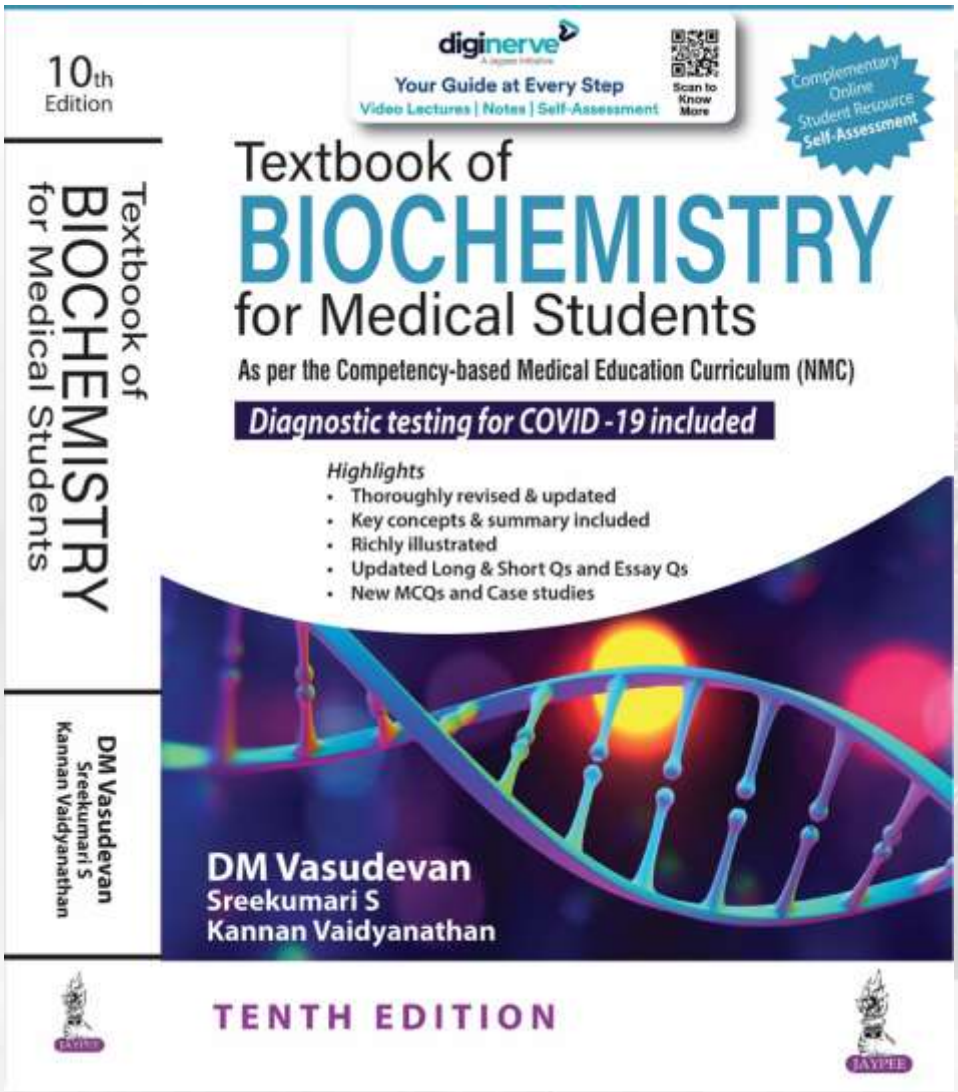


Chapter 14:

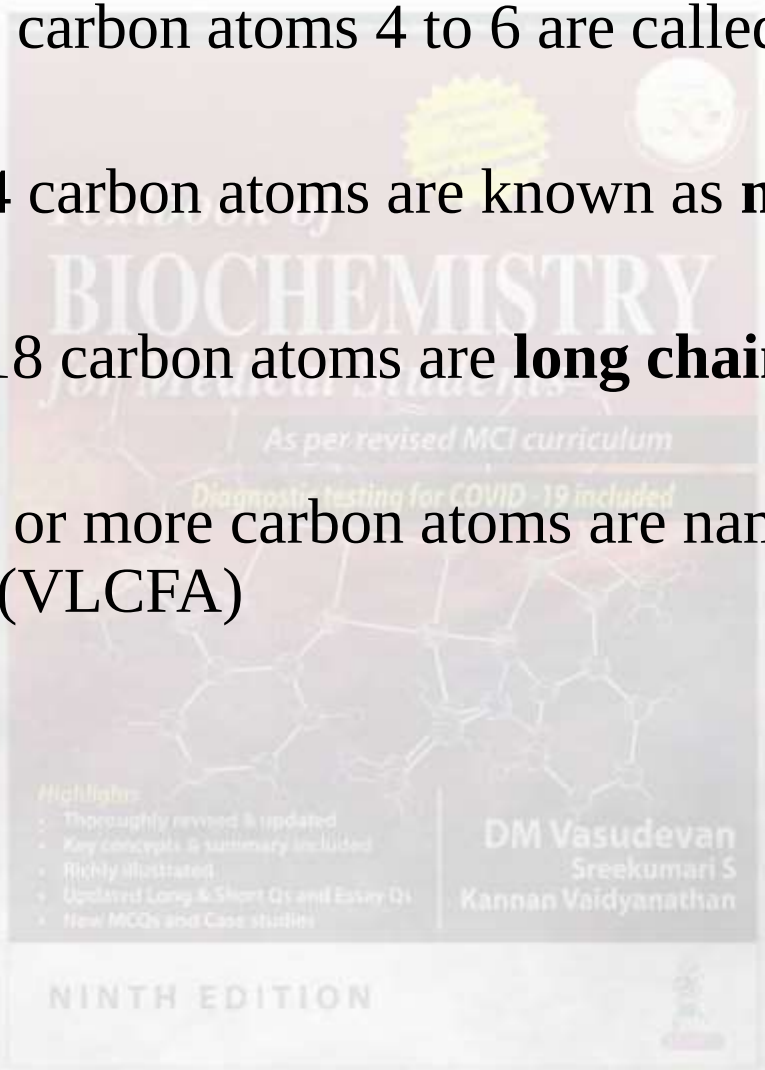
Medium Chain Fatty Acid, Polyunsaturated Fatty Acid, Prostaglandins and Compound Lipids

Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

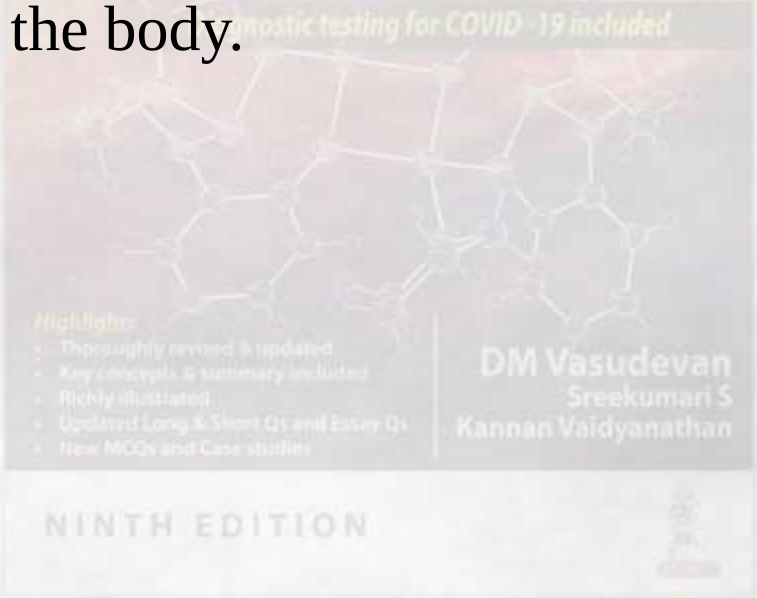
TENTH EDITION

- Fatty acids having carbon atoms 4 to 6 are called **small chain fatty acids** (SCFA)
- Those with 8 to 14 carbon atoms are known as **medium chain fatty acids** (MCFA)
- Those with 16 to 18 carbon atoms are **long chain fatty acids** (LCFA);
- Those carrying 20 or more carbon atoms are named as **very long chain fatty acids** (VLCFA)



Small chain fatty acids (SCFA)

- The SCFAs, butyric acid (4C) and caproic acid (6C) are seen in butter and ghee; the name butyric is derived from butter.
- MCFAs, capric acid (10C), lauric acid (12C) and myristic acid (14C) are present in coconut oil and **human milk**.
- Normal skin has a very thin layer of sebum secretion with MCT (medium chain triglyceride) containing lauric acid, which prevents bacterial entry into the body.



Differences in metabolisms of SCFA and LCFA containing triglycerides

	Short and medium chain fatty acids	Long chain fatty acids
Examples	Butyric acid (C = 4) in butter and lauric acid (C = 12) in coconut oil	Palmitic acid (C=16) and stearic acid (C=18) in vegetable oils, animal fats
Digestion in stomach	Hydrolysed	Not hydrolysed
Pancreatic lipase	Not necessary	Essential
Bile salts	Not necessary	Absolutely essential
Inside intestinal cells	TAG is hydrolysed to fatty acids	Free fatty acids are re-esterified

Differences in metabolisms of SCFA and LCFA containing triglycerides

	Short and medium chain fatty acids	Long chain fatty acids
Absorbed as	Free fatty acid carried by albumin	TAG, carried by chylomicrons
Immediate fate	Oxidised by peripheral cells	Deposited in the adipose tissue
Carnitine	is not required for oxidation	is required for oxidation
Clinical application	No effect on atherosclerosis	Hypercholesterolemia and atherosclerosis

Very Long Chain Fatty Acids (VLCFA)

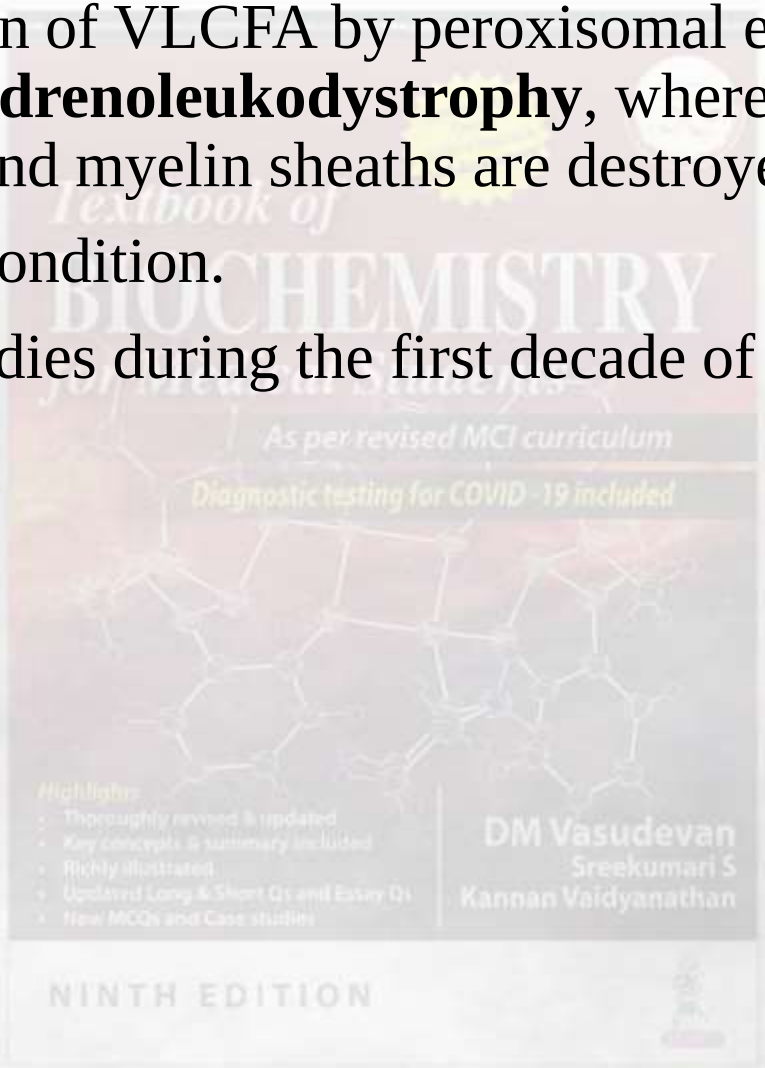
- Fatty acids having 20 or more carbon atoms are called very long chain fatty acids (VLCFA).
- Eicosapentaenoic acid (**EPA**) (C-20, 5 double bonds) and docosahexaenoic acid (**DHA**) (C-22, 6 double bonds) are good examples of VLCFA.
- DHA is synthesized in liver from linolenic acid (Omega-3, C-18, 3 double bond).
- DHA is available in large quantities in **fish oils**.
- DHA is especially required for the development of **brain and retina**.
- Low level of DHA in blood is seen in patients with **retinitis pigmentosa.**

VLCFA, continued

- In human beings, DHA accumulates in brain before birth and for up to 12 weeks afterwards.
- Outer segments of retinal rods contain high concentrations of DHA, which gives high fluidity to the membranes.
- This is required for the lateral and rotational movement of **rhodopsin** within the membrane during photoactivation.
- VLCFAs (20C and above) are partly oxidized in peroxisomes to smaller (18C) fatty acids, which then leave peroxisomes to enter mitochondria.
- This **peroxisomal oxidation** differs from beta-oxidation in that the electrons from FADH2 (step 1 of beta-oxidation) are directly donated to oxygen to form **hydrogen peroxide**.
- So this step does not produce ATP.

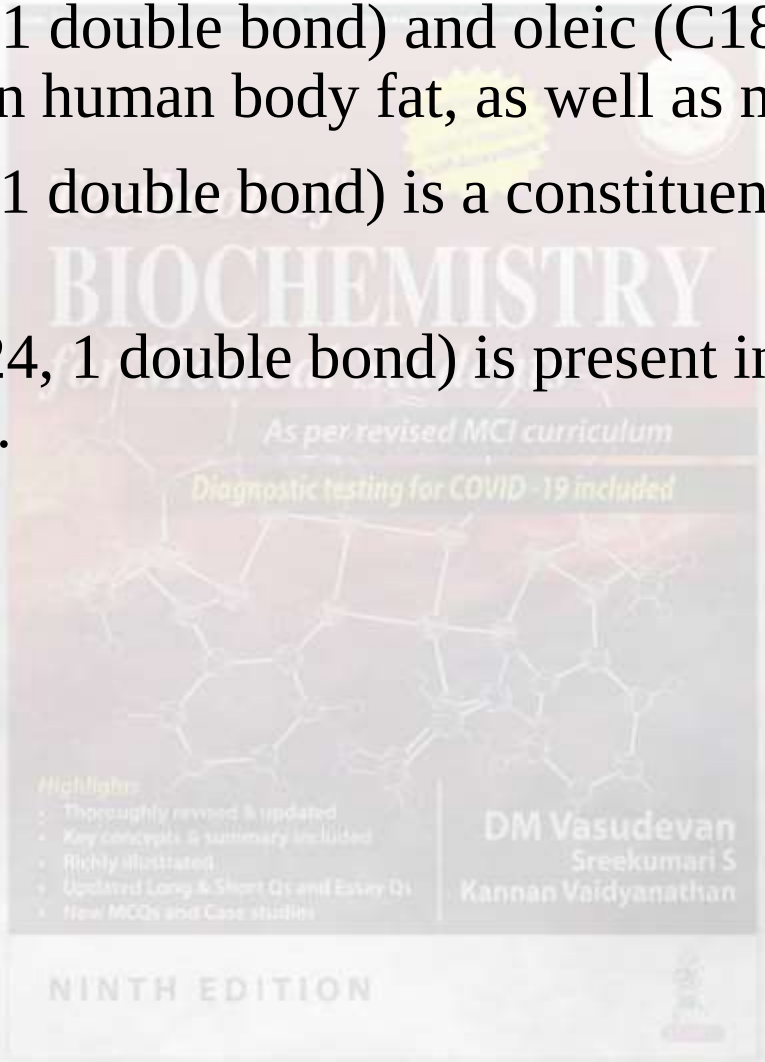
VLCFA, continued

- Deficient oxidation of VLCFA by peroxisomal enzyme systems leads to **adrenoleukodystrophy**, where VLCFAs are accumulated and myelin sheaths are destroyed.
- It is an X-linked condition.
- The child usually dies during the first decade of life.



Monounsaturated Fatty Acids (MUFA)

- Palmitoleic (C16, 1 double bond) and oleic (C18, 1 double bond) acids are present in human body fat, as well as many vegetable oils.
- Erucic acid (C22, 1 double bond) is a constituent of mustard oil and rapeseed oil.
- Nervonic acid (C24, 1 double bond) is present in substantial quantities in brain.



Modified beta-oxidation of MUFA

- The oxidation of unsaturated fatty acids proceeds as in the case of saturated fatty acids, till the double bond is reached.
- Thus palmitoleic acid (16 C monounsaturated) undergoes 3 cycles of beta-oxidation to yield D3-cis enoyl-CoA with 10 carbon atoms. Here the double bond is cis type; the dehydrogenase cannot act on that bond.
- Therefore, an **isomerase** changes the cis D3 double bond to D2-trans double bond. The double bond between 3rd and 4th carbon atoms is shifted to between 2nd and 3rd carbon atoms.
- It will then undergo 2nd, 3rd and 4th step reactions of beta-oxidation.
- So in this cycle the **FAD dependent dehydrogenation is not needed.**
- Thus in the case of unsaturated fatty acids, the **energy yield is less by 1.5 ATP molecules per double bond.**

Polyunsaturated Fatty Acids (PUFA)

- The important poly unsaturated fatty acids are:
  1. **Linoleic acid** (18C, 2 double bonds)
  2. **Linolenic acid** (18C, 3 double bonds)
  3. **Arachidonic acid** (20C, 4 double bonds)
- They are present in significant quantities in **vegetable oils** such as sunflower oil.
- They are used to esterify cholesterol, whereby the latter can be excreted.
- So, PUFA in general are **antiatherogenic**.
- Fish oils contain PUFAs with 5 or 6 double bonds.
- They are important for development of human brain.

Significance of PUFA

1. PUFAs are seen in vegetable oils.
2. They are nutritionally essential; and are called **essential fatty acids**.
3. **Prostaglandins**, thromboxanes and leukotrienes are produced from arachidonic acid.
4. PUFAs form integral part of mitochondrial membranes. In deficiency of PUFA, the efficiency of **biological oxidation** is reduced.
5. They are components of **membranes**. Arachidonic acid is 10–15% of the fatty acids of membranes.

Significance of PUFA, continued

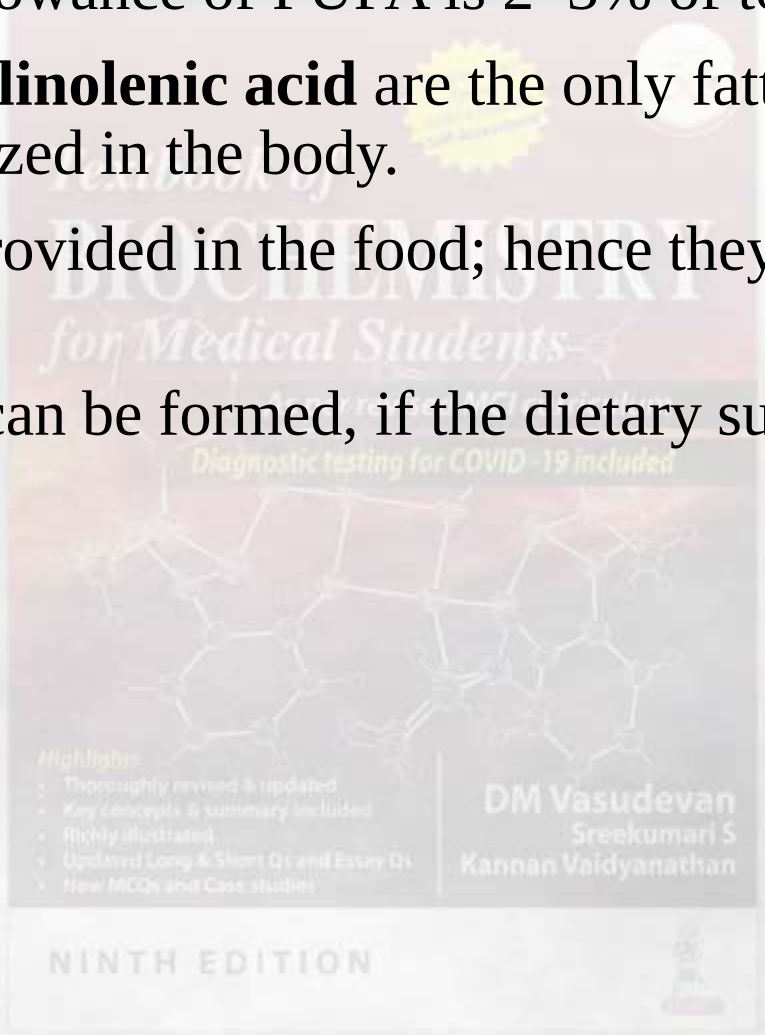
6. As double bonds are in cis configuration; the PUFA molecule cannot be closely packed. So PUFAs will **increase the fluidity** of the membrane.
7. As PUFAs are easily liable to undergo peroxidation, the membranes containing PUFAs are more prone for damage by free radicals.
8. The production of docosa hexenoic acid (DHA) from alpha linolenic acid is limited. DHA is present in high concentrations in fish oils. DHA is present in high concentrations in retina, cerebral cortex and sperms.

Clinical significance of PUFA and EFA

1. Persons with normal diet will not have any deficiency; but those who are on parenteral nutrition for long periods will have deficiency.
2. PUFAs are used for esterification and excretion of cholesterol. PUFA will reduce serum cholesterol level.
3. Deficiency of EFA causes acanthocytosis, hyperkeratosis, acrodermatitis and hypercholesterolemia.
4. EFA deficiency is connected with acrodermatitis enteropathica, hepatorenal syndrome and CNS manifestations.
5. Elevated PUFA levels are seen in Zellweger's syndrome.
6. DHA levels in blood are low in patients with retinitis pigmentosa.
7. Trans fatty acids will compete with EFAs and may increase the EFA deficiency and decrease fluidity of membranes.
8. Trans fatty acids decrease HDL-cholesterol and may cause atherosclerosis.

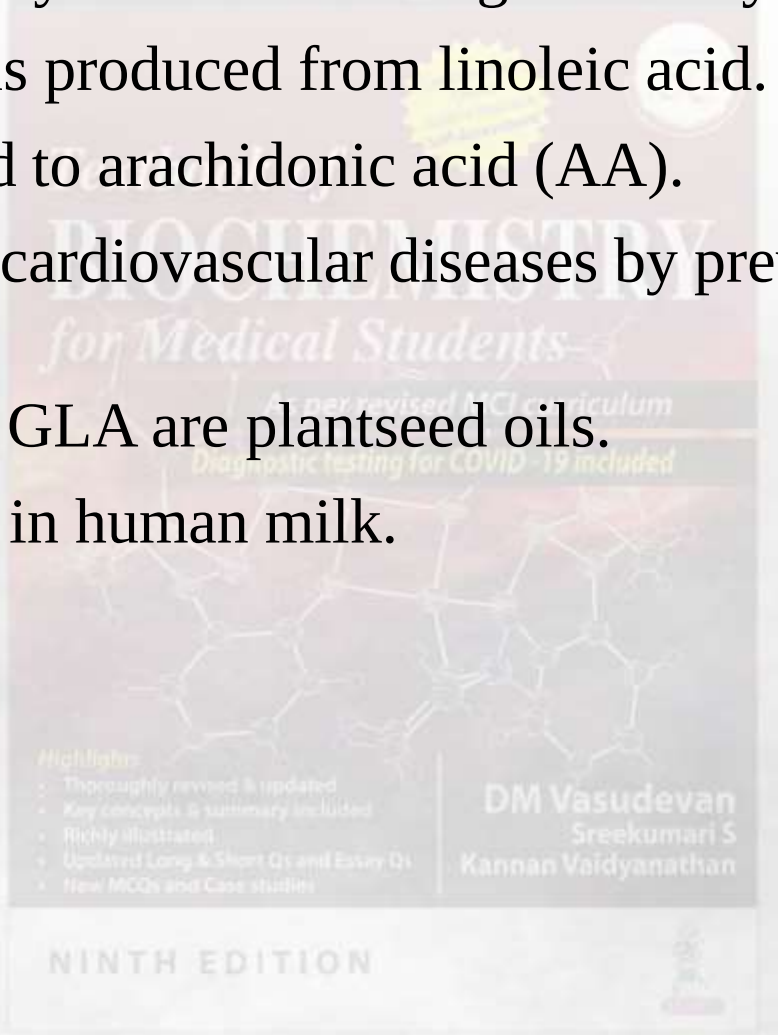
Essential Fatty Acids (EFA)

- Normal dietary allowance of PUFA is 2–3% of total calories.
- **Linoleic acid** and **linolenic acid** are the only fatty acids which cannot be synthesized in the body.
- They have to be provided in the food; hence they are essential fatty acids.
- Arachidonic acid can be formed, if the dietary supply of linoleic acid is sufficient.



Gamma-Linolenic Acid (GLA)

- It is an essential fatty acid of the omega-6 family.
- In the body, GLA is produced from linoleic acid.
- GLA is desaturated to arachidonic acid (AA).
- GLA may prevent cardiovascular diseases by preventing atherosclerosis.
- Dietary sources of GLA are plantseed oils.
- GLA is also found in human milk.

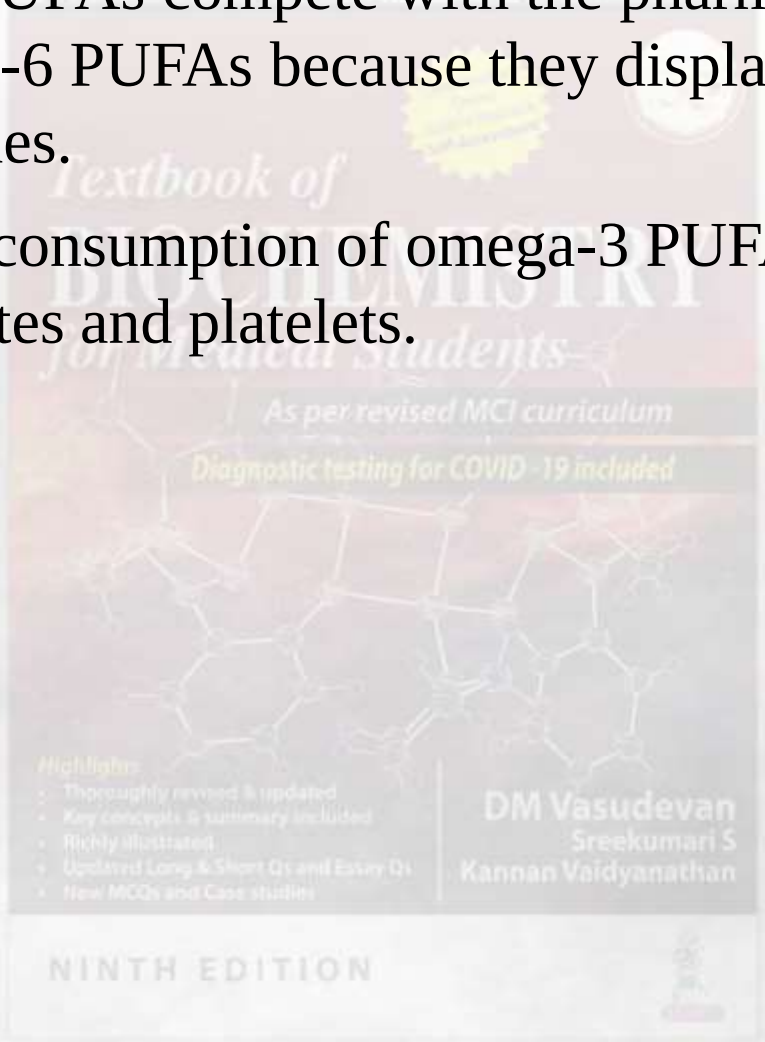


Clinical Significance of Omega-3 and Omega-6 PUFAs

- There are three major types of omega-3 fatty acids in foods; these are ALA (alpha linolenic acid), eicosa pentaenoic acid (EPA), and docosa hexaenoic acid (DHA).
- The body converts ALA to EPA and then to DHA.
- Most of the ALA consumed in the diet comes from fruits and nuts.
- The highest concentrations of EPA and DHA are found in cold water fishes such as salmon, tuna, and herring.
- The most important PUFAs, biologically, are EPA and DHA.
- Most of the omega-6 PUFAs consumed in the diet are from vegetable oils such as soybean oil, corn oil, etc.
- Linoleic acid is converted to arachidonic acid.
- When gamma-linolenic acid (GLA) is available in food, GLA is converted to arachidonic acid.

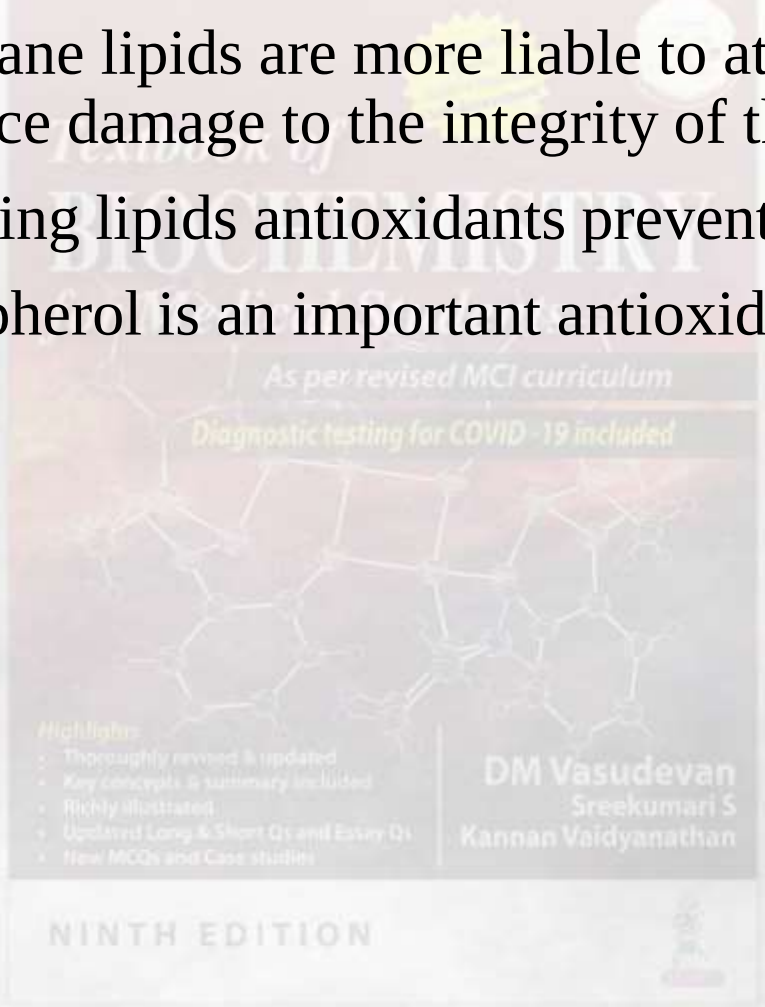
- Omega-3 and omega-6 fatty acids are incorporated into cell membranes.
- These membrane lipids serve as precursors for the synthesis of important signalling molecules involved in cell growth and inflammation.
- The most important omega-6 PUFA is arachidonic acid.
- On stimulation of the cell, arachidonic acid is released from cell membranes through the action of phospholipase A*2* (PLA*2*).
- The released arachidonate then serves as the precursor for the synthesis of the prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs).
- These eicosanoids will cause platelet and leukocyte activation, signaling of pain, induction of bronchoconstriction, and regulation of gastric secretions.
- These activities are targets of nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, and leukotriene antagonists.

- Dietary omega-3 PUFAs compete with the pharmacological activities of omega-6 PUFAs because they displace arachidonic acid from cell membranes.
- Increasing dietary consumption of omega-3 PUFAs will reduce the activity of leukocytes and platelets.



Lipid Peroxidation

- In vitro, peroxidation would lead to rancidity of fats and oils.
- In vivo the membrane lipids are more liable to attack by free radicals and produce damage to the integrity of the membrane.
- In naturally occurring lipids antioxidants prevent lipid peroxidation.
- Vitamin E or tocopherol is an important antioxidant in the human body.

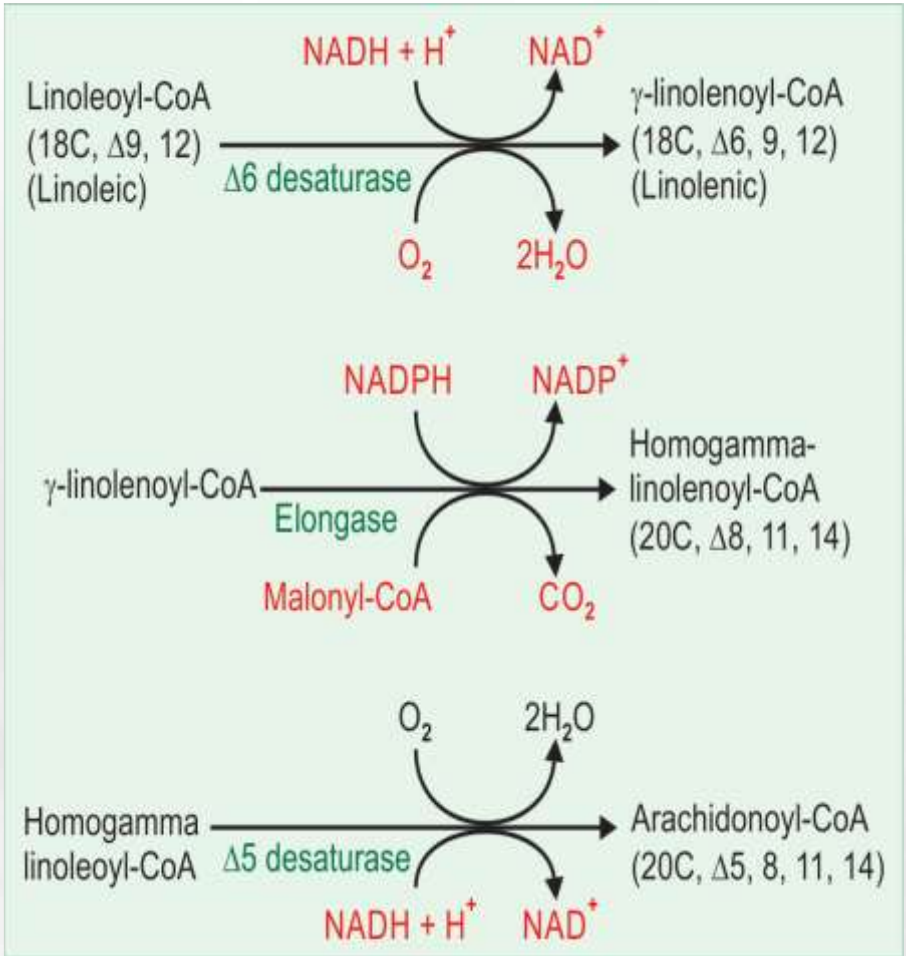


Elongation of Fatty Acids

- The **Microsomal system** (microsomal fatty acid elongase system) elongates saturated or unsaturated fatty acyl-CoA by successive addition of two-carbon units.
- Malonyl-CoA is the donor of two carbon acetyl groups.
- NADPH is required for the reaction.
- This system can elongate fatty acids having 10 carbon units onwards up to the length of 22 or 24 carbons.
- The steps in elongation are similar to de novo synthesis.

Desaturation of Fatty Acids

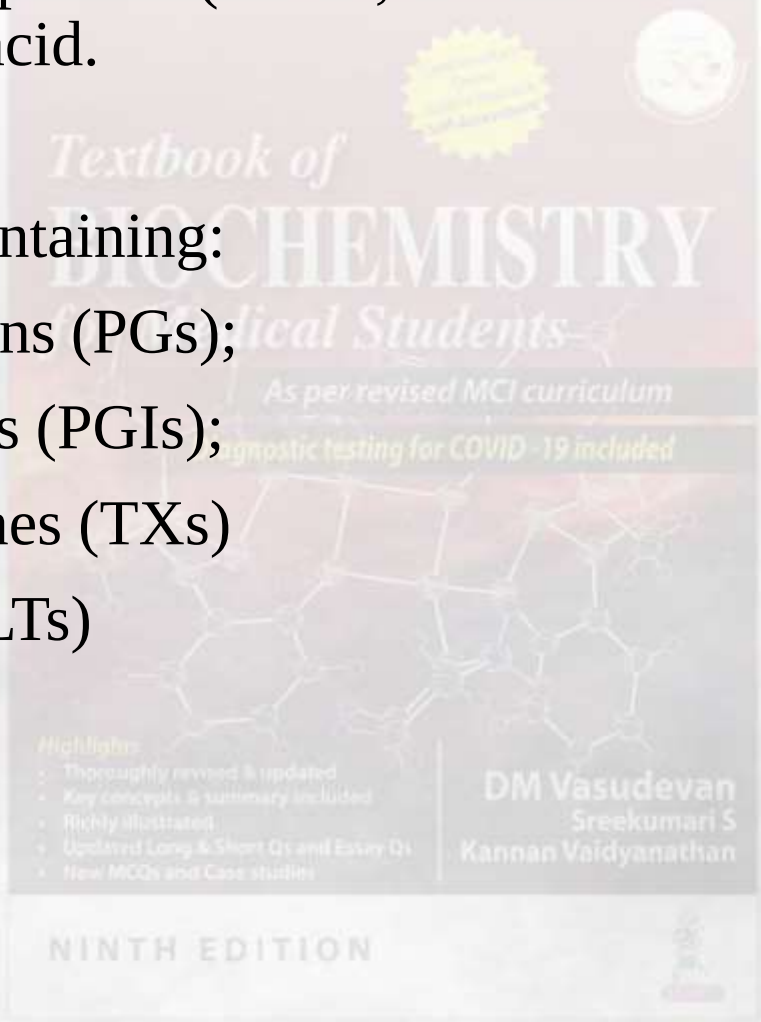
- Monounsaturated fatty acids can be synthesized from saturated fatty acids by a D9 desaturase enzyme system present in the **endoplasmic reticulum**.
- The reaction utilizes NADH and molecular O2 and cytochrome b5.
- Thus stearic acid is desaturated to form oleic acid.
- The introduction of double bonds is possible only between an existing double bond and carboxyl end of the fatty acid (but not between the omega end and an existing double bond).
- Hence, linoleic acid cannot be synthesized from oleic acid.
- However, **linoleic acid can be converted to arachidonic acid** by elongation and desaturation.



Desaturation and elongation of linoleic acid to arachidonic acid.

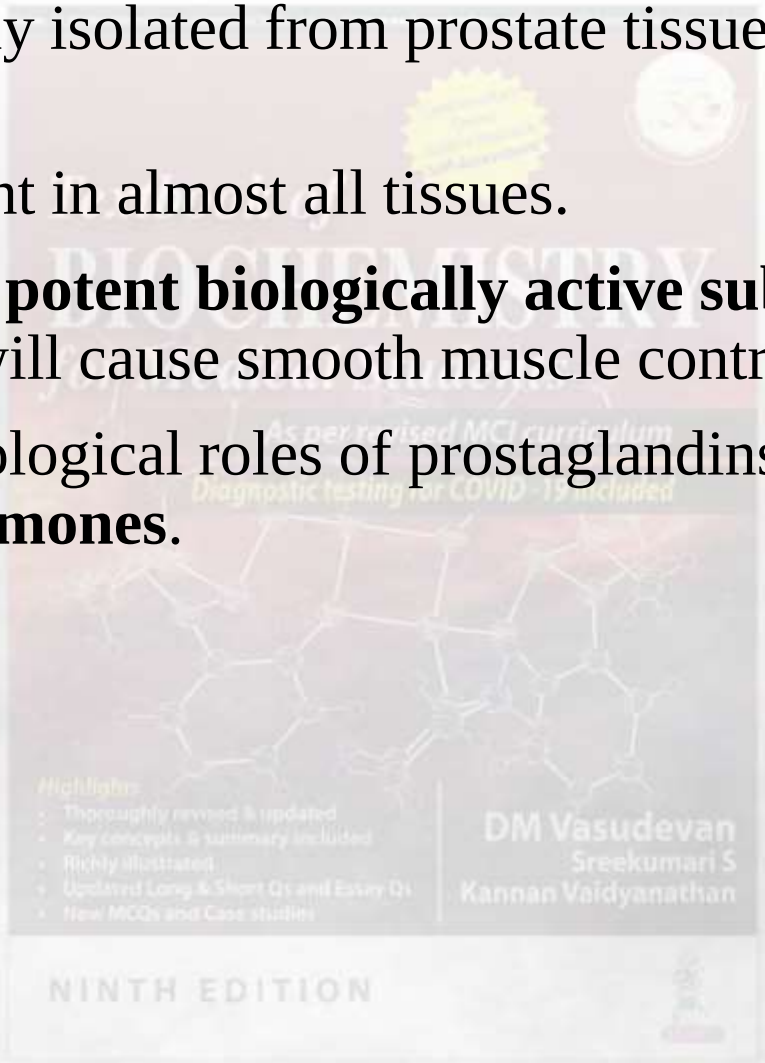
Eicosanoids

- They are 20C compounds (Greek, eikosi = twenty), derived from arachidonic acid.
- Their names are:
  1. Prostanoids, containing:
     a. Prostaglandins (PGs);
     b. Prostacyclins (PGIs);
     c. Thromboxanes (TXs)
  2. Leukotrienes (LTs)



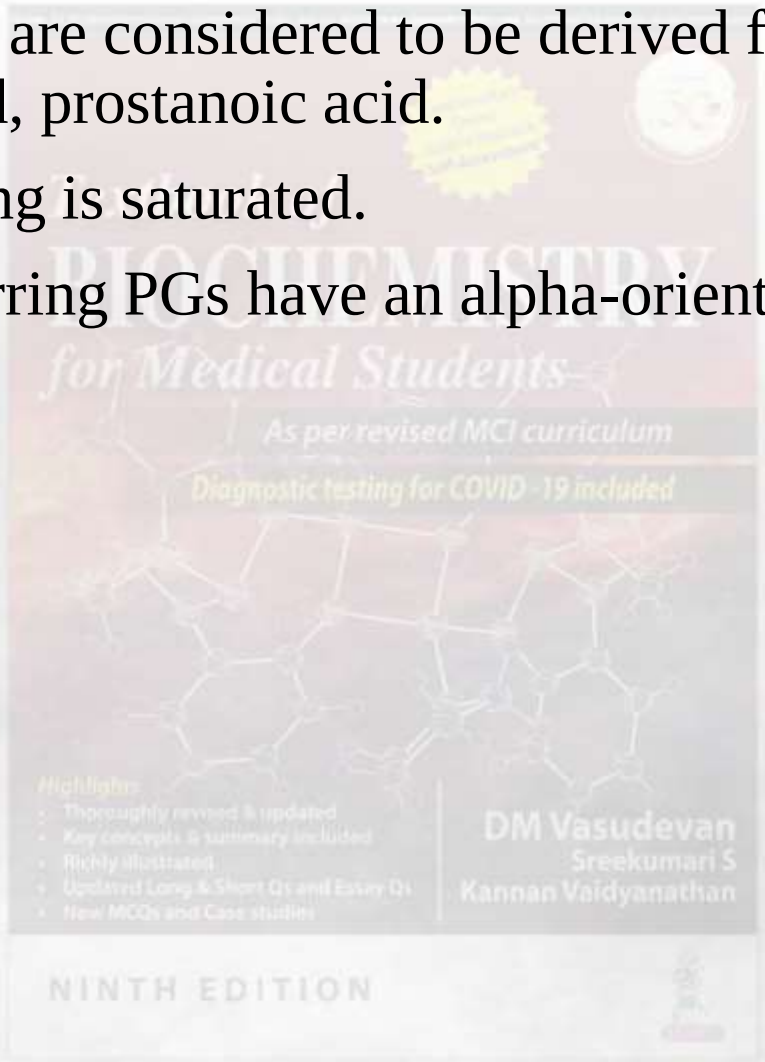
Prostaglandins (PGs)

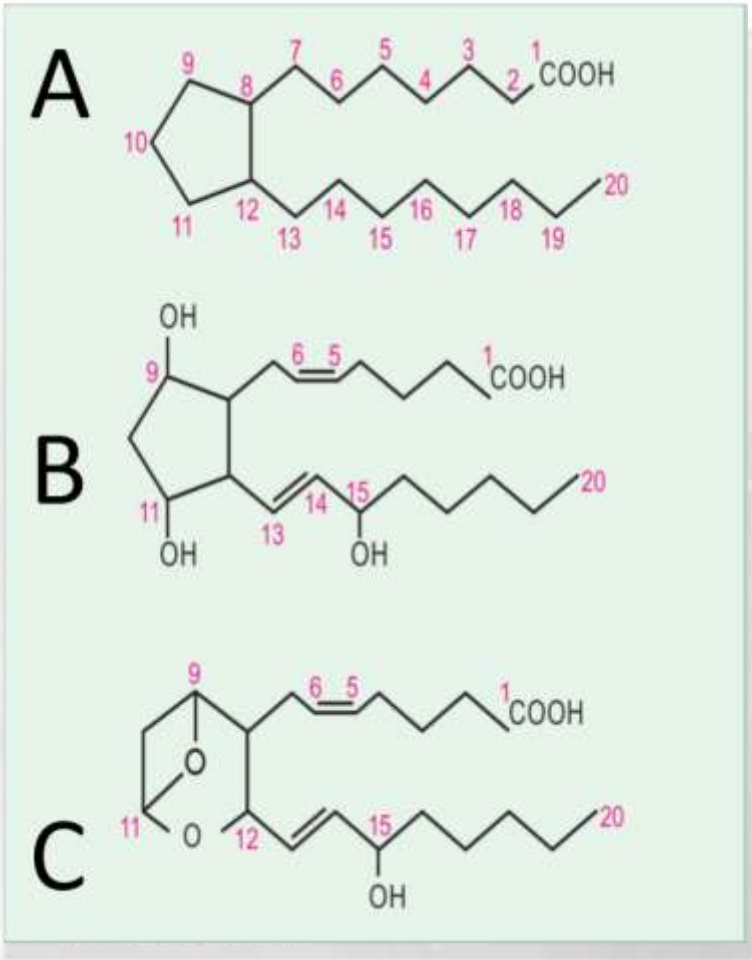
- PGs were originally isolated from prostate tissue and hence the name.
- But they are present in almost all tissues.
- They are the **most potent biologically active substances**; as low as one ng/ml of PG will cause smooth muscle contraction.
- The diverse physiological roles of prostaglandins confer on them the status of **local hormones**.



Chemical Structure

- All prostaglandins are considered to be derived from the 20C cyclic saturated fatty acid, prostanoic acid.
- The five carbon ring is saturated.
- All naturally occurring PGs have an alpha-oriented **OH group at C15.**





(A) Prostanoic acid; (B) Prostanglandin-F2; (C) Thromboxane A2

Salient features of prostaglandins

Name	Substituent groups
PGA	Keto group at C9; double bond C10 and 11
PGB	Keto group at C9; double bond C8 and 12
PGD	OH group at C9; keto group at C11
PGE	Keto group at C9; OH group at C11
PGF	OH groups at C9 and C11 (Fig.14.2)
PGG	Two oxygen atoms, interconnected to each other, and bonded at C9 and C11; hydroperoxide group at C15
PGH	Same ring as PGG; but C15 has OH group
PGI	Double ring. Oxygen attached to C6 and C9, to form another 5-membered ring. Hence called prostacyclin.

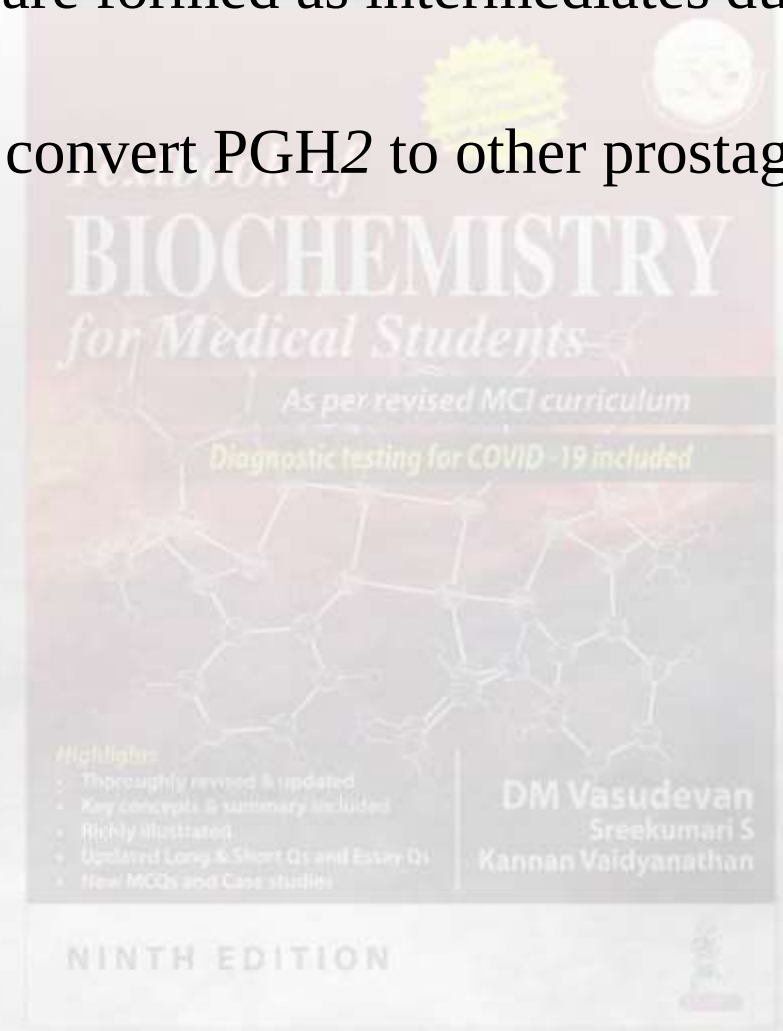
Classification of Prostaglandins

- According to the attachment of different substituent groups to the ring, PGs are named with capital letters such as A, B, E and F.
- PGF is designated as alpha to denote the projection of the OH group in naturally occurring prostaglandins.
- In the same series, depending on number of double bonds on the side chains they are denoted by a subscript after the capital letter, e.g. PGE1, PGE2, PGE3, etc.
- The primary prostaglandins PGG and PGH, (the endoperoxides) are intermediates in the synthesis of others.
- **Only 5 PGs are widely** distributed in the body.
- They are PGD2, PGE2, PGF2 and PGI2 and thromboxane A2.

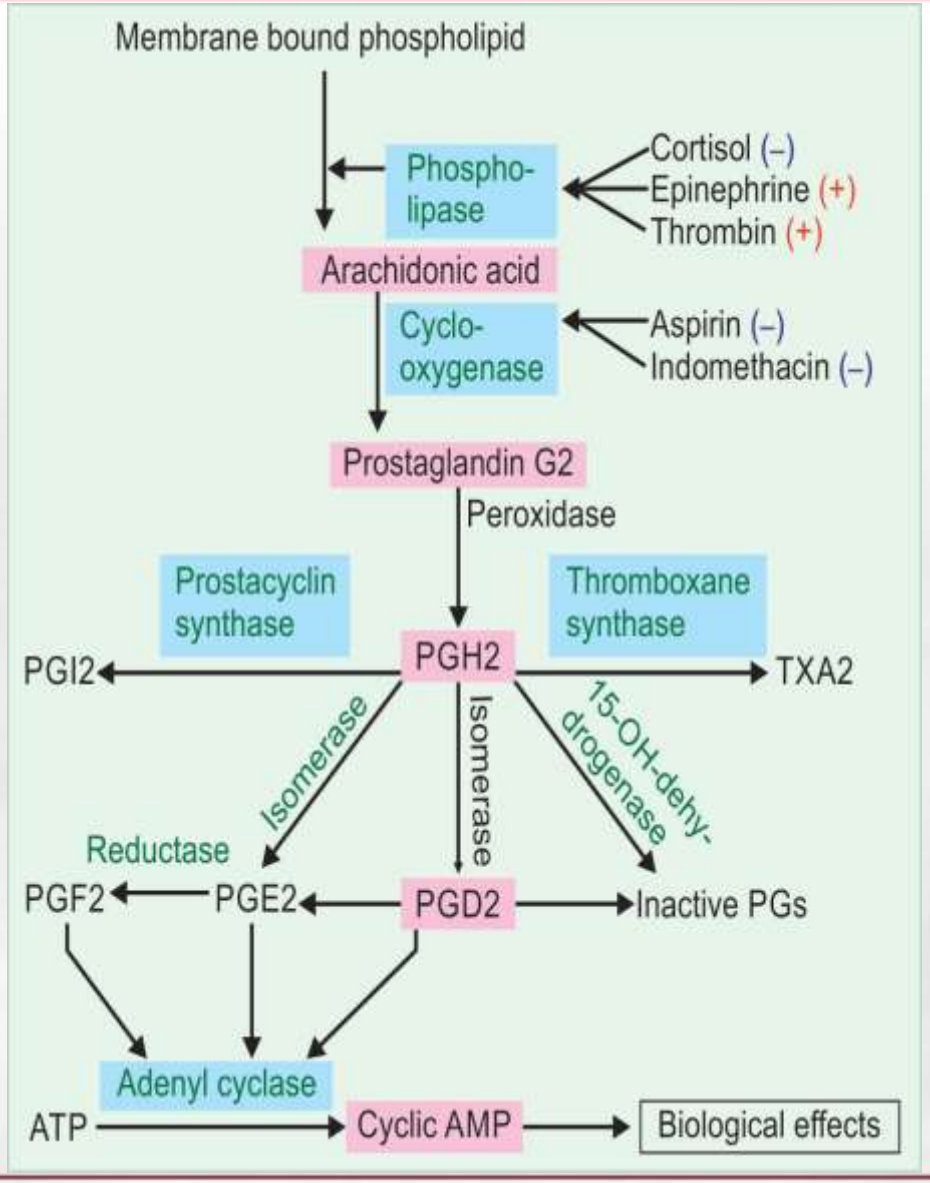
Biosynthesis of Prostaglandins

- Prostaglandins are derived from the following PUFA.
  1 series (1 double bond)—from Linoleic acid
  2 series (2 double bonds)—from Arachidonic acid
  3 series (3 double bonds)—Eicosapentaenoic acid
- Naturally occurring PGs belong to the 2 series.
- PGs are not stored as such; the precursor fatty acids are present in membrane as phospholipids.
- The arachidonic acid is released by the action of **phospholipase A2** on phospholipids.
- Synthesis is catalyzed by prostaglandin H synthase **(PGHS)**.
- It contains two separate enzyme activities, **cyclo-oxygenase** and peroxidase.

- PGG*2* and PGH*2* are formed as intermediates during the synthesis of other PGs.
- Specific enzymes convert PGH*2* to other prostaglandins.



Biosynthesis of Prostaglandins



Regulation of Synthesis

- The **phospholipase** (PL) is activated by epinephrine, thrombin, angiotensin II, bradykinin and vasopressin.
- Steroids inhibit PL and prevent release of arachidonic acid from membranes.
- **Cyclo-oxygenase** is activated by catecholamines and inhibited by nonsteroid anti-inflammatory drugs (NSAIDs).
- **Aspirin** acetylates serine at the active site and irreversibly inhibits the cyclo-oxygenase.
- Cyclo-oxygenase is a **"suicide" enzyme,** self catalysed destruction rapidly inactivates the enzyme.
- This would prevent excessive production of PGs.
- Cyclo-oxygenase exists in two different forms.

- COX- 1, the **constitutive form** produces prostaglandins, that mediate gastric, renal and platelet functions.
- The **inducible form** mediates the inflammatory response.
- Prostaglandins have only very short half-life, of about 30 seconds.
- Prostaglandins are **local hormones.**
- They function through G-protein coupled receptors.
- In most tissues, PGE increases cAMP (**cyclic AMP**) level.
- But in adipose tissue and in renal tubular cells, PGE lowers cAMP level.
- PGI activates adenyl cyclase and TXA inhibits it.

Mechanism of action of aspirin

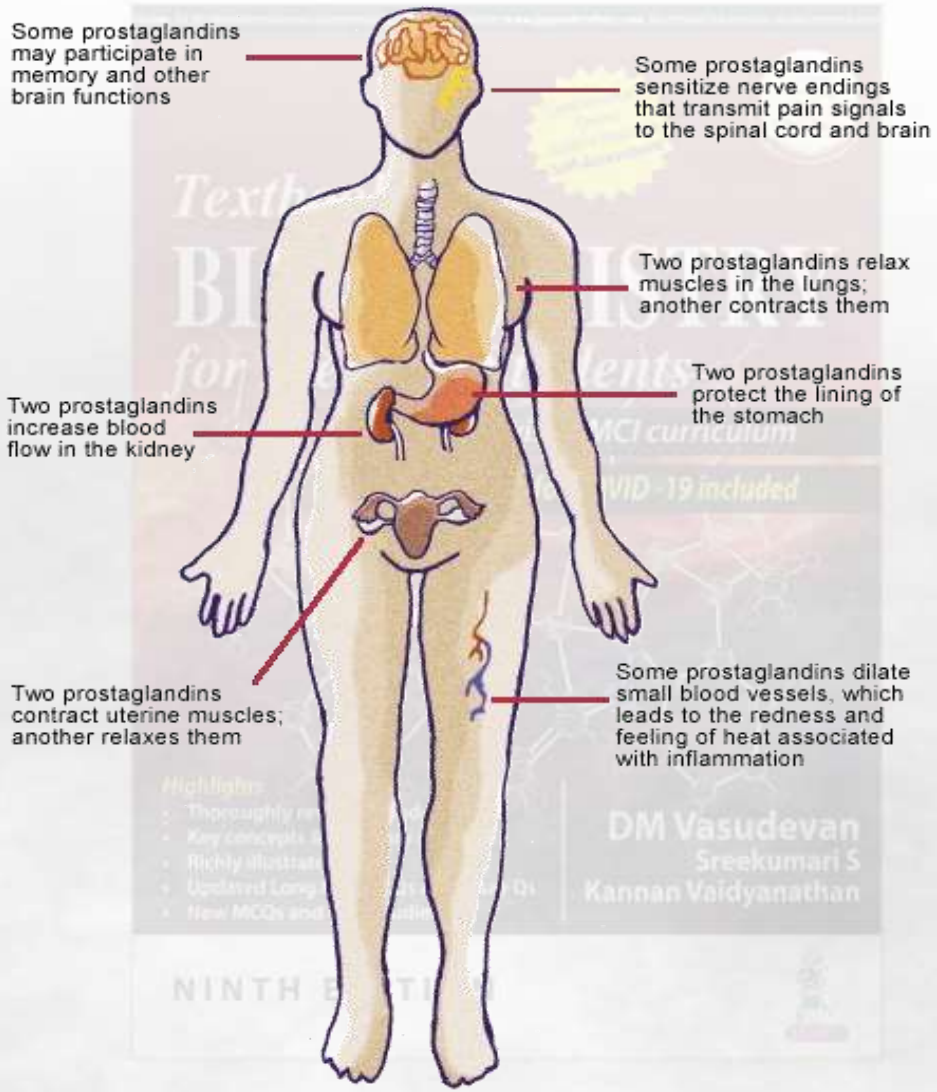
- Aspirin irreversibly acetylates and inhibits **cyclo-oxygenase**.
- Platelets cannot regenerate cyclo-oxygenase and so thromboxane A2 is not formed in platelets.
- Hence, there is decreased platelet aggregation.
- Therefore, aspirin is useful in prevention of **heart attacks**.
- By inhibiting cyclo-oxygenase, aspirin also reduces PGI2; but endothelial cells after a few hours will resynthesize cyclo-oxygenase.
- So aspirin completely blocks TXA2, but only partially inhibits PGI2.
- Other anti-inflammatory drugs (*indomethacin and ibuprofen*) also cause irreversible inhibition of enzyme.
- **Paracetamol** is a reversible inhibitor.

Biological Actions and Clinical Applications

- *Effects on CVS*
- **Prostacyclin** or PGI2 is synthesized by the vascular endothelium.
- Major effect is **vasodilatation**.
- It also **inhibits platelet aggregation** and has a protective effect on vessel wall against deposition of platelets.
- But any injury to the vessel wall would inhibit PGI2 synthesis so that platelet aggregation occurs to promote thrombus formation.
- **Thromboxane** (TXA2) is the main PG produced by platelets.
- The major effects are **vasoconstriction** and **platelet aggregation**.
- Prostacyclin and thromboxane are opposing in activity.
- Prostaglandins lower the blood pressure.

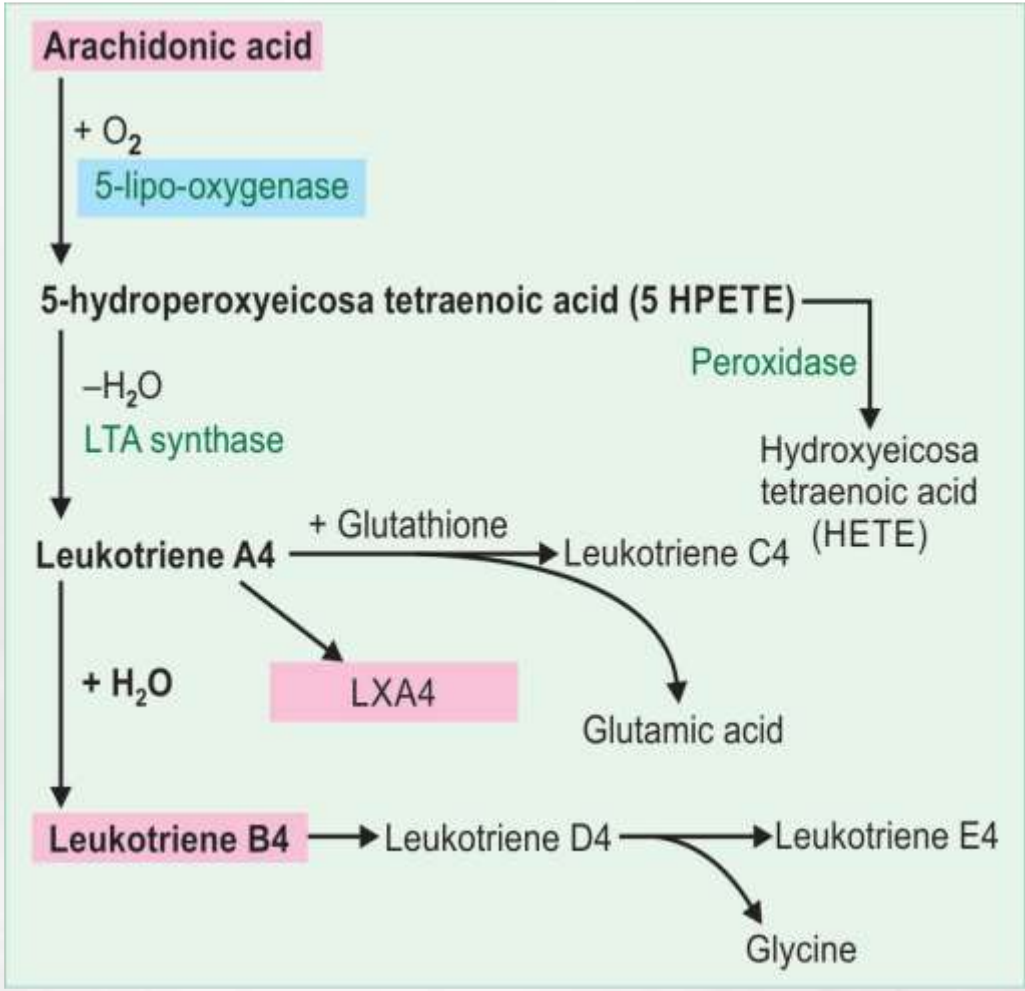
- *Effects on Ovary and Uterus*
- The PGF2 stimulates the uterine muscles.
- Hence PGF2 may be used for medical **termination of pregnancy**.
- Yet another use is in **inducing labor** and arresting postpartum **hemorrhage**.
- PGs are involved in LH induced ovulation.
- In cattle, if PG is given, luteolysis takes place and animal goes into estrus.
- Better fertilization rate is achieved with timely artificial insemination.

- *Effects on Respiratory Tract*
- The PGF is a constrictor of bronchial smooth muscle; but PGE is a potent **bronchodilator**.
- PGE series are used in aerosols for relieving bronchospasm.
- *Effects on Immunity and Inflammation*
- The PGE*2* and D*2* produce inflammation by increasing capillary permeability.
- Erythema and wheal are produced at the site of injury.


Some prostaglandins may participate in memory and other brain functions
Some prostaglandins sensitize nerve endings that transmit pain signals to the spinal cord and brain
Two prostaglandins relax muscles in the lungs; another contracts them
Two prostaglandins protect the lining of the stomach
Two prostaglandins increase blood flow in the kidney
Two prostaglandins contract uterine muscles; another relaxes them
Some prostaglandins dilate small blood vessels, which leads to the redness and feeling of heat associated with inflammation

Leukotrienes (LTs)

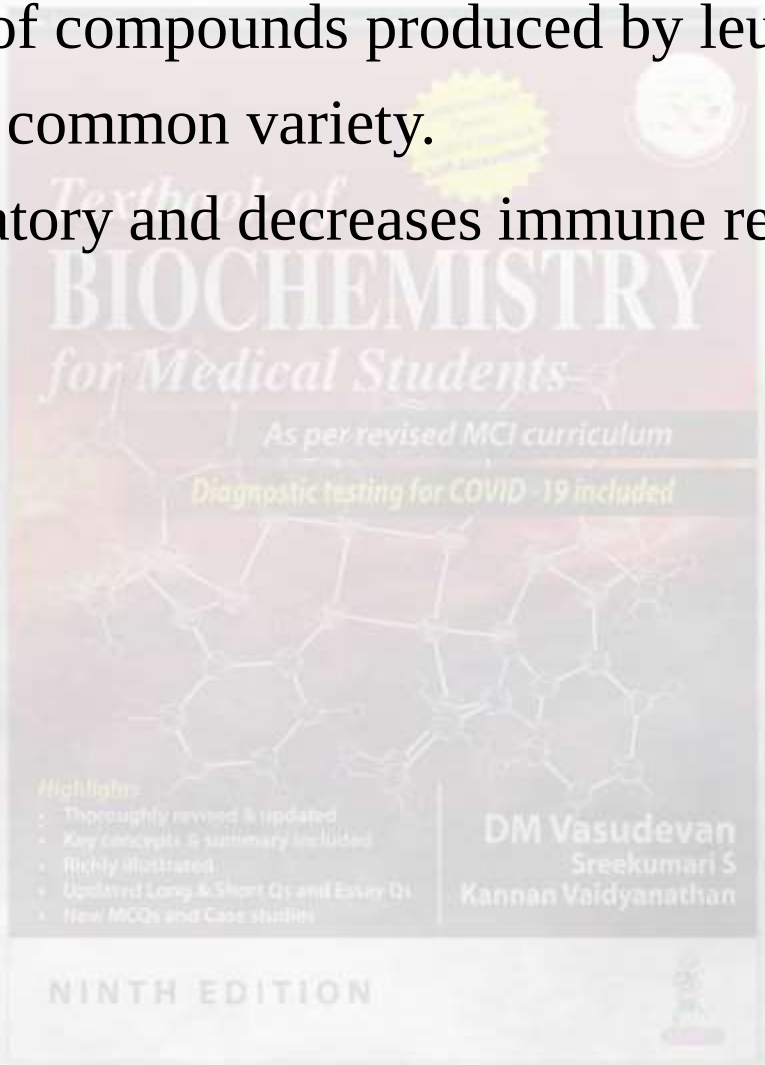
- They are produced **from arachidonic acid**.
- LT B4 is produced in neutrophils; it is the most potent **chemotactic** agent (factor attracting cells to the inflammatory site).
- The number 4 denotes that there are 4 double bonds in the structure.
- The **slow reacting substance of anaphylaxis** (**SRS-A**) contains LTC4, LTD4 and LTE4.
- They cause smooth muscle contraction, constrict the bronchioles and produce vasoconstriction.
- SRS is the mediator of hypersensitivity reactions such as asthma.
- LTB4 is a potent inflammatory molecule through its action on neutrophils.



Synthesis of leukotrienes.
(LT: leukotriene; LXA: lipoxin; HETE: hydroxyeicosa tetraenoic acid)

Lipoxins

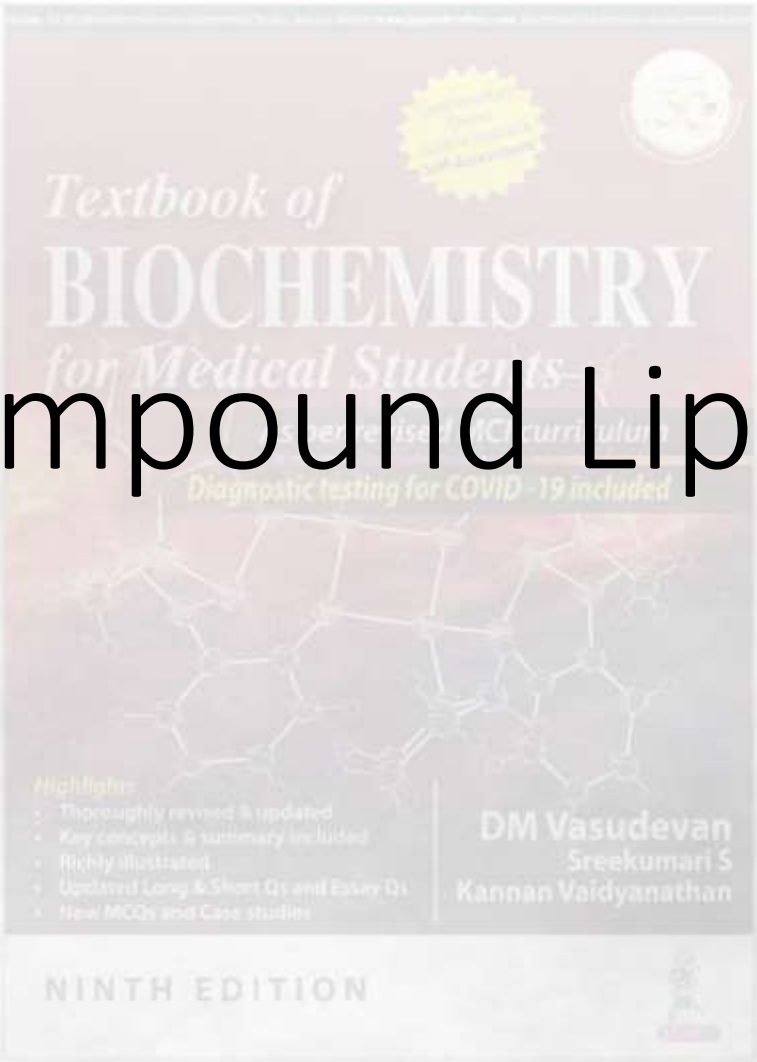
- They are a group of compounds produced by leukocytes.
- LXA4 is the most common variety.
- It is anti-inflammatory and decreases immune response.



Prostacyclins and Thromboxane

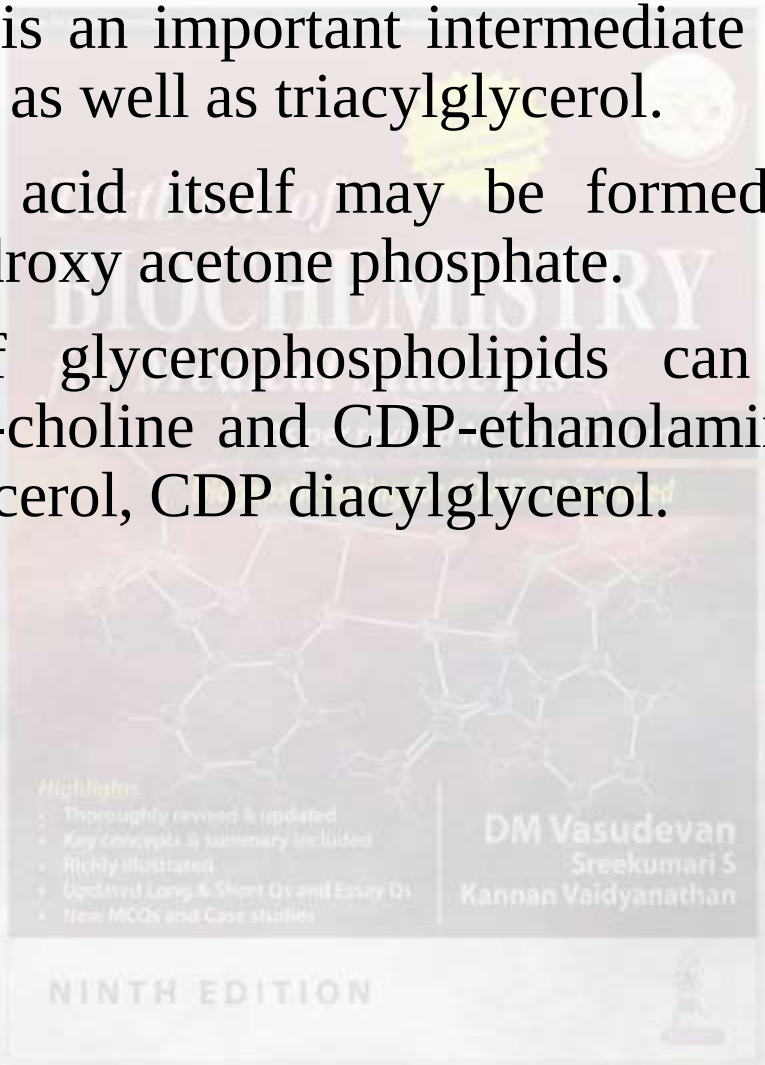
	PGI2	TXA2
Structure	Cyclopentane ring	Oxane ring
Site of formation	Endothelium	Platelets
Cyclic AMP level	Increased	Decreased
Platelet aggregation	Inhibited	Enhanced
Blood vessel	Vasodilatation	Constriction
Bronchioles	Relaxation	Constriction

Compound Lipids



Synthesis of Glycerophosphatides

- Phosphatidic acid is an important intermediate in the synthesis of phosphoglycerides as well as triacylglycerol.
- The phosphatidic acid itself may be formed from glycerol-3-phosphate or dihydroxy acetone phosphate.
- The synthesis of glycerophospholipids can occur either by activation to CDP-choline and CDP-ethanolamine or by formation of active diacylglycerol, CDP diacylglycerol.

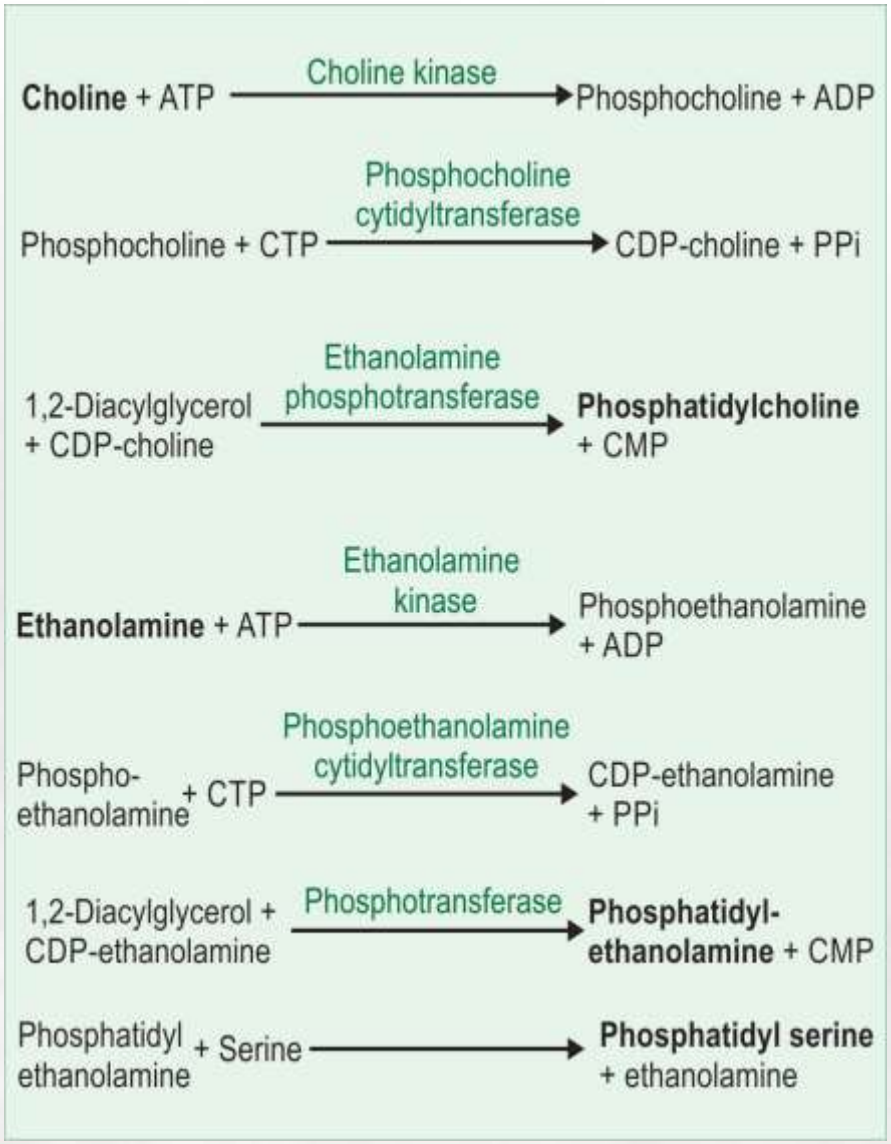


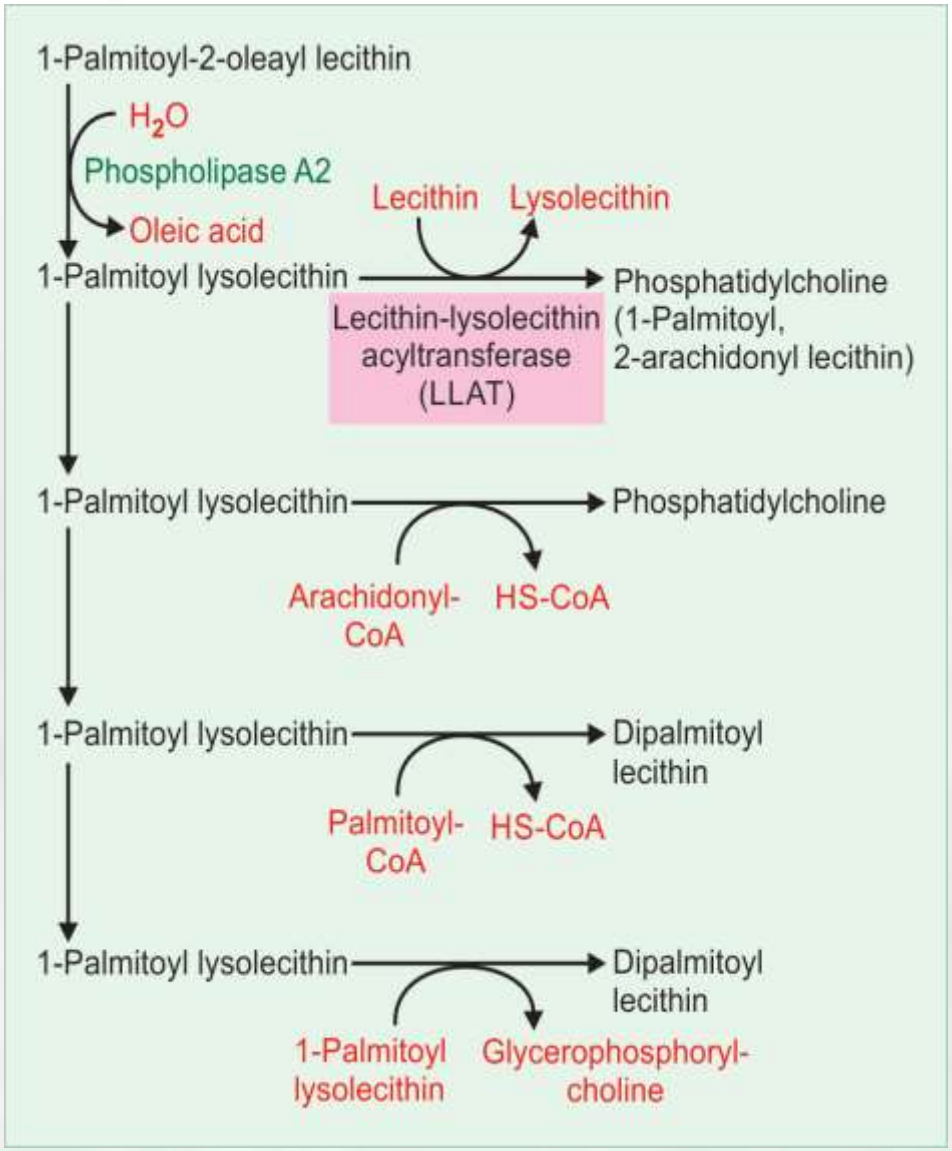
Synthesis of Phosphatidylinositol

- In the CDP-diacylglycerol pathway, phosphatidic acid first reacts with CTP to form CDP-diacylglycerol.
- The CDP diacylglycerol can react with the alcoholic group of serine or inositol to form the corresponding phosphoglyceride and releasing CMP.
- The phosphatidylinositol undergoes further phosphorylation by a specific kinase to form phosphatidylinositol diphosphate (**PIP2**) which acts as a signal transducer.

Synthesis of Phosphatidyl Choline

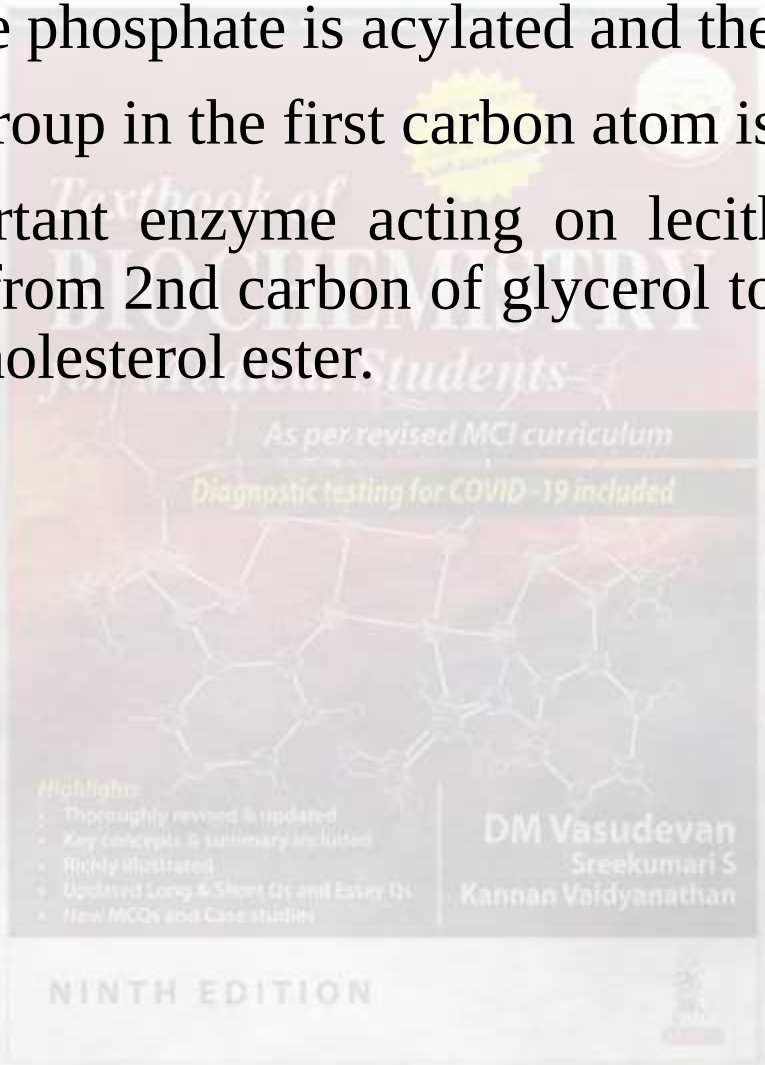
- The major pathway for lecithin and cephalin synthesis, especially in liver and brain, involves the activation of choline or ethanolamine to phosphorylated derivative and then to form the CDP derivative.
- Finally phosphocholine or phosphoethanolamine is transferred to diacylglycerol to form the corresponding phospholipid.
- First one fatty acid residue is removed from glycerol.
- Then, arachidonic acid is added by the action of LLAT (Lecithin-lysolecithin acyltransferase).


Choline + ATP
Choline kinase
Phosphocholine + ADP
Phosphocholine + CTP
Phosphocholine cytidyltransferase
CDP-choline + PPi
1,2-Diacylglycerol + CDP-choline
Ethanolamine phosphotransferase
Phosphatidylcholine + CMP
Ethanolamine + ATP
Ethanolamine kinase
Phosphoethanolamine + ADP
Phospho-ethanolamine + CTP
Phosphoethanolamine cytidyltransferase
CDP-ethanolamine + PPi
1,2-Diacylglycerol + CDP-ethanolamine
Phosphotransferase
Phosphatidyl-ethanolamine + CMP
Phosphatidyl ethanolamine + Serine
Phosphatidyl serine + ethanolamine


1-Palmitoyl-2-oleayl lecithin
H_2O
Phospholipase A2
Oleic acid
Lecithin
Lysolecithin
1-Palmitoyl lysolecithin
Lecithin-lysolecithin acyltransferase (LLAT)
Phosphatidylcholine (1-Palmitoyl, 2-arachidonyl lecithin)
1-Palmitoyl lysolecithin
Phosphatidylcholine
Arachidonyl-CoA
HS-CoA
1-Palmitoyl lysolecithin
Dipalmitoyl lecithin
Palmitoyl-CoA
HS-CoA
1-Palmitoyl lysolecithin
Dipalmitoyl lecithin
1-Palmitoyl lysolecithin
Glycerophosphoryl-choline

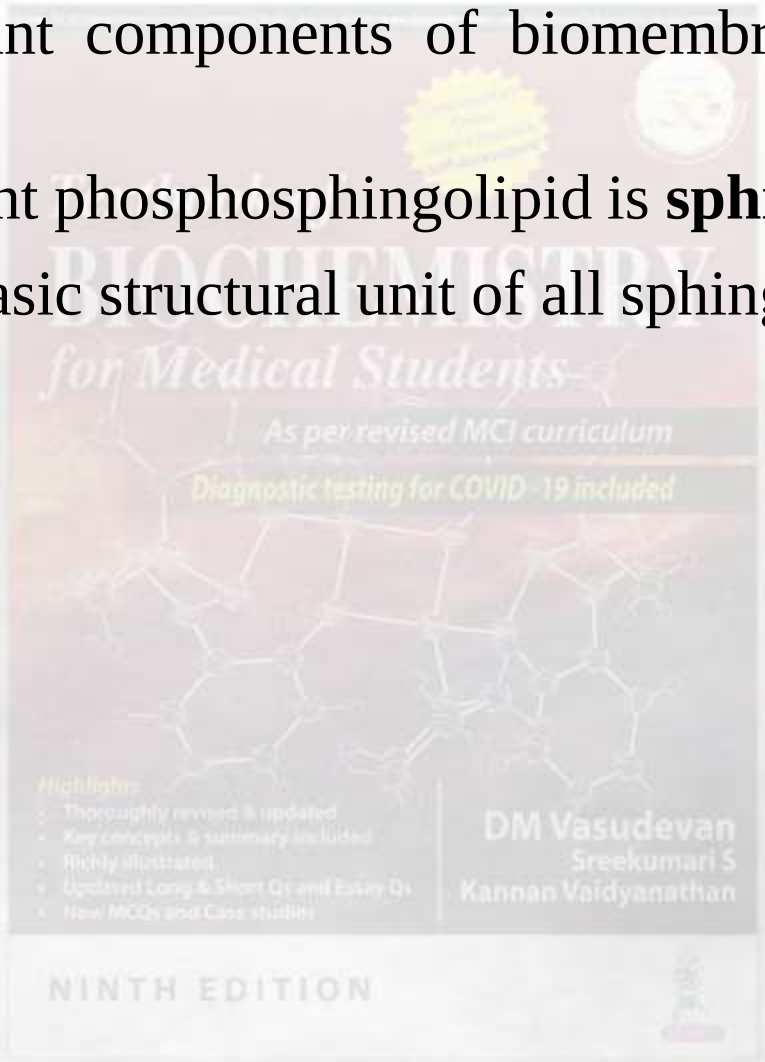
Plasmalogens

- Dihydroxy acetone phosphate is acylated and then choline is added.
- Finally the alkyl group in the first carbon atom is desaturated.
- Yet another important enzyme acting on lecithin is **LCAT** which transfers a PUFA from 2nd carbon of glycerol to cholesterol forming lysolecithin and cholesterol ester.



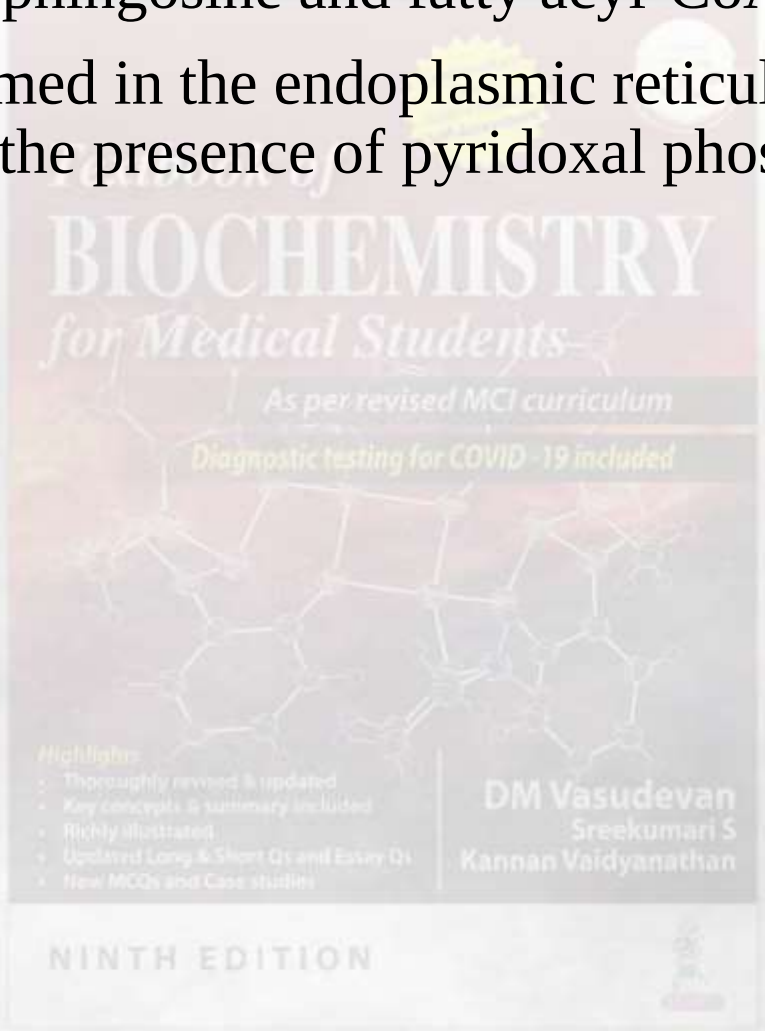
Synthesis of Sphingolipids

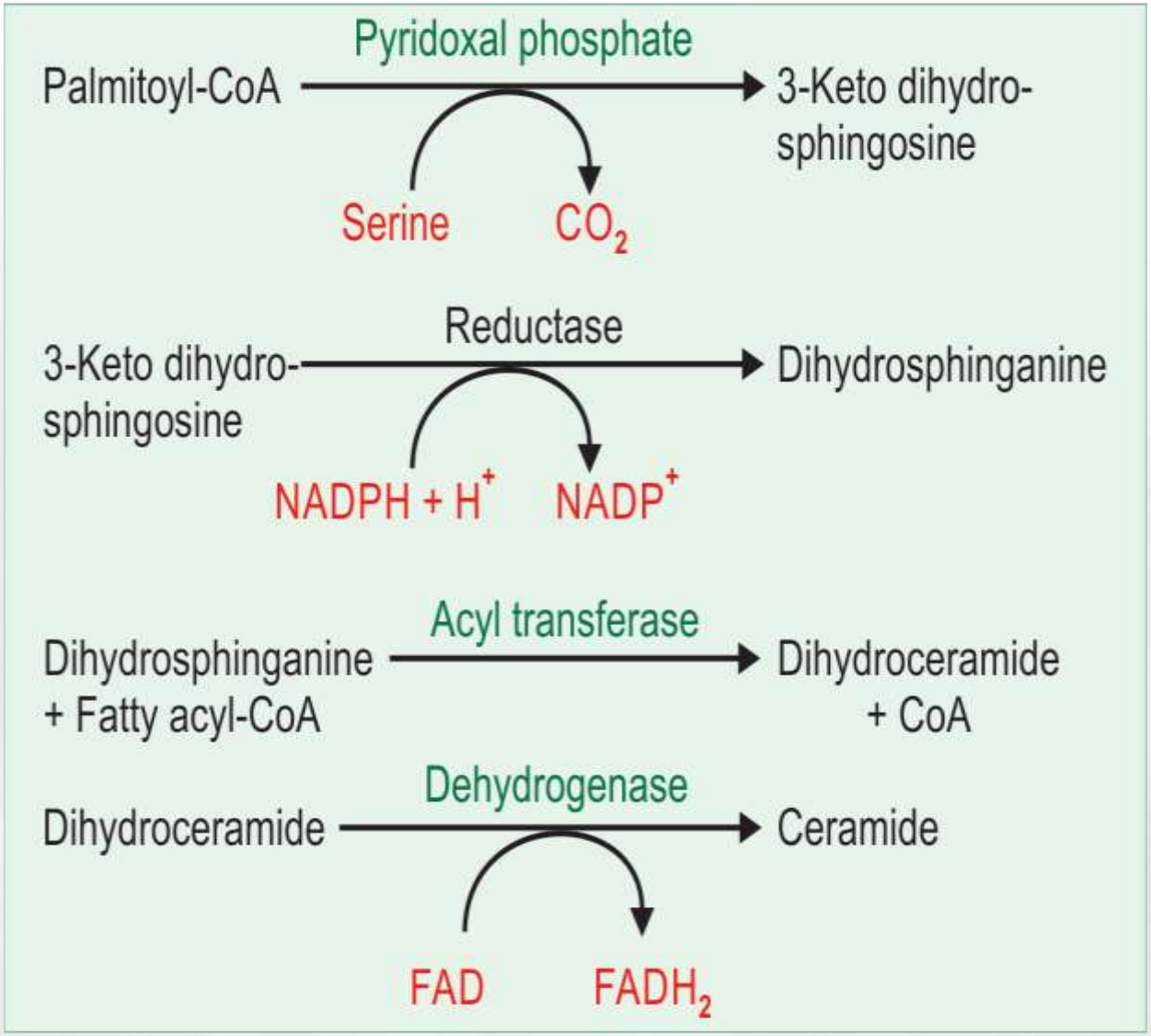
- They are important components of biomembranes as well as the brain.
- The most important phosphosphingolipid is **sphingomyelin.**
- Ceramide is the basic structural unit of all sphingolipids.



Synthesis of Ceramide

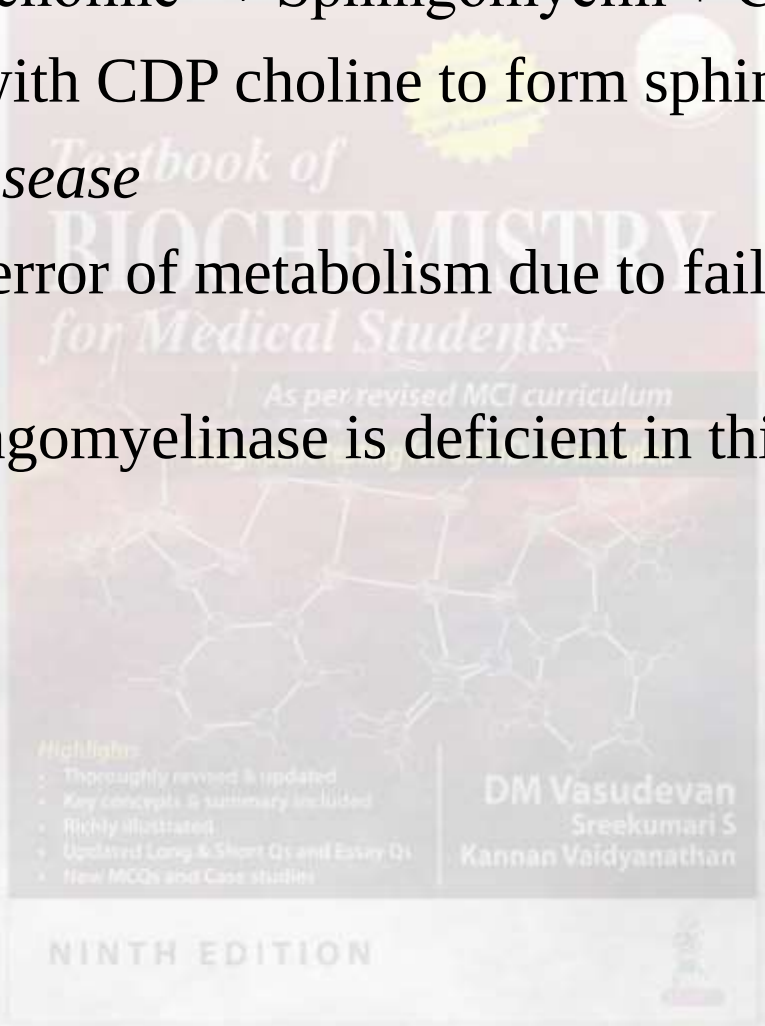
- It is formed from sphingosine and fatty acyl-CoA.
- Sphingosine is formed in the endoplasmic reticulum from palmitoyl-CoA and serine in the presence of pyridoxal phosphate.




Pyridoxal phosphate
Palmitoyl-CoA
3-Keto dihydro-sphingosine
Serine
CO_2
Reductase
3-Keto dihydro-sphingosine
Dihydrosphinganine
$NADPH + H^+$
$NADP^+$
Acyl transferase
Dihydrosphinganine + Fatty acyl-CoA
Dihydroceramide + CoA
Dehydrogenase
Dihydroceramide
Ceramide
FAD
$FADH_2$

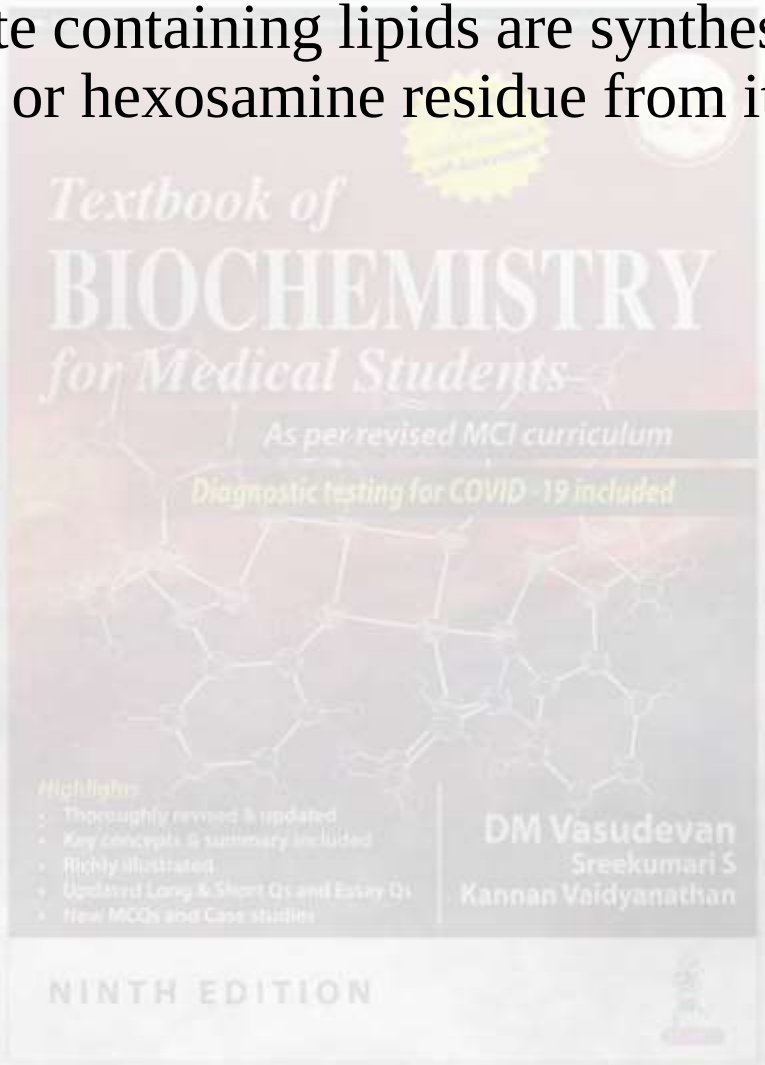
Synthesis of Sphingomyelin

- Ceramide + CDP choline → Sphingomyelin + CMP
- Ceramide reacts with CDP choline to form sphingomyelin.
- *Niemann Pick's disease*
- This is an inborn error of metabolism due to failure of degradation of sphingomyelin.
- The enzyme sphingomyelinase is deficient in this condition.



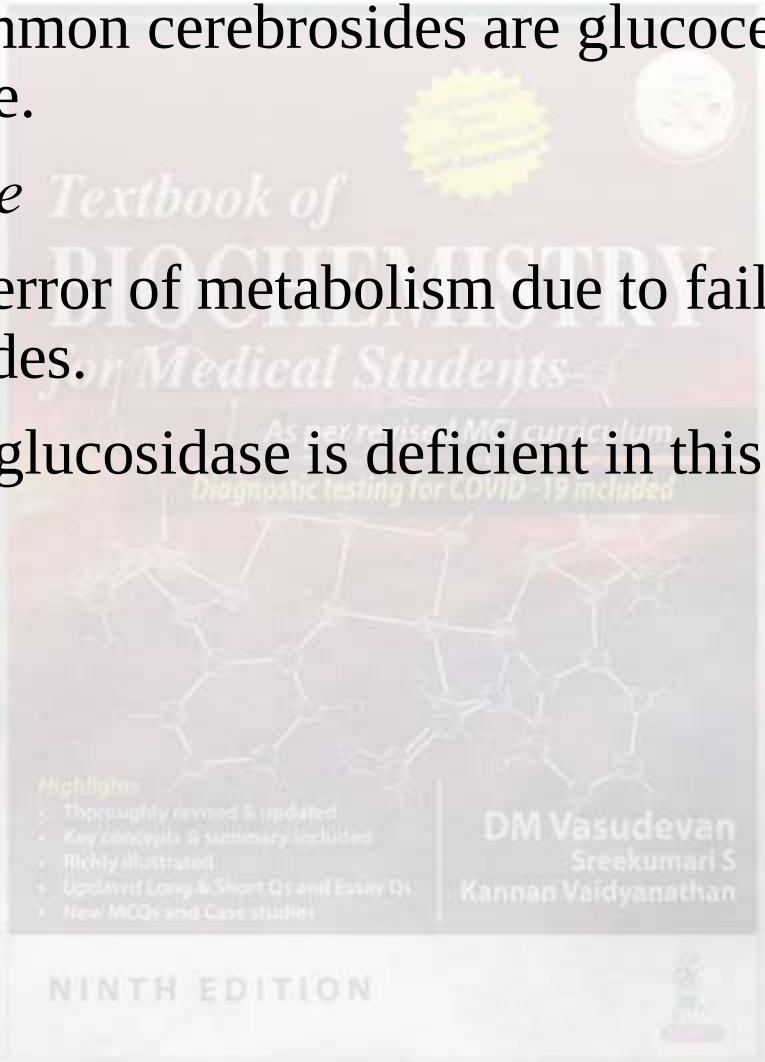
Synthesis of Glycosphingolipids

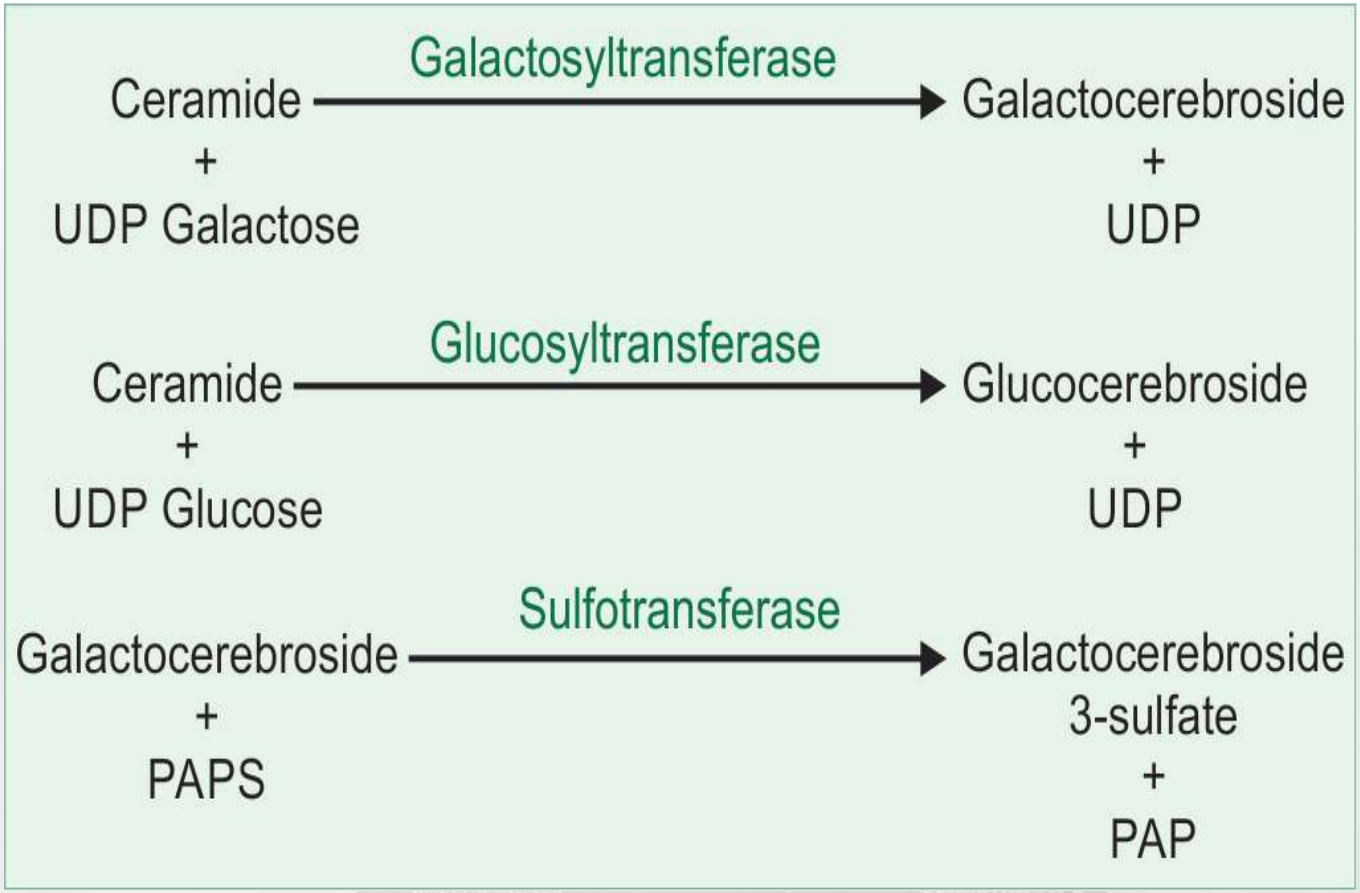
- These carbohydrate containing lipids are synthesized by transfer of an active glycosyl or hexosamine residue from its UDP derivative.



Synthesis of Cerebrosides

- The two most common cerebrosides are glucocerebroside and galactocerebroside.
- *Gaucher's Disease*
- This is an inborn error of metabolism due to failure of degradation of glucocerebrosides.
- The enzyme beta glucosidase is deficient in this condition

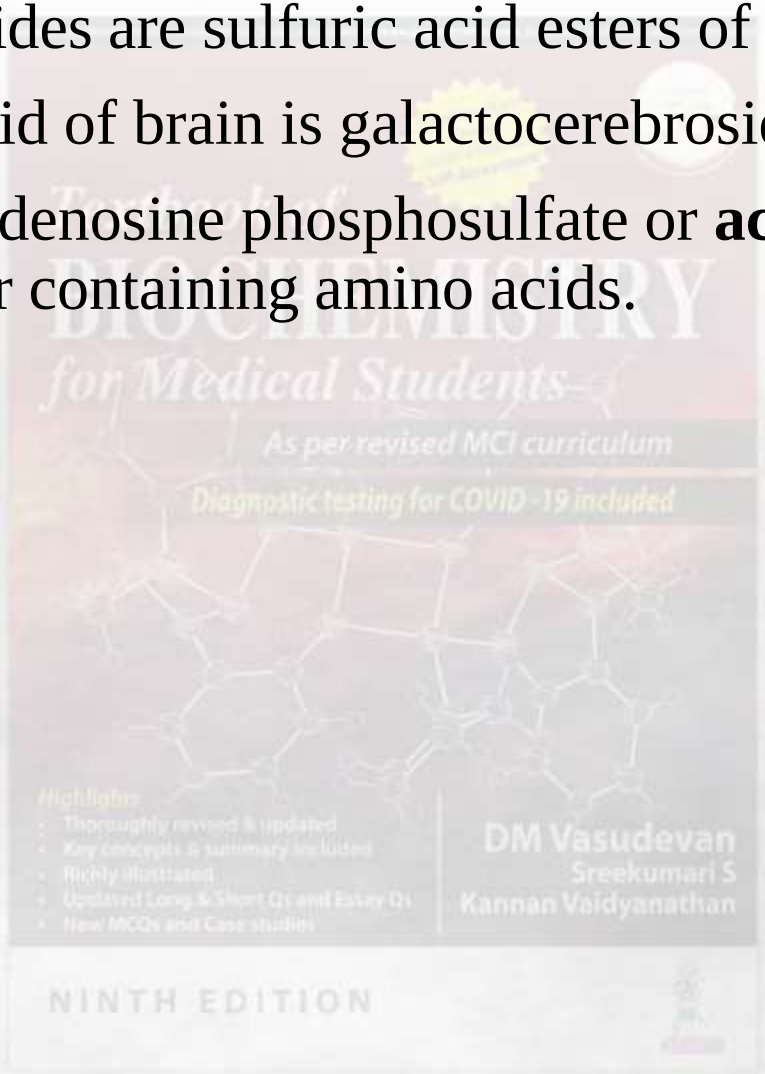




Synthesis of cerebrosides

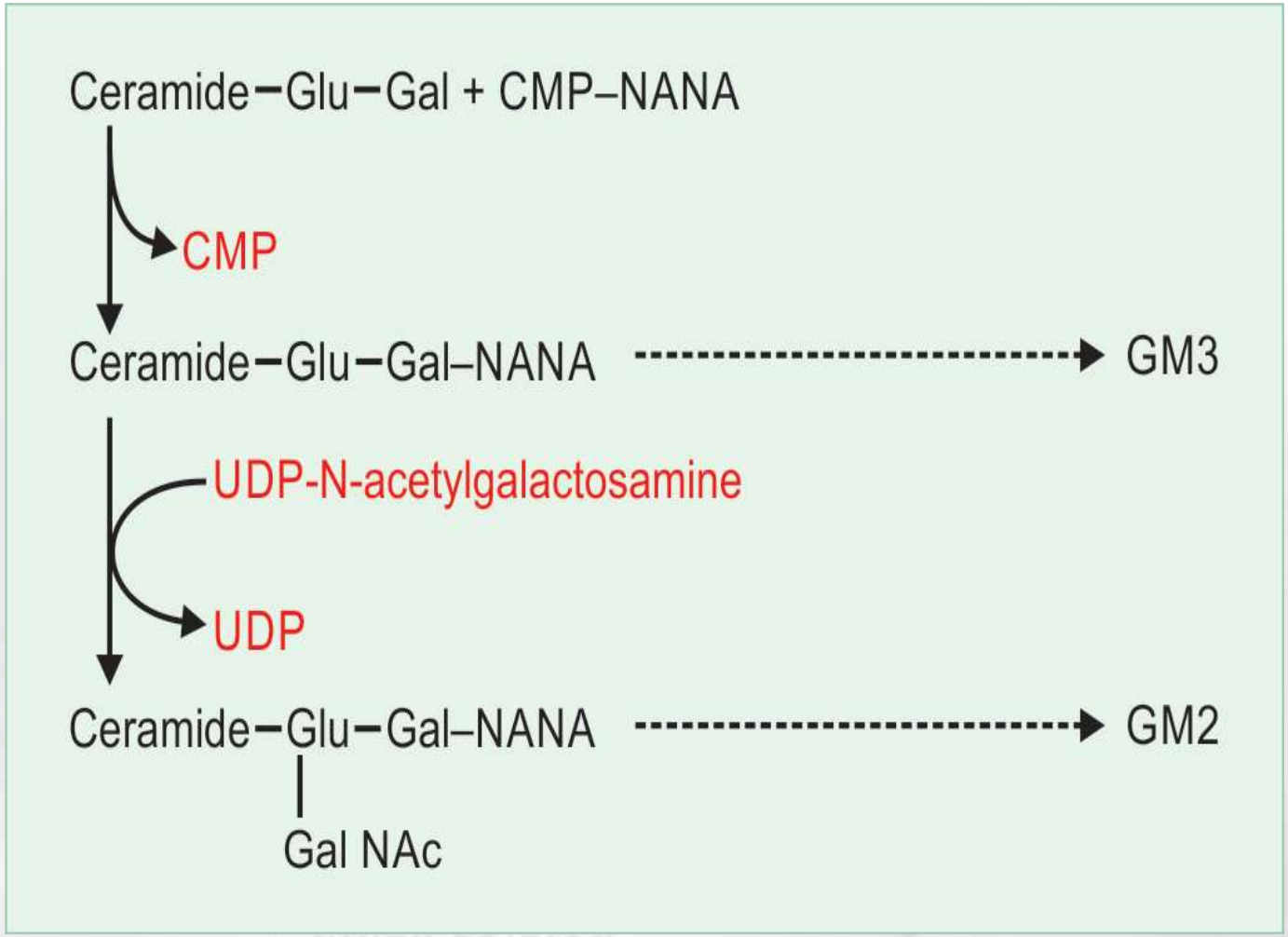
Synthesis of Sulfatides

- Cerebroside sulfatides are sulfuric acid esters of cerebrosides.
- The major sulfolipid of brain is galactocerebroside-3-sulfate.
- **PAPS** is phosphoadenosine phosphosulfate or **active sulfate** formed from sulfur containing amino acids.



Synthesis of Gangliosides

- Gangliosides contain one or more sialic acid residues.
- They are present in high concentrations in the CNS and also on surface of membranes.
- For ganglioside synthesis, the active form of NANA (N-acetyl neuraminic acid) is used.
- **Tay-Sachs Disease**
- This is an inborn error of metabolism due to failure of degradation of gangliosides.
- The enzyme hexosaminidase A is deficient in this condition



Synthesis of gangliosides.

Lipid Storage Diseases (Sphingolipidoses)

- They form a group of lysosomal storage diseases.
- The sphingolipids are normally catabolized by a series of bond specific lysosomal hydrolases like alpha and beta glucosidases, galactosidase, neuraminidase, hexosaminidase and arylsulfatase.
- The diseases result from failure of breakdown of a particular sphingolipid due to deficiency of a single enzyme.
- The children afflicted by these diseases are severely retarded mentally and seldom survive for long.

Sphingolipidoses, continued

- All these diseases can be diagnosed prenatally by amniocentesis and culture of amniotic fluid cells.
- Children have serious mental deficits.
- Replacement of deficient enzyme has been tried in Gaucher's disease, with limited success.
- Rate of synthesis of the lipid is normal, only degradation is affected.
- The extent of the enzyme deficiency is the same in all tissues.

Sphingolipidoses or lipid storage diseases

No	Disease	Enzyme defect	Lipid accumulating	Salient features
1.	Gaucher's disease	Beta glucosidase	Gluco-cerebroside	3 types—adult, infantile, juvenile. Hepatosplenomegaly, erosion of bone, moderate anemia.
2.	Niemann-Pick disease	Sphingo-myelinase	Sphingomyelin	Severe CNS damage, mental retardation, hepatosplenomegaly. Cherry red spot in macula. Death occurs by 2 years of age.

Sphingolipidoses or lipid storage diseases

No	Disease	Enzyme defect	Lipid accumulating	Salient features
3.	Krabbe's leukodystrophy	Beta-galactosidase	Galacto-cerebroside	Severe mental retardation. Total absence of myelin in CNS. Globoid bodies in white matter.
4.	Metachromatic leukodystrophy	Sulfatide sulfatase	Sulfogalacto-cerebroside	Accumulates in most tissues. Neurological deficit, difficulty in speech and optic atrophy. Demyelination is also seen.

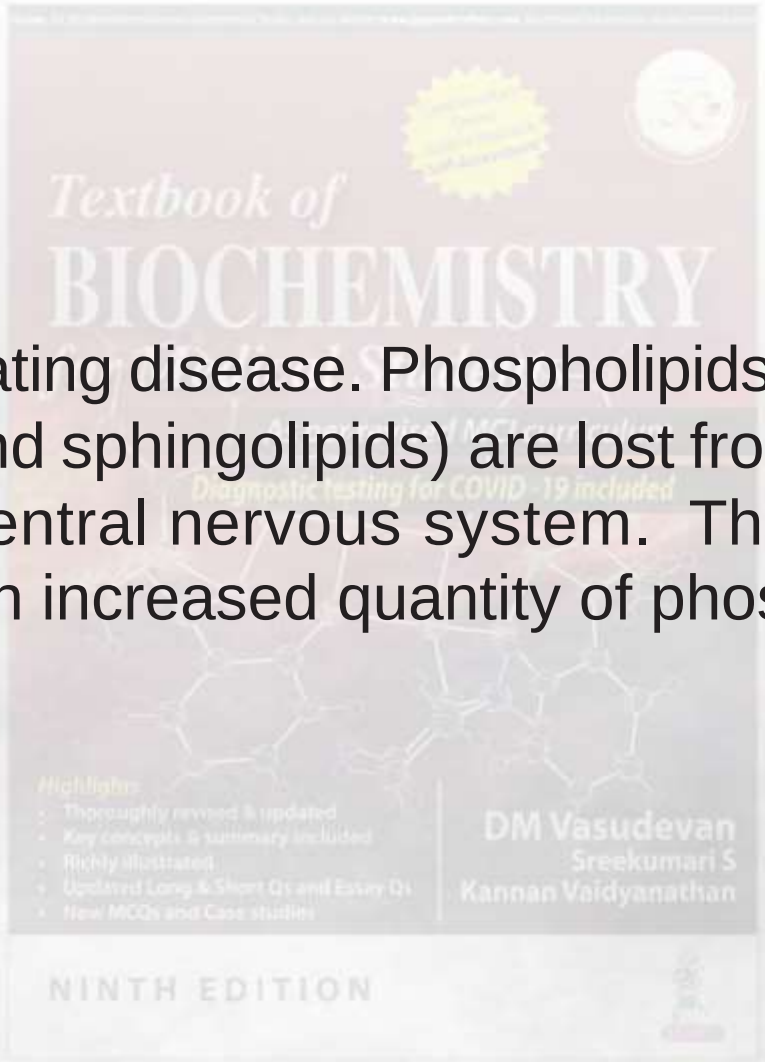
Sphingolipidoses or lipid storage diseases

No	Disease	Enzyme defect	Lipid accumulating	Salient features
5.	Fabry's disease	alpha-galactosidase	Ceramide trihexoside	Kidney is the site of accumulation. Progressive renal failure. Death by 5 years of age. Purplish papules appear. 'X' linked inheritance.
6.	Tay Sachs disease	Hexosaminidase A	Ganglioside (GM2)	Incidence 1 in 6000 births. Mental Retardation. Cherry red spot in the macula. Progressive deterioration. Death by 3-4 years.

Sphingolipidoses or lipid storage diseases

No	Disease	Enzyme defect	Lipid accumulating	Salient features
7.	Generalized gangliosidoses	Beta-galactosidase	Ganglioside (GM1)	Mental retardation, hepatomegaly, skeletal deformities. Foam cells in bone marrow. Cherry red spot in the retina.
8.	Lactosyl ceramidoses	Beta-galactosidase	Lactosyl ceramide	Mainly CNS and reticulo-endothelial system affected.
9.	Sandhoff's disease	Hexosaminidase A and B	Globoside	Neurological deficit, mental retardation.

Multiple Sclerosis



It is a demyelinating disease. Phospholipids (ethanolamine plasmalogen and sphingolipids) are lost from the white matter of the central nervous system. The cerebrospinal fluid contains an increased quantity of phospholipids.