Metabolism of lipids VI:

Sphingolipids

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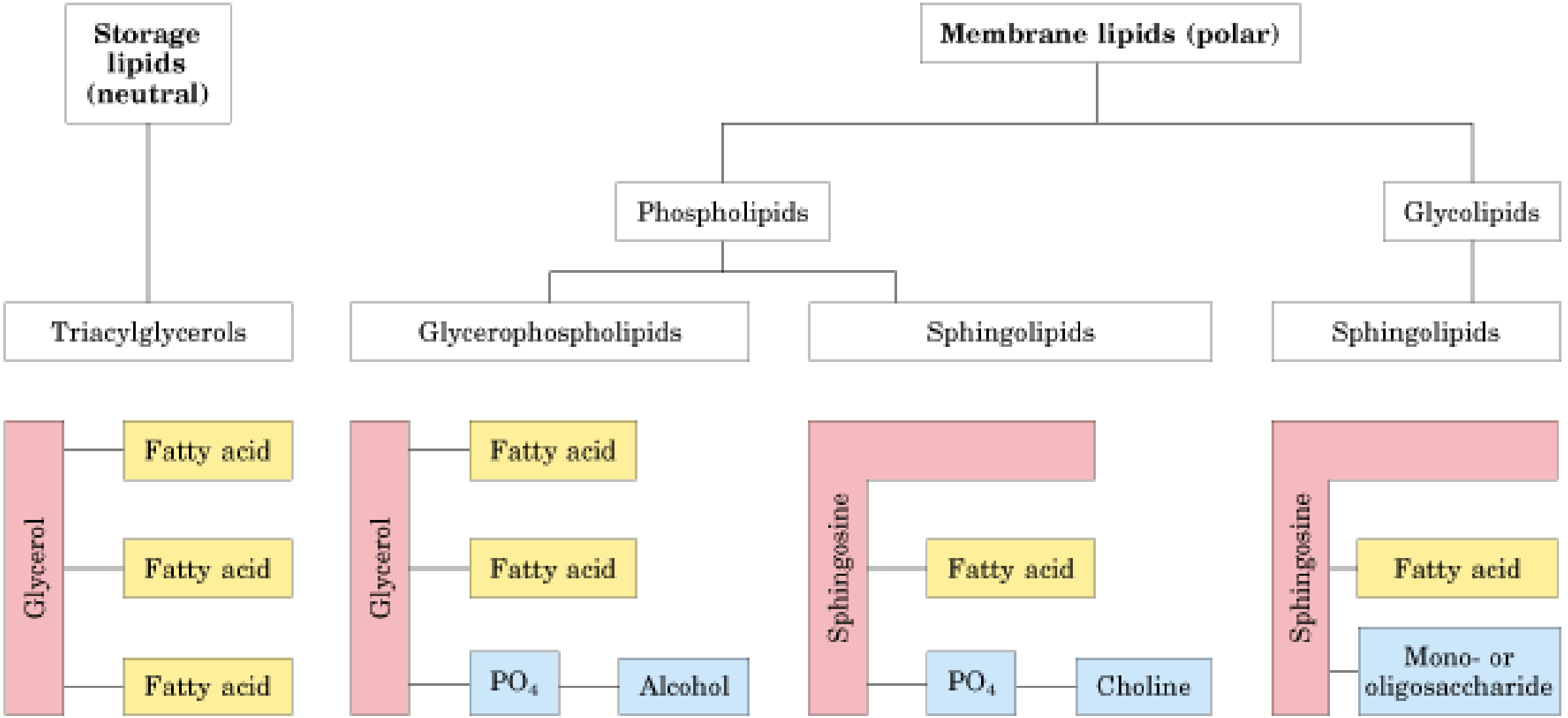
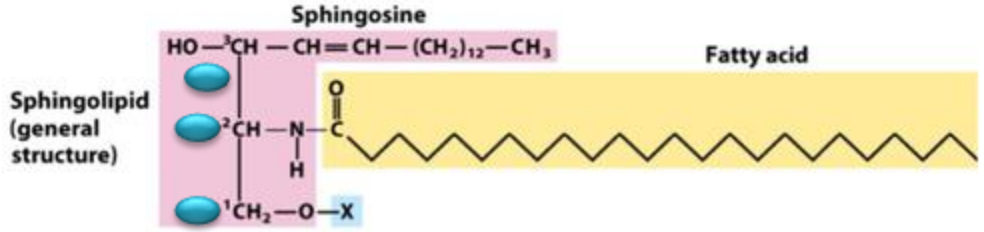
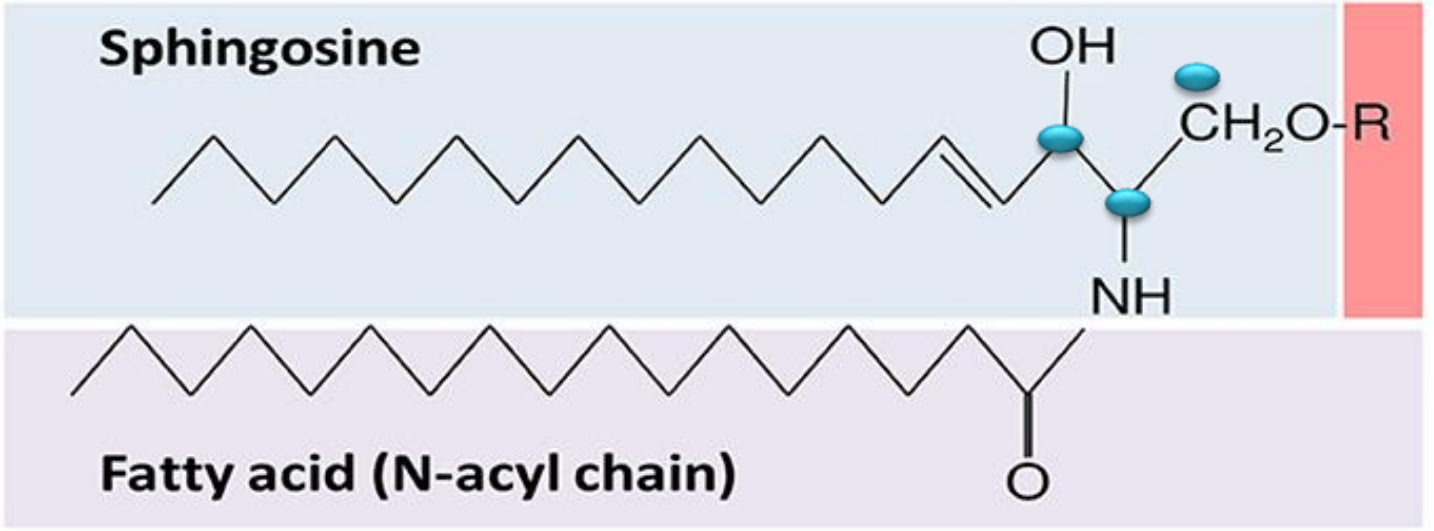
Resources

- This lecture
- Lippincott's Biochemistry, Ch. 17


Storage lipids (neutral)
Membrane lipids (polar)
Phospholipids
Glycolipids
Triacylglycerols
Glycerophospholipids
Sphingolipids
Sphingolipids
Glycerol
Fatty acid
Fatty acid
Fatty acid
Glycerol
Fatty acid
Fatty acid
PO_4
Alcohol
Sphingosine
Fatty acid
PO_4
Choline
Sphingosine
Fatty acid
Mono- or oligosaccharide

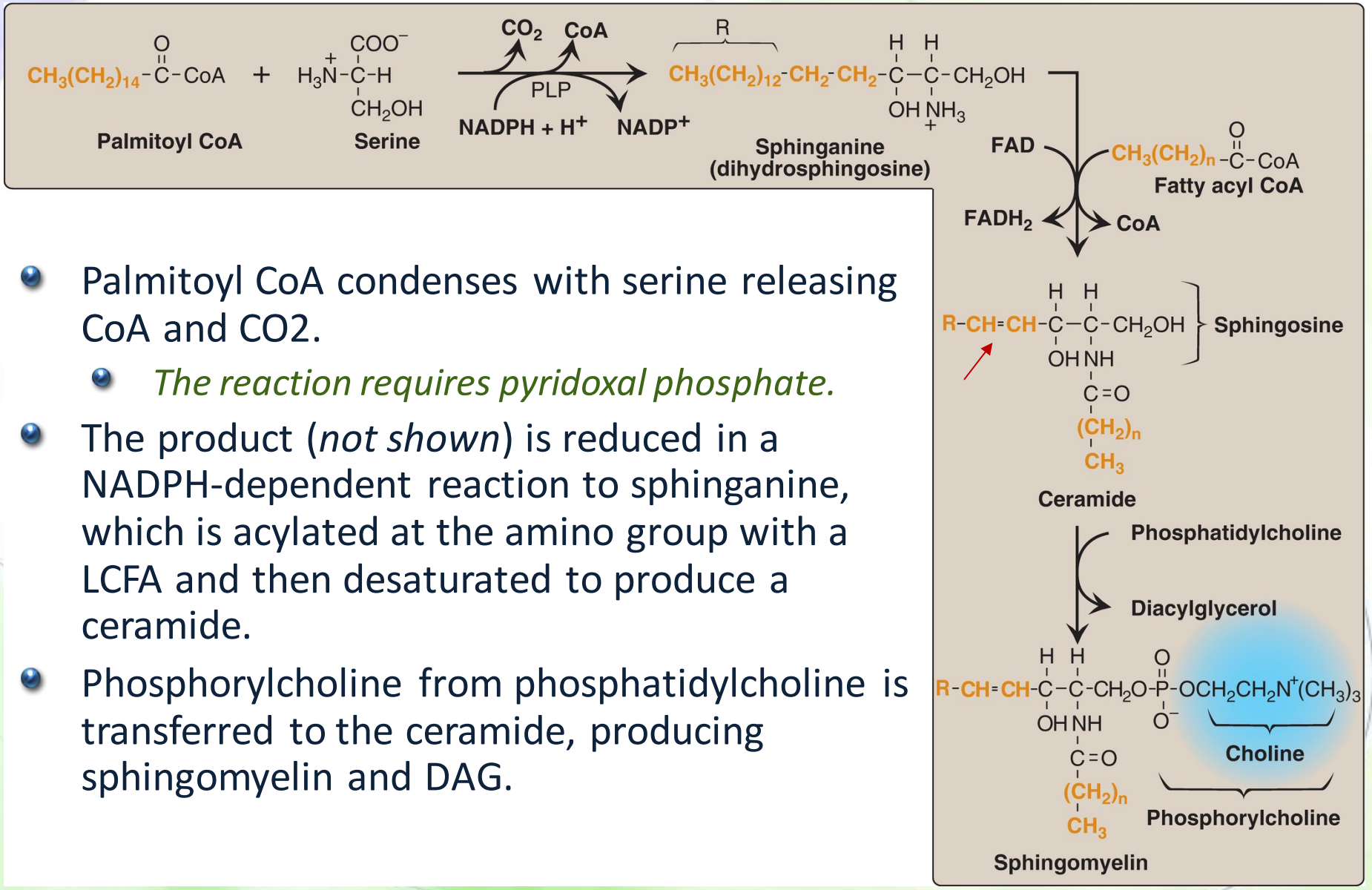
Structure of sphingolipids





Substituent (R)	Sphingolipid
H	Ceramides
Phosphocholine	Sphingomyelins
Sugar (s) - Single sugar (glucose or galactose) - Lactose (disaccharide) - Oligosaccharide - Sugar + sulfate	Glycosphingolipids - Cerebrosides - Lactosylceramides - Gangliosides - Sulfatides

Synthesis of sphingomyelin

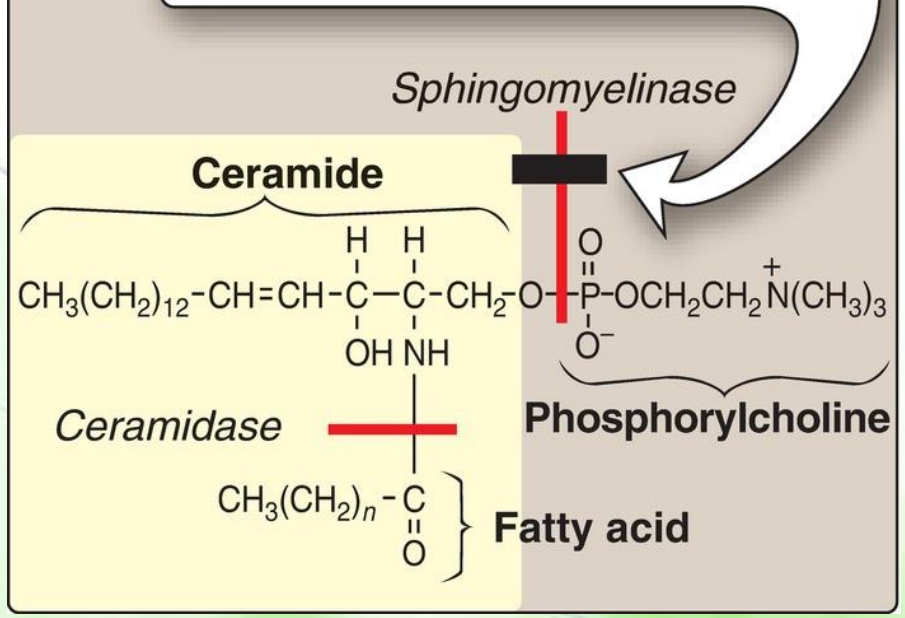


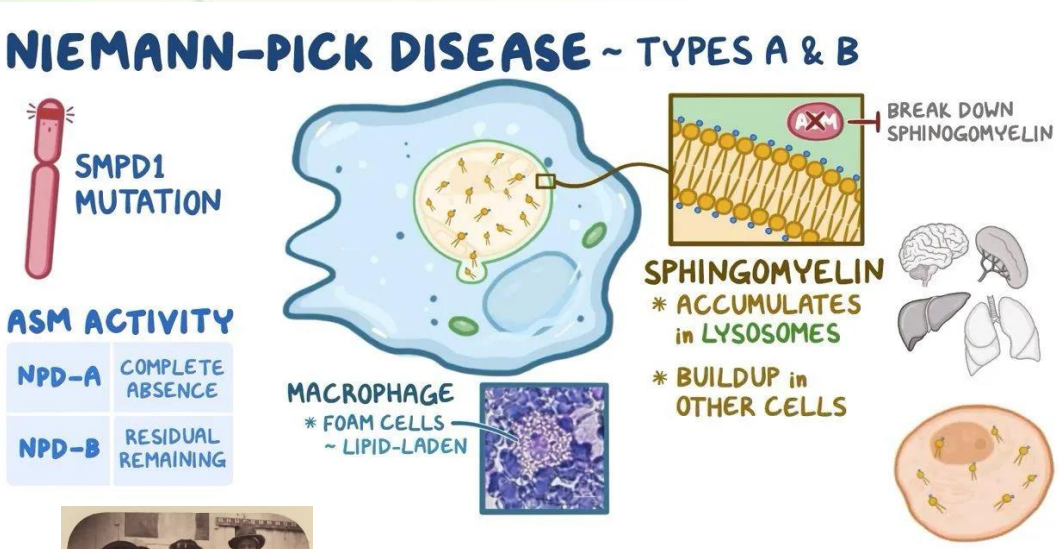
- Palmitoyl CoA condenses with serine releasing CoA and CO2.
  - *The reaction requires pyridoxal phosphate.*
- The product (*not shown*) is reduced in a NADPH-dependent reaction to sphinganine, which is acylated at the amino group with a LCFA and then desaturated to produce a ceramide.
- Phosphorylcholine from phosphatidylcholine is transferred to the ceramide, producing sphingomyelin and DAG.

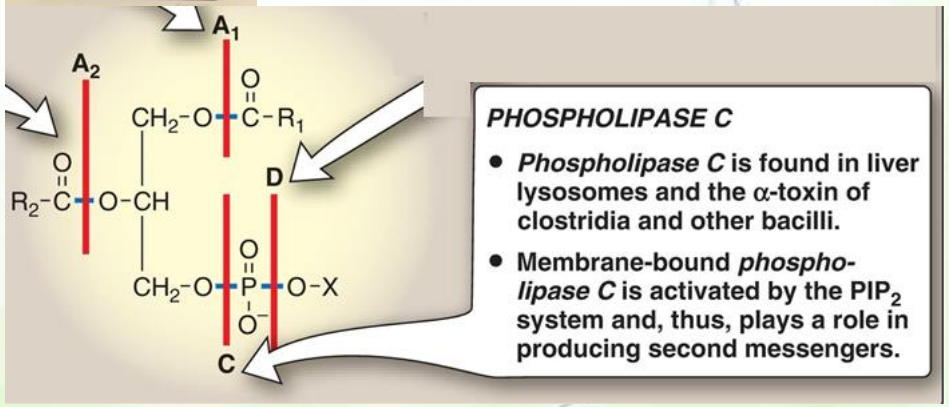
Deficiency of sphingomyelinase

NIEMANN-PICK DISEASE

- *Sphingomyelinase* deficiency
- Enlarged liver and spleen filled with lipid
- Severe intellectual disability and neurodegeneration (type A)
- Death in early childhood (type A)

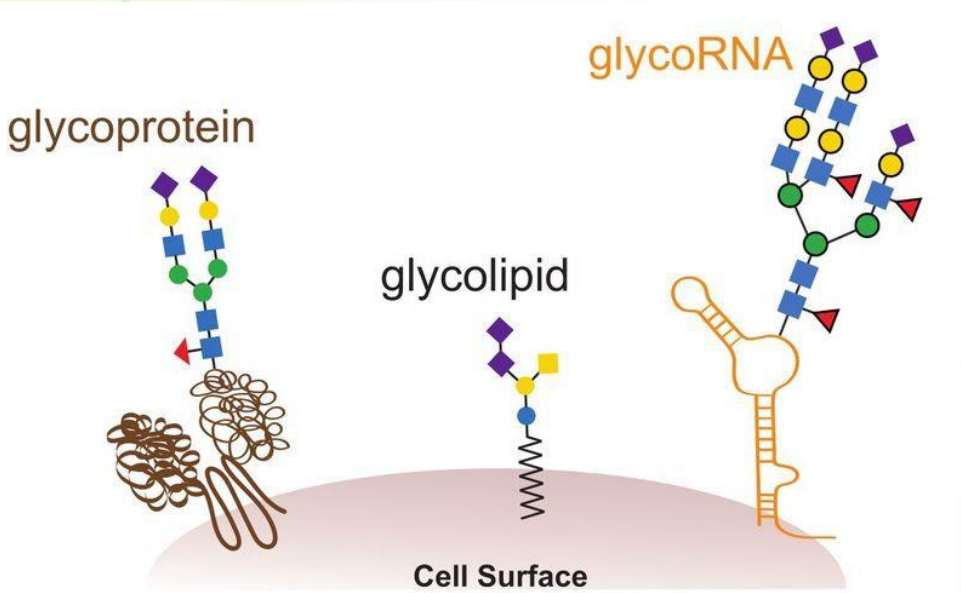


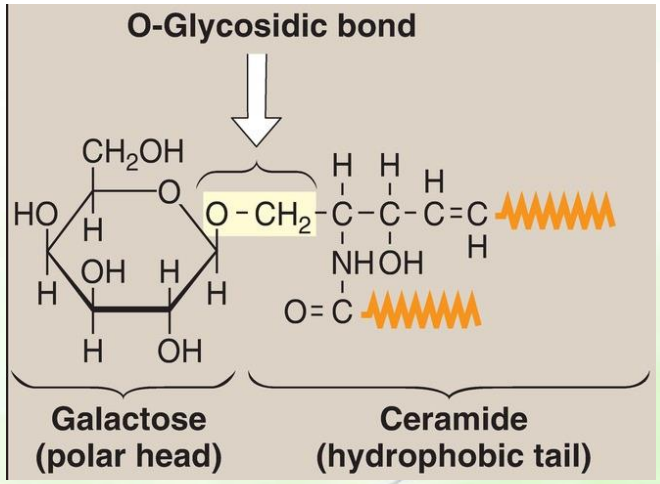




Glycosphingolipids (glycolipids)

- They are made of ceramide (precursor).
- They are localized in the outer leaflet of the plasma membrane (adhesion, recognition, and signaling).
- A sugar(s) is attached to ceramide by an O-glycosidic bond.
- The number and type of carbohydrate moieties present determine the type of glycosphingolipid.

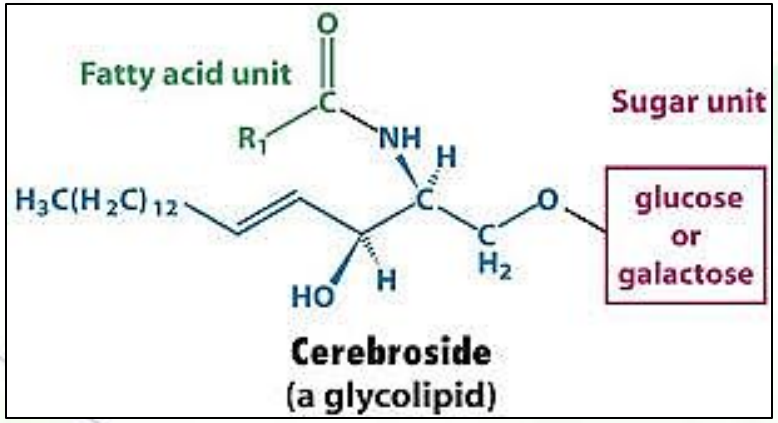




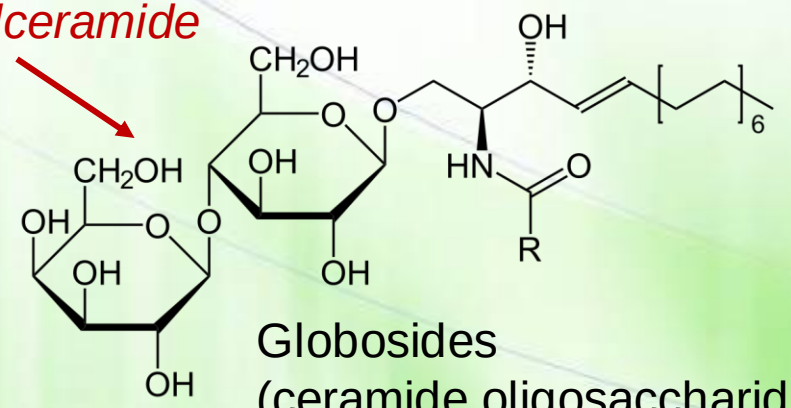
Types of glycolipids

Neutral glycosphingolipids

- Cerebrosides are the simplest.



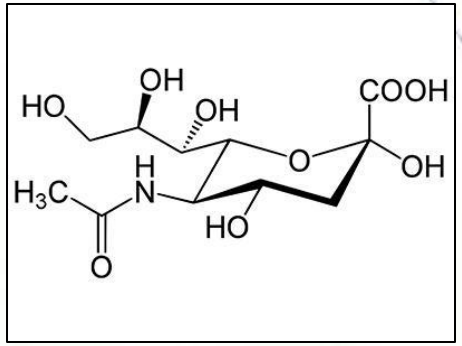
Lactosylceramide

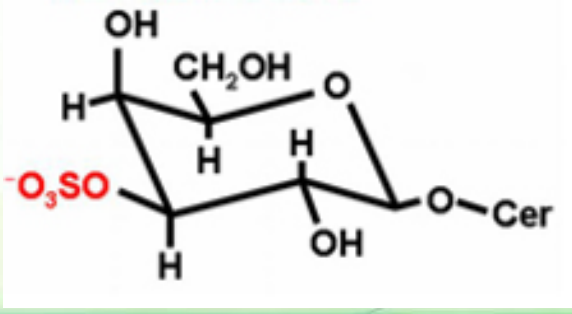


Globosides
(ceramide oligosaccharides)

Acidic glycosphingolipids

- They are negatively charged at physiologic pH due to attachment of N-acetylneuraminic acid ([NANA], a sialic acid, in gangliosides or by sulfate groups in sulfatides.

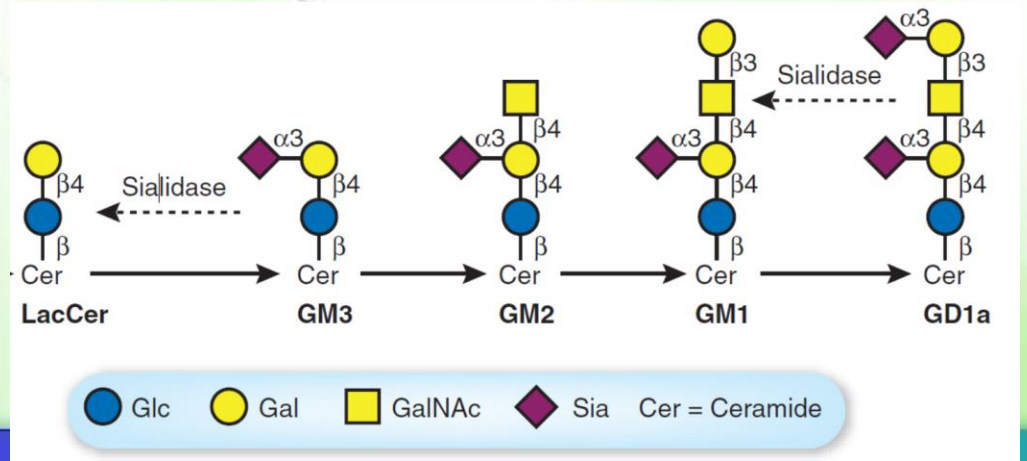




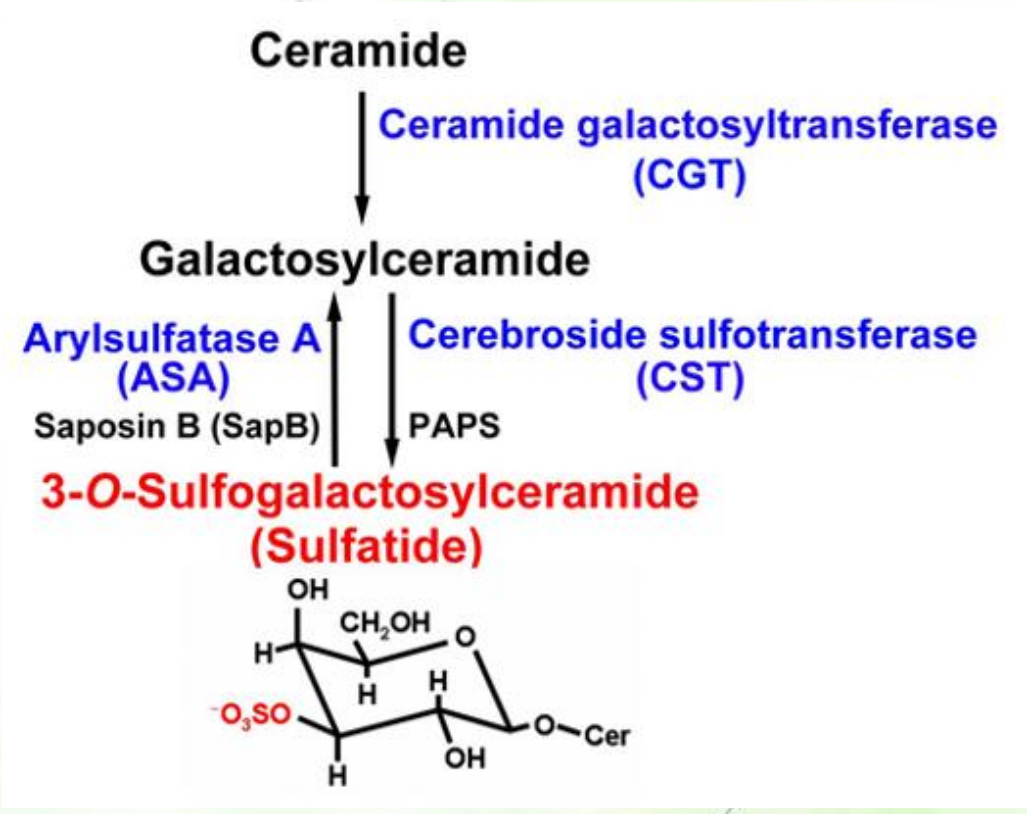
More on gangliosides and sulfatides

Gangliosides

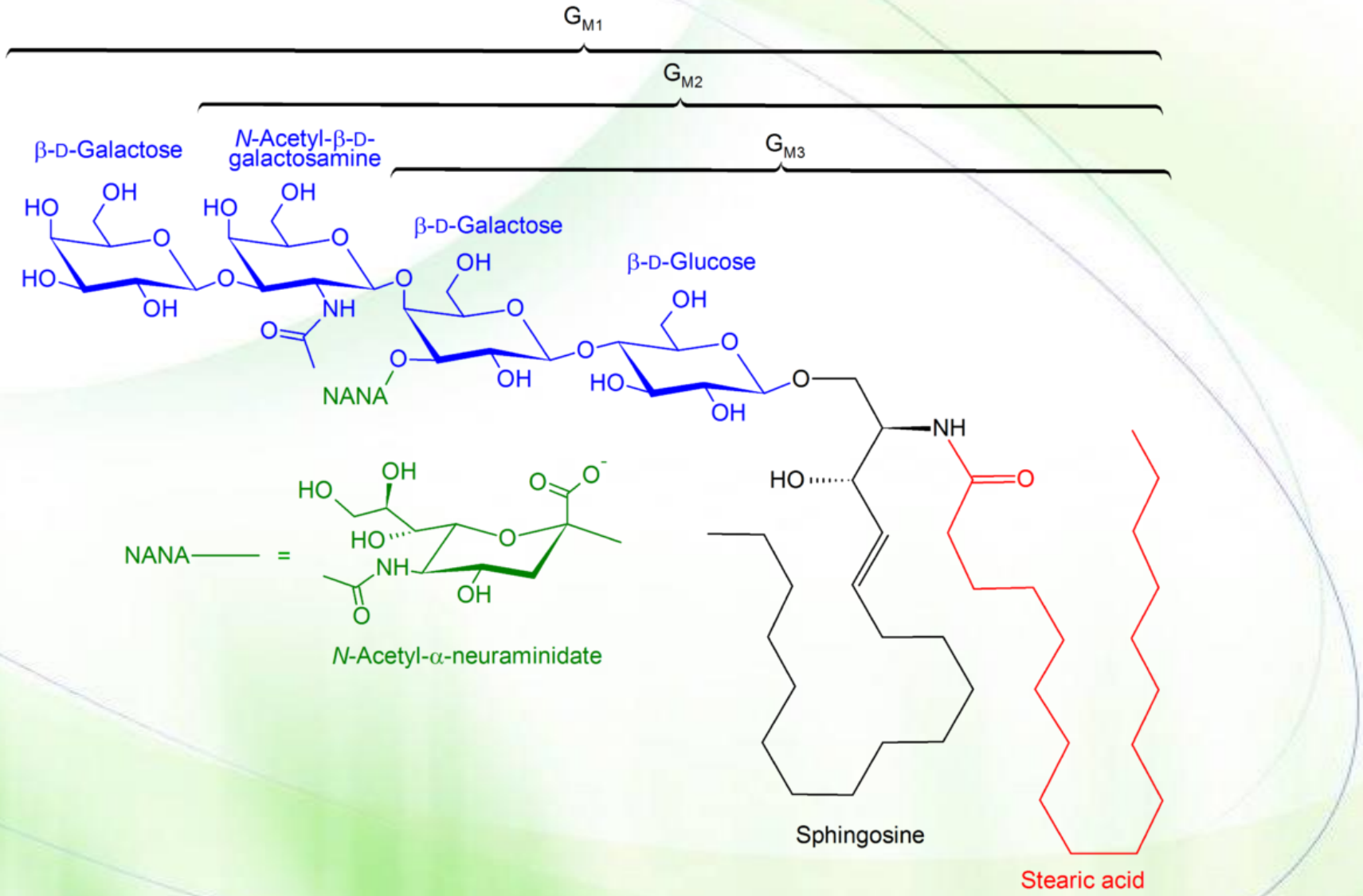
- They are designated as G (for ganglioside) plus a subscript (M, D, T, or Q) to indicate number of sialic acid molecules: 1 (mono), 2 (di), 3 (tri), or 4 (quatro), and then numbers to indicate **indirectly** the number of sugar residues subtracted from 5:
  - GM1 contains 5–1 = 4 sugar residues
  - GD3 contains 5–3 = 2 sugar residues



Sulfatides

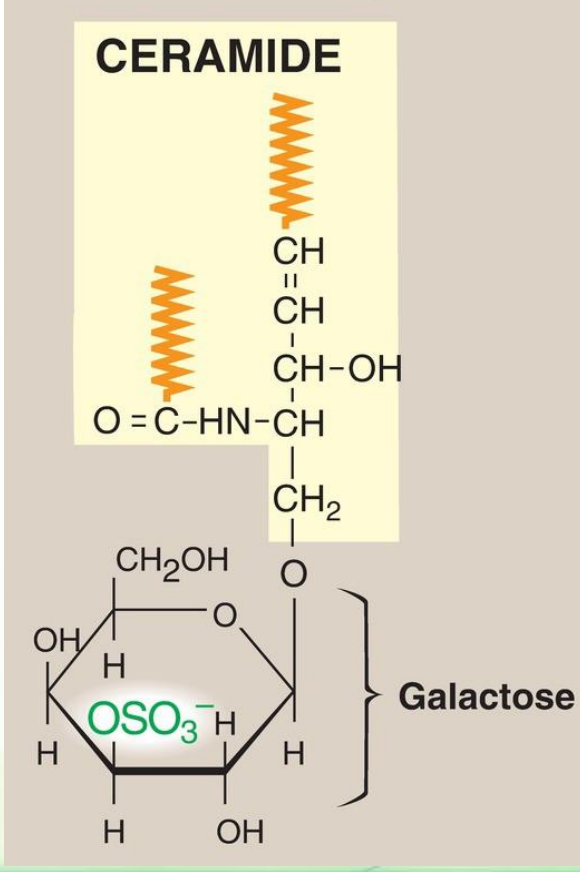


An example

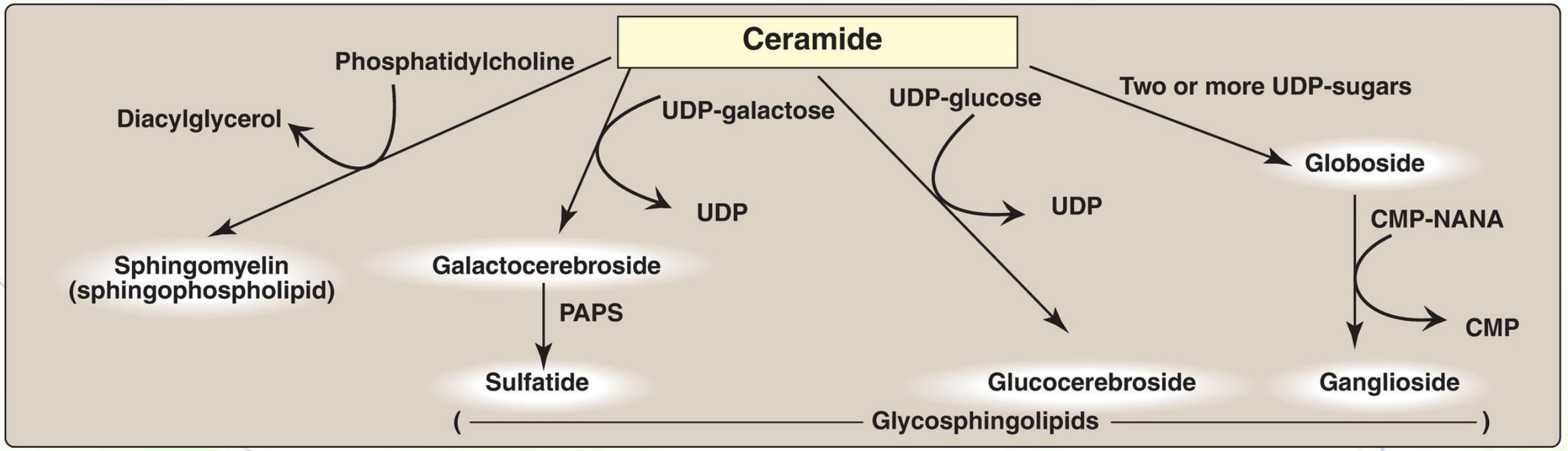

G_M1
G_M2
G_M3
β-D-Galactose
N-Acetyl-β-D-galactosamine
β-D-Galactose
β-D-Glucose
NANA
NANA —— =
N-Acetyl-α-neuraminidate
Sphingosine
Stearic acid

Synthesis of glycosphingolipids I

- Synthesis of glycosphingolipids occurs primarily in the Golgi apparatus by sequential addition of glycosyl monomers transferred from UDP-sugars to the acceptor molecule by glycosyltransferases.
- A sulfate group from the sulfate carrier 3′-phosphoadenosine-5′-phosphosulfate ([PAPS], is added by a sulfotransferase to the 3′-hydroxyl group of the galactose in a galactocerebroside, forming the sulfatide galactocerebroside 3-sulfate.

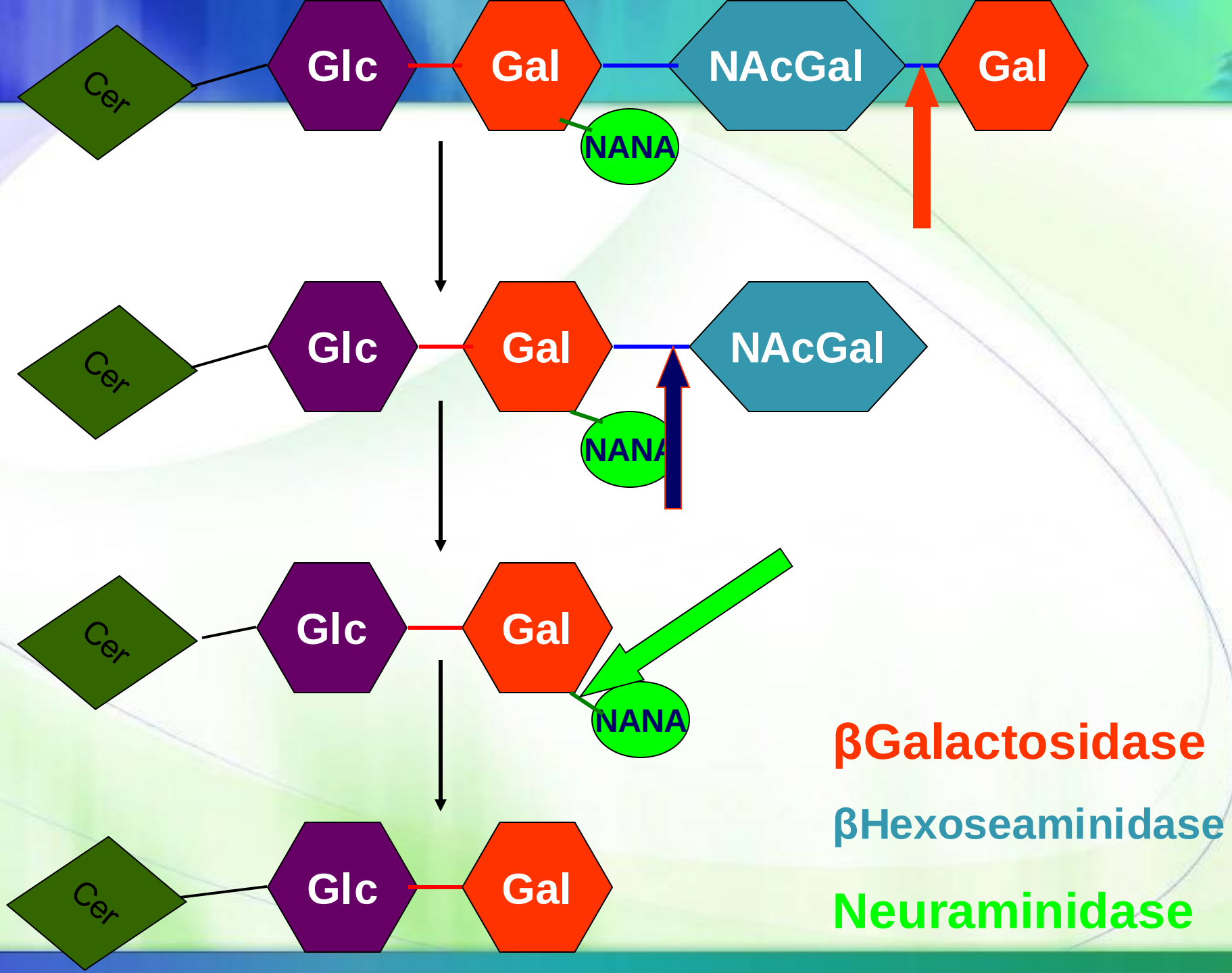


Synthesis of glycosphingolipids II



Glycosphingolipid degradation

- Glycosphingolipids are internalized by phagocytosis into the lysosomes that fuse with the phagosomes.
- The lysosomal enzymes hydrolytically and irreversibly remove the sugars sequentially starting with the last one added and ending with the first one added.
- Defect in the degradation of glycosphingolipid, as well as glycosaminoglycans and glycoproteins, causes “lysosomal storage diseases”.
  - Sphingolipidoses: disorders related to defective degradation of sphingolipids



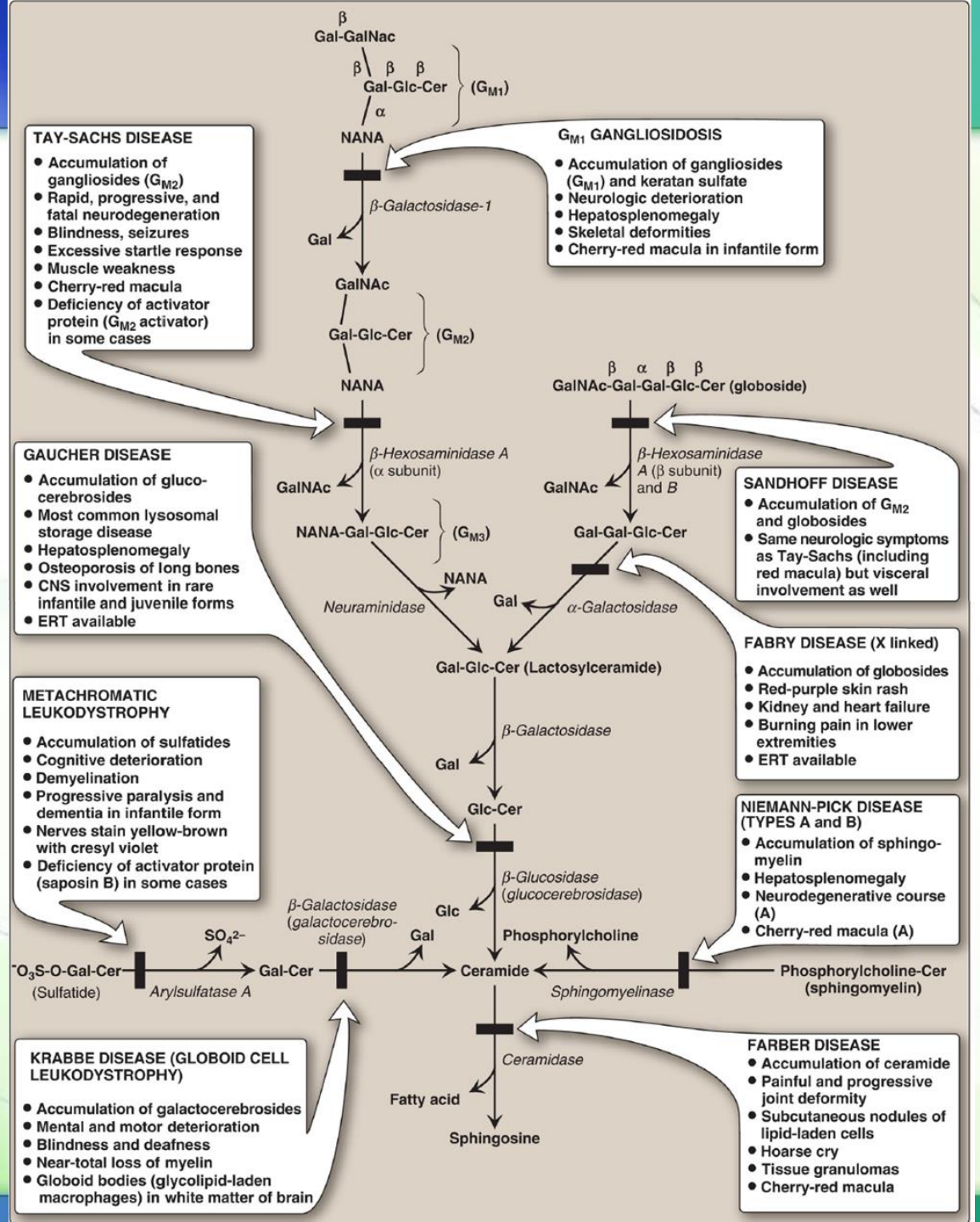
βGalactosidase

βHexoseaminidase

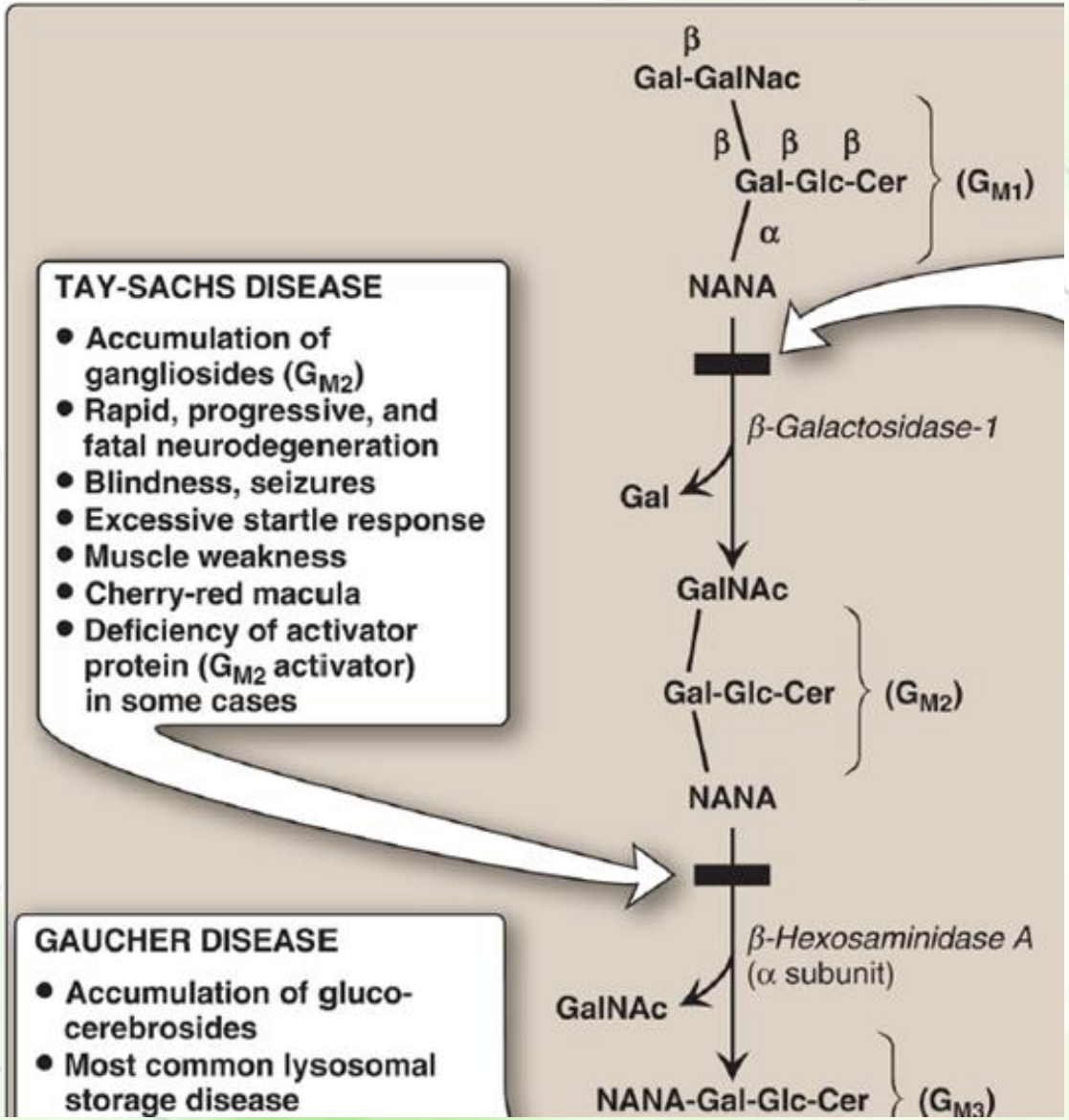
Neuraminidase

Sphingolipidoses

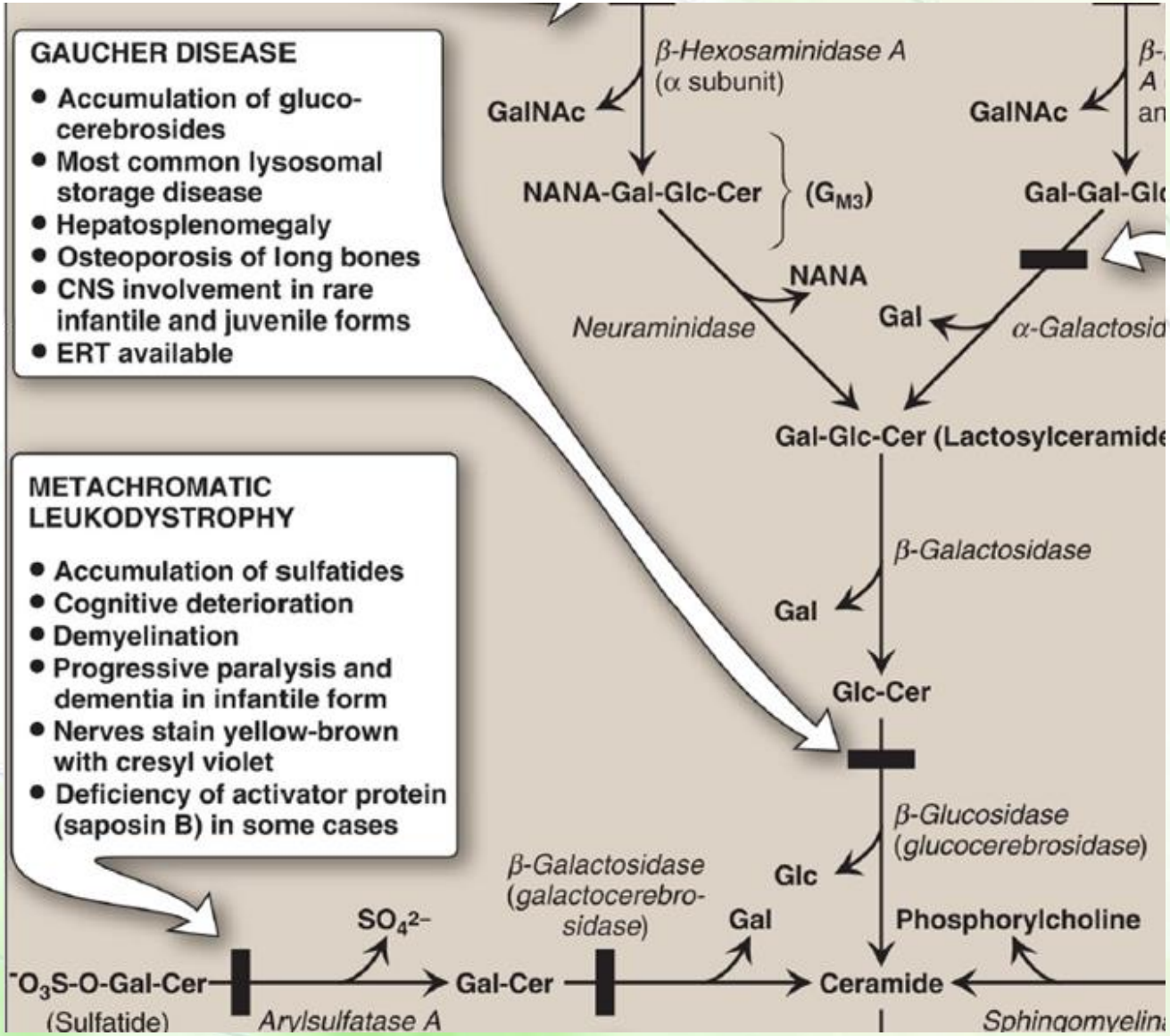
- The rate of biosynthesis of the accumulating lipid is normal.
- Usually, only a single sphingolipid (the substrate for the deficient enzyme) accumulates in the involved organs.
- The disorders are progressive and can be fatal.
- There is extensive phenotypic variability due to:
  - Allele heterogeneity: The defective gene that causes the disorder (the clinical type)
  - Locus heterogeneity: the type of mutation within the gene that produces the defective enzyme.
- They are autosomal-recessive disorders, except for Fabry disease, which is X linked.
- The incidence of the sphingolipidoses is low in most populations, except for Gaucher and Tay-Sachs diseases, which, like Niemann-Pick disease, show a high frequency in the Ashkenazi Jewish population.


β
Gal-GalNac
β β β
Gal-Glc-Cer
(GM1)
α
NANA
TAY-SACHS DISEASE
• Accumulation of gangliosides (GM2)
• Rapid, progressive, and fatal neurodegeneration
• Blindness, seizures
• Excessive startle response
• Muscle weakness
• Cherry-red macula
• Deficiency of activator protein (GM2 activator) in some cases
GM1 GANGLIOSIDOSIS
• Accumulation of gangliosides (GM1) and keratan sulfate
• Neurologic deterioration
• Hepatosplenomegaly
• Skeletal deformities
• Cherry-red macula in infantile form
β-Galactosidase-1
Gal
GalNAc
Gal-Glc-Cer
(GM2)
NANA
β α β β
GalNAc-Gal-Gal-Glc-Cer (globoside)
β-Hexosaminidase A
(α subunit)
GalNAc
β-Hexosaminidase A (β subunit) and B
GalNAc
GAUCHER DISEASE
• Accumulation of gluco-cerebrosides
• Most common lysosomal storage disease
• Hepatosplenomegaly
• Osteoporosis of long bones
• CNS involvement in rare infantile and juvenile forms
• ERT available
SANDHOFF DISEASE
• Accumulation of GM2 and globosides
• Same neurologic symptoms as Tay-Sachs (including red macula) but visceral involvement as well
NANA-Gal-Glc-Cer
(GM3)
Gal-Gal-Glc-Cer
NANA
Neuraminidase
Gal
α-Galactosidase
Gal-Glc-Cer (Lactosylceramide)
FABRY DISEASE (X linked)
• Accumulation of globosides
• Red-purple skin rash
• Kidney and heart failure
• Burning pain in lower extremities
• ERT available
METACHROMATIC LEUKODYSTROPHY
• Accumulation of sulfatides
• Cognitive deterioration
• Demyelination
• Progressive paralysis and dementia in infantile form
• Nerves stain yellow-brown with cresyl violet
• Deficiency of activator protein (saposin B) in some cases
β-Galactosidase
Gal
Glc-Cer
β-Glucosidase (glucocerebrosidase)
Glc
β-Galactosidase (galactocerebro-sidase)
Gal
Phosphorylcholine
NIEMANN-PICK DISEASE (TYPES A and B)
• Accumulation of sphingo-myelin
• Hepatosplenomegaly
• Neurodegenerative course (A)
• Cherry-red macula (A)
SO_4^{2-}
^-O_3S-O-Gal-Cer
(Sulfatide)
Arylsulfatase A
Gal-Cer
Ceramide
Sphingomyelinase
Phosphorylcholine-Cer
(sphingomyelin)
KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)
• Accumulation of galactocerebrosides
• Mental and motor deterioration
• Blindness and deafness
• Near-total loss of myelin
• Globoid bodies (glycolipid-laden macrophages) in white matter of brain
Ceramidase
Fatty acid
Sphingosine
FARBER DISEASE
• Accumulation of ceramide
• Painful and progressive joint deformity
• Subcutaneous nodules of lipid-laden cells
• Hoarse cry
• Tissue granulomas
• Cherry-red macula

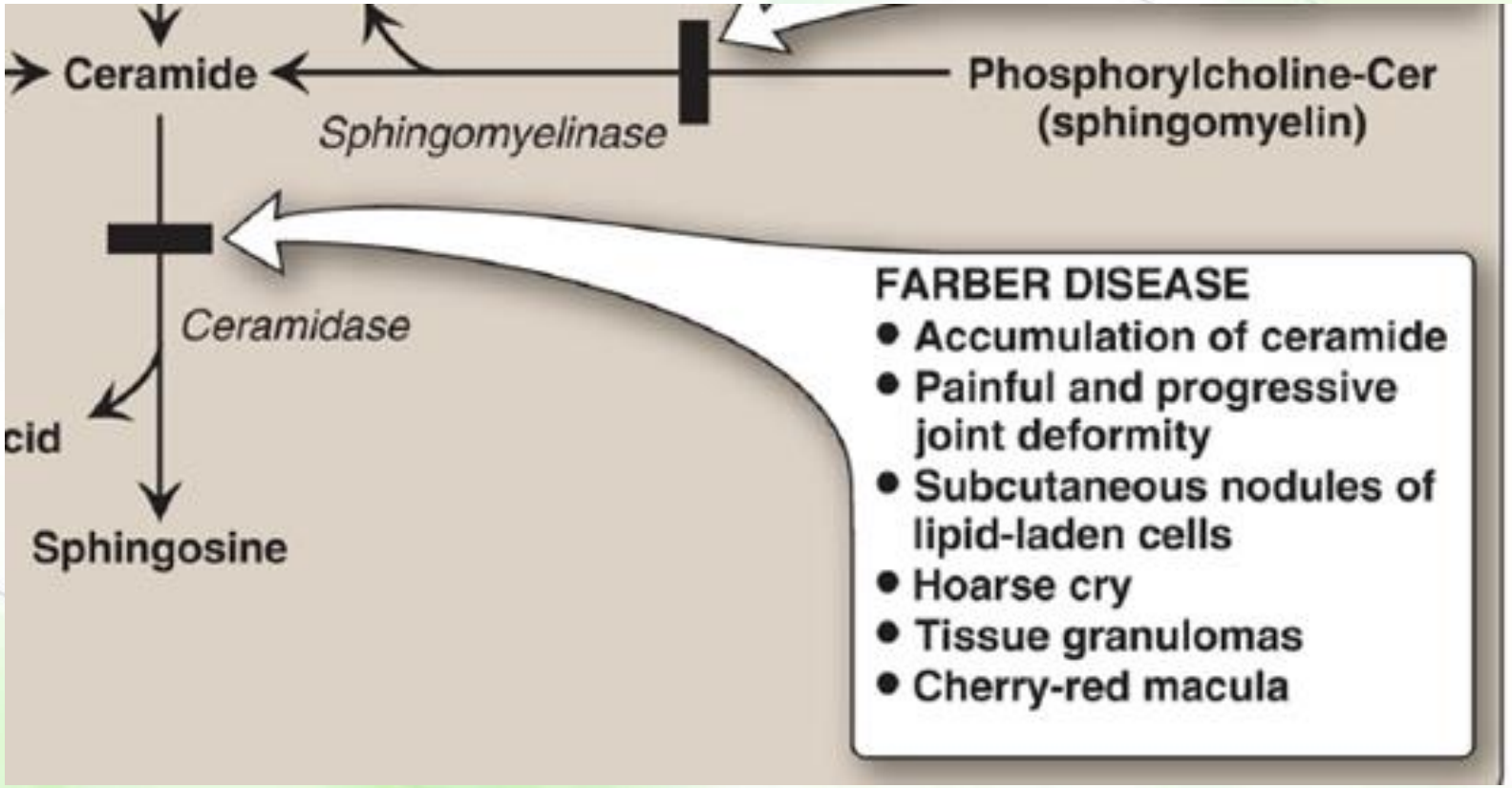
Tay-Sachs disease



Gaucher disease



Farber disease



Diagnosis and treatment

- Diagnosis:
  - Measure enzyme activity in cultured fibroblasts or peripheral leukocytes
  - Analyzing DNA
- Treatment:
  - Recombinant human enzyme replacement therapy
    - Gaucher disease and Fabry disease (expensive)
  - Bone marrow transplantation:
    - Gaucher disease
- Substrate reduction therapy
  - Gaucher disease: Pharmacologic reduction of glucosylceramide