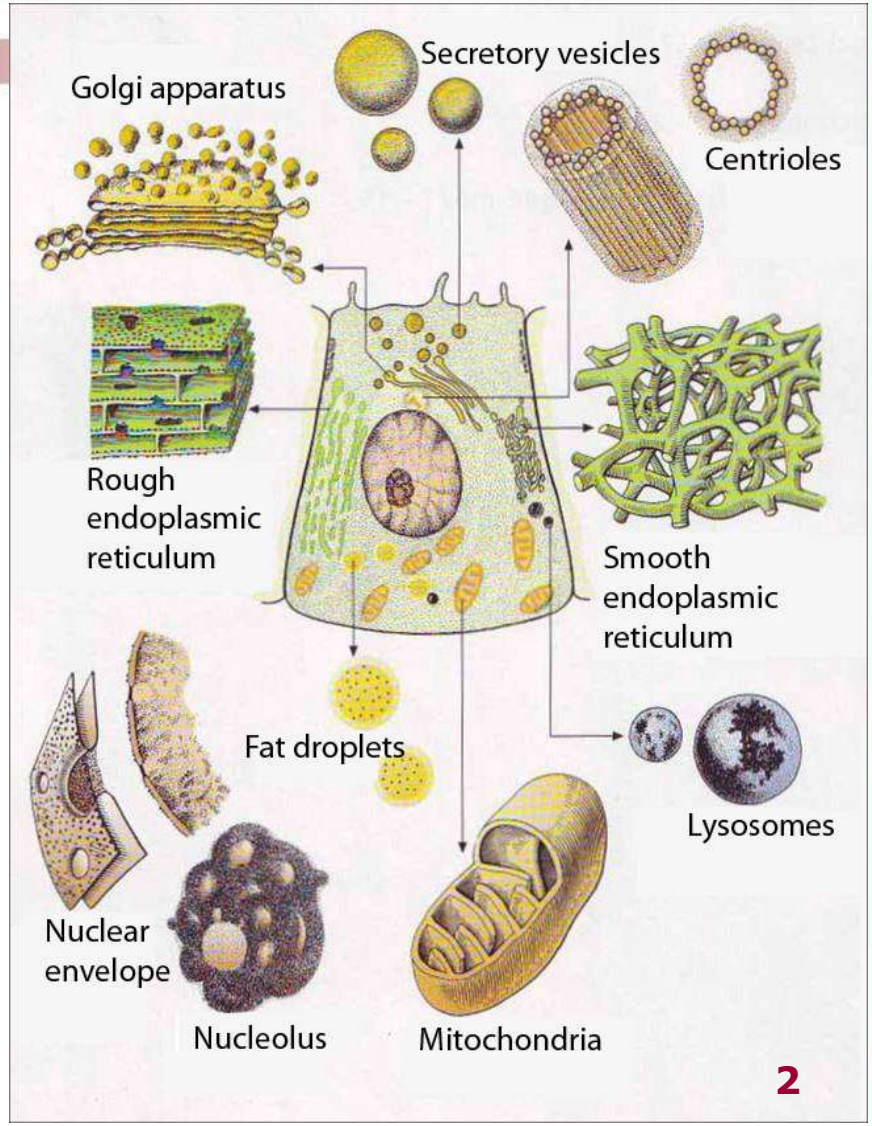
Membranous Organelles

1. **Endoplasmic reticulum:**
   - ✓ **Rough Endoplasmic Reticulum (RER)**
   - ✓ **Smooth Endoplasmic Reticulum (SER)**
2. **Annulate lamellae**
3. **Golgi apparatus**
4. **Secretory vesicles (granules)**
5. **Lysosomes**
6. **Peroxisomes (microbodies)**
7. **Mitochondria**
8. **Coated vesicles**

Membrane-limited organelles

- ✓ Endoplasmic reticulum
- ✓ Annulate lamellae
- ✓ Transport vesicles
- ✓ Golgi apparatus
- ✓ Secretory vesicles
- ✓ Lysosomes
- ✓ Proteasomes
- ✓ Peroxisomes
- ✓ Mitochondria
- ✓ Coated vesicles
- ✓ Nucleus



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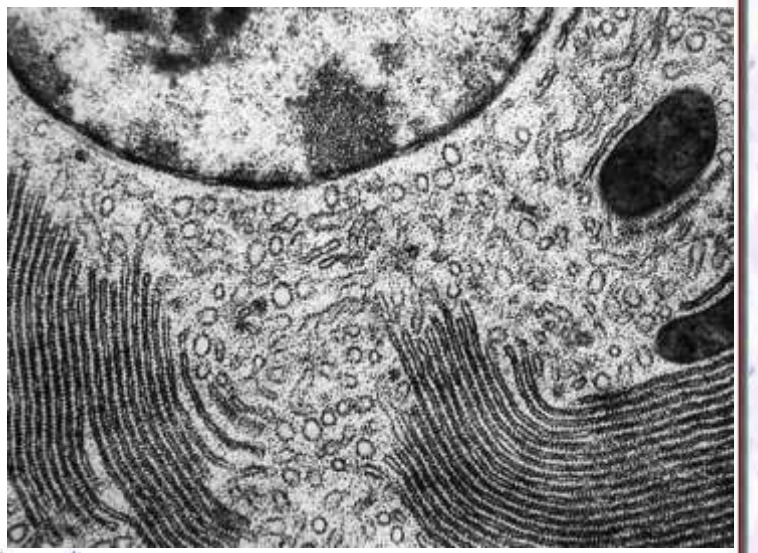
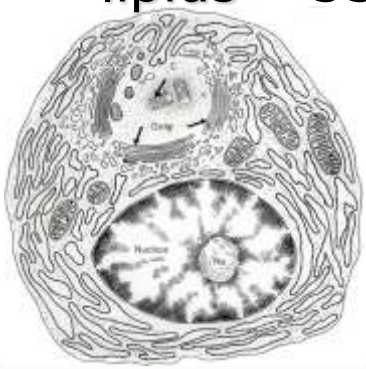
Ergastoplasm

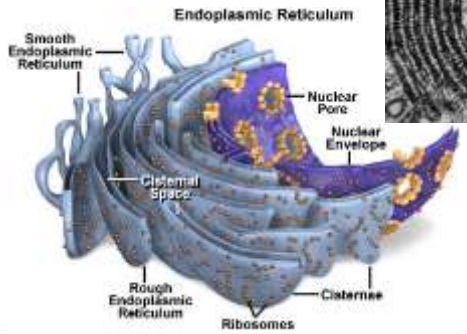
Keith Roberts Porter
(1912-1997)

Albert Claude
(1899-1983)

- Garnier – basophilic substance (RNA), ergastoplasm (Etymology: Gr. *ergaster*, worker + *plasma,* to mold)
- Ultrastructure: Porter, Claude, Fullam, 1945
- An interconnected network (reticulum) of:
  - ✓ cisternae (flattened sacs)
  - ✓ vacuoles
  - ✓ up to 10% of cell volume
- Chemical composition:
  - ✓ proteins – 60-65%
  - ✓ lipids – 35-40%







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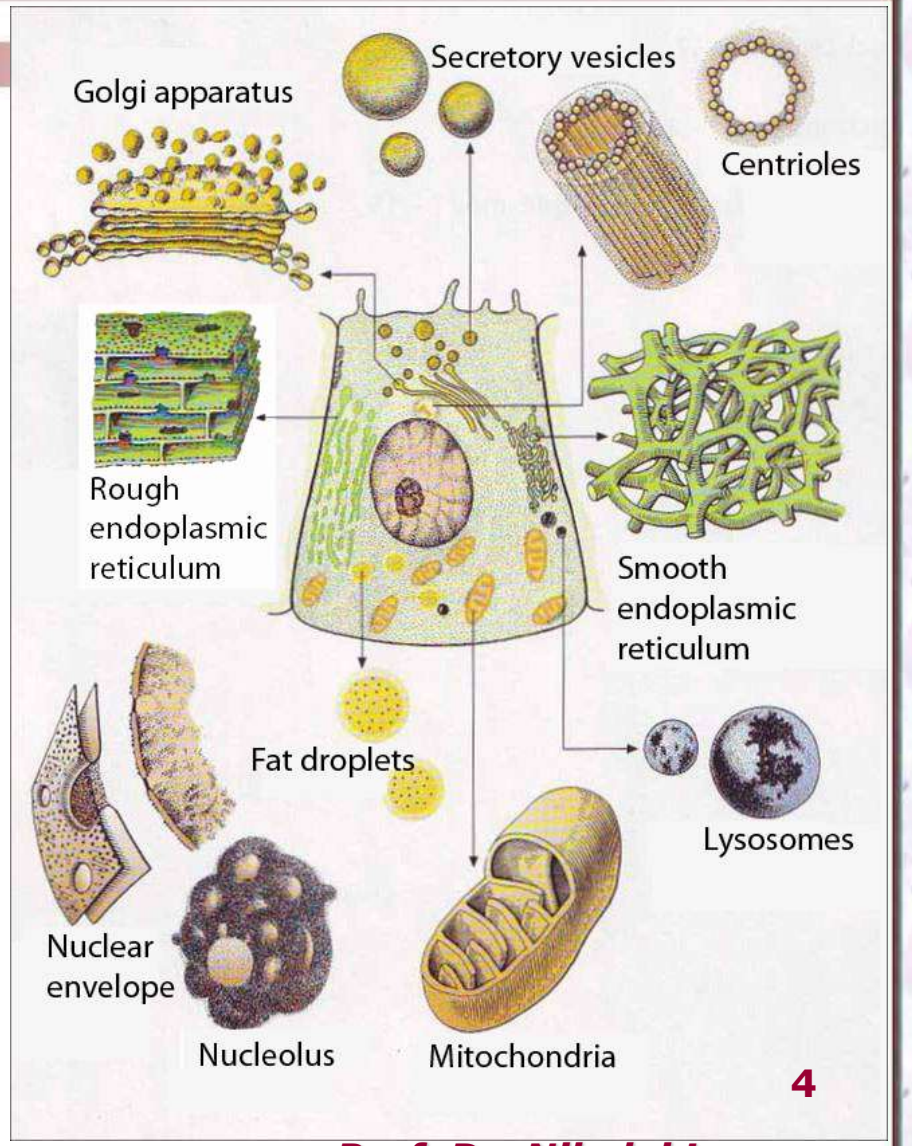
Endoplasmic reticulum

- Endoplasmic reticulum:
  - ✓ rough
  - ✓ smooth

rough endoplasmic reticulum

protein synthesis



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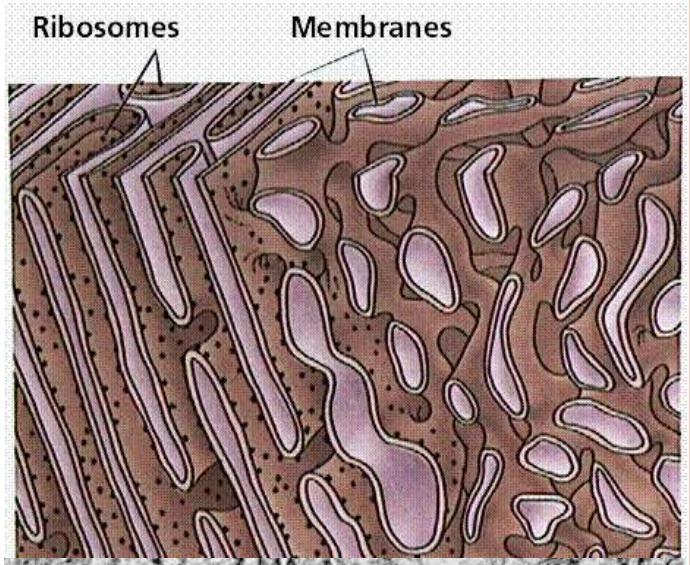
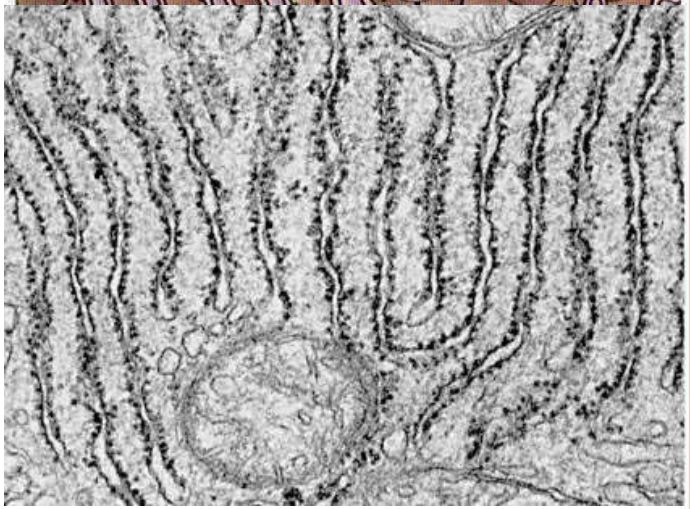
Rough (granular) endoplasmic reticulum

- Structure:
  - ✓ cisternae – 7-8 nm
  - ✓ ribosomes
- Functions:
  - ✓ protein synthesis and segregation:
    - ➢ intracellular utilization
    - ➢ extracellular export
  - ✓ initial glycosylation of glycoproteins
  - ✓ phospholipid synthesis
- Prominent in protein-synthesizing cells:
  - ✓ blast cells
  - ✓ exocrine gland cells
  - ✓ plasma cells
  - ✓ neurons





Rough (granular) endoplasmic reticulum

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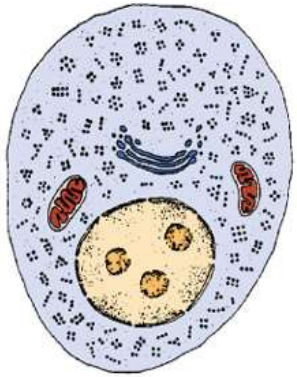
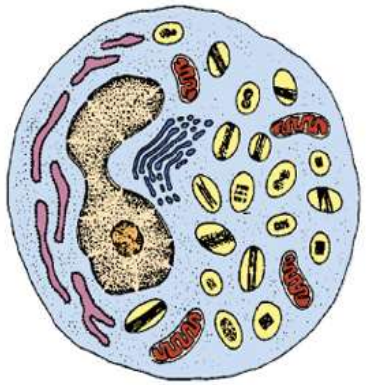
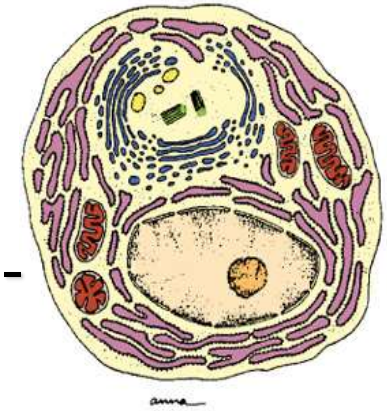
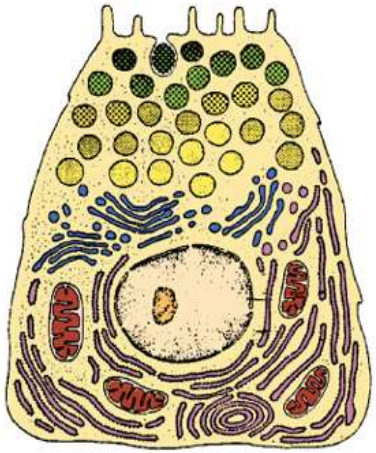

A Erythroblast


B Eosinophilic leukocyte


C Plasma cell


D Pancreatic acinar cell

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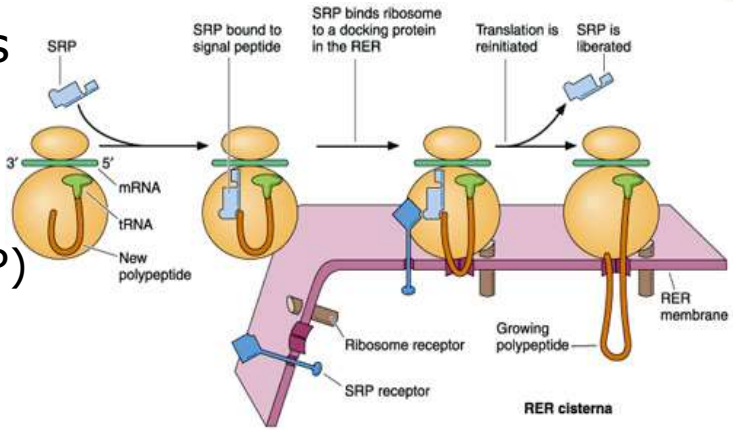
Protein synthesis

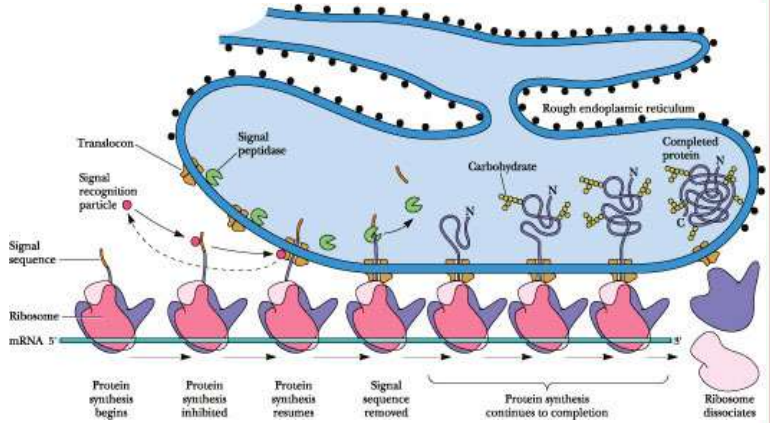
- Signal hypothesis for the synthesis of secretory proteins:

✓ signal sequence of mRNA – 20-25 hydrophobic amino acids

✓ integral membrane proteins
  - ribophorins I and II
  - signal-recognition particle (SRP)
  - docking protein (SRP receptor protein)
  - translocon (translocator or translocation channel)

✓ steps:
  - initial (core) glycosylation
  - formation of disulfide bounds
  - protein folding and assembly – chaperones
  - proteolytic release of newly synthesized protein





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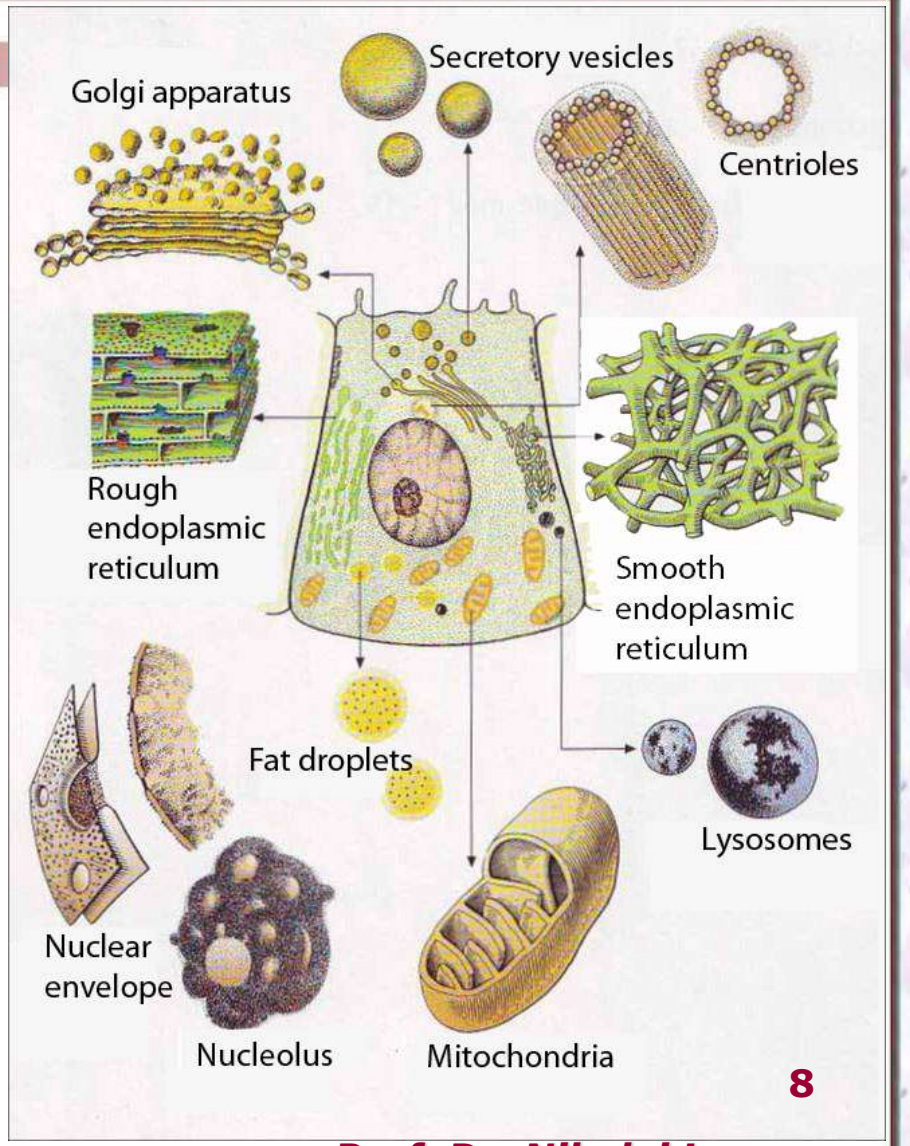
Endoplasmic reticulum

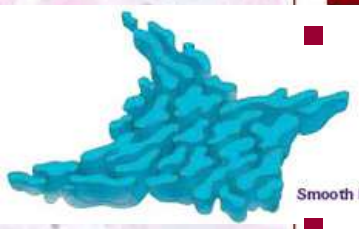
- Endoplasmic reticulum:

smooth endoplasmic reticulum

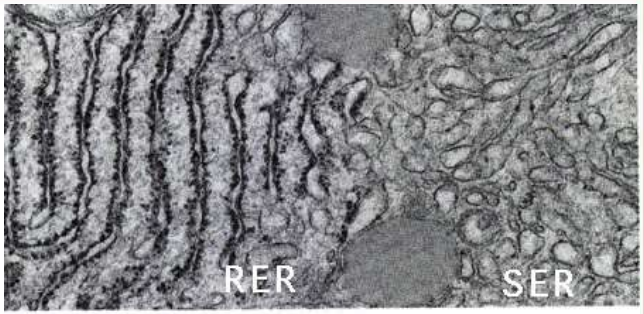
lipid synthesis
steroid synthesis
detoxification

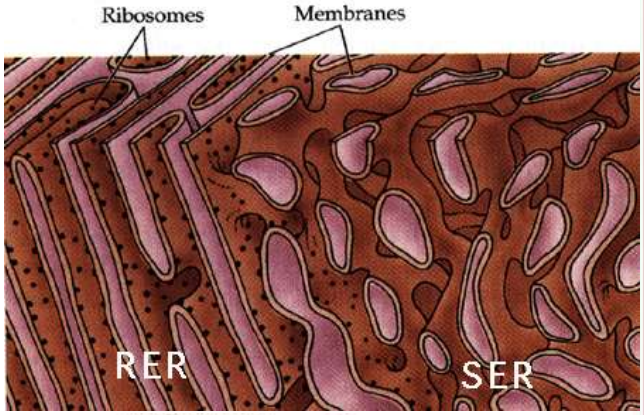


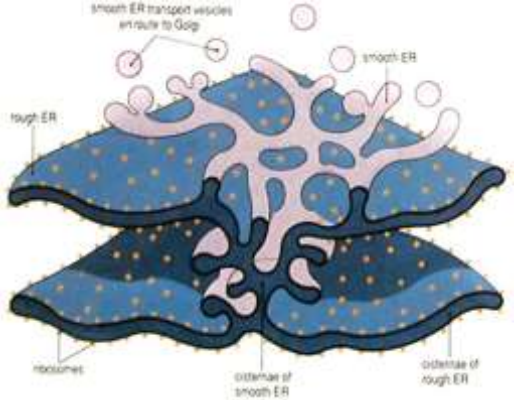
Smooth (agranular) endoplasmic reticulum



- Structure:
  - ✓ tubular cisternae – 6-7 nm
  - ✓ lacks the associated ribosomes
- Functions:
  - ✓ lipid absorption and metabolism
  - ✓ glycogen metabolism
  - ✓ synthesis of steroid hormones
  - ✓ regulation of Ca^{2+} concentration
  - ✓ drug detoxification
- Well-developed in:
  - ✓ steroid-producing cells:
    - ➢ cells of adrenal cortex
    - ➢ interstitial cells of gonads
  - ✓ other cell types:
    - ➢ liver cells (hepatocytes)
    - ➢ skeletal and cardiac muscle cells – sarcoplasmic reticulum
    - ➢ nerve cells (neurons)
    - ➢ glandular cells

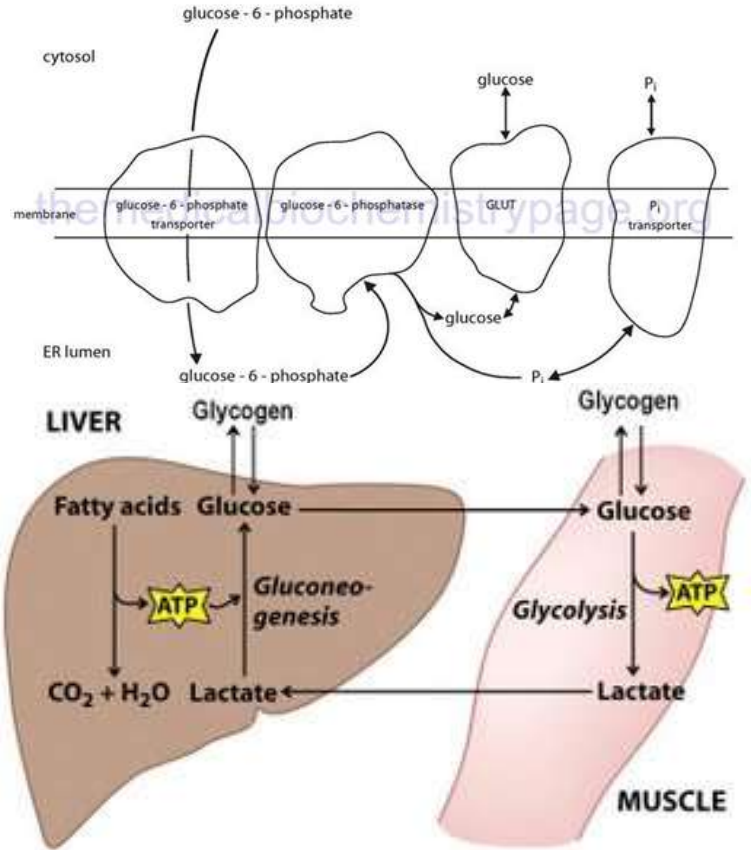


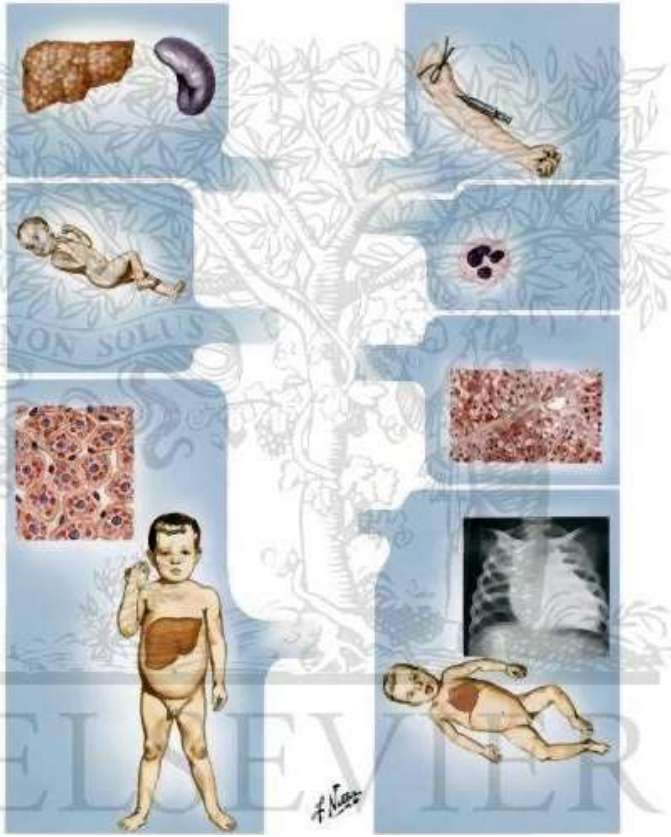




Endoplasmic reticulum: clinical significance

- Morbus von Gierke – type I glycogen storage disease:
  - ✓ gene deficiency of the enzyme glucose-6-phosphatase
  - ✓ increased glycogen storage in liver and kidneys





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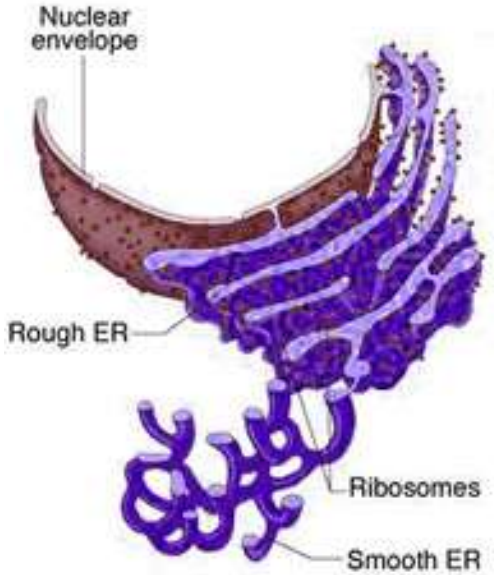
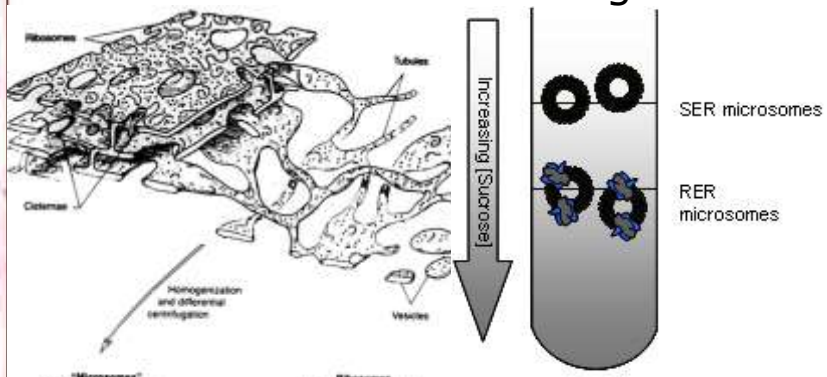
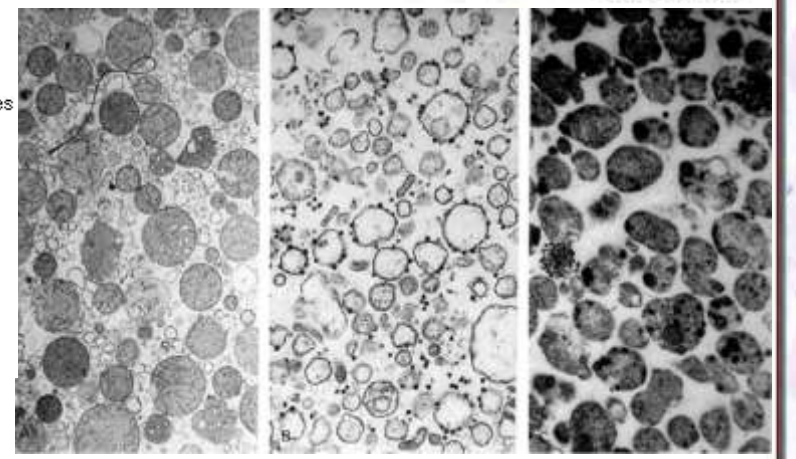
Endoplasmic reticulum: origin

- rough ER:
  - ✓ continuous with the outer layer of the nuclear envelope
- smooth ER:
  - ✓ degranulation of rough ER
- microsomes – 100 nm
  - ✓ not ordinarily present in living cells
  - ✓ vesicle-like artifacts formed from the ER
  - ✓ last-order fraction, achieved by differential centrifugation

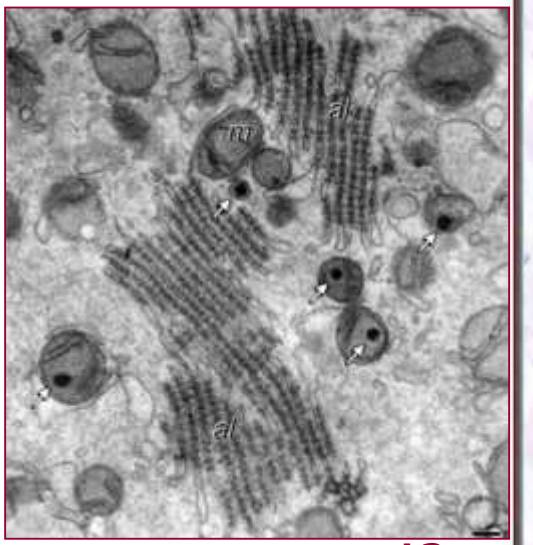


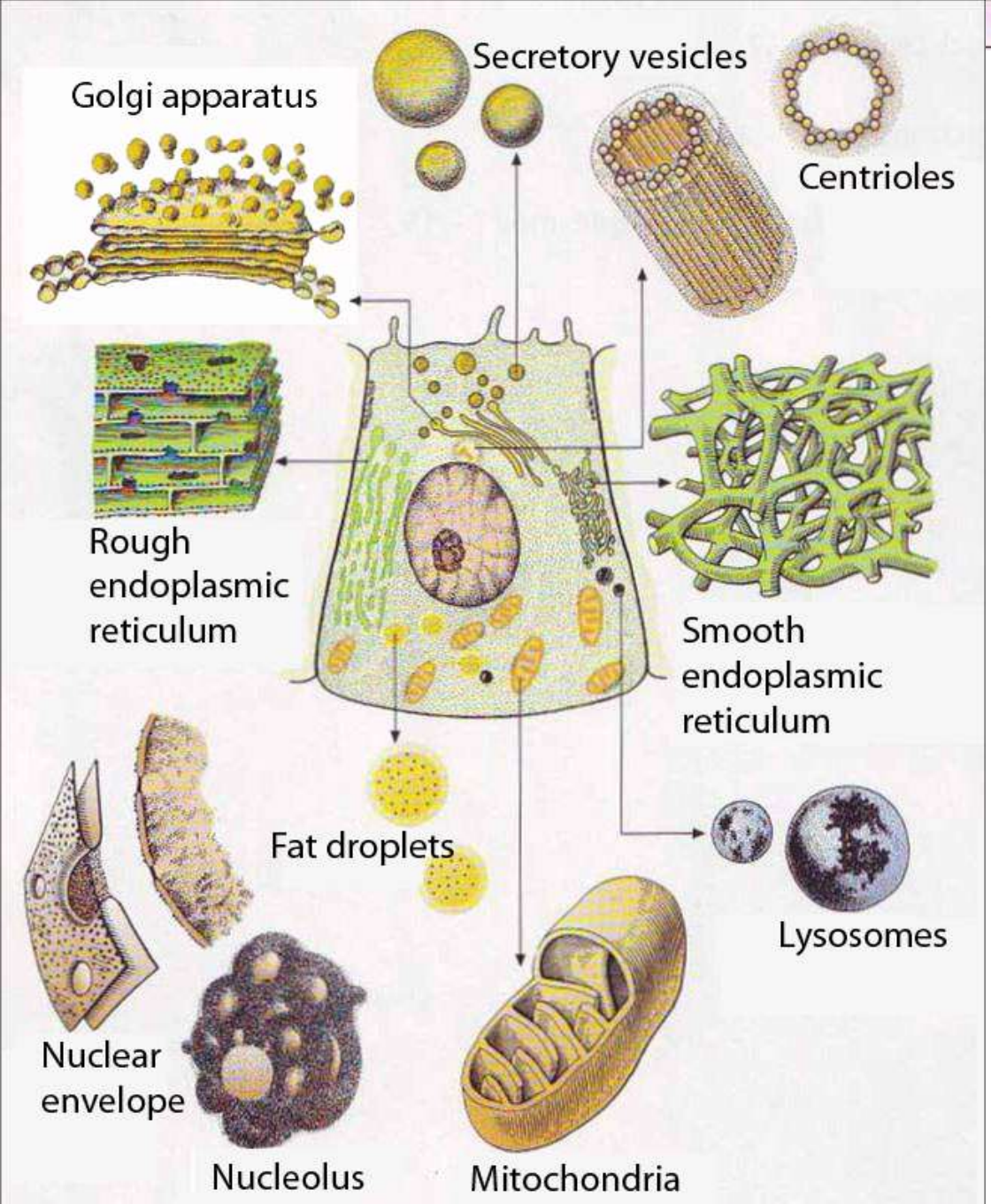




Annulate lamellae

- Structure:
  - ✓ stacks of flat, membranous cisternae
  - ✓ contain numerous pore complexes
  - ✓ frequently seen as extensions of RER cisternae
  - ✓ intermediate stage between the ER and the nuclear envelope
- Origin:
  - ✓ derived from the nuclear envelope
- Abundant in:
  - ✓ human oocytes
  - ✓ spermatozoa
  - ✓ Sertoli cells in testis
  - ✓ tumor cells
- Function:
  - ✓ largely unknown
  - ✓ attachment sites for stored RNA
  - ✓ reserve fund for nuclear envelope

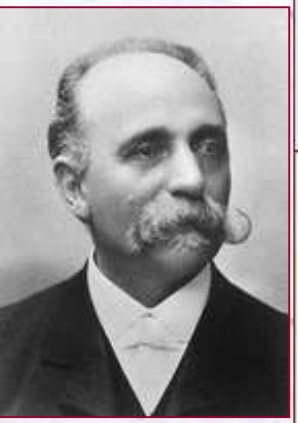




Membranous Organelles

Golgi Apparatus

sorting

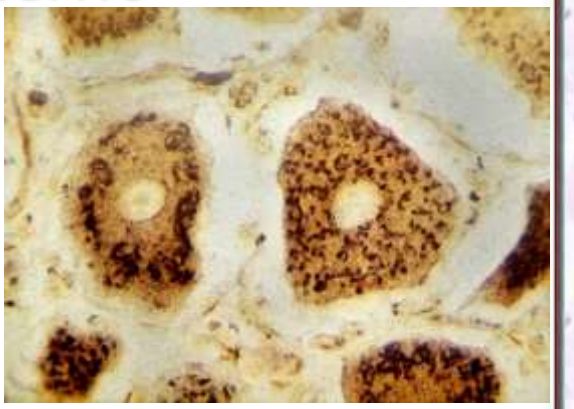


Cammillo Golgi
(1843-1926)

Golgi Apparatus

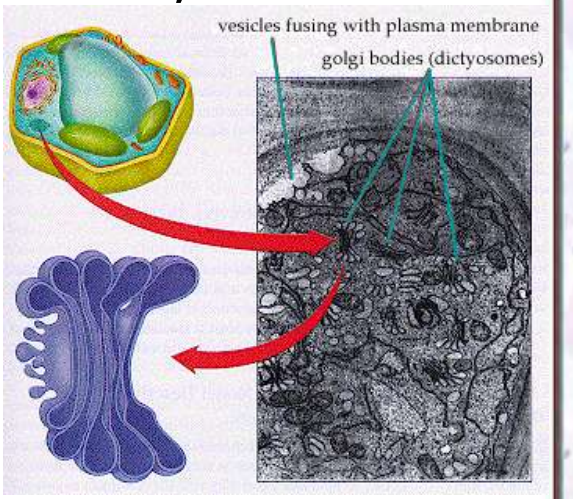
The Nobel Prize in Physiology or Medicine 1906

- *ital*. – *apparato reticolare interno:* Cammillo Golgi, 1886, 1898
- Synonyms:
  - ✓ Golgi complex
  - ✓ Golgi zone
  - ✓ Golgi bodies
- Ultrastructure: A. Dalton, M. Felix, 1953



Dictyosome:

- stacks of smooth membrane-limited:
  - ✓ 3-12 flattened cisternae (50-200 nm)
  - ✓ vesicles (30-50 nm)
  - ✓ large, clear vacuoles (200-300 nm)



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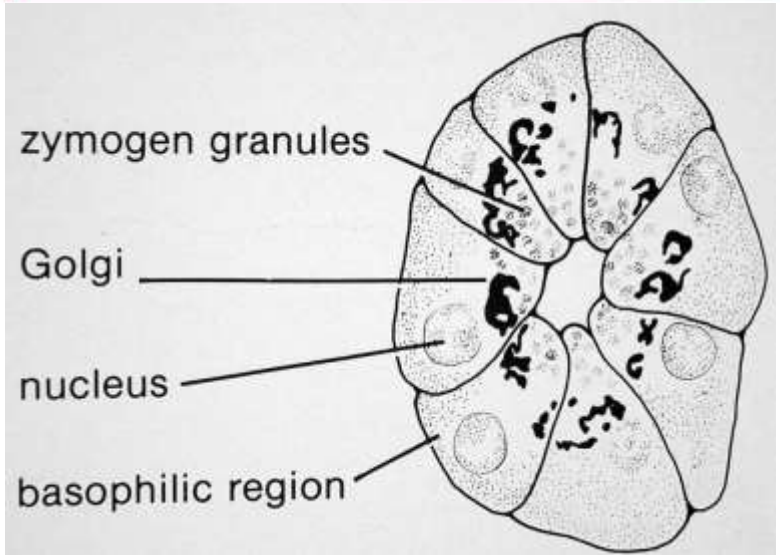
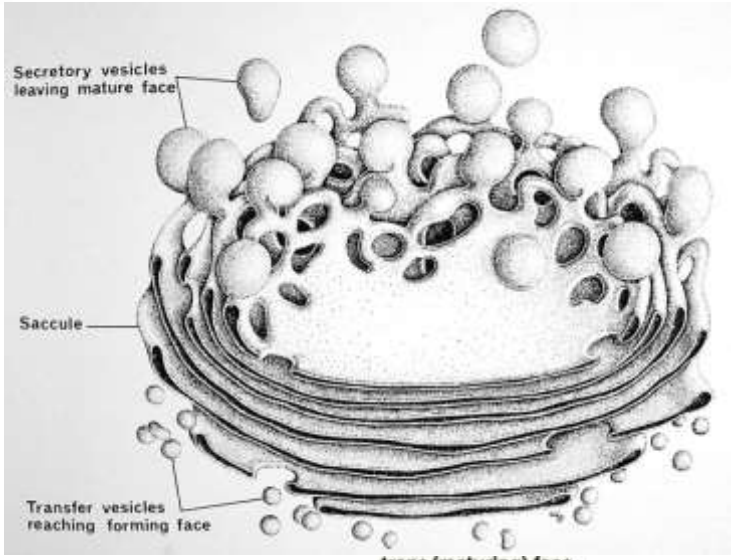
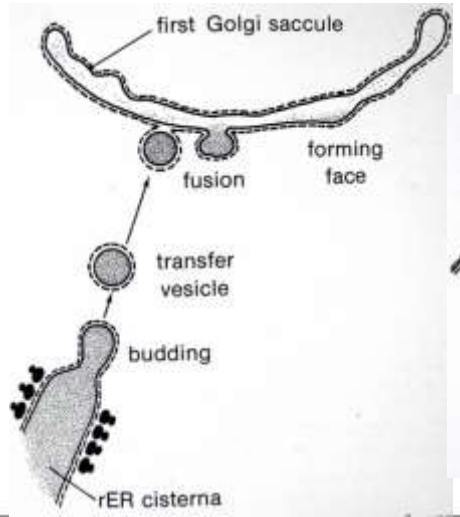
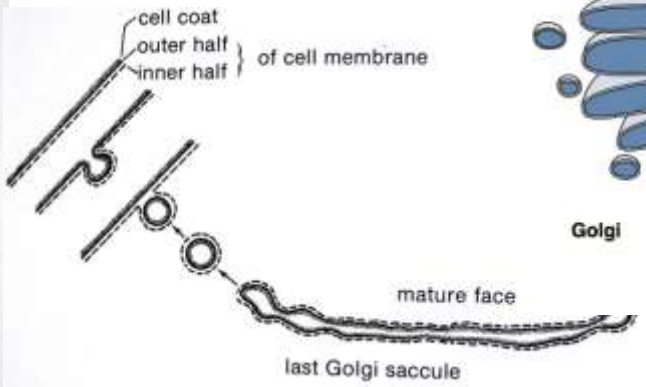
Golgi Apparatus – structure

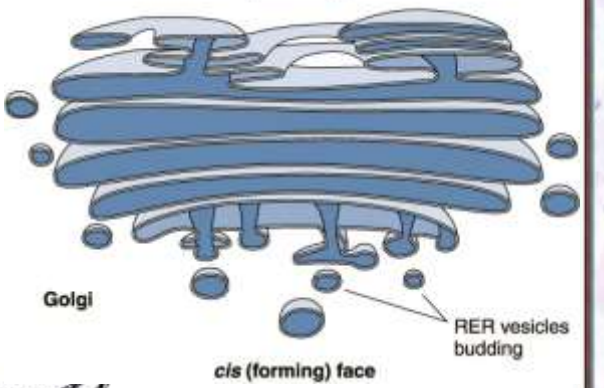
- both morphologically and functionally polarized structure:

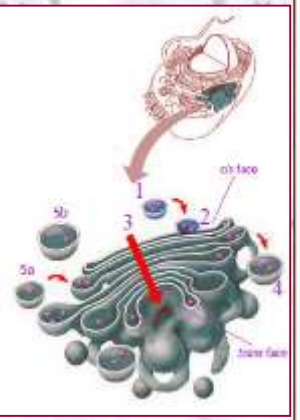












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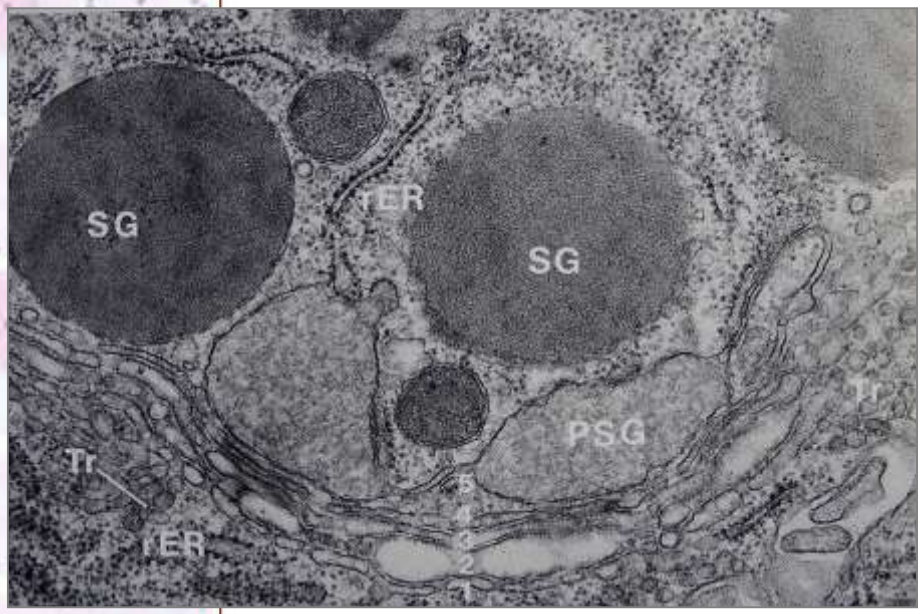
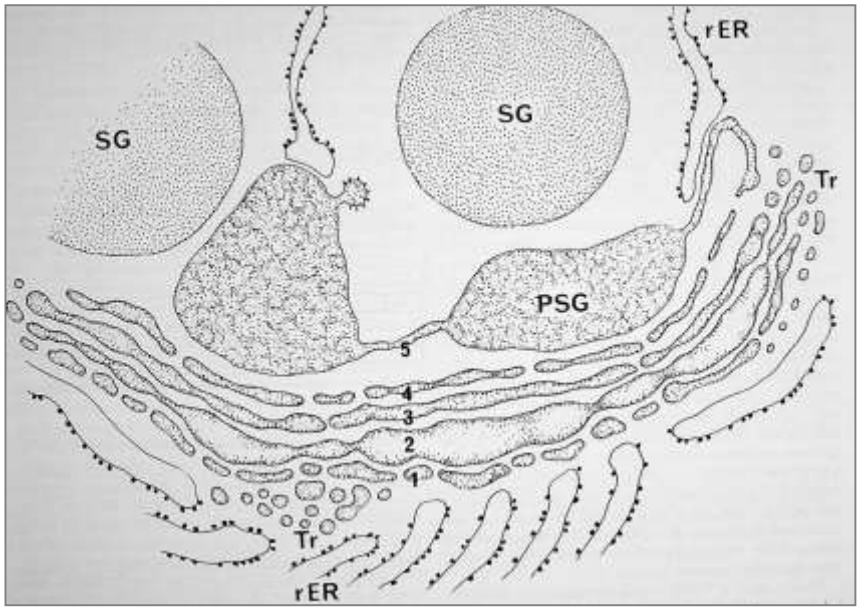
Golgi Apparatus – internal polarity





GERL* concept – *zone of Novikoff (1964)

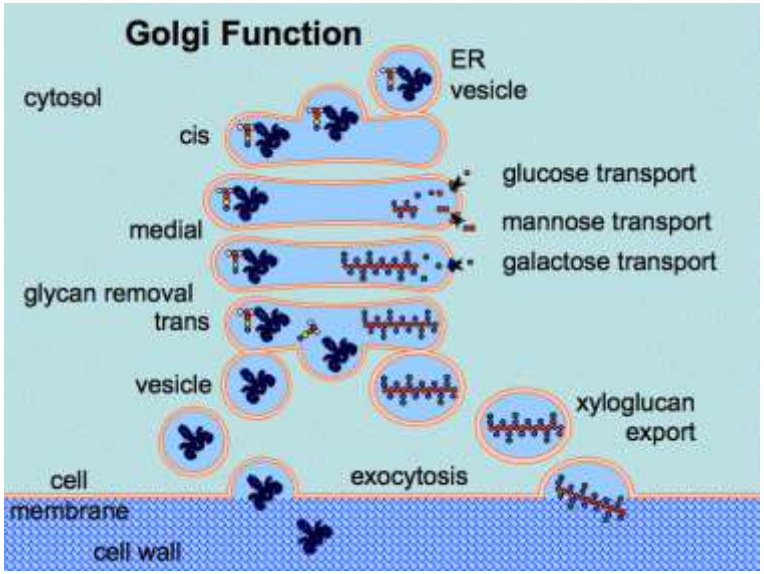
G – ***Golgi apparatus***

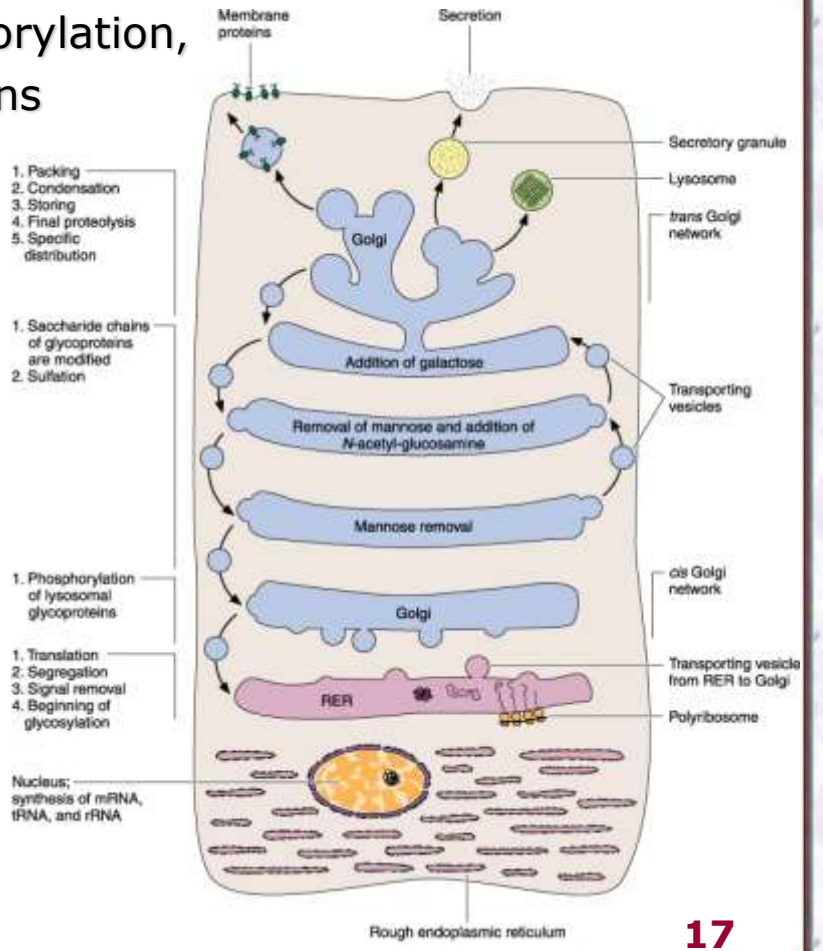
ER – ***Endoplasmic Reticulum***

L – ***Lysosomes***

Golgi Apparatus – functional polarity

- trafficking and sorting of proteins:
  - ✓ glycosylation, sulfation, phosphorylation, and limited proteolysis of proteins
  - ✓ initiates packing, concentration, and storage of secretory products





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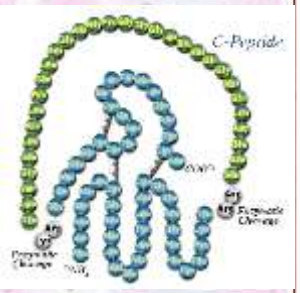
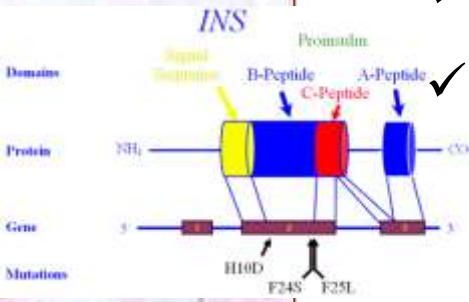
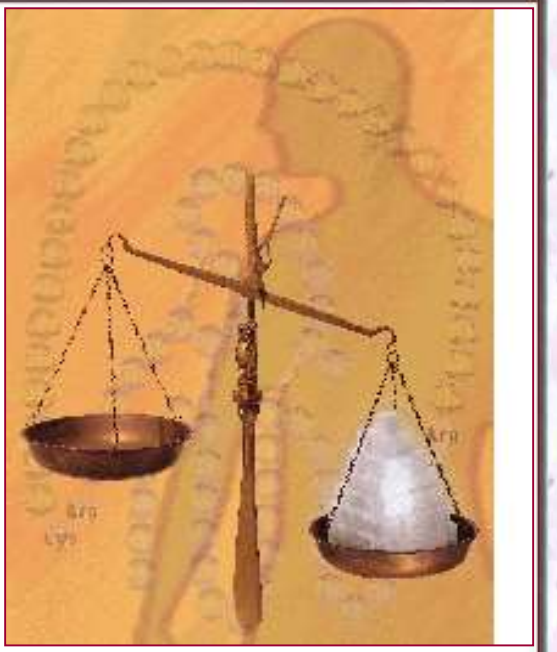
Golgi Apparatus – clinical relevance





- Hyperproinsulinaemia:
  - ✓ immature forms of insulin make up the majority of circulating insulin
- Mucolipidosis – a group of inherited metabolic disorders in which mucopolysaccharides and lipids accumulate in tissues:
  - ✓ type I (sialidosis) – a deficiency of the lysosomal enzyme sialidase
  - ✓ type II (inclusion, I-cell disease) - a deficiency in a phosphorylating enzyme normally present in the Golgi complex ⇨ lysosomes contain large inclusions of undigested glycosaminoglycans and glycolipids
  - ✓ type III (pseudo-Hurler polydystrophy) – the glycoproteins are not destined for lysosomes
  - ✓ type IV – alterations of a protein in the cell that is believed to be involved in the movement of molecules such as calcium across cell membranes



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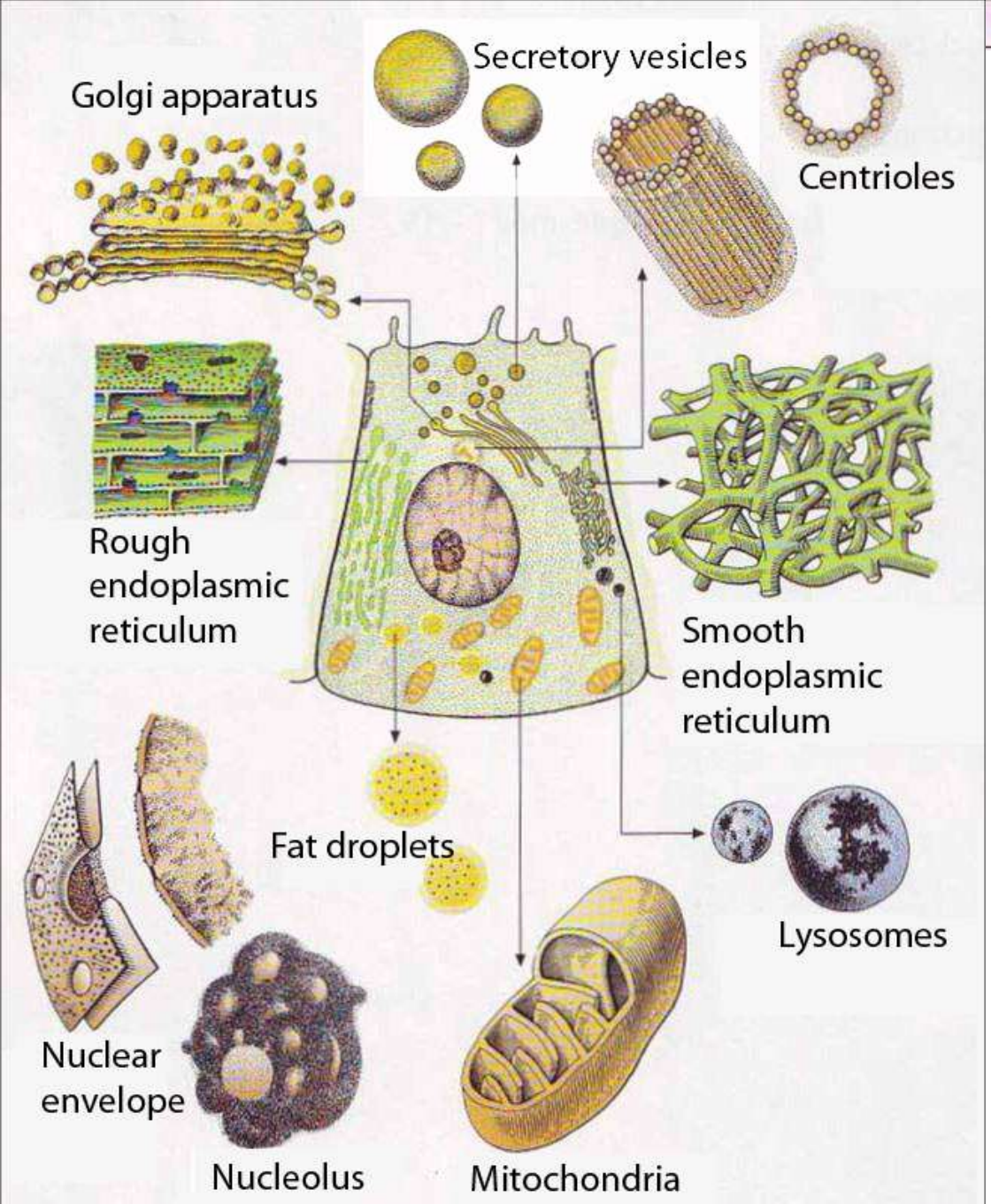
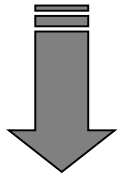
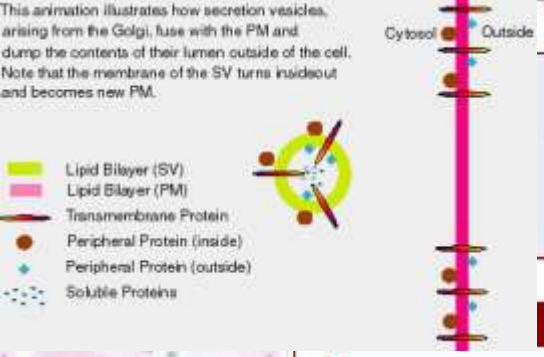


Membranous Organelles

Secretory vesicles (granules)

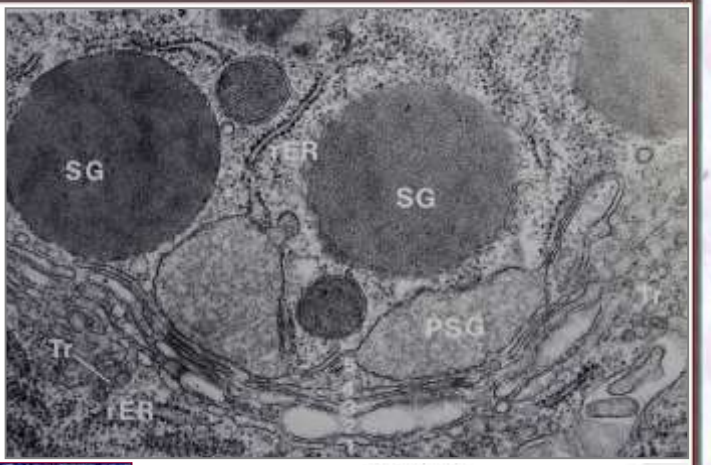


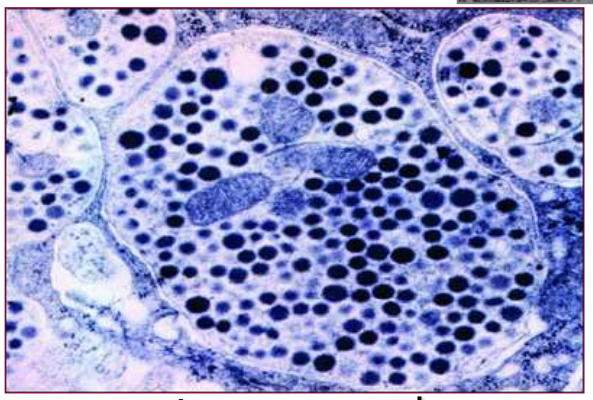
storage and release of secretory products



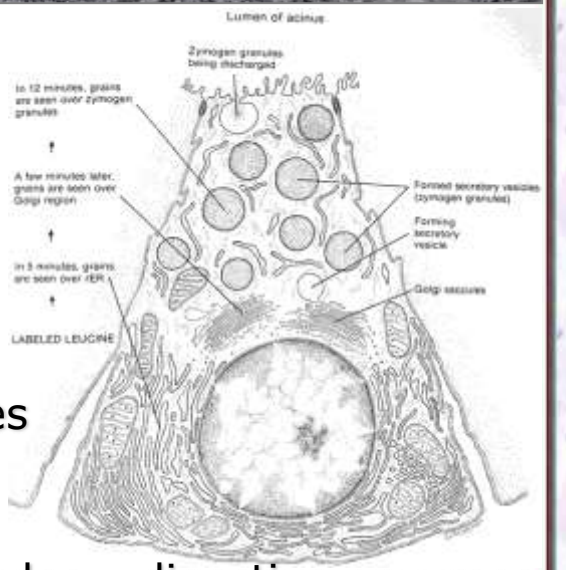
Secretory vesicles

- Secretory granules:
  - ✓ shape – spherical
  - ✓ diameter – 0.15 μm->1 μm
  - ✓ clathrin-coated vesicles
  - ✓ core – histamine, chromogranin B, secretogranin II





Neurosecretosomes – hormones



Zymogen granules – digestive enzymes

Synaptic vesicles – transmitters

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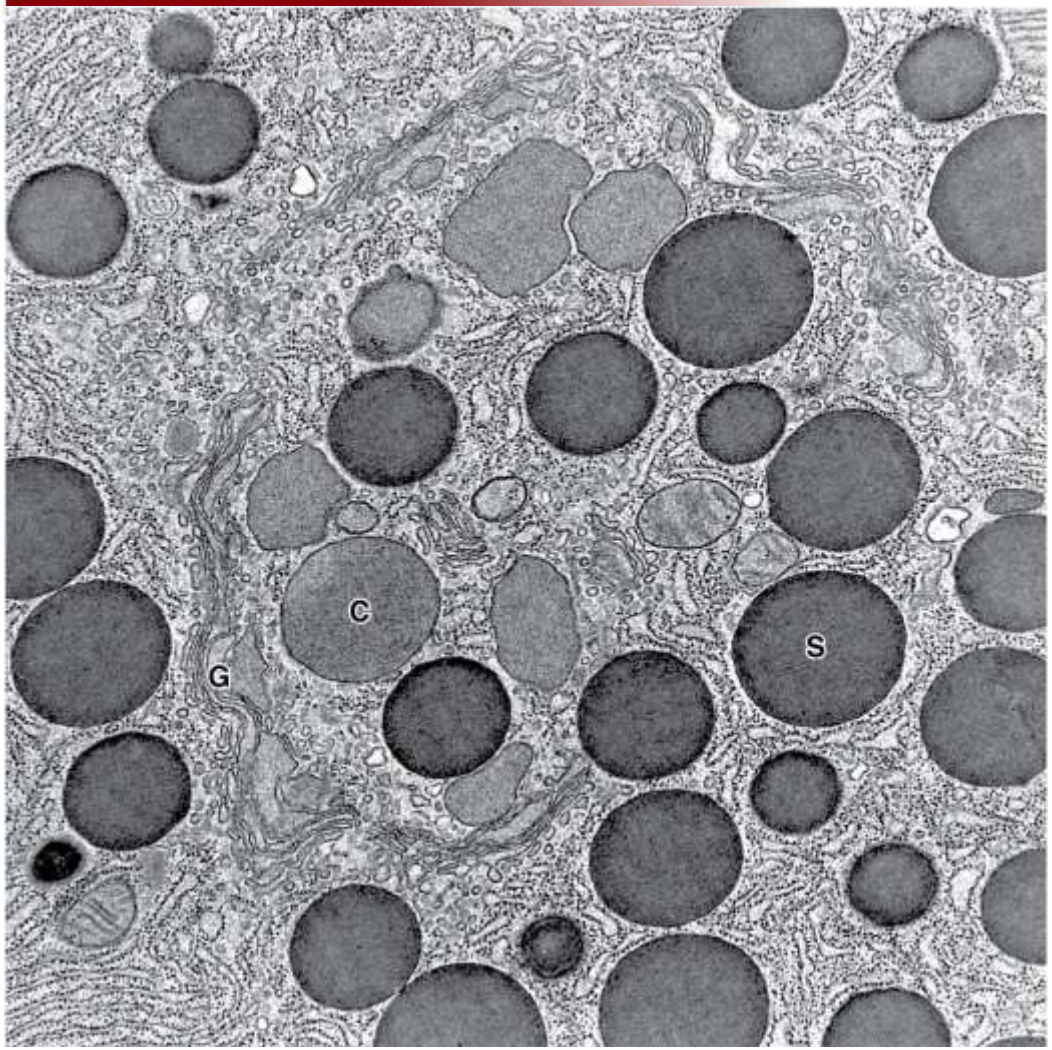
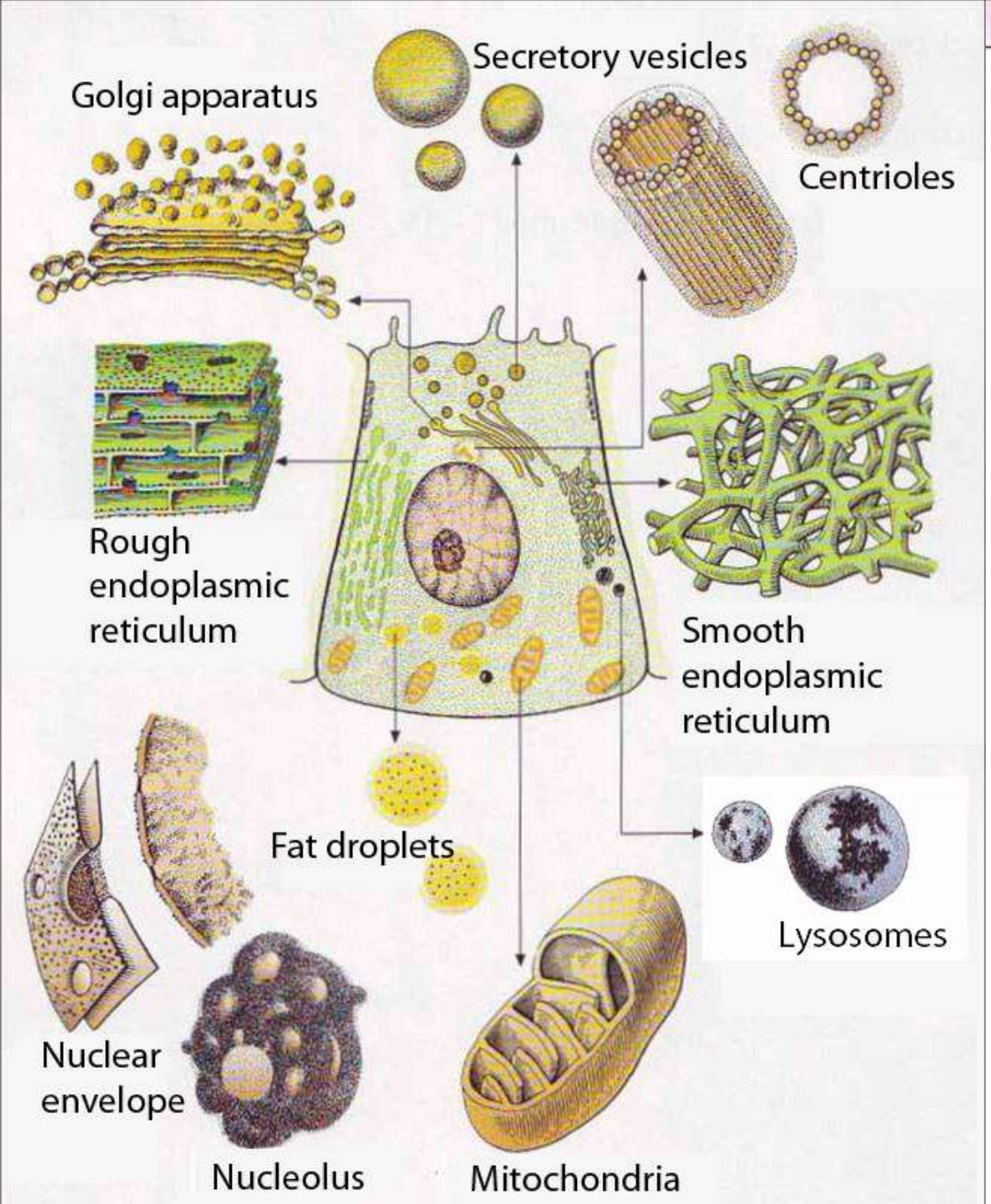
Secretory vesicles





Membranous Organelles

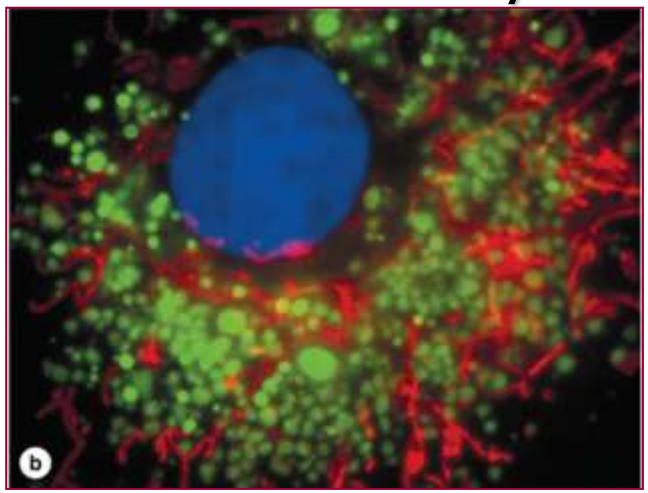
Lysosomes

intracellular digestion

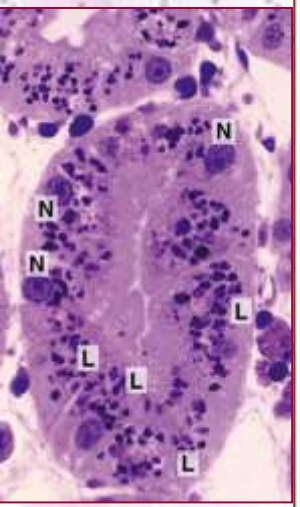
Christian de Duve
(1917-2013)

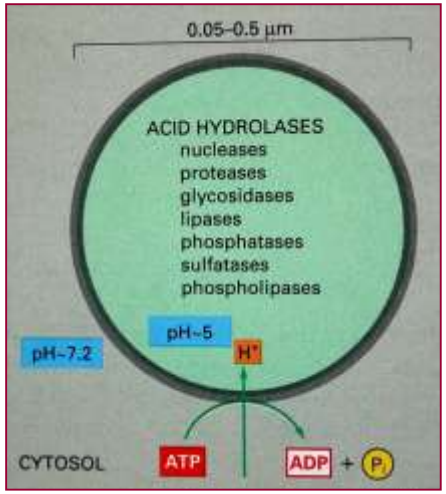
Lysosomes

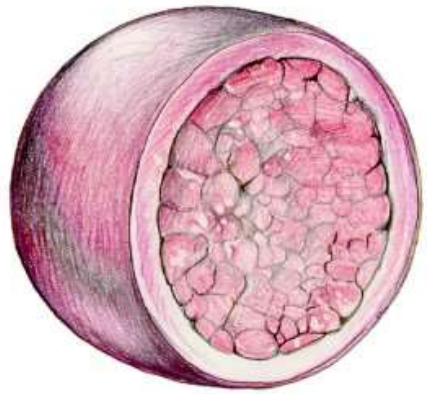
- (Gr. *lysis*, dissolution or destruction + *soma*, body)
- Discovered by Christian de Duve, 1955



The Nobel Prize in Physiology or Medicine 1974



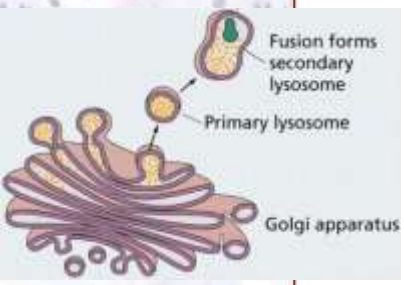


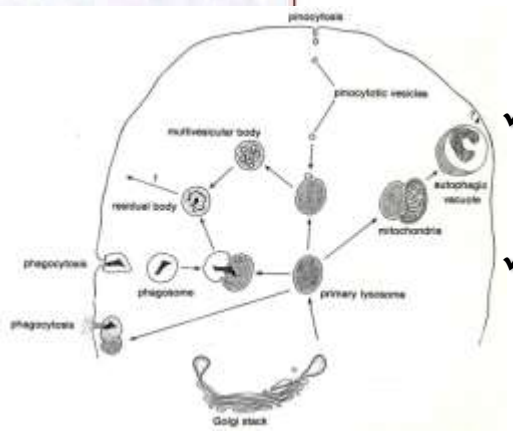


Spherical organelles:

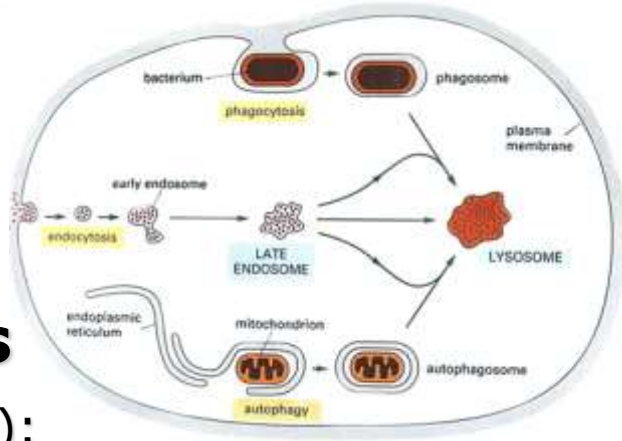
- ✓ size – 0.05-0.5 μm
- ✓ single layer (unit) membrane – 6 nm
- ✓ lysosomal matrix – pH 5 ⇨ favorable for enzymatic activity
- ✓ more than 40 hydrolytic enzymes

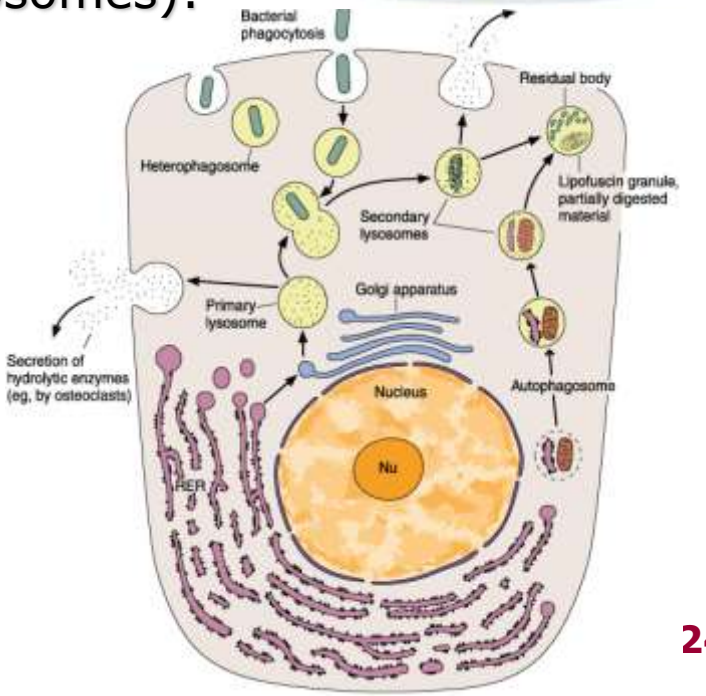
Lysosomes – stages





- **Primary lysosomes:**
  inactive enzymes
- **Secondary lysosomes**
  (phagosomes, phagolysosomes):
  - ✓ heterolysosomes (heterophagosomes)
  - ✓ autophagosomes (autophagic vacuoles)
  - ✓ residual bodies (telolysosomes)
    ⇨ lipofuscin droplets
  - ✓ pinocytotic vesicles
  - ✓ multivesicular bodies





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Lysosomes – ultrastructure

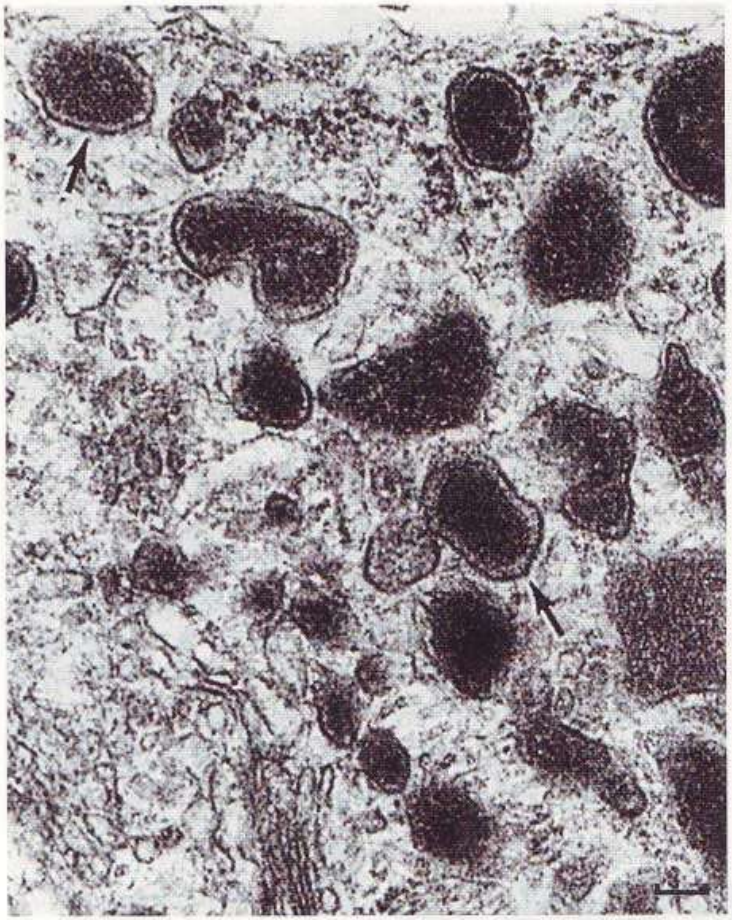
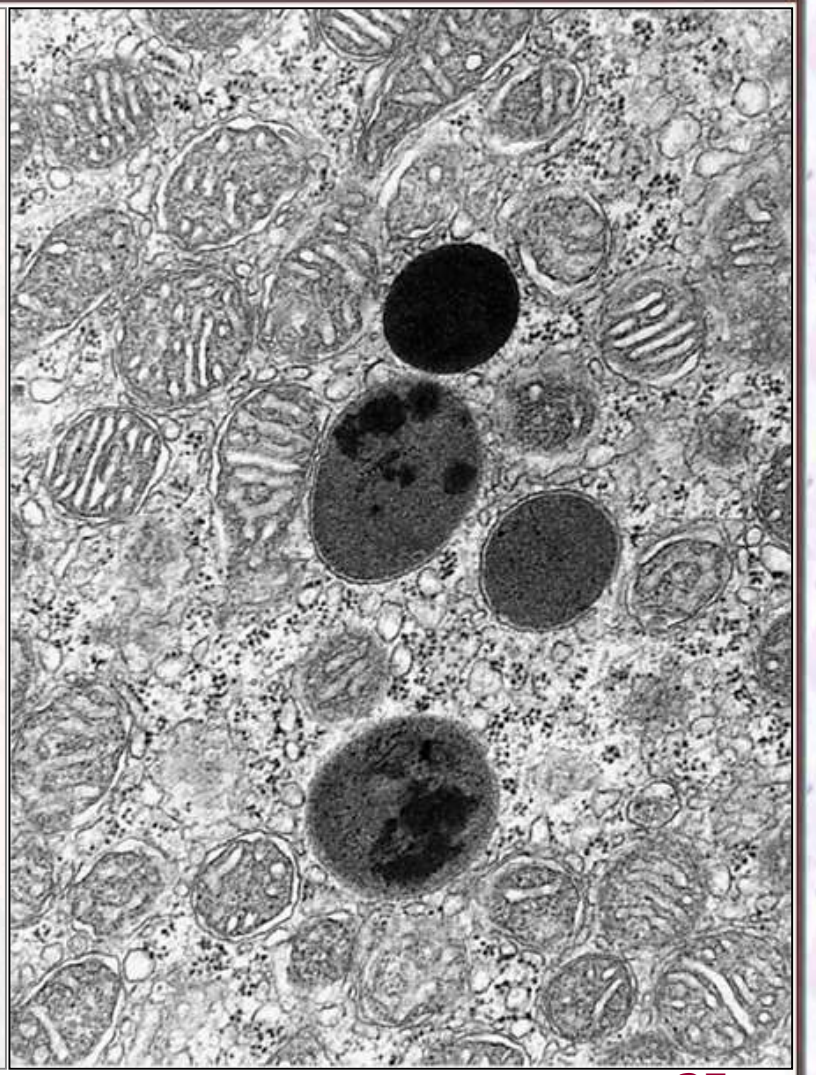
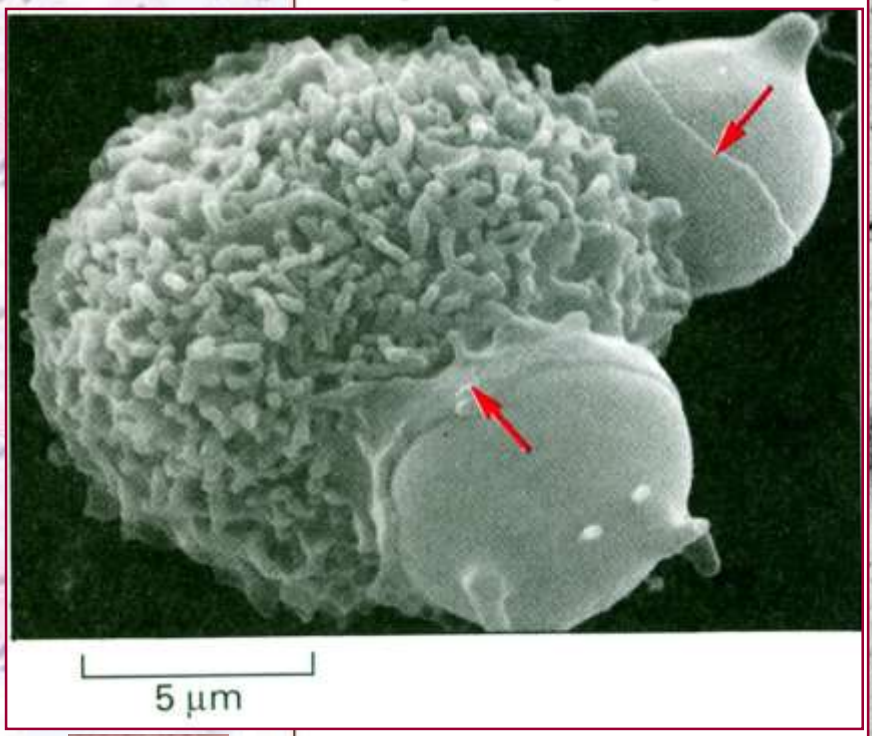


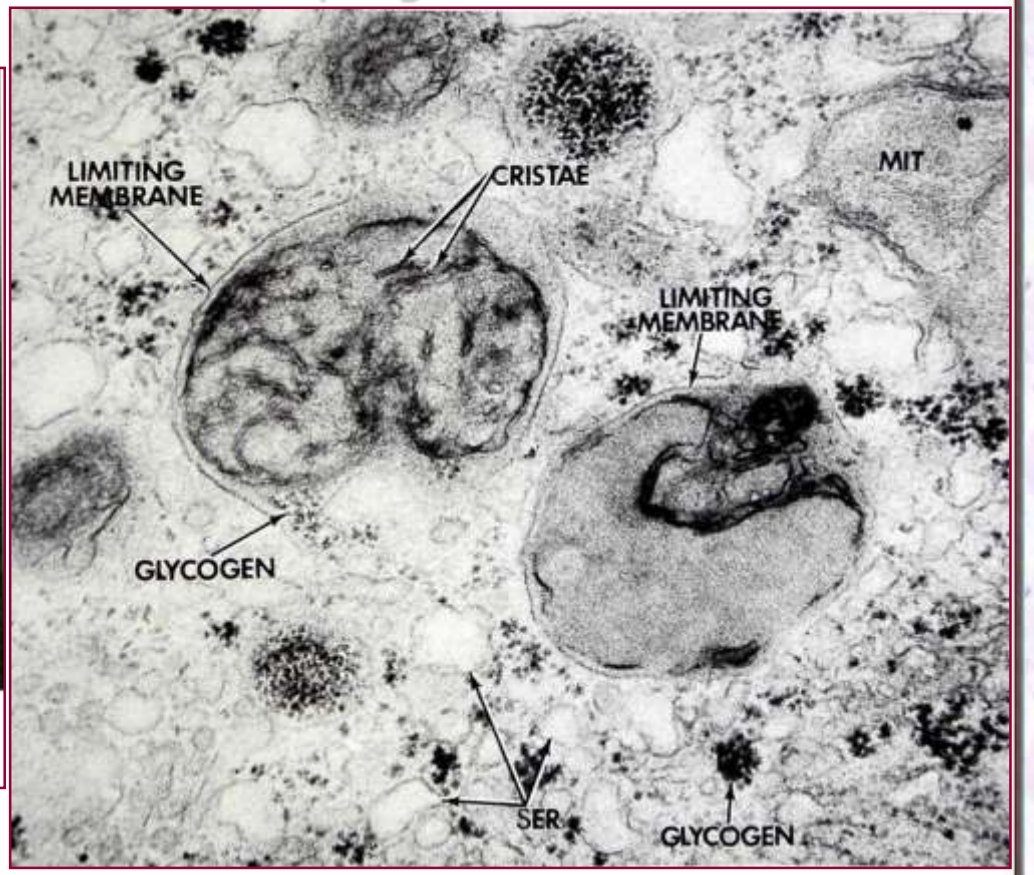
Abb. 1.19. Primäre Lysosomen eines Makrophagen bei stärkerer Vergrößerung. Die *Pfeile* deuten auf die die Organellen umgebende Membran. Balken = 0,1 µm. (Aus Junqueira et al. 1998)



Lysosomes – "suicide-bags" or "suicide-sacs"

- (autophagy – self-eating, Gr. *auto*, self + *phagein*, to eat)
- controlled digestion of damaged organelles within a cell
- autophagic cell death – a form of programmed self destruction (autolysis)



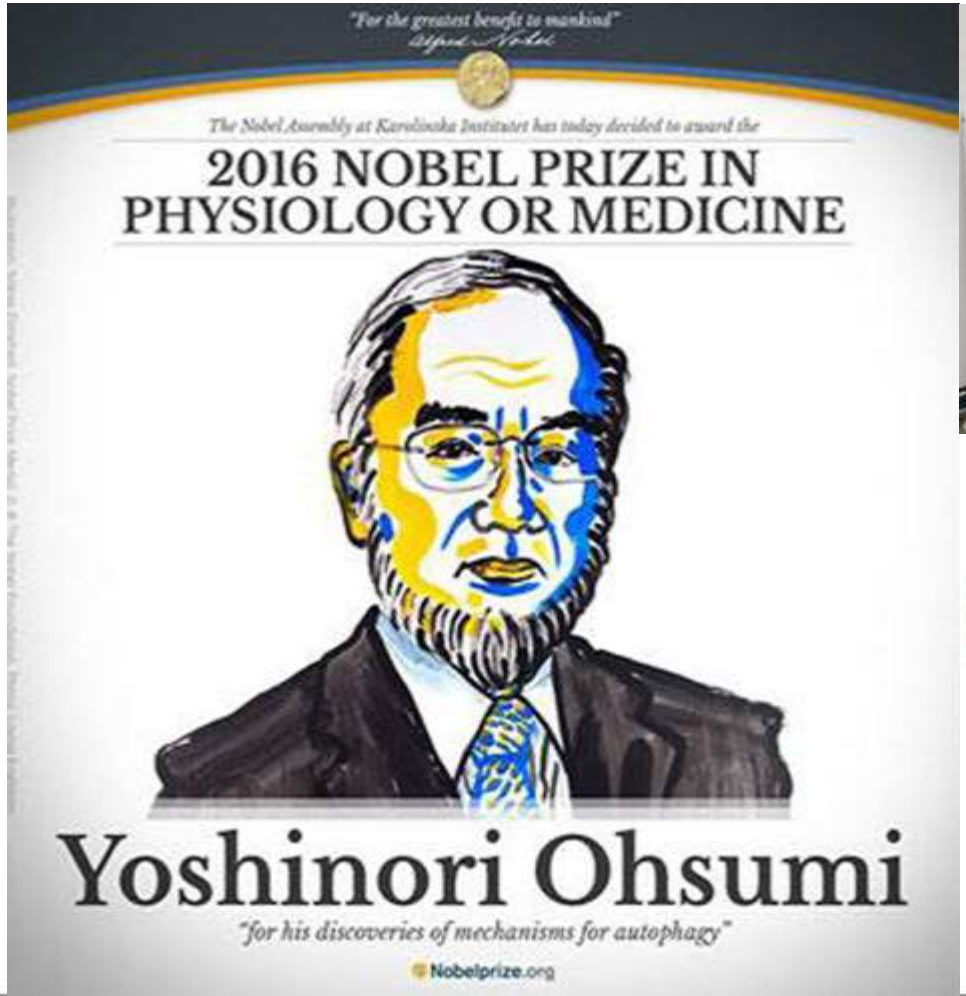


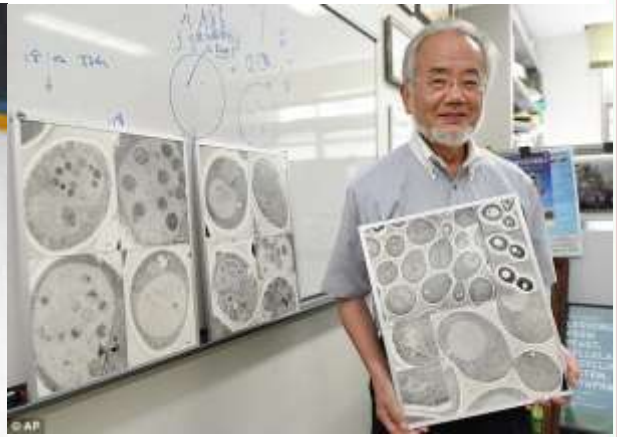
- the cells' garbage disposal system

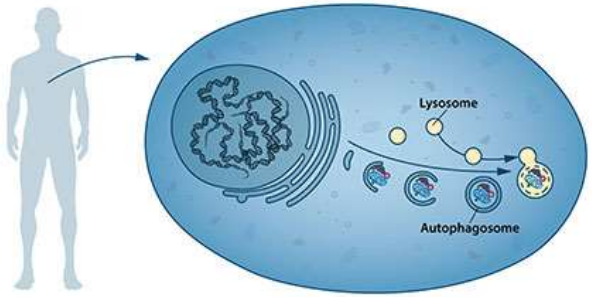
"For the greatest benefit to mankind"
Alfred Nobel

2016 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Yoshinori Ohsumi

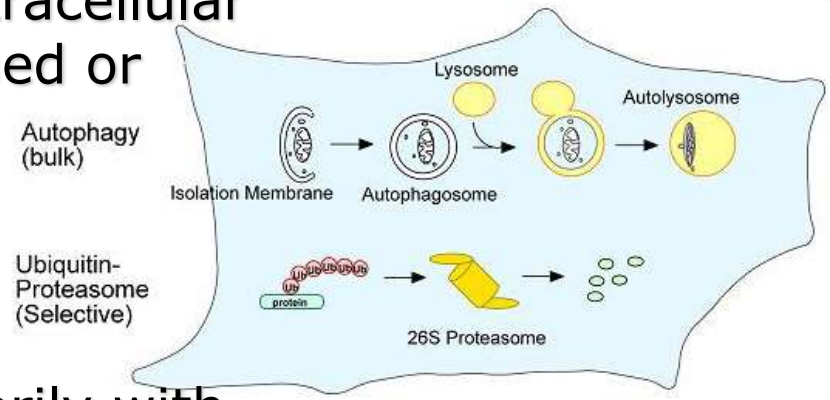




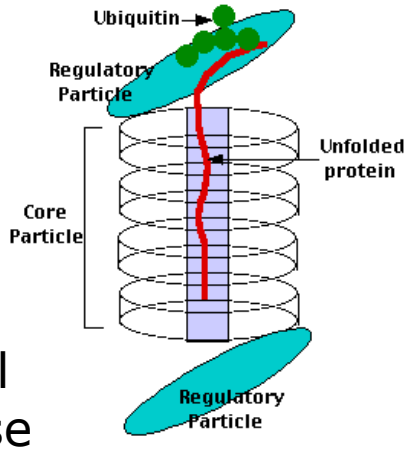


Proteasomes

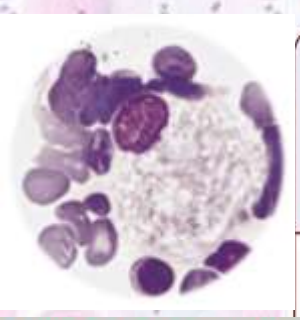
- multiple-protease complexes that digest proteins targeted
- There are two major intracellular devices in which damaged or unneeded proteins are broken down:
  - ✓ lysosomes
  - ✓ proteasomes



- Proteasomes deal primarily with proteins as individual molecules, whereas lysosomes digest bulk material introduced into the cell or whole organelles and vesicles
- Proteasome has:
  - ✓ a core particle with the shape of a barrel
  - ✓ a regulatory particle that contains ATPase



The Nobel Prize in Chemistry 2004 was awarded to Aaron Ciechanover, Avram Hershko and Irwin Rose "for the discovery of ubiquitin-mediated protein degradation"



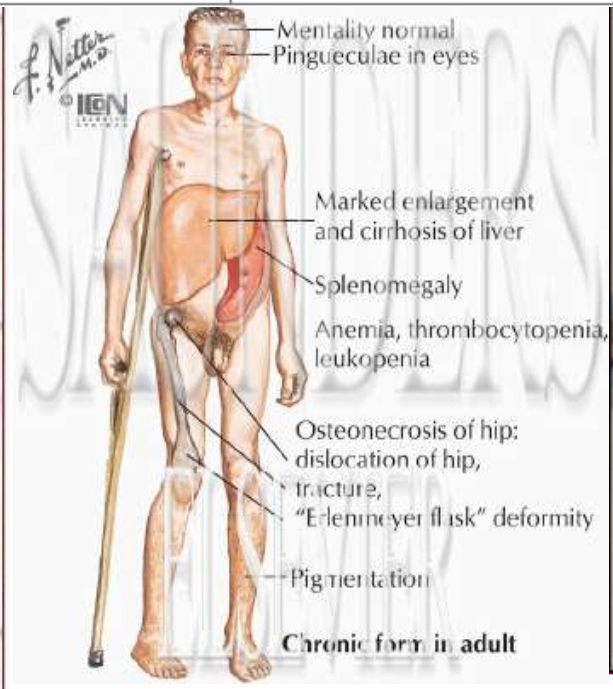
Lysosomes – clinical relevance

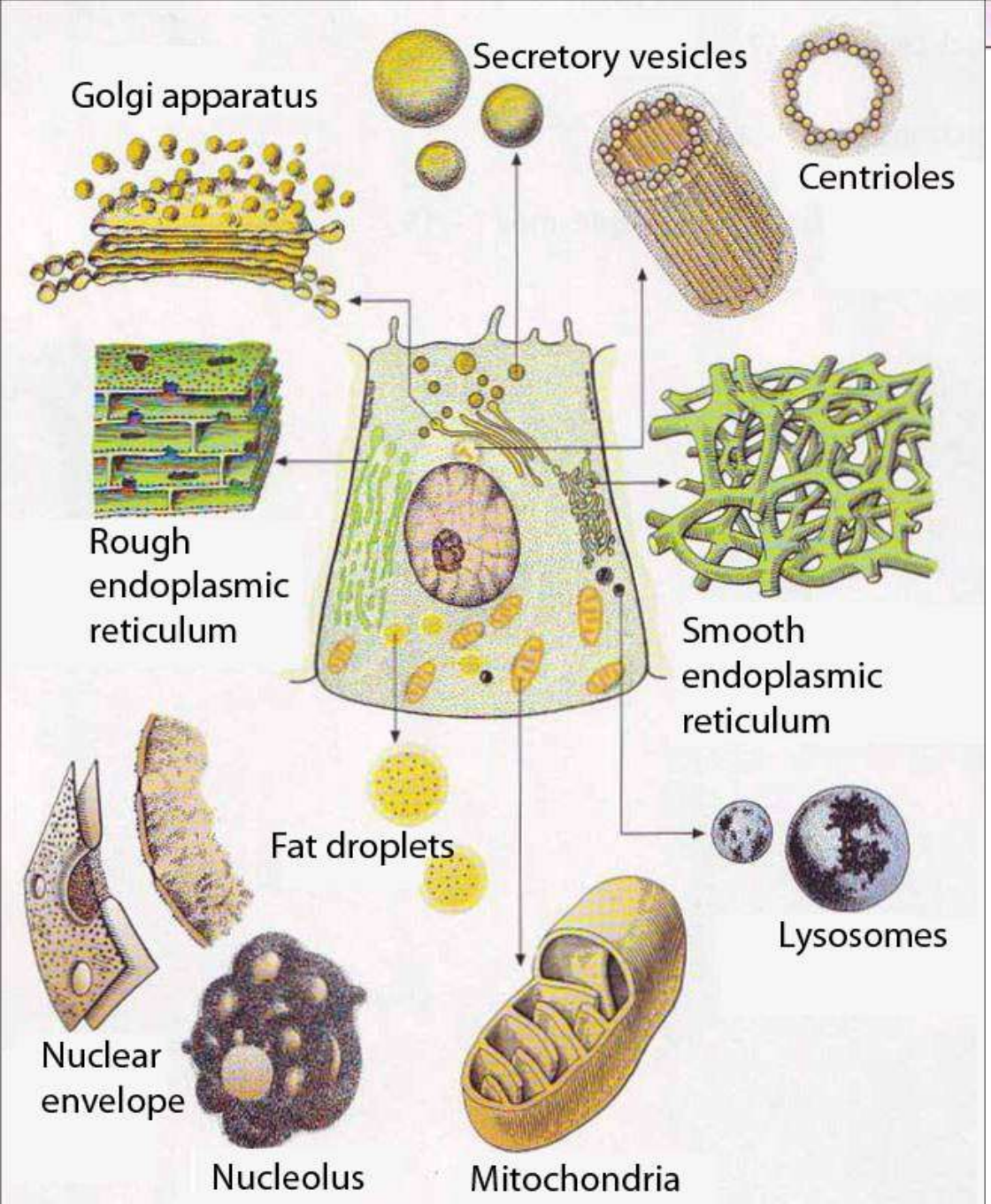
- Lysosomal storage diseases:

Table 2–3. Examples of Diseases Caused by Lysosomal Enzyme Failure and Accumulation of Undigested Material in Different Cell Types.

Disease	Faulty Enzyme	Main Organs Affected
Hurler disease	α-L-Iduronidase	Skeleton and nervous system
Sanfilippo syndrome A	Heparan sulfate sulfamidase	Skeleton and nervous system
Tay-Sachs	Hexosaminidase-A	Nervous system
Gaucher	β-D-Glycosidase	Liver and spleen
I-cell disease	Phosphotransferase	Skeleton and nervous system

Phillippe Gaucher (1854-1918)





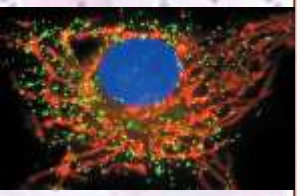
Membranous Organelles

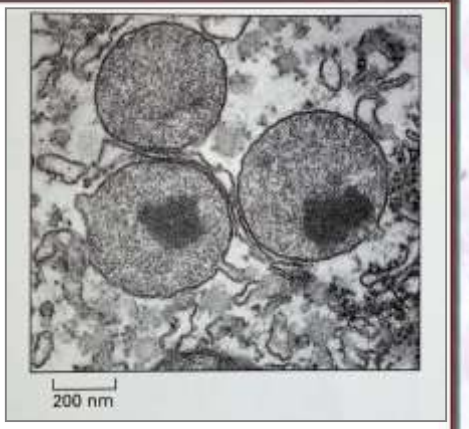
Peroxisomes

sites for oxygen utilization

Peroxisomes (microbodies)

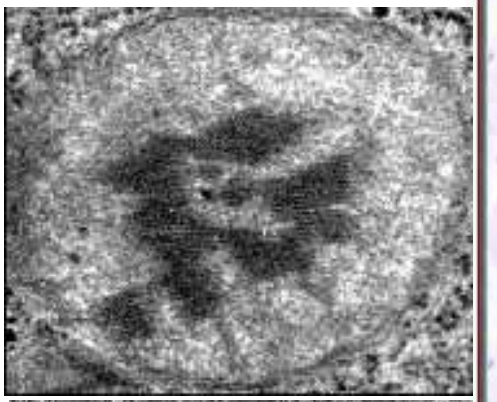
- identified by EM as organelles by Christian de Duve, 1967
  - *Gr.* peroxide + *soma,* body
  - microbodies: Rhodin, 1954

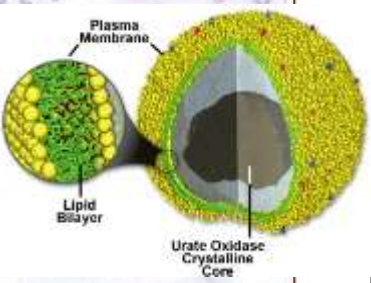


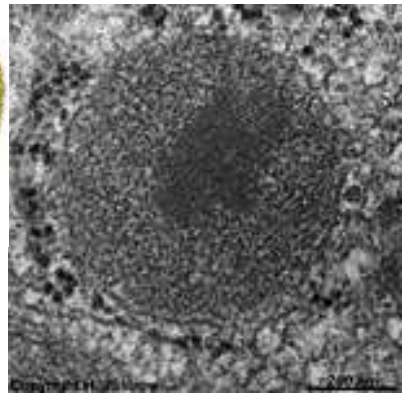


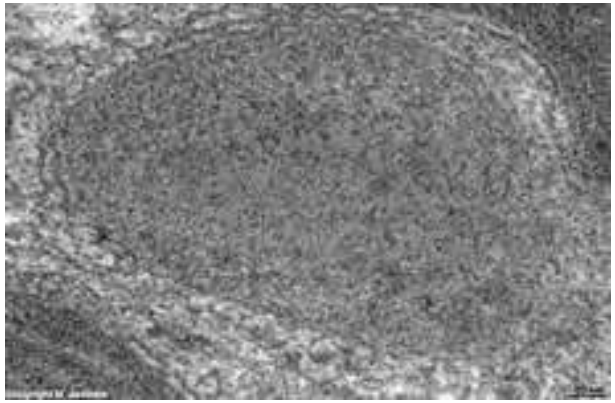
Spherical organelles: 70-100/cell

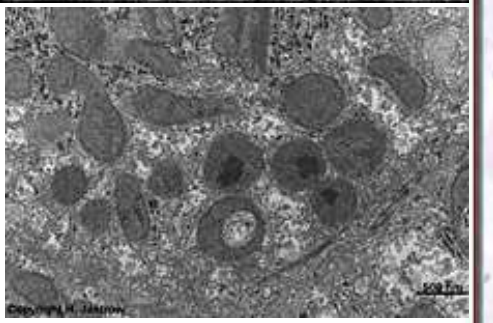
- ✓ size – 0.5-3 μm (macroperoxisomes)
- ✓ microperoxisomes – 0.1-0.3 μm
- ✓ homogeneous matrix (crystalloid core or nucleoid)
- ✓ marginal plate
- ✓ single layer membrane – 6-8 nm











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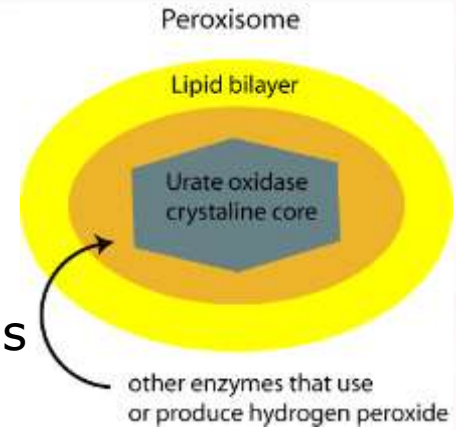
Peroxisomes – structure and function

- ***Enzymes***: >50
  - ✓ catalase – 40%
  - ✓ peroxidase
  - ✓ β-oxydase of very long-chain fatty acids
  - ✓ D- and L-amino oxydases
  - ✓ urate oxidase

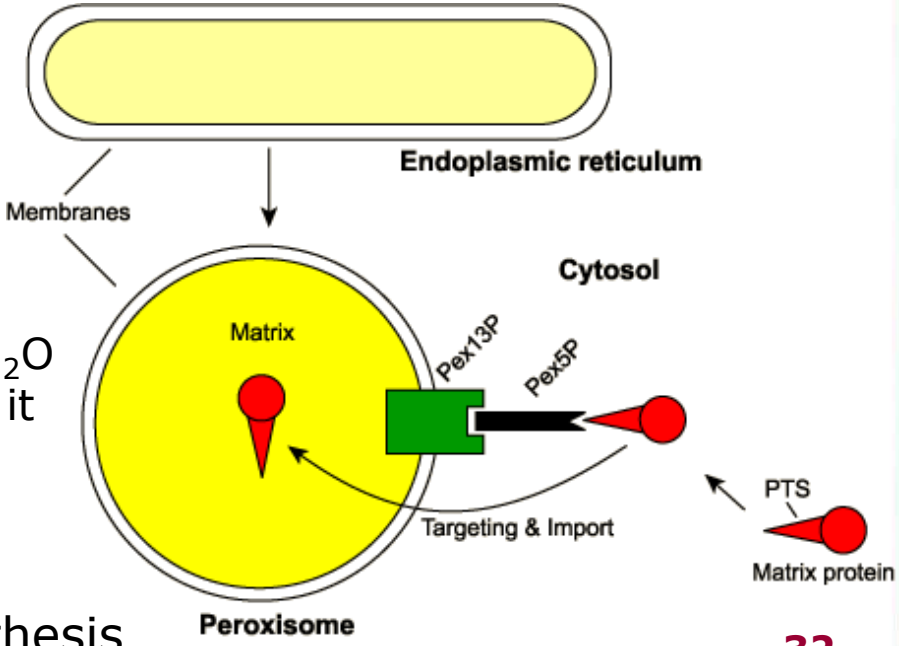


- ***Functions***:

✓ a compartment for oxidation reactions:
  - ➢ decomposes H_2O_2 to H_2O and O_2 and eliminates it
  - ➢ degrades several toxic molecules and prescription drugs

✓ involved in lipid biosynthesis

✓ important role in cellular respiration



Peroxisomes – clinical relevance

- Peroxisomal disorders –

  17 inherited metabolic diseases:

  ✓ Refsum's disease – leukodystrophy:
  - faulty enzymes during the alpha-oxidation of phytanic acid

  ✓ Zellweger syndrome:
  - deficiency in the protein import can lead to empty peroxisomes

  ✓ X-chromosome-linked adrenoleukodystrophy:
  - a defective integral membrane protein that participates in transporting very long-chain fatty acids into the peroxisome for β-oxidation

Sigvald Bernhard Refsum

(1907–1991)

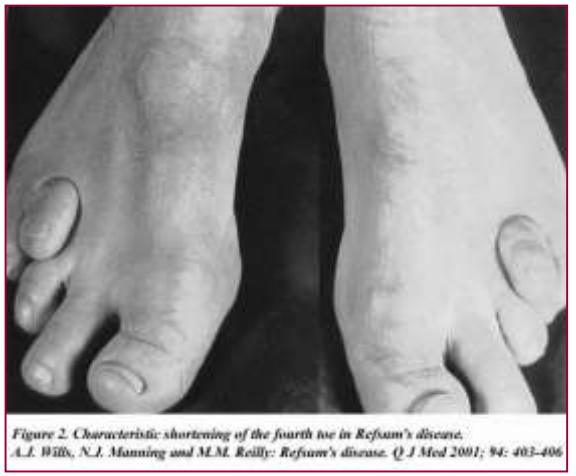
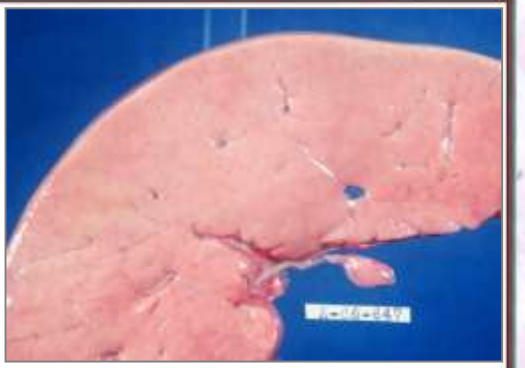


Figure 2. Characteristic shortening of the fourth toe in Refsum's disease.
A.J. Wills, N.J. Manning and M.M. Reilly: Refsum's disease. Q J Med 2001; 94: 403-406

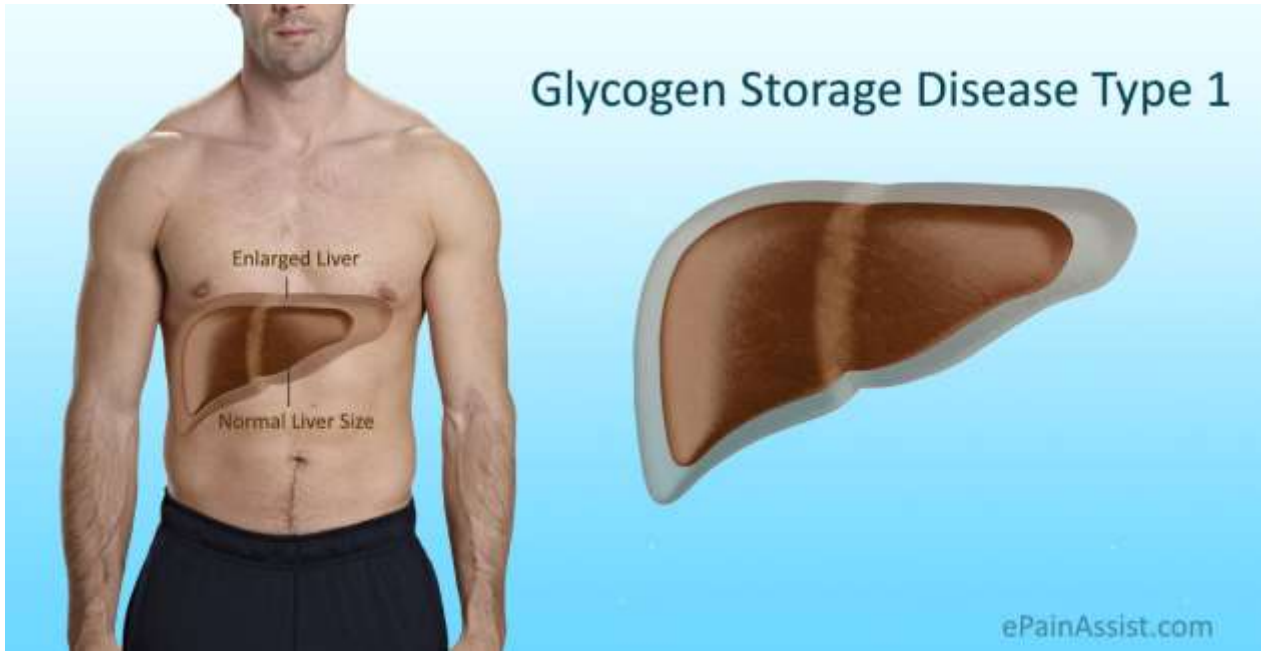
Peroxisomes – clinical relevance

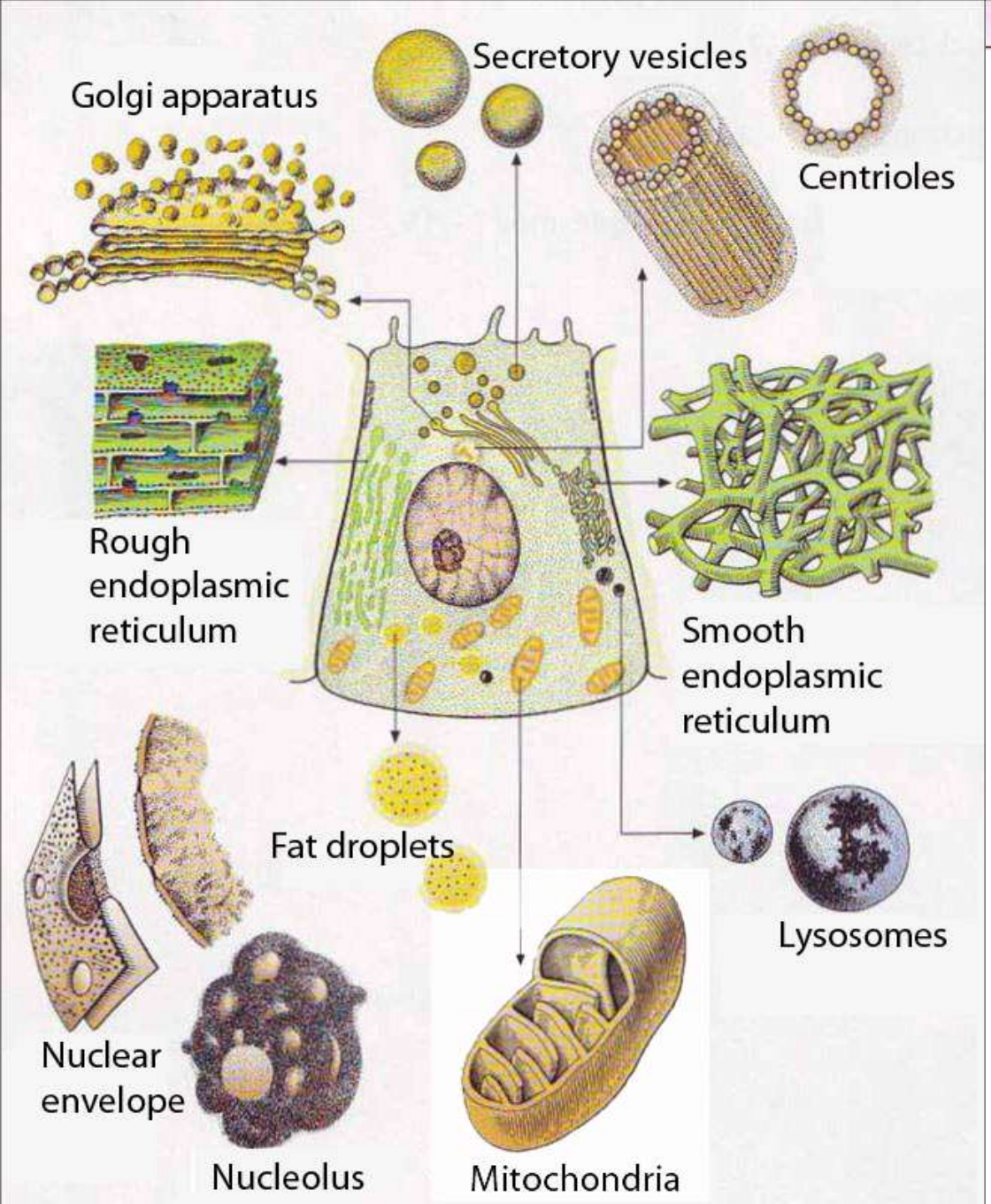
Edgar Otto Conrad von Gierke

(1877–1945)



- ✓ Von Gierke disease:
  - ➢ glycogen storage disease type 1
  - ➢ impairment of glycogenolysis:
    - ✓ hypoglycemia
    - ✓ hyperlipidemia (excess acetyl CoA)
    - ✓ accumulation of glycogen in the liver and kidneys





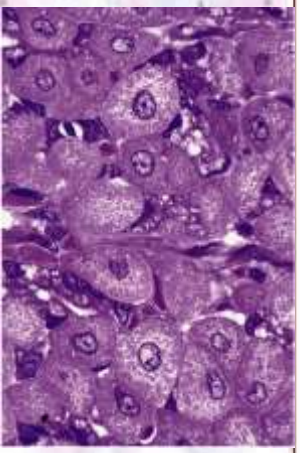
Membranous Organelles

Mitochondria

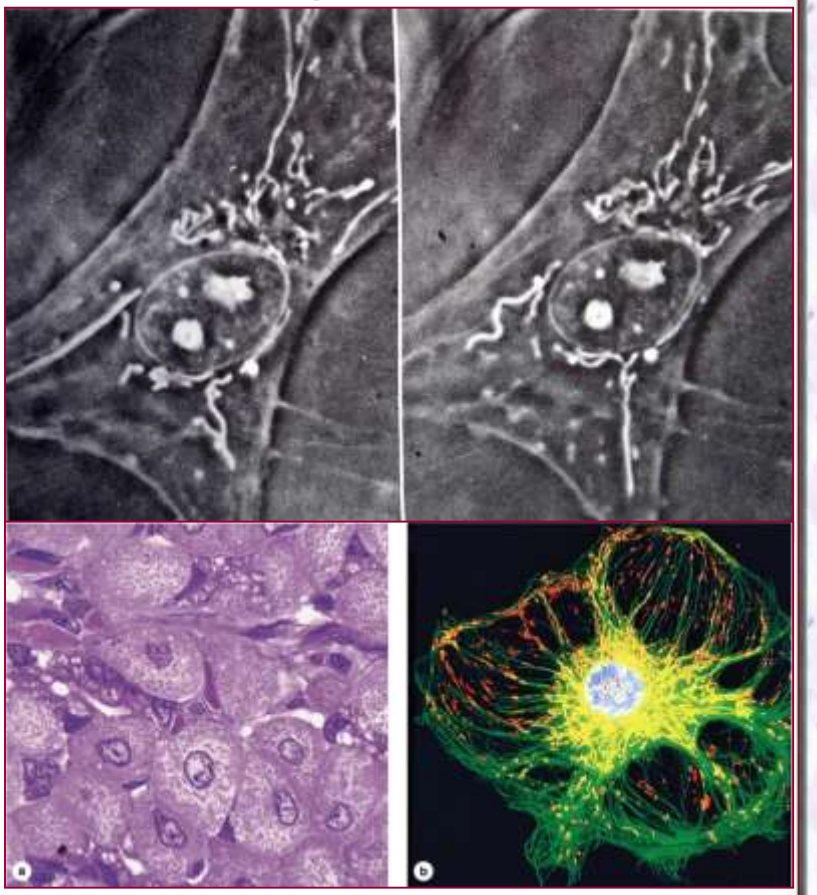
ATP and steroid synthesis

Mitochondria

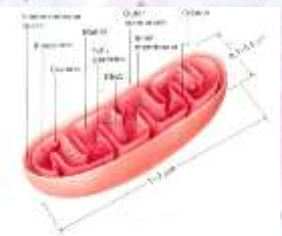
- vitally staining – Janus green B



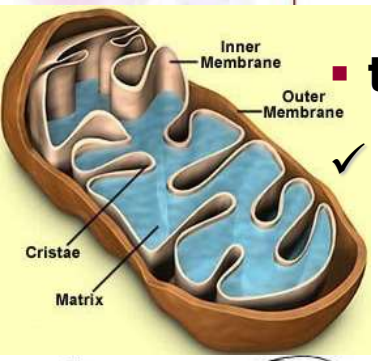
- Gr. *mitos*, thread + *chondros*, granule:
  Carl Benda, 1898
- First observations:
  - ✓ Kölliker, 1850
  - ✓ Flemming, 1882
  - ✓ R. Altmann, 1890: bioblasts
- Size:
  - ✓ 0.5-1 μm wide
  - ✓ length up to 10 μm
- Number – varying:
  - ✓ fibroblasts – 100
  - ✓ hepatocytes – 800 (25%)
  - ✓ oocytes – 300 000



Mitochondria – structure

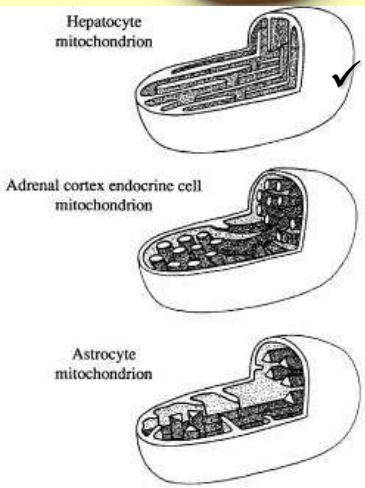


- Ultrastructure: G. Palade, F.S. Sjöstrand, 1952

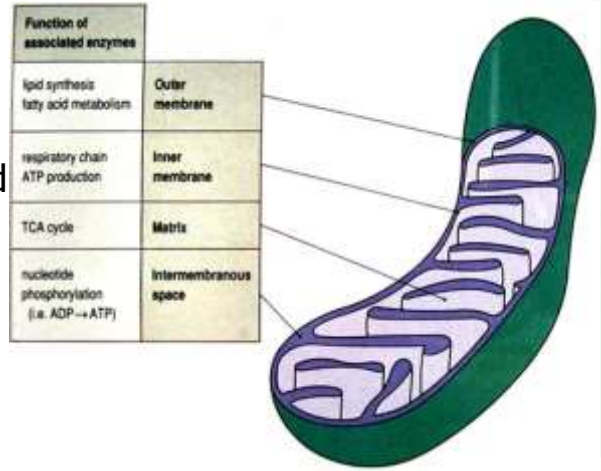


- **two mitochondrial membranes:**

✓ **outer** (6-7 nm) ~50% proteins and lipids:
- transport proteins (porin)
- enzymes: oxidases, hydrolases, transferases, enzymes of fatty acid metabolism, cytochromes



✓ **inner**: 80% proteins and cardiolipin
- reductases, oxidases, dehydrogenases, ATP synthase, transferases, cytochromes
- enzymes for oxidative phosphorylation and for electron transport system (cytochromes)
- forms cristae (tubules) – intracristal space
- attached elementary particles

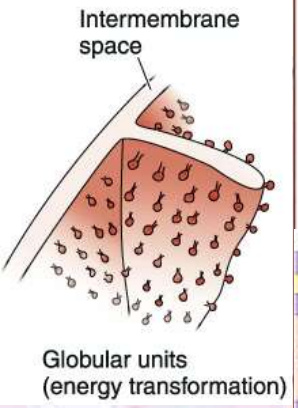


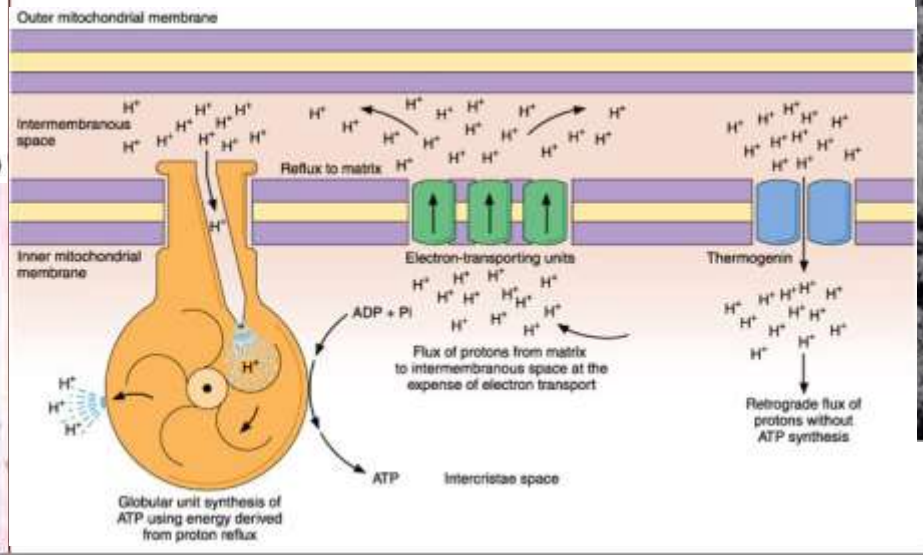
- **intramembranous space (outer chamber) – 4-10 nm**
- **matrix –** intercristal (matrix) space

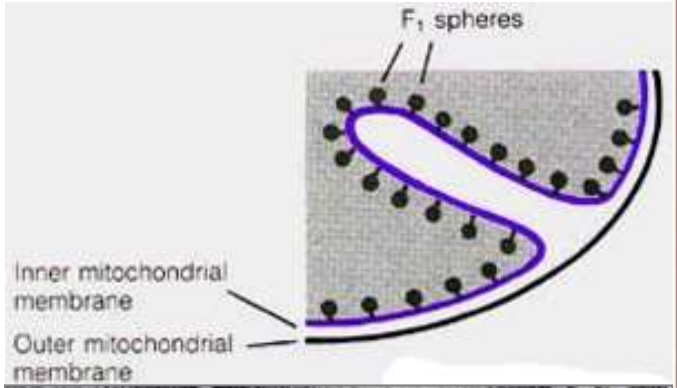
Humberto Fernández Morán *(1924-1999)*

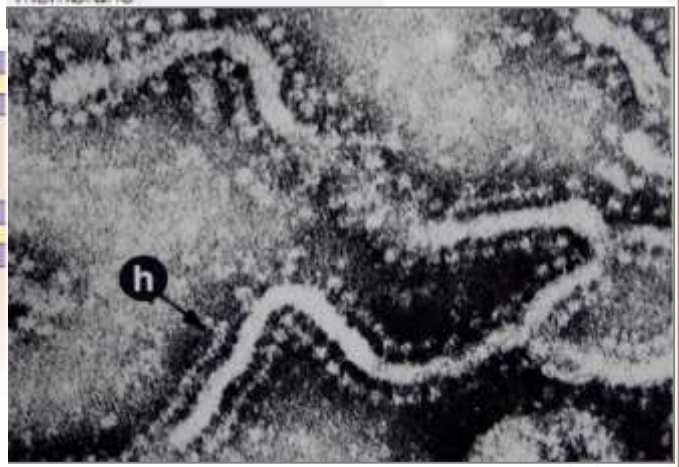
Mitochondria – structure

- **Elementary particles**: *Fernández-Morán*, 1962-1964
  (F_1-spheres, oxisomes, ATP somes) = 10000-100000/cell; ~ 8-9 nm
  - ✓ tennis racquet-shaped structures:
    - ➢ spherical head 9-10 nm, ATP synthase
    - ➢ cylindrical stalk – 4-5 nm
    - ➢ basis – 11 nm
- ➢ oxidative phosphorylation
- ➢ synthesis of ATP
- ➢ electron transport system (400 nm^2)
- ➢ artifact structures



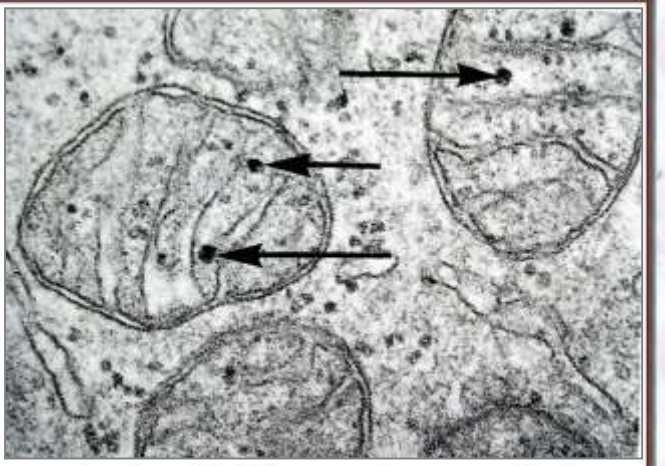




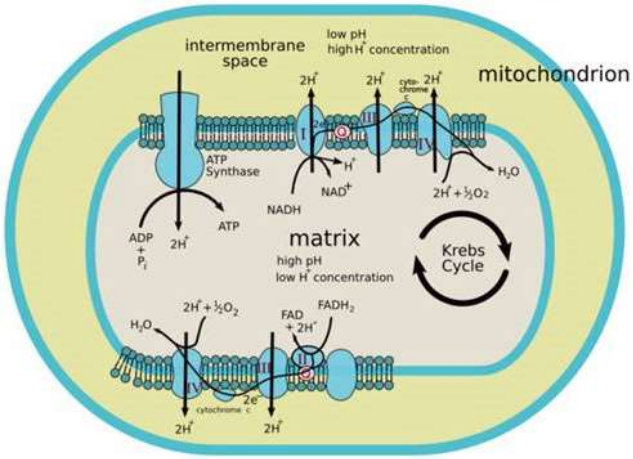


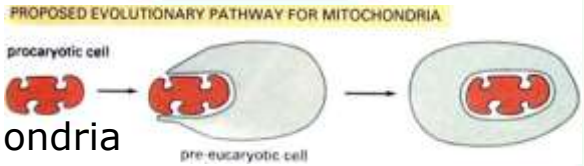
Mitochondria – structure and function

- **Mitochondrial matrix:**
  (intercristal space; inner chamber)
  rich in proteins, DNA, RNA
  - ✓ matrix granules: 30-50 nm; storage site for divalent cations – Ca^{2+}, Mg^{2+}
  - ✓ mitoribosomes (mrRNA): 15-20 nm
  - ✓ mitochondrial mRNA, tRNA
  - ✓ circular DNA: 2-3 nm
  - ✓ RNA- and DNA-polymerases
  - ✓ Krebs cycle enzymes
  - ✓ enzymes for lipid synthesis
  - ✓ enzymes for protein synthesis
- **Origin of mitochondria:**
  - ✓ evolutionary from an ancestral aerobic prokaryote adapted to an endosymbiotic life (intracellular symbiosis)
  - ✓ new mitochondria – from preexisting mitochondria by growth and subsequent division (fission)



Mitochondrial Electron Transport Chain





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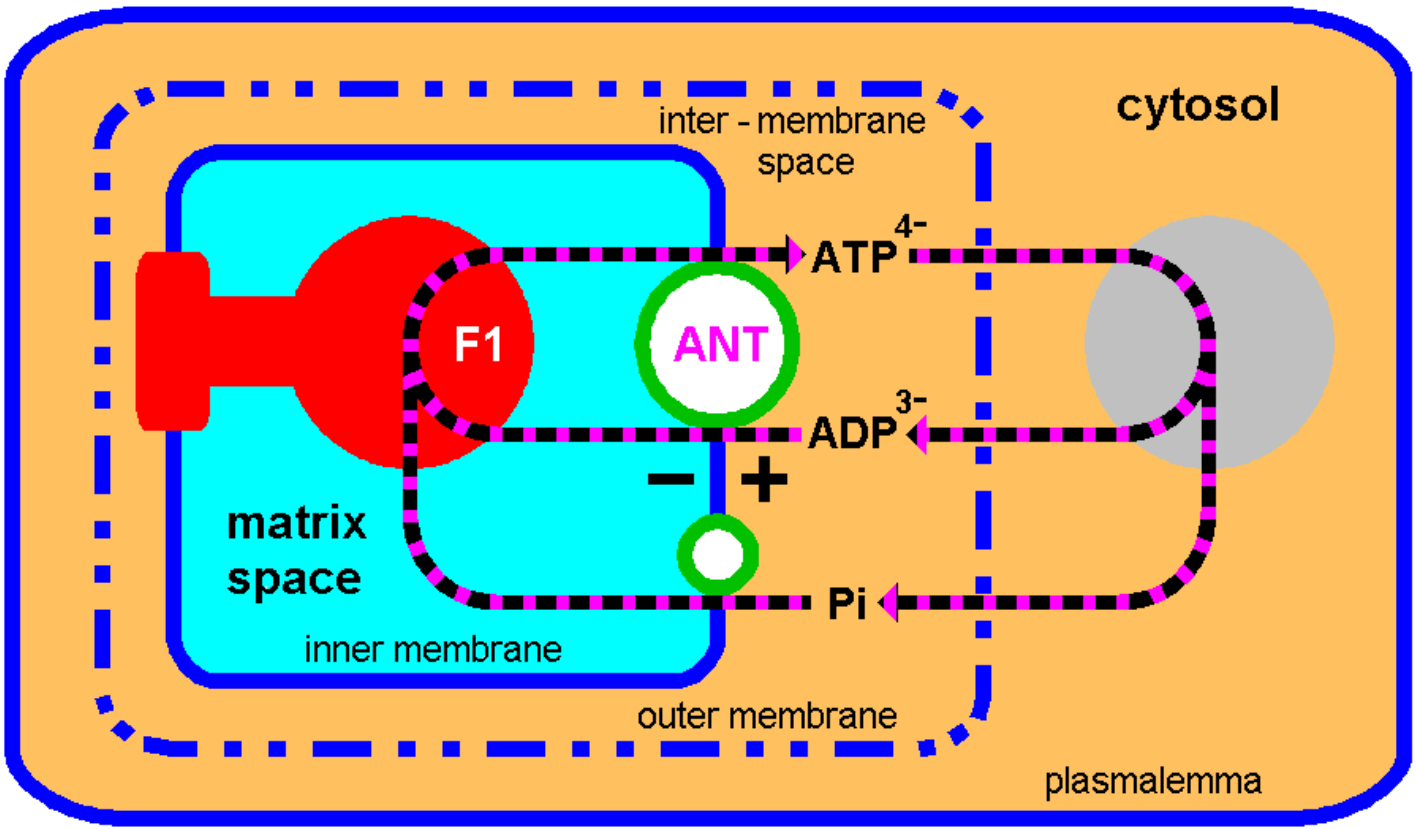
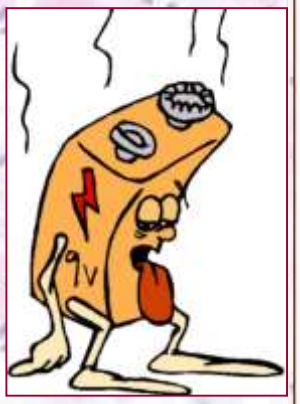
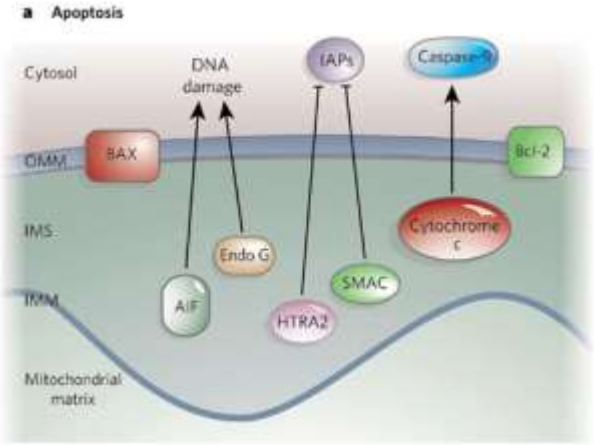
Mitochondria – the power plants of the cell

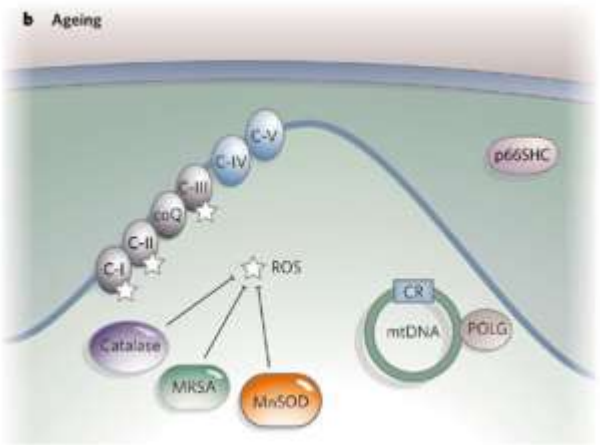


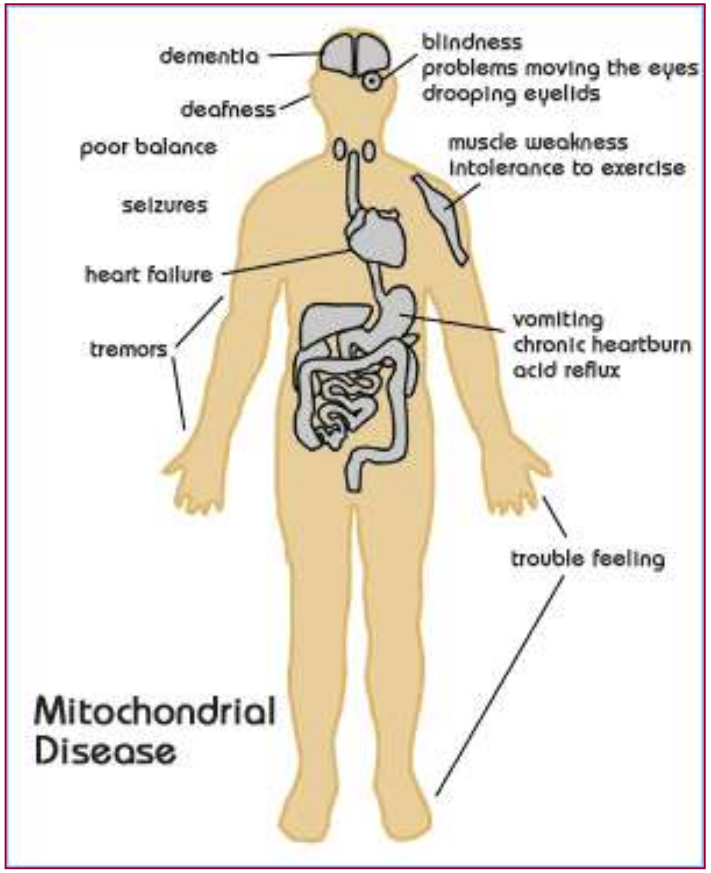
Mitochondrial diseases



- ✓ mitochondrial disorders – more than 40 entities
- ✓ possible relationships to aging and death







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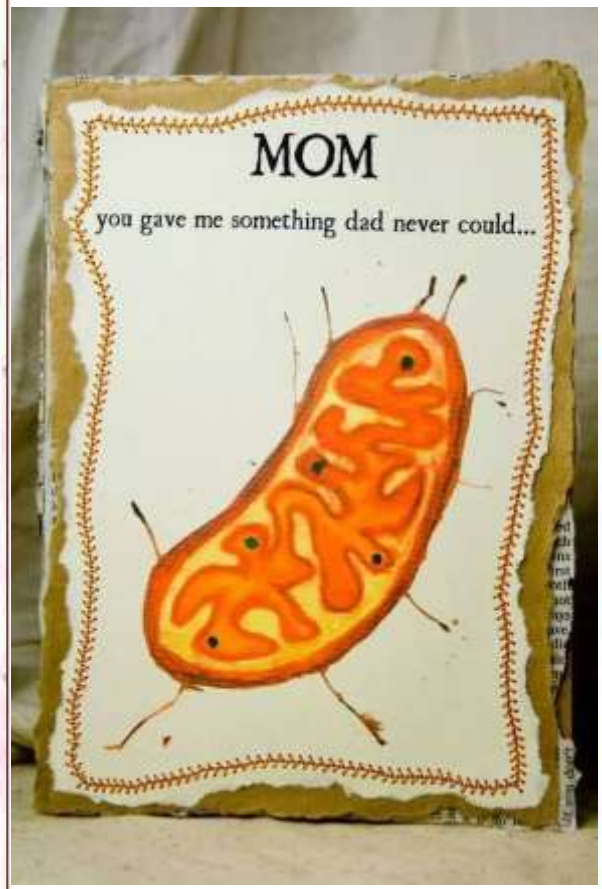
Mitochondria – "the cell's brain"



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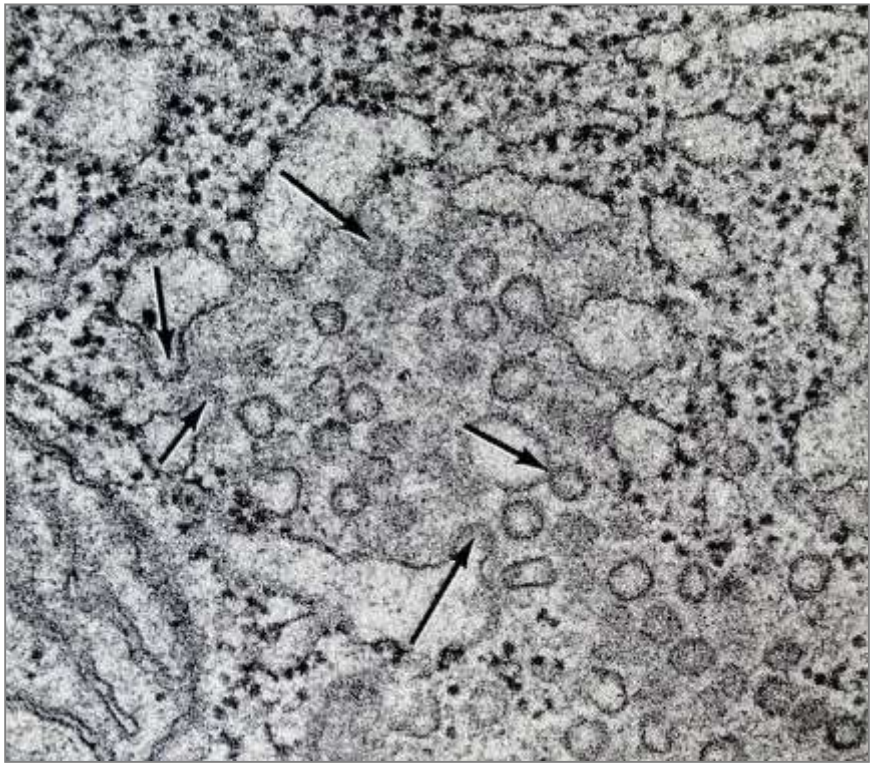
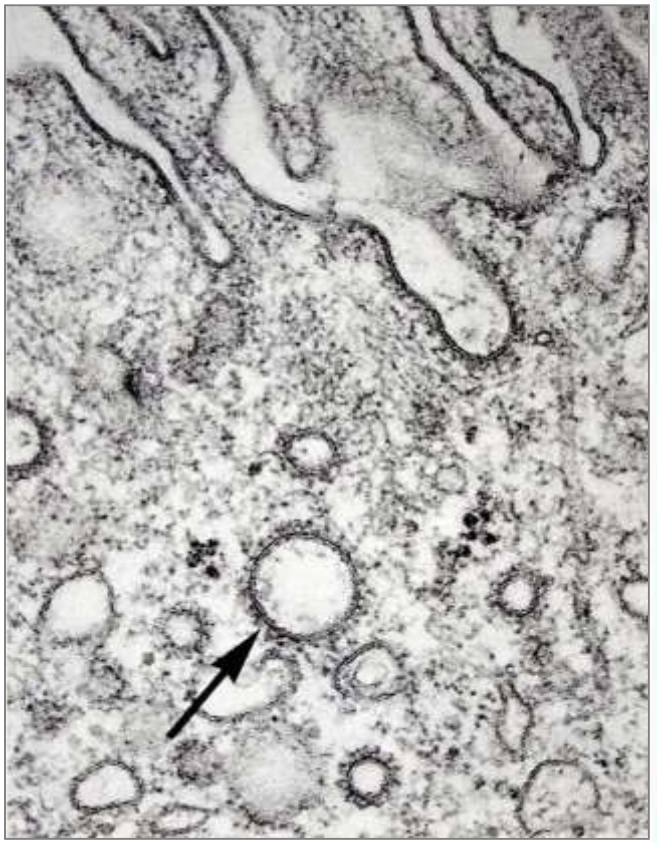
Coated vesicles

E.G. Gray, 1962 – coated vesicles

- ✓ size – 20-250 nm
- ✓ 6-8 nm spines
- ✓ single membrane – 7.5-8 nm





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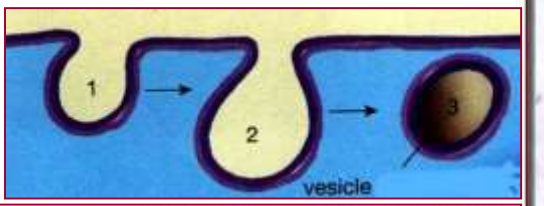
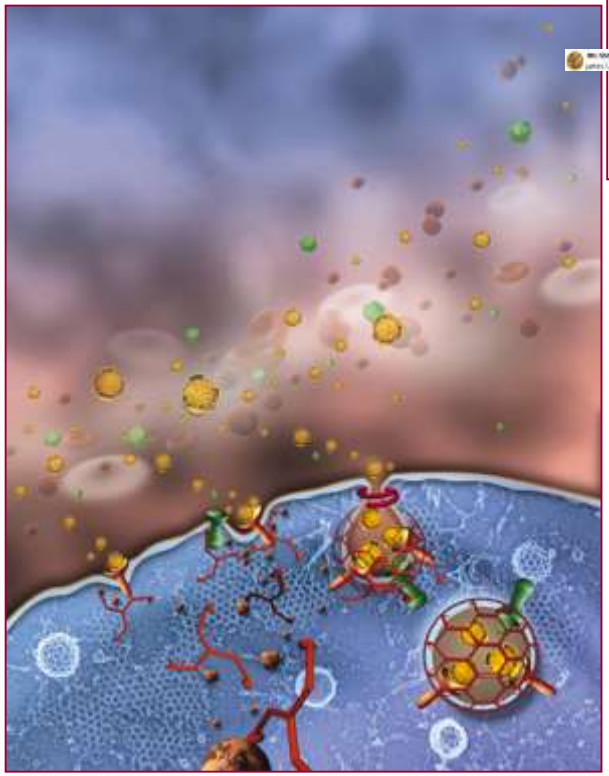
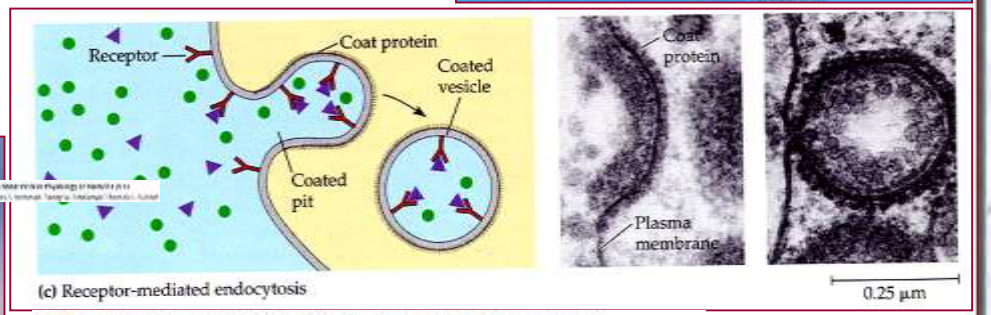
Coated vesicles – types

- 3 types coated vesicles:
  - ✓ clathrin-coated vesicles – 6-8 nm spines
  - ✓ coatomer-coated vesicles
  - ✓ caveolae







The Nobel Prize in Physiology or Medicine 2013

James E. Rothman, Randy W. Schekman, Thomas C. Südhof

"for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells".

Photo: A. Mahmoud

James E. Rothman

Photo: A. Mahmoud

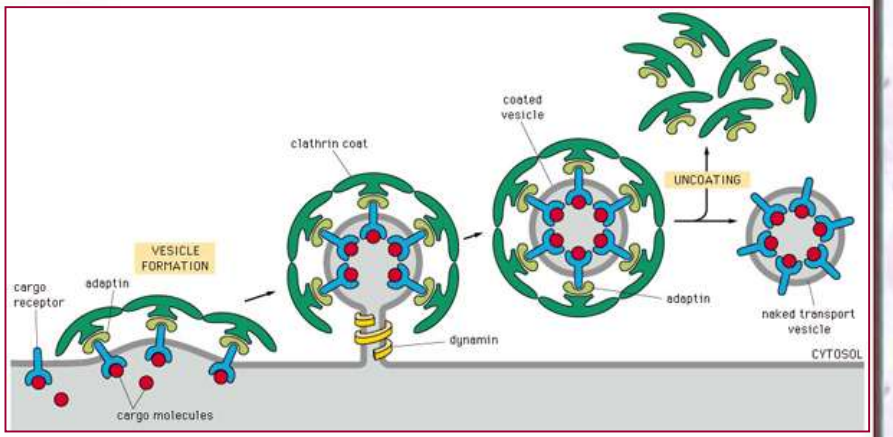
Randy W. Schekman

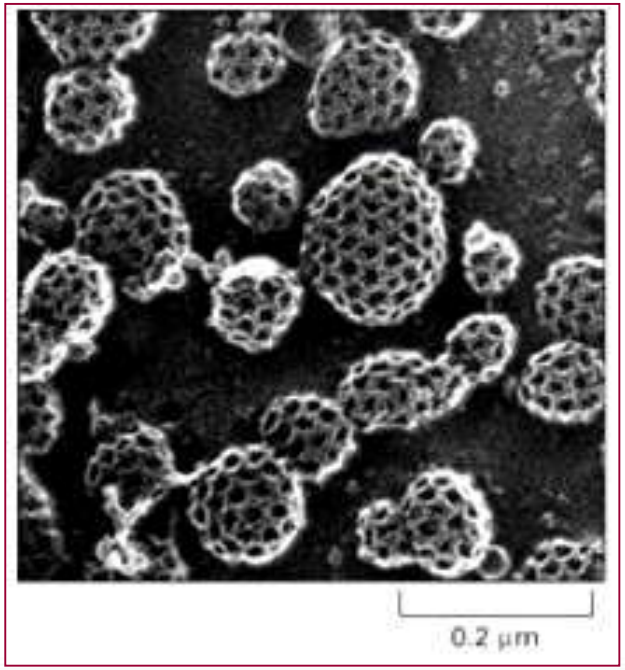
Photo: A. Mahmoud

Thomas C. Südhof

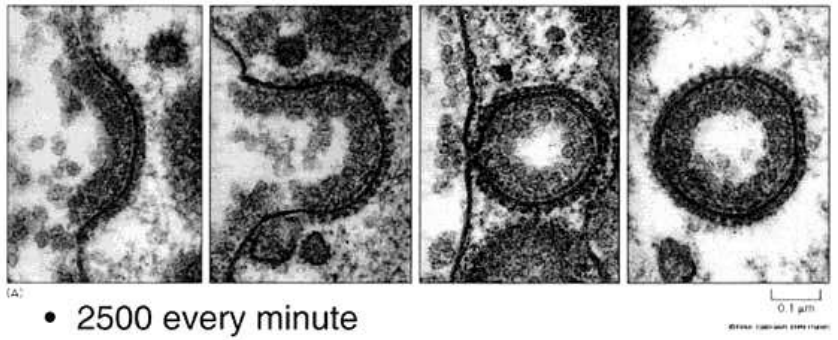
Clathrin-coated vesicles

- ✓ mediate selective transport of transmembrane receptors
- ✓ transmembrane proteins (spines) 6-8 nm
- ✓ clathrin molecules, bound via adaptin
- ✓ formed by endocytosis or from the Golgi apparatus





Formation of Clathrin-Coated Vesicles



- 2500 every minute
- CCV uncoat within seconds

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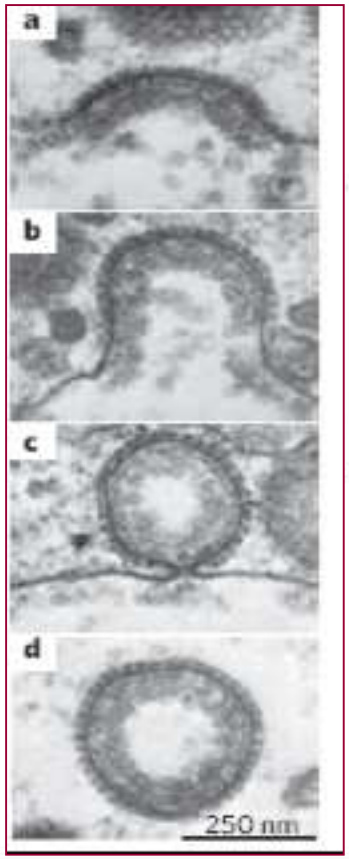
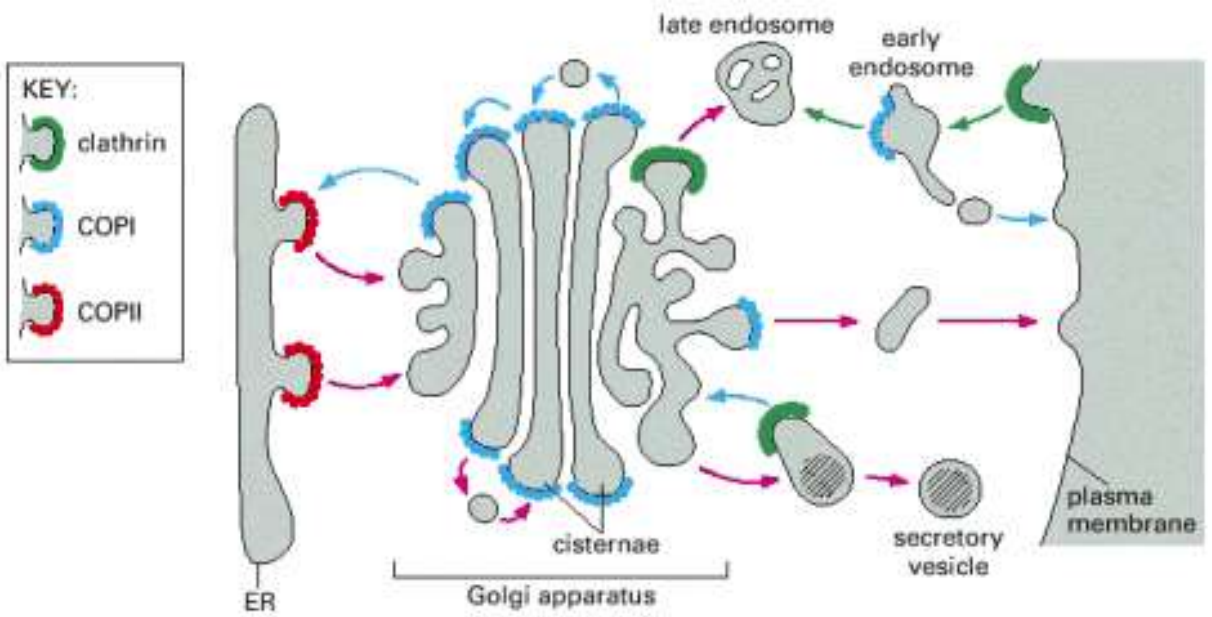
Coatomer-coated vesicles

- ✓ COPII (α-COP) – responsible for anterograde transport from the endoplasmic reticulum to the Golgi complex
- ✓ COPI (β-COP) – involved in Golgi to endoplasmic reticulum (retrograde) vesicle transport, and possibly also in intra-Golgi transport





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Caveolae

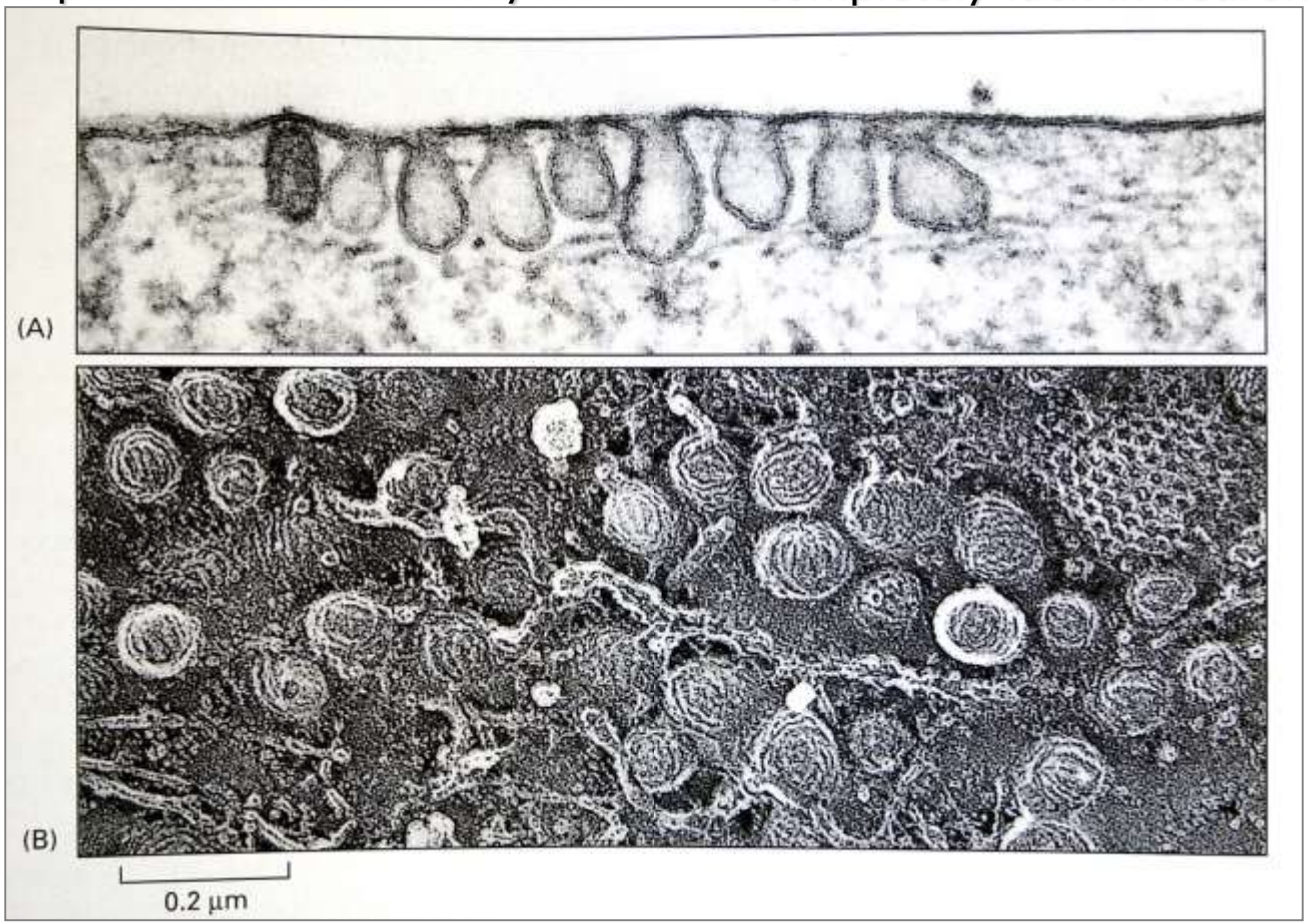
- Lat. for *little caves*

✓ potocytosis – a type of receptor-mediated endocytosis

✓ small (50–100 nm) invaginations of the plasma membrane

✓ in endothelial cells and adipocytes

✓ completely lack in neurons



Thank you…