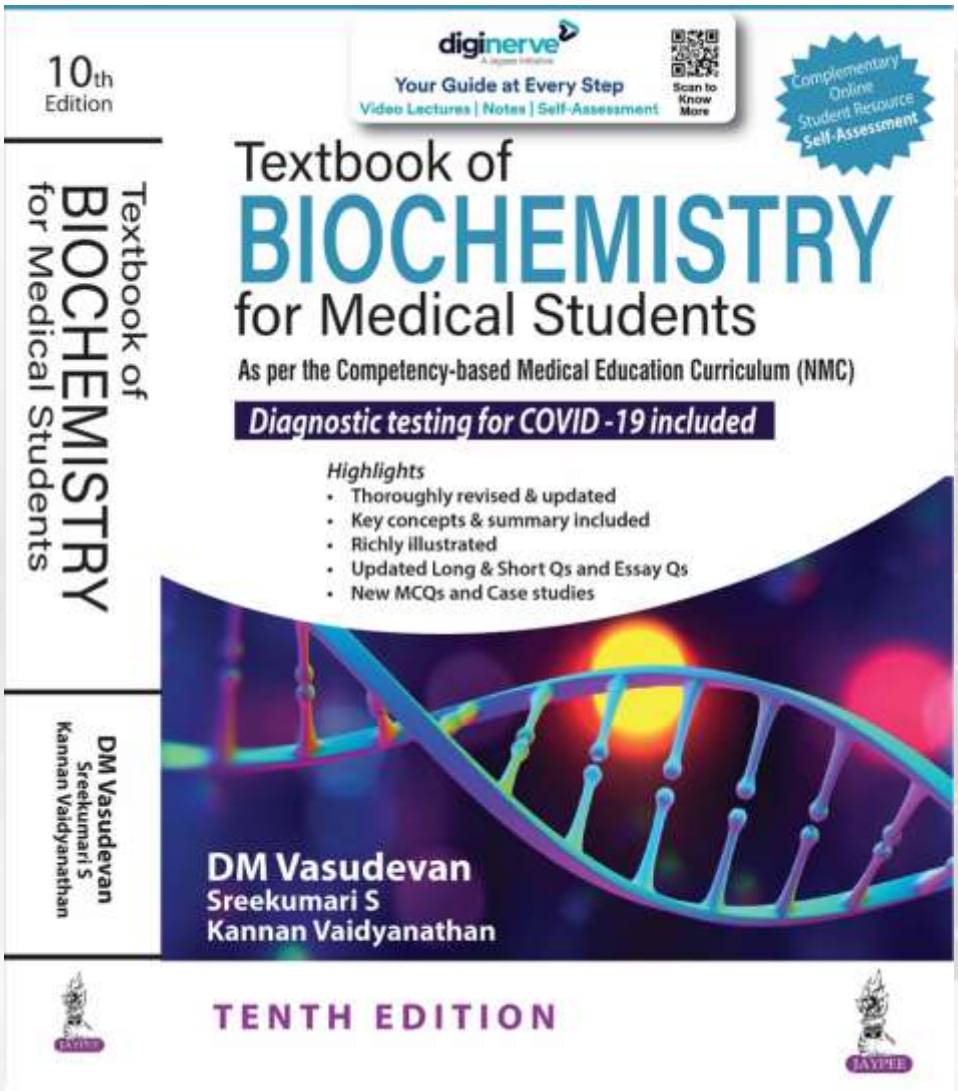


Chapter 10:

Metabolic Pathways of Carbohydrates, other than Glucose (Fructose, Galactose, Alcohol, Methanol, GAG, Glycoproteins)

Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

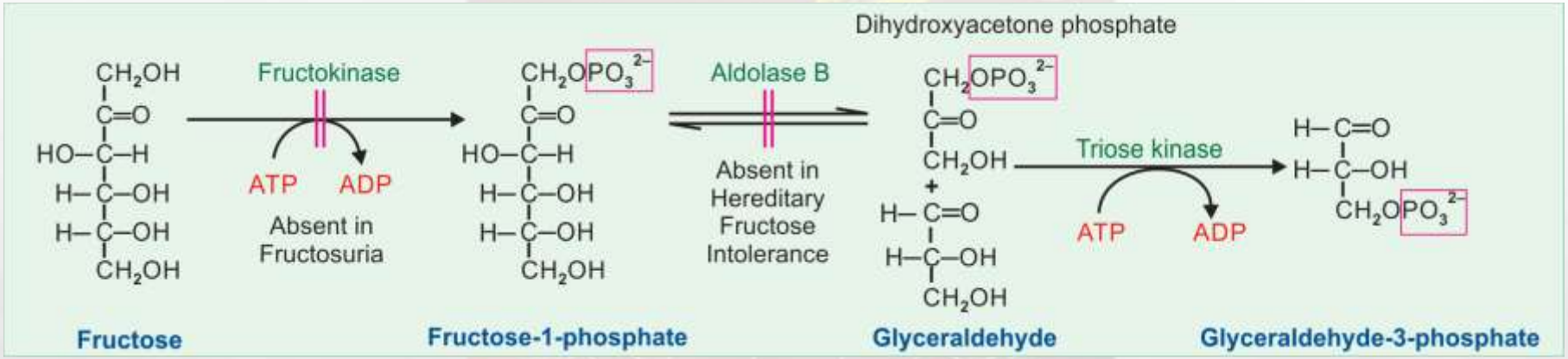
Fructose Metabolism

Fructose is a ketohexose present in fruits, honey and sucrose.

Fructose is promptly metabolized by the liver.

Fructokinase; absent in Fructosuria

- Fructose is phosphorylated by **fructokinase**.
- Fructokinase phosphorylates at **1st position,** whereas hexokinase action is on the 6th position.
- Fructokinase is not dependent on insulin.


Dihydroxyacetone phosphate
Fructokinase
ATP
ADP
Absent in Fructosuria
Aldolase B
Absent in Hereditary Fructose Intolerance
Triose kinase
ATP
ADP
Fructose
Fructose-1-phosphate
Glyceraldehyde
Glyceraldehyde-3-phosphate

Free fructose is seen in large quantities in **seminal plasma.**

- **The energy for mobility of spermatozoa** is mainly derived from fructose.
- Fructose is secreted by seminal vesicles. In some persons azoospermia is seen due to a block in the duct.
- In such persons fructose is estimated in semen.
- If fructose is present, the block is above the seminal vesicular duct; if absent, block is after the seminal vesicles.

Hereditary Fructose Intolerance (HFI)

Autosomal recessive
Inborn error of metabolism
1 in 70 persons are carriers of abnormal gene

The defect is in Aldolase-B

Manifested by vomiting and loss of appetite.
Hepatomegaly and jaundice may occur.

When sucrose or fructose is introduced in diet of infants usually around 6 months.

Fructose is excreted in urine ;
urine gives positive Benedict's test.

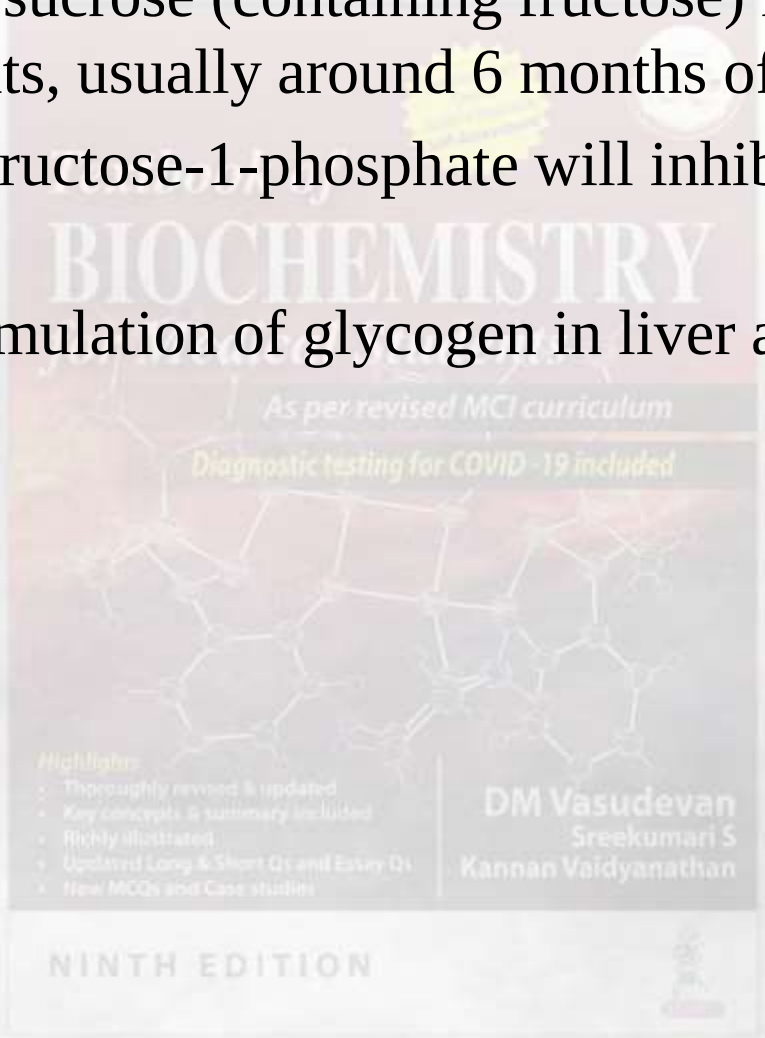
Accumulation of fructose-1-phosphate will inhibit glycogen phosphorylase.

This leads to accumulation of glycogen in liver and associated hypoglycemia

The infants often fail to thrive.
If liver damage progresses,
Cirrhosis, Death.

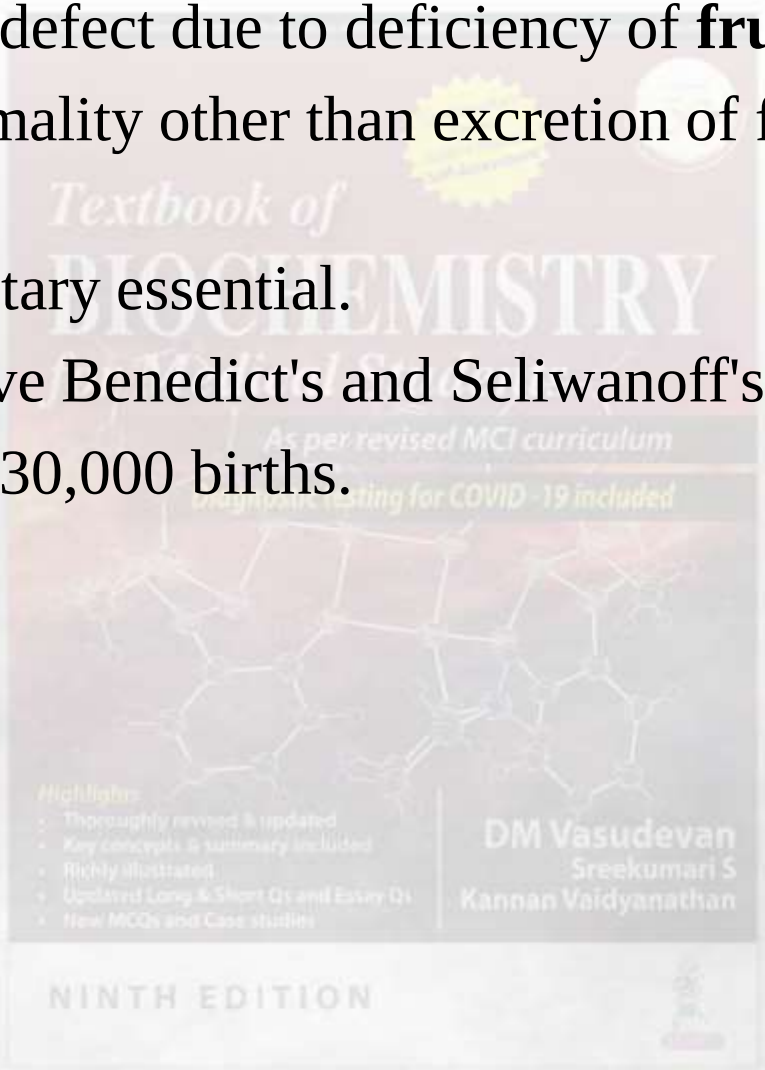
Withdrawal of fructose from the diet will immediately relieve the symptoms.

- This is seen when sucrose (containing fructose) is introduced in the diet of infants, usually around 6 months of age.
- Accumulation of fructose-1-phosphate will inhibit glycogen phosphorylase.
- This leads to accumulation of glycogen in liver and associated **hypoglycemia.**



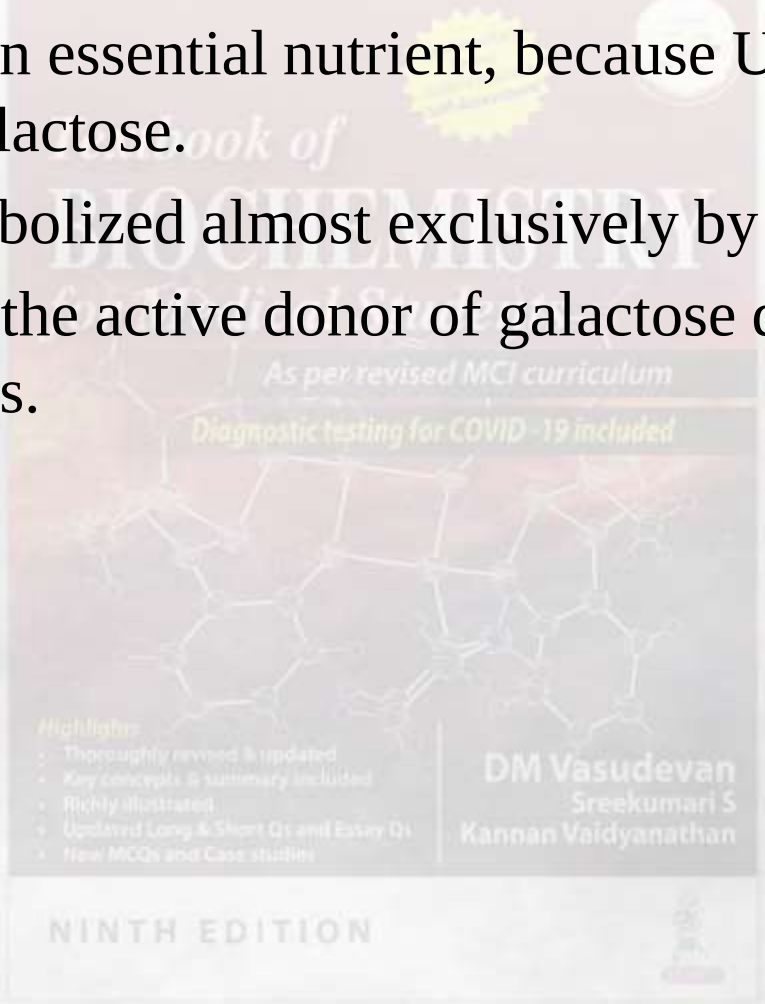
Fructosuria

- Benign metabolic defect due to deficiency of **fructokinase.**
- There is no abnormality other than excretion of fructose in urine.
- Fructose is not dietary essential.
- Urine gives positive Benedict's and Seliwanoff's tests.
- Incidence is 1 in 130,000 births.



Galactose Metabolism

- Galactose is a constituent of lactose, milk sugar.
- Galactose is not an essential nutrient, because UDP glucose can form UDP galactose.
- Galactose is metabolized almost exclusively by the liver.
- UDP galactose is the active donor of galactose during synthetic reactions.



- Galactose is necessary for synthesis of the following.

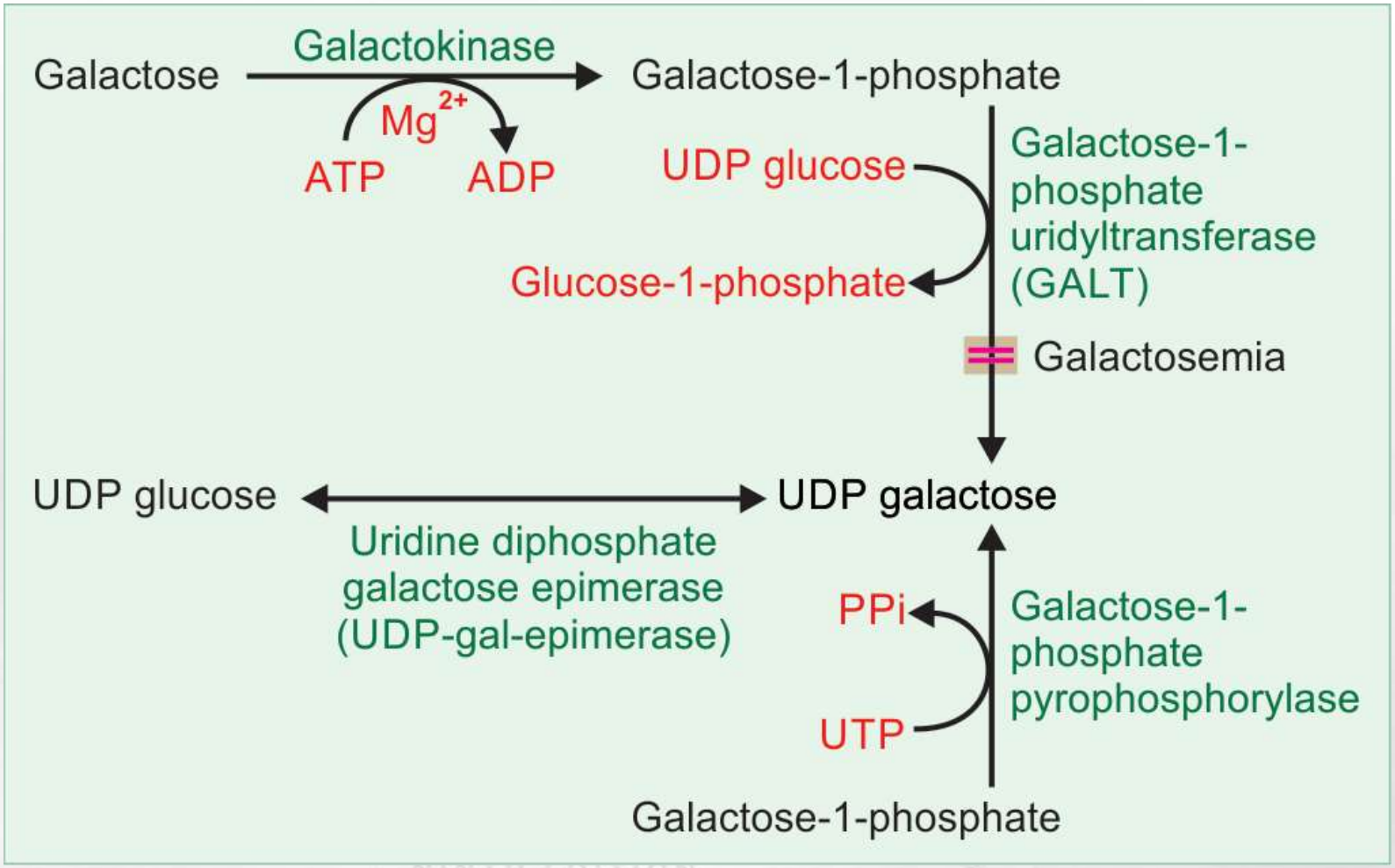
i. Lactose Synthesis

$$\text{UDP glucose} \xrightarrow{\text{Epimerase}} \text{UDP galactose}$$

$$\text{UDP galactose} + \text{glucose} \xrightarrow{\text{Lactose synthase}} \text{Lactose}$$

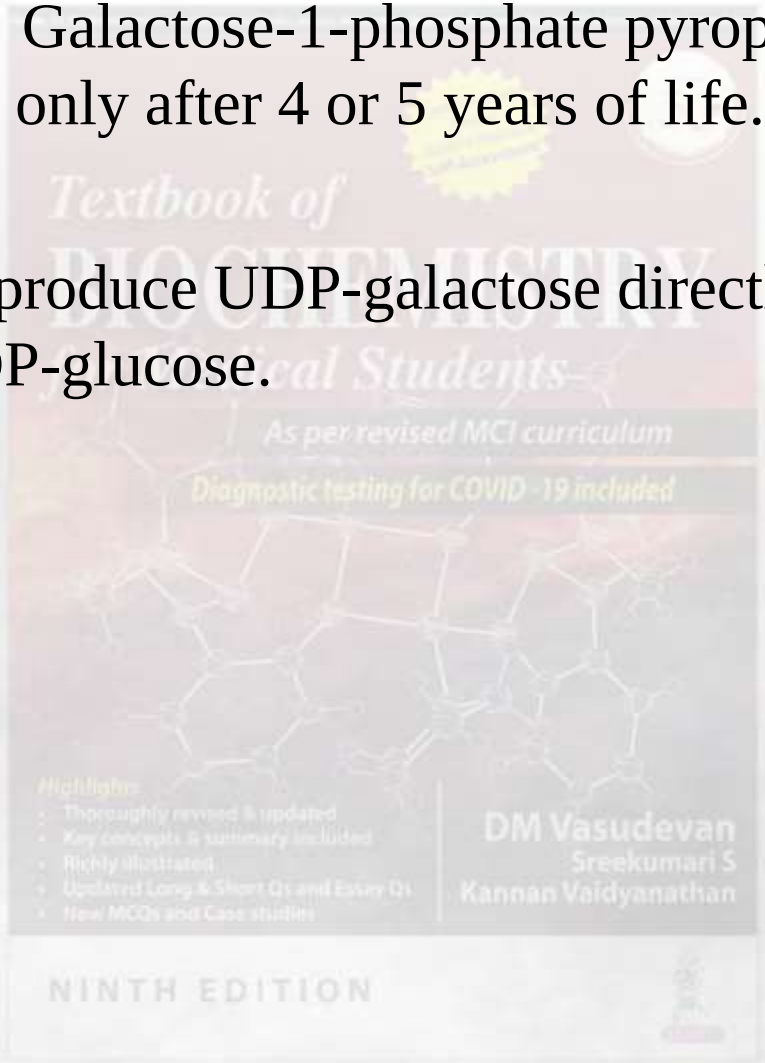
- Lactose synthesis is seen in lactating mammary glands.

ii. Synthesis of glycosaminoglycans
iii. Synthesis of cerebrosides
iv. Synthesis of glycolipids
v. Synthesis of glycoproteins.


Galactose
Galactokinase
Mg2+
ATP
ADP
Galactose-1-phosphate
UDP glucose
Glucose-1-phosphate
Galactose-1-phosphate uridyltransferase (GALT)
Galactosemia
UDP glucose
UDP galactose
Uridine diphosphate galactose epimerase (UDP-gal-epimerase)
PPi
UTP
Galactose-1-phosphate pyrophosphorylase
Galactose-1-phosphate

Alternate pathway: Galactose-1-phosphate pyrophosphorylase in liver becomes active only after 4 or 5 years of life.

- The enzyme will produce UDP-galactose directly which can be epimerized to UDP-glucose.



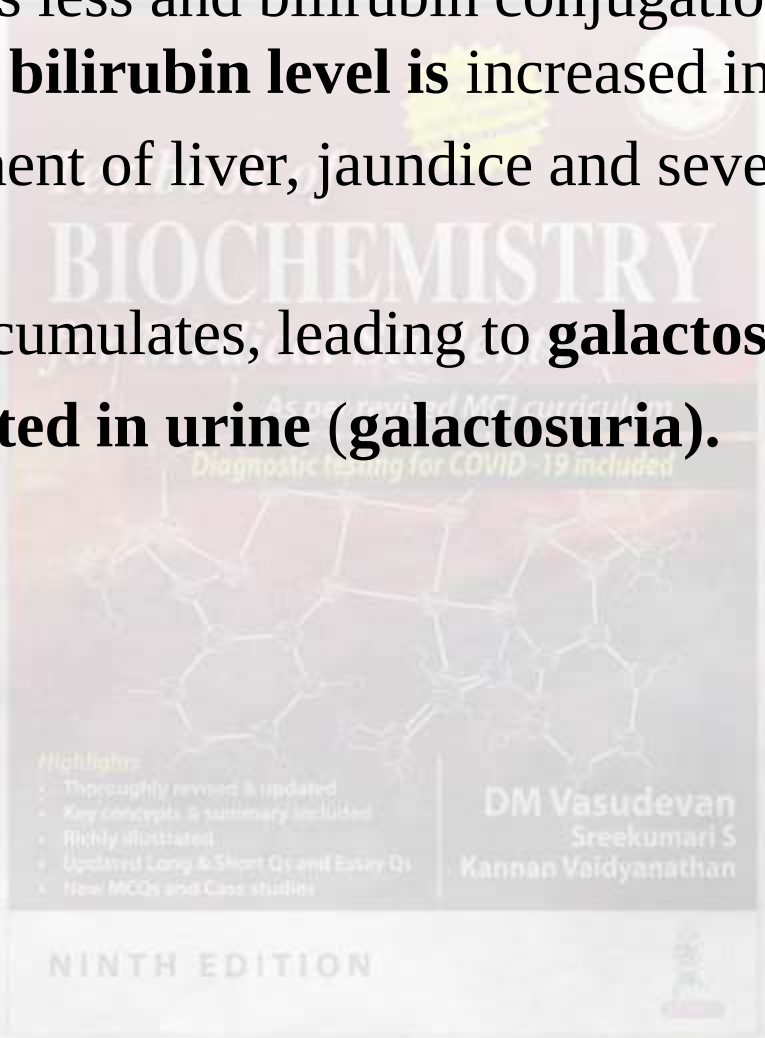
Galactosemia

Inborn error of metabolism.
The incidence is 1 in 35,000 births.

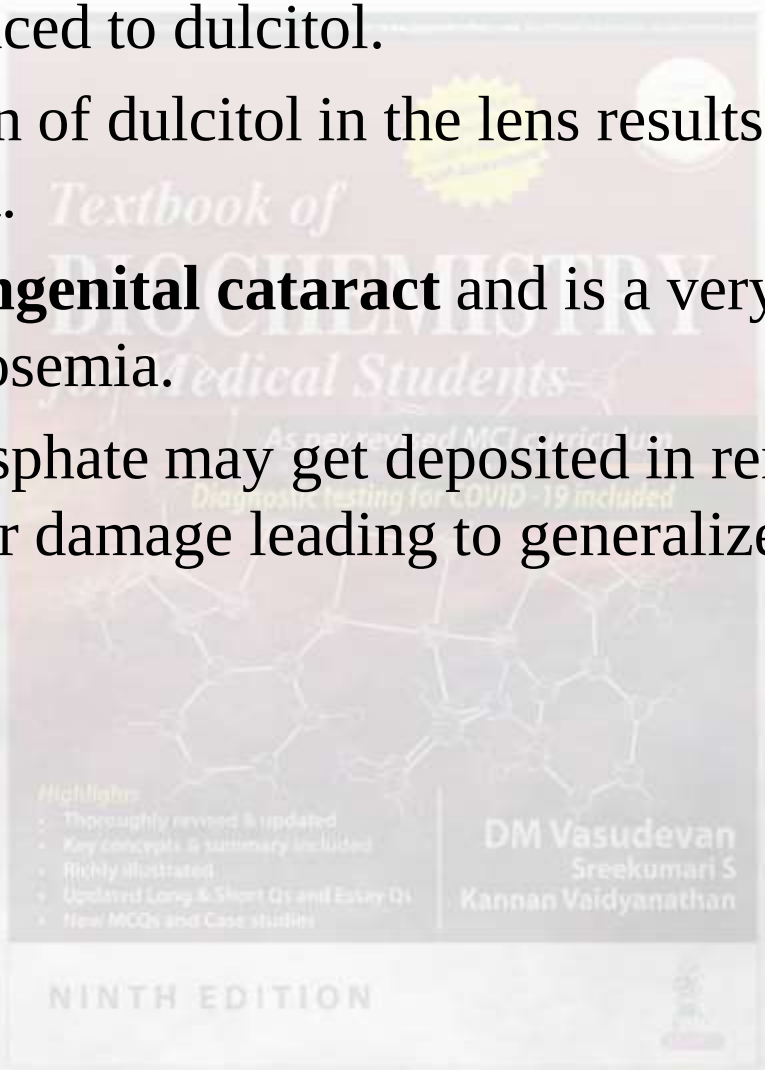
Deficiency of the enzyme
galactose-1-phosphate uridyl transferase.

Galactose-1-phosphate accumulates in liver, which inhibits glycogen phosphorylase.
Neonatal hypoglycemia

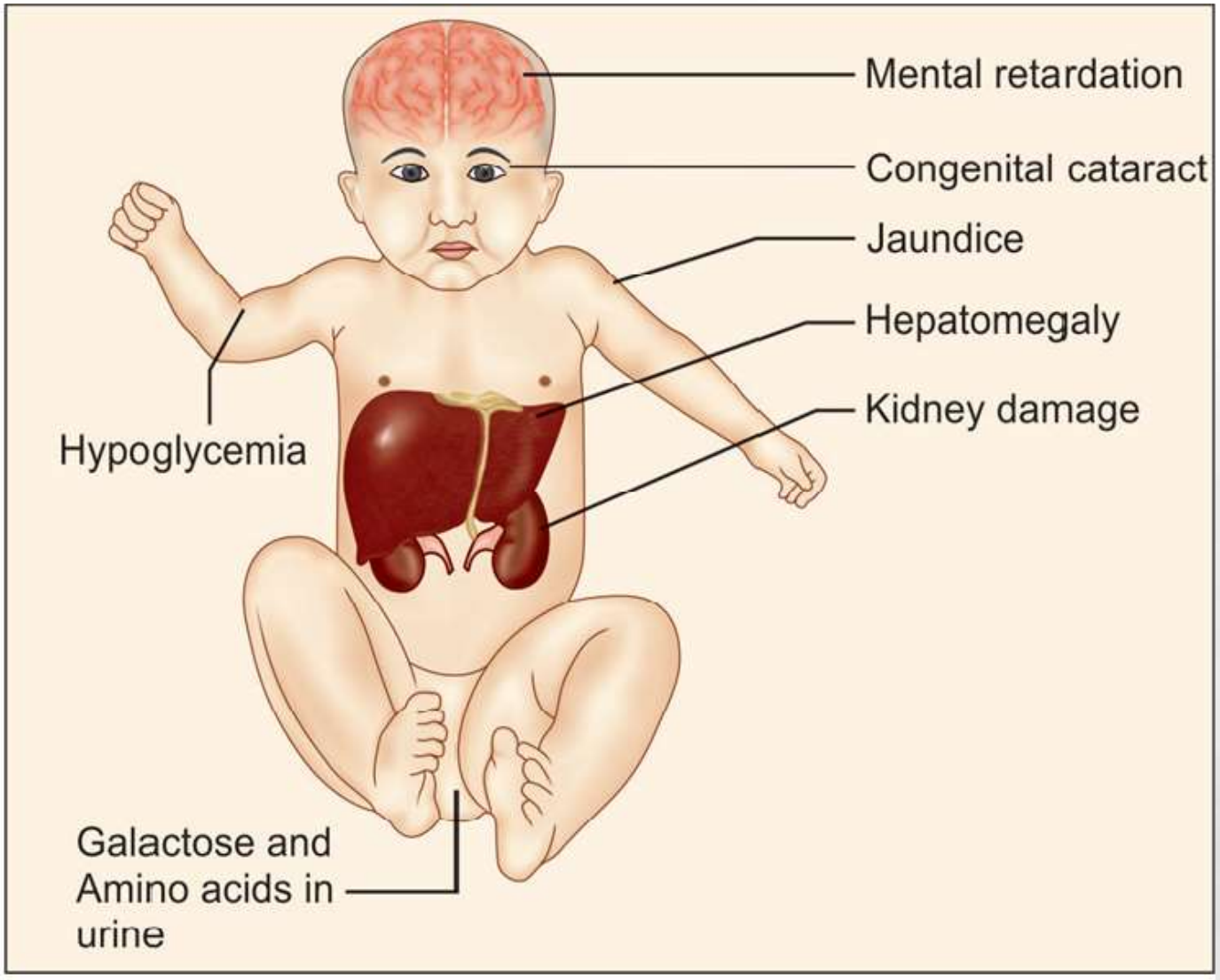
- Bilirubin uptake is less and bilirubin conjugation is reduced; so **unconjugated bilirubin level is** increased in blood.
- There is enlargement of liver, jaundice and severe **mental retardation.**
- Free galactose accumulates, leading to **galactosemia.**
- **It is partly excreted in urine (galactosuria).**



- Galactose is reduced to dulcitol.
- The accumulation of dulcitol in the lens results in cataract due to its osmotic effect.
- This is called **congenital cataract** and is a very characteristic feature of galactosemia.
- Galactose-1-phosphate may get deposited in renal tubules, producing tubular damage leading to generalized **amino aciduria.**



Clinical Features of Galactosemia

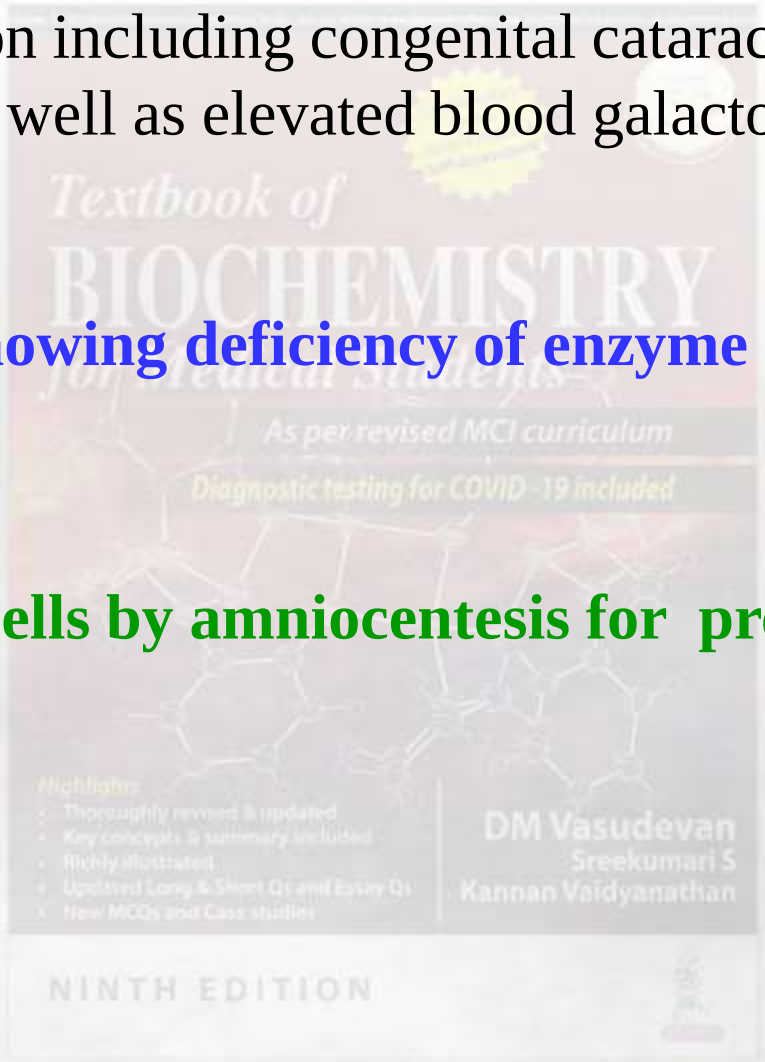


Diagnosis of Galactosemia

Clinical manifestation including congenital cataract and presence of galactose in urine as well as elevated blood galactose levels will help in the diagnosis.

Confirmation by showing deficiency of enzyme activity in WBCs.

Collection of fetal cells by amniocentesis for prenatal diagnosis.



Treatment of Galactosemia

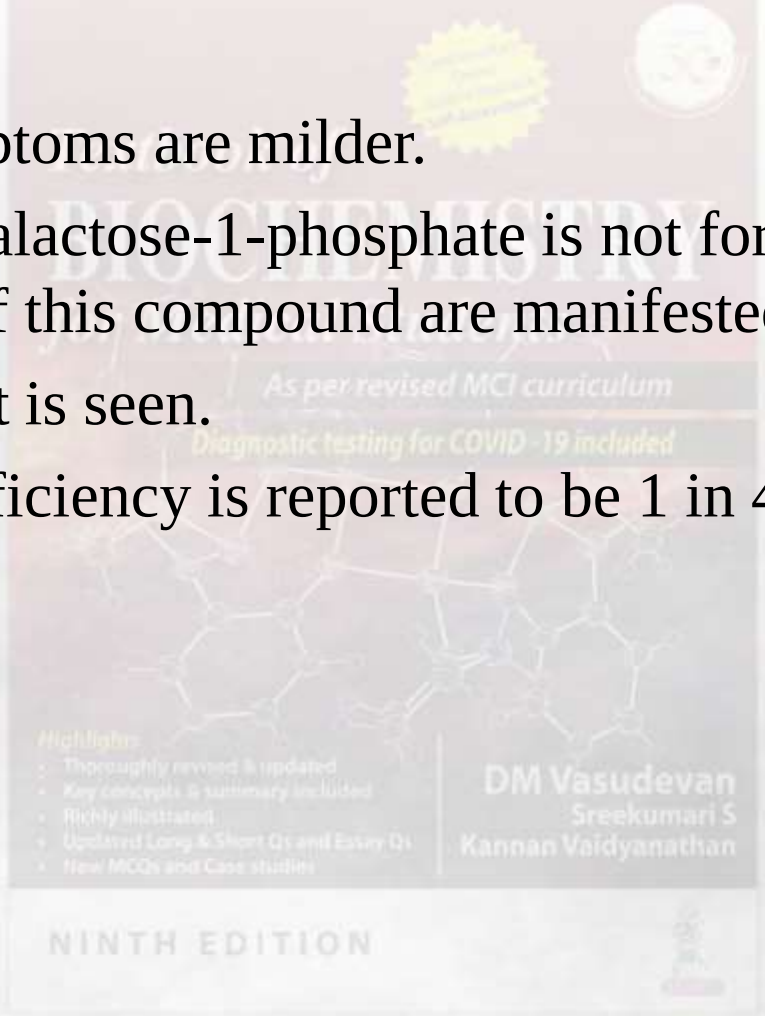
Lactose-free diet.
Special diet may be withdrawn after 4 years, when galactose-1-phosphate pyrophosphorylase becomes active.

If lactose is withdrawn from the diet, most of the symptoms recede.

But mental retardation, when established, will not improve.
Hence early detection is most important.

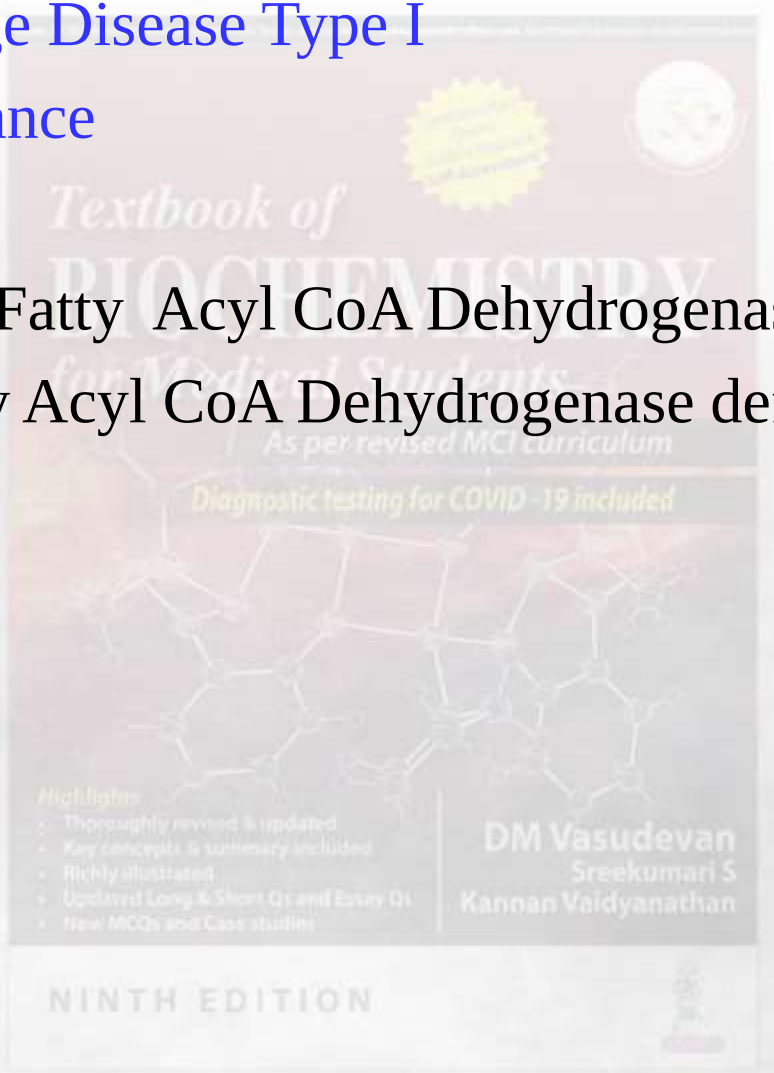
Galactokinase Deficiency

- A variant of the disease occurs due to the deficiency of galactokinase.
- But here the symptoms are milder.
- This is because galactose-1-phosphate is not formed and hence no toxic effects of this compound are manifested.
- However, cataract is seen.
- Galactokinase deficiency is reported to be 1 in 40,000 births.



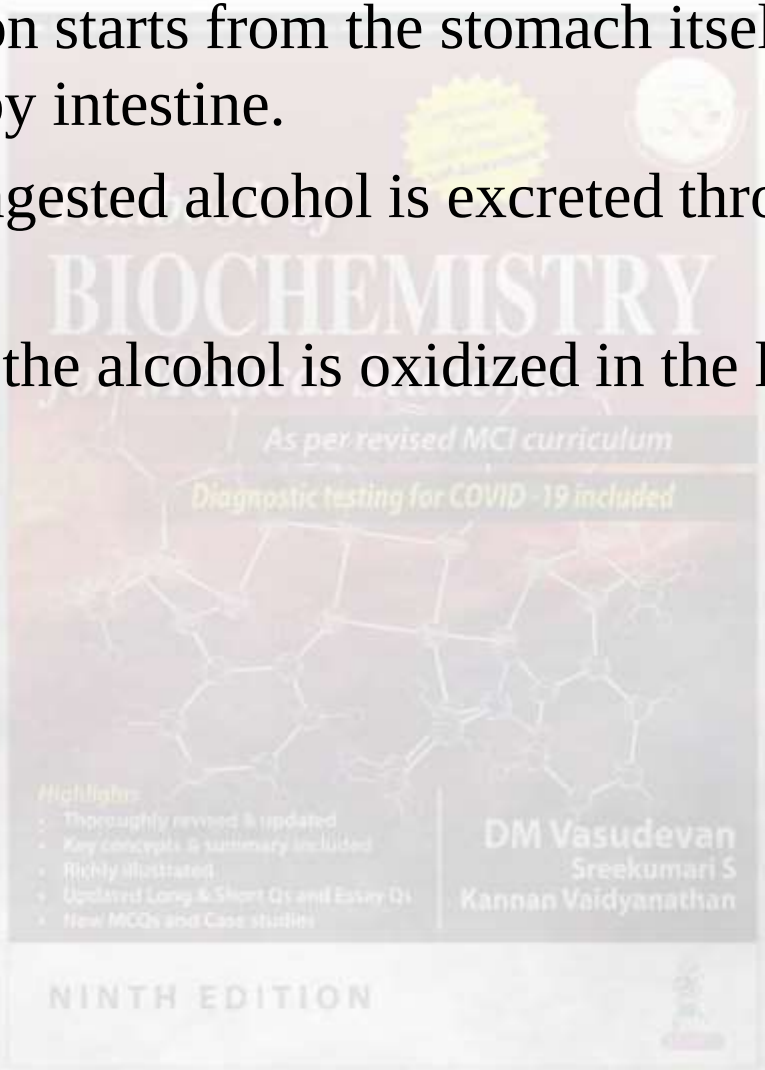
Neonatal hypoglycemia

1. Glycogen Storage Disease Type I
2. Fructose Intolerance
3. Galactosemia
4. Medium Chain Fatty Acyl CoA Dehydrogenase deficiency
5. Long Chain Fatty Acyl CoA Dehydrogenase deficiency



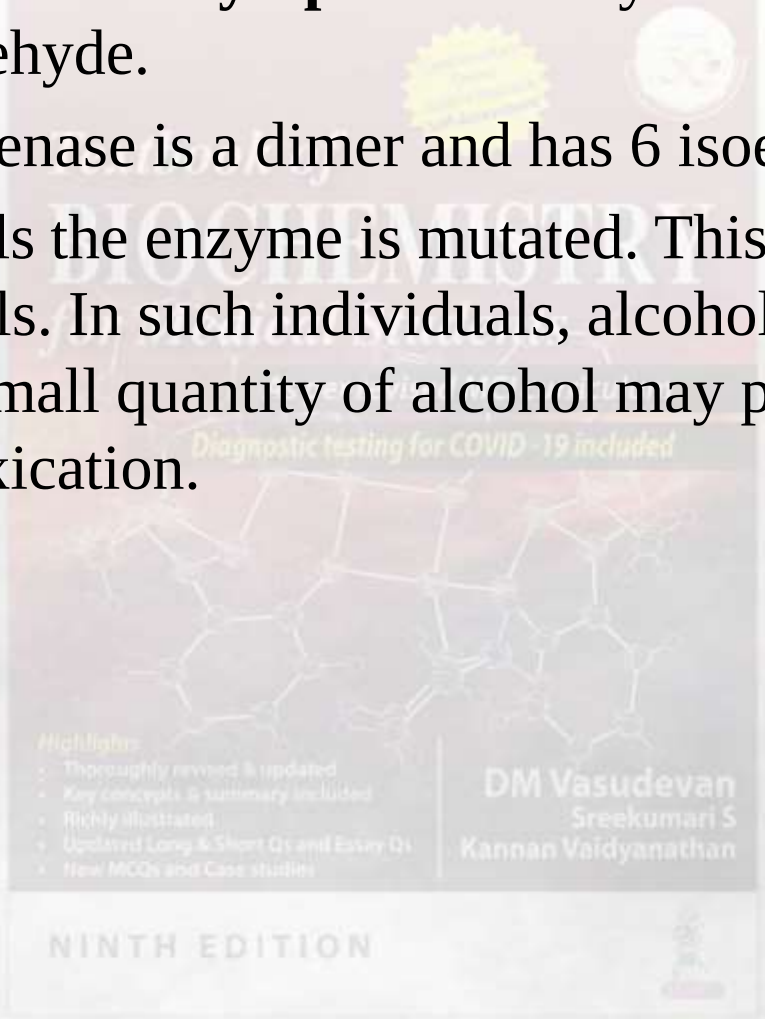
Metabolism of alcohol

- Alcohol absorption starts from the stomach itself, but most of it is absorbed by intestine.
- Only 1% of the ingested alcohol is excreted through the lungs or urine.
- Major fraction of the alcohol is oxidized in the liver.



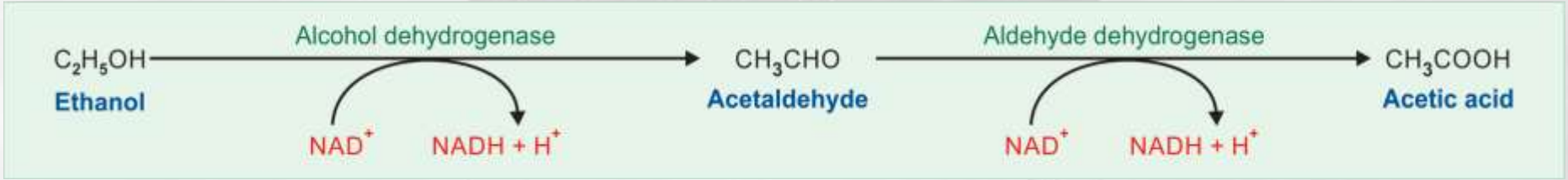
Alcohol Dehydrogenase (ADH)

- It is an NAD+ dependent **cytoplasmic** enzyme that oxidizes ethanol to acetaldehyde.
- Alcohol dehydrogenase is a dimer and has 6 isoenzymes.
- In some individuals the enzyme is mutated. This mutation rate is more in Orientals. In such individuals, alcohol metabolism is slower and even small quantity of alcohol may produce symptoms of intoxication.



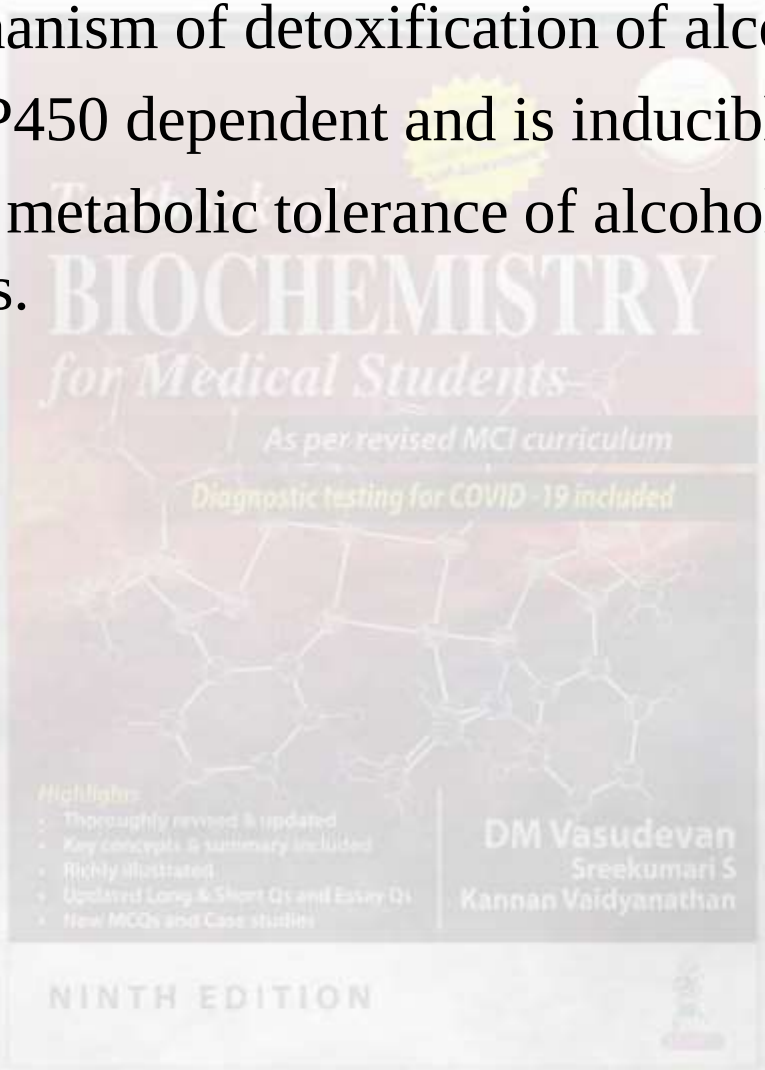
Aldehyde Dehydrogenase

- Acetaldehyde is further oxidized to acetate by a **mitochondrial** NAD+ dependent enzyme.
- The acetate is then converted to acetyl CoA.
- The activity of alcohol dehydrogenase is more than aldehyde dehydrogenase.
- So acetaldehyde accumulates in liver.
- **Aldehyde is toxic**, which in excess may lead to cell death.
- The activity of aldehyde dehydrogenase is less in Indians, when compared to Europeans.



Microsomal Ethanol Oxidizing System (MEOS)

- It is another mechanism of detoxification of alcohol.
- It is cytochrome P450 dependent and is inducible.
- This accounts for metabolic tolerance of alcohol observed in chronic alcoholics.



Biochemical Alterations in Alcoholism

- Both the oxidation steps of alcohol produces NADH, resulting in a high NADH / NAD+ ratio.
- As a result, several metabolic adaptations occur:

i. In the cytoplasm, the high NADH level favours conversion of pyruvate to lactate, leading to **lactic acidosis**.

ii. Deficiency of pyruvate leads to inadequate formation of oxaloacetate. This results in depression of gluconeogenesis, leading to **hypoglycemia**.

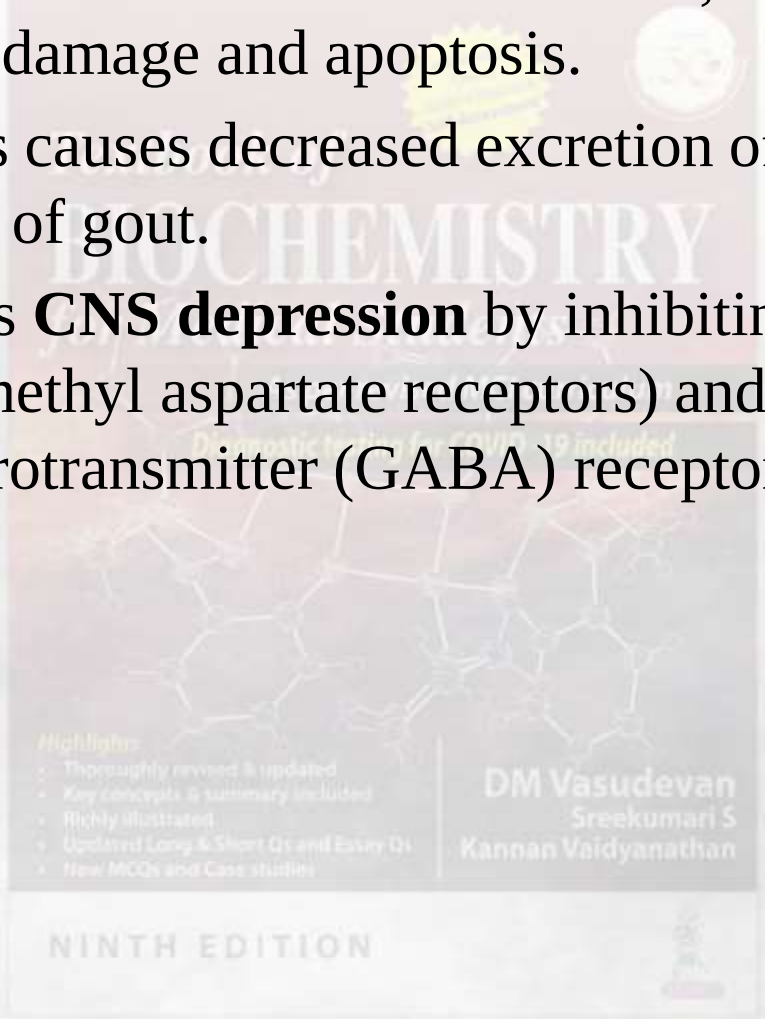
iii. Reduced oxaloacetate, decreased pyruvate and high NADH level causes suppression of TCA cycle. So Acetyl CoA is accumulated, which favors **ketogenesis**.

iv. Increased level of acetyl CoA causes increased fatty acid synthesis; but fatty acid is not oxidized. So fat is accumulated in liver, resulting in **fatty liver** and steatosis.

v. Alcohol also increases the release of ROS, leading to mitochondrial damage and apoptosis.

vi. Lactic acidosis causes decreased excretion of uric acid, resulting in acute attack of gout.

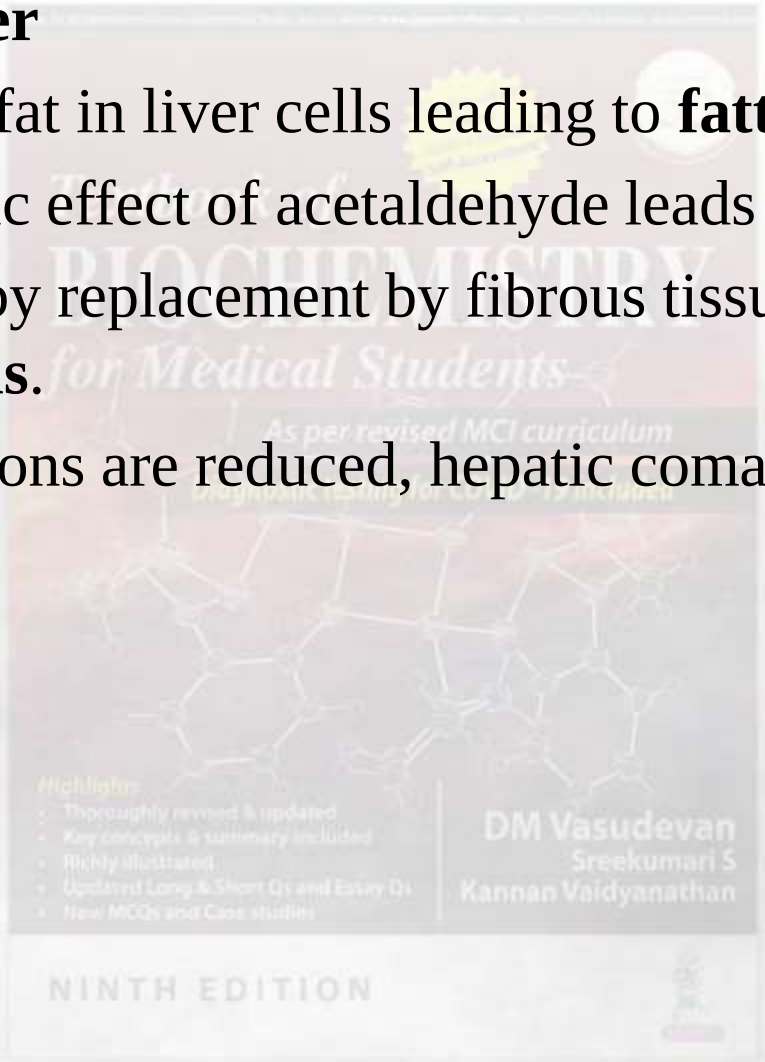
vii. Alcohol causes **CNS depression** by inhibiting excitatory receptors (N-methyl aspartate receptors) and by potentiating inhibitory neurotransmitter (GABA) receptors.



Chronic Alcoholism

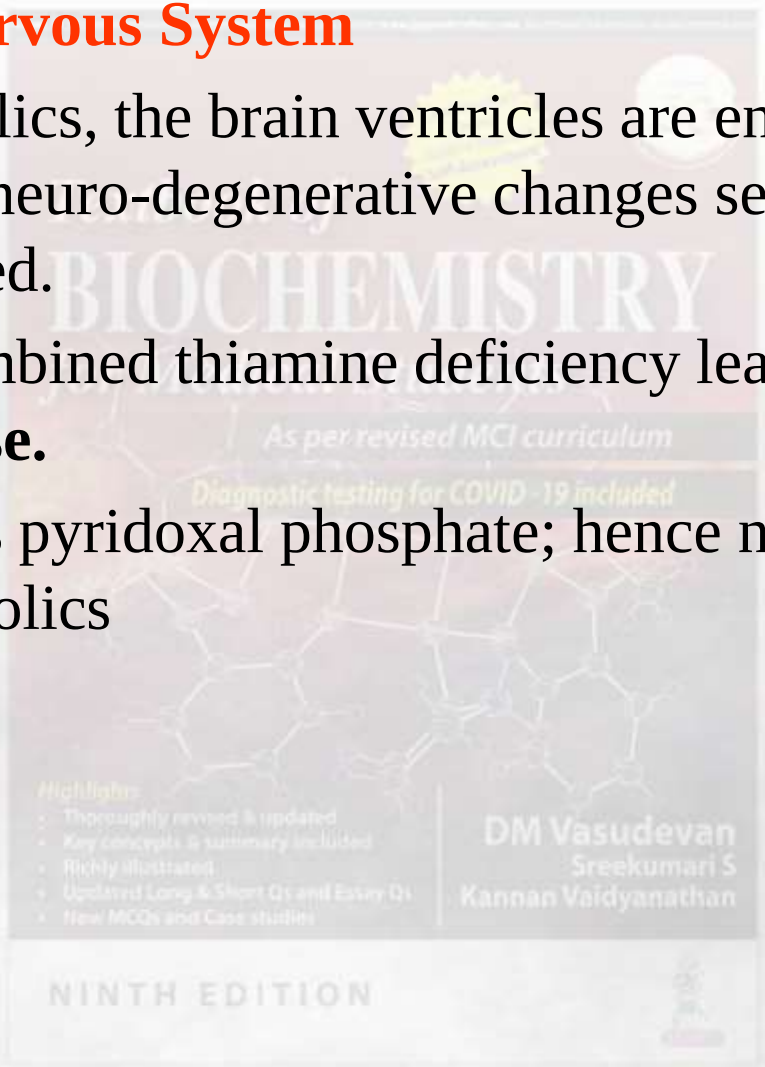
Alcoholism and liver

- Accumulation of fat in liver cells leading to **fatty liver**.
- Accumulated toxic effect of acetaldehyde leads to cellular death.
- This is followed by replacement by fibrous tissue. Fibrosis of liver is called **Cirrhosis**.
- When liver functions are reduced, hepatic coma results.



Alcoholism and Nervous System

- In chronic alcoholics, the brain ventricles are enlarged, neurons are lost, neuro-degenerative changes set in the memory is affected.
- In alcoholics, combined thiamine deficiency leads to **Wernick's disease.**
- Aldehyde inhibits pyridoxal phosphate; hence neuritis is very common in alcoholics



Laboratory Findings in Chronic Alcoholism

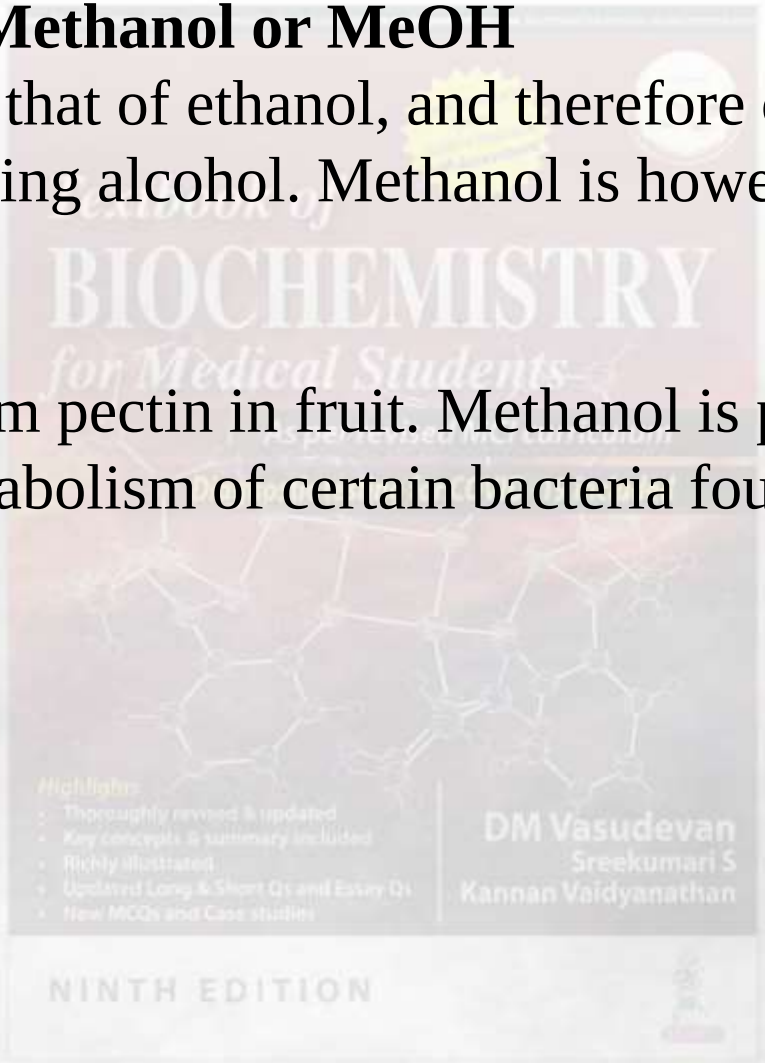
- Increase in serum levels of gamma-glutamyl transferase (GGT) and alanine transaminase (ALT).
- Decrease in aldehyde dehydrogenase activity (in liver cells and RBCs) is the best marker for alcohol abuse.
- **Desialylated transferrin** level in blood is a highly sensitive marker for chronic alcohol abuse.

Metabolism of Methanol

Methyl alcohol or Methanol or MeOH

Its odor is similar to that of ethanol, and therefore often used for adulteration of drinking alcohol. Methanol is however far more toxic than ethanol.

This is produced from pectin in fruit. Methanol is produced naturally in the anaerobic metabolism of certain bacteria found in the environment.



Methanol Toxicity

As little as 10 mL of pure methanol can cause permanent blindness by destruction of the optic nerve, while 30 mL is fatal. Toxic effects begin hours after ingestion

It is metabolized to formaldehyde by the ADH in the liver. This formaldehyde is further converted to formic acid (formate) by ALDH. Formate is toxic because it inhibits mitochondrial cytochrome c oxidase, causing cellular hypoxia and metabolic acidosis.

Major toxicity manifestation is loss of vision. Decreased vision may start as early as 12 hours after exposure. This may be accompanied by vomiting, abdominal pain, decreased consciousness. Death may occur even after drinking a small amount.

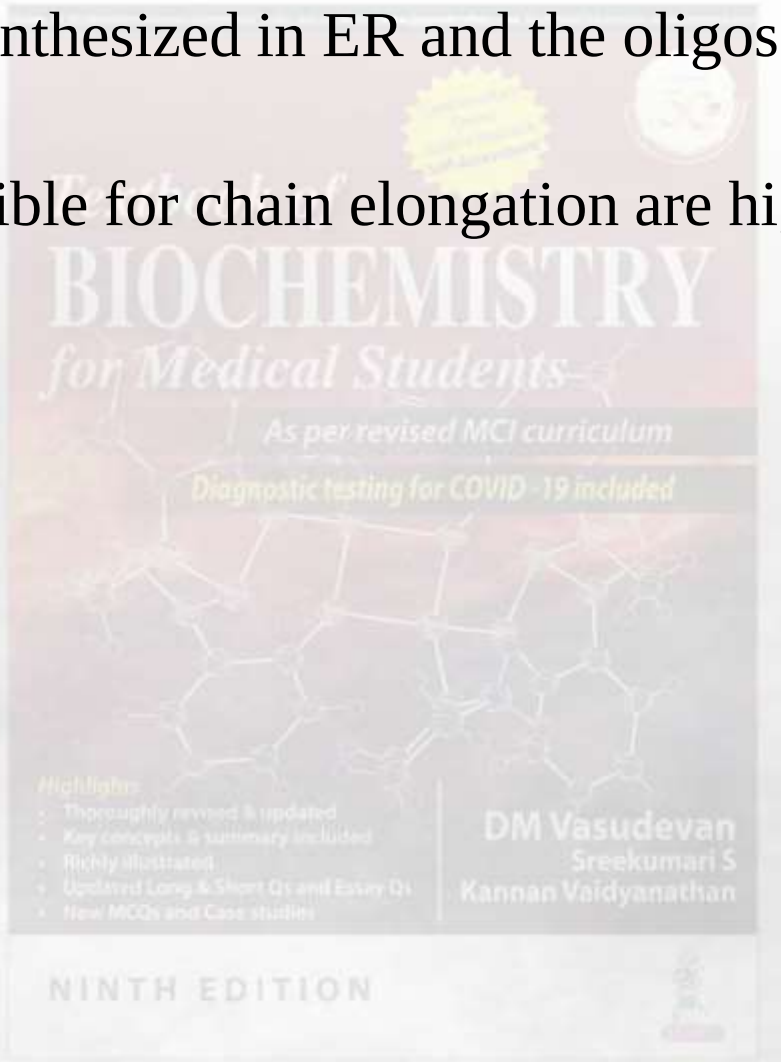
Treatment for methyl alcohol toxicity Early treatment increases the chance of a good outcome. The preferred antidote is fomepizole. If it is not available, ethanol can be used. Ethyl alcohol will competitively inhibit methanol. Ethanol will bind more effectively to the enzyme ADH, thus blocking the metabolism of methanol. The remaining methanol is excreted by the kidneys, without producing the toxic formic acid. Additional treatment may include sodium bicarbonate for metabolic acidosis, and hemodialysis to remove methanol and formate from the blood.

Glycosaminoglycans

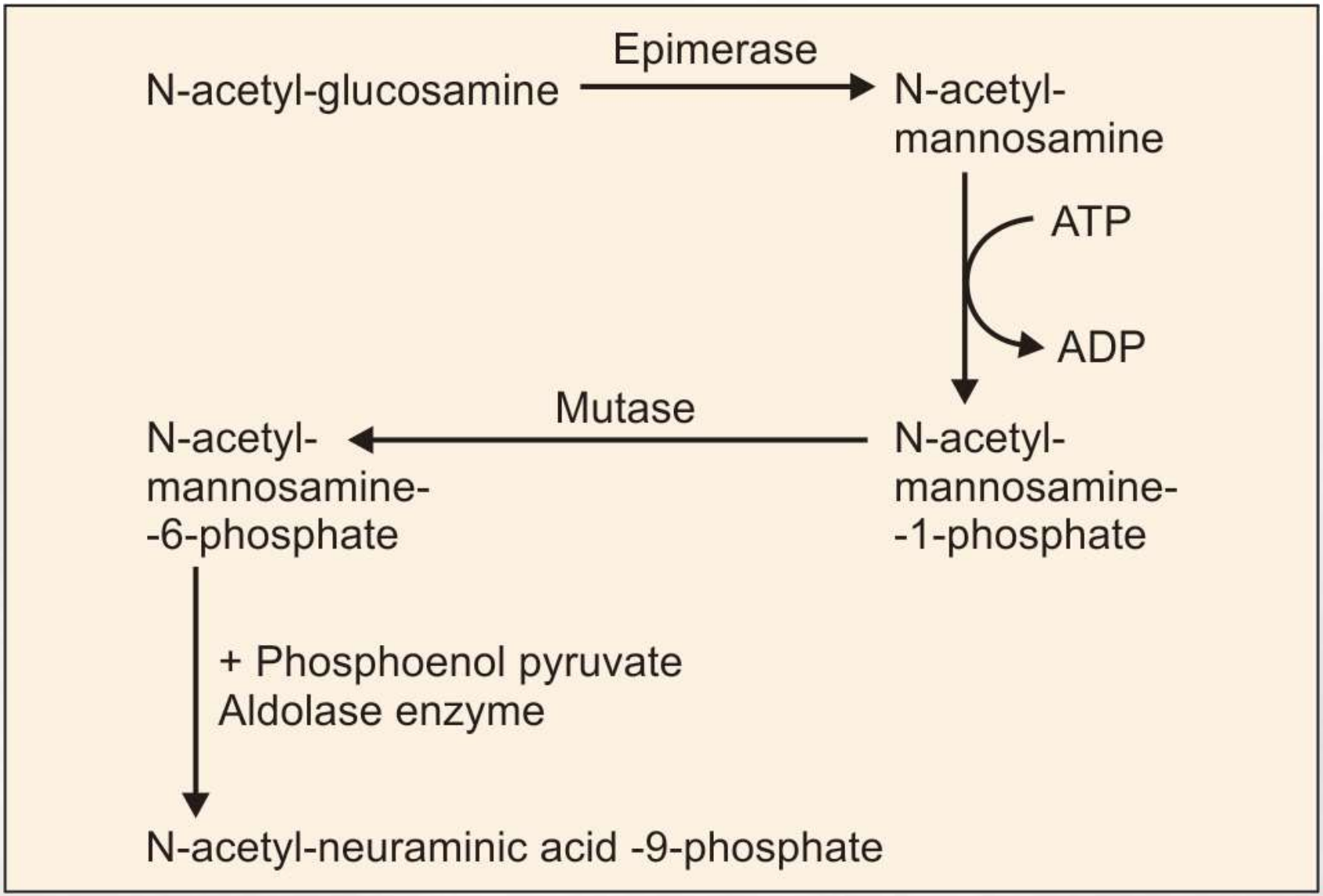
GAG	Repeating sugar units	Linkage	Tissues
Hyaluronic acid	N-Acetyl glucosamine and Glucuronic acid	beta-1,3	Synovial fluid, vitreous humor
Chondroitin sulphate	N-Acetyl galactosamine Glucuronic acid	beta-1,3	Cartilage, bone, cornea
Keratin sulphate Types I and II	N-Acetyl glucosamine and Galactose	beta-1,4	Cornea, cartilage
Heparan	N-Acetyl glucosamine	alpha-1,4	Skin

Synthesis of Glycosaminoglycans.

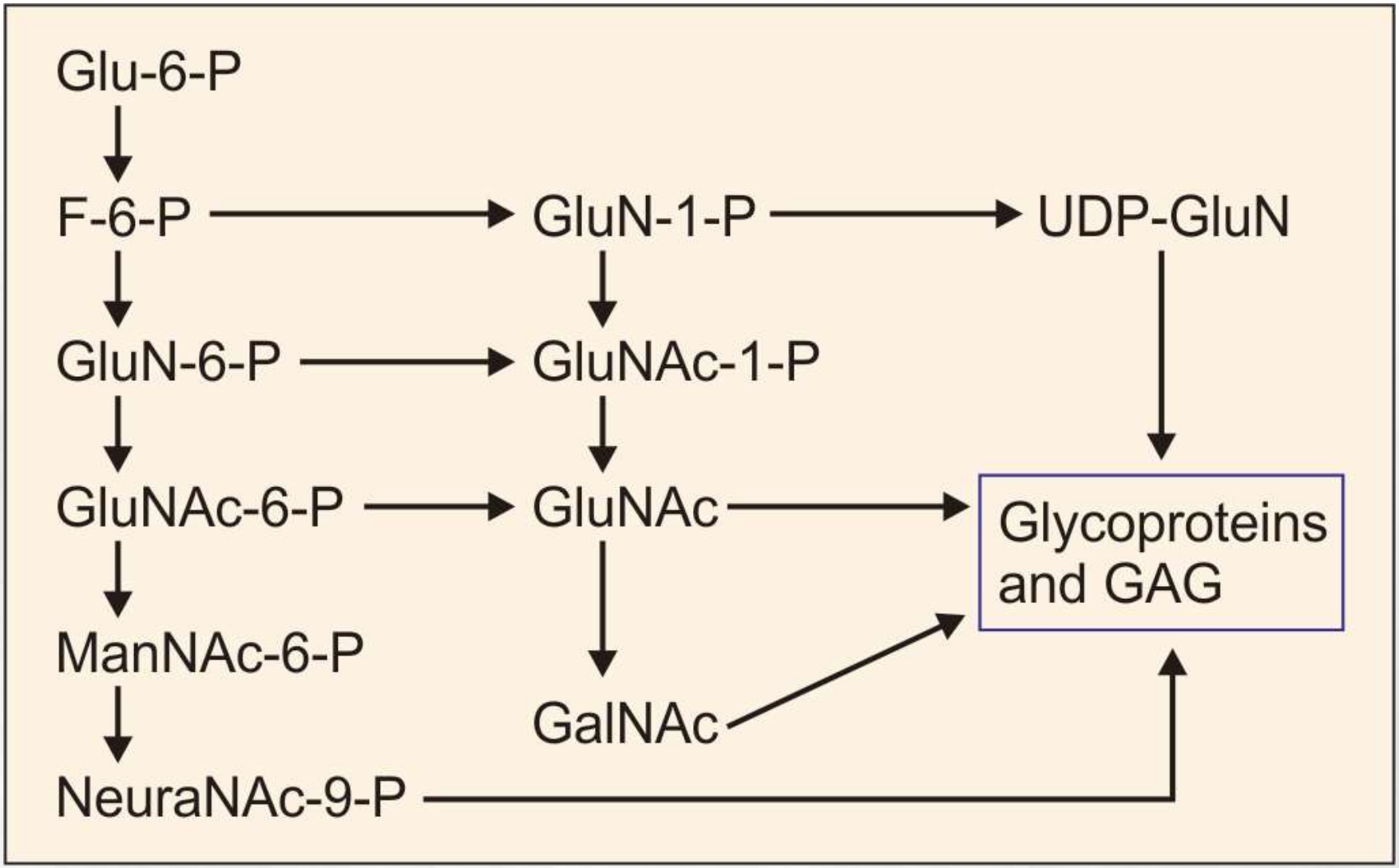
- Core protein is synthesized in ER and the oligosaccharide moiety is added in Golgi.
- Enzymes responsible for chain elongation are highly specific.



Synthesis of N-acetyl neuraminic acid

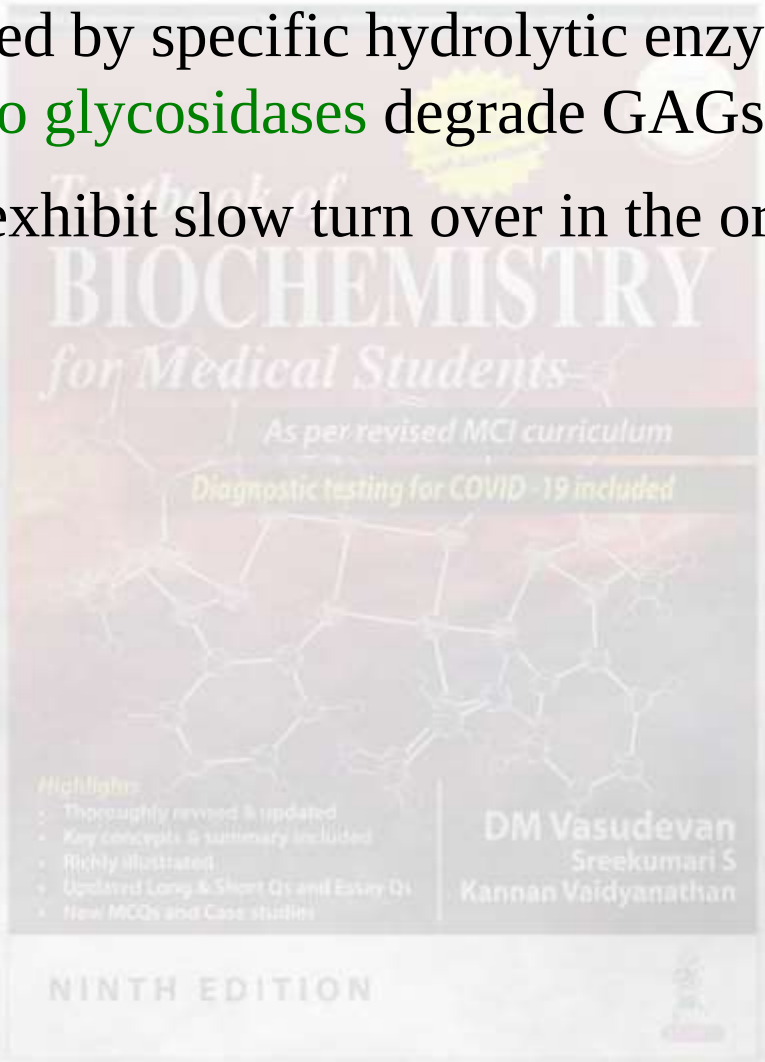


Interrelations of amino sugars



Degradation of Glycosaminoglycans

- GAGs are degraded by specific hydrolytic enzymes in lysosomes. Both exo and endo glycosidases degrade GAGs.
- GAGs generally exhibit slow turn over in the order of days and weeks.

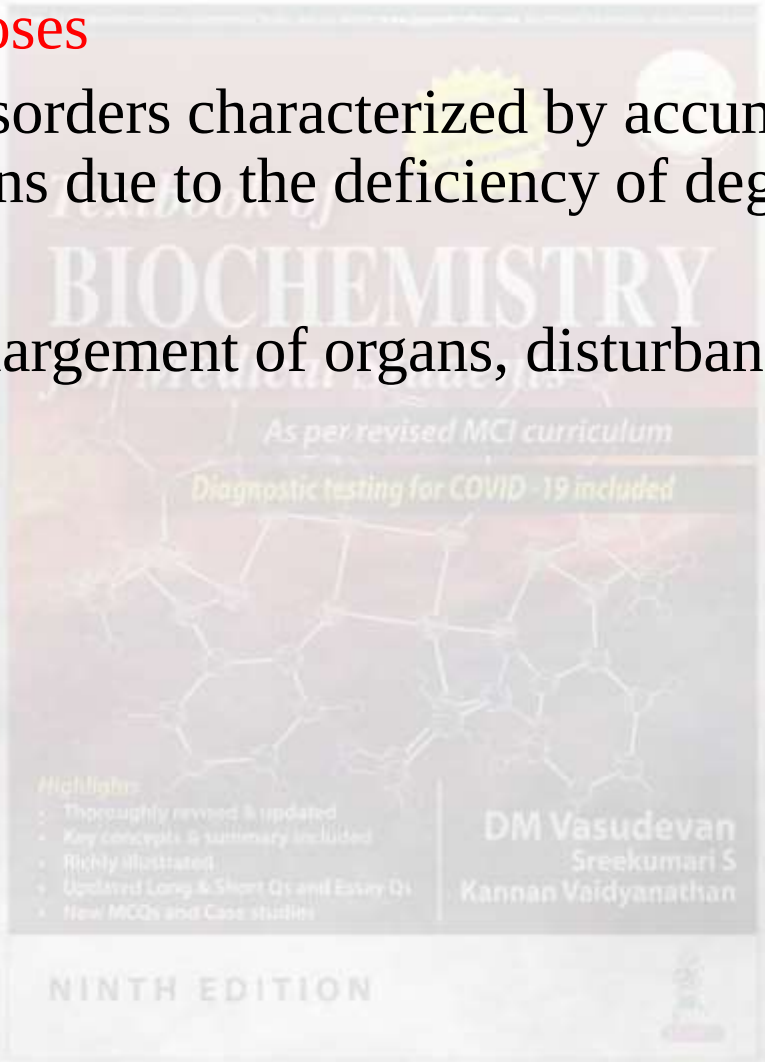


Clinical Significance

Mucopolysaccharidoses

- Are a group of disorders characterized by accumulation of substrates in organs due to the deficiency of degrading enzymes.

- This results in enlargement of organs, disturbances in structure of bone, skin etc.



Mucopolysaccharidoses 7 different Types

Disease	Defective enzyme	GAG in urine
Hurler	L Iduronidase	DS, HS
Hunter*	Iduronate Sulfatase	DS, HS
Sanfilippo	NAc Glcaminidase	HS
Morquis	NGal Sulfatase	KS,CS
Scheie's*	L Iduronidase	DS
Maroteaux	NAc Gal 4 sulfatase	DS
Slys	Beta Glucuronidase	DS, HS

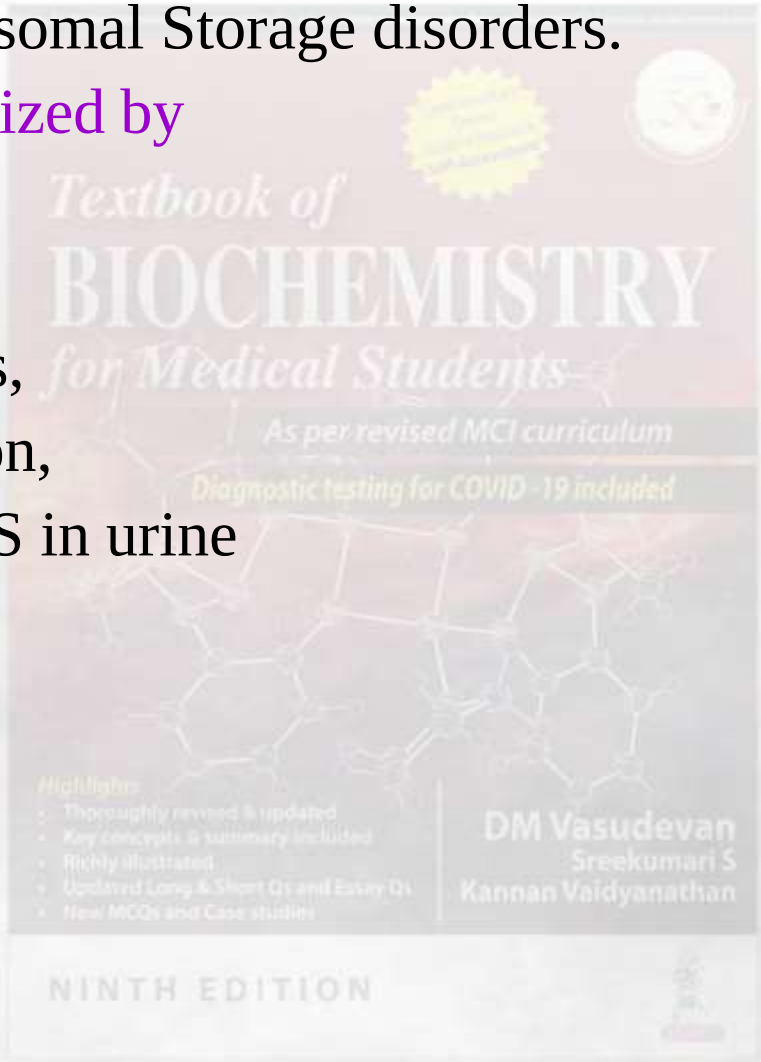
*** X linked recessive** *** No mental retardation**

Mucopolysaccharidoses

- Included in Lysosomal Storage disorders.

Disease is characterized by

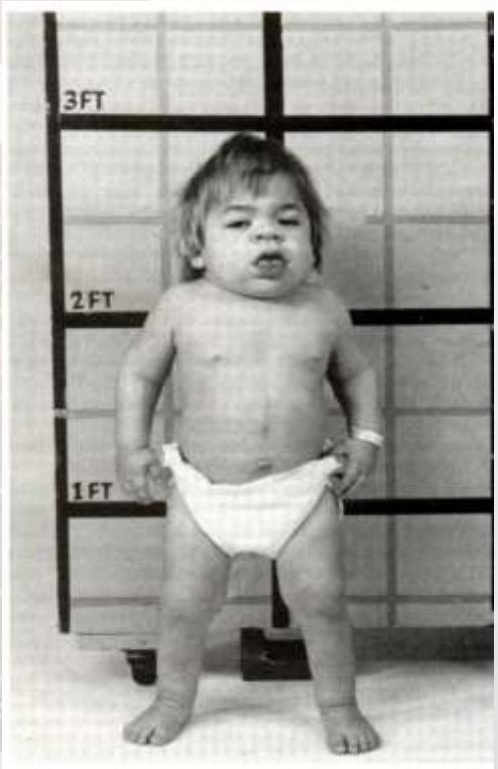
- Coarse features,
- Thick skin,
- Corneal opacities,
- Mental retardation,
- Excretion of MPS in urine



Mucopolysaccharidoses – Hurler

A four year old boy presenting with

- Delayed milestones,
- Hepatomegaly
- Short stature
- Enlarged tongue
- Nasal discharge
- Hydrocephalus



The disease was progressive and at the age of 8 he died of respiratory arrest.

Mucopolysaccharidoses – Hunter's

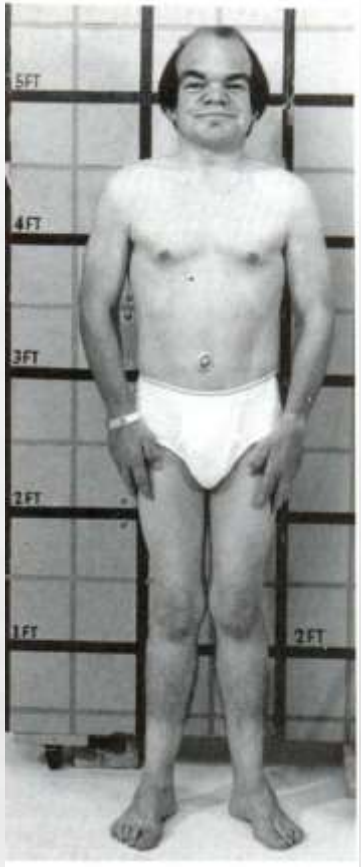
6 year old boy diagnosed of having severe MPS II at the age of one. Presented with

- Hepatomegaly
- Joint stiffness
- Umbilical hernia
- Severe hearing loss
- Developmental delay
- Recurrent ear infections
- Hyperactive

The disease was progressive and at the age of 20, he died.

Mucopolysaccharidoses – Hunter's
A 48 year old man, suffering from mild MPS II

- At the age of 13, diagnosis was made.
- He had joint stiffness, coarse facial features, heart murmur
- Normal intelligence.
- He has a good career Mode of inheritance- X linked recessive



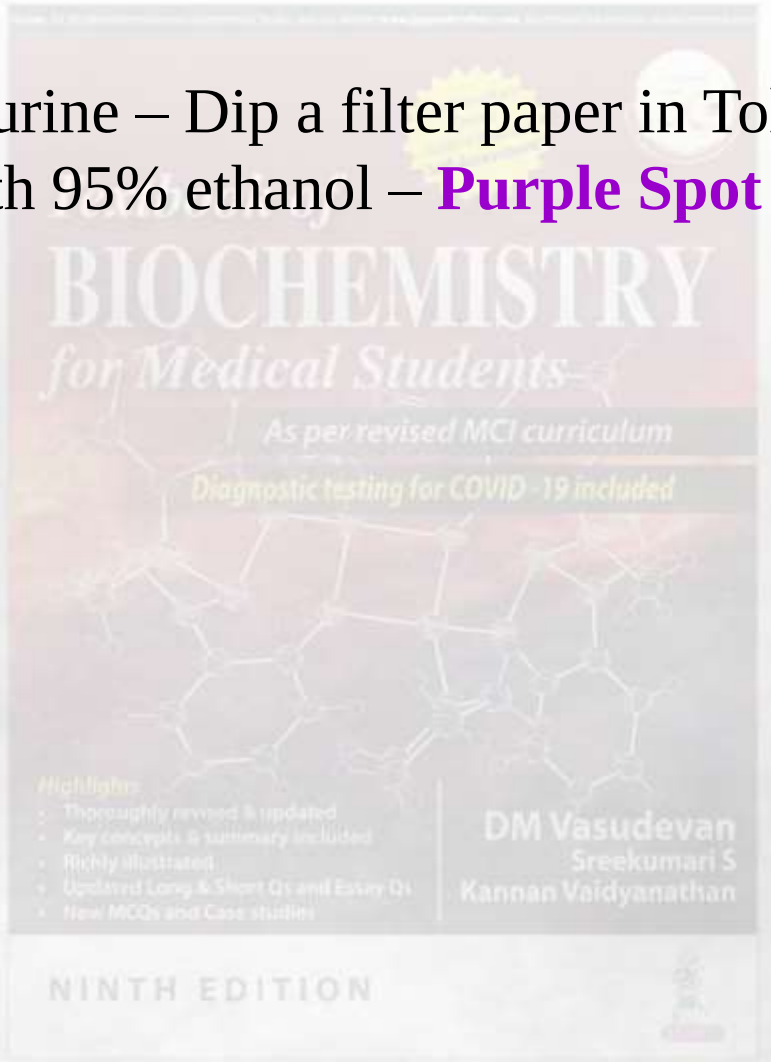
Mucopolysaccharidoses

Diagnosis

- Screening test in urine – Dip a filter paper in Toludine blue of pH 2. wash with 95% ethanol – **Purple Spot - + ve**
  - Amniocentesis

Treatment

- Gene Therapy



Features of mucopolysaccharidoses

Ty-pe	Epo-nym	Deficient enzyme	Clinical findings
I	Hurler's	L-Iduronidase	MR+++; Skeletal deformity++; Corneal opacity++; DS and HS in urine.
II	Hunter's	Iduronate sulphatase	MR+; Skeletal deformity++; deafness; no corneal clouding; DS and HS in urine
III	Sanfili-ppo's	N-Acetyl glucosami-nidase, Heparan sulfatase	MR++; Skeletal deformity+; corneal clouding+; HS in urine; 3 different types are reported.

MR = mental retardation; CS = chondroitin sulphate; KS = keratan sulphate; HS = heparan sulphate; DS = dermatan sulphate

Features of mucopolysaccharidoses

Ty-pe	Epo-nym	Deficient enzyme	Clinical findings
IV	Mor-quio's	Galactosamine sulfatase, beta-D-galactosidase	MR+; Skeletal deformity+; epiphyseal dysplasia+; Corneal opacity +; KS and CS in urine
V	Sch-eie's	L-Iduronidase	No MR; Mild skeletal changes; corneal opacity++; DS in urine
VI	Maro-teaux-Lamy's	N-Acetyl-beta-D-Galactosamino-4-Sulfatase	Skeletal deformity+++; corneal opacity++; No MR; DS in urine
VII	Sly's	beta-Glucuronidase	MR+; DS and HS in urine

Glycoproteins and Mucoproteins

When the carbohydrate chains are attached to a polypeptide it is called a **proteoglycan.**

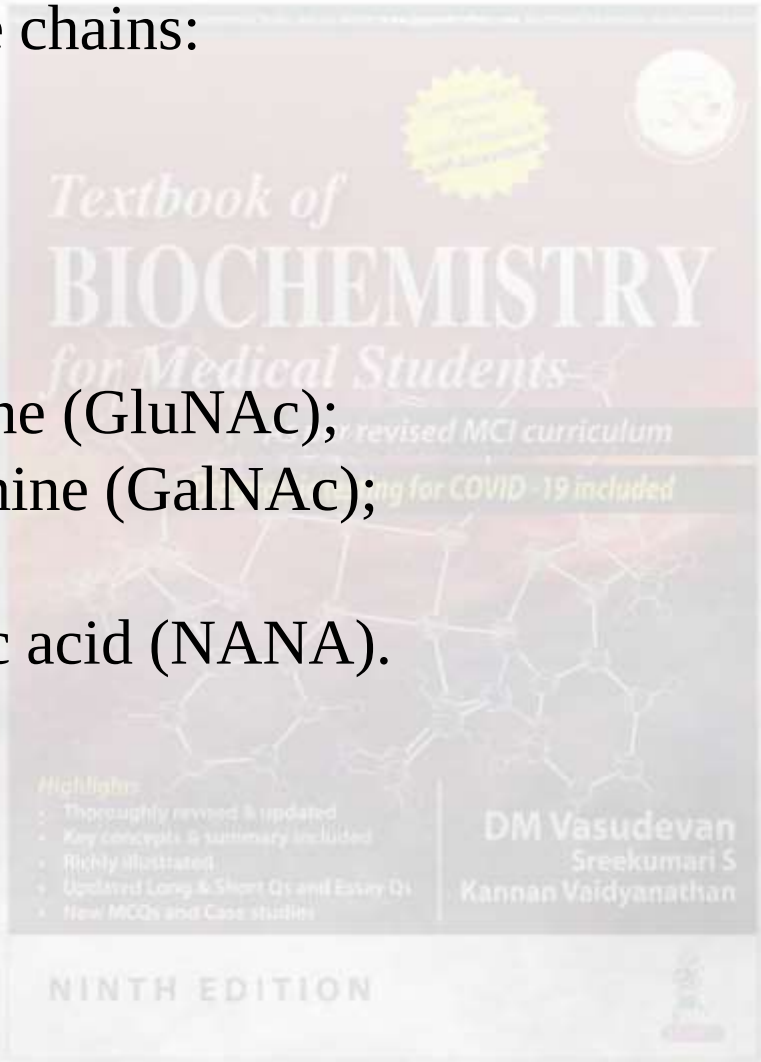
If the carbohydrate content is less than 10%, it is generally named as a **glycoprotein.**

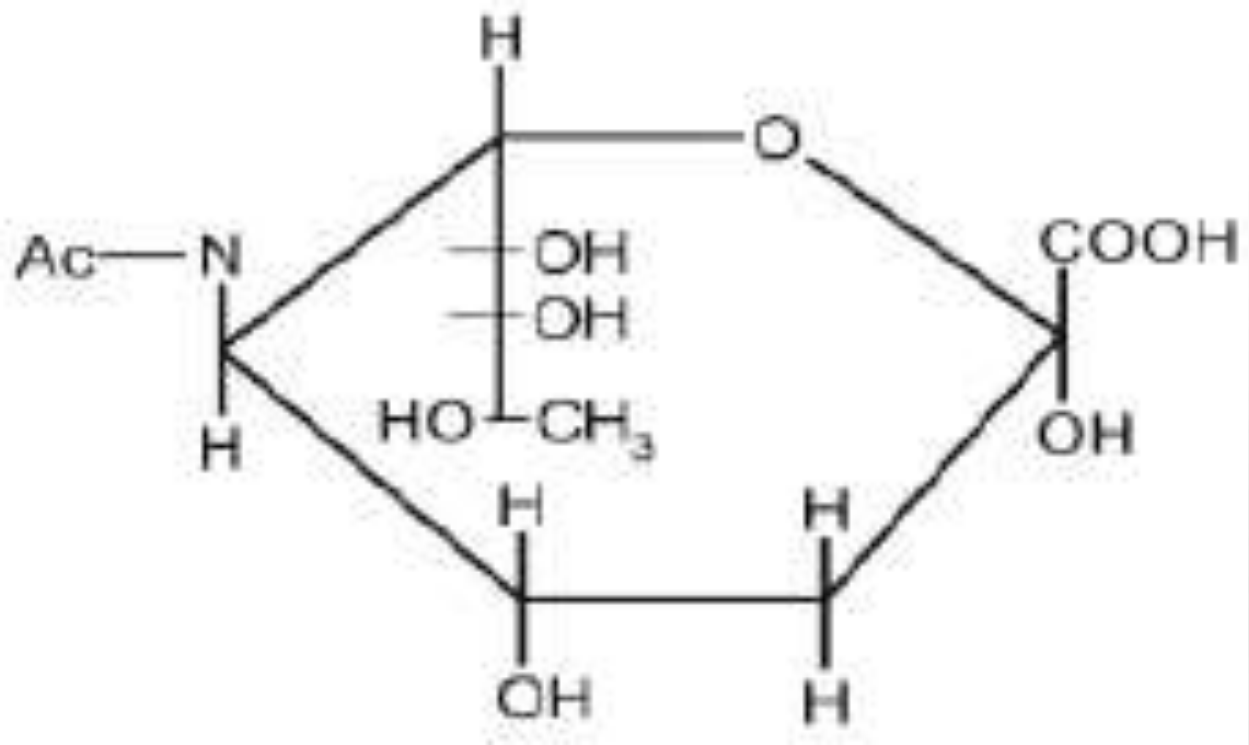
If the carbohydrate content is more than 10% it is a **mucoprotein**.

Functions: enzymes, hormones, transport proteins, structural proteins and receptors.

The oligosaccharide chains:

Glucose (Glu);
mannose (Man);
galactose (Gal);
N-acetyl glucosamine (GluNAc);
N-acetyl galactosamine (GalNAc);
L-fucose (Fuc) and
N-acetyl neuraminic acid (NANA).





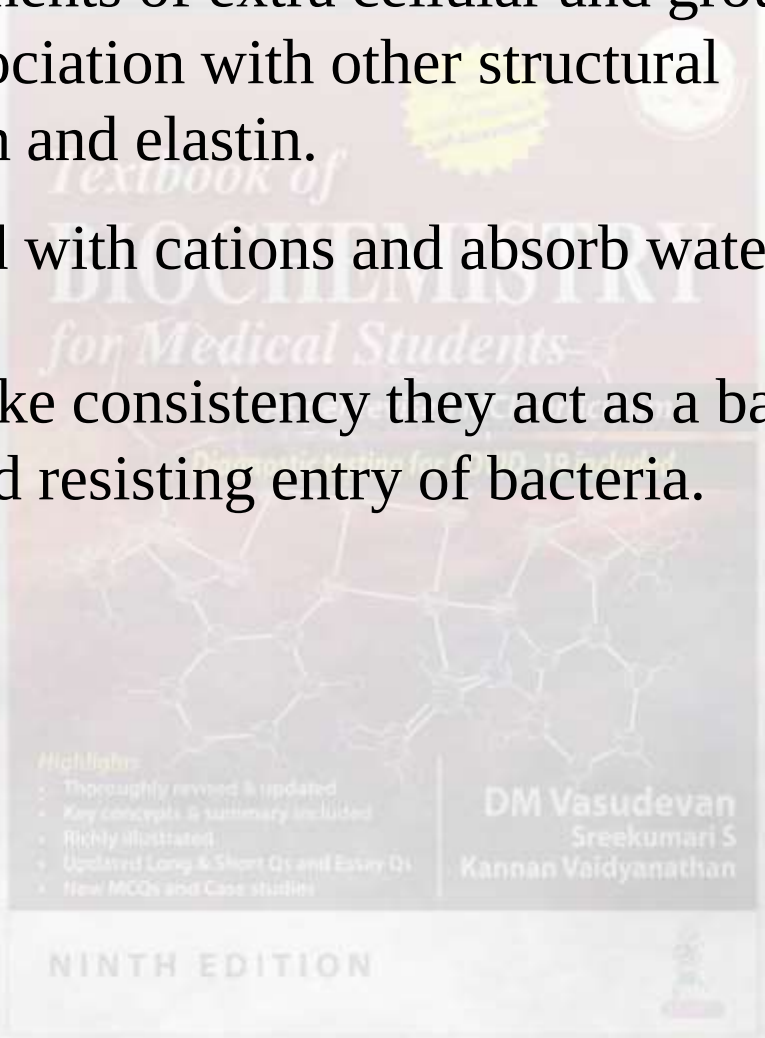
Structure of NANA

Functions of Glycosaminoglycans

- Structural components of extra cellular and ground substances in association with other structural elements-collagen and elastin.

Poly anions can bind with cations and absorb water by osmosis

Because of the gel like consistency they act as a barrier permitting entry of nutrients and resisting entry of bacteria.



Functions of Glycosaminoglycans

Role in Disease and Ageing:

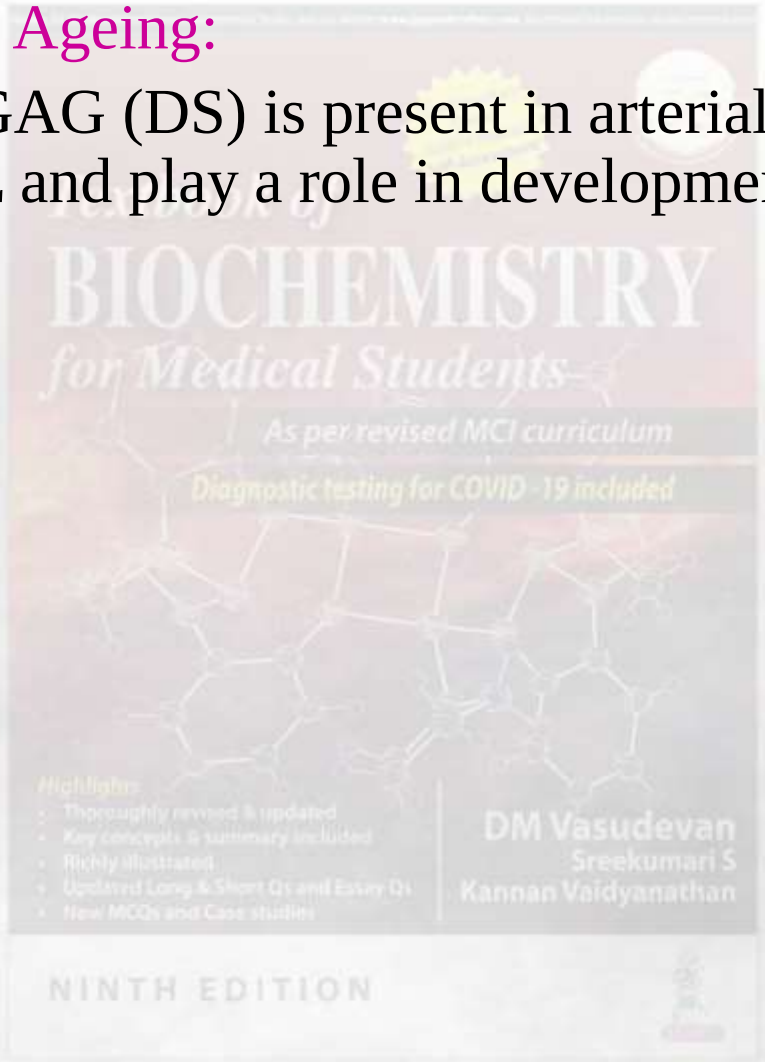
- Tumor cells induce fibroblasts to synthesize large amount of GAG and facilitate metastasis.

Proteoglycans have got a role in development of arthritis. They act as auto-antigens and contribute to pathogenesis.

Functions of Glycosaminoglycans

Role in Disease and Ageing:

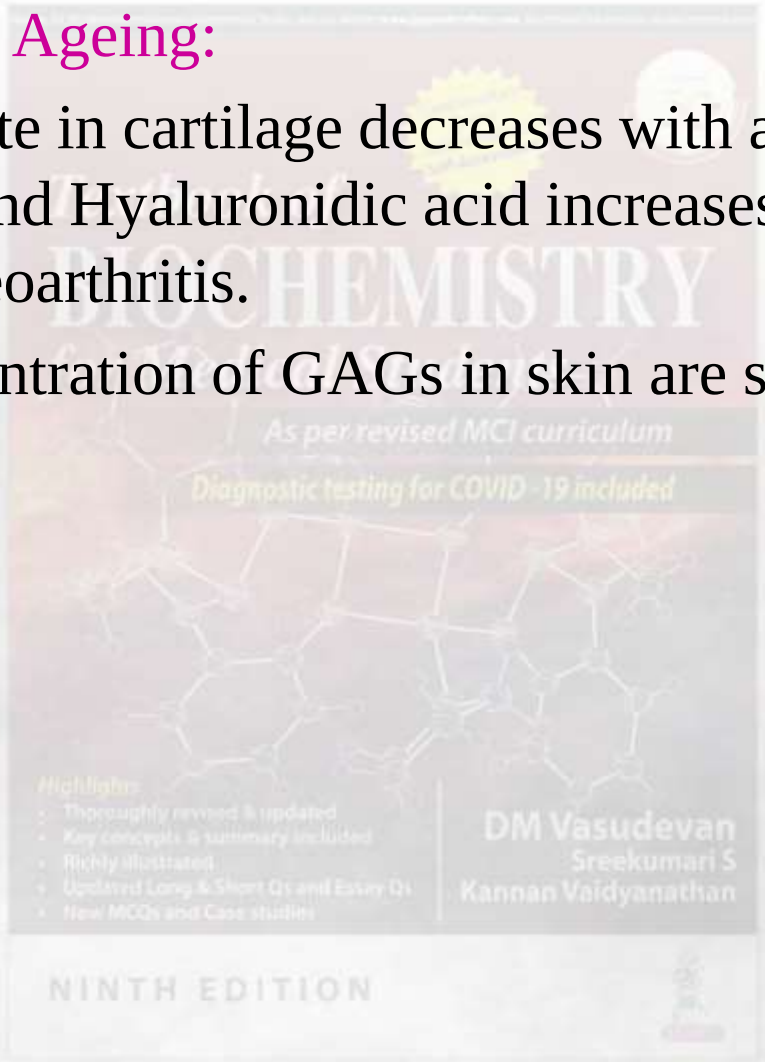
- High amount of GAG (DS) is present in arterial walls. They get bound to LDL and play a role in development of atherosclerosis.



Functions of Glycosaminoglycans

Role in Disease and Ageing:

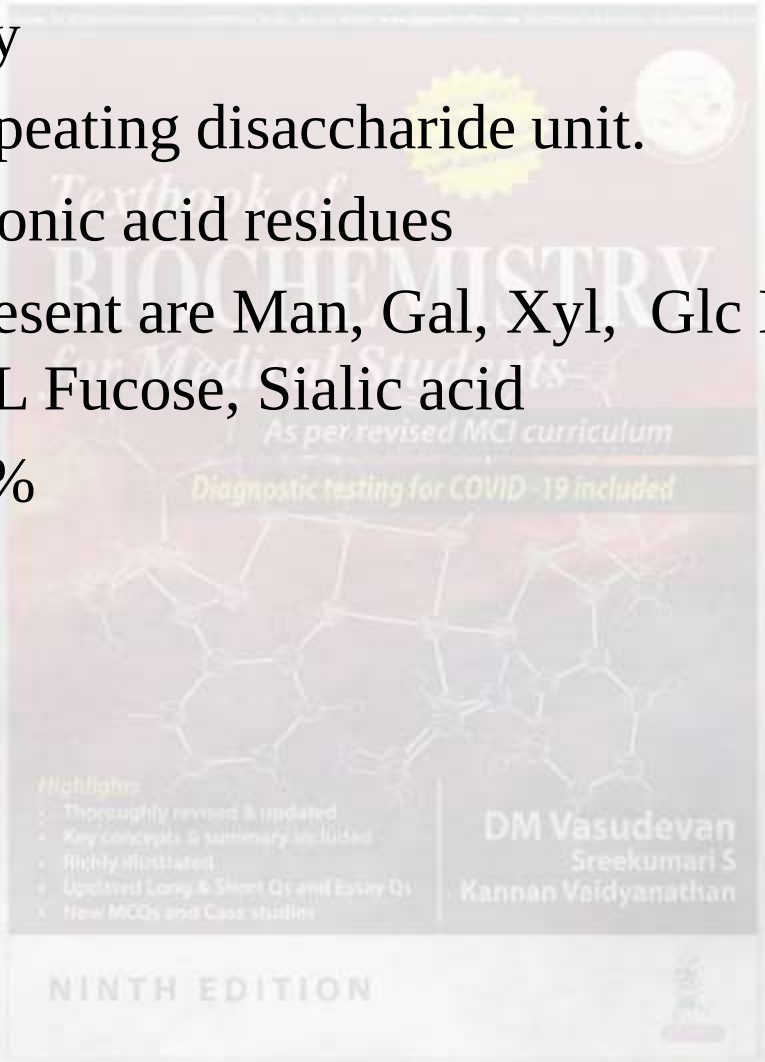
- Chondroitin sulfate in cartilage decreases with age where as Keratan Sulfate and Hyaluronidic acid increases. These changes contribute to Osteoarthritis.
- Changes in concentration of GAGs in skin are seen with ageing.



Glycoproteins - Mucoproteins

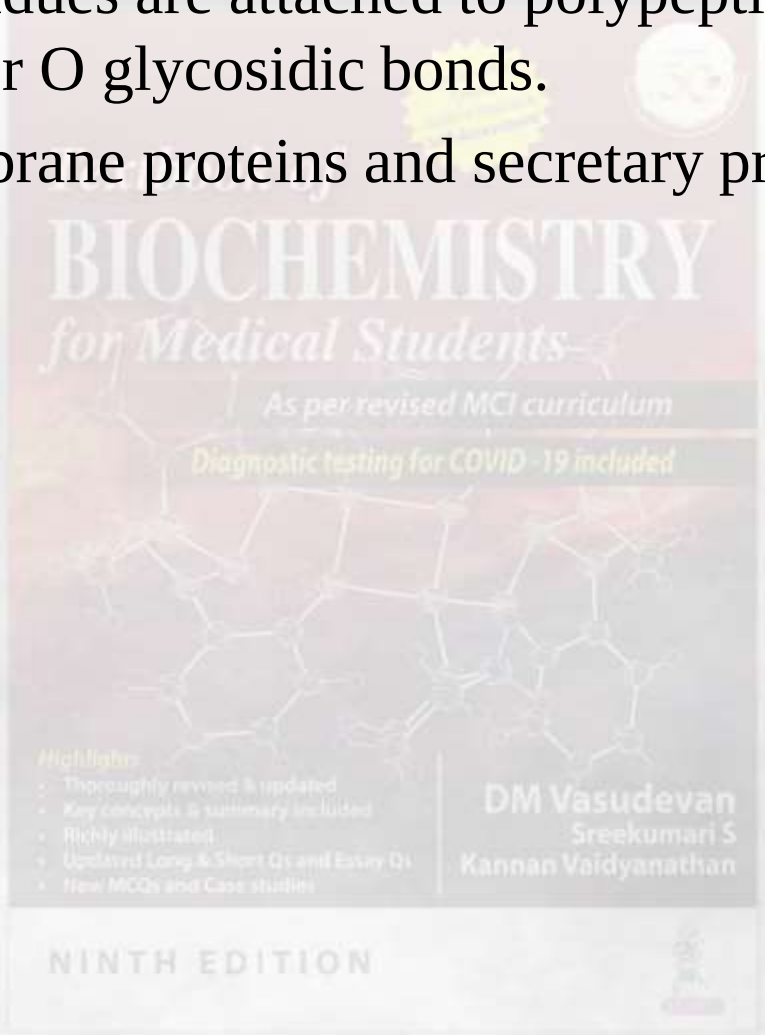
Differ from GAG by

- Do not contain repeating disaccharide unit.
- Do not contain uronic acid residues
- Sugar residues present are Man, Gal, Xyl, Glc NAC, Gal NAc, Arabinose, L Fucose, Sialic acid
- CHO residue < 4%



Glycoproteins

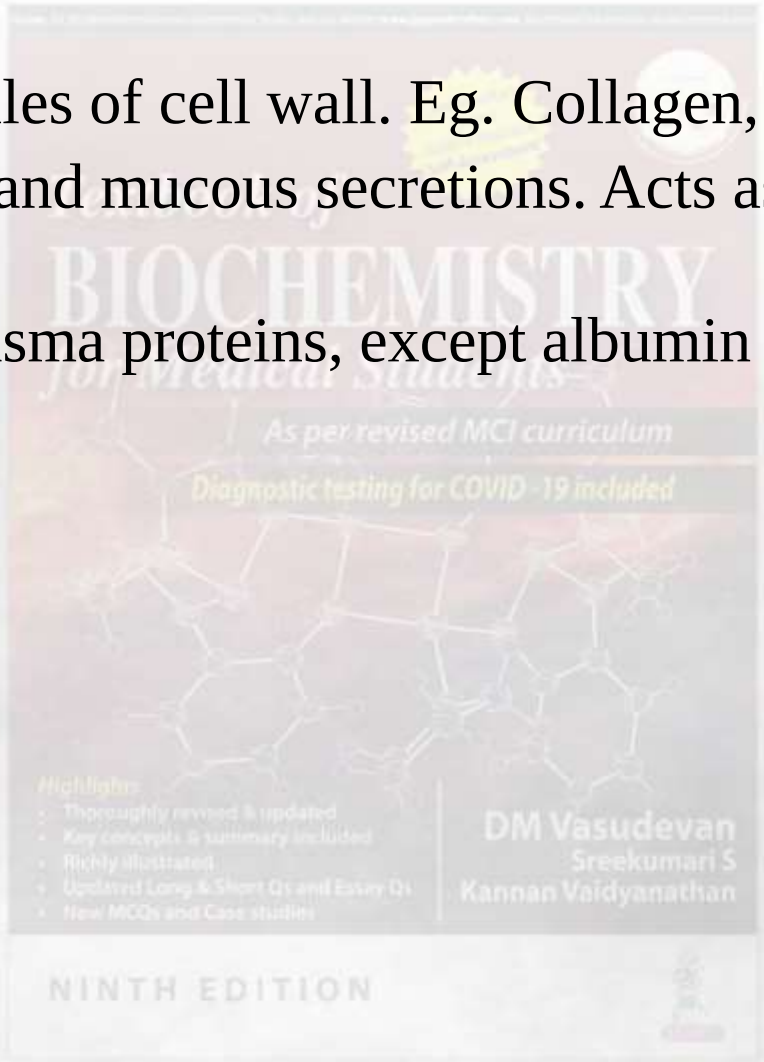
- Carbohydrate residues are attached to polypeptide chains covalently by N or O glycosidic bonds.
- Most of the membrane proteins and secretary proteins are Glycoproteins.



Glycoproteins

Functions:

- Structural molecules of cell wall. Eg. Collagen, elastin, fibrin.
- Present in mucin and mucous secretions. Acts as lubricant and protective agent.
- Almost all the plasma proteins, except albumin are glycoproteins.



Glycoproteins

- Act as transporters of vitamins, minerals, hormones, drugs etc.

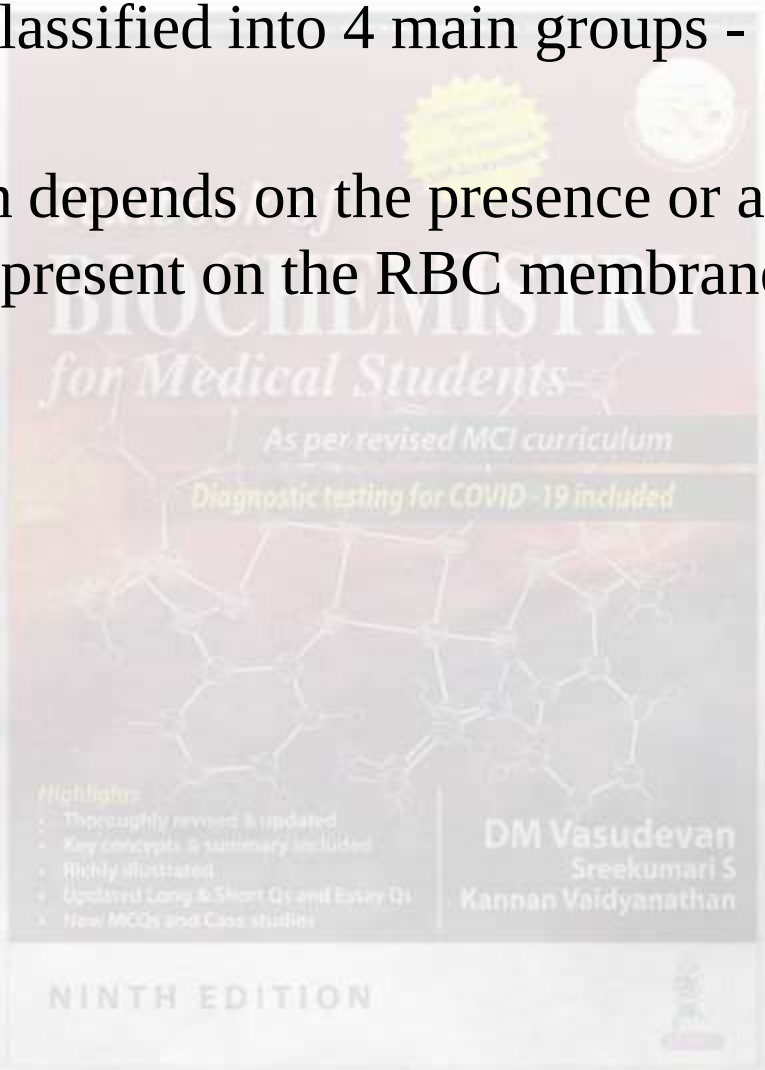
  Ceruloplasmin- Copper, Transferrin - Iron
- Constituent of Immunoglobulins, Complements etc.
- Many of the Hormones and enzymes are Glycoproteins.

  eg.- Chorionic gonadotropin, TSH

Functions of glycoproteins	
Function	**Example of glycoprotein**
Structural substance	**Collagen, bacterial cell walls**
Enzymes	**Ribonuclease-B, Prothrombin**
Transport proteins	**Ceruloplasmin, Transferrin**
Hormones Immunity	**Thyroglobulin, Erythropoietin, TSH, Immunoglobulins, Blood group**
Lubricant	**Mucin**
Signal transduction	**Receptor proteins on cell surfaces**
Cell adhesion	**Selectins and integrins**

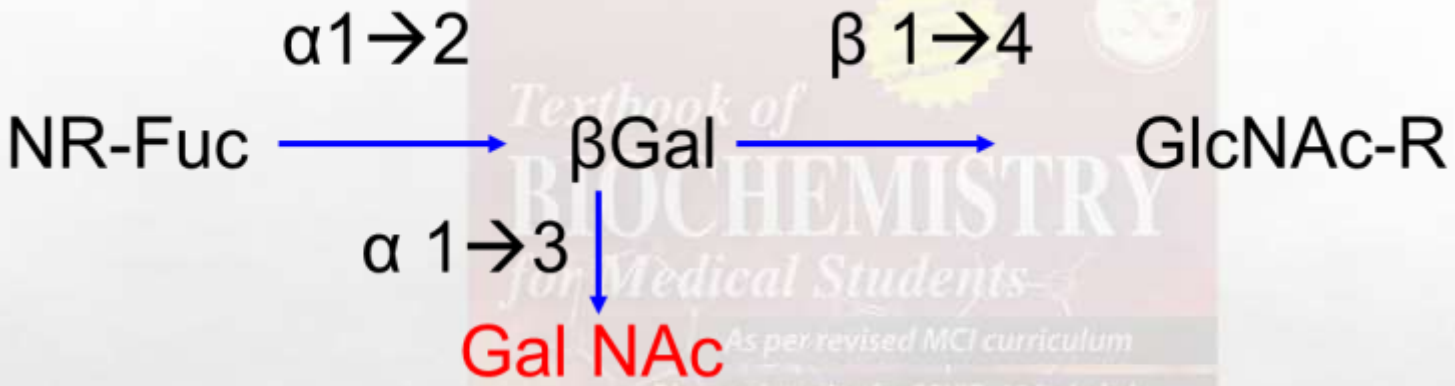
Blood Group Substances

- Human blood is classified into 4 main groups - **A, B, AB and O**
- This classification depends on the presence or absence of blood group substances present on the RBC membrane.



Blood Group Substances

A Group



B Group

Biosynthesis of Glycoproteins

- The **biosynthesis** of GAG is taking place in the endoplasmic reticulum and Golgi bodies, with the help of specific glycosyltransferases.
- At the endoplasmic reticulum, along with the protein being synthesized, these carbohydrate units are added one by one.
- Certain amino acid sequences in the protein will code for the attachment of the glycans; specific enzymes will add the glycans sequentially.
- There are carrier systems (transporters) to transport sugars across Golgi membrane.
- Termination of the oligosaccharide chain occurs following sulphation of the sugar residues.

Selectins

- The name “selectin” is derived from the words “selected” and “lectins”. They belong to a family of cell adhesion molecules (CAMs).
- There are three subsets of selectins: E-selectin in endothelial cells, L-selectin in lymphocytes, monocytes and granulocytes and P- selectin in platelets.
- Tumor cells exploit the selectin-dependent mechanisms mediating cell tethering and rolling interactions through recognition of carbohydrate ligands on tumor cells to enhance distant organ metastasis.

Integrins

They are transmembrane receptors that facilitate cell adhesion to the extracellular matrix (ECM). Upon ligand binding, integrins activate signal transduction pathways that mediate regulation of the cell cycle, organization of the intracellular cytoskeleton, movement of new receptors to the cell membrane and cell to cell and cell to matrix interaction. Ligands for integrins include fibronectin, vitronectin, collagen and laminin. Integrins have two main functions, a) attachment of the cell to the ECM and b) signal transduction from the ECM to the cell. Integrins are involved in cell growth, cell division, cellular differentiation, apoptosis (programmed cell death), immunity, cell migration, and binding to cells by certain viruses (adenovirus, echovirus).

Proteoglycans

- **Proteoglycans** are complex molecules having glycosaminoglycans (GAG) and proteins. As the carbohydrate content is increased, viscosity is increased and solubility is decreased.
- The carbohydrate content of mucins is generally more than 50%. **Mucus** consists of 5-10% of mucins. These monomers are further linked together by disulfide linkages, to form oligomers. **Mucins** will form a protective barrier on epithelial surfaces. They are also found in secretions of the gastro-intestinal, respiratory and urogenital tract.
- The GAGs containing repeating disaccharide units are covalently bound to the peptide chain to form proteoglycans.

Inborn errors associated with carbohydrate metabolism

Name	Defective enzyme	Salient features
Glycogen storage disease, Type I (von Gierke's disease)	Glucose-6-phosphatase	Hepatomegaly, cirrhosis, hypoglycemia, ketosis, hyperuricemia
Do, type II (Pompe's disease)	Lysosomal maltase	Glycogen deposit; lysosomal storage disease
Do, type III (Cori's disease)	Debranching enzyme	Hepatomegaly, cirrhosis
Do, type IV (Andersen's disease)	Branching enzyme	Do

Inborn errors associated with carbohydrate metabolism

Name	Defective enzyme	Salient features
Do, type V (McArdle's disease)	Muscle phosphorylase	Exercise intolerance
Do, type VI (Hers' disease)	Liver phosphorylase	Hepatomegaly, hypoglycemia
Do, type VII (Tarui's disease)	Phosphofructo-kinase	
Do, type VIll	Phosphorylase kinase	
Lactose intolerance	Lactase	Milk induced diarrhea
Fructose intolerance	Aldolase B	Hypoglycemia, vomiting, hepatomegaly

Inborn errors associated with carbohydrate metabolism

Name	Defective enzyme	Salient features
Fructosuria	Fructokinase	**Benign; urine sugar**
Galactosemia	Gal-1-P-uridyl transferase	**Hypoglycemia ; hepatomegaly; mental retardation; jaundice; congenital cataract**
Do, variant	Galactokinase	**Congenital cataract**
Essential pentosuria	**Xylitol dihydro-genase**	**Benign**

Inborn errors associated with carbohydrate metabolism

Name	Defective enzyme	Salient features
PC deficiency	Pyruvate carboxylase	Mental retardation
GPD deficiency	Glucose-6-phosphate dihydro-genase	Drug-induced hemolytic anemia
HK deficiency	Hexokinase	Hemolytic anemia
PK deficiency	Pyruvate kinase	Hemolytic anemia
PDH deficiency	Pyruvate dihydro-genase	Neuronal loss in brain; muscular hypotonia; lactic acidosis