life and hereditary.

- A genetic mutation results in the synthesis of a defective enzyme/protein molecule.

- Inherited deficiencies in specific enzymes/protein molecules are the causes of the disorders.

- Autosomal recessive pattern of inheritance is observed in all the diseases considered in this presentation.

- As a result of defective enzyme/protein molecule a metabolic block occurs at that step in the metabolic pathway. This leads to accumulation of the metabolite (intermediate).

- In an attempt to reduce the amount of the accumulated metabolite, it goes through alternate/secondary pathways forming additionally various other compounds.

- All the accumulated metabolites are generally excreted in the urine. Identification of these metabolites affords a mechanism for diagnosis of the disease.

- Very often one or more of the accumulated metabolites are extremely toxic causing mild/severe clinical symptoms. This could result in physical and mental retardation.

- Clinical symptoms may appear within the first few days of life. Hence early diagnosis in neo-natal life is very important. With poor health care system in our country, the diseases remain routinely undiagnosed leading to death of the infant.

- Ideal way to treat the disorder would be to introduce the correct gene so that the right type of the gene product (protein) is synthesized. This constitutes gene therapy. However this is not available at the present moment.

- Alternatively only symptomatic treatment is possible-to reduce the ill effects/ pain or to prevent the disease from progressing to more severe consequences. Nutritional intervention does provide relief in many instances. However nutritional management is difficult, needs constant biochemical monitoring, very often expensive and requires one-to-one monitoring for becoming successful.

- Apart from gene therapy, a large number of the diseases have no known method of treatment, leading to inevitable end, death of the patient in infancy or early childhood.

- Hence prenatal diagnosis followed by counseling for medical termination of pregnancy will help the mother from going through the stress of pregnancy and childbirth.

- Prenatal diagnosis is currently possible for many diseases which involves analysis of amniotic fluid cells for the defective enzyme, the metabolite which accumulates or for the defective product.

- Mass screening programs conducted in at risk populations would help to ascertain the carriers of the disease.

12.8 GLOSSARY

Allosteric mechanisms	:	regulation of enzyme activity by exerting effect at a site other than the catalytic site.
Amniotic fluid	:	fluid protecting the embryo.
Ascites	:	accumulation of fluid in peritoneal cavity.
Autosomal	:	a chromosome that is not a sex chromosome.
Autosomal recessive	:	an abnormal gene on one of the autosomal chromosomes (one of the first 22 "non-sex" chromosomes) from each parent is required to cause the disease. People with only one abnormal gene in the gene pair are called carriers, but since the gene is recessive they do not exhibit the disease. In other words, the normal gene of the pair can supply the function of the gene so that the abnormal gene is described as acting in a recessive manner.
Bacteriophage	:	a virus that infects a bacterium.
Calculi	:	stones.
Ceramide	:	a combination of sphingosine (alcohol) and fatty acid.
Chimeric DNA	:	DNA containing sequences derived from two different species (eg. bacteria and human being).
Chromosomes	:	long pieces of DNA contained in the nucleus of cells.
Cloning	:	a process of obtaining a large number of cells or molecules that are identical with a single parent cell or molecule.
Congenital	:	existing at birth.
Duplex	:	twofold.
Gene	:	a segment of DNA chain that contains the instructions for the complete protein.
Genetic engineering	:	process of altering chemical structure of genes.
Genetic mutation	:	a mutation occurs when a DNA gene is damaged or changed in such a way as to alter the genetic message carried by that gene.
Gout	:	hereditary condition of uric acid metabolism.
Hepatomegaly	:	enlargement of liver.
Hyperkeratosis	:	disease of the skin characterized by an excessive overgrowth of the cornified epithelium.
Keratitis	:	inflammation of the cornea.
Lipidosis	:	lipid-storage disease.
Lysosomes	:	membrane bound particles within cells, which aid in intracellular digestive function.
Melanocyte	:	pigment containing cell.
Oedema	:	excessive accumulation of fluid in tissue spaces.
Ochronosis	:	pigmentation of the connective tissue.

Organomegaly	:	enlargement of organs.
Oxalosis	:	widespread deposit of oxalate crystals through the body.
Panethnic	:	involving various ethnic groups.
Plasmid	:	a small extramicrosomal circular molecule of DNA that replicates independently of the host DNA.
Recombinant DNA	:	the altered DNA that results from the insertion of a sequence of deoxynucleotides not previously present into an existing molecule of DNA by enzymatic or chemical means.
Supraphysiologic	:	much greater than normal (physiologic) dose.
Syndrome	:	combination of several symptoms characteristic of a disease.
Vasooclusion	:	block in blood vessel.
Vector	:	plasmid or bacteriophage into which foreign DNA can be introduced for the purpose of cloning.

12.10 ANSWERS TO CHECK YOUR PROGRESS EXERCISES

Check Your Progress Exercise 1

1) Inborn errors of metabolism are a number of metabolic abnormalities that are congenital, present throughout life and hereditary. This can be because the enzyme molecule is completely absent and is unable to do its work. Or more likely, the protein molecule is present, but there is a genetically determined mutation at the reactive site. It may also be possible that the enzyme is present and structurally normal too, but unable to function properly because of alterations within the cell. A deficiency of cofactors or the presence of inhibitors could produce such an effect.

2) The identification of the intermediate metabolic products in urine aids in diagnosis of the genetic diseases.

   Treatment is still only symptomatic i.e. alleviating the pain etc. or preventing the disease from progressing to more severe consequences. Nutritional management has been useful in many instances. However the ideal treatment would be adoption of devices which would enable the cell to start synthesizing the right kind of protein.

3)

Amino Acid	Disease	Defective Enzyme
Tyrosine	Alcaptonuria	Homogentisate oxidase
Phenylalanine	Phenylketonuria	Phenylalanine hydroxylase
Tyrosine	Albinism	Tyrosinase

4) a) In PKU patients, there is an inability of the enzyme phenylalanine hydroxylase to convert phenylalanine into tyrosine. Hence, tyrosine becomes an essential amino acid for PKU patients.

   b) The urine upon standing becomes dark in colour in Alcaptonuria due to a defect in the enzyme homogentisate oxidase. The defect causes a block in the metabolic pathway at homogentisic acid and leads to its accumulation in blood and hence imparts a dark colour to the urine.

c) Hematin (hydroxide of heme with iron in ferric state) compensates the decreased biosynthesis of heme.

d) The accumulated metabolites of phenylalanine especially phenyllactate can cause damage to the CNS resulting in acute neurological abnormalities.

e) Patients with albinism have red pupil and pink or bluish iris and hence become sensitive to light leading to photophobia.

5) a) - iv)

   b) - i)

   c) - ii)

   d) - iii)

   e) - v)

Check Your Progress Exercise 2

1) a) In MSUD, intake of 3 branched chain amino acids is restricted and so very little natural protein intake is recommended. Hence, to maintain height and weight of the patient, a high calorie intake is suggested.

   b) Since three essential amino acids are involved in MSUD, an intake of all the 3 branched-chain amino acids must be restricted. Hence very little of natural protein can be given. Appropriate IV therapy must be initiated to correct acidosis and electrolyte imbalances which may occur by the time diagnosis is made. Further, constant fluctuation in the tolerance for the amino acids involved, requires frequent monitoring of blood for the 3 branched chain amino acids.

   c) Due to the reduced activity of the enzyme cystathionine β-synthase, the homocysteine formed from methionine cannot be further metabolized to cystathionine and ultimately cysteine. Hence, it becomes must to include cyteine in the diet.

   d) Cystinosis is characterized by the accumulation of cystine in tissues throughout the body, which can cause certain organs to malfunction.

   e) Excess homocysteine forms homocysteine thiolactone, a highly reactive intermediate that thiolates free amino groups in low density lipoproteins (LDL) and causes them to aggregate and be endocytosed by macrophages (phagocytic cells).

2) a) Cystathionine β-synthase

   b) Arginase

   c) Histidase

   d) α-ketoacid decarboxylase

   e) Glycine oxidase

3) a) MSUD

   b) one enzyme

   c) ammonia

   d) cystinosis

   e) nephrolithiasis

Check Your Progress Exercise 3

1) Pentose (5-carbon) and hexose (6-carbon) sugars are invovled in disorders of carbohydrate metabolism. Pentosuria, fructosuria and galactosemia are the three disorders of carbohydrate metabolism.

2) a) Muscles have abnormally high content of glycogen (2.5-4.0%). Little or no lactate in blood after exercise since muscle glycogen unavailable as fuel. Hence, there is a marked diminished tolerance to exercise in patients with MCArdle's disease.

b) In galactosemia galactose accumulates leading to galactosemia which is accompanied by galactosuria. Excess galactose is reduced by aldose reductase in the eye to the corresponding alcohol (galactitol) which accumulates causing cataract.

c) All the inorganic phosphate (Pi) is tied up as fructose-1-phosphate in hereditary fructose intolerance and thus is not available for phosphorylation of ADP to form ATP. Thus there is depletion of Pi (inorganic phosphate) and ATP.

d) Nutritional intervention should be started as early as possible in galactosemia since breast milk contains lactose.

e) The defective enzyme in Andersen's disease is brancher enzyme, which leads to an accumulation of glycogen with few branch points leading to cirrhosis, hepatosplenomegaly with bleeding tendencies.

3) a) Glucose-6-phosphatase

b) NADP- dependent Xylitol dehydrogenase

c) Hepatic fructokinase

d) Brancher

e) Galactose-1-phosphate uridyl transferase

4) i) - b)

ii) - e)

iii) - a)

iv) - c)

v) - d)

Check Your Progress Exercise 4

1) The disorders of lipid metabolism lead to a condition in which there is storage of lipids in the cells i.e. lipidosis. These diseases have recessive autosomal pattern of inheritance. Gene therapy is the only hope.

2) a) In Gaucher's disease, glucocerebroside accumulates in the cells of the reticuloendothelial (blood forming) system. Thus these cells become enlarged. The cytoplasm of such cells is replaced entirely by the lipid and under the microscope the cells appear as large pale cells.

b) The defective enzyme is *sphingomyelinase* in Niemann-Pick disease, which normally cleaves sphingomyelin forming phosphorylcholine and ceramide (sphingosine + long-chain fatty acid). Hence sphingomyelin accumulates in the cytoplasm of cells of spleen, liver, bone marrow and lymph nodes.

c) In Tay-sachs disease, there is a severe deficiency of the enzyme Hexoaminidase A, which in normal persons catabolizes the lipid called gangliosides. Gangliosides are present in high concentration in ganglion cells (nerve cells). In Tay-Sachs disease, GM2 accumulates and very severe symptoms are encountered. There is motor weakness and mental and motor deterioration progresses rapidly after 1 year of age, with death occurring by 3 years of age.

3) a) Glucocerebrosidase; neuronopathic and CNS involvement.

    b) Sphingomyelinase; respiratory and feeding difficulties with CNS involvement.

    c) Hexoaminidase A; motor weakness and convulsions.

Check Your Progress Exercise 5

1) Haemoglobinopathies are those conditions where haemoglobin (Hb) is unable to perform its function. Sickle cell anaemia and thalassemia are the two disorders caused due to it.

2) a) HbF (which does not contain β-chain) when present in the cells of persons carrying HbS is beneficial. Thus the newborn is not affected until HbF synthesis declines.

    b) In thalassemias, due to genetic mutation, synthesis of the protein globin is affected.

    c) To prevent hemosiderosis, thalassemics have to take iron-chelation drugs (desferal or kelfer) to drain the excess iron out of the system. These drugs chelate readily with iron and the complex is excreted.

3) a) False, it is a reversible process.

    b) False, it is seen in case of β-thalassemia disease.

    c) True

    d) True

    e) False, hepatosplenomegaly is observed in thalassemias.

SUGGESTED READINGS

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West E.S., Todd W.R., Mason H.S. and Van Bruggen J.T., *Textbook of Biochemistry*

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List of Abbreviations

ACP	:	Acyl Carrier Protein
ACTH	:	Adrenocorticotropin Hormone
ADH	:	Antidiuretic Hormone
ADP	:	Adenosine Diphosphate
AMP	:	Adenosine Monophosphate
ATP	:	Adenosine Triphosphate
BMR	:	Basal Metabolic Rate
cAMP	:	cyclic Adenosine Monophosphate
CAT	:	Catalase
CBS	:	Cystathionine beta-synthase
CDP	:	Cytidine diphosphatidyl choline
CE	:	Condensing Enzyme
cGMP	:	cyclic Guanosine Monophosphate
CNS	:	Central Nervous System
CPT	:	Carnitine Palmitoyl Transferase
CRBP	:	Cellular Retinol-Binding Protein
CRH	:	Corticotropin Releasing Hormone
CT	:	Calcitonin
CVD	:	Cardio Vascular Disease
DNA	:	Deoxyribonuleic Acid
DOPA	:	3,4-dihydroxyphenylalanine
ECF	:	Extra Cellular Fluid
EFA	:	Essential Fatty Acid
ER	:	Endoplasmic Reticulum
FAD	:	Flavin Adenine Dinucleotide
FAS	:	Fatty Acid Synthase
FDP	:	Farnesyl Diphosphate
FMN	:	Flavin mononucleotide
GDP	:	Guanosine Diphosphate
GH	:	Growth Hormone
GI	:	Gastro-intestinal tract
GLUT	:	Glucose Transporter
GPCR	:	G-Protein Coupled Receptors
GSH	:	Glutathione

GTP	:	Guanosine Triphosphate
HDL	:	High-Density Lipoprotein
HEXA	:	Hexosaminidase A
HMG	:	Hydroxymethyl glutarate
HMP	:	Hexose monophosphate
HPETE	:	5-Hydroxy 6,8,11,14 – eicosatetraenoic acid
ICMR	:	Indian Council of Medical Research
IDL	:	Intermediate Density Lipoprotein
IDP	:	Isopentenyl Diphosphate
IEM	:	Inborn Errors of Metabolism
IGF	:	Insulin-like Growth Factor
IQ	:	Intelligence Quotient
IRP	:	Iron Regulator Protein
IV	:	Intra venous
LDL	:	Low Density Lipoprotein
LPL	:	Lipoprotein Lipase
mRNA	:	messenger Ribonucleic Acid
MSUD	:	Maple Syrup Urine Disease
MT	:	Metallothionein
NAD	:	Nicotinamide Adenine Dinucleotide
PC	:	Phosphatidyl Choline
PCAT	:	Phosphatidylcholine Cholesterol Acyl transferase
PE	:	Phosphatidyl ethanolamine
PEPCK	:	Phosphoenolpyruvate Carboxykinase
PFK	:	Phosphofructokinase
PG	:	Phosphatidyl Glycerol
PI	:	Phosphatidyl Inositol
PKA	:	Protein Kinase A
PKG	:	cGMP dependent Protein Kinase
PKU	:	Phenylketonuria
PS	:	Phosphatidyl Serine
PTH	:	Parathyroid Hormone
PUFA	:	Poly Unsaturated Fatty Acid
RBC	:	Red Blood Cells

RBP	:	Retinol Binding Protein
RNA	:	Ribonucleic Acid
SAM	:	S-Adenosyl Methionine
SOD	:	Superoxide dismutase
TDP	:	Thiamine diphosphate
THF	:	Tetra hydrofolate
TMP	:	Thymidine monophosphate
TPP	:	Thiamin Pyrophosphate
TRE	:	Thyroid Response Element
TSD	:	Tay Sach's Disease
TSH	:	Thyroid Stimulating Hormone
VLDL	:	Very Low Density Lipoprotein

Inborn error of metabolism

Inborn errors of metabolism (IEM) are rare genetic (inherited) disorders in which the body cannot properly turn food into energy. The disorders are usually caused by defects in specific proteins (enzymes) that help break down (metabolize) parts of food.

In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds.

- IEM comprise a large class of genetic diseases involving disorders of metabolism.

- The majority are due to defects of single genes that code for enzymes that facilitate conversion of various substances (substrates) into others (products).

- In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal function, or to the effects of reduced ability to synthesize essential compounds.

Inborn errors of metabolism are now often referred to as **congenital metabolic diseases** or **inherited metabolic diseases**

Phynylketonuria

- **Phenylketonuria (PKU)** is an <u>inborn error of metabolism</u> that results in decreased <u>metabolism</u> of the <u>amino acid phenylalanine.</u>
- The enzyme <u>phenylalanine hydroxylase</u> normally converts the <u>amino acid</u> <u>phenylalanine</u> into the amino acid <u>tyrosine</u>.
- If this reaction does not take place, phenylalanine accumulates and tyrosine is deficient.
- This results in the build up of dietary phenylalanine to potentially toxic levels.
- It is <u>autosomal recessive</u> meaning that both copies of the gene must be mutated for the condition to develop.
- There are two main types, classic PKU and variant PKU.

Diagnosis

PhenylAlanine Hydroxylase deficiency can be diagnosed by newborn screening

A normal blood phenylalanine level is about 1mg/dl and

In PKU:
Blood phenylalanine >6 -10 mg/dl or (360-600 μmol/L)

Blood tyrosine < 3mg/dl (165 μmol/L)

The normal metabolism of phenylalanine (pathways a and b)

Dietary sources, particularly plant proteins → **PHENYLALANINE**

PHENYLALANINE HYDROXYLASE

PHENYLALANINE →(a)→ TYROSINE

PHENYLALANINE →(b)→ BODY PROTEINS

TYROSINE → BREAKDOWN

TYROSINE → BODY PROTEINS
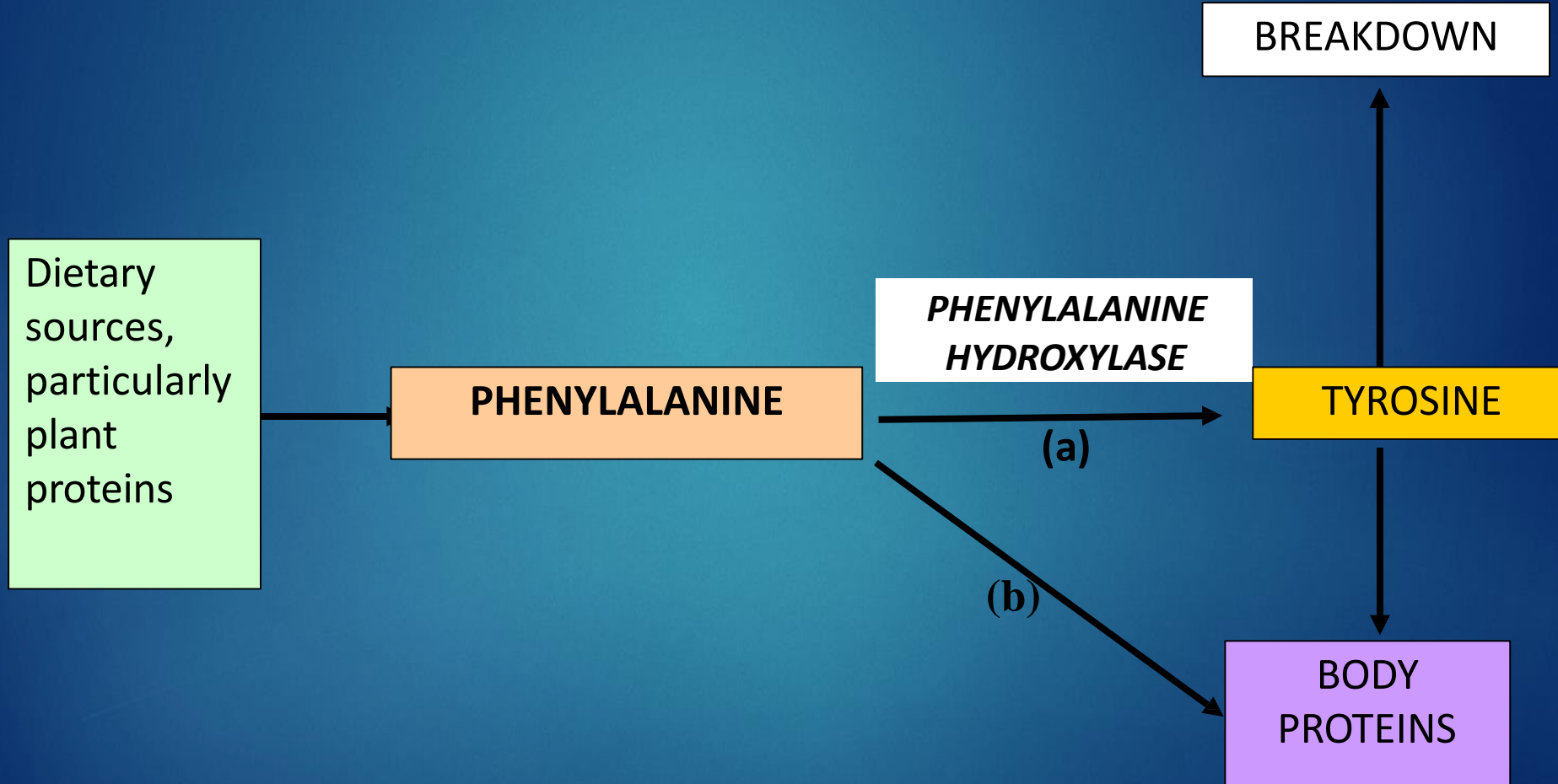
The abnormal metabolism in phenylketonuric subjects (pathway c)

HYDROXYPHENYLACETIC ACID

Dietary sources, particularly plant proteins

(c)

PHENYLALANINE*

PHENYLALANINE HYDROXYLASE

(a)

(c)

(b)

PHENYLACETIC ACID*

BODY PROTEINS
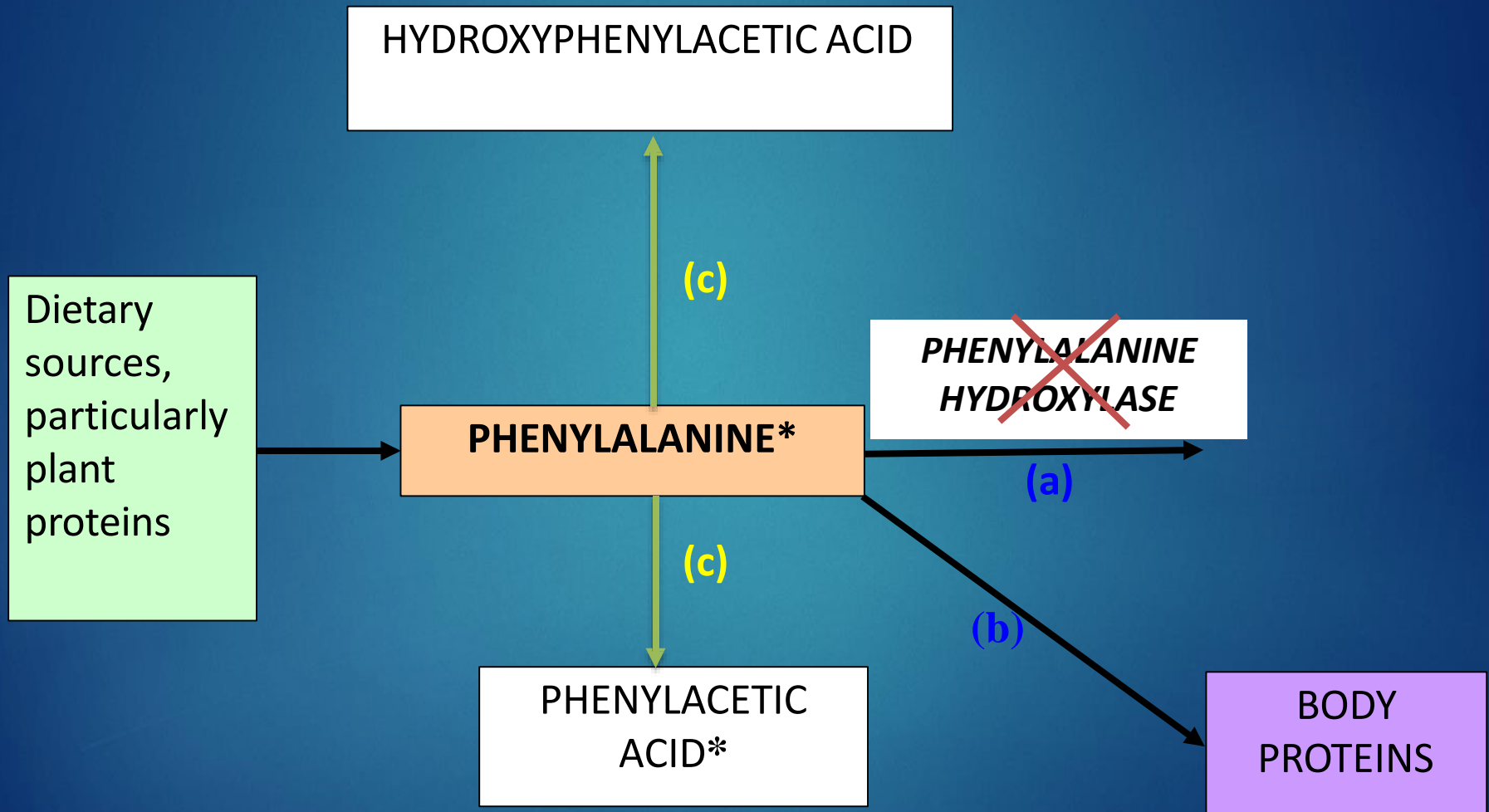
*Agents, thought to be responsible for mental retardation

SYMPTOMS OF PKU (About 50% of untreated infants have the following early symptoms)

- Infants with classic PKU appear normal until they are a few months old.

- Without treatment with a special low-phenylalanine diet, these children develop permanent intellectual disability.

- Seizures, delayed development, behavioral problems, and psychiatric disorders

- Untreated individuals may have a musty or mouse-like odor as a side effect of excess phenylalanine in the body.

- Children with classic PKU tend to have lighter skin and hair and are also likely to have skin disorders such as eczema.

- Vomiting and Irritability

- Unusual odor to urine

- Nervous System Problems(increased muscle tone, more active muscle tendon reflexes)

- Microcephaly

- Decreased body growth and prominent cheek and jaw bones widely spaced teeth and poor development of tooth enamel

Medical Management
- Regular monitoring of blood phenylalanine
- To maintain at 1-6 mg/dl (60-350 µmol/L)

Nutrition assessment
- Assess parental and family support for important nutrition therapy

Nutrition care
- Phenylalanine – free formula/medical food
- Low phenylalanine foods
- Supplement with tyrosine
- Education of family and child about formula/medical food preparation
- Adequate nutritional intake
- Regular monitoring of growth
- Education on label reading and food choices

Medical Nutrition Therapy

✓For PKU dietary therapy is planned around the use of a formula/medical food and protein source with L-amino acid, Phe removed from the protein.

✓Carbohydrate sources are corn syrup solids, modified tapioca starch, sucrose, and hydrolyzed cornstarch. Fat is provided by a variety of oils. Some formulas and medical foods contain no fat or carbohydrate; therefore these components must be provided from other sources.

✓Phe-free formula is supplemented with regular infant formula or breast milk during infancy and cow's milk in early childhood to provide high-bv protein, nonessential amino acids, and sufficient Phe to meet the individualized requirements of the growing child.

✓The optimal amount of protein substitute depends on the individual's age (and thus requirements for growth) and enzyme activity and must be individually prescribed.

✓The Phe-free formula and milk mixture should provide about 90% of the protein and 80% of the energy needed by infants and toddlers.

✓Certain vegetables, fruits, and some grains can then be added in to the diet after infancy.

✓Regular meats, eggs, fish, milk, and cheese are never to be added into the diet.

✓Diet drinks and foods that contain the artificial sweetener aspartame (which contains Phe) must always be avoided. Ex: Nutrasweet or Equal

✓Phe-free formula needs to be followed throughout childhood and adolescence because protein is needed for development.

Tyrosinemia

- Inborn error in the degradation of the tyrosine. People have problems breaking down an <u>amino acid</u> <u>tyrosine</u> from the food they eat.
- Hereditary – autosomally recessive.

Three types

- Type I – deficiency of the enzyme fumarylacetoacetate hydrolase (FAH).
- Type II – deficiency of the enzyme tyrosine aminotransferase (TAT).
- Type III – deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD).

Type I Tyrosinemia

- Tyrosinemia 1 occurs when an enzyme, called fumarylacetoacetase (FAH), is either missing or not working properly.
- There is a mutation in the FAH gene that encodes for the FAH enzyme.
- When FAH is not working, it cannot break down tyrosine. Tyrosine and other harmful substances then build up in the blood.
- Can be either chronic or acute.
  - Acute – infancy
  - Chronic – later in life

Symptoms of Type I Tyrosinemia

- Failure to gain weight or grow
- Diarrhea, bloody stools and vomiting
- Jaundice of skin and eyes
- Cabbage-like odor to the skin or urine
- Increased tendency to bleed (esp. nosebleeds)
- extreme sleepiness
- irritability
- enlarged liver
- yellowing of the skin
- tendency to bleed and bruise easily
- swelling of the legs and abdomen
- Liver cirrhosis and/or hepatocellular carcinoma (chronic)
- Kidney problems
- rickets
- delays in walking

Type II Tyrosinemia

Caused by a mutation in the TAT gene that encodes for the hepatic (liver) TAT enzyme.
Also known as "Richner-Hanhart syndrome"

  TAT gene –
❑ Codes for tyr aminotransferase
Which is responsible for converting tyrosine to 4-hydroxyphenylpyruvate. TAT is the enzyme involved in the first of a series of five reactions of tyrosine degradation.
Occurs in cytosol
Pyridoxal 5'-phosphate (PLP) dependent enzyme Transaminates tyrosine and   α-ketogluterate into p-hydrophenylpyruvate and glutamate.

Symptoms of Type II Tyrosinemia

Elevated serum and plasma tyrosine levels

Lesions of skin and eyes Due to clumping of cellular tyrosine crystals.

Excessive tearing, abnormal sensitivity to light (photophobia), lacrimation, burning eye pain, inflamed conjunctiva

Microcephaly - Mental retardation (caused by elevated blood tyrosine levels)

Blistering lesions on the palms and soles

delay behavioral problems and self injurious behaviors also occurring frequently Symptoms often begin in early childhood

Type III Tyrosinemia

Deficiency of 4-hydroxyphenylpyruvate dioxygenase (HPPD)

Caused by a mutation in the HPPD gene that encodes for the enzyme HPPD

Second enzyme involved in tyrosine catabolism pathway

Requires Fe(II), oxygen and a alpha-keto acid substrate (typically alpha- ketoglutarate)

Symptoms of Type III Tyrosinemia

Mild mental retardation Seizures
Loss of balance and coordination
(intermittent ataxia)
High blood and urine concentrations of
tyrosine and HPP

Diagnosis

Newborn screen
Tandem mass spectrometry

Maintaining tyrosine levels below 800μmol/l appears to be protective against pathology including neurological squeal

Goals of dietary management:

1. Support an appropriate rate of growth
2. Support normal intellectual development
3. Maintain optimal nutritional status
4. Provide adequate nourishment
5. Prevent neurological crisis
6. Prevent liver and renal function problems
7. Prevent formation of tyrosine crystals in the eyes (this occurs with elevated plasma tyrosine levels)

Nutritional treatment

The diet is made up of foods that are very low in tyrosine and phenylalanine (aim is below 500 µmol/L) and it is made up of special medical formula. There are other medical foods such as special flours, pastas, and rice that are made especially for people with tyrosinemia 1.

There is a need to limit foods such as: cow's milk
Meat eggs and cheese regular flour dried beans
Nuts and peanut butter

Maple Syrup Urine Disease

➢ It is an autosomal recessive, metabolic disorder affecting branched-chain amino acids.

➢ It is one type of "organic acidemia" the disease is named for the presence of sweet- smelling urine, with an odor similar to that of maple syrup.

➢ is a potentially deadly disorder that affects the way the body breaks down three amino acids, leucine, isoleucine, and valine. (used as supplements for body (muscle) building.)

➢People with MSUD have a mutation that results in a deficiency for one of the 6 proteins that make up this complex. Therefore, they can't break down leucine, isoleucine, and valine.

➢They end up with dangerously high levels of these amino acids in their blood, causing the rapid degeneration of brain cells and death if left untreated.

Mechanism

MSUD is a metabolic disorder caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC), leading to a buildup of the branched-chain amino
acids (leucine, isoleucine, and valine) and their toxic by-products (ketoacids) in the blood and urine.

As a result, these amino acids and their by- products build up in the body.

Because high levels of these substances are toxic to
the brain and other organs, this accumulation leads to the serious medical problems associated with maple syrup urine disease.

SYMPTOMS

- There are several types of maple syrup urine disease. The *most common (classic) form* typically will produce symptoms in newborn infants aged 4-7 days. These symptoms may include:
- Poor feeding
- Vomiting
- Poor weight gain
- Increasing lethargy (difficult to wake up)
- Characteristic burned sugar smell to urine
- Changes in muscle tone, muscle spasms, and seizures

DIAGNOSIS

➤ In some states, all babies are screened for MSUD within 24 hours after birth.

➤ A blood sample taken from the baby's heel is analyzed for high leucine levels.

➤ If maple syrup urine disease is suspected based on the physical symptoms, especially the characteristic urine odor, a blood test for amino acids can be done.

Treatment

➢ Treatment involved dietary restriction of the amino acids leucine, isoleucine, and valine.

➢ This treatment must begin very early to prevent brain damage.

➢ Babies with the disease must eat a special formula that does not contain the amino acids leucine, isoleucine, and valine.

➢ As the person grows to adulthood, he or she must always watch their diet, avoiding high protein foods such as meat, eggs, and nuts.

➤ If levels of the three amino acids still get too high, patients can be treated with an **intravenous** (given through a vein) solution that helps the body use up excess leucine, isoleucine, and valine for protein synthesis.

➤ **Gene therapy** is also a potential future treatment for patients with MSUD.
This would involve replacing the mutated gene with a good copy, allowing the patient's cells to generate a functional BCKD protein complex and break down the excess amino acids

Homocystinuria

Homocystinuria or cystathionine beta synthase deficiency is an autosomal recessive inherited disorder of methionine metabolism.

Methionine is an essential, non-polar α-amino acid. Under normal conditions methionine undergoes conversion to homocysteine.

This in turn undergoes trans- sulfuration to ultimately yield cysteine. This step is catalyzed by the enzyme Cystathionine beta synthase (CBS). People suffering from this disease are unable to synthesize CBS, hence leading to an inability to metabolize methionine.

Symptoms

Homocystinuria is accompanied by a variety of clinical and pathological abnormalities, which show major involvement in four organ systems:- the eye, skeletal, central nervous system, and vascular system. Ectopia lentis and high myopia are the major ocular manifestation of classical homocystinuria. The most striking changes however is that of skeleton.

One of the distinguishing features of classical homocystinuria patients is the presence of osteoporosis, especially spinal osteoporosis.

Ectopia Lentis

Normal eye — Ectopia lentis

Iris — Pupil

Zonule fibers — Lens — Dislocated lens — Torn zonule fibers

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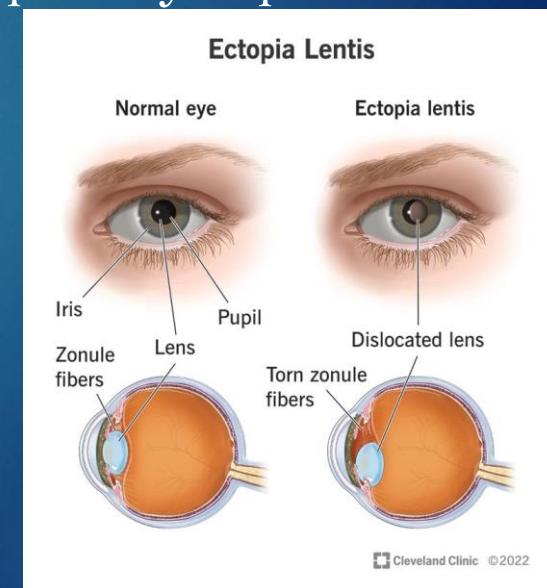
Another well known symptom of homocystinuria is thromboembolism, affecting both large and small arteries and veins. It is also the most striking cause of serious complications and mortality in the disease.

Mental Retardation is the most frequent Central Nervous System abnormality and Is often the first recognizable sign of homocystinuria. These patients show a wide variation in their IQ levels with a median IQ of 64.

DIAGNOSIS

• Newborns are tested for homocystinuria before they leave the hospital. The test usually looks for high levels of MET. If the test is positive, blood or urine tests can be done to confirm the diagnosis. These tests can detect high levels of MET, homocystine, and other sulphur-containing amino acids. Tests to detect an enzyme deficiency (such as cystathionine synthetase) can be done as well.

• If a child is not tested at birth, a doctor may later discover the disorder based on symptoms. At that point, the following may be done:

• Blood tests to confirm the diagnosis
• X-rays to look for bone problems
• An eye exam to look for eye problems

TREATMENT

- Effective treatment requires early diagnosis and initiation of therapy

- Try pyridoxine in all

- Methionine restricted, cystine supplemented diet for those who do not respond to pyridoxine

- Methionine restriction has been shown to prevent mental retardation and reduce the rate of lens dislocation and seizure activity

- Pyridoxine supplementation for responders (usually 50% of affected patients)

▪Pyridoxine treatment of those who are detected late, reduces the rate of thromboembolic events

▪There is no cure for homocystinuria. However, many people respond to high doses of vitamin B6 (also known as pyridoxine).

▪Slightly less than half of patients respond to this treatment.
▪Neither a low-methionine diet nor medication will improve existing mental retardation.

▪ Medication and diet should be closely supervised by a physician with experience treating homocystinuria.

Galactosemia

❖Galactose is a C-4 epimer of glucose. It is found in dairy products, sugar beets, and other gums and mucilages. It is also synthesized by the body, where it forms part of glycolipids and glycoprotein in several tissues.

❖Galactosemia is a rare disorder that affect the body ability to breakdown a food sugar called galactose.

❖Galactosemia is an autosomal recessive disorder caused by deficient or absent activities of one of the three enzymes involved in the galactose metabolic pathway: galactokinase, galactose-1-phosphate uridyltransferase and UDP-galactose 4'-epimerase

❖Galactosemia is an inherited autosomal- recessive disorder of galactose metabolism.

❖People with galactosemia cannot tolerate any form of milk.

❖The sugar lactose (a disaccharide present in milk) is made up of equal parts of glucose and galactose; thus a deficiency of the enzymes involved in galactose metabolism can lead to severe clinical consequences.

❖The classical and most severe form is caused by a deficiency of the enzyme *galactose-1- phosphate uridyl transferase* (GALT).

Galactose-1-phosphate uridylyl transferase (GALT) is an enzyme responsible converting ingested galactose to glucose.

Signs and Symptoms

Early symptoms may include:
- ❖ Jaundice(yellowing) of the skin and whites of the eyes
- ❖ Vomiting
- ❖ Poor weight gain
- ❖ Low blood sugar (hypoglycemia)
- ❖ Feeding difficulties
- ❖ Irritability
- ❖ Lethargy
- ❖ Convulsions

Later signs and symptoms may include:
- Opaque lenses of the eyes (Cataract)
- Enlarged liver, enlarged spleen
- Mental retardation
- Sepsis caused by a specific bacteria (*Escherichia coli*)
- Cirrhosis liver failure
- Kidney problems
- Swelling of the extremities or stomach

Long-term complications include:
- Poor growth
- Learning disabilities
- Speech and language problems
- Fine and gross motor skill delays
- Ovarian failure (in girls)
- Cataracts (usually regress with dietary treatment, leaving no residual visual impairment)
- Decreased bone mineral density

Treatment

- The Treatment for Galactosemia is the removal of galactose from your diet. All lactose products must be totally avoided. Milk and milk products contain the most amount of lactose; however it is also present in other foods such as legumes, organ meats and processed meats.

- Infants will need to be fed with food that is lactose free such as soy formula, meat-base formula, or Nutramigen (a protein hydrolysate formula)

- There is no definite cure for Galactosemia, the condition is life long and it can only be controlled. Doctors advise a calcium supplement for patients with Galactosemia as Milk is an important source of calcium for a growing child.

THANK YOU

WILSON'S DISEASE

Copper (Cu)

- Total body copper is about 100mg

- Sources :liver, fish, meat, lentils

  milk is a poor source

- RDA: 1-3mg/day

Functions

- Mobilization of iron

$$Fe^{2+} \xrightarrow{\text{Ceruloplasmin}} Fe^{3+}$$
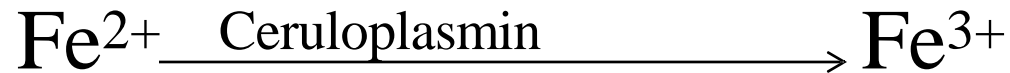
- Formation of enzymes
  dopamine oxidase, serum ferroxidase,
  ALA synthase, monoamine oxidase,
  tyrosinase etc.
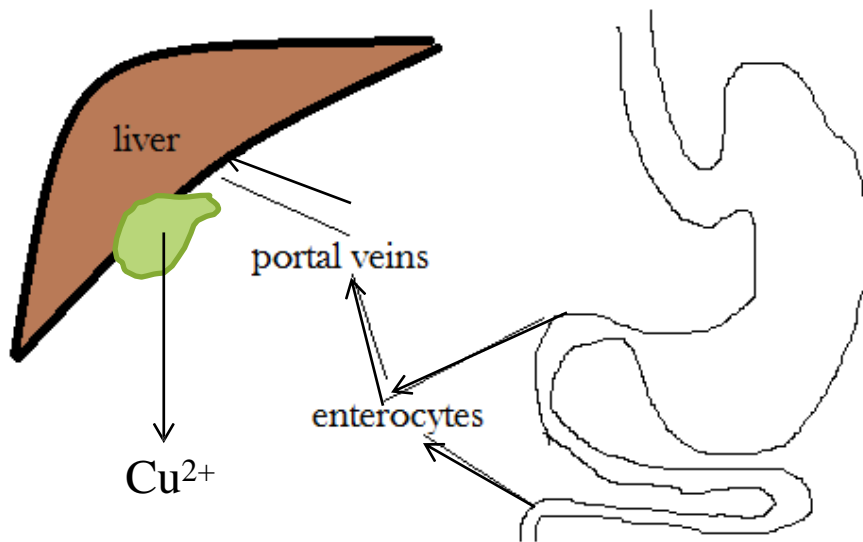
- Absorption : from duodenum
- **Metallothionein** – facilitates absorption

- Phytates, **zinc** and **molybdenum** decrease Cu uptake

Excretion of copper
90% Bile $\longrightarrow$ fecal Cu
10% urine

Functions of ATP7B
1) Binds Cu to Apoceruloplasmin
2) Packages Cu into vesicles for exocytosis in bile

Excess of Cu

Initially bound to metallothionein, but as this storage capacity is exceeded , liver damage begins

$$Cu^{2+} \xrightarrow{\ H_2O_2\ } Cu^{2+} + {}^{*}OH + {}^{-}OH$$

$\downarrow$
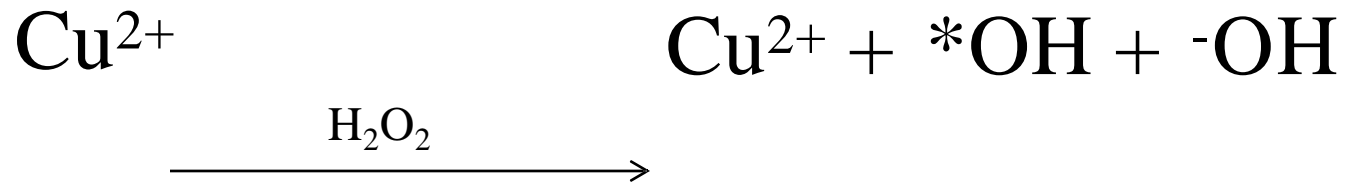
Free radical

$\downarrow$

Tissue damage

DEFINITION

- Wilson's disease occurs due to a defect of copper transport by the hepatic lysosomes.

- Genetic defect in excretion of Cu resulting in excess deposition of Cu in body tissues.

- It is autosomal recessive disorder.

ETIOLOGY

- Mutations in the ATP7B gene,

A membrane bound, copper transporting ATPase.

WD-PATHOPHYSIOLOGY
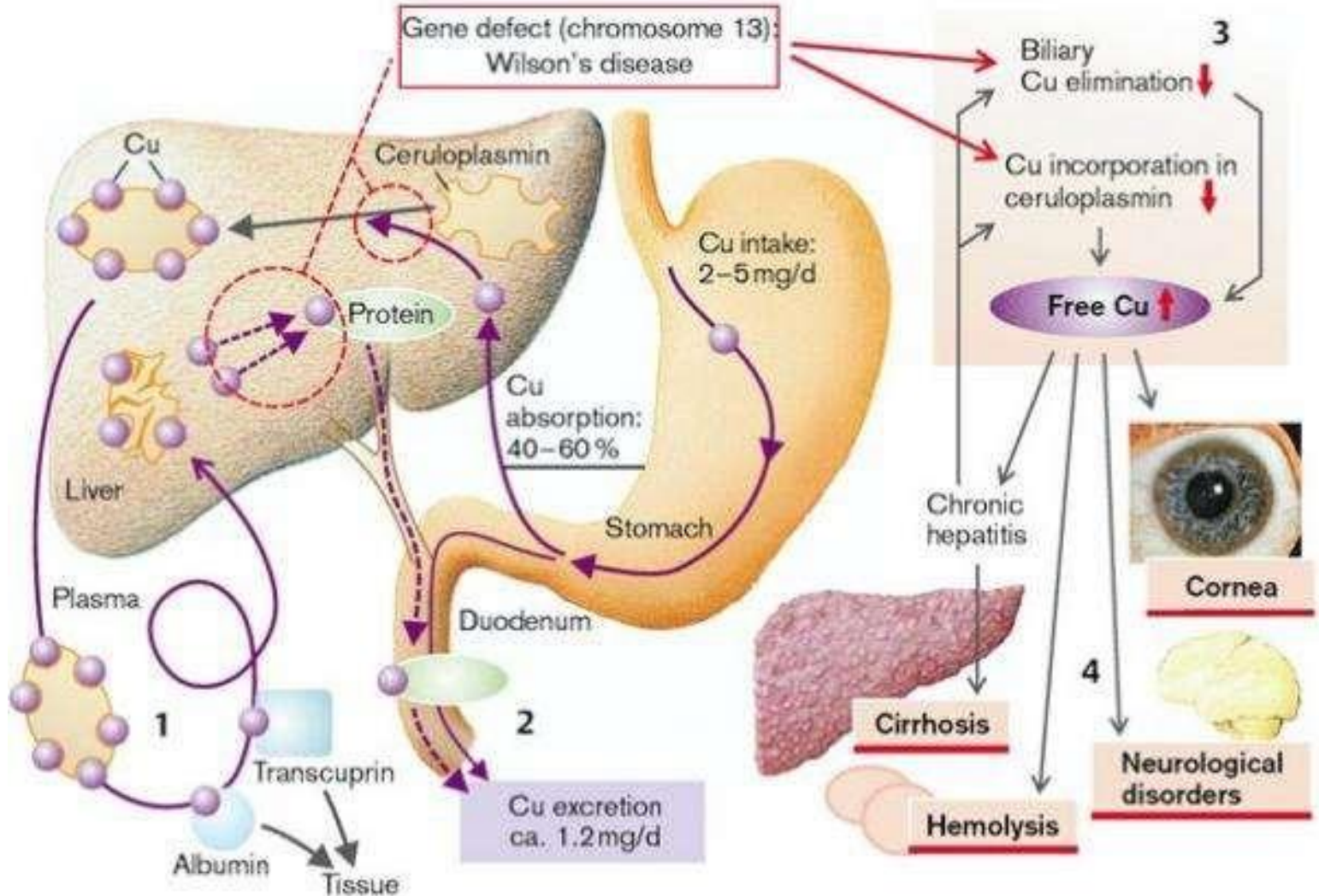
Normal copper metabolism

Normal *Cu uptake* is 2–5mg daily, of which 40–60% are absorbed in the stomach and upper duodenum.

It is then incorporated mainly into *ceruloplasmin* (CP) in the liver

Ceruloplasmin bound copper is secreted into plasma which accounts for 90-95% of serum copper
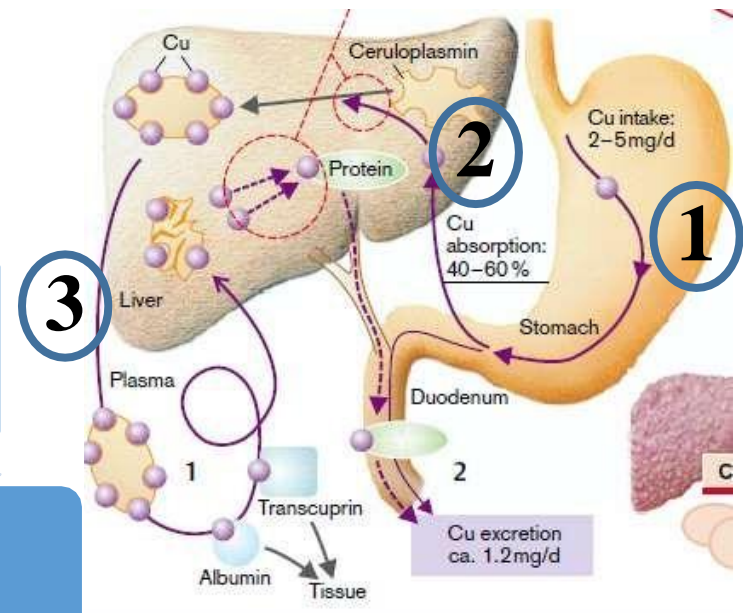
Normal copper metabolism

CP binds six to seven Cu atoms firmly, is apparently important for the oxidation of Fe2+ in plasma

Cu that is bound to *transcuprin and albumin is released into tissue for metabolic needs.*

Old (desialysed) CP is broken down in the liver and the liberated Cu binds to biliary proteins and excreted **into the bile.**
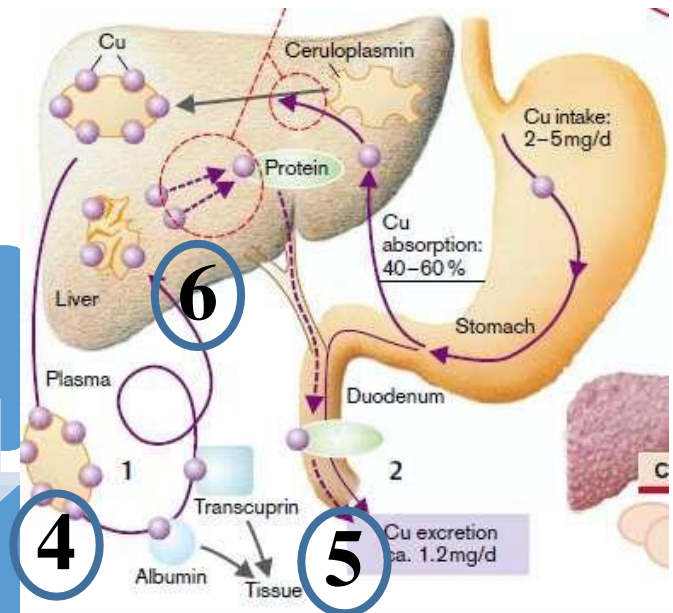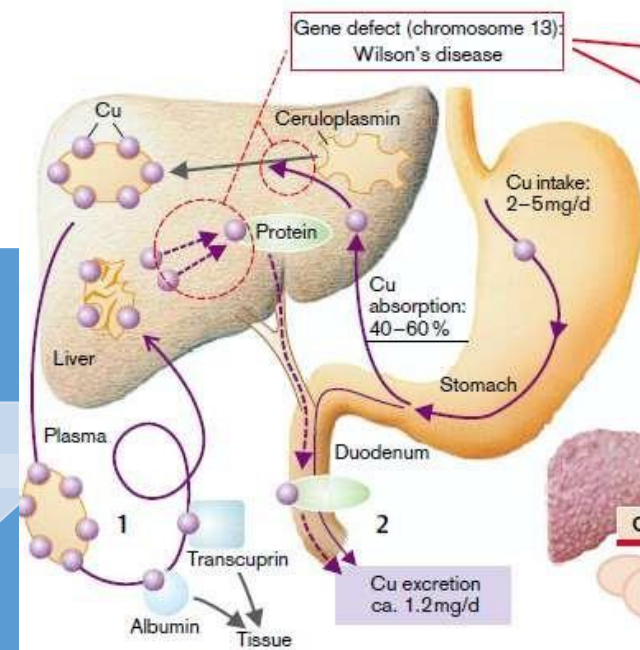
What happens in wilson's disease?

Initial steps of copper absorption and transport to the liver are normal.

But liver fails to excrete sufficient Cu via the bile, and the ability to incorporate Cu into CP is diminished

Due to loss of function mutations of the ATP7B gene on chromosome 13, which encodes a copper-transporting ATPase (ATP7B)
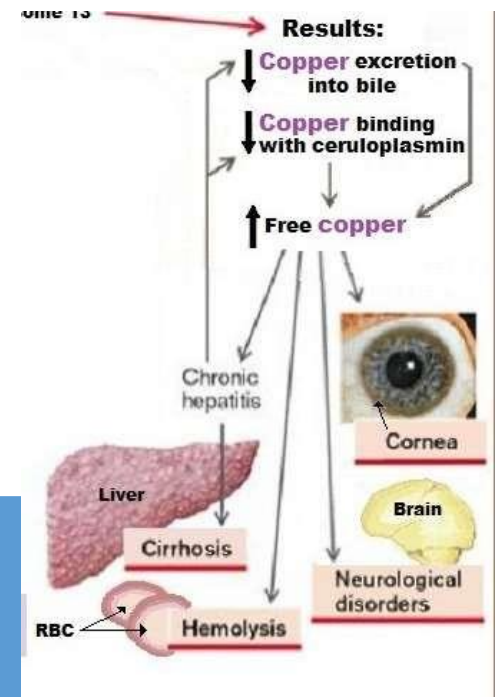
What happens in wilson's disease?

Free or only loosely bound Cu progressively accumulates in the liver.

Free copper escape from the overloaded, damaged hepatocytes into the circulation.
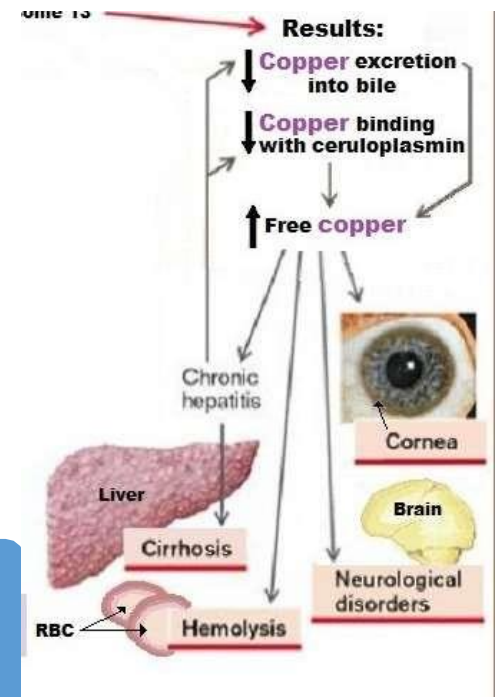
And in other organs

Cont….

Free copper is cytotoxic because it promotes the formation of O2 radical

Causing hemolytic anemia and chronic active hepatitis that can later change to cirrhosis.

If the hepatitis takes a fulminant course, large amounts of Cu are suddenly released from the necrotic liver and this may trigger a hemolytic crisis.
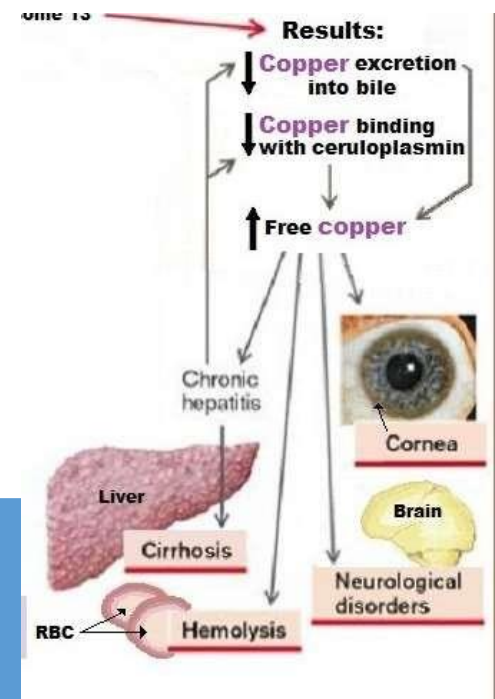
Cont…..

Accumulation of Cu in the CNS cause neurological, neuromuscular, and psychogenic abnormalities.

Cu deposited in Descemet's membrane of the eye giving a Kayser–Fleischer ring

The kidneys, skeleton and heart can also be affected.

Results:
↓ Copper excretion into bile
↓ Copper binding with ceruloplasmin
↑ Free copper
Chronic hepatitis
Cornea
Liver
Brain
Cirrhosis
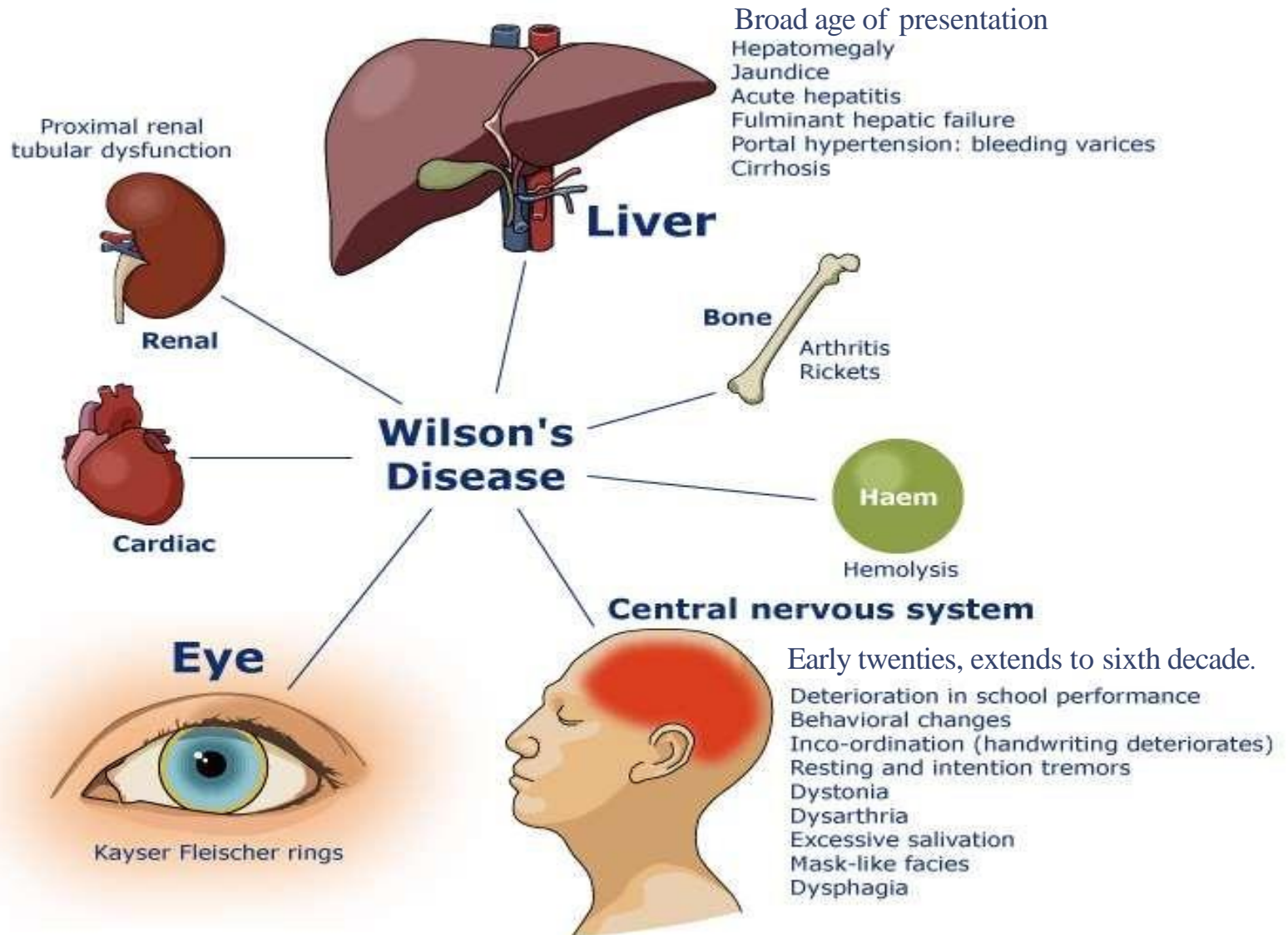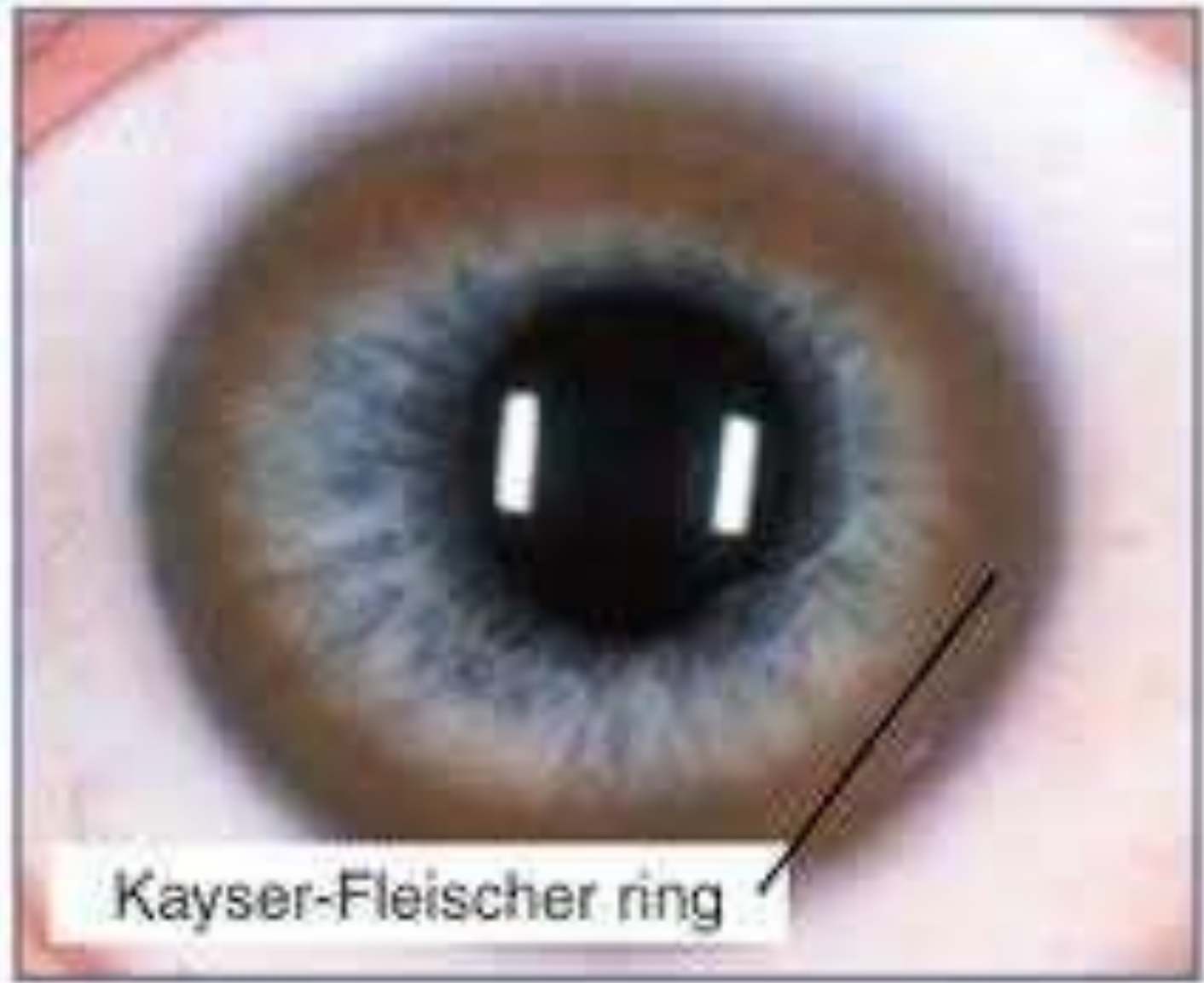Neurological disorders
RBC → Hemolysis

LIVER

Slice of enlarged liver shows micro and macronodular cirrhosis.

Inset demonstrates copper deposits within hepatocytes on rubeanic acid stain. Inset: Rubeanic acid

CLINICAL FEATURES

Broad age of presentation

Liver
Hepatomegaly
Jaundice
Acute hepatitis
Fulminant hepatic failure
Portal hypertension: bleeding varices
Cirrhosis

Renal
Proximal renal tubular dysfunction

Bone
Arthritis
Rickets

Wilson's Disease

Haem
Hemolysis

Cardiac

Eye
Kayser Fleischer rings

Central nervous system

Early twenties, extends to sixth decade.

Deterioration in school performance
Behavioral changes
Inco-ordination (handwriting deteriorates)
Resting and intention tremors
Dystonia
Dysarthria
Excessive salivation
Mask-like facies
Dysphagia

Kayser-Fleischer ring

Neurological	Movement abn – tremor, involuntary movements Dysarthria Rigidity/spasticity Pseudobulbar palsy Dysautonomia Migraine headaches Insomnia Seizures Muscle spasms Drooling	**Psychiatric**	Depression Neurotic behaviours Personality changes Psychosis Mood disturbances Early subtle findings of deterioration of schoolwork, decrease in previous good hand-eye coordination, micrographia etc.
Ophthalmologic	Kayser-Fleischer rings Sunflower cataracts	**Endocrine**	Hypoparathroidism
Cutaneous	Lunulae ceruleae	**Gynecological**	Menstrual irregularities Infertility Repeated miscarriages
Renal	Aminoaciduria Nephrolithiasis Acute renal failure Recurrent hypokalemia → recurrent muscle wkness	**Other**	Pancreatitis Coombs-negative hemolytic anemia (transient episodes of jaundice)
Musculoskeletal	Premature osteopororosis Arthritis		

Confirmatory work-up

Biochemical

↓

Raised 24 hr urinary
Copper (>100mg/24hr)
Low serum cerruloplasmin
copper

Ophthalmic

↓

Slip lamp confirmed
Kayser-Fleisher ring

Radiological

↓

USG Abdomen
  cirrhotic liver
  portal hypertension
MRI Brain
  bilateral basal ganglia changes
  tectal plate changes
  CPM like features and
   combination of basal ganglia
   Brainstem signal changes

Genetics

↓

Genetic analysis
For mutations

INVESTIGATIONS

- Biochemical
  - Serum ceruloplasmin ↓   <20mg/dL
  - 24hr Urinary Copper   >100micg/d
  - Serum free copper   >10micg/dL
  - Liver Copper   >250micg/g
- Ophthalmological
  - Slit lamp   KF ring
- Imaging
  - X-ray   Osteoporosis
  - Ultrasound   Cirrhosis
  - CT Scan
  - MRI
- Genetics

MRI in WD

a. 'Face of giant panda' sign;
b. MRSS: decreased NAA and therefore a decreased ratio with other products
c. Bright lateral putamen or claustral sign;
d. Pallidal hyperintensity

TABLE 360-1 Useful Tests for Wilson's disease

Test	Usefulness[a]	Normal Value	Heterozygous Carriers	Wilson's disease
Serum ceruloplasmin	+	180–350 mg/L (18–35 mg/dL)	Low in 20%	Low in 90%
KF rings	++	Absent	Absent	Present in 99% + if neurologic or psychiatric symptoms present Present in 30–50% in hepatic presentation and presymptomatic state
24-h urine Cu	+++	0.3–0.8 µmol (20–50 µg)	Normal to 1.3 µmol (80 µg)	>1.6 µmol (>100 µg) in symptomatic patients 0.9 to >1.6 µmol (60 to >100 µg) in presymptomatic patients
Liver Cu	++++	0.3–0.8 µmol/g (20–50 µg per g tissue)	Normal to 2.0 µmol (125 µg)	>3.1 µmol (>200 µg) (obstructive liver disease can cause false-positive results)
Haplotype analysis	++++ (Siblings only)	0 Matches	1 Match	2 Matches

Treatment Options

- Reduced Copper intake
  - Low copper diet
- Reduce copper absorption
  - Zinc
- Increase copper excretion
  - Penicillamine
  - Trentine
  - Tetrathiomolybdate
- Liver Transplantation
- Gene Therapy

Prognosis

- Life long treatment is needed to control Wilson's disease.
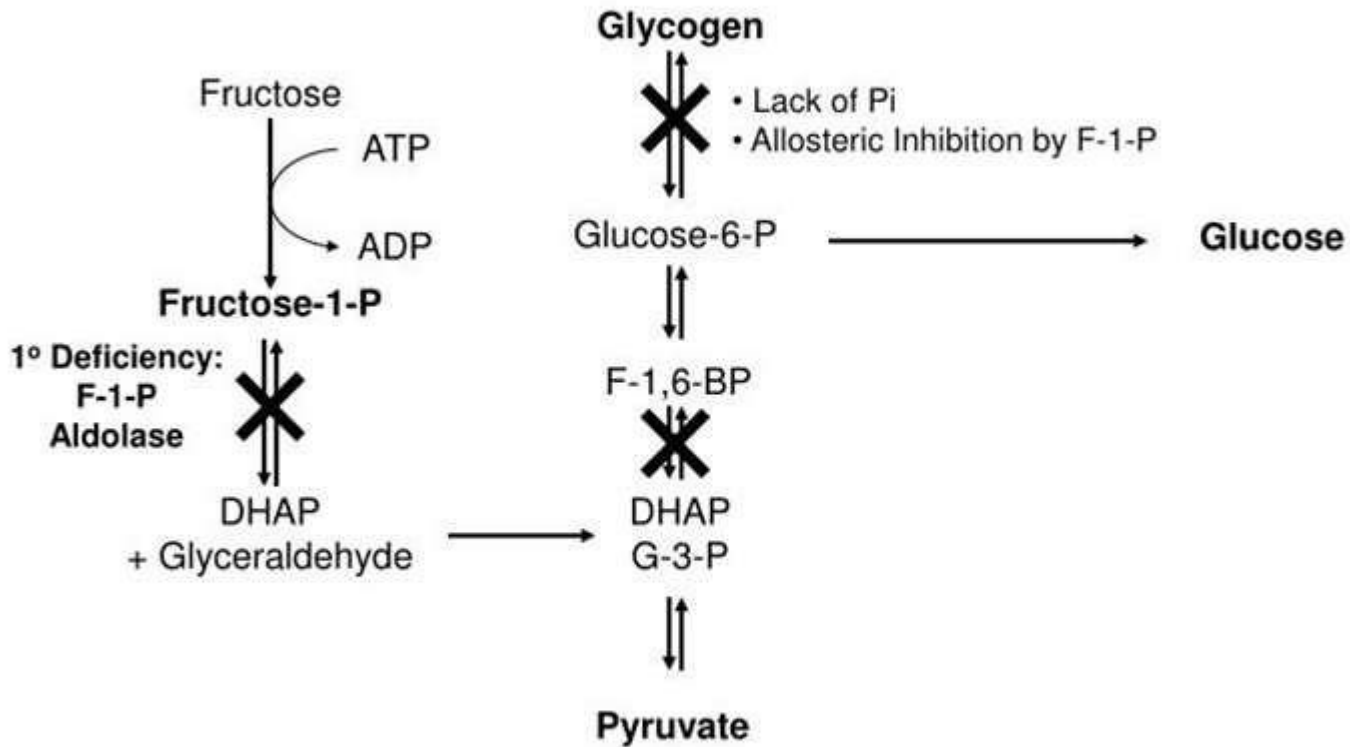- If not treated early, Wilson's disease is fatal.

HEREDITARY FRUCTOSE INTOLERANCE

INTRODUCTION

o Fructose intolerance, occurs when cells on the surface of the intestines aren't able to break down fructose efficiently.

o Fructose is a simple sugar, known as a monosaccharide, that comes mostly from fruit and some vegetables.

o Fructose intolerance is a rare genetic condition occurs because the body doesn't make the enzyme needed to break down fructose.

o This can lead to serious health issues such as liver failure if a strict fructose-free diet isn't followed.

- **HFI is an autosomal recessive disorder of fructose metabolism due to a deficiency of fructose-1-phosphate aldolase (EC 2.1.2.13) activity, which results in an accumulation of fructose-1- phosphate in the liver, kidney, and small intestine.**

- **The accumulated fructose-1-phosphate inhibits glycogen breakdown and glucose synthesis, thereby causing severe hypoglycaemia following ingestion of fructose**

- **Prolonged fructose ingestion in infants leads ultimately to hepatic and/or renal failure and death.**

Fructose Intolerance

Fructose

ATP

ADP

Fructose-1-P

1° Deficiency:
F-1-P
Aldolase

DHAP
+ Glyceraldehyde

Glycogen

- Lack of Pi
- Allosteric Inhibition by F-1-P

Glucose-6-P → **Glucose**

F-1,6-BP

DHAP
G-3-P

Pyruvate

Genetic Condition of Fructose Intolerance

O Mutations in the **ALDOB gene** (generally found in liver) cause hereditary fructose intolerance. The ALDOB gene provides instructions for making the aldolase B enzyme. This enzyme is found primarily in the liver and is involved in the breakdown (metabolism) of fructose so this sugar can be used as energy.

Causes

Fructose intolerance is fairly common, affecting up to 1 in 3 people.

Fructose Intolerance can be due to many causes that include:

o imbalance of good and bad bacteria in the gut.

o high intake of refined and processed foods.

o preexisting gut issues such as irritable bowel syndrome (IBS).

o Stress.

Symptoms

Symptoms for fructose Intolerance include:

o Nausea.

o Bloating.

o Gas.

o Abdominal pain.

o Diarrhea.

o Vomiting.

Diagnosis

- The only definitive way to diagnose if one is suffering from HFI is to have one of two test.

- An enzymatic assay to determine aldolase activity.

  O - The aldolase is obtained from patient liver tissue in an invasive surgical procedure called **liver biopsy.**

- A **fructose tolerance test,** fructose is injected introvenously under controlled condition where acute glucose, fructose & phosphate levels are monitered.

o Hydrogen breathe test is a method currently used to diagnosis following ingestion of fructose, the hydrogen concentration of the patients breathe is measured at various time intervals. The normal range for hydrogen is 20ppm in 60 minutes.

Clinical Diagnosis

The aldolase test was used to look for liver or muscle damage. Doctors use more specific blood tests, including:

o creatine kinase (CK) [**normal range** is 22 to 198 U/L (units per liter)].

o alanine aminotransferase (ALT) [The **normal value for ALT** in blood ranges from 29 to 33 units per liter (IU/L) for males and 19 to 25 IU/L for females]

o aspartate aminotransferase (AST) [The normal range of values for AST is about 5 to 40 units per liter of serum.

Treatment

O Treatment of HFI is currently done through a **strict fructose free diet**.

O Read nutrition labels and ingredients lists carefully to determine what foods are safe and which ones you want to avoid.

Foods To Avoid :

Fruits

O Although you can safely consume fruit on a low fructose diet, it is important to know which ones are high in fructose.

O High fructose fruits include watermelon, pineapple, oranges, apples, pears, peaches and mangoes.

O However, some people can tolerate eating some of these fruits in small amounts and in combination with other foods.

Sweeteners

o Sweet foods are likely to contain some form of fructose.

o High fructose corn syrup is one that you should limit or avoid if you are maintaining a low fructose diet.

o Soda, candy, yogurt, jam and some sports drinks contain this sweetener.

o Any food sweetened with sorbitol, fruit juice or honey should also be limited.

What to Eat

O There are plenty of foods you can eat on a low fructose diet so that you are covering your nutrient needs and staying healthy.

O Recommended diet are meat, dairy, eggs, beans and vegetables.

Meat :-

O Fresh meat contain no fructose. They are also high in protein and iron, and low in carbs. Chicken are lean and contain no fructose.

Vegetables :-

The   majority of   vegetables   are   low in fructose. Such as peppers, Cabbage ,Radishes etc.

Cont.

Dairy

o Dairy products, such as cheese, milk and buttermilk are low in fructose. These items are high in calcium, protein and fat.

Eggs

o Eggs contain no fructose, are low in carbs and are high in protein and fat.

Beans

Beans in their natural state are free of fructose. They are also high in fiber, protein and complex carbohydrates.

THANK YOU