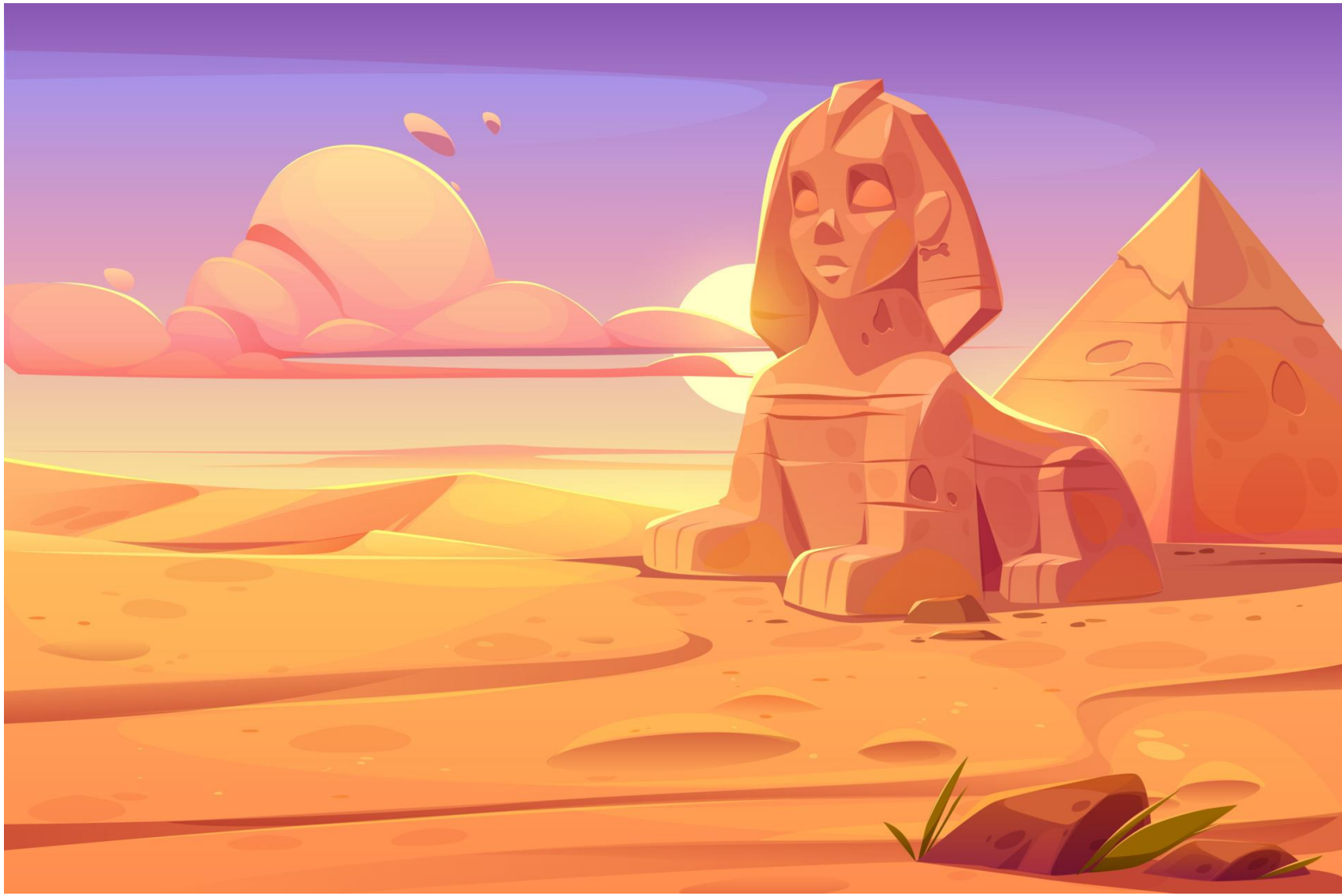
# Metabolism of Sphingolipids



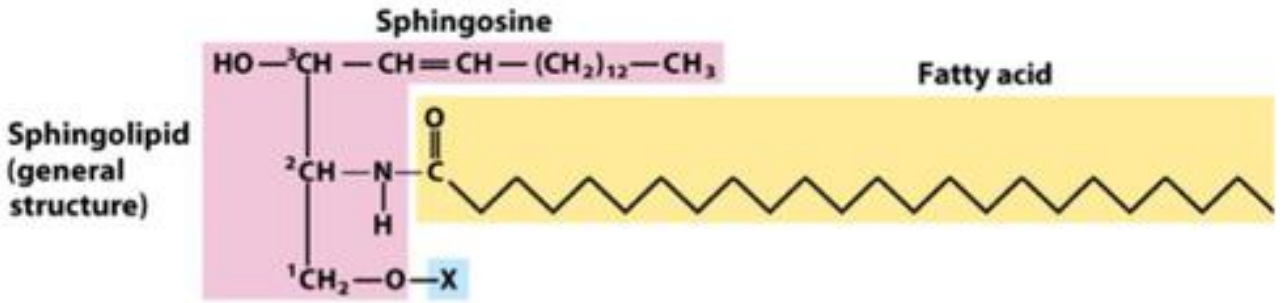
Dr. Diala Abu-Hassan

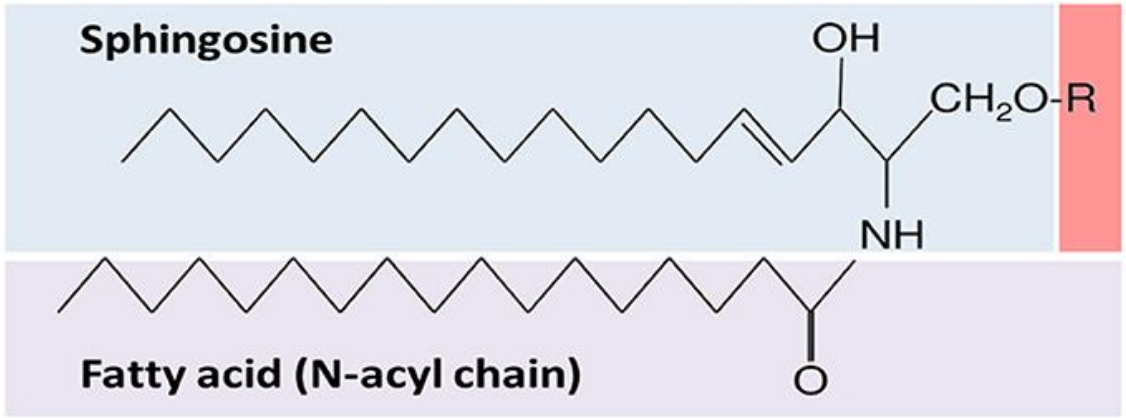
Lippincott's Biochemistry, Ch. 17

# Structure of sphingolipids

Sphingomyelin

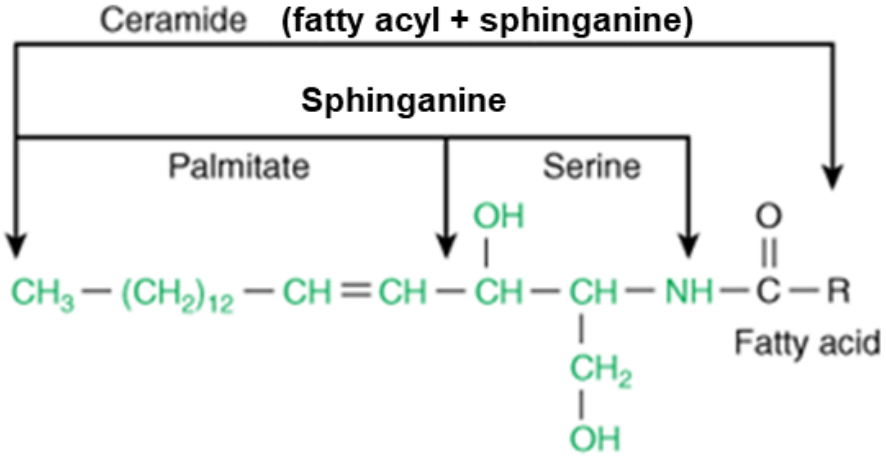
Glycolipids

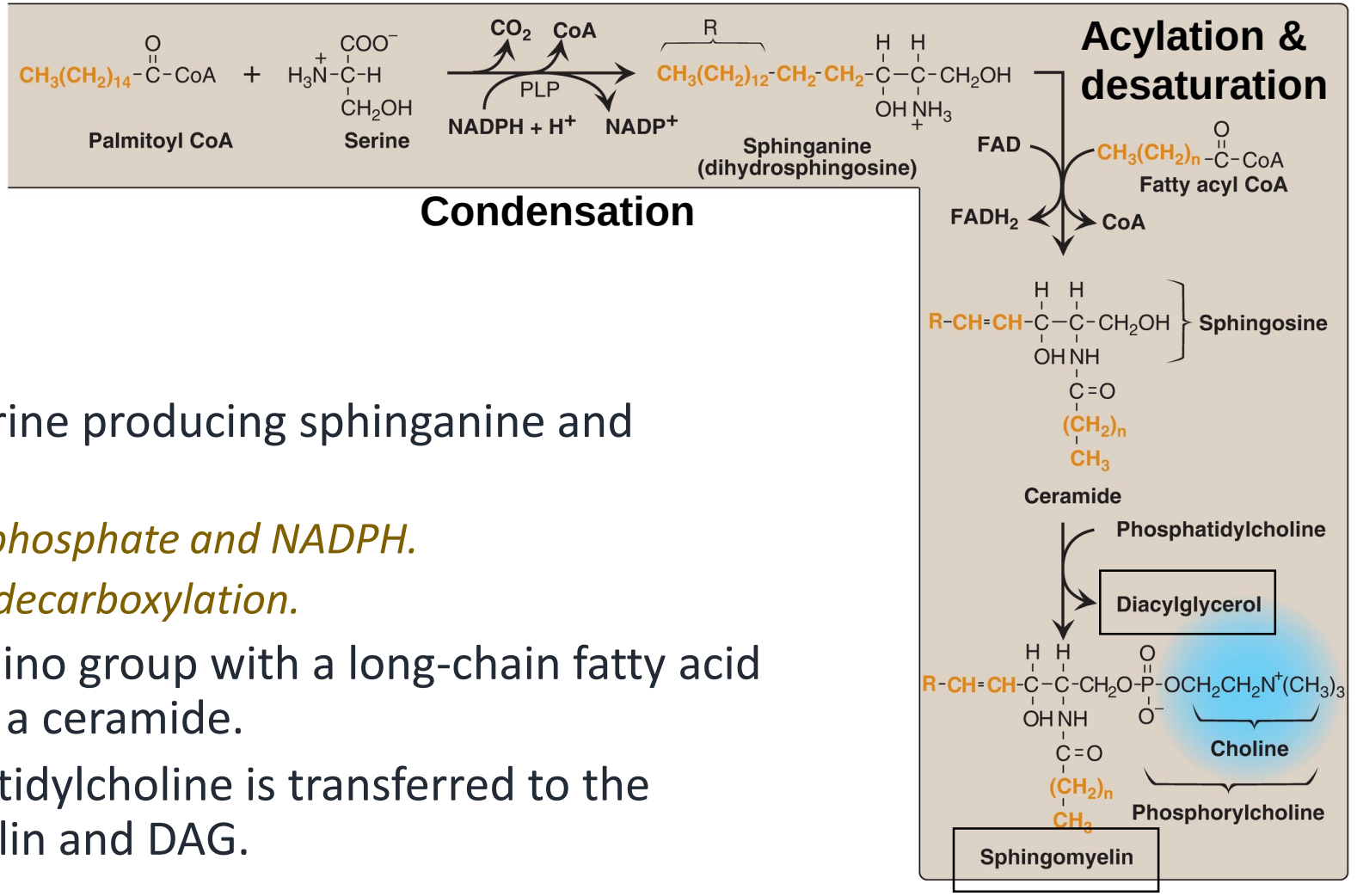



| Substituent (R) | Sphingolipid |
|---|---|
| H | Ceramides |
| Phosphocholine | Sphingomyelins |
| Sugar (s)<br>- Single sugar (glucose or galactose)<br>- Lactose (disaccharide)<br>- Oligosaccharide<br>- Sugar + sulfate | Glycosphingolipids<br>- Cerebrosides<br>- Lactosylceramides<br>- Gangliosides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

# Synthesis of sphingomyelin

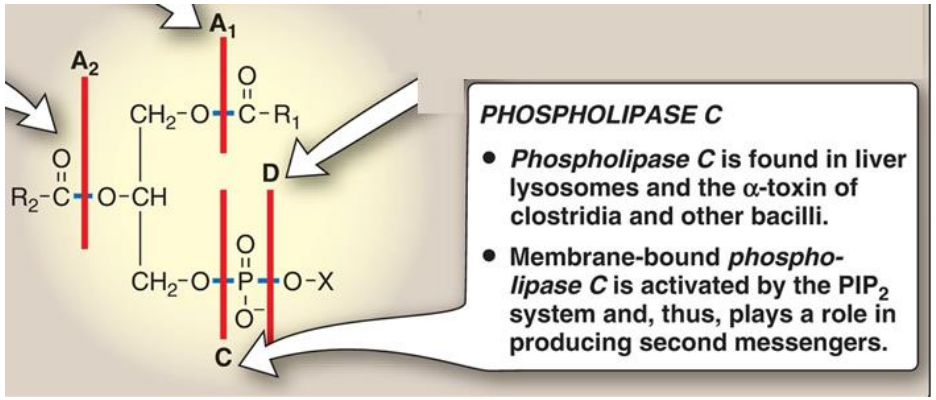


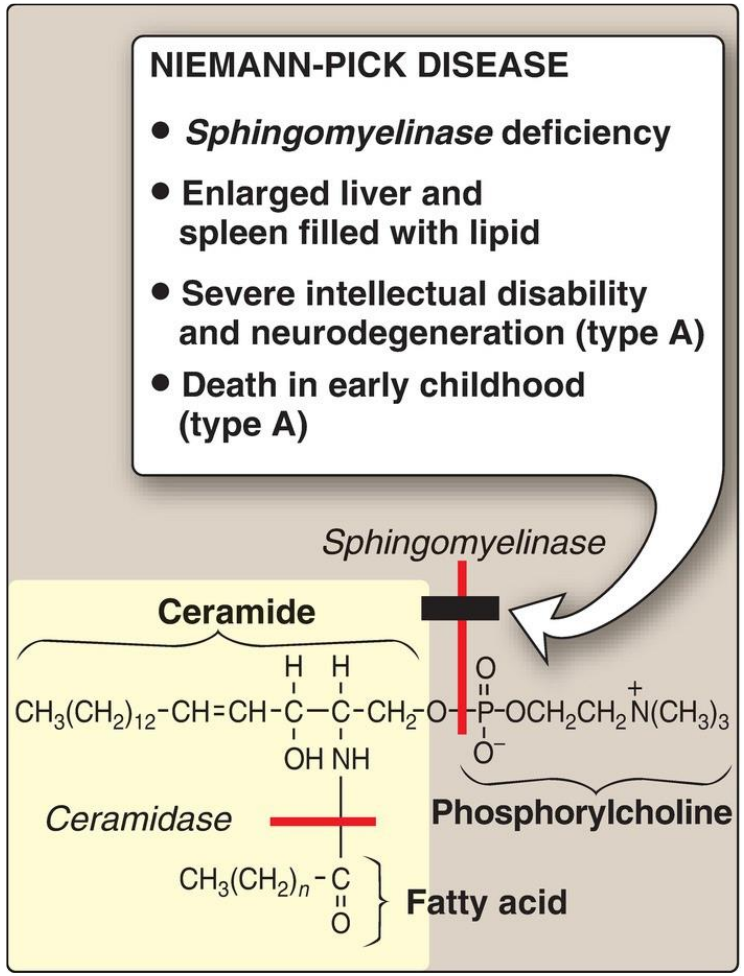




- Palmitoyl CoA condenses with serine producing sphinganine and releasing CoA and $CO_2$.
  - *The reaction requires pyridoxal phosphate and NADPH.*
  - *The needed energy comes from decarboxylation.*
- Sphinganine is acylated at the amino group with a long-chain fatty acid and then desaturated to produce a ceramide.
- Phosphorylcholine from phosphatidylcholine is transferred to the ceramide, producing sphingomyelin and DAG.

# Degradation of sphingomyelin and the deficiency of sphingomyelinase

- ✓ Sphingomyelin is degraded by sphingomyelinase, a lysosomal enzyme and a type of phospholipase C
- ✓ The ceramide is cleaved by ceramidase into sphingosine and a free fatty acid
- ✓ The ceramide and sphingosine released regulate signal transduction pathways by influencing the activity of protein kinase C and they also promote apoptosis.
- ✓ Niemann-Pick disease (Types A and B) is an autosomal recessive disease (lysosomal storage disease)
- ✓ Enlarger liver and spleen because of lipid deposits
- ✓ Type A is more severe than B
- ✓ Niemann-Pick disease occurs in all ethnic groups
- ✓ Type A is more frequent in the Ashkenazi Jewish population



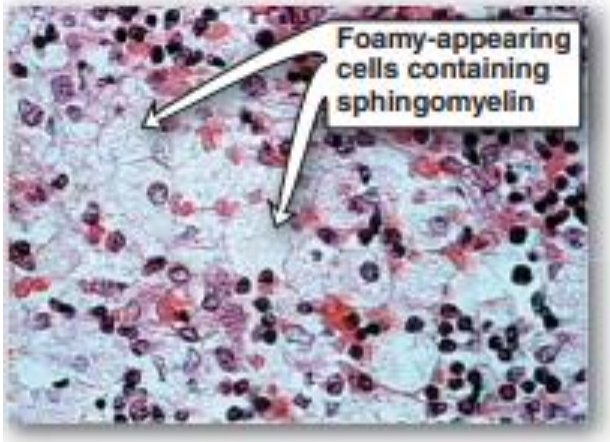
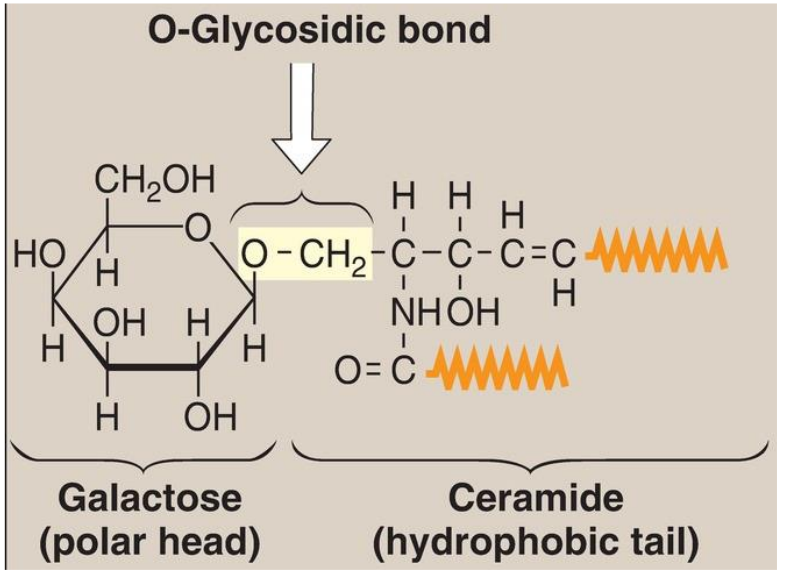
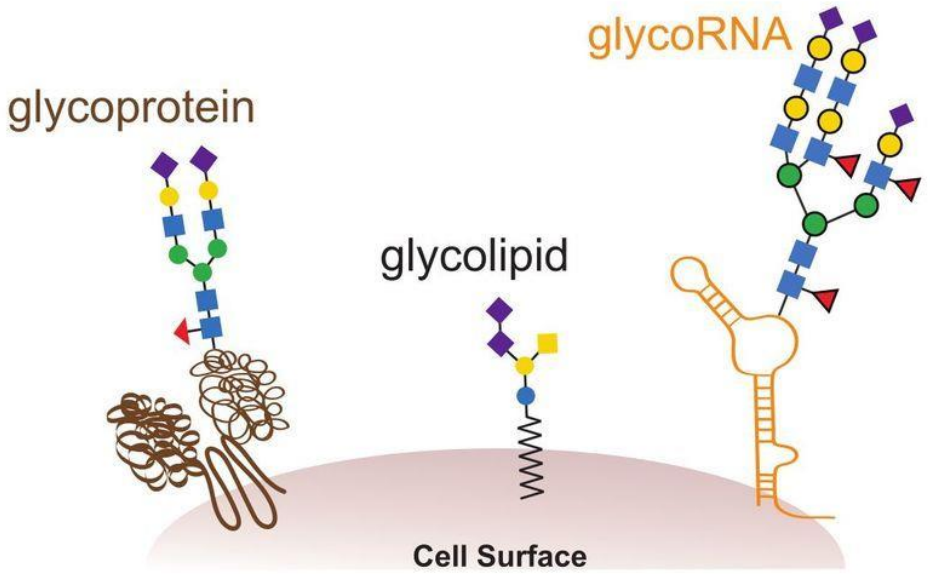




**Figure 17.13**
Accumulation of lipids in spleen cells from a patient with Niemann-Pick disease.

# Glycosphingolipids (glycolipids)

- They are made of ceramide (precursor).
- A sugar(s) is attached to ceramide by an O-glycosidic bond.
- The number and type of carbohydrate moieties determine the type of glycosphingolipid.
- They are localized in the outer leaflet of the plasma membrane and exposed extracellularly (adhesion, recognition, and signaling).
- Their hydrophobic ceramide tail inserts into the outer phospholipid leaflet, while the glycan headgroup extends outwardly.

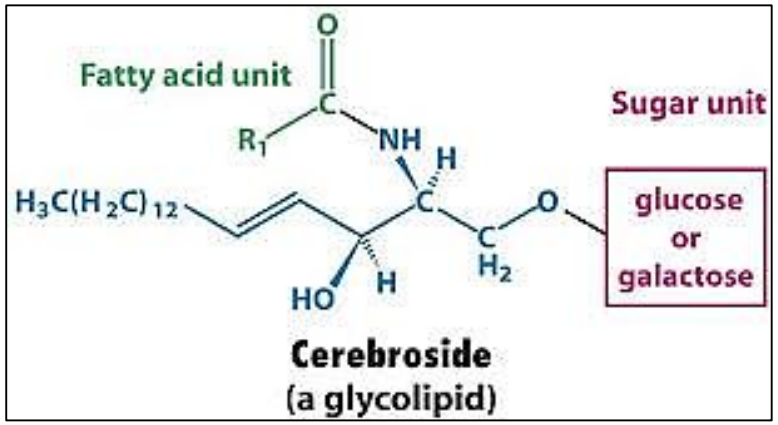


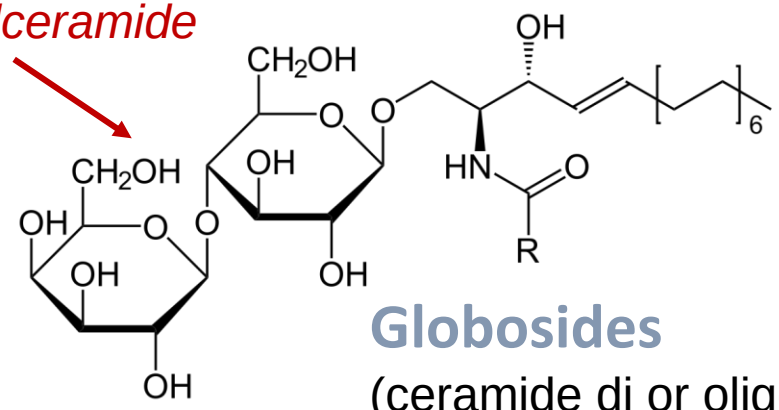
# Types of glycolipids

**Neutral glycosphingolipids**

- **Cerebrosides** are the simplest.
- Gluco- or Galactocereobrosides




*Lactosylceramide*

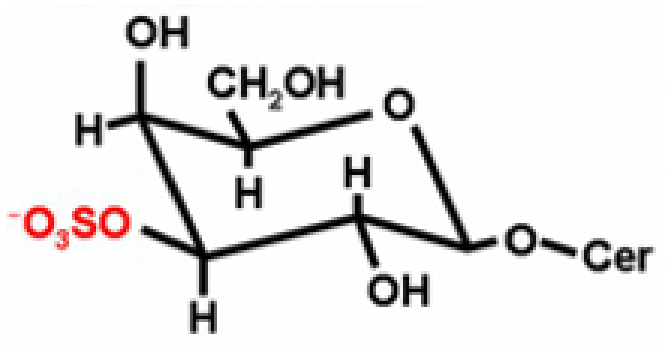


**Globosides**

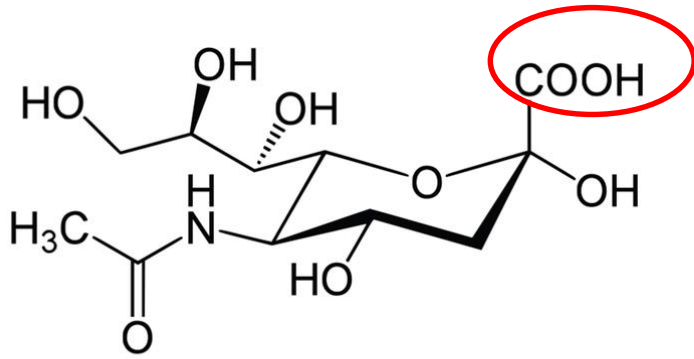
(ceramide di or oligosaccharides)

**Acidic glycosphingolipids (gangliosides)**

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



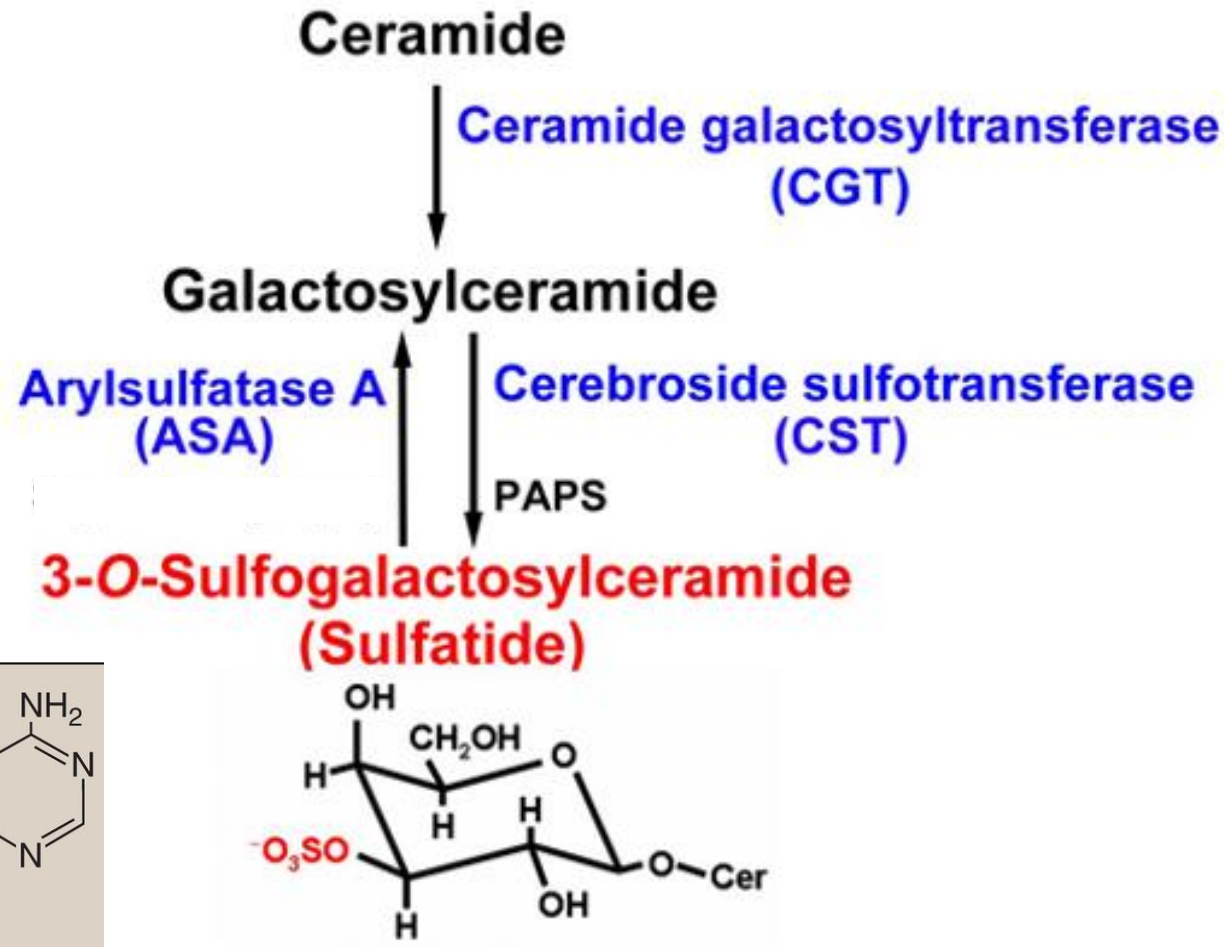
Sulfatide

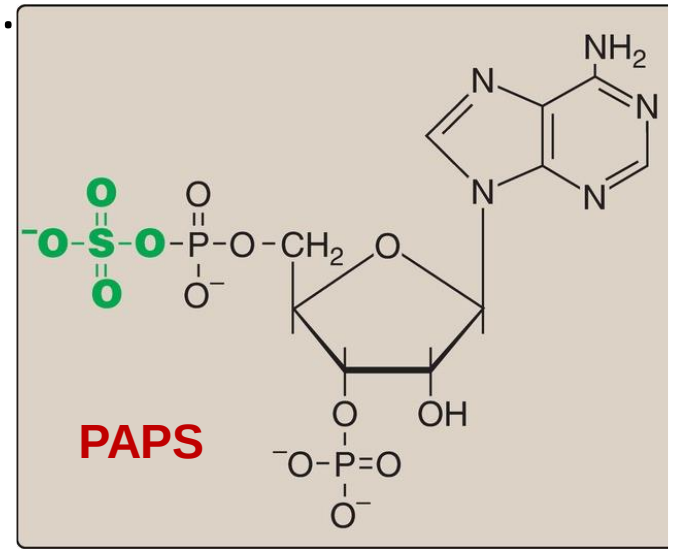


***N*-acetylneuraminic acid**

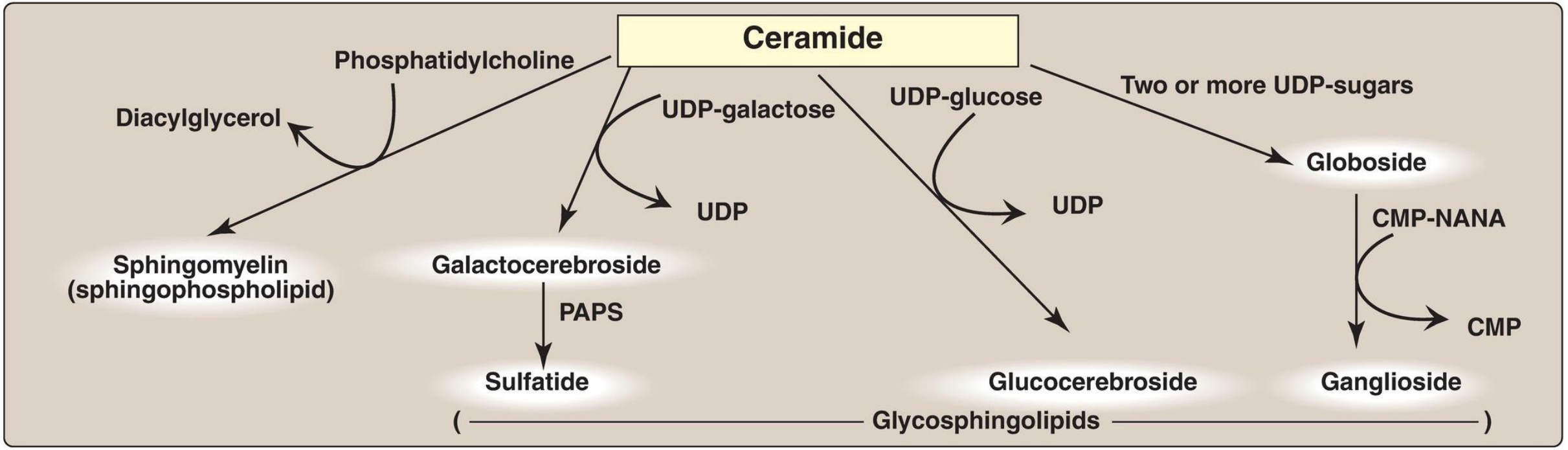
# Synthesis of Glycosphingolipids and Sulfatides

- 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 a galactose in a galactocerebroside, forming the sulfatide galactocerebroside sulfate.



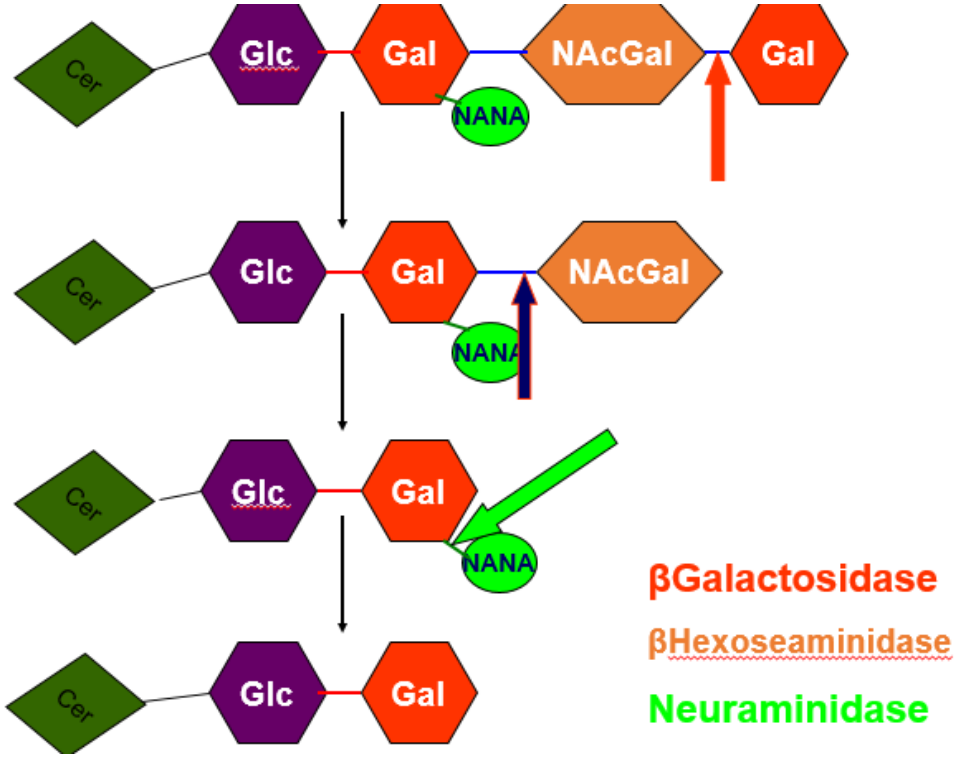



# Synthesis of Glycosphingolipids and Sulfatides



# Glycosphingolipid (GSL) degradation

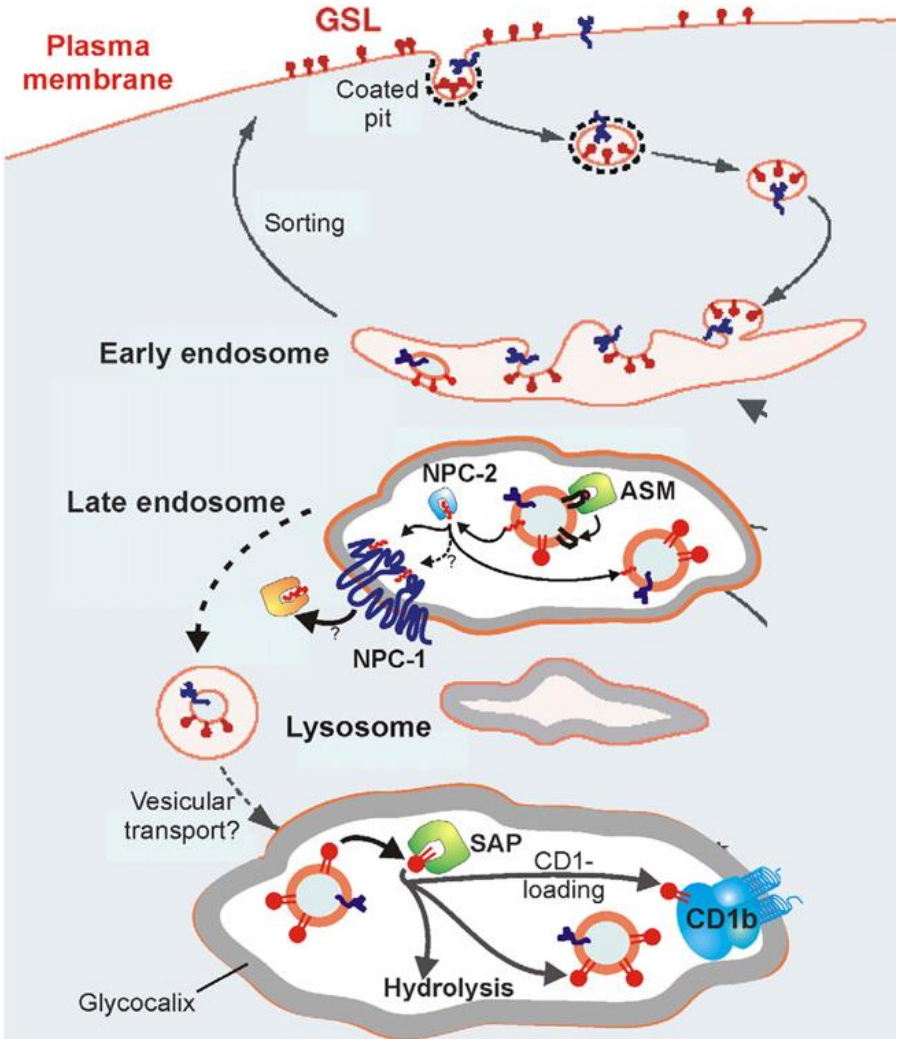
- Glycosphingolipids are phagocytosed into the endosomes that fuse with the lysosomes.
- The lysosomal hydrolases remove the sugars sequentially starting with the last one added and ending with the first one added.




βGalactosidase

βHexoseaminidase

Neuraminidase

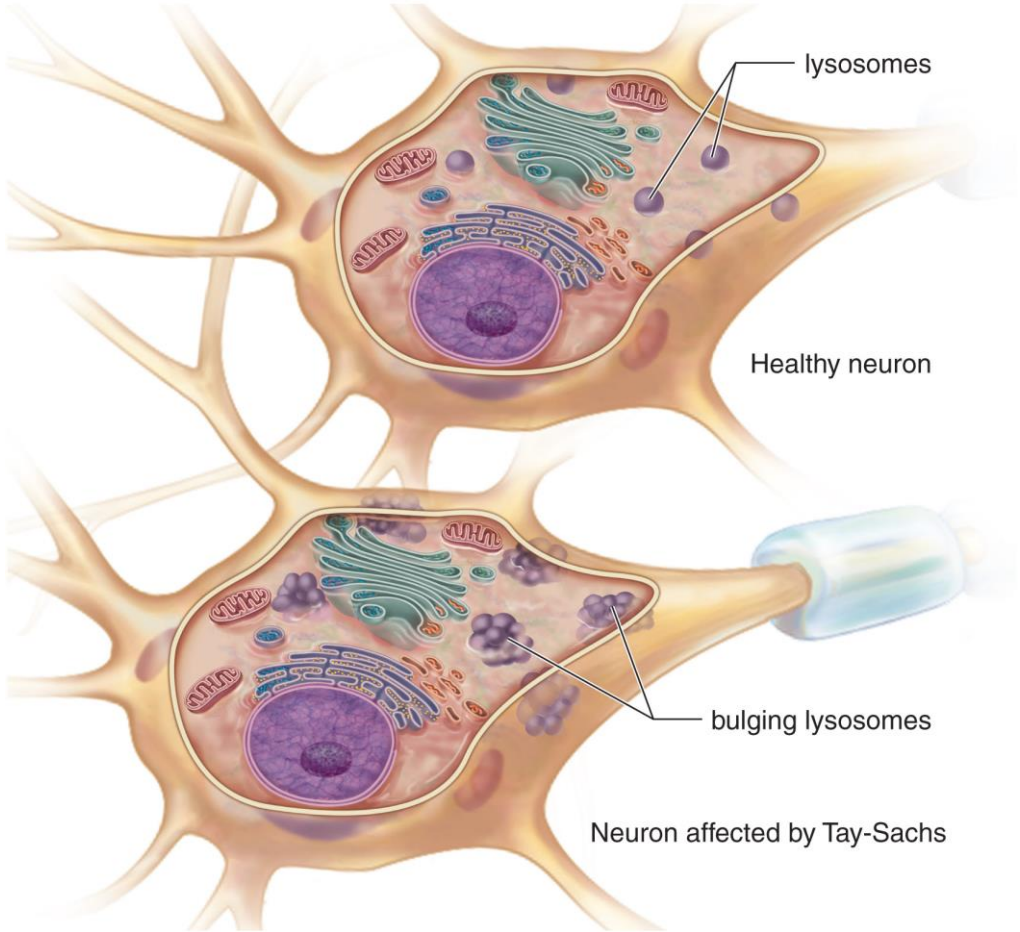


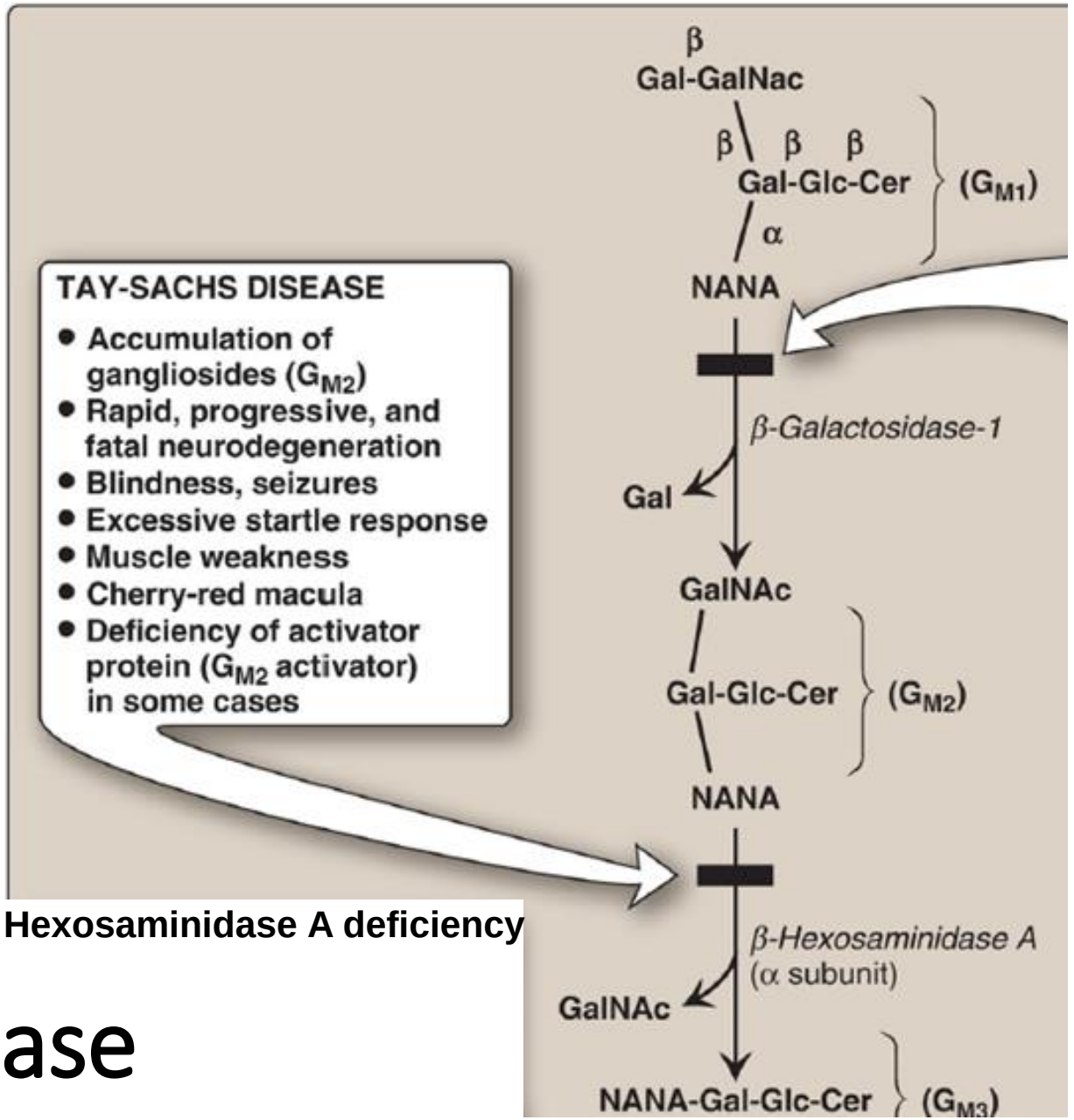

- Defect in the degradation of glycosphingolipid, glycosaminoglycans, and glycoproteins causes “lysosomal storage diseases”.
- Sialidase (neuroaminidase) is the glycosidase that removes sialic acid during ganglioside degradation

# Application: Sphingolipidoses (lysosomal disease)

- Sphingolipidoses: **lysosomal** diseases characterized by mutations in genes that encode lysosomal hydrolases or activator proteins engaged in the intralysosomal **degradation of sphingolipids.**

- Usually, only a single sphingolipid (the substrate for the deficient enzyme) accumulates in the involved organs.
- The disorders are progressive becoming more severe with aging and can be fatal.
- There is extensive phenotypic variability due to:
  - Allele heterogeneity: different mutations within the same gene (different alleles)
  - Locus heterogeneity: different genes are defective (locus = position, location).
- They are autosomal-recessive disorders, except for Fabry disease, which is X linked.
- The incidence of 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.

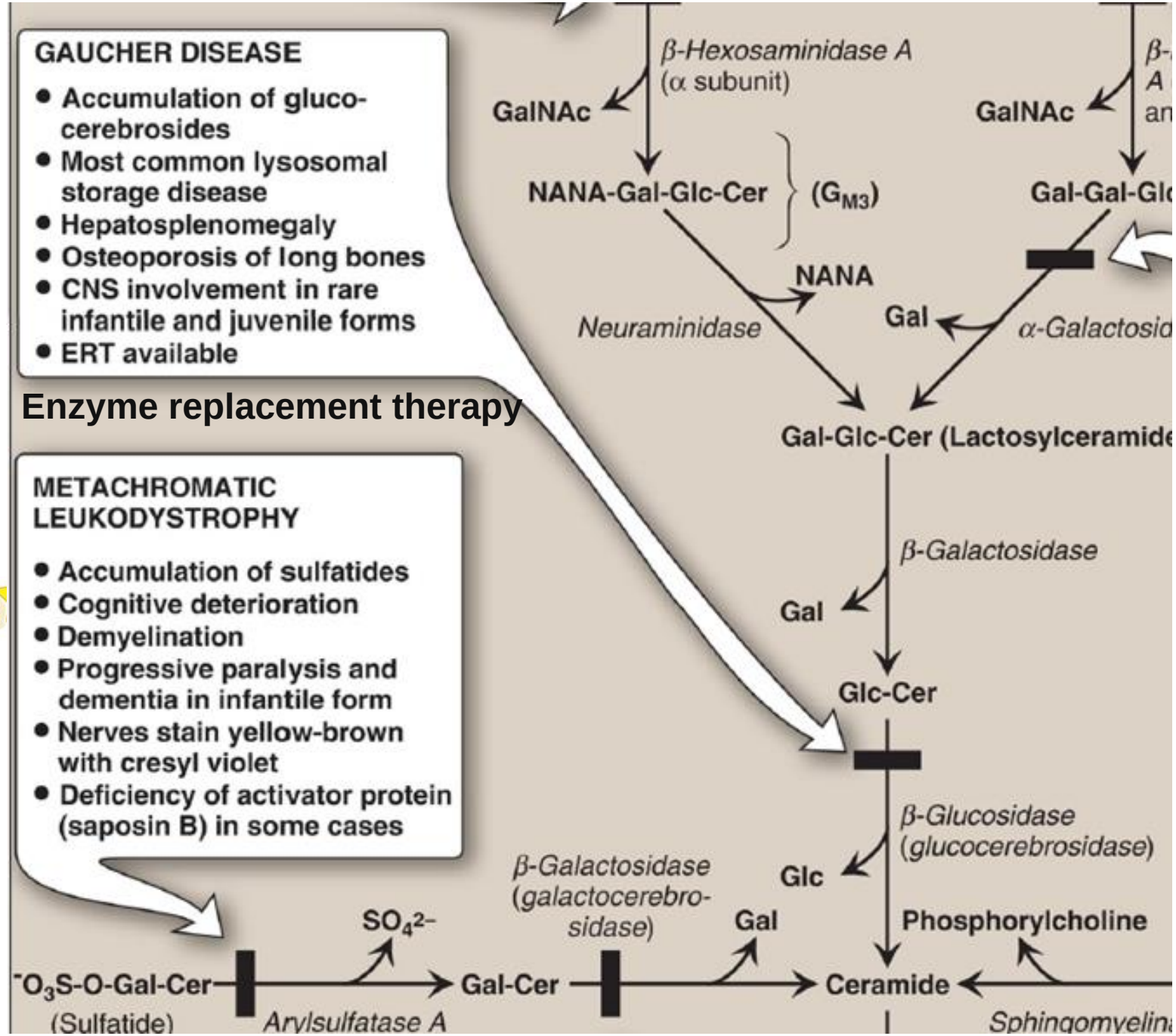



# Tay-Sachs disease

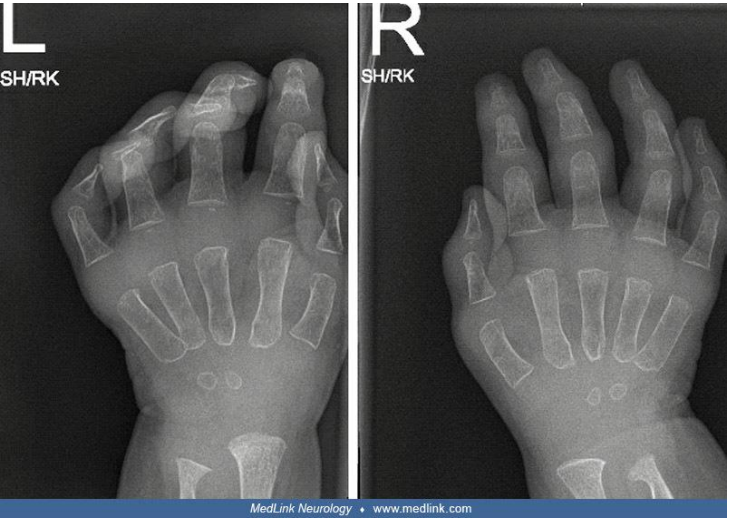
# Gaucher disease

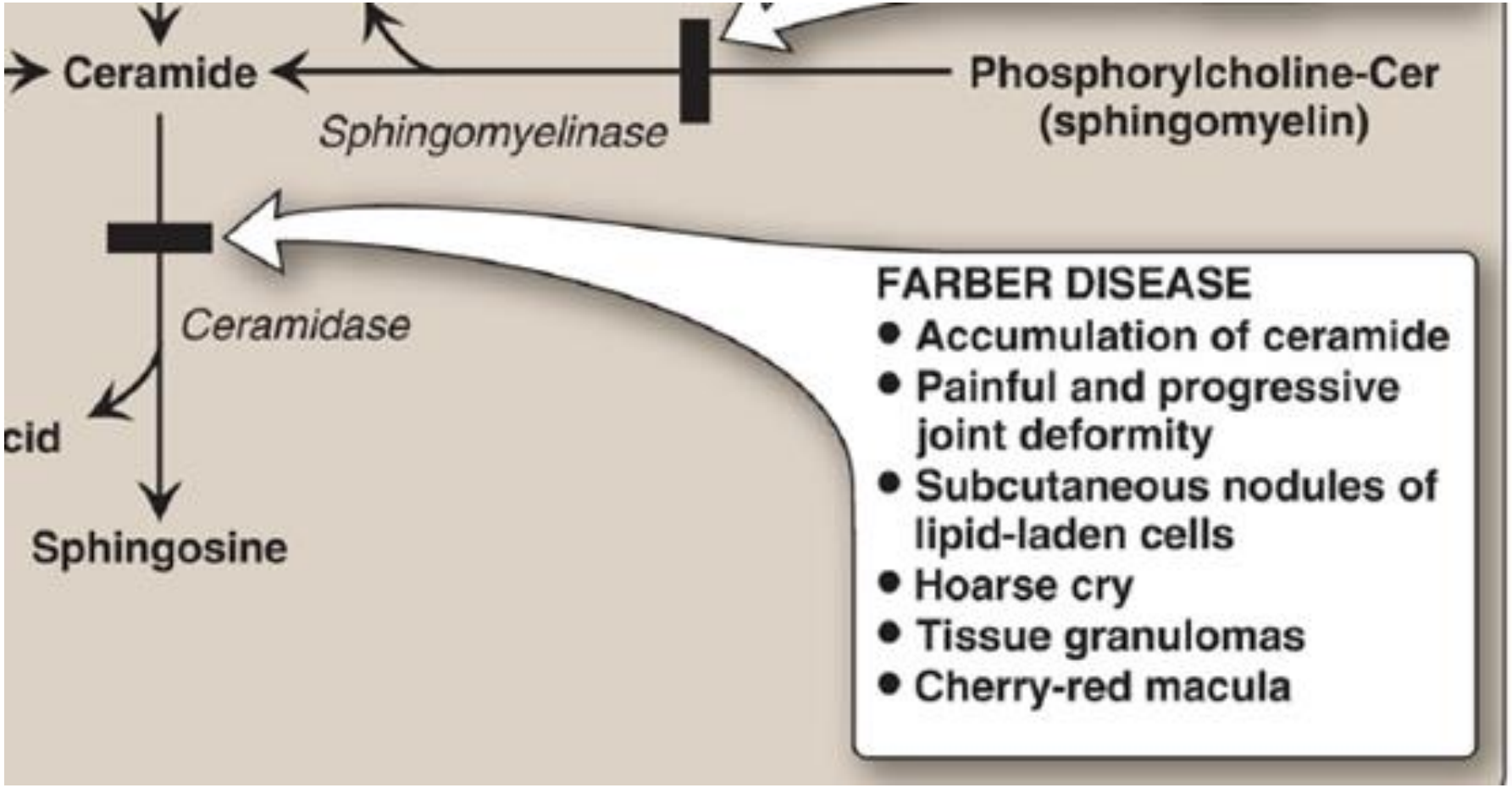
* MOST COMMON LYSOSOMAL STORAGE DISORDER



# Farber disease


**Deformed joints**



# 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: reducing the amount of glucocerebroside produced in the body pharmacologically