SPHINGOLIPIDS AND MYELIN STRUCTURE

OUTLINES

- Objectives.
- Background.
- Key principles.
- Take home messages.

OBJECTIVES

By the end of this lecture, the students should be able to:

- Recognize the Sphingolipids class of lipids as regard their chemical structure, tissue distribution and functions.
- Be familiar with the biochemical structure and function of myelin.
- Learn the basics of biosynthesis of sphingolipids.
- Be introduced to Sphingolipidoses.

BACKGROUND

There are two classes of phospholipids based on the backbone:

- Glycerol (from glucose).
- Sphingosine (from serine and palmitate).

BACKGROUND *(Cont'd…)*

- Essential component of membranes.
- Abundant in nervous tissue.
- Also exist extra-nervous tissue:

e.g. Receptors for:

Cholera toxins

Diphtheria toxins

Viruses.

BACKGROUND *(Cont'd…)*

- Regulation of growth and development.
- Very antigenic:

  Blood group antigen

  Embryonic antigen

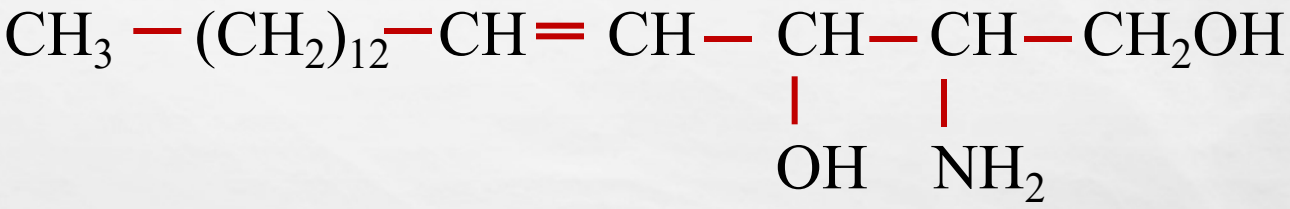
  Tumor antigen
- Cell transformation.

KEY PRINCIPLES

- Chemical structure of Sphingolipids.
- Types:
  - Glycosphingolipids (Glycolipids).
  - Sphingophospholipids, e.g. Sphingomyelin.
- Myelin structure and function.
- Sphingolipidoses.

SPHINGOLIPIDS: STRUCTURE AND TYPES

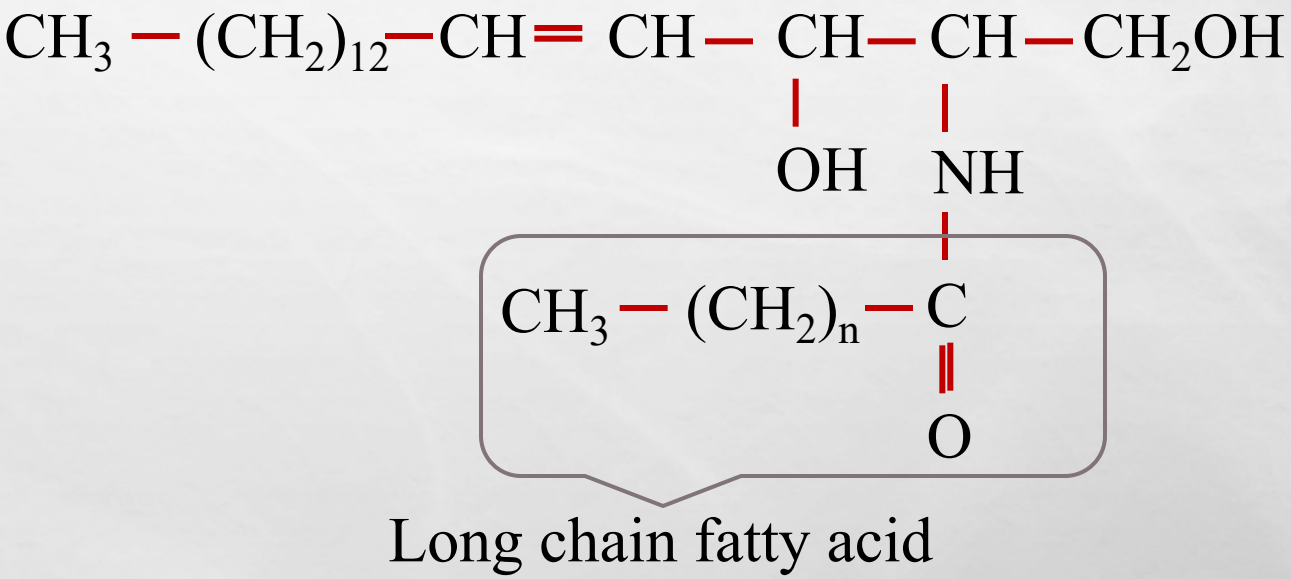
SPHINGOSINE



Long chain, unsaturated amino alcohol

CERAMIDE

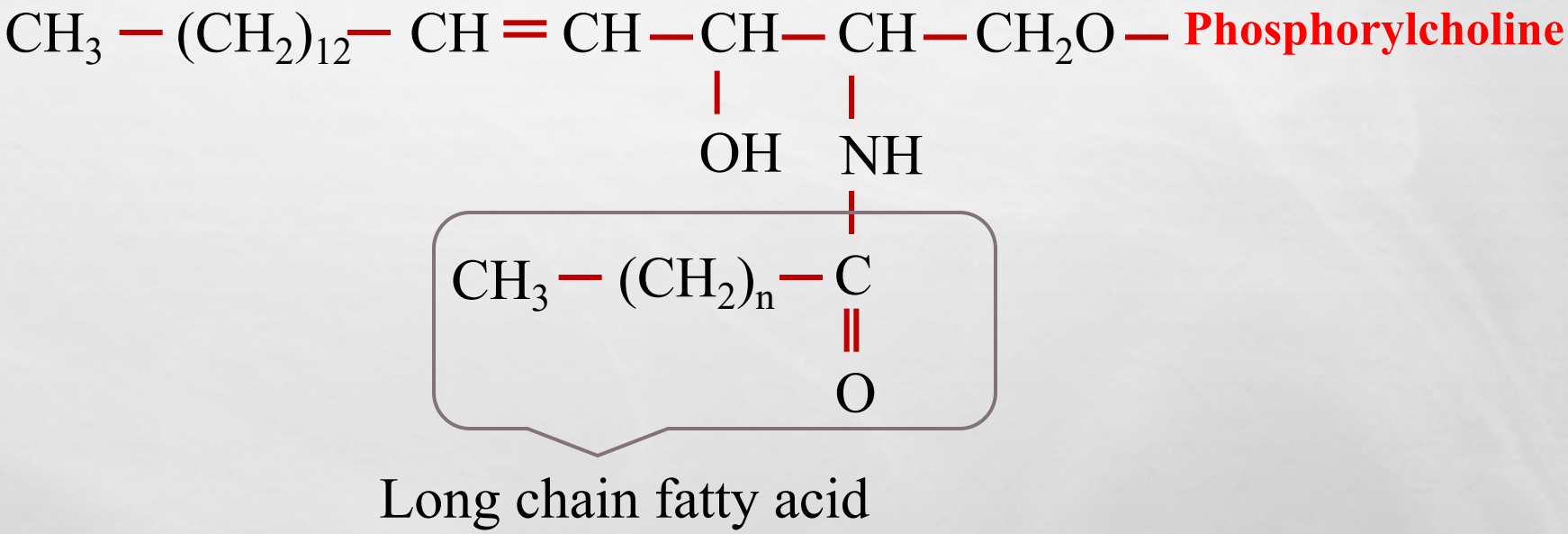
Ceramide = Sphingosine + Fatty acid



- *Ceramide play a key role in maintaining the skin's water-permeability barrier.*
- *Decreased ceramide levels are associated with a number of skin diseases.*

SPHINGOMYELIN

Sphingomyelin = Ceramide + Phosphorylcholine

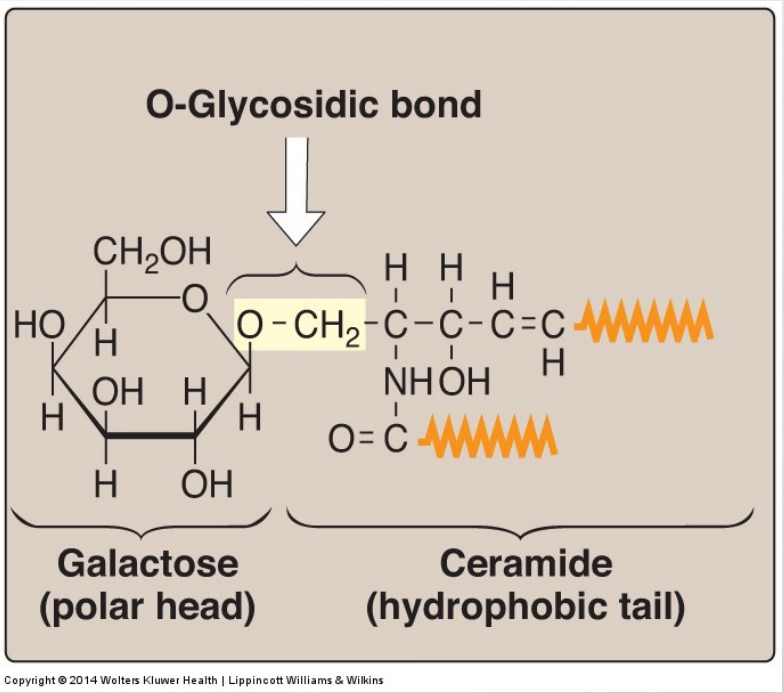


- *Sphingomyelin is the only significant sphingolipid in humans*

CEREBROSIDES

Cerebrosides = Ceramide + Monosaccharides

e.g. Galactocerebroside.



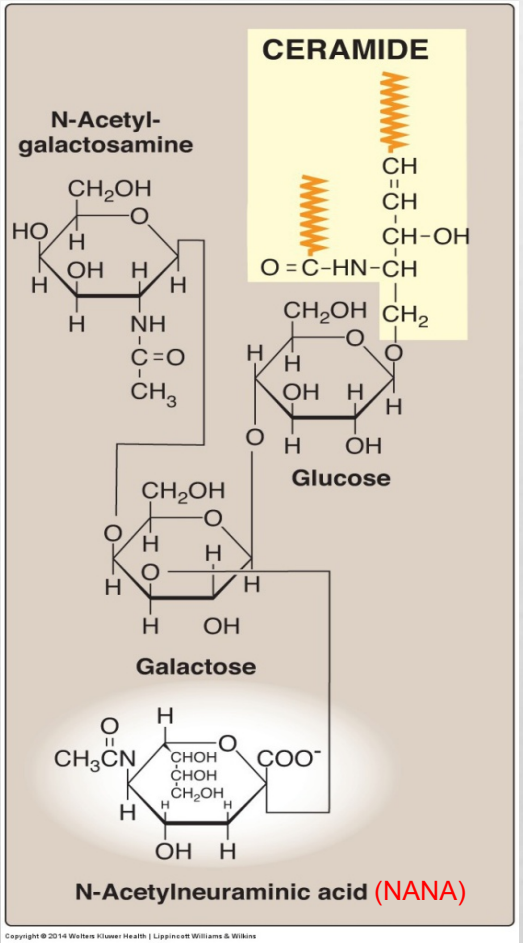
GANGLIOSIDES

Gangliosides = Ceramide oligosaccharides

+

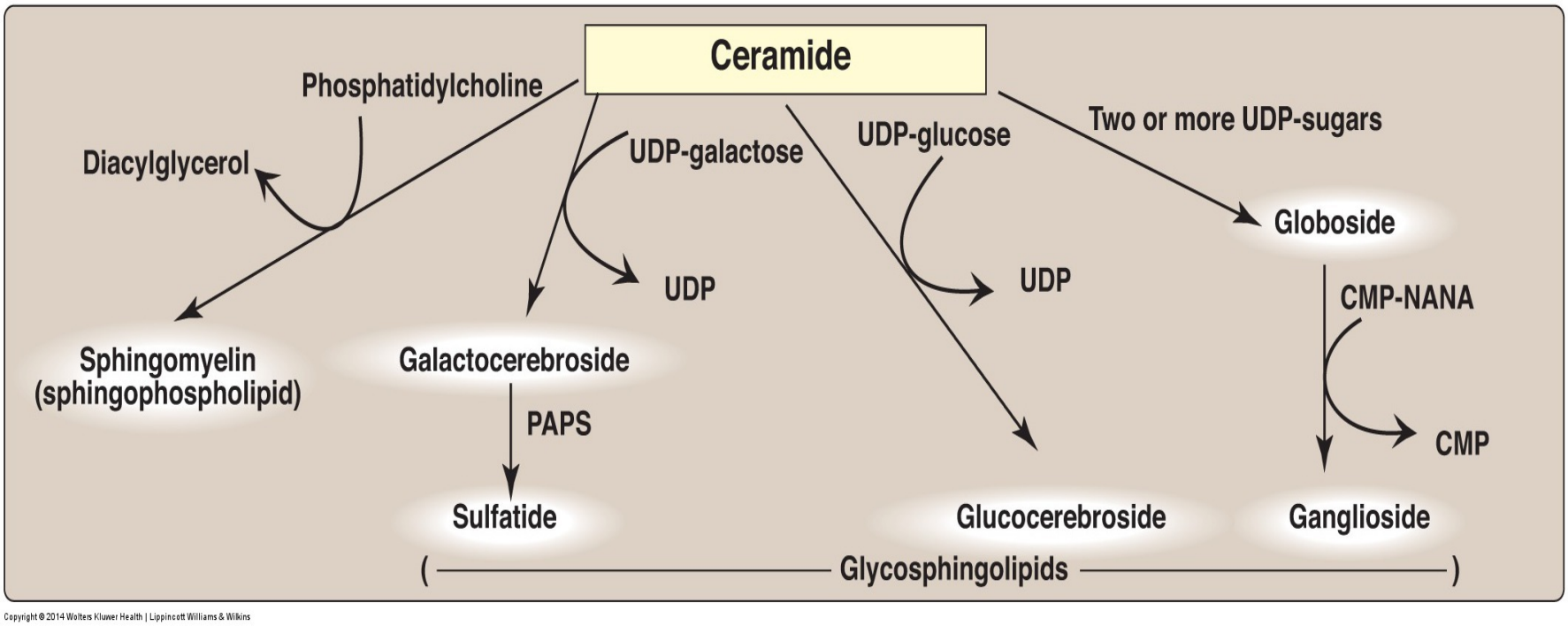
NANA

e.g. G_{M2}.



- *For G_{M2}: G=ganglioside; M=mono molecule of NANA; 2=the monomeric sequence of the carbohydrate attached to the ceramide*

SPHINGOLIPIDS' SYNTHESIS



MYELIN STRUCTURE

Myelin is a specialized cell membrane that ensheathes an axon to form a myelinated nerve fiber.

Myelin is produced by:

Schwann cells: Peripheral nerves.

Oligodendrocytes: CNS.

Myelin composition:

Lipids (80%): Main component: Cerebrosides

Other component: Sphingomyelin

Proteins (20%): e.g. Myelin basic protein

MYELIN STRUCTURE

Fatty acid of Sphingomyelin:

Myelin sheath:

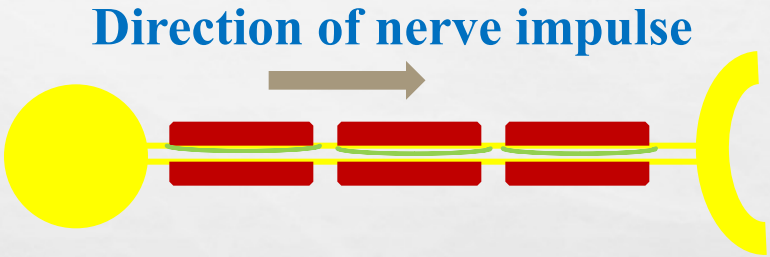
Very long chain fatty acids

Lignoceric 24:0

Nervonic 24:1(15)

MYELIN STRUCTURE AND FUNCTION

Myelin sheath insulates the nerve axon to avoid signal leakage and greatly speeds up the transmission of impulses along axons.



Multiple sclerosis:

Neuro-degenerative, auto-immune disease.

Breakdown of myelin sheath (demyelination).

Defective transmission of nerve impulses.

SPHINGOLIPIDOSES

- A partial or total missing of a specific lysosomal acid hydrolase leads to accumulation of a sphingolipid.
- Lysosomal lipid storage diseases caused by these deficiencies are called **sphingolipidoses**.

SPHINGOLIPIDOSES *(Cont'd…)*

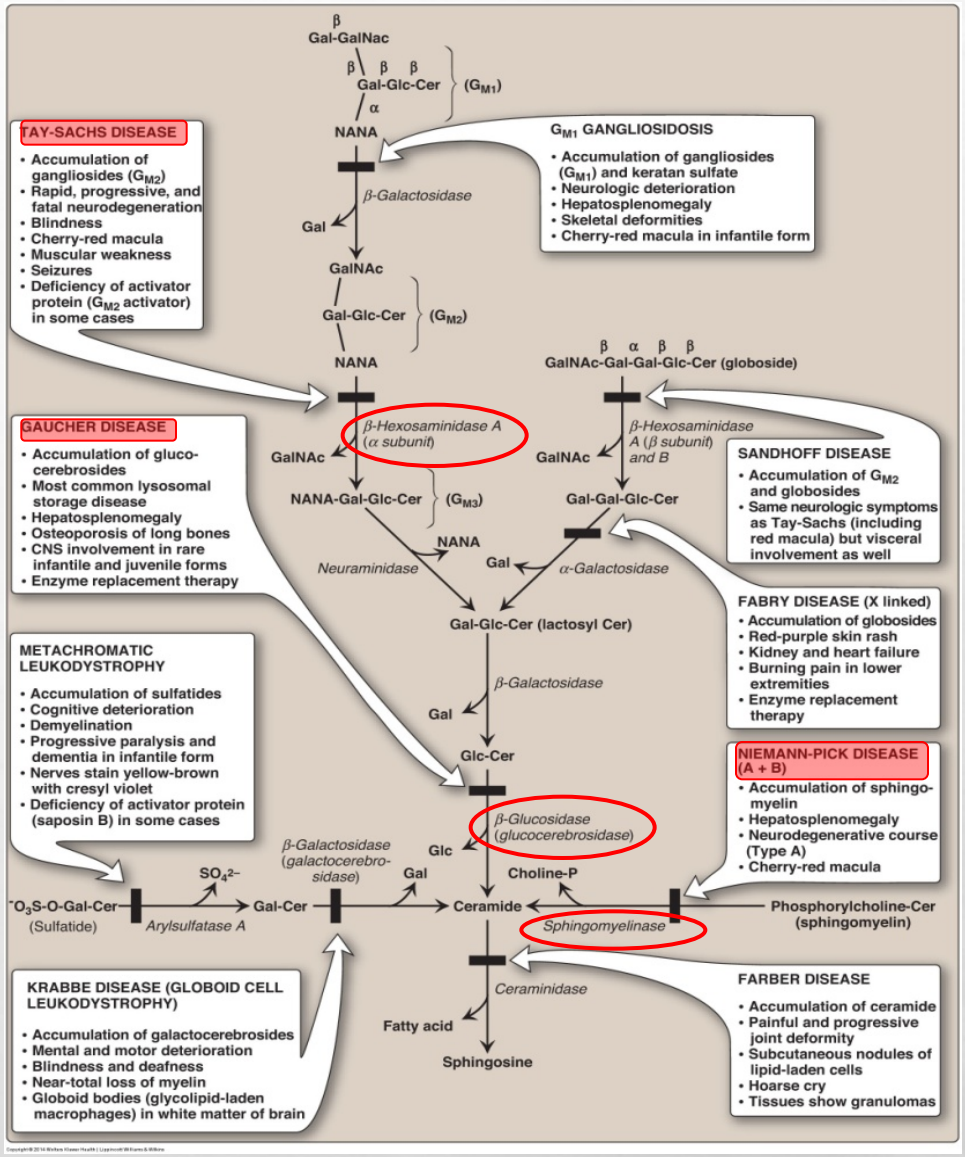
- Synthesis (Normal); Degradation (Defective).
- Substrate accumulates in organs..
- Progressive, early death.
- Phenotypic and genotypic variability.
- Autosomal recessive (mostly).
- Rare, Except in Ashkenazi Jewish.

- *Usually only a single sphingolipid accumulates in the involved organs in each disease*

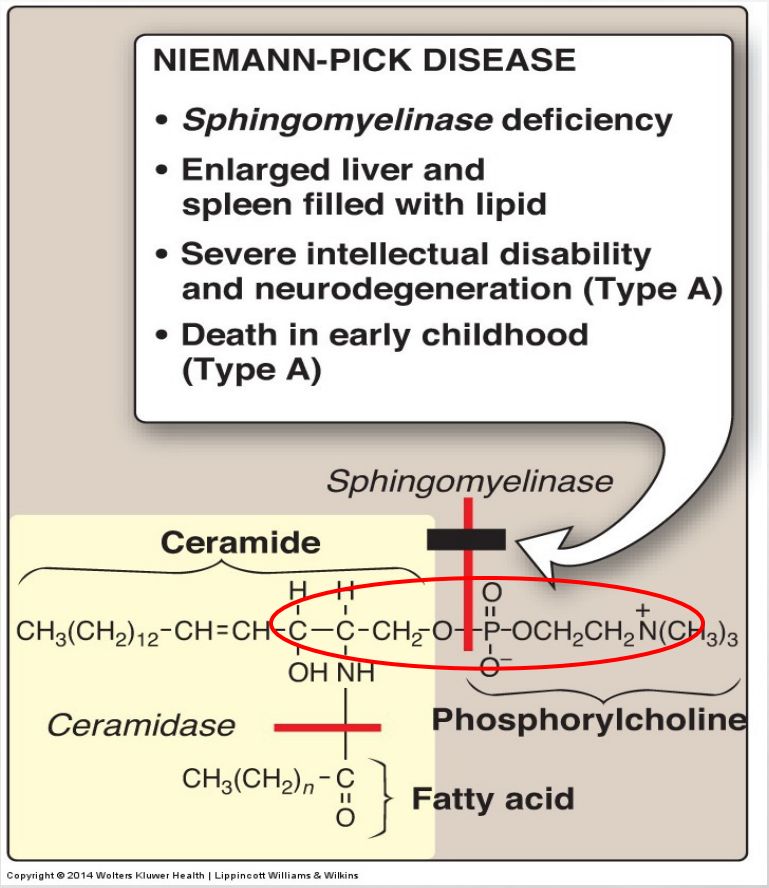
SPHINGOLIPIDOSES *(Cont'd…)*

- **Diagnosis:**
  - Measure enzyme activity:
    - Cultured fibroblasts or peripheral leukocytes.
    - Cultured amniocytes or chorionic villi (prenatal).
  - Histologic examination.
  - DNA analysis.
- **Treatment: e.g. for Gaucher disease:**
  - Replacement Therapy (e.g. recombinant human enzyme).
  - Bone marrow transplantation.

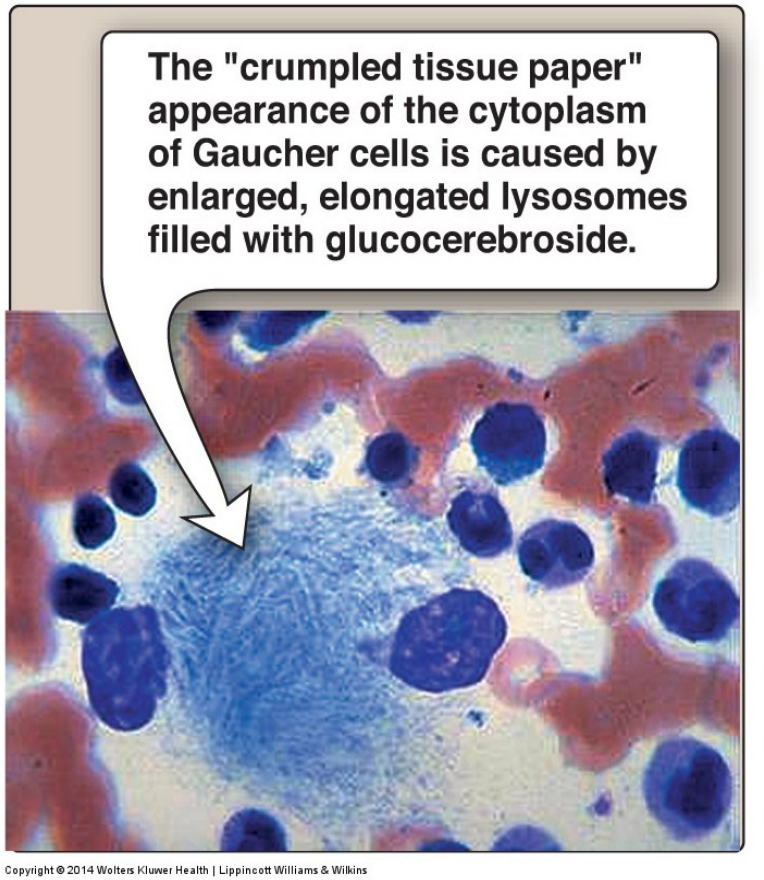
SPHINGOLIPIDOSES



NIEMANN-PICK DISEASE



GAUCHER DISEASE



TAKE HOME MESSAGES

- Sphingolipids are complex lipids that includes sphingo-phospholipids and glycolipids.
- Ceramide is the precursor of all sphingolipids.
- Sphingolipids are present mainly in nerve tissue, but they are also found extra-neural.
- Myelin sheath insulates the nerve axon to avoid signal leakage and speed up impulse transmission.
- Sphingolipidoses are rare genetic diseases due to defective degeneration of sphingolipids.

REFERENCE

Lippincott Illustrated Review of Biochemistry, 6th edition, 2014, Unit 3, Chapter 17, Pages 201-218.