Lecture 4:
Lysosomes

Dr. Diala Abu-Hassan

School of Medicine

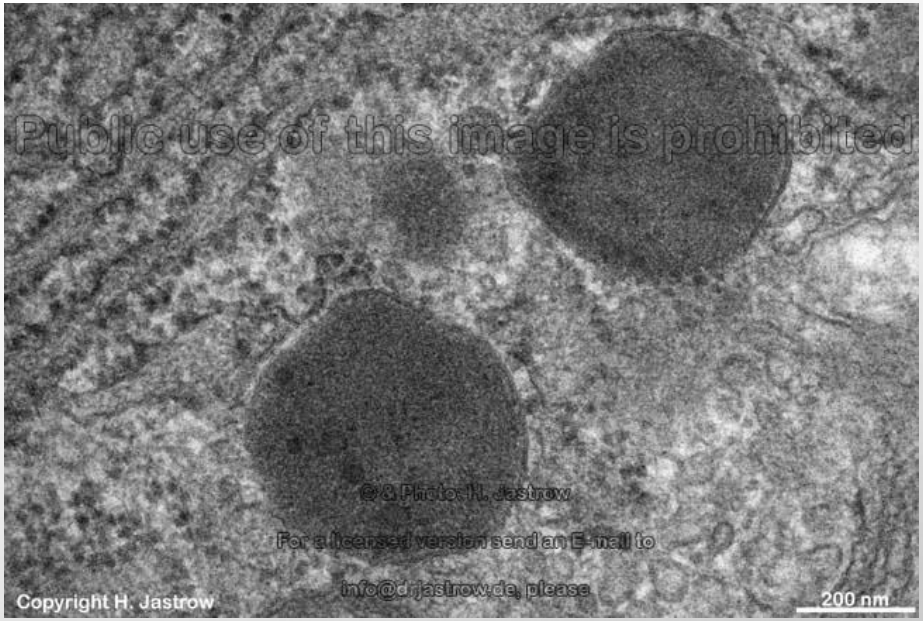
dr.abuhassand@gmail.com

Principles of Genetics and Molecular Biology

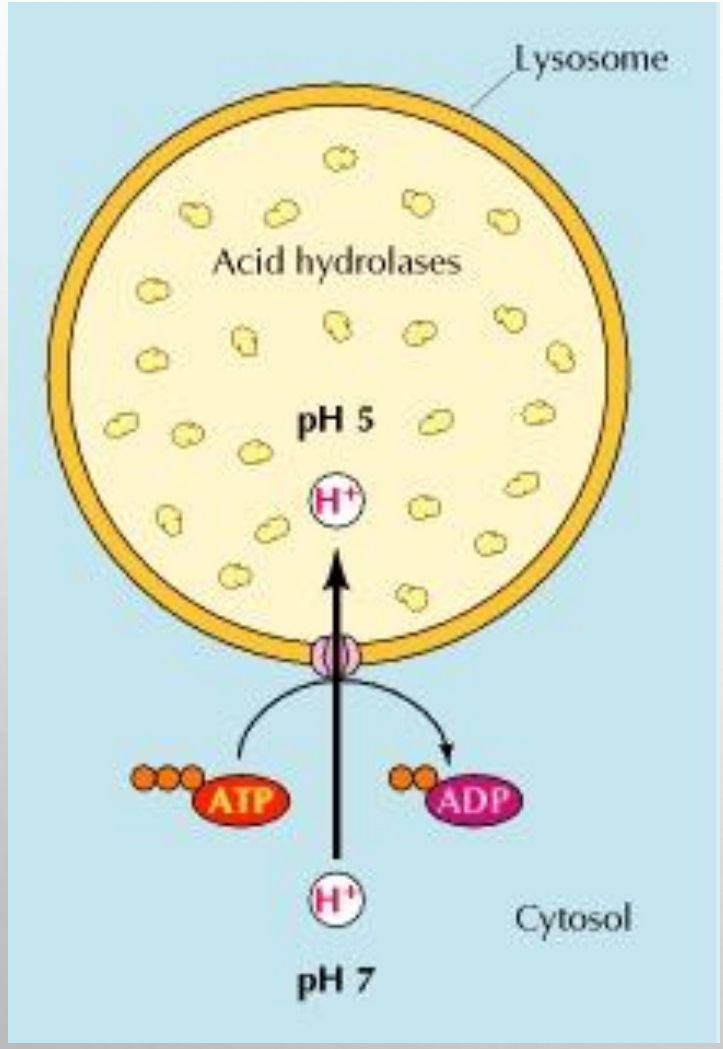
LYSOSOMES

STRUCTURE

- Lysosomes are membrane-enclosed organelles that contain various enzymes that break down all types of biological polymers.
- Lysosomes degrade material taken up from outside and inside the cell.
- Variable in size and shape.

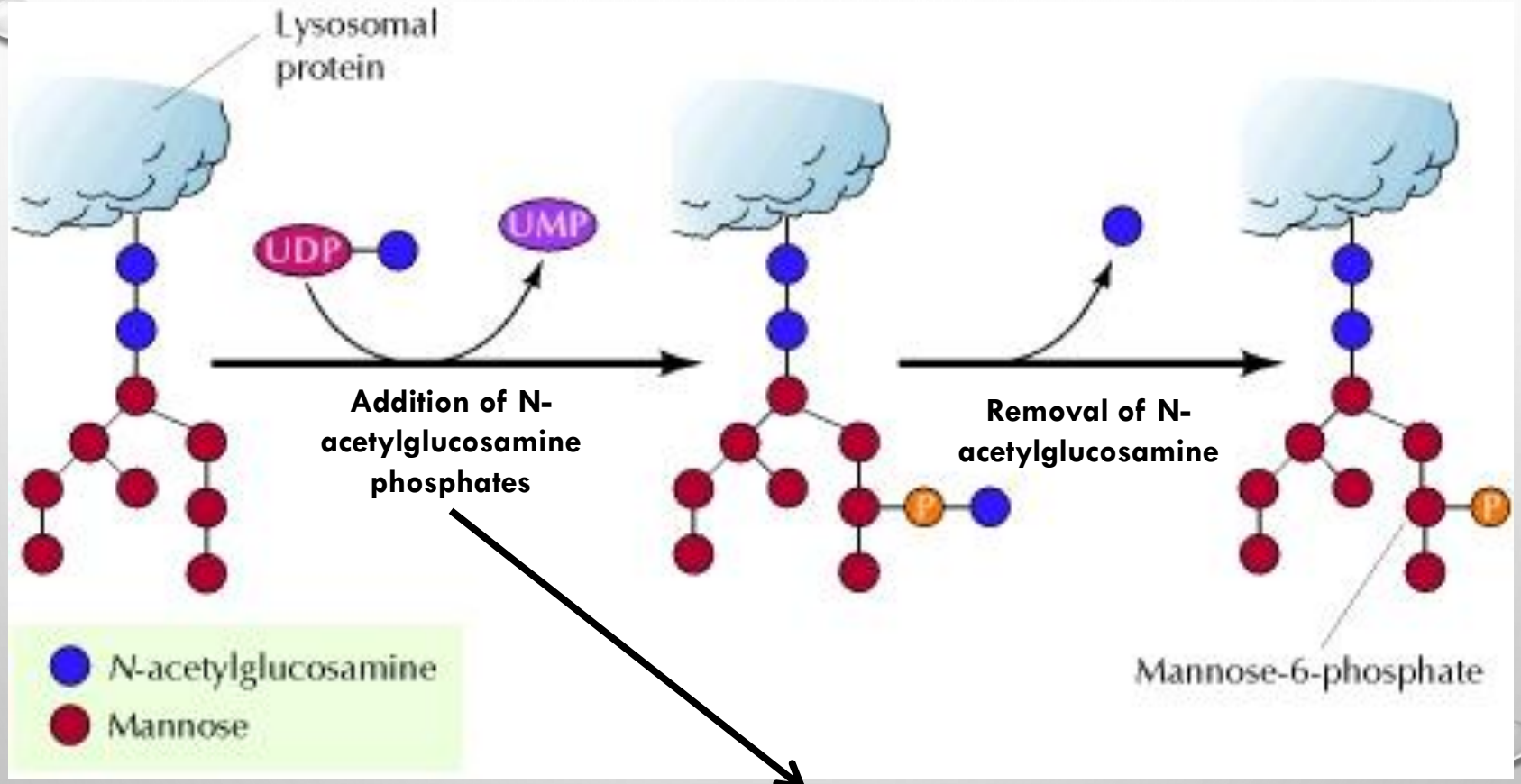


Lysosomal enzymes



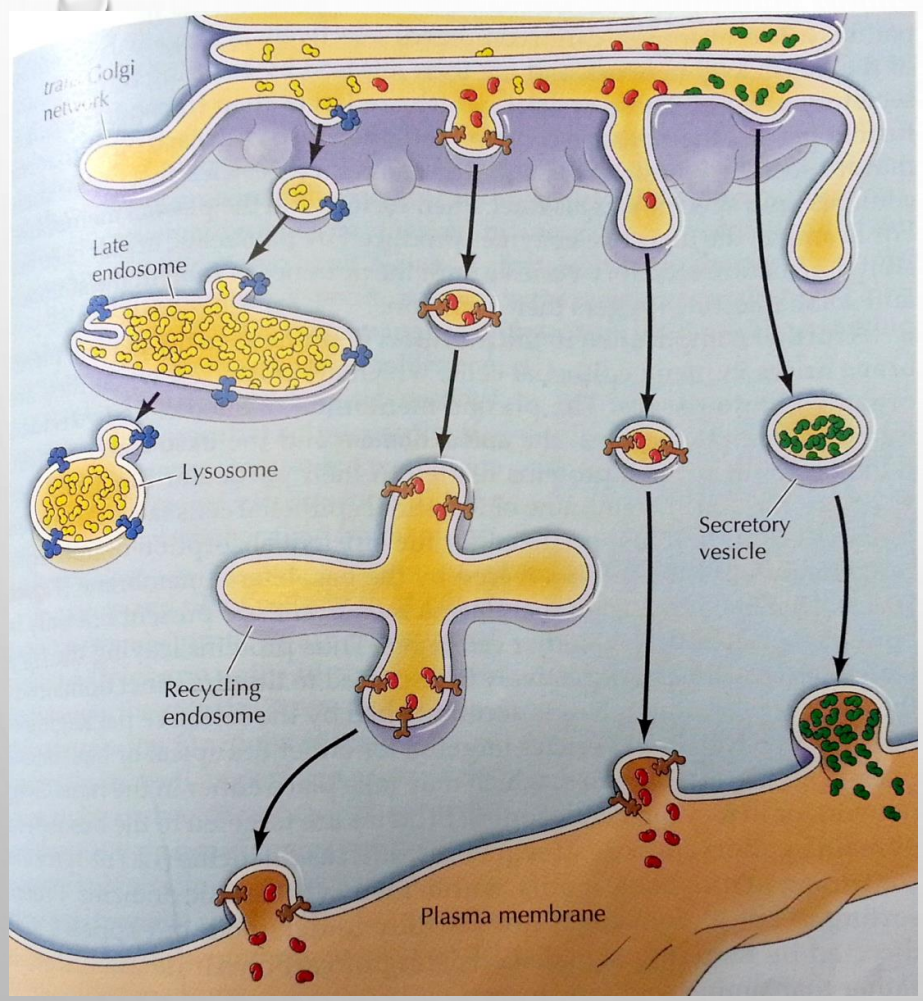
- Lysosomes contain ~50 different acid hydrolases.
- Enzymes hydrolyze proteins, DNA, RNA, polysaccharides and lipids.
- The enzymes are active at the acidic pH (about 5) that is maintained within lysosomes.
- Levels of Protection:
  - Containment
  - Inactive if released
- A proton pump maintains lysosomal pH.

Processing of lumenal lysosomal proteins



The enzyme recognizes a signal patch (a three-dimensional structural determinant) not a sequence.

Transport of lysosomal proteins



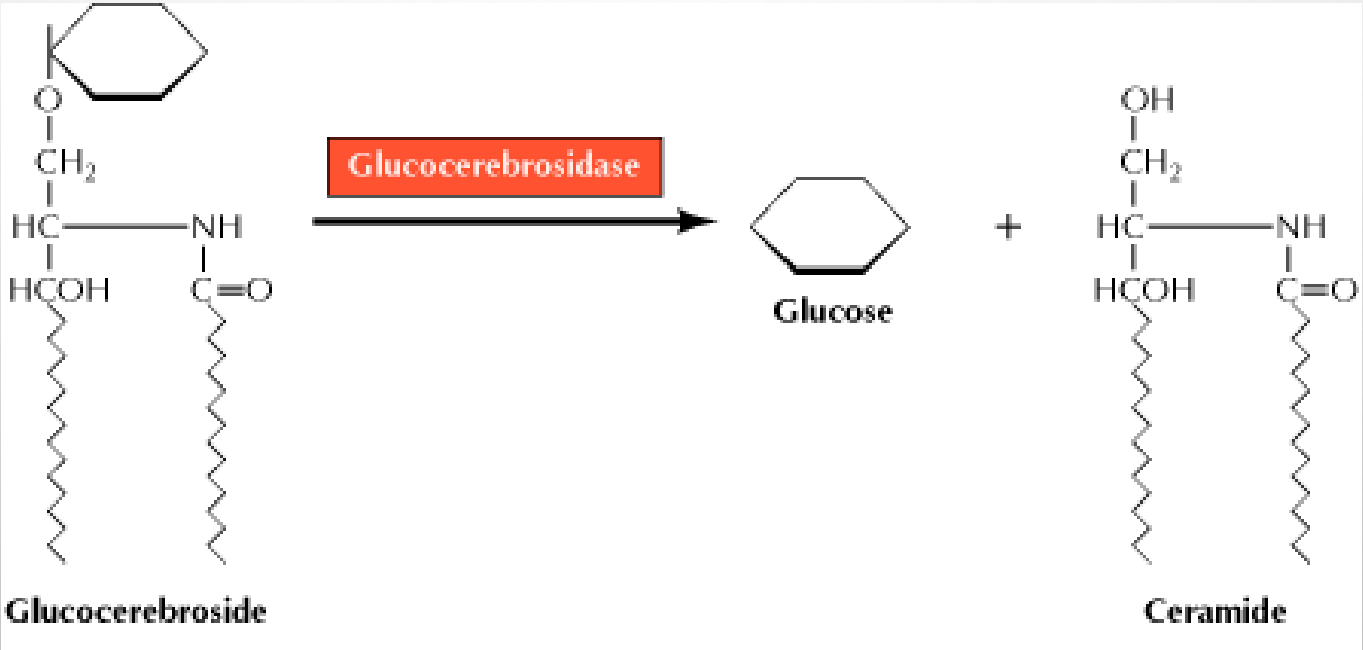
- **Lumenal** lysosomal proteins marked by **mannose-6-phosphates** bind to a mannose-6-phospahte receptor.
- The complexes are packaged into transport vesicles destined for late endosomes, which mature into lysosomes.
- Lysosomal **membrane** proteins are targeted by **sequences in their cytoplasmic tails,** rather than by mannose-6-phosphates.

Lysosomal storage diseases

- **Glycolipidoses** (*sphingolipidoses*)
- **Oligosaccharidoses**
- **Mucopolysaccharidoses**: *deficiencies in lysosomal hydrolases of GAGs (heparan, keratan and dermatan sulfates, chondroitin sulfates).*
  - *They are chronic progressively debilitating disorders that lead to severe psychomotor retardation and premature death.*

Glucocerebroside

- Glucocerebroside is a glycolipids (a monosaccharide attached directly to a ceramide unit
- It is a byproduct of the normal recycling of red blood cells, which are phagocytosed by macrophages, degraded and their contents recycled to make new cells.

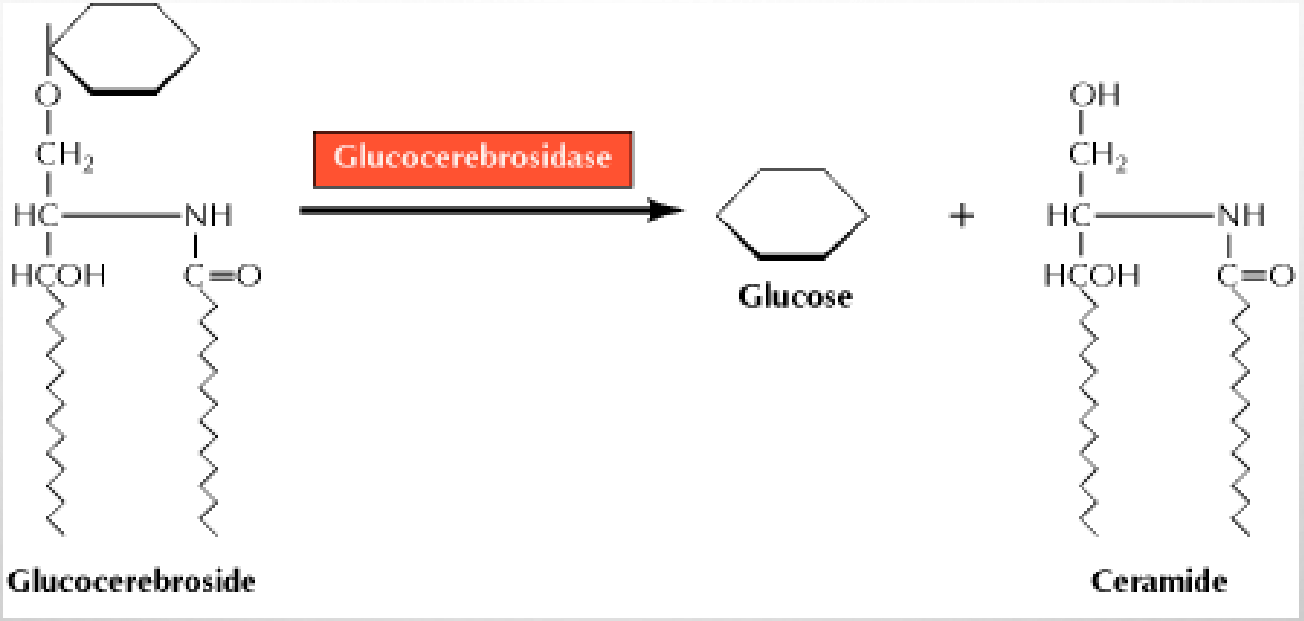


Types

- Three types according to severity and nervous system involvement
  - **Type 1:** (least severe, most common) the nervous system is not involved; spleen and liver enlargement, development of bone lesions
  - **Types 11 and 111** (more severe, much rarer): the only cells affected in Gaucher's disease are macrophages
    - Macrophages eliminate aged and damaged cells by phagocytosis that involves continuous ingestion of large amounts of lipids in lysosomes for degradation

Gaucher disease (glucocerebrosidase deficiency)

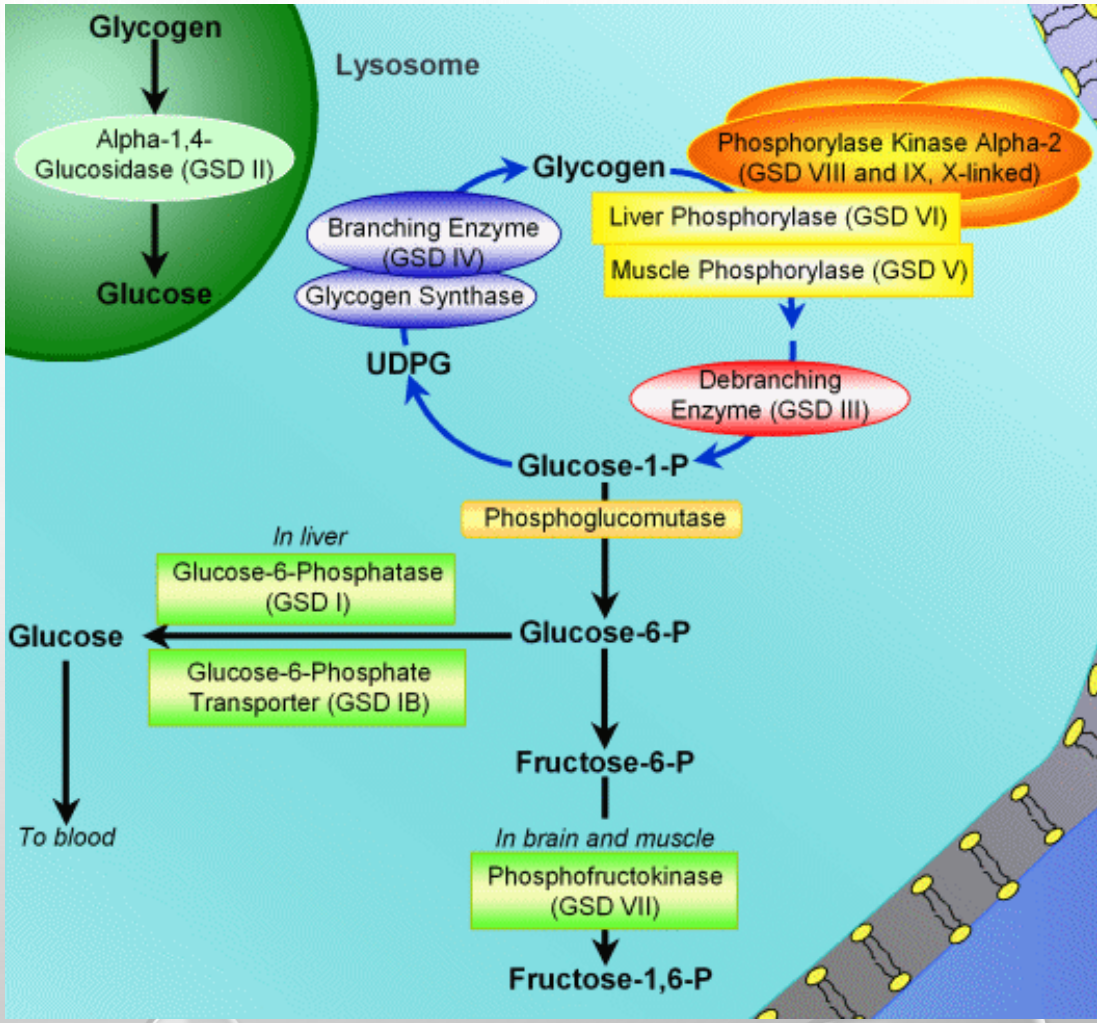
- The most common lysosomal storage disease
- Caused by mutation in the gene encoding acid-beta glucosidase, or glucocerebrosidase.



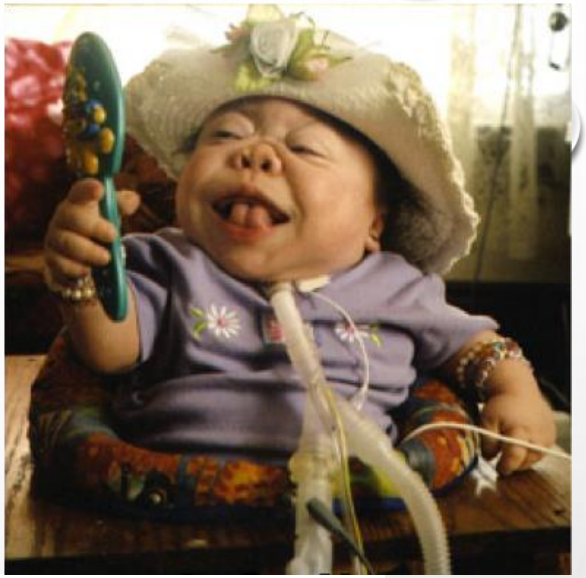
- Failure of lysosomes to degrade substances that they normally break down.
- The accumulation of non-degraded compounds leads to an increase in the size and number of lysosomes within the cell.

Oligosaccharidoses-Pompe disease (type II)

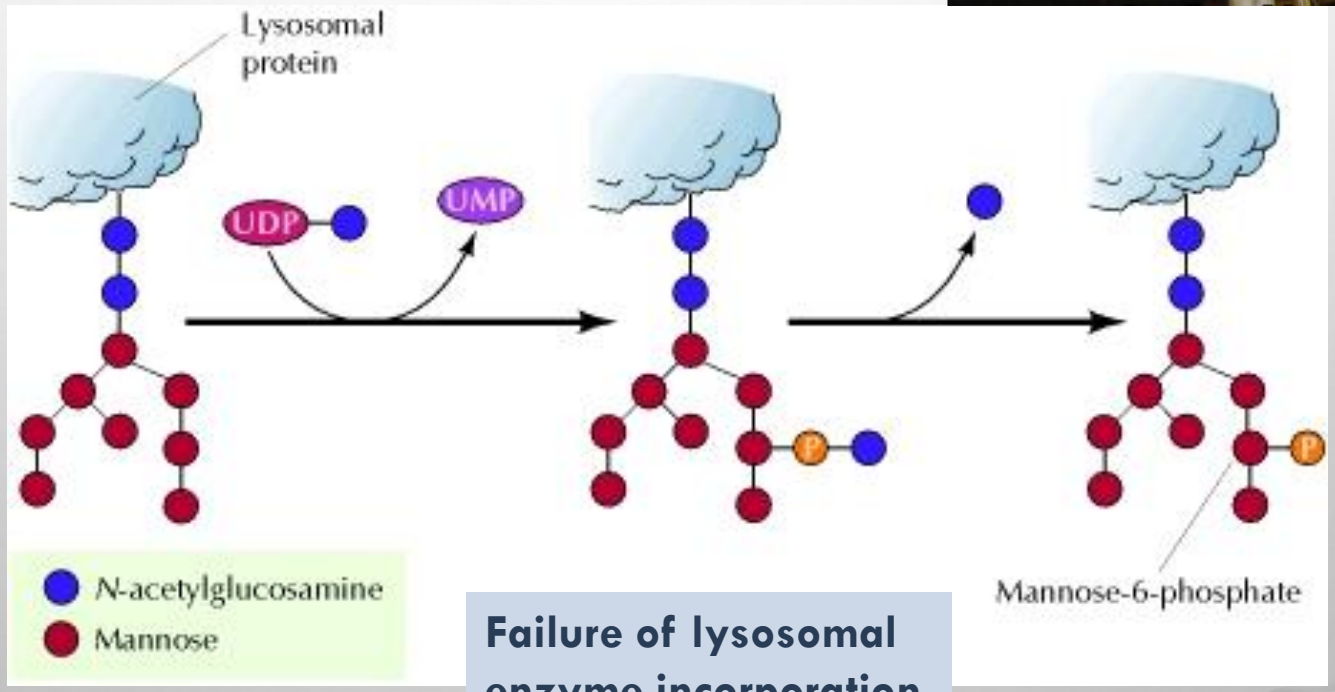
- Lysosomes become engorged with glycogen because they lack α-1,4-glucosidase, a hydrolytic enzyme confined to these organelles
- Glycogen structure is normal, but its amount is excessive



I-cell disease

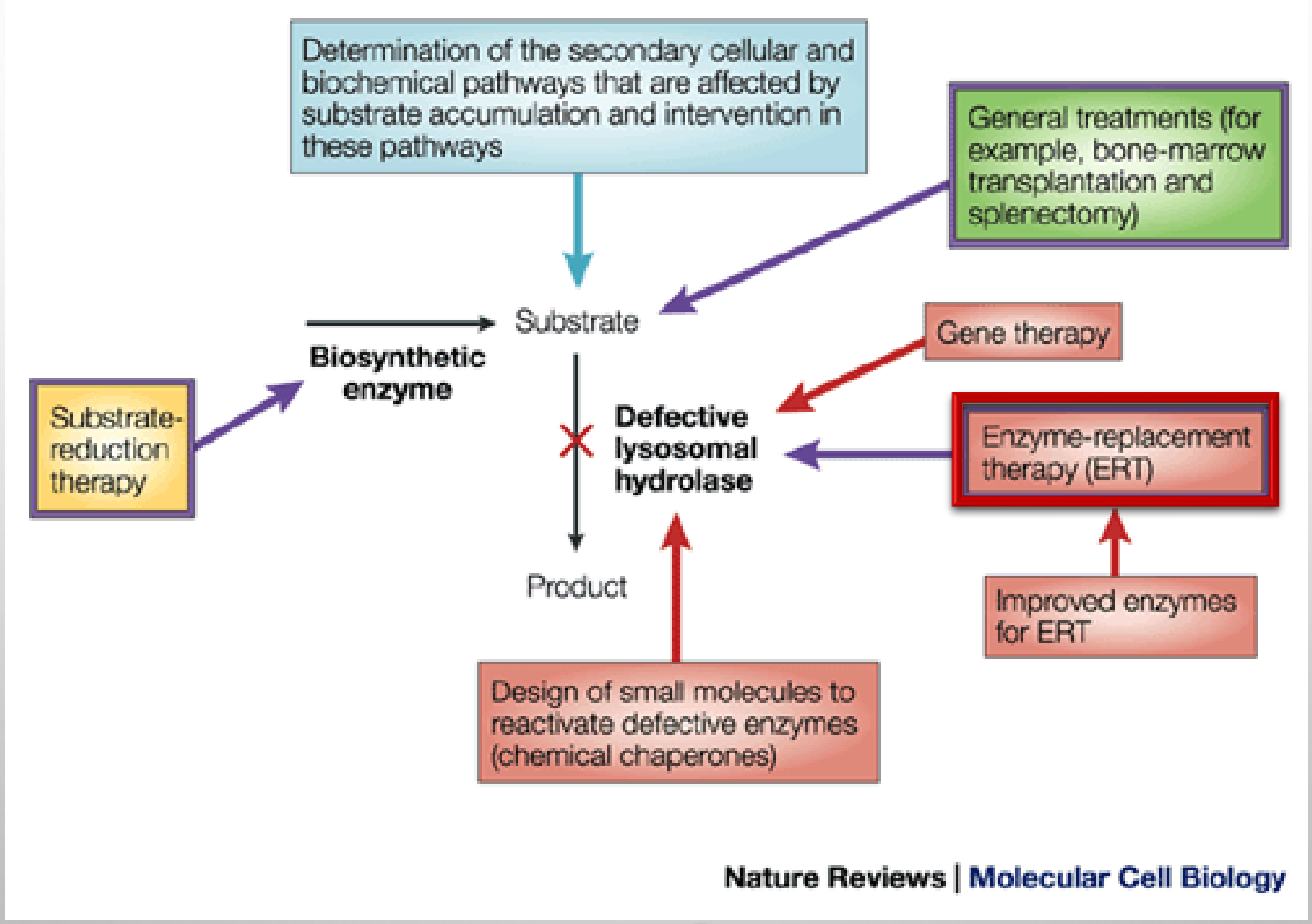


- Lack of targeting of lysosomal enzymes from Golgi
- A deficiency in tagging enzyme
- Features: severe psychomotor retardation that rapidly progresses leading to death between 5 and 8 years of age.



Failure of lysosomal enzyme incorporation into the lysosomes

TREATMENT


Determination of the secondary cellular and biochemical pathways that are affected by substrate accumulation and intervention in these pathways
General treatments (for example, bone-marrow transplantation and splenectomy)
Substrate
Biosynthetic enzyme
Substrate-reduction therapy
Gene therapy
Defective lysosomal hydrolase
Enzyme-replacement therapy (ERT)
Product
Improved enzymes for ERT
Design of small molecules to reactivate defective enzymes (chemical chaperones)
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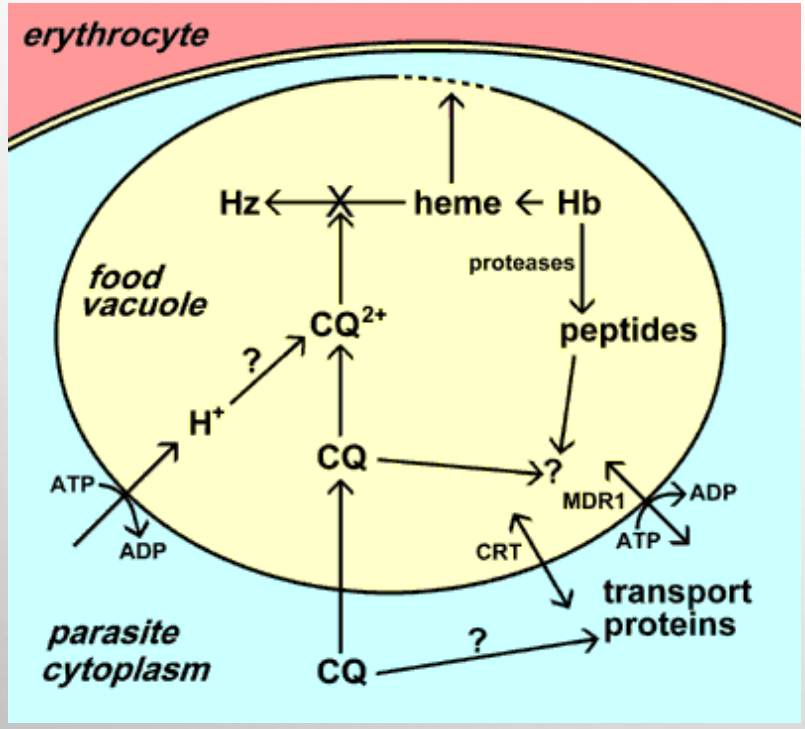
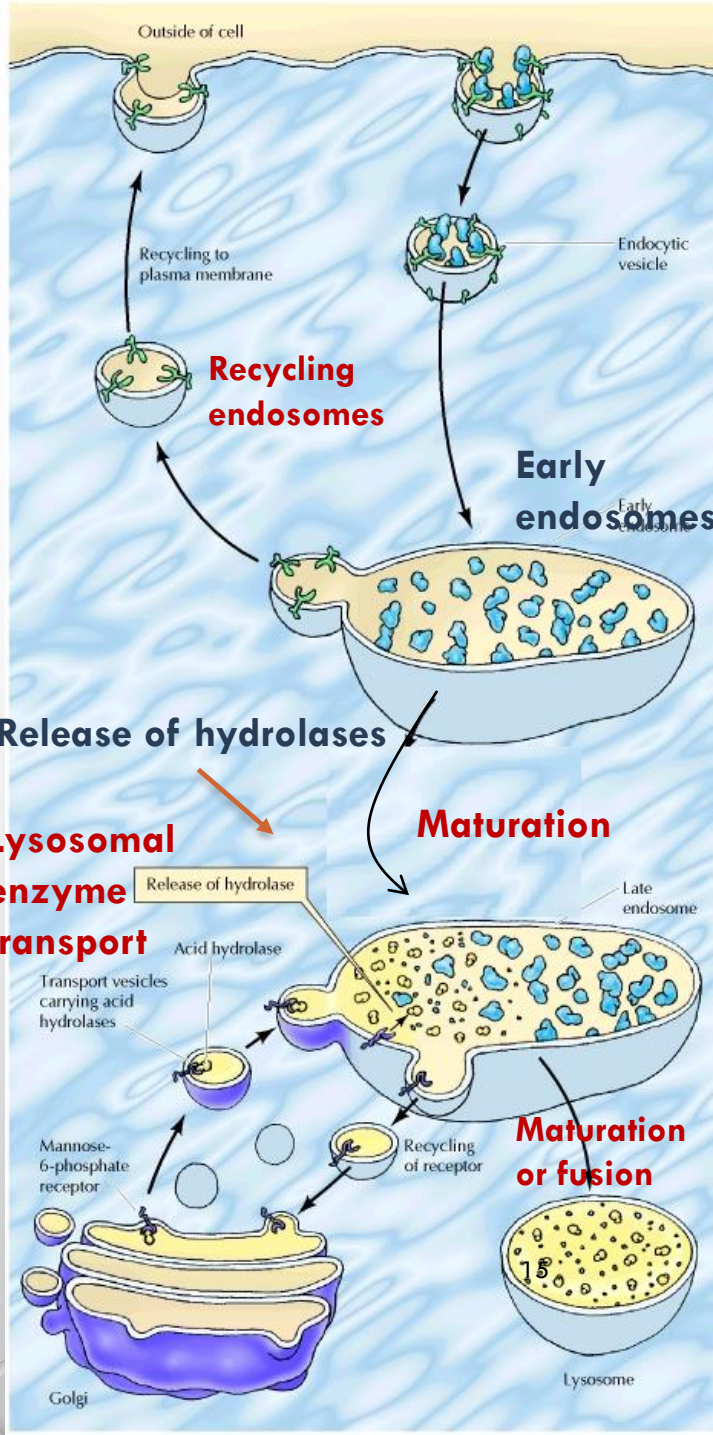
Application: Chloroquine



- Anti-malarial agent
- In the parasite's vaculoe, hemoglobin is digested and heme is modified by heme polymerase.
- If heme is not modified, it is toxic to the parasite.
- Chloroquine crosses membranes into the malarial digestive vacuole and inhibits the enzyme.
- It is a weak base that becomes protonated at acidic pH

Endocytosis

- Molecules are taken up from outside the cell in endocytic vesicles, which fuse with early endosomes.
- Early endosomes separate molecules targeted for recycling from those targeted for degradation.
- Membrane receptors are recycled via recycling endosomes.
- Early endosomes mature into late endosomes.
- Transport vesicles carrying acid hydrolases from the Golgi fuse with late endosomes, which mature into lysosomes.
- The acid hydrolases dissociate from the mannose-6-phosphate receptor and the receptors are recycled to the Golgi.



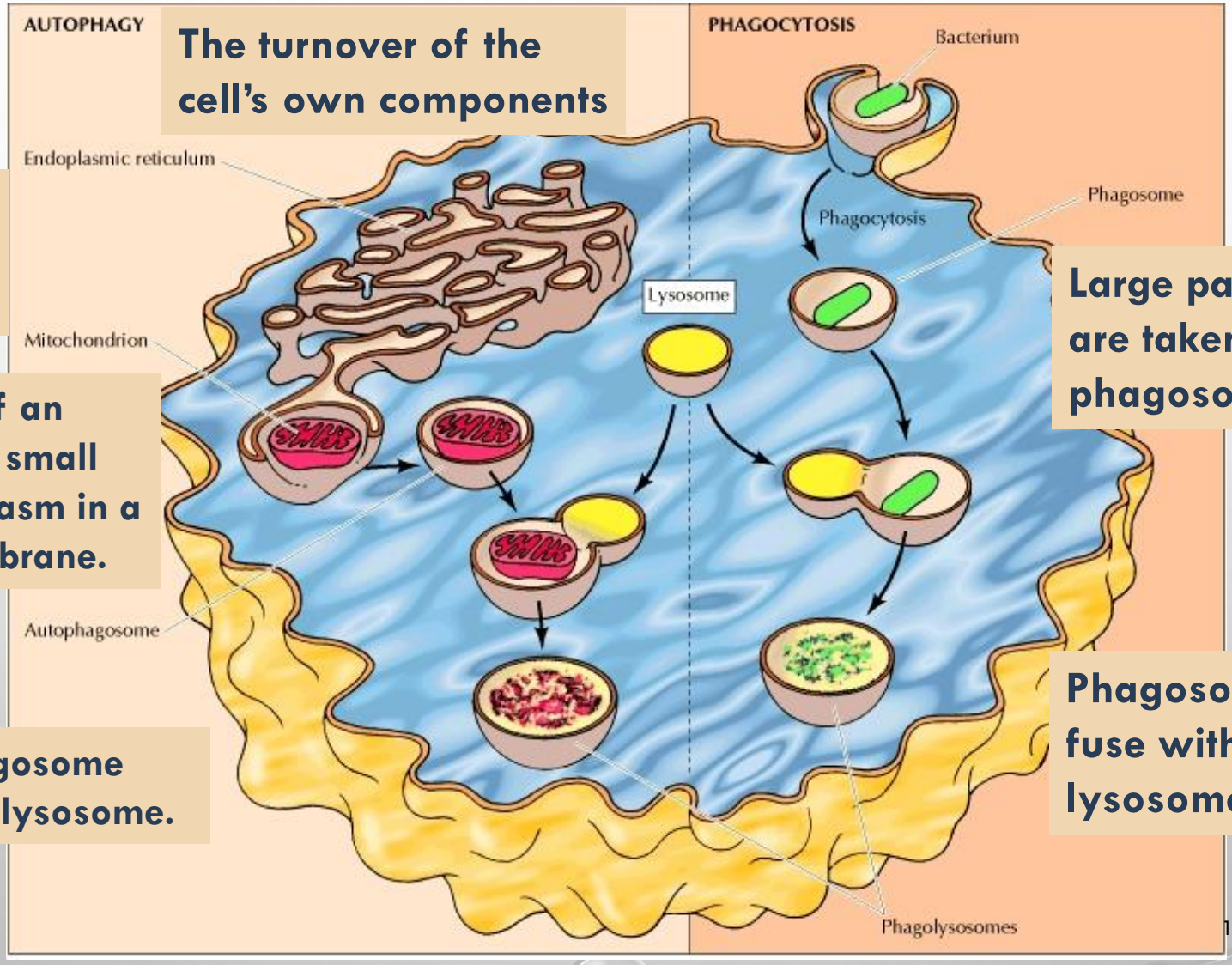
Phagocytosis and autophagy

The turnover of the cell's own components

1. Embryonic development
2. Apoptosis

1. Enclosure of an organelle or a small area of cytoplasm in a cytosolic membrane.

2. Autophagosome fusion with lysosome.



Large particles are taken up by phagosomes

Phagosomes fuse with lysosomes