3. RER, GOLGI, and SECRETION

Undergraduate – Graduate
Histology Lecture Series

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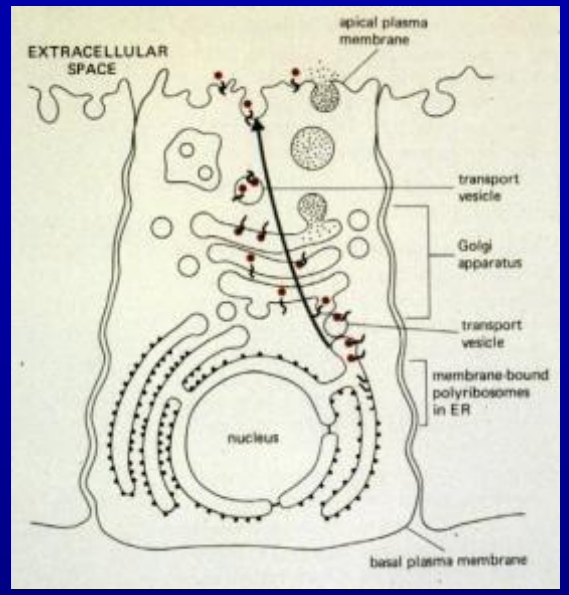
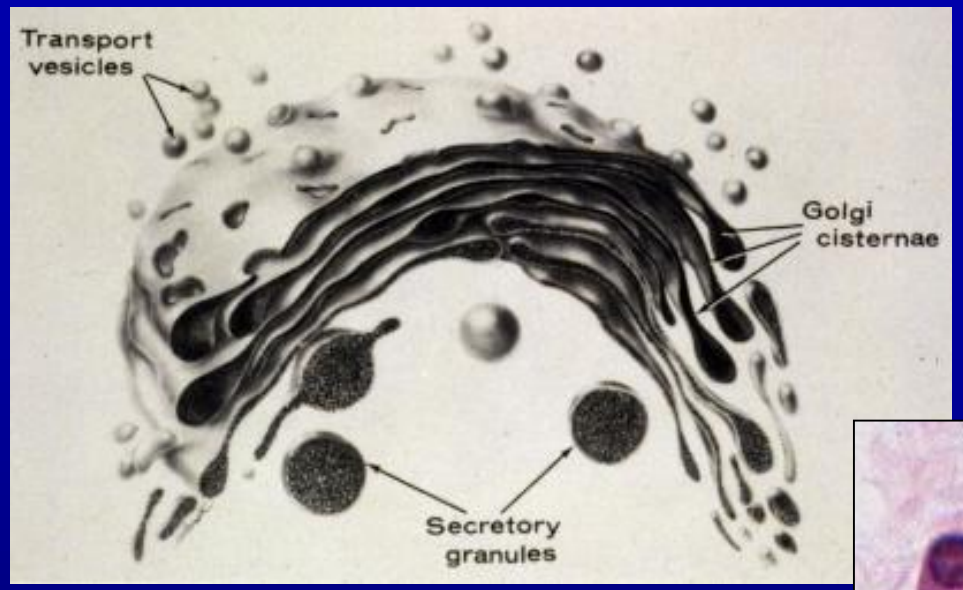
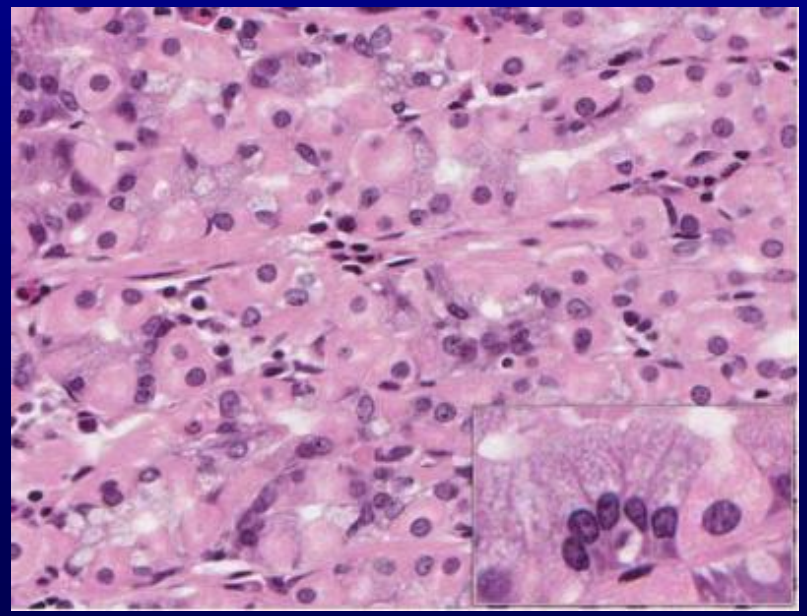
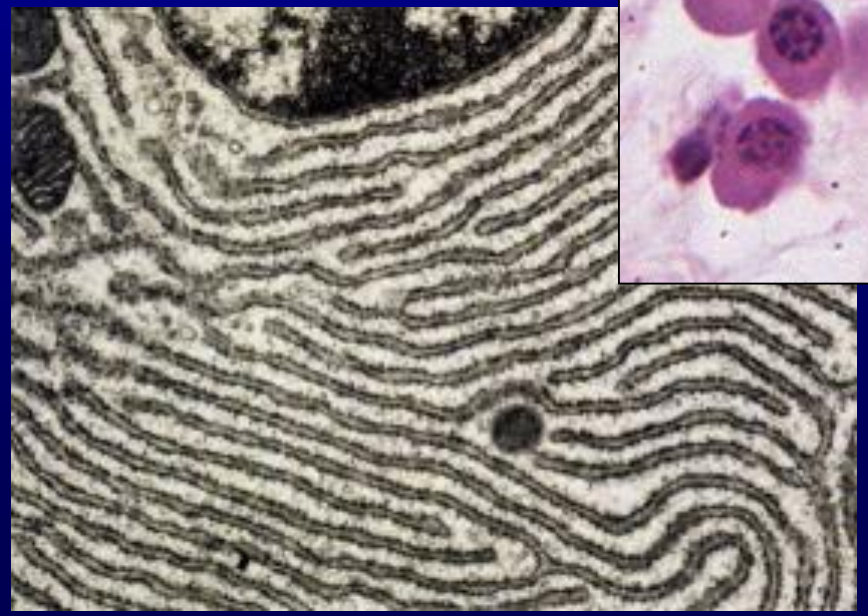
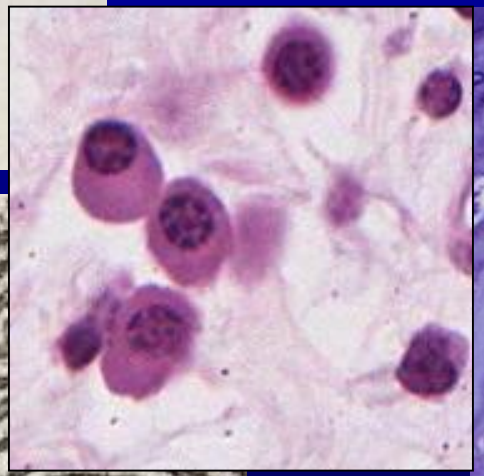
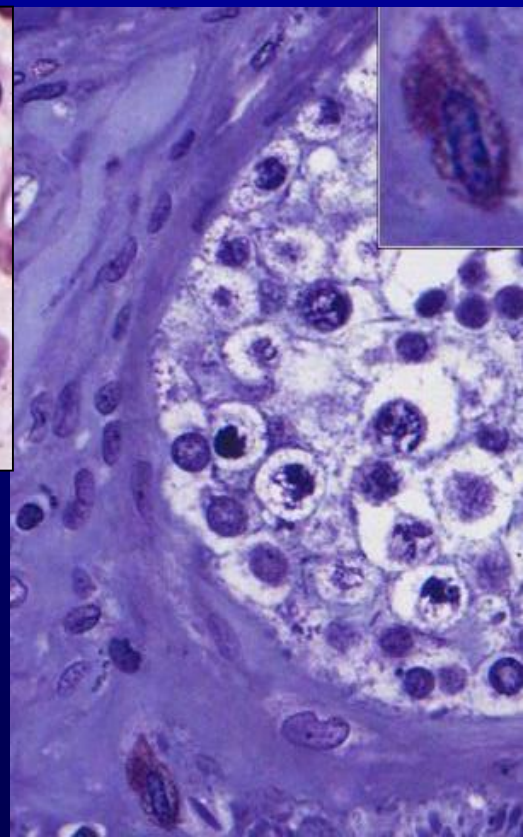












Objectives

Ultrastructural features

Production pathway followed by proteins

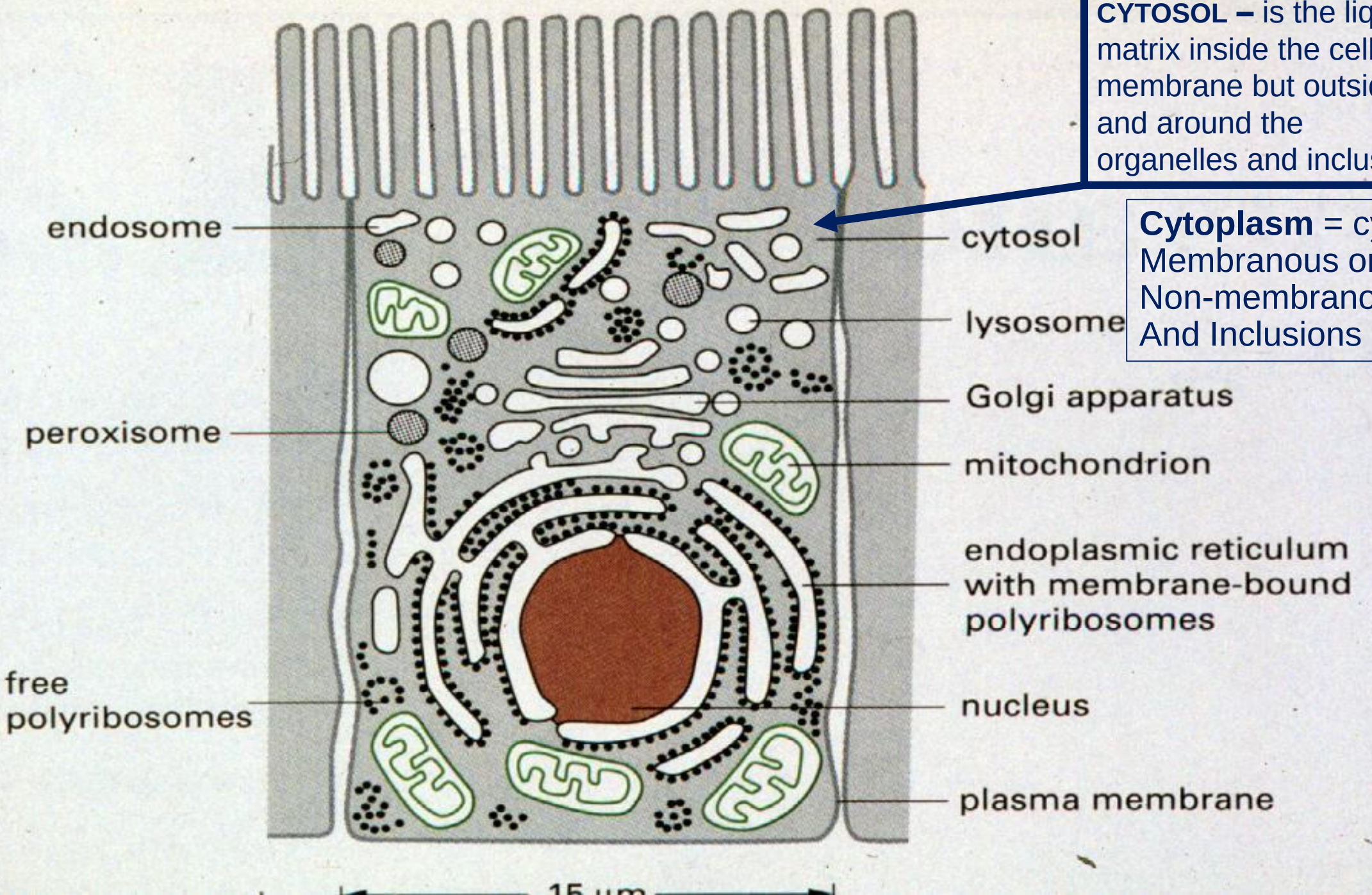
Cell biological and biochemical evidence of the pathway

Mechanisms for protein sorting

Post-translational modification of proteins

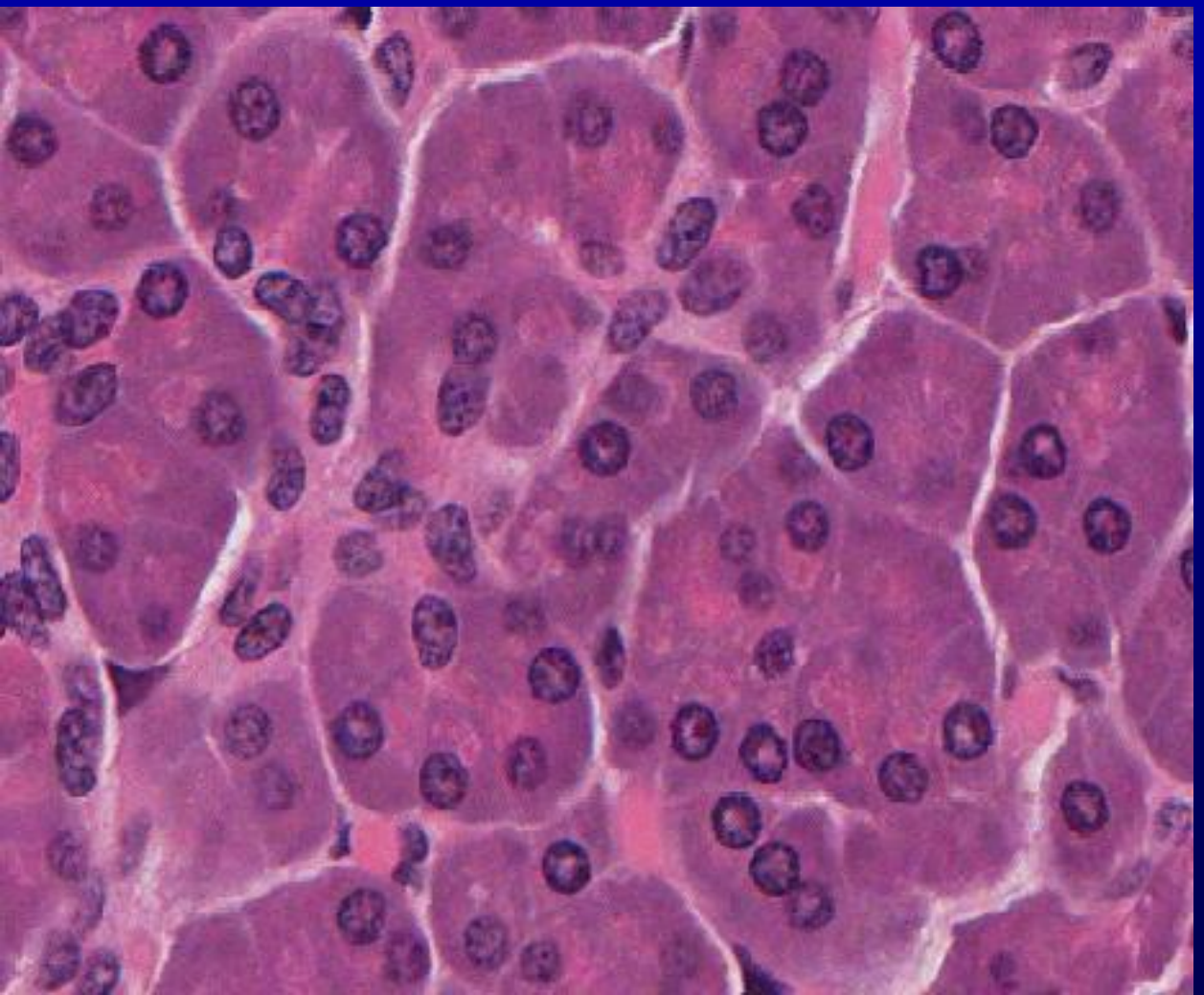
CYTOSOL – is the liquid matrix inside the cell membrane but outside and around the organelles and inclusions

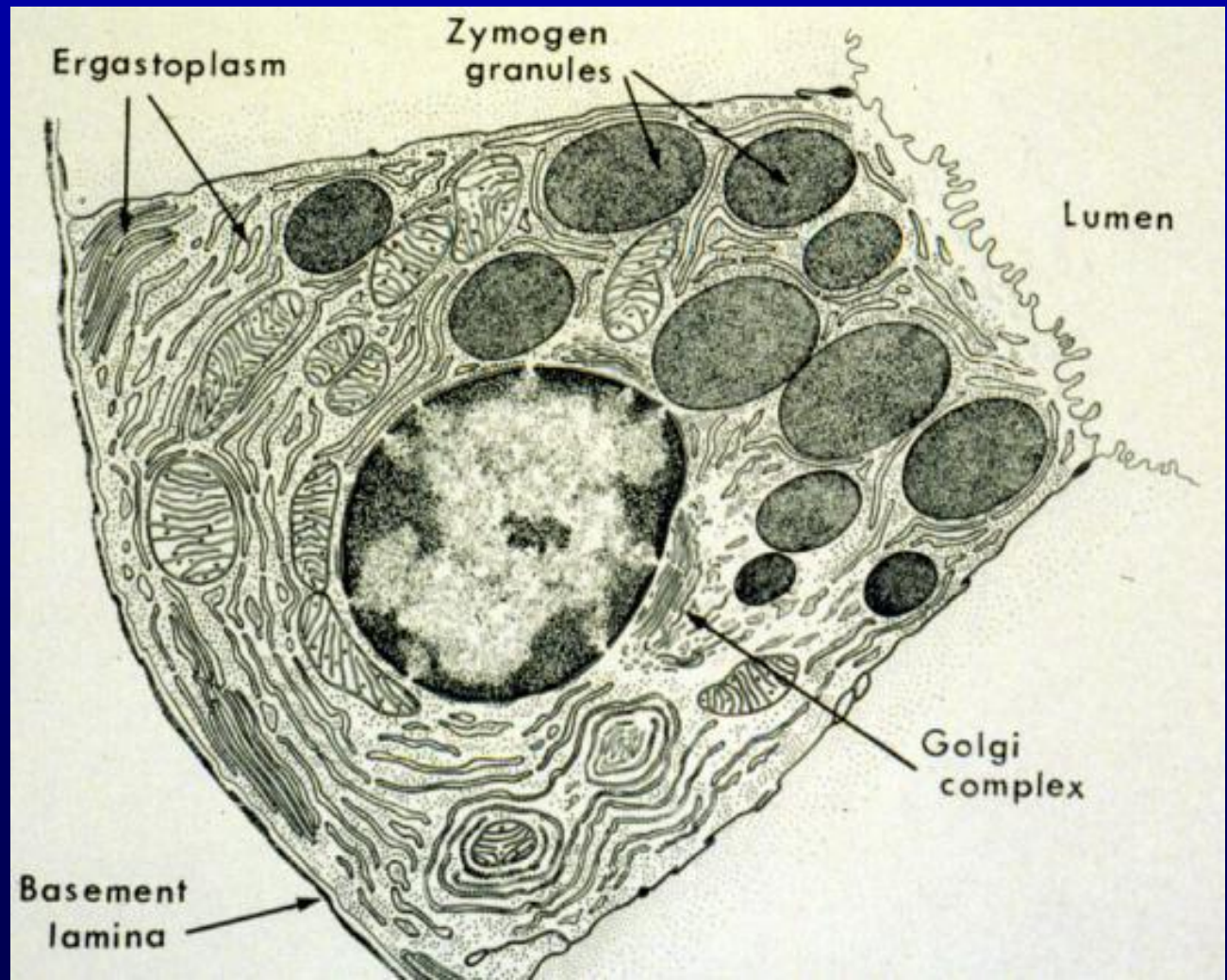
Cytoplasm = cytosol +
Membranous organelles
Non-membranous organelles
And Inclusions



Examples of secretory cells

Pancreatic acinar cell - digestive enzymes

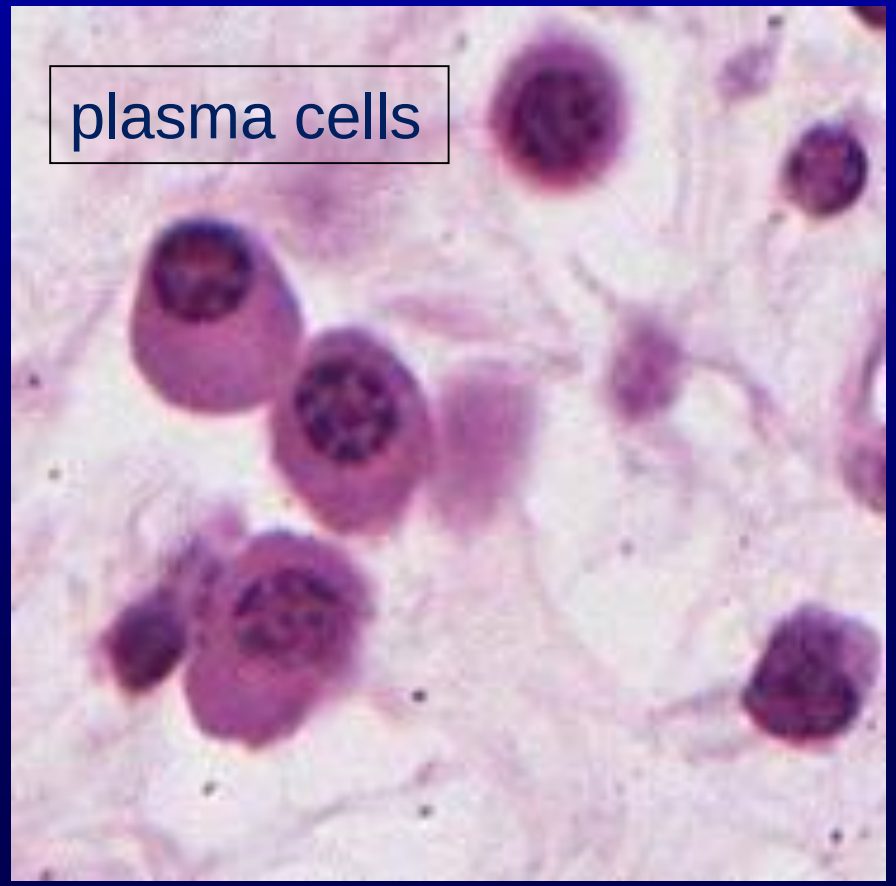


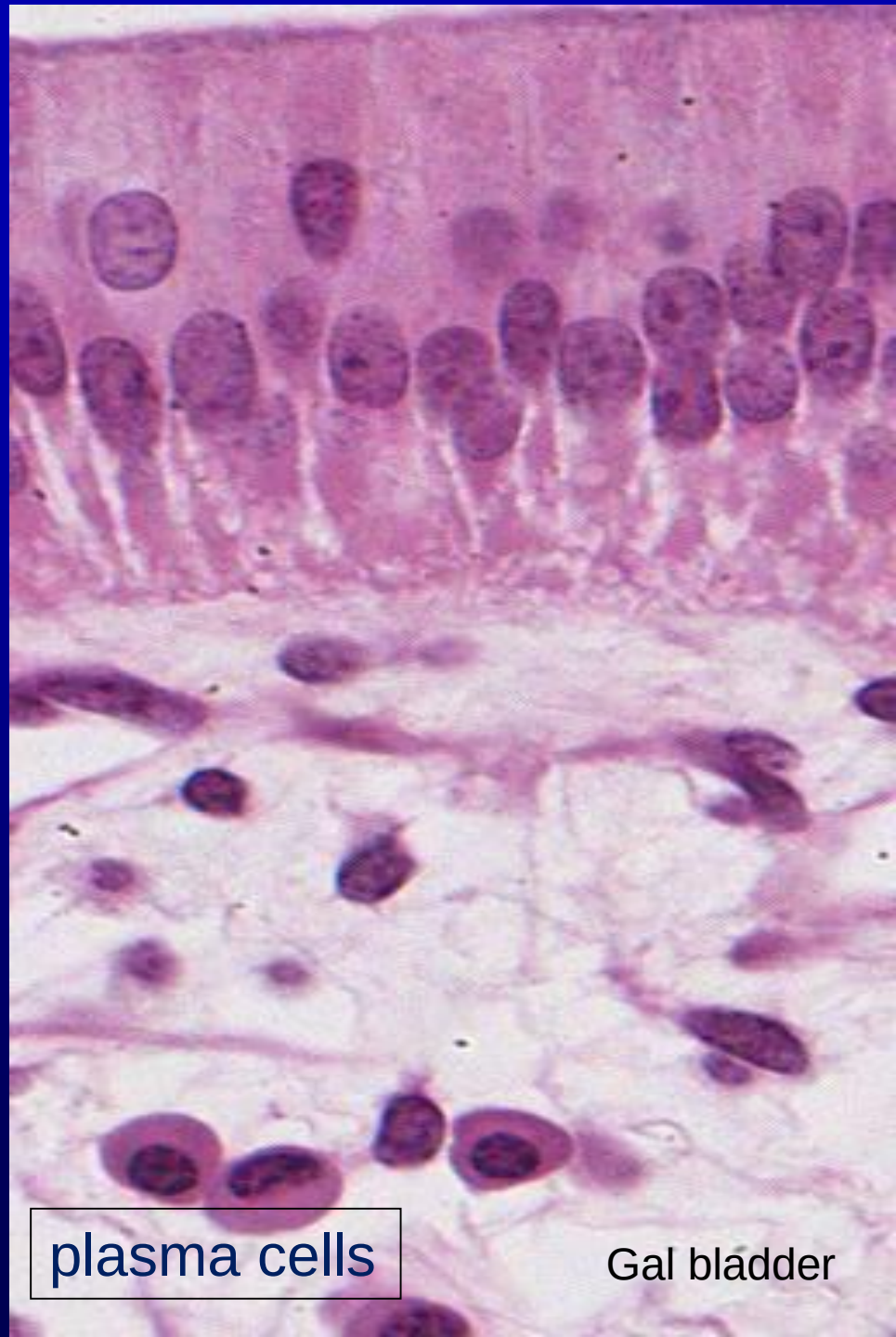


Examples of secretory cells Con't

Pancreatic acinar cell - digestive enzymes

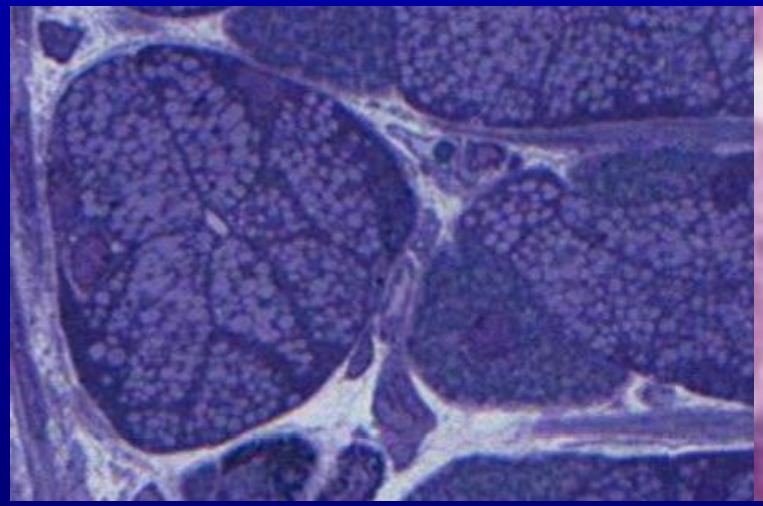
Plasma cell – antibodies





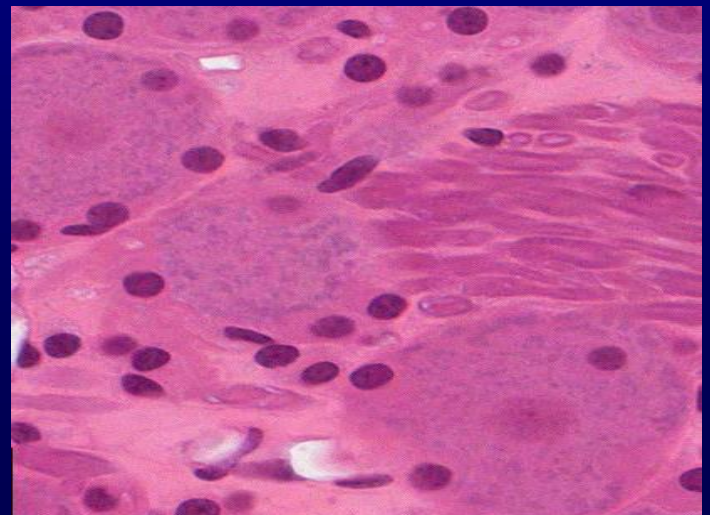
Examples of secretory cells Con't

Pancreatic acinar cell - digestive enzymes



Plasma cell –
antibodies

Chief cells in stomach

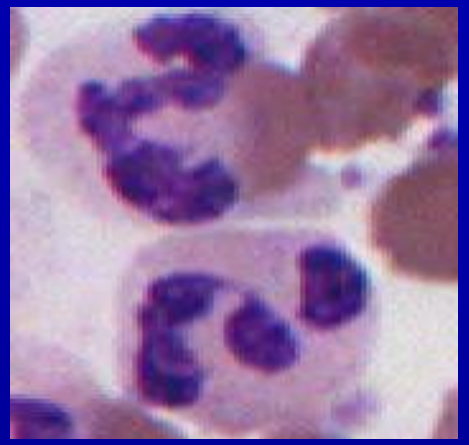


Neurons

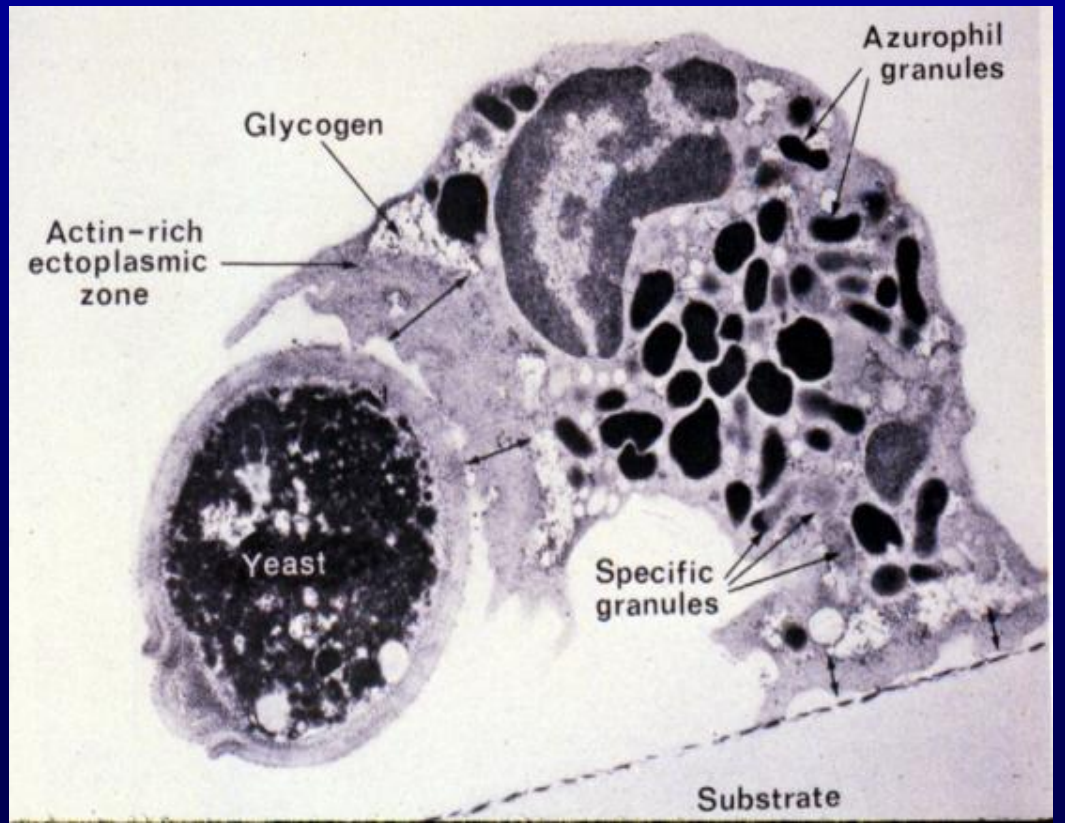
Examples of secretory cells Con't

Neutrophils –
lysosomes to kill
ingested bacteria

All cells housekeeping –
cell membranes,
lysosomes

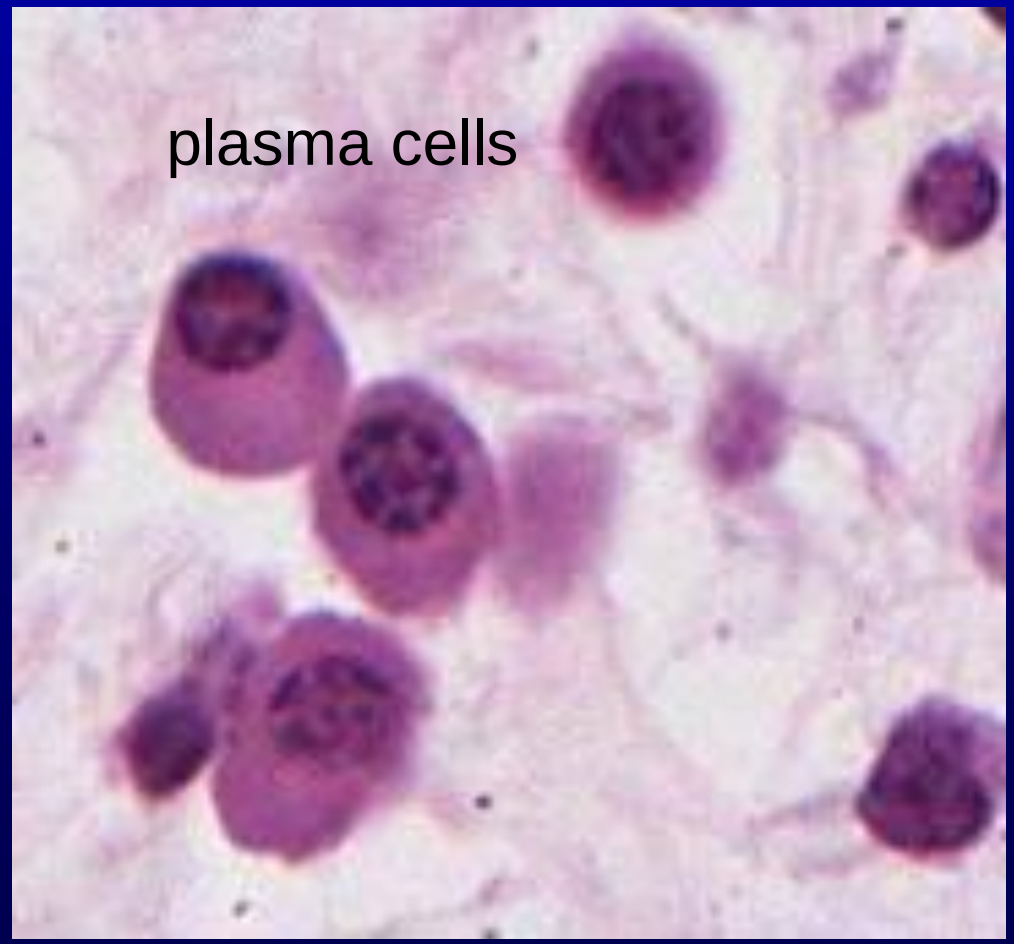


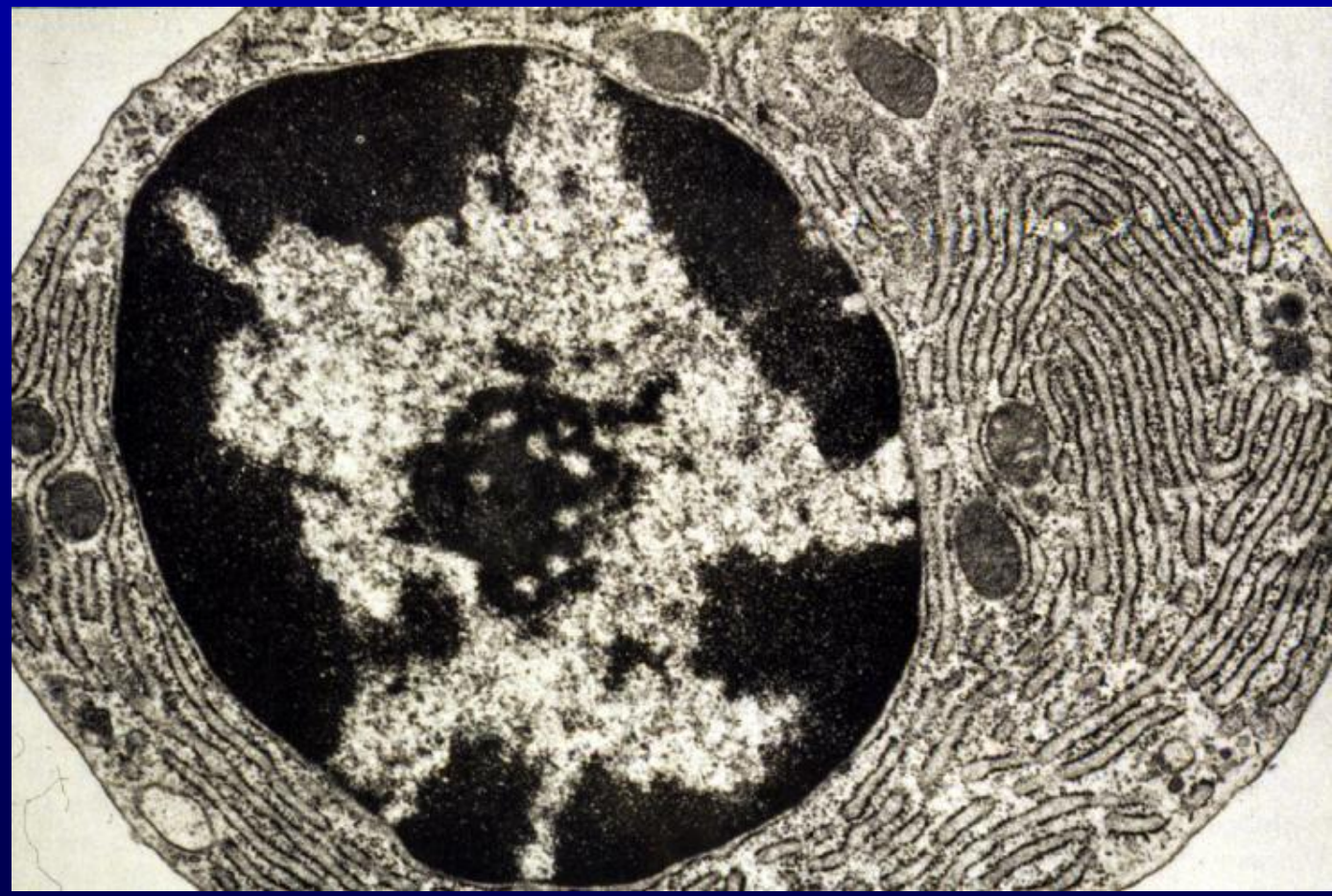
Neutrophils



Secretory Cells have Two types of Release

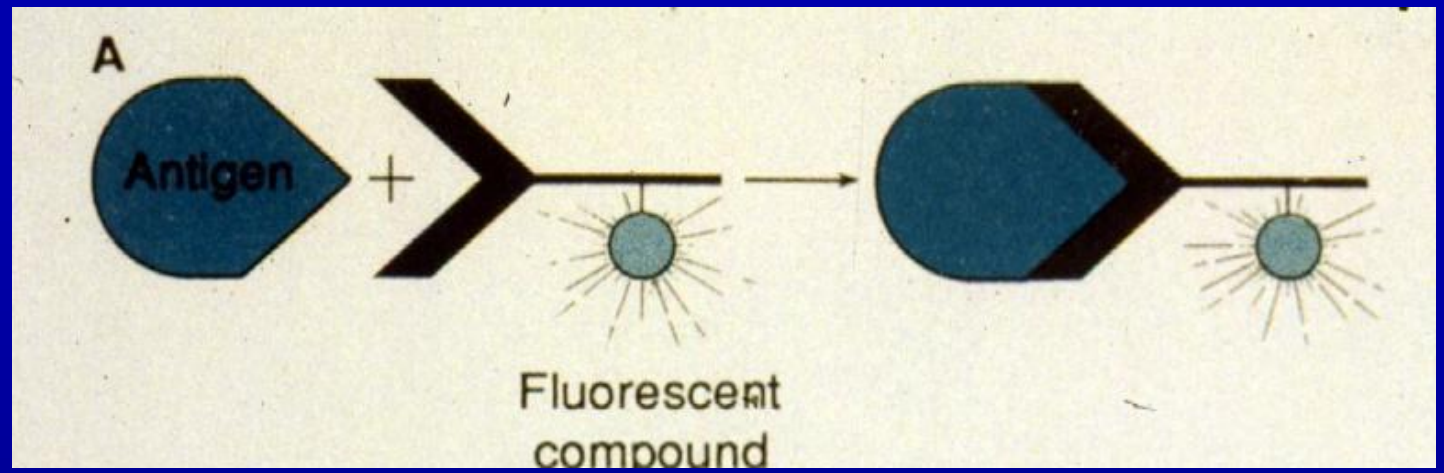
1. <u>Constitutive</u> - consistently releasing without storage granules
e.g., Plasma cell

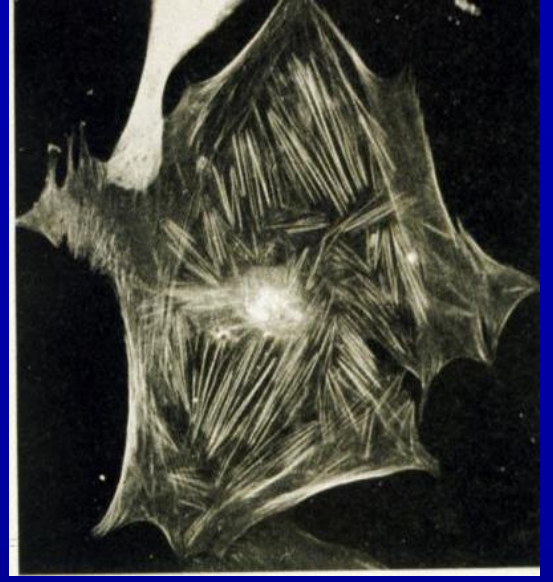




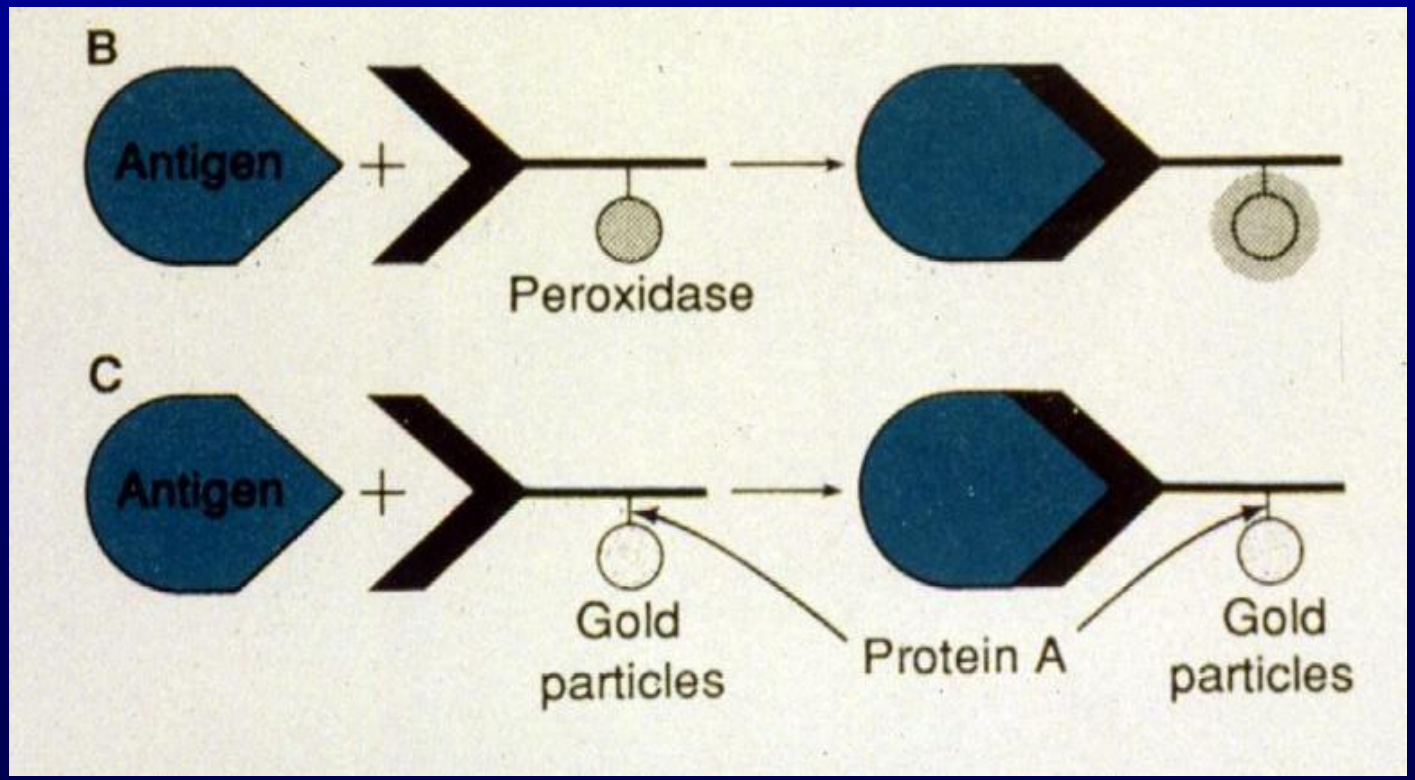
Method to detect release types

Light microscopy

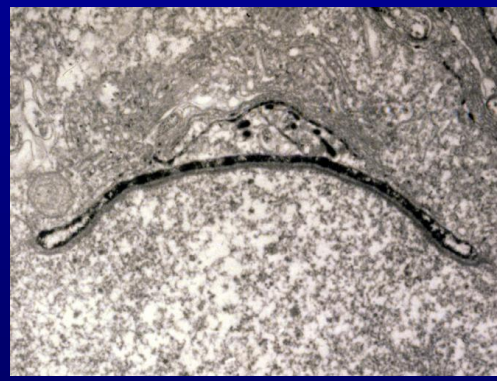


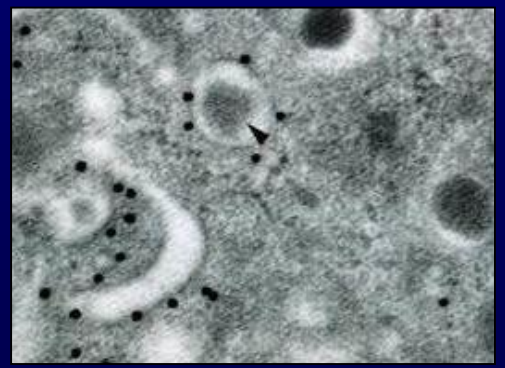


Electron microscopy (TEM) = electron opaque



Histochemical reaction creates e-opaque deposit using the enzymatic activity of the peroxidase





Plasma cells

Typical as seen by TEM

Dense reaction product is seen in the cisternae of the RER indicating the location of antibody protein in plasma cells with no storage of antibody in secretory granules

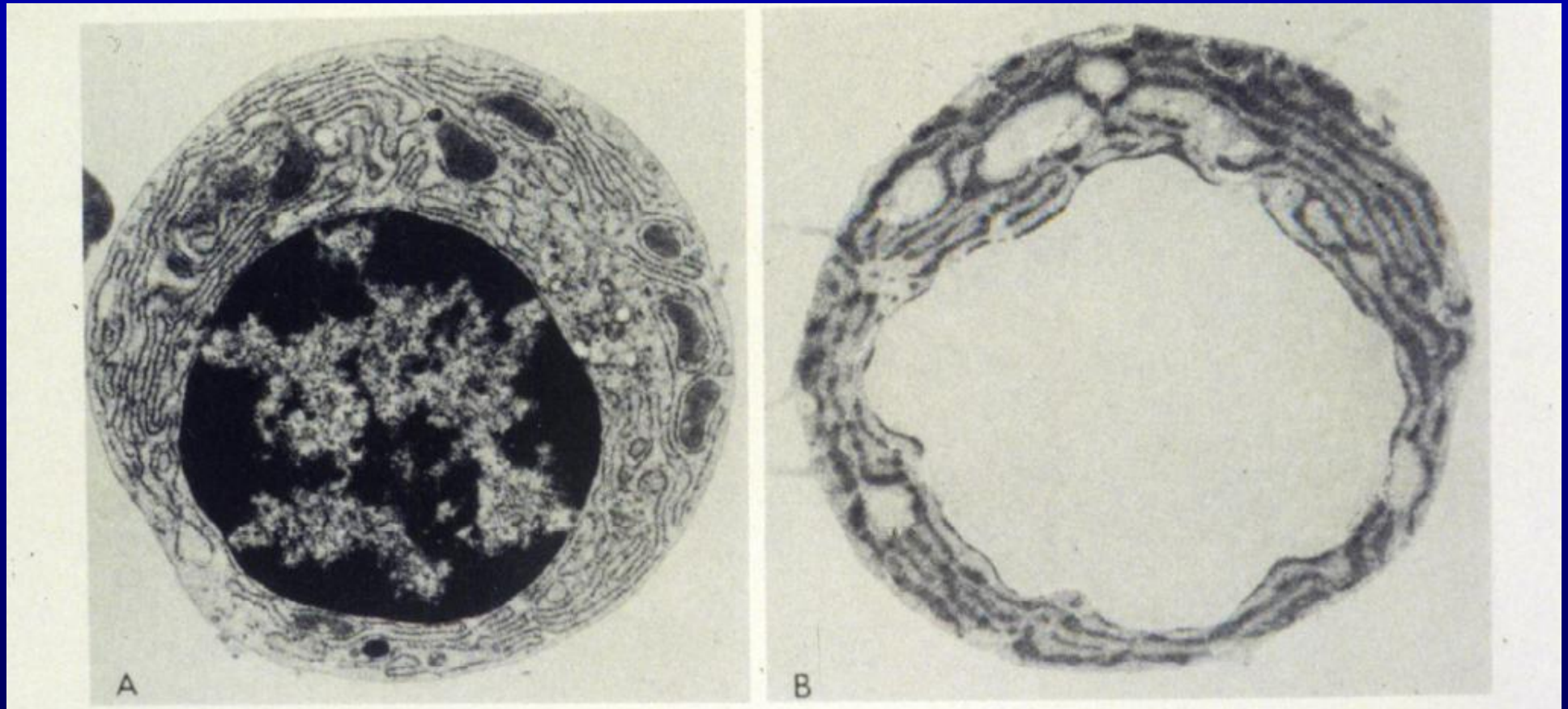
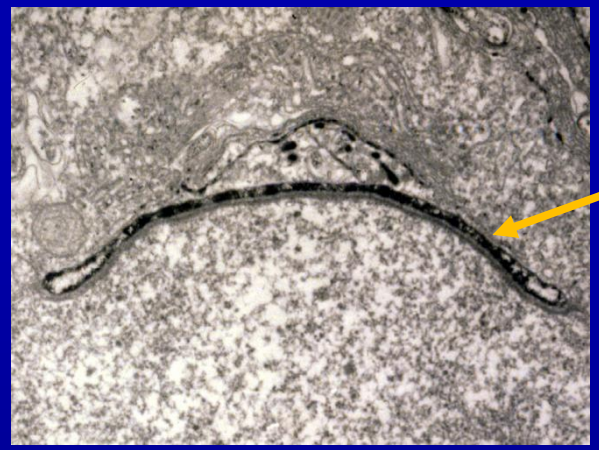


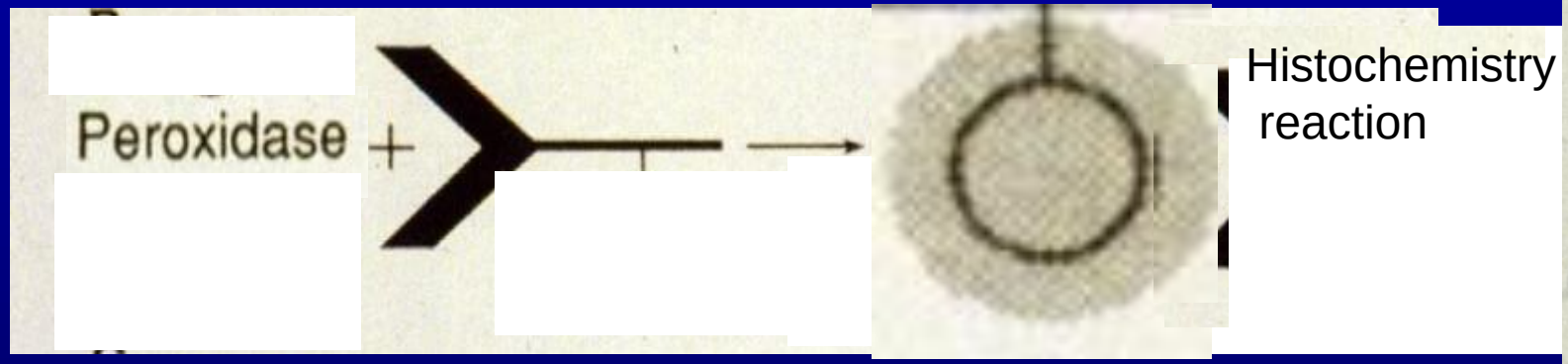
Figure 13–7. (A) Electron micrograph of a plasma cell from the rat spleen. The cytoplasm displays a highly developed rough endoplasmic reticulum. (B) Plasma cell from the spleen of a rabbit, which was injected with horseradish peroxidase, used as an antigen. (B) The spleen cells were subsequently exposed to the peroxidase antigen and stained by the histochemical reaction for demonstrating peroxidase activity. The dense reaction product is seen in the cisternae of endoplasmic reticulum, indicating the presence of anti-peroxidase antibody. (Micrograph courtesy of E.D. Leduc and S. Avrameas.)

Evidence for Constitutive secretion of plasma cells

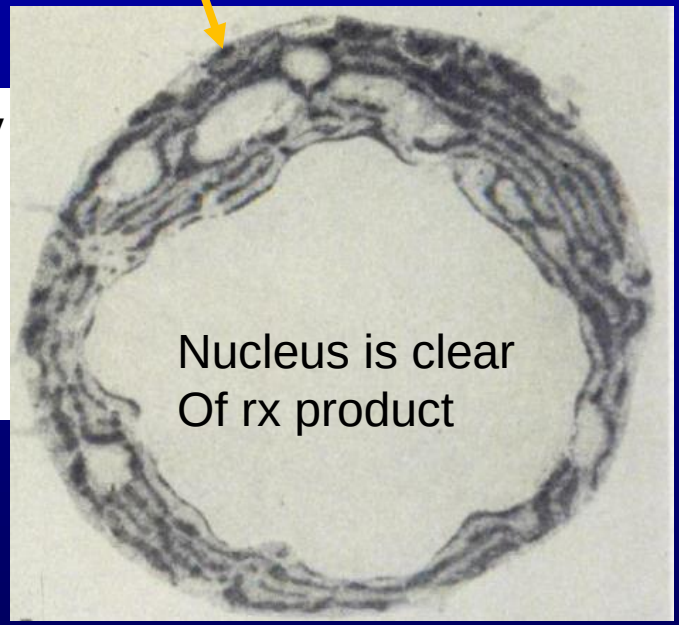
Histochemistry reaction where by native enzymes within the mature face of Golgi reacted with substrate to produce electron opaque participate



horseradish peroxidase reaction product is electron opaque with EM



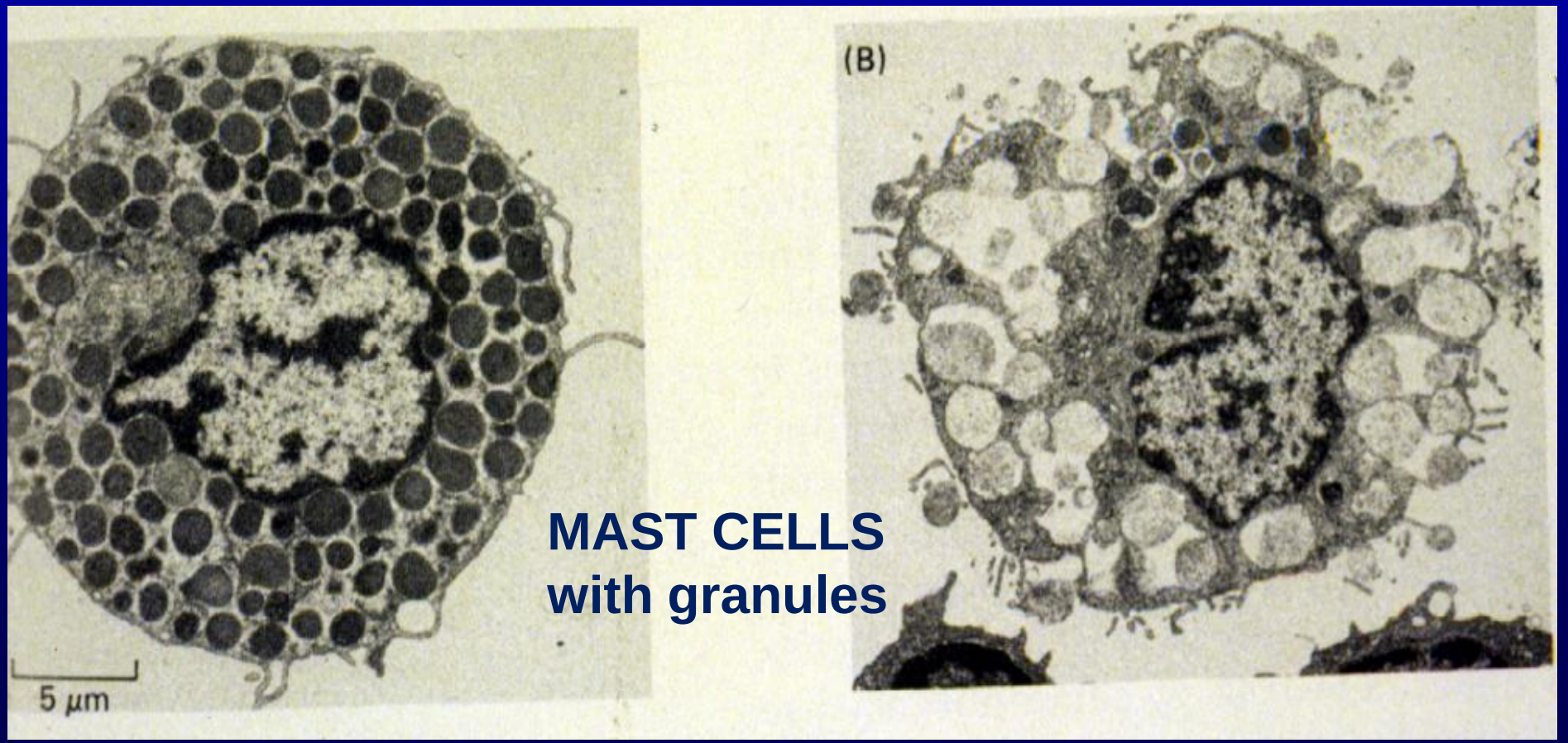
Histochemistry reaction



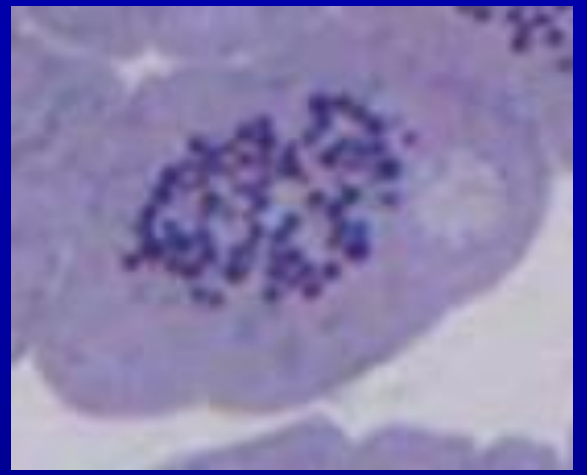
Injection of animal with horseradish peroxidase caused its plasma cells to produce antibodies against peroxidase (and the antibodies are located where they are produced in the cisternae of RER) and bind to peroxidase when exposed to the cell by experimental treatment followed by histochemical reaction induction of a electron opaque participate

Secretory Cells have Two types of Release

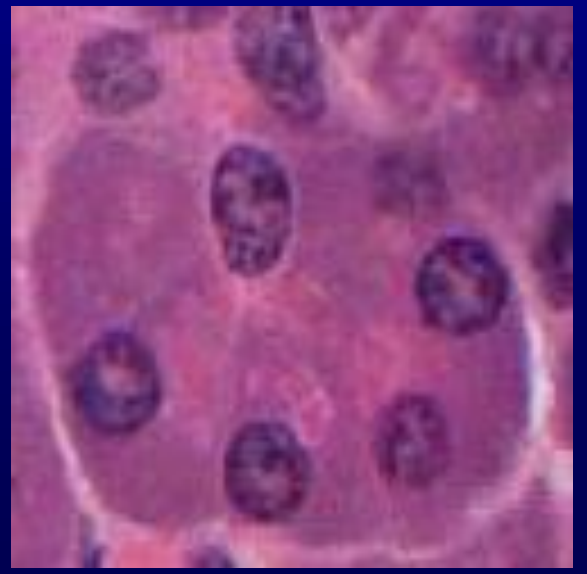
2. <u>Induced</u> – release from storage granules after signal received (hormone/antibody binding) e.g., Pancreatic acinar cell and mast cell



MAST CELLS with granules

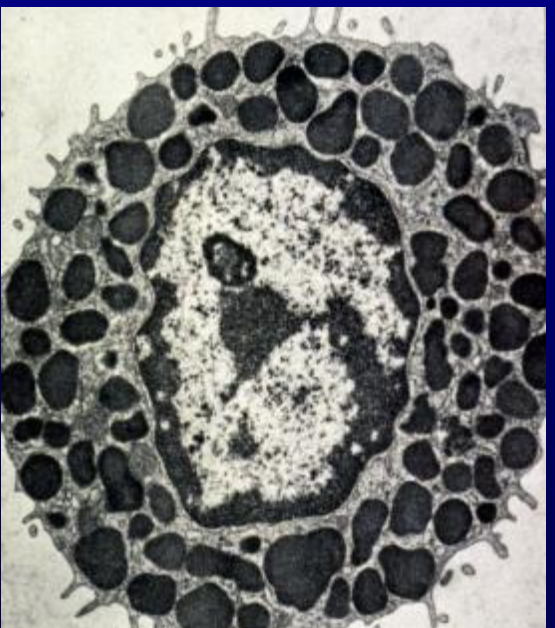


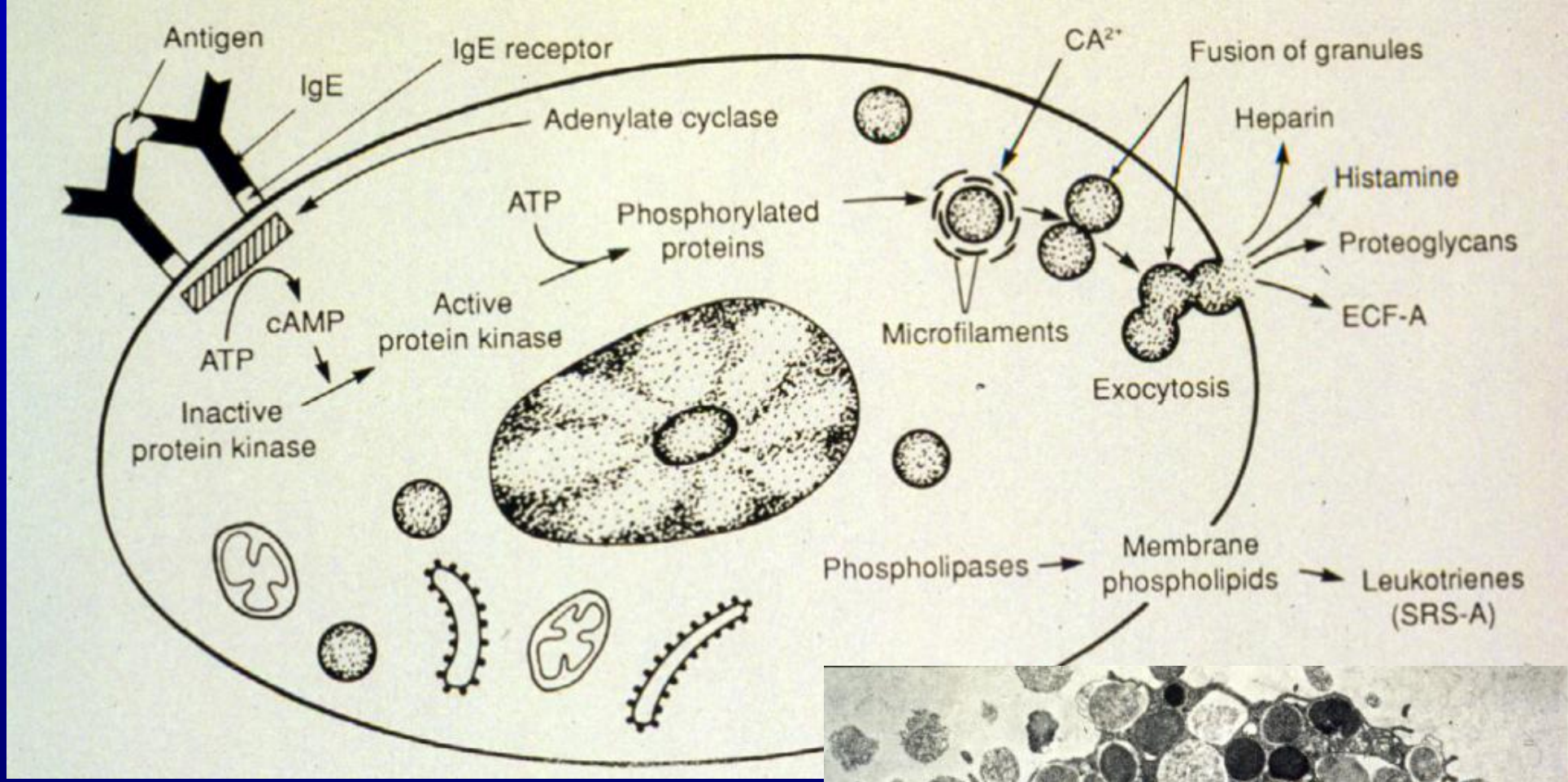
Insulin induces release of secretions Pancreatic acinar cell



Receptors on mast cell surface bind IgE antibodies and cAMP is produces inside the cell when the antibodies bind to their specific antigens

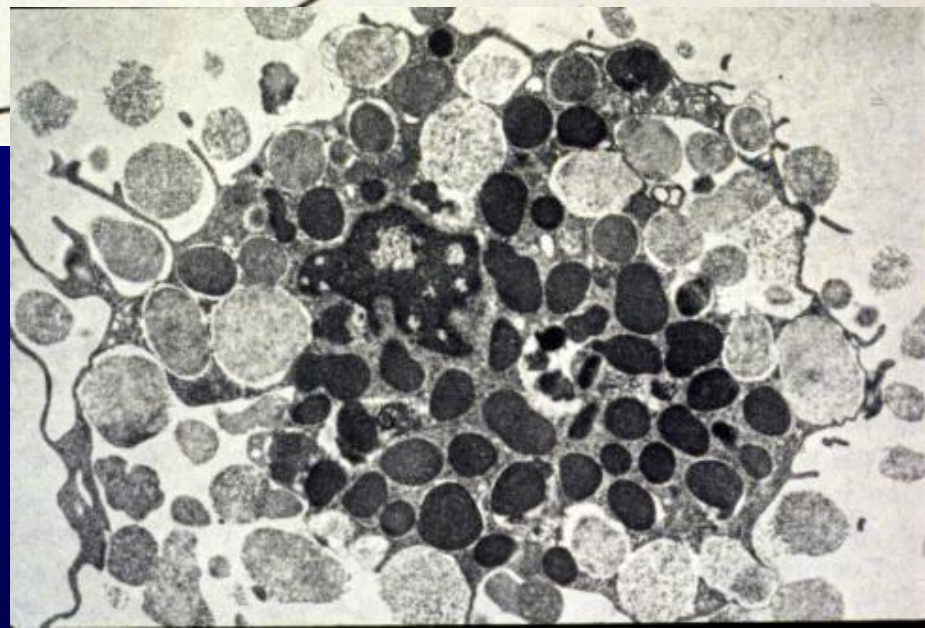
This allows several antigens to induce mast cell degranulation depending on antigen present.



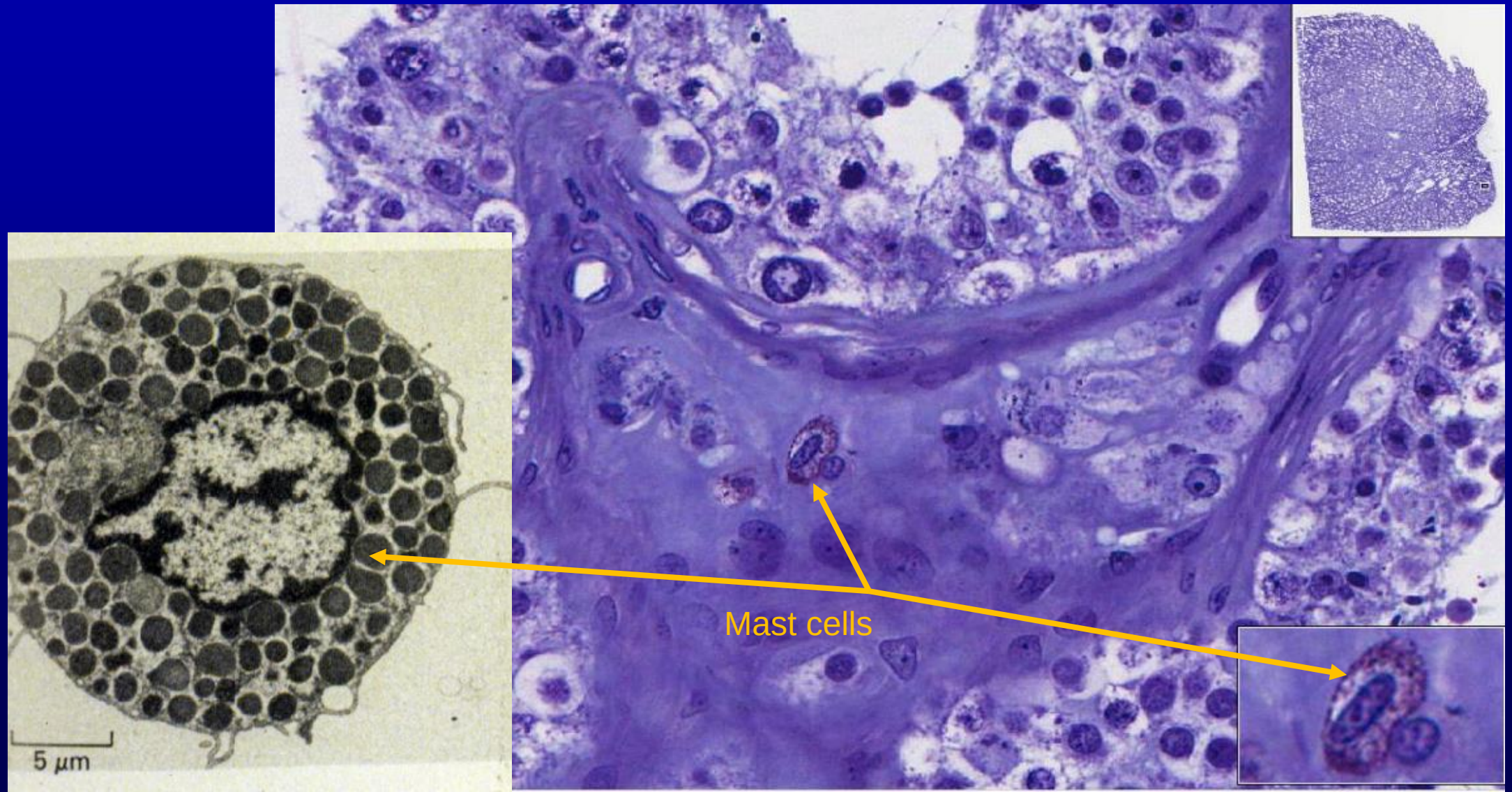


Induced degranulation of mast cells

Antibody-antigen induced mechanism makes mast cells respond to specific antigens. Hence, it gives specificity to mast cells.



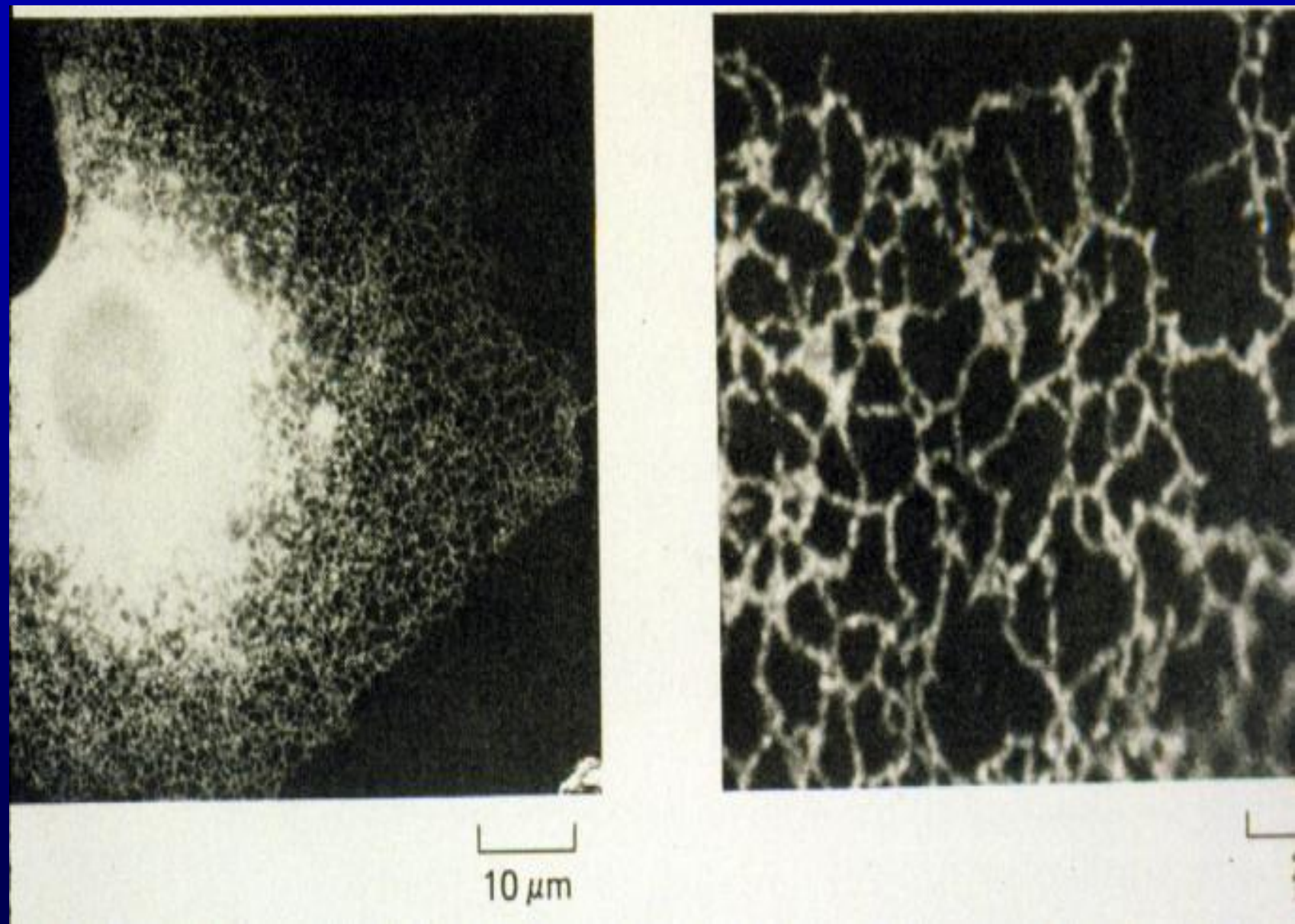
19709 Mast cells in stained testicular tissue



Endoplasmic reticulum in secretion

General:

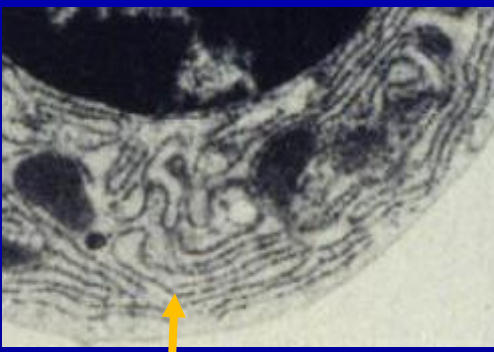
- **Membrane-bound canaliculi**
- **Loose network of branching and anastomosing tubules (SER)**

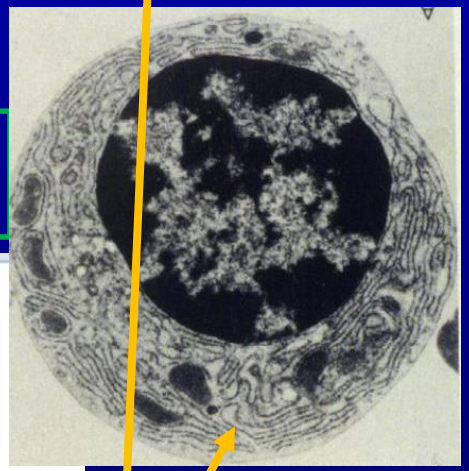


Endoplasmic reticulum in secretion

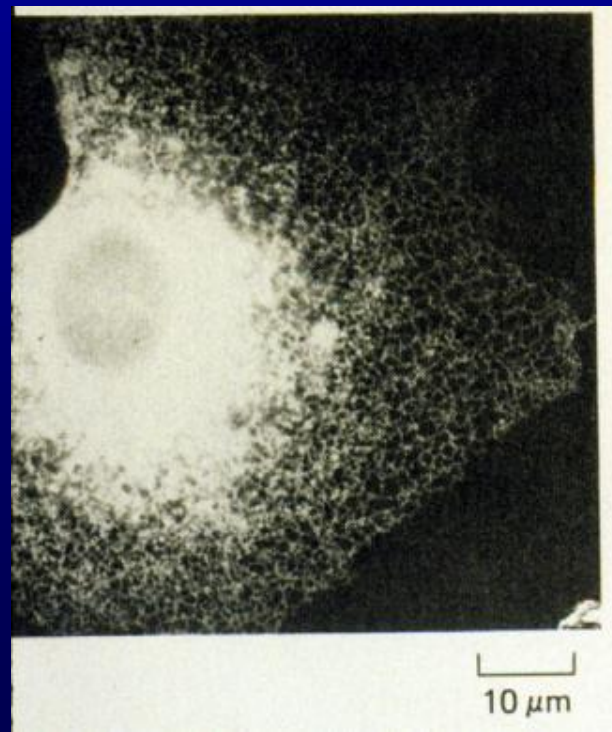
General:

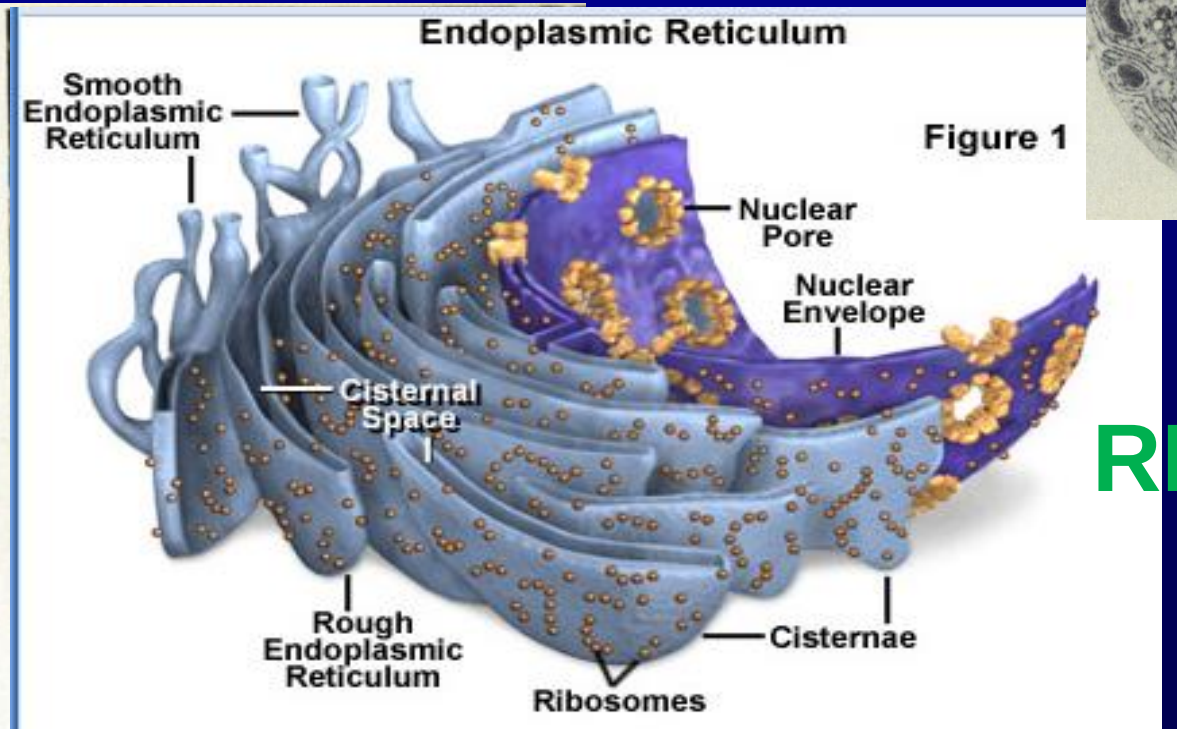
- **Membrane-bound canaliculi**
- **Loose network of branching and anastomosing tubules (SER)**
- **Cisternae - flattened sacks (RER) with ribosomes**





SER

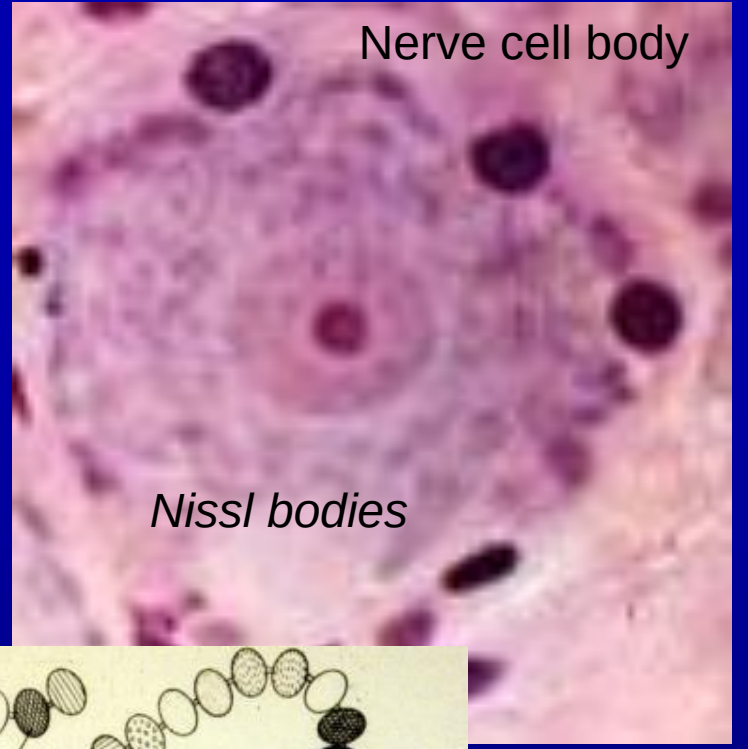


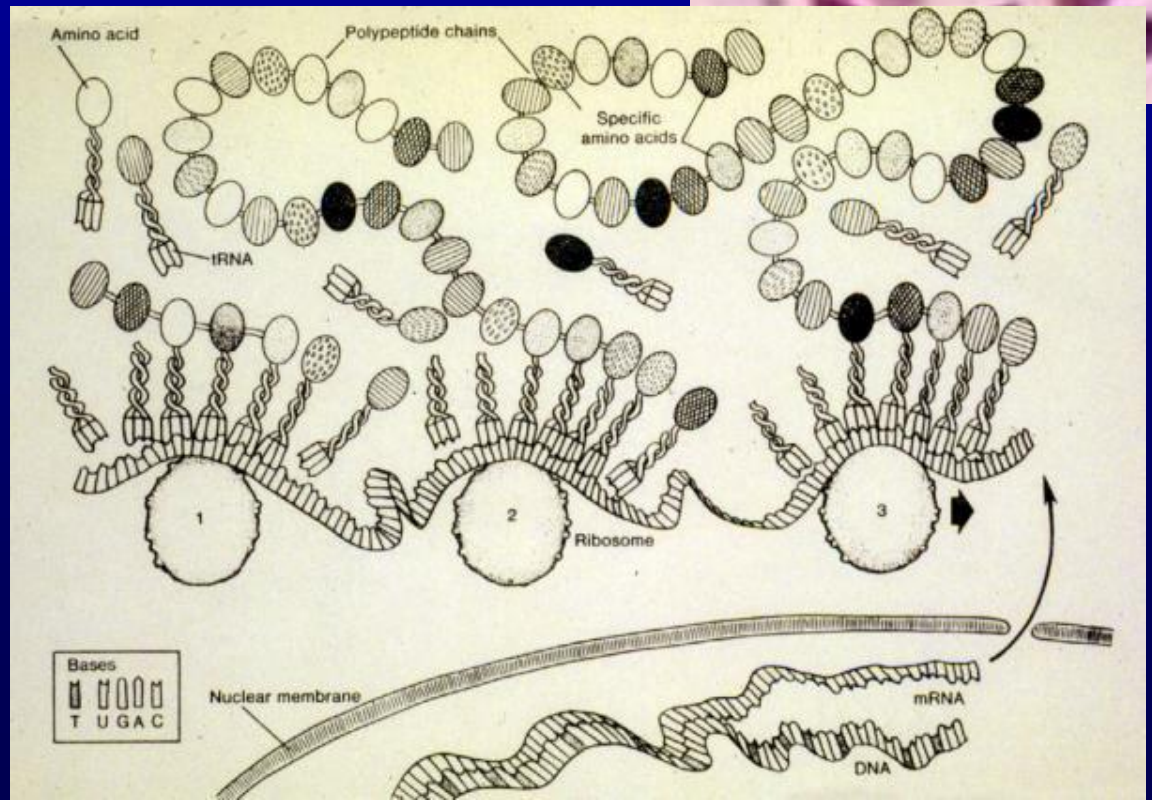


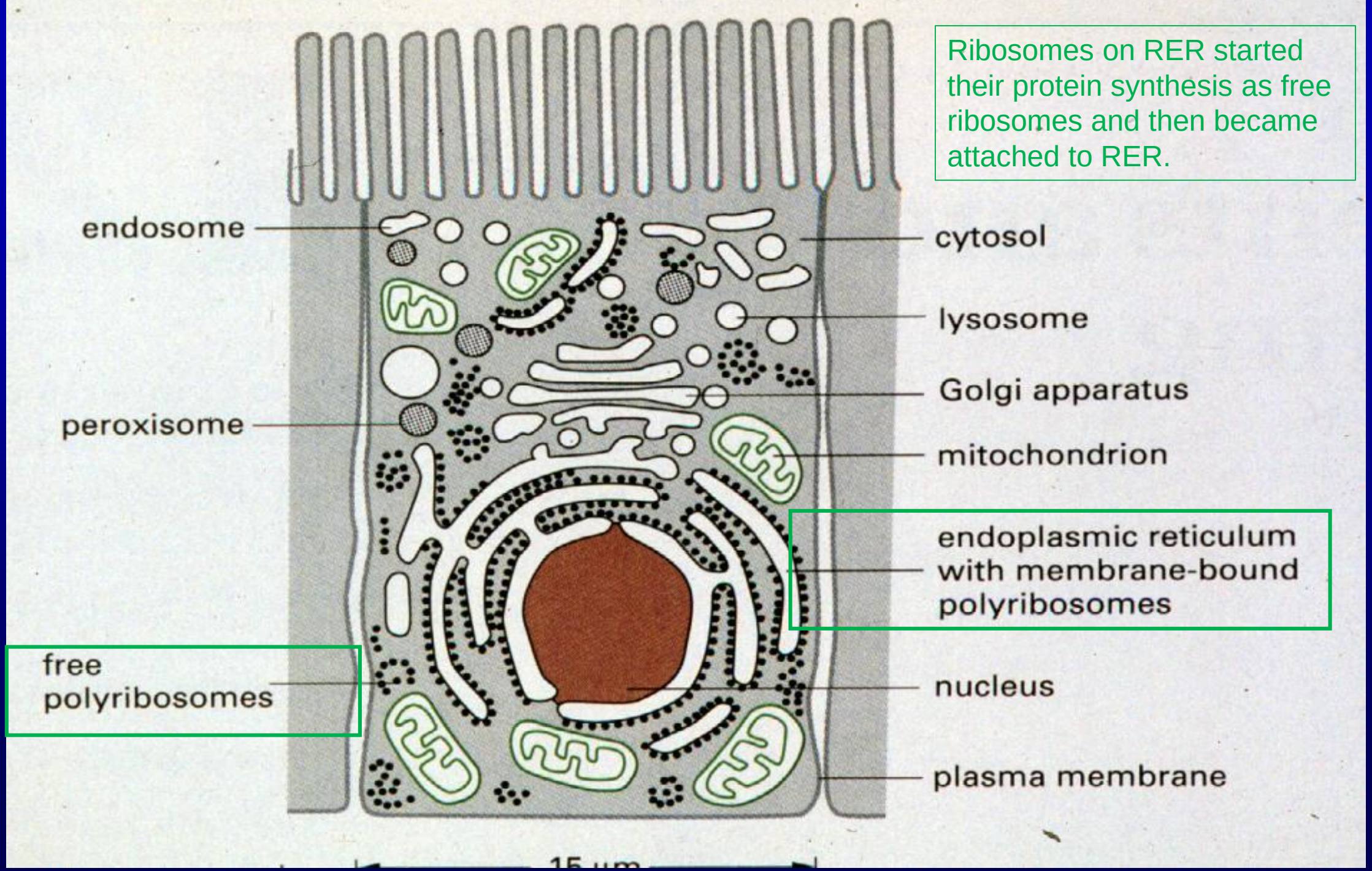
RER

Ribosomes make RER rough

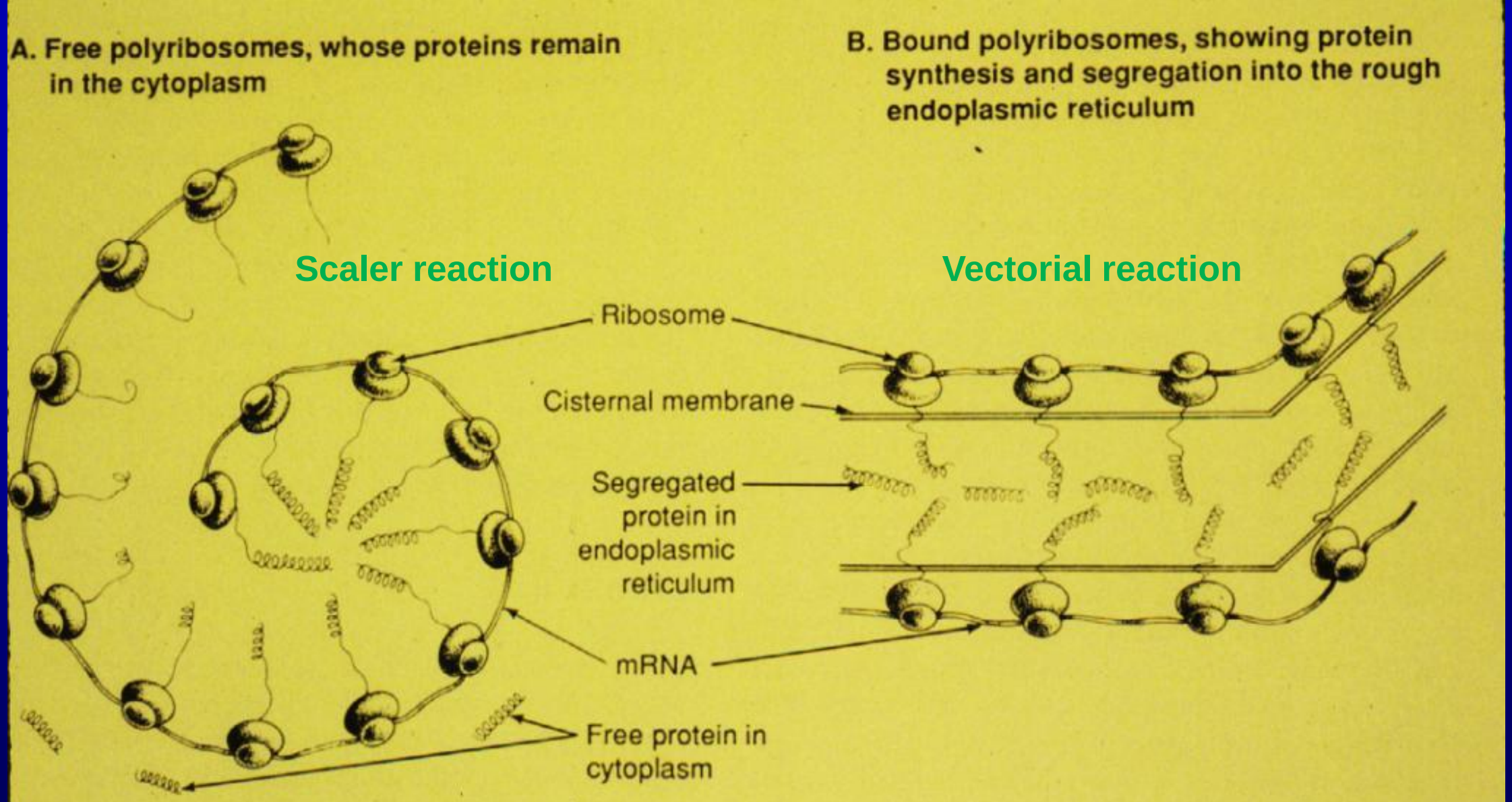
- Ribosomal RNA and protein
- Basophilic due to phosphate groups
  - (Nissl bodies of nerve cell bodies)
- Polyribosomes - group attached by common mRNA carrying code for amino acid sequence
- Function-decoding (translating) mRNA during protein synthesis







Ribosomes on RER started their protein synthesis as free ribosomes and then became attached to RER.



gure 3–8. This diagram illustrates **(A)** the concept that cells synthesizing proteins (represented here by spirals) that e to remain within the cytoplasm possess (free) polyribosomes (ie, nonadherent to the endoplasmic reticulum). In **B,** ere the proteins are segregated in the endoplasmic reticulum and may eventually be extruded from the cytoplasm xport proteins), not only do the polyribosomes adhere to the membranes of rough endoplasmic reticulum, but the

Reactions

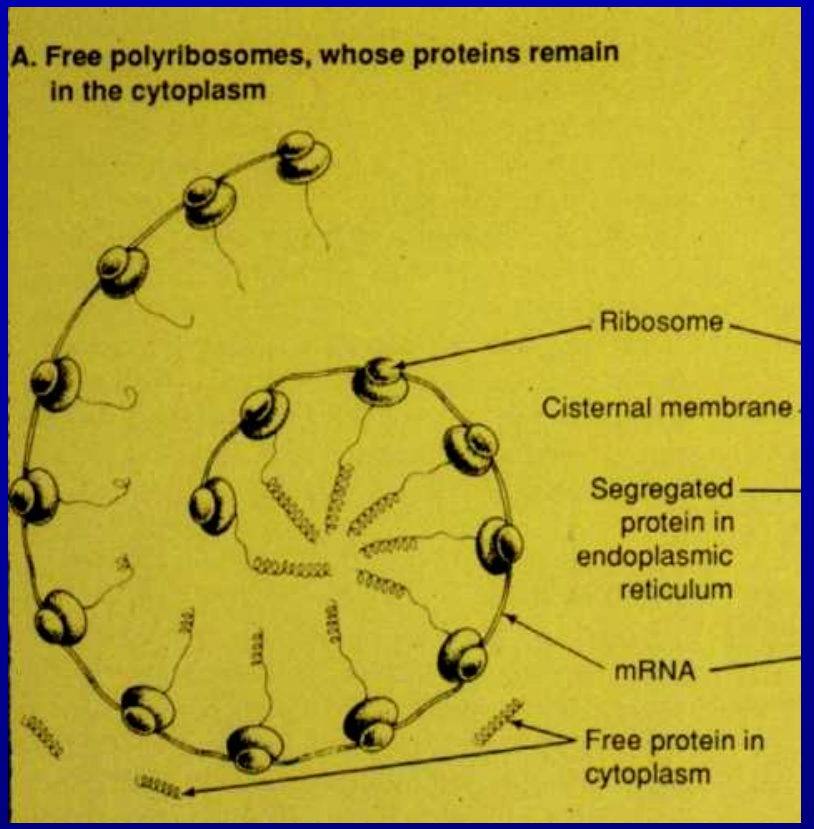
- **Scaler reactions**

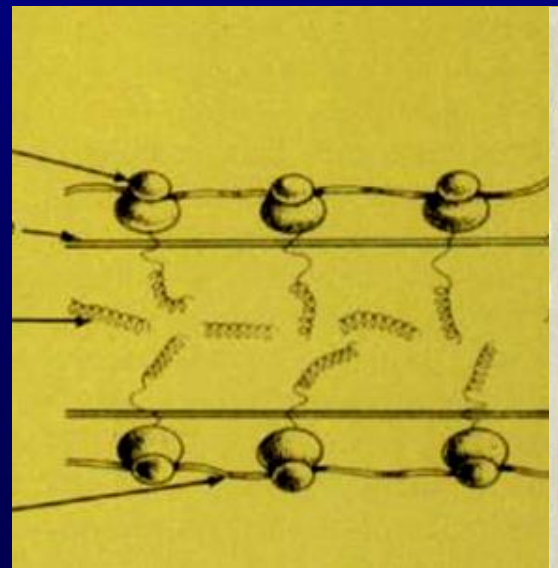
$$a + b = c$$

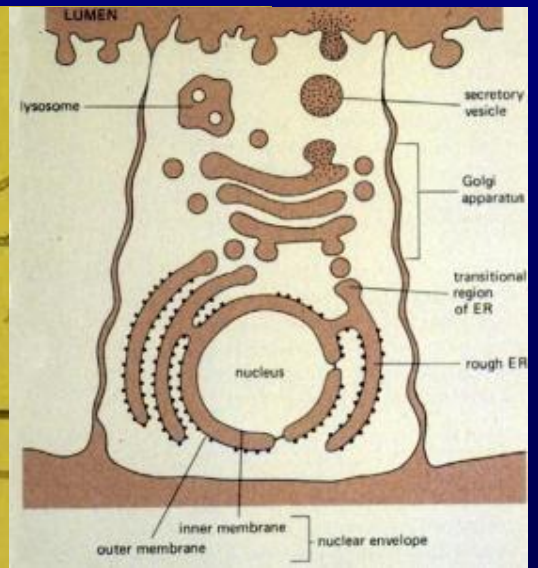
- **Vectorial reactions**

$$a + b = c$$

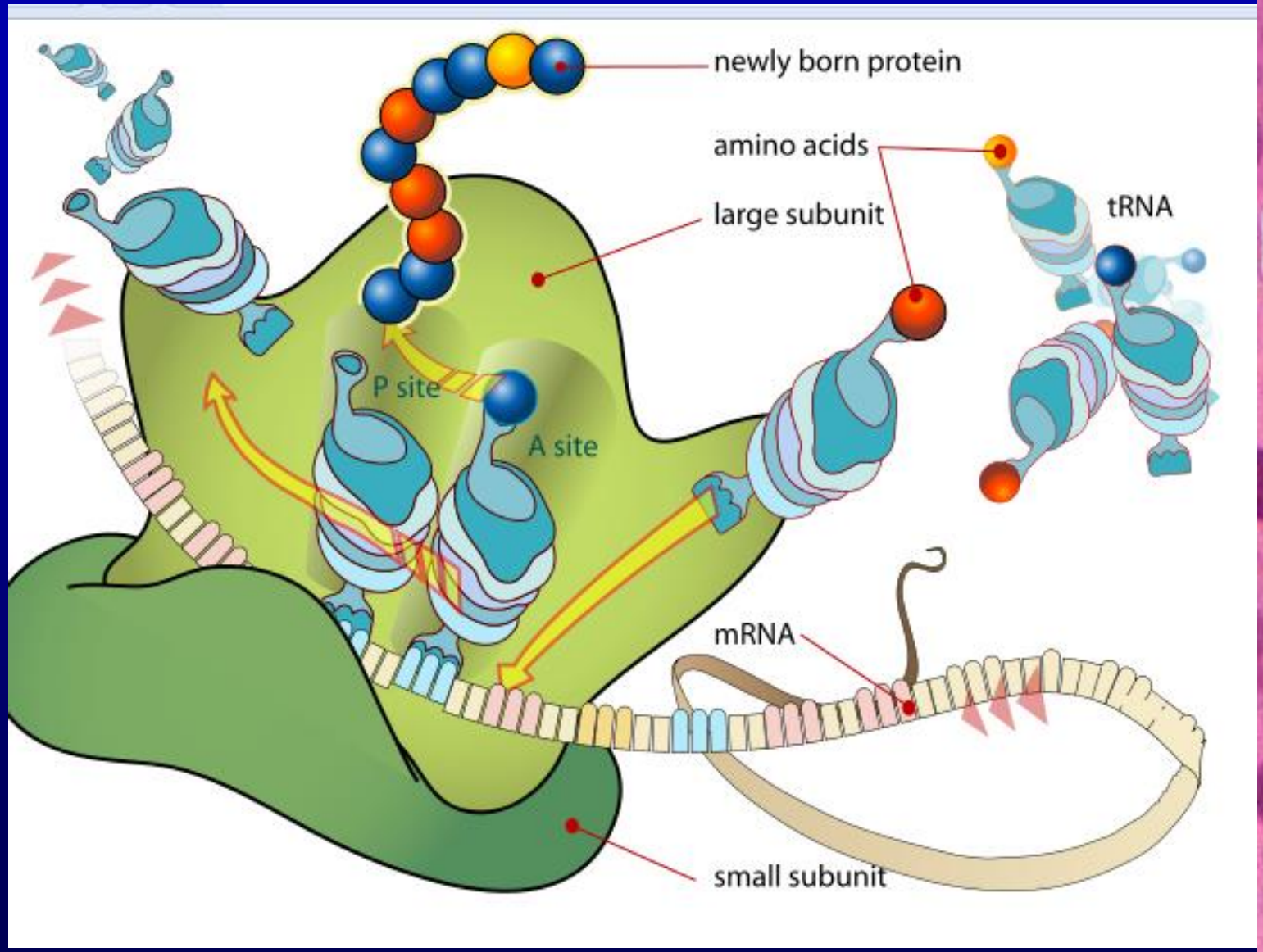
Membranes separate



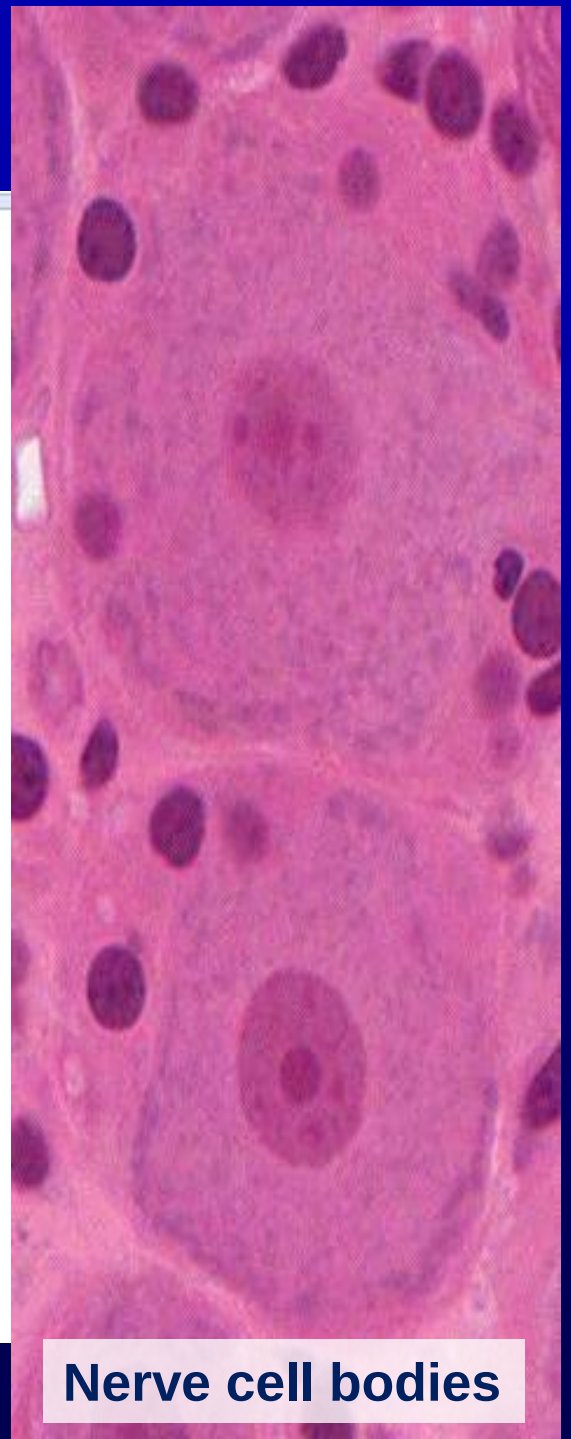




Ribosomes

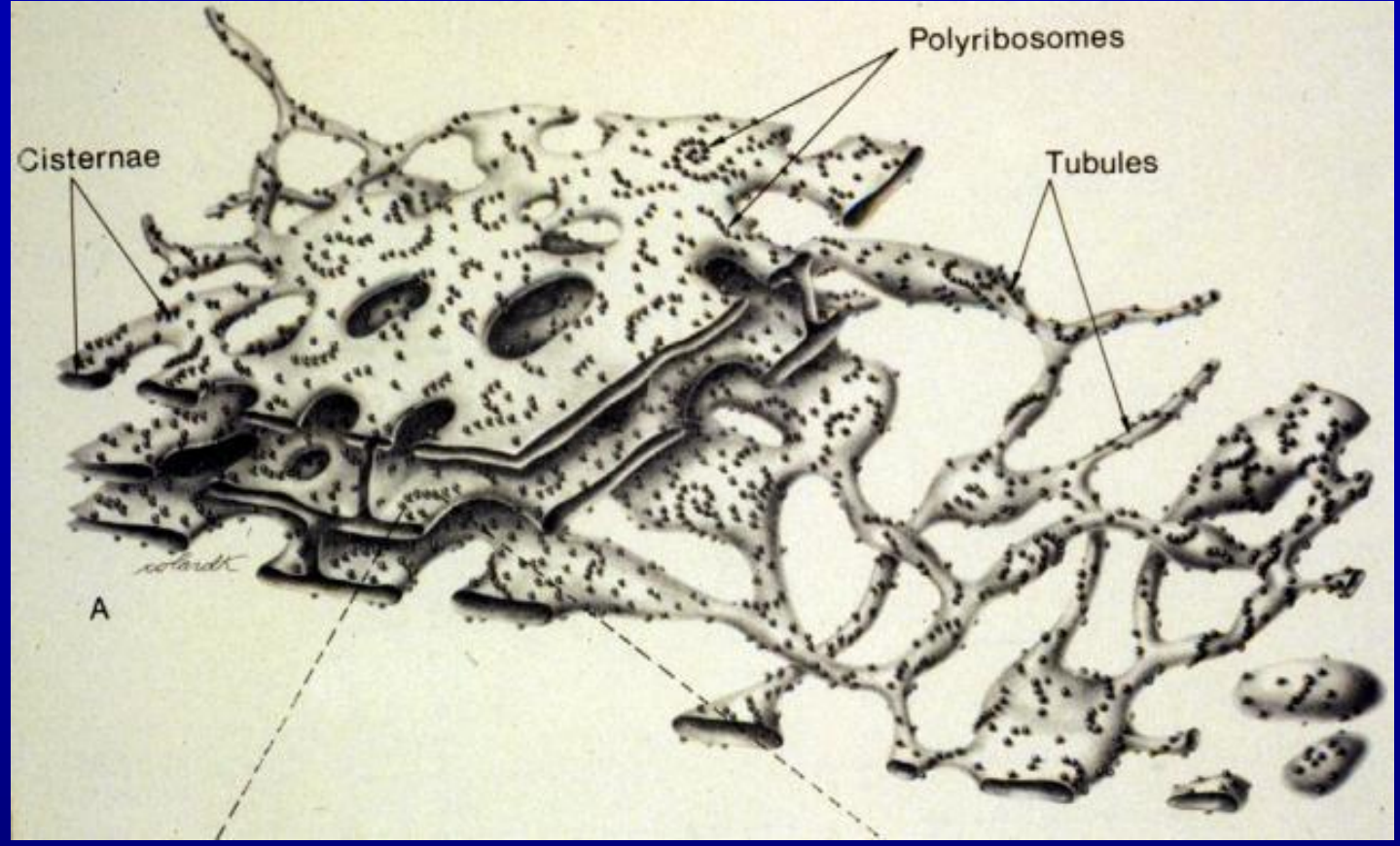


Nissl bodies of nerve cell bodies = ribosomes



Nerve cell bodies

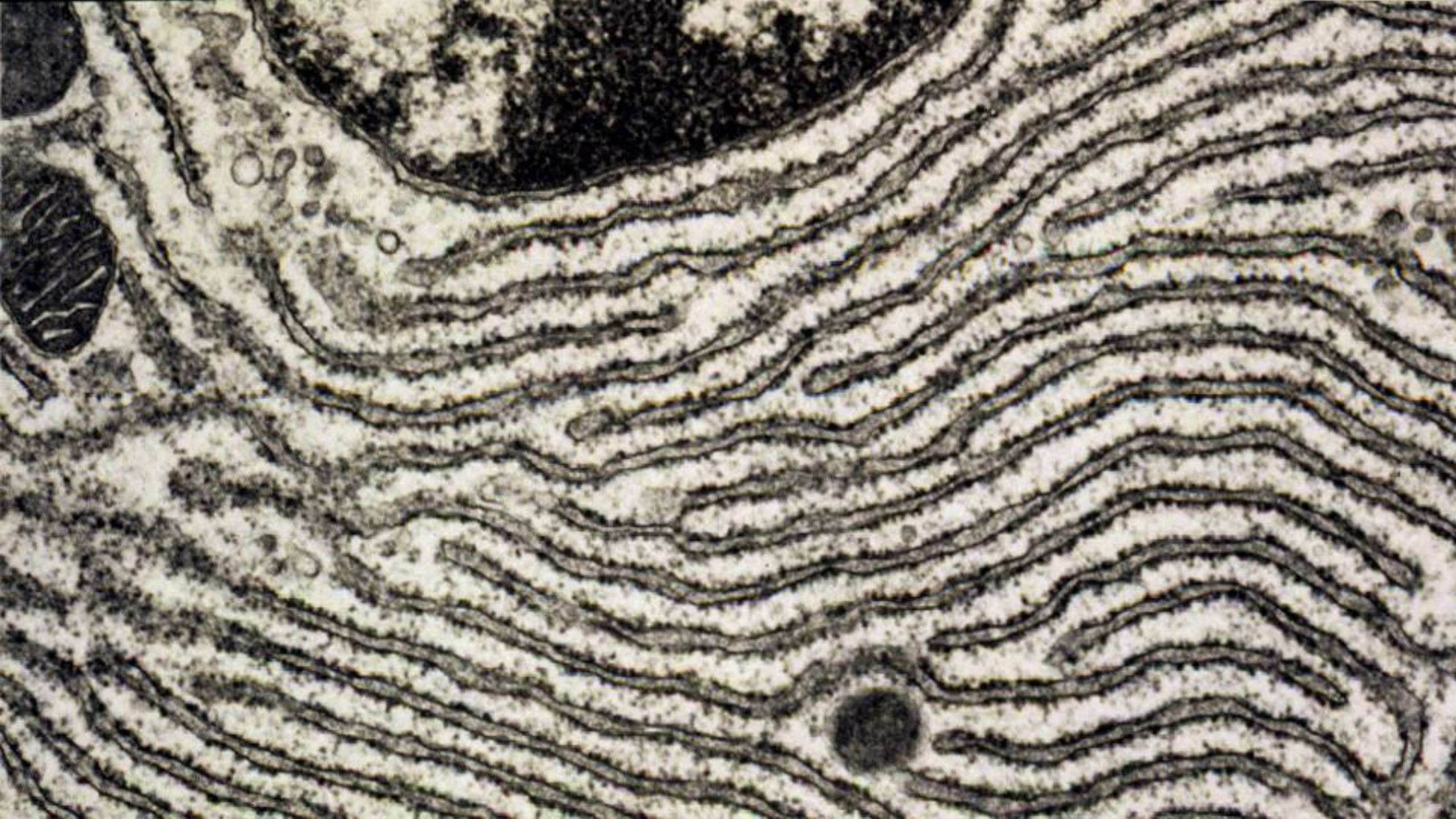
Ribosomes



<u>Free</u> –
intracellular proteins

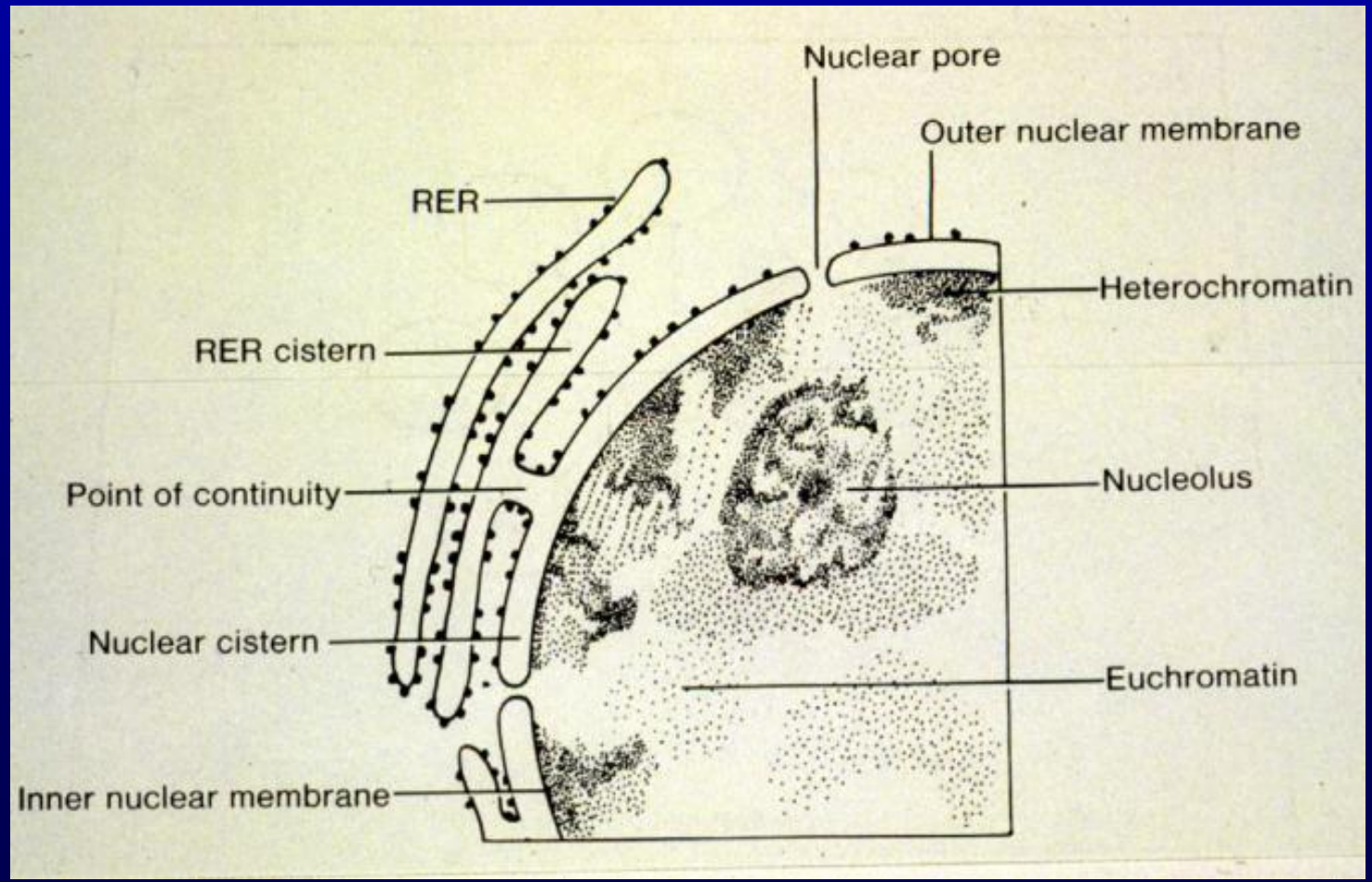
<u>Attached to RER</u> –
secretory proteins

- **Signal sequence - attach new protein to RER**
- **Stop transfer sequence**
- **Docking protein on RER for protein synthesis to continue**
- **Ribophorins - attach ribosomes to RER**



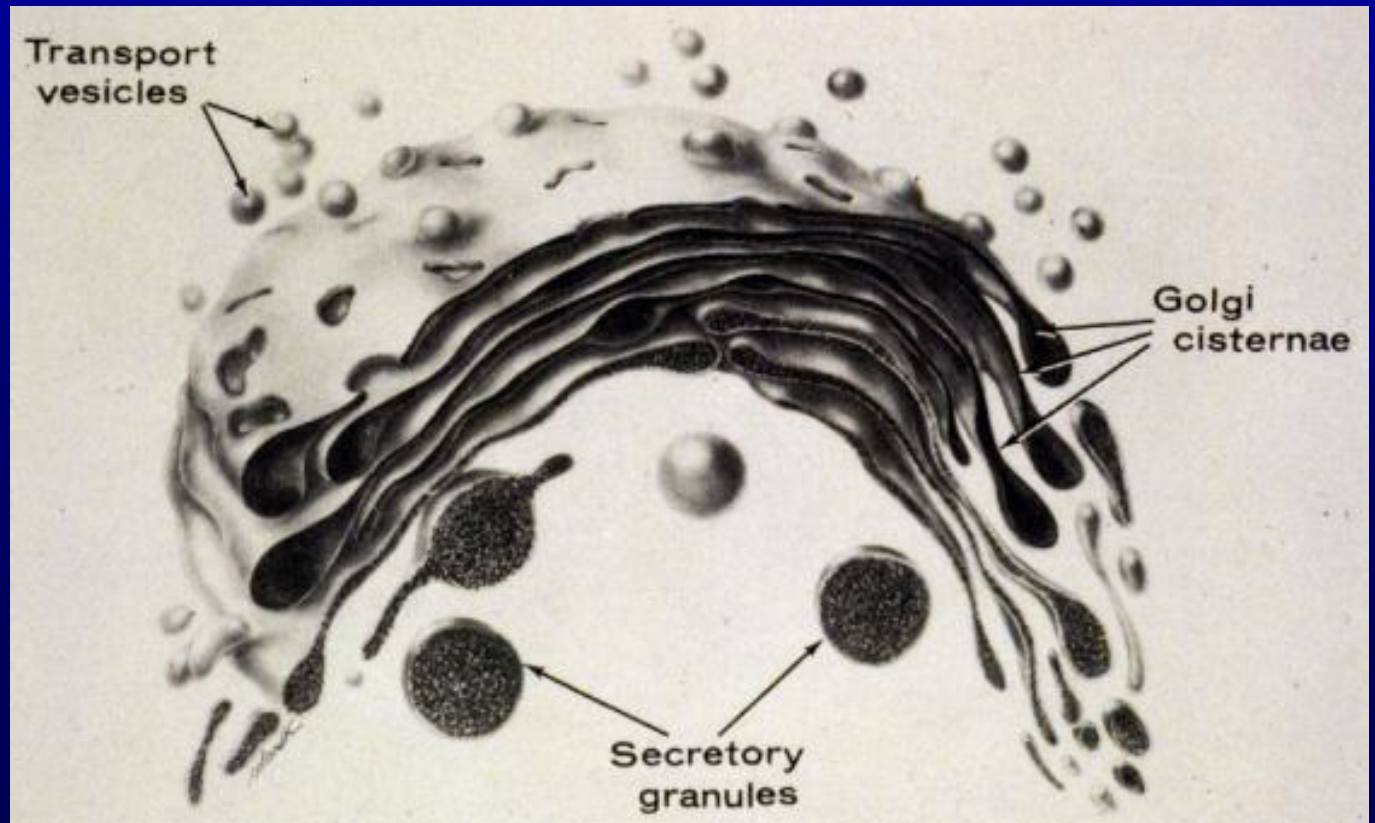
Rough endoplasmic reticulum

- Ribosomes
- Protein synthesis and initial glycosylation > Golgi > plasma membrane
- Nuclear envelope



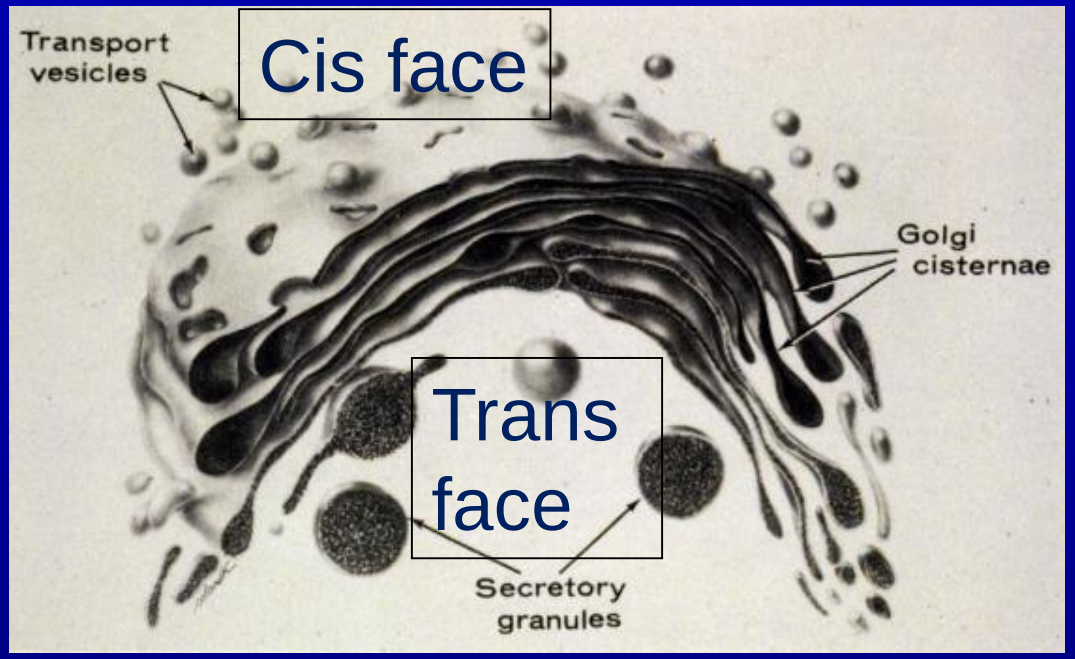
Golgi in secretion

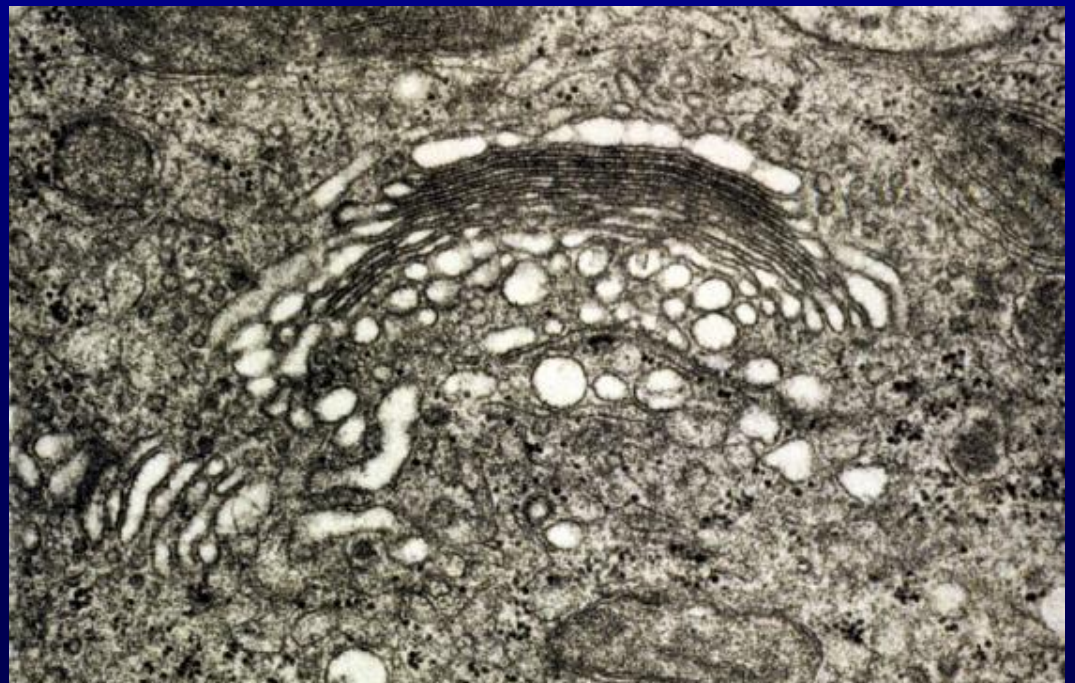
- Present in nearly all eukaryotic cells
- Function - concentration, chemical modification and packaging of secretory products and production of lysosomes

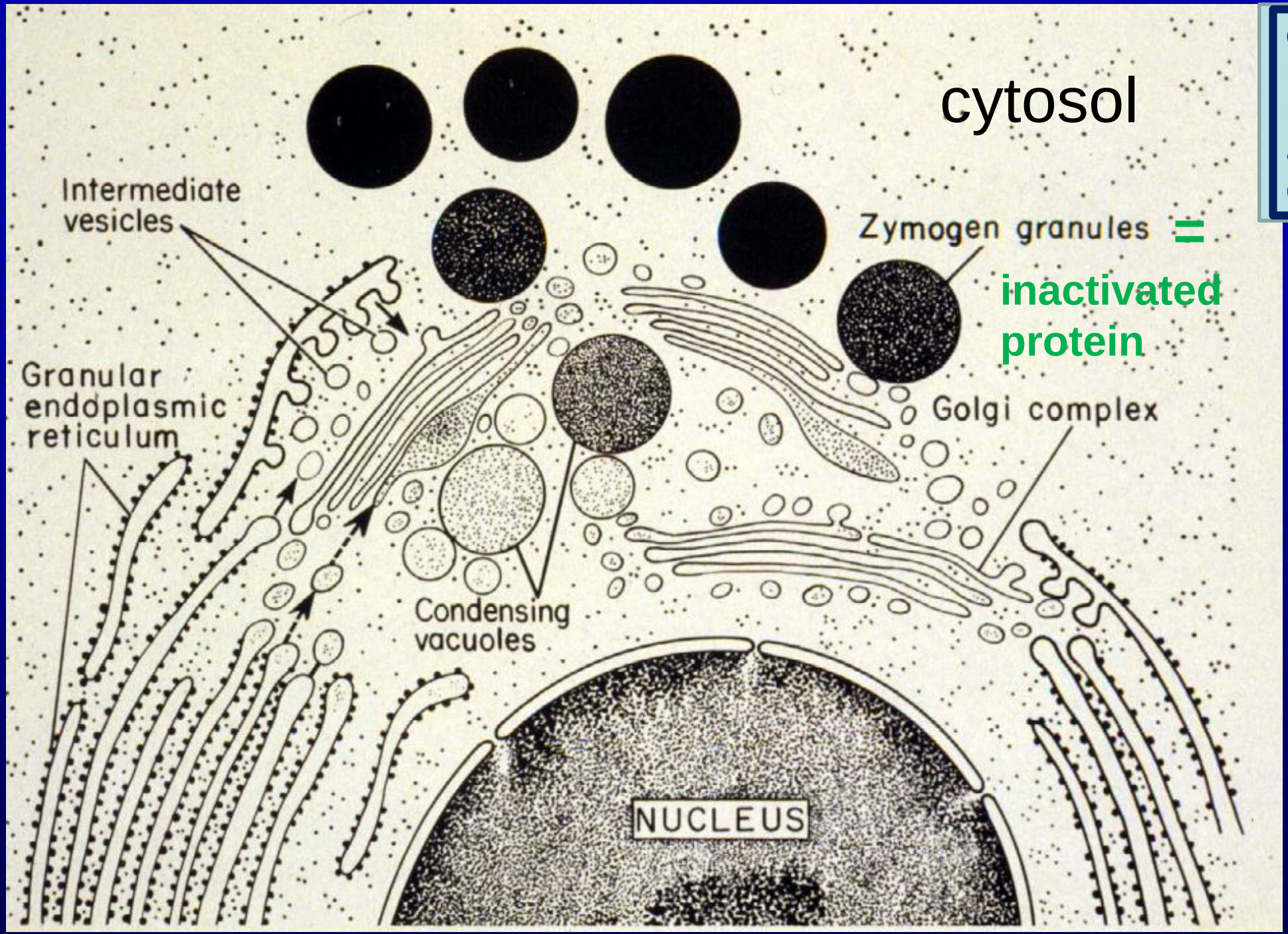


Golgi

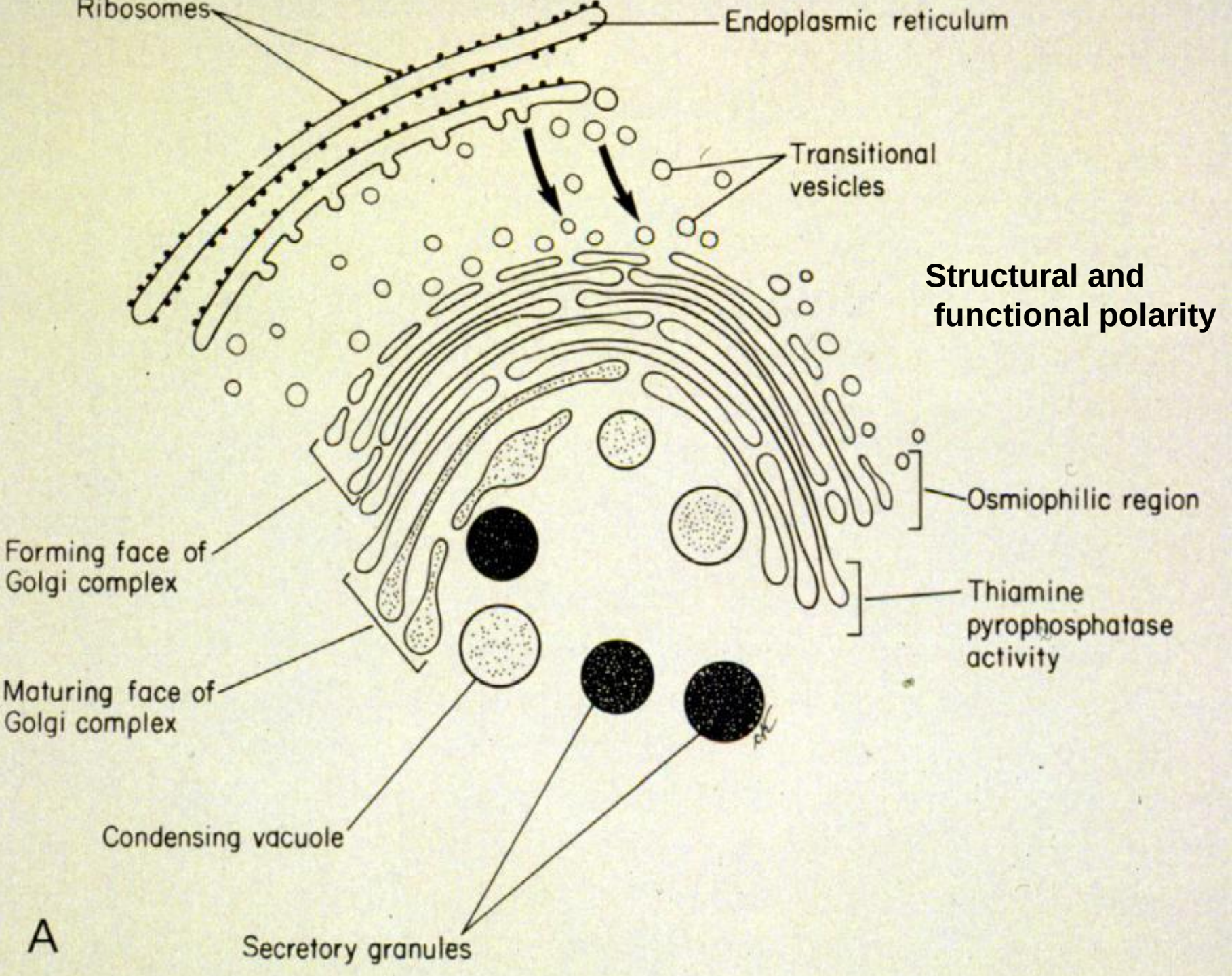
- **Structural and functional polarity**
- **Glycosylation of proteins from RER**

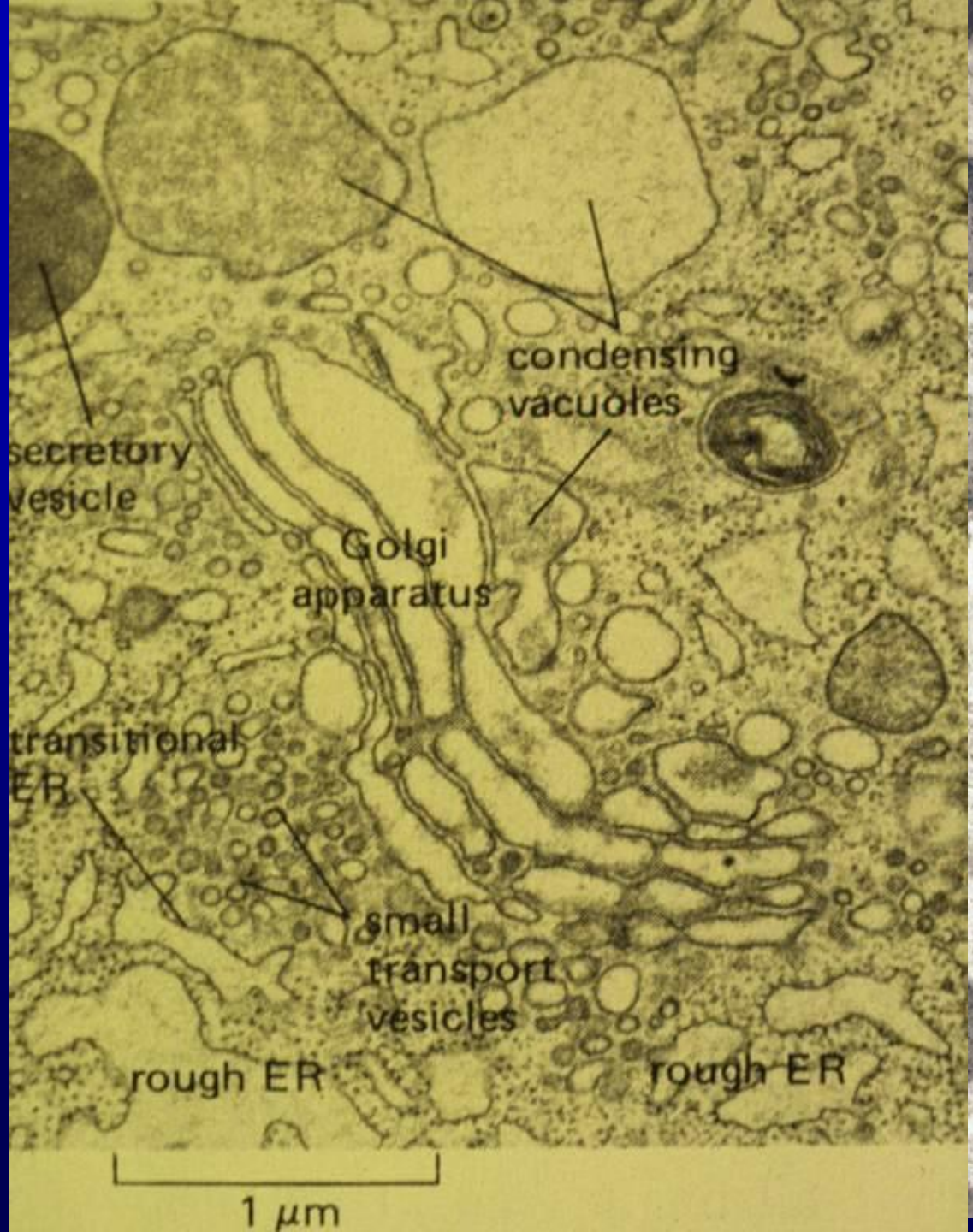


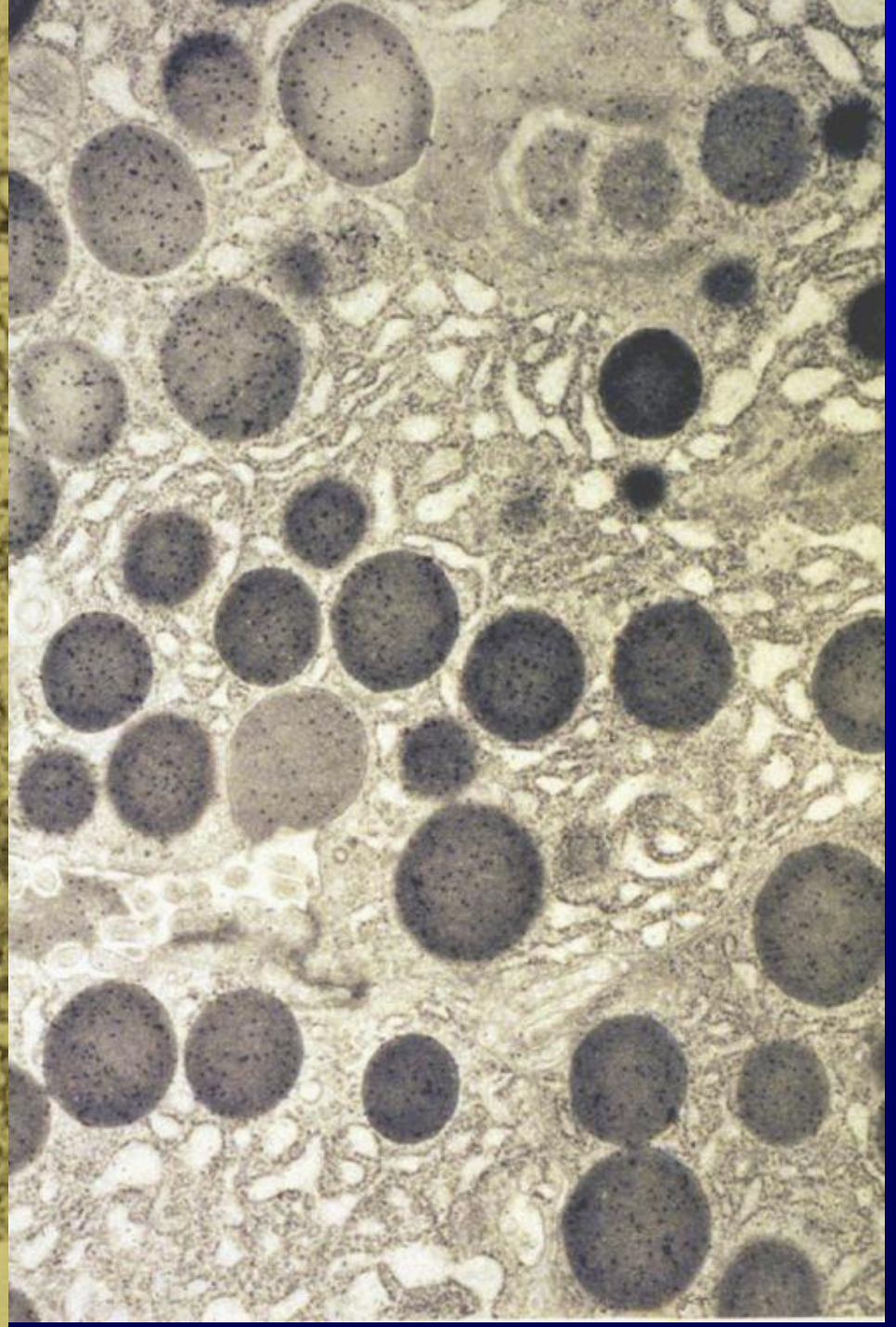




CYTOSOL – is the liquid matrix inside the cell membrane but outside and around the organelles and inclusions

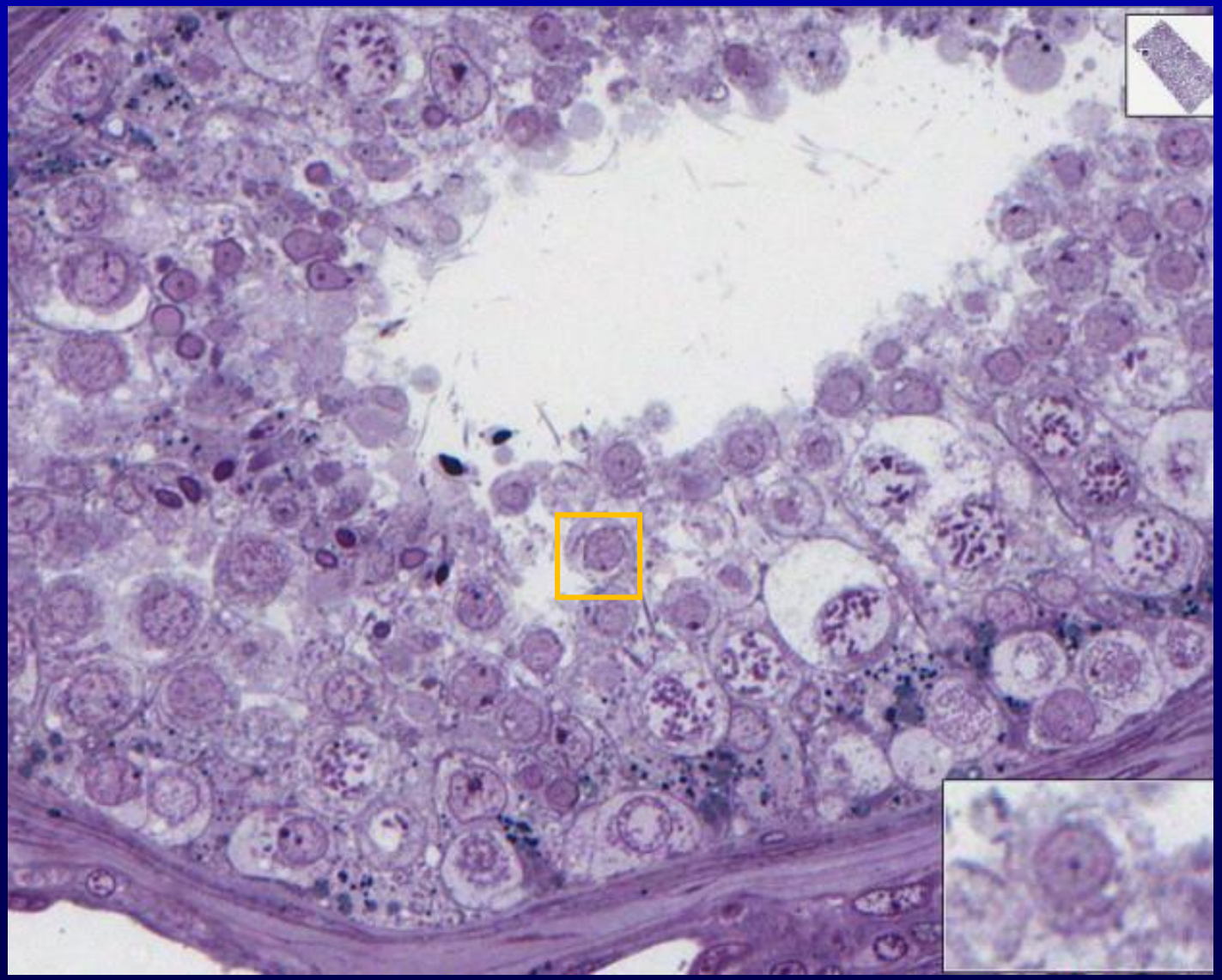

Ribosomes
Endoplasmic reticulum
Transitional vesicles
Structural and functional polarity
Osmiophilic region
Forming face of Golgi complex
Thiamine pyrophosphatase activity
Maturing face of Golgi complex
Condensing vacuole
A
Secretory granules


condensing
vacuoles
secretory
vesicle
Golgi
apparatus
transitional
ER
small
transport
vesicles
rough ER
rough ER
1 μm



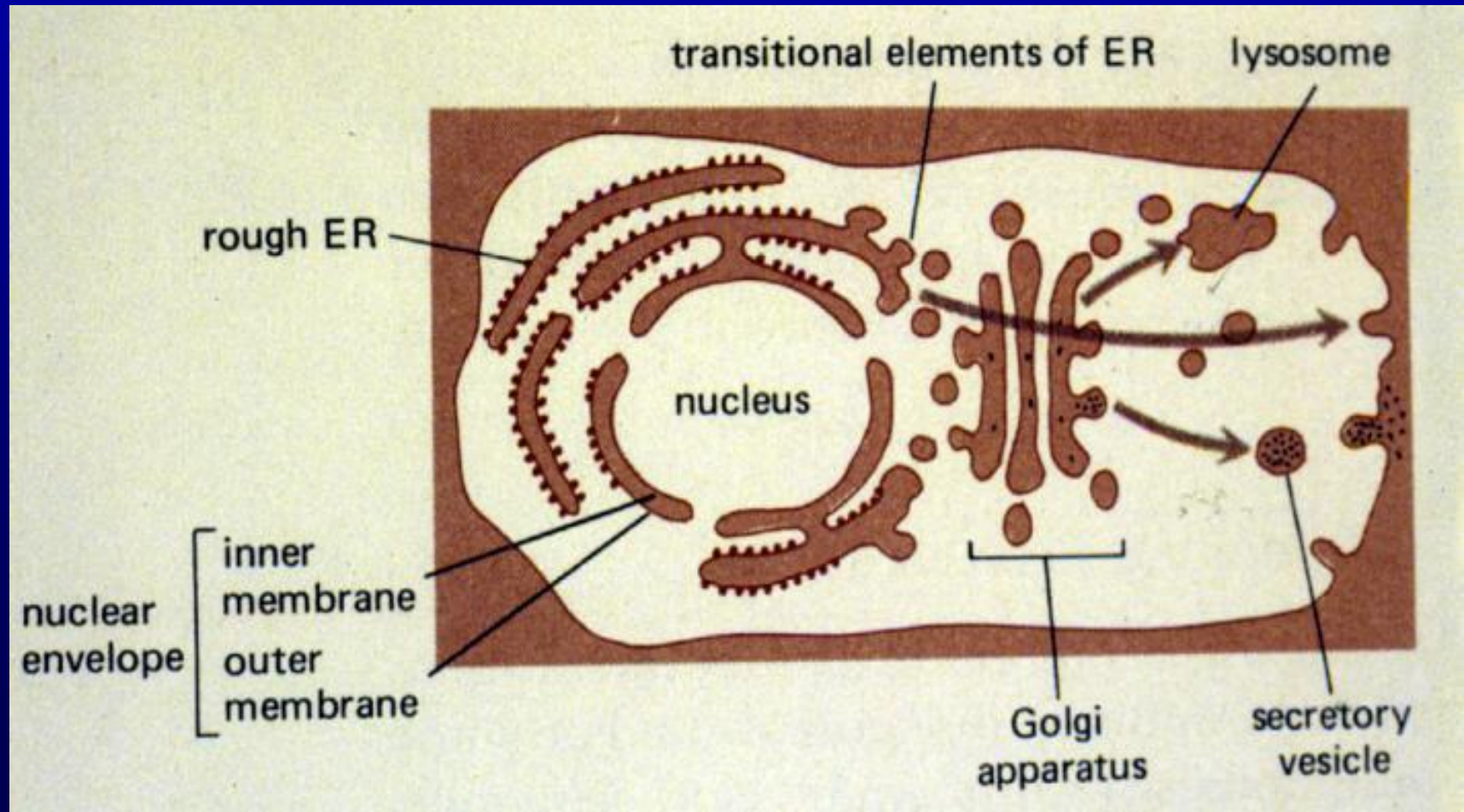
Cells that use the same pathway of protein secretion

- Pancreatic acinar cell
- Plasma cell
- Mast cells
- Neutrophils
- Chief cells
- Spermatids
- Most all cells



Key characteristics of the pathway

- Directional
- Deliver from organelle to organelle by small vesicles
- Specificity of end destination



Evidence for protein pathway

Temporal appearance of radioactive proteins in different organelles

(Produced from radioactive precursors e.g., labeled AA)

Detected by:

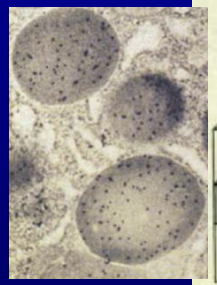
Autoradiography -

visual

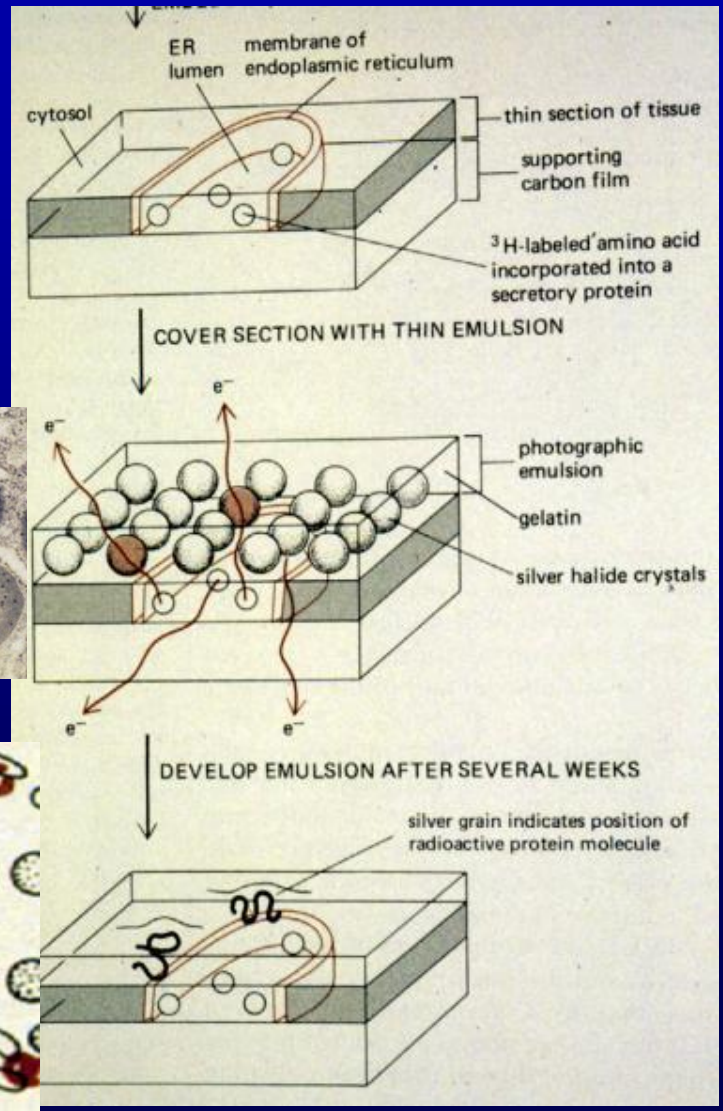
Cell fractionation -

biochemical

LM



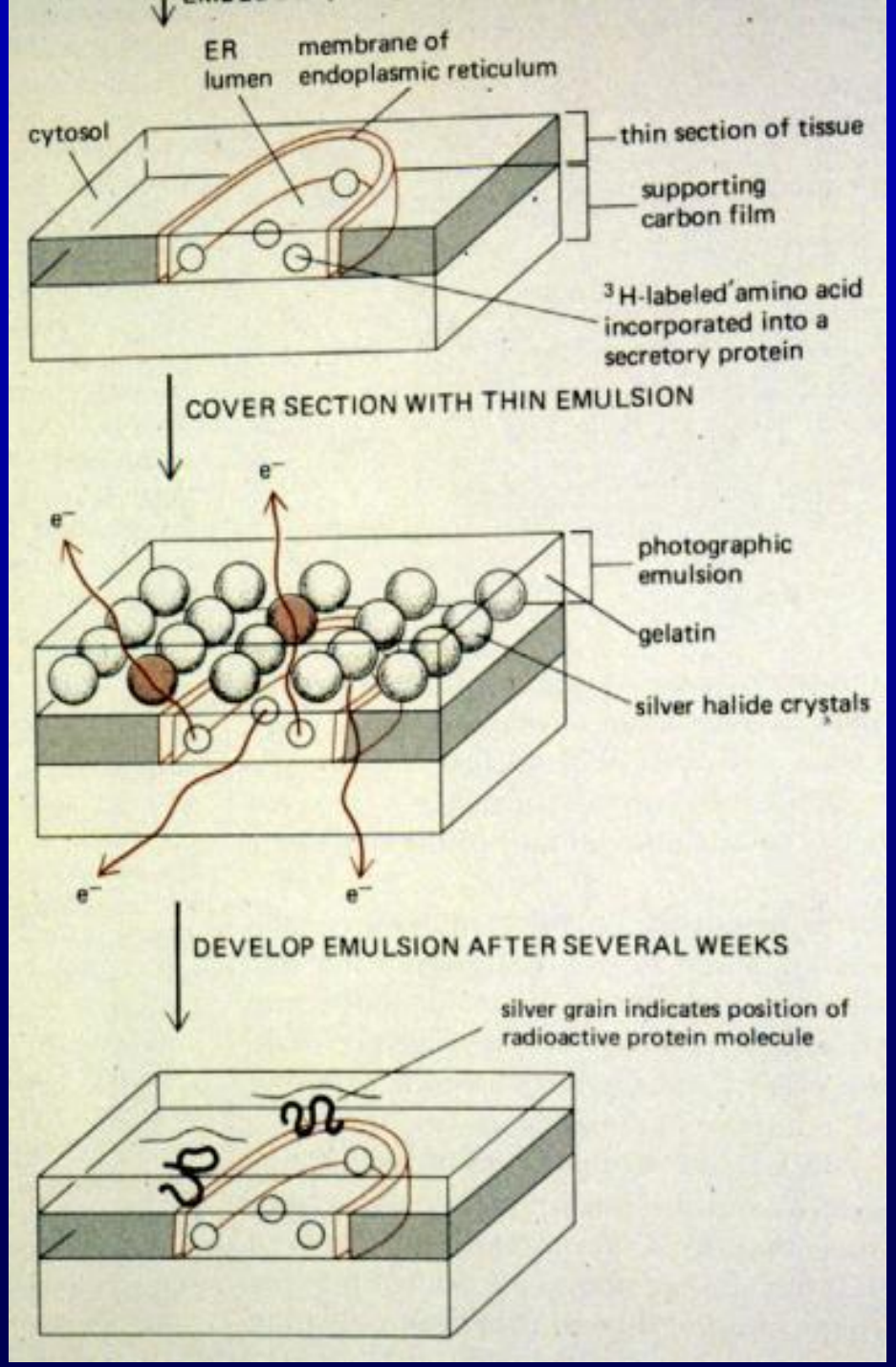
EM



Evidence for protein pathway

Autoradiography

Procedure to localize a product (e.g., protein) within a cell or gel that is self-radioactive due to the cell's incorporation of radioactive precursors (e.g., radioactive amino acids) into that product that is visualized in a photographic emulsion.



A pulse – chase experiment to detect the temporal appearance of radioactive proteins in different organelles

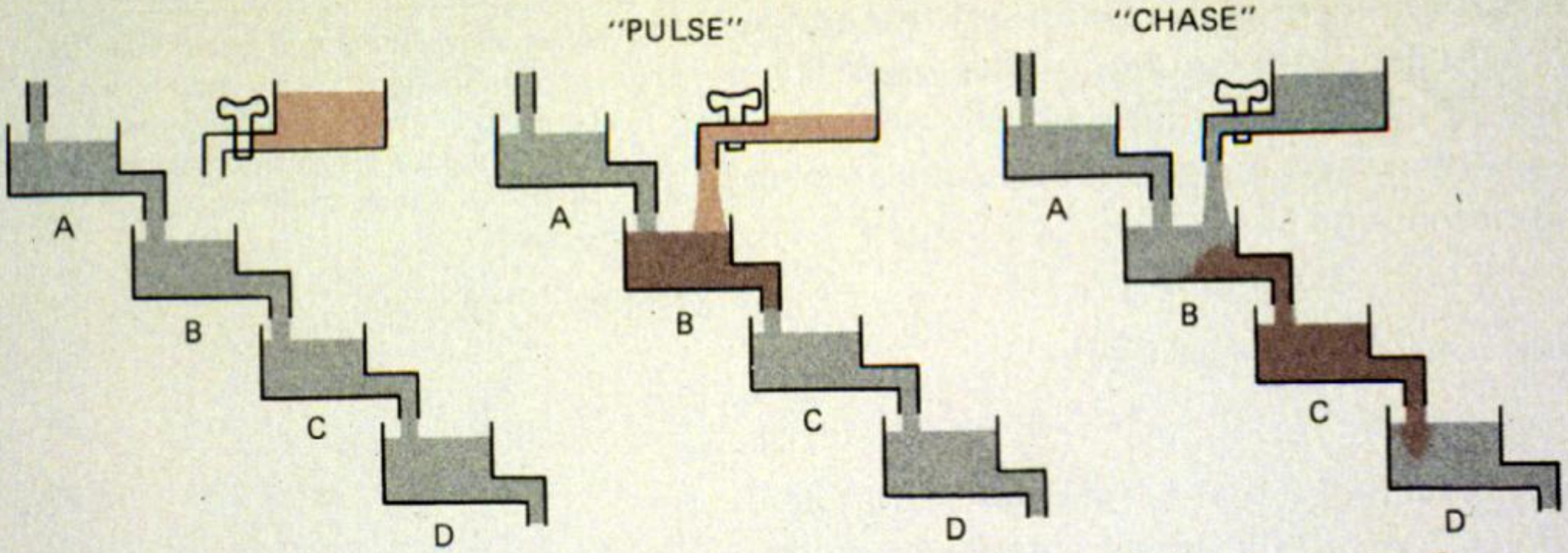


Figure 4–41 Schematic diagram outlining the logic of a typical pulse-chase experiment using radioisotopes. The chambers labeled A, B, C, and D represent either different compartments in the cell (detected by autoradiography or by cell fractionation experiments) or different chemical compounds (detected by chromatography or other chemical methods).

Pulse = radioactive precursors

Chase = non-radioactive precursors following the pulse

Do the :

Pulse – chase experiment

Look for the :

Temporal appearance of silver grains in the photographic emulsion over organelles of interest

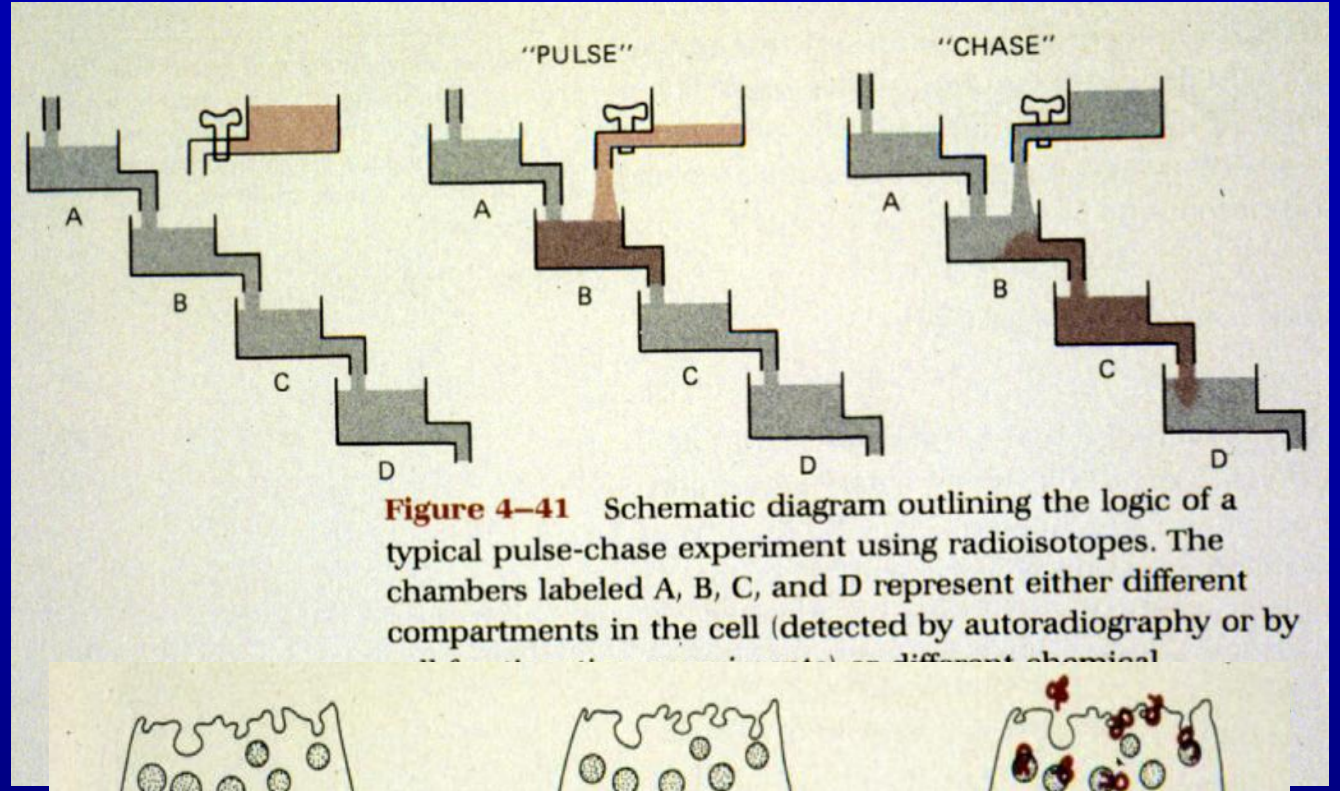
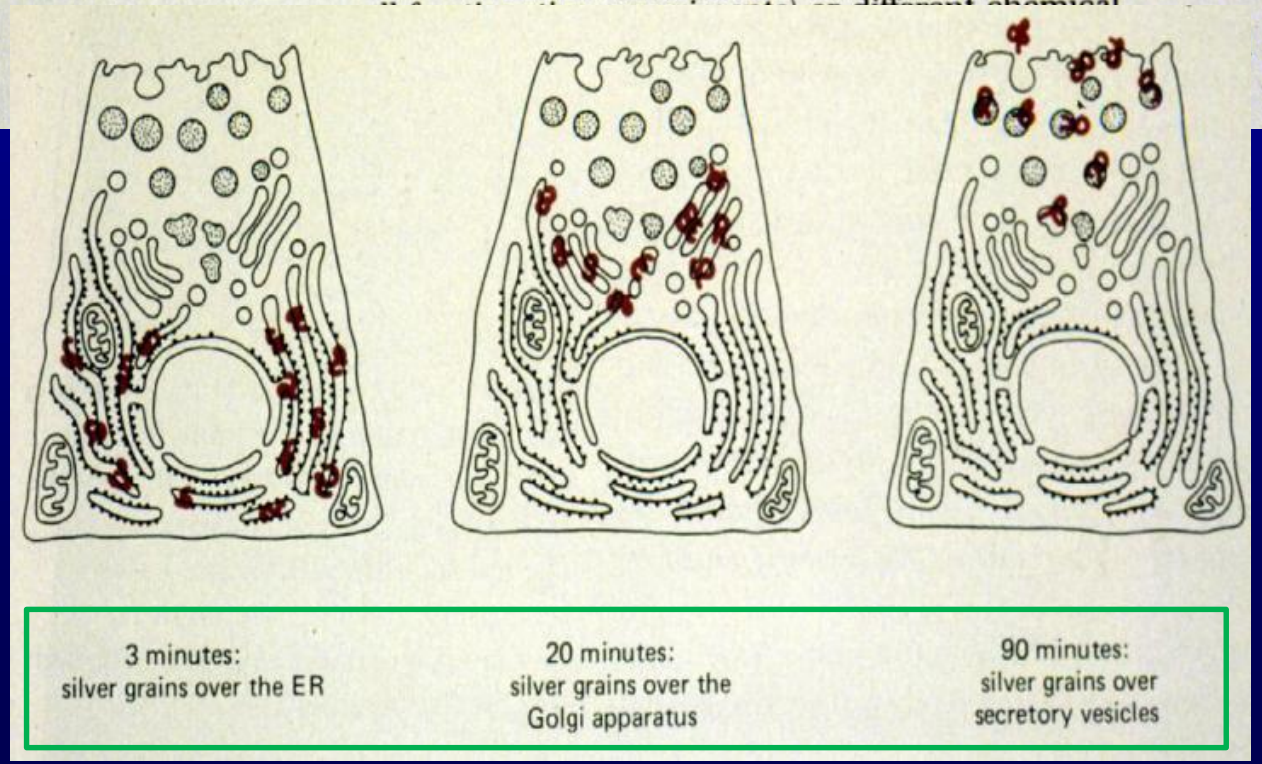


Figure 4–41 Schematic diagram outlining the logic of a typical pulse-chase experiment using radioisotopes. The chambers labeled A, B, C, and D represent either different compartments in the cell (detected by autoradiography or by



Temporal differences = changes with time

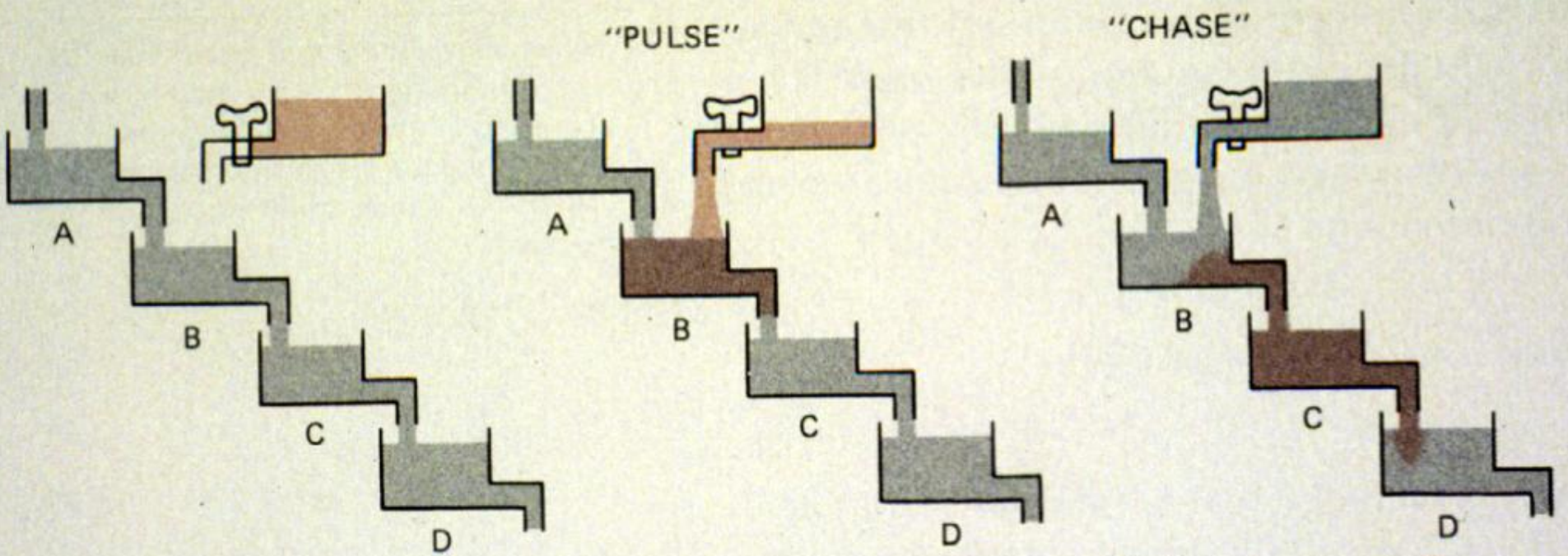
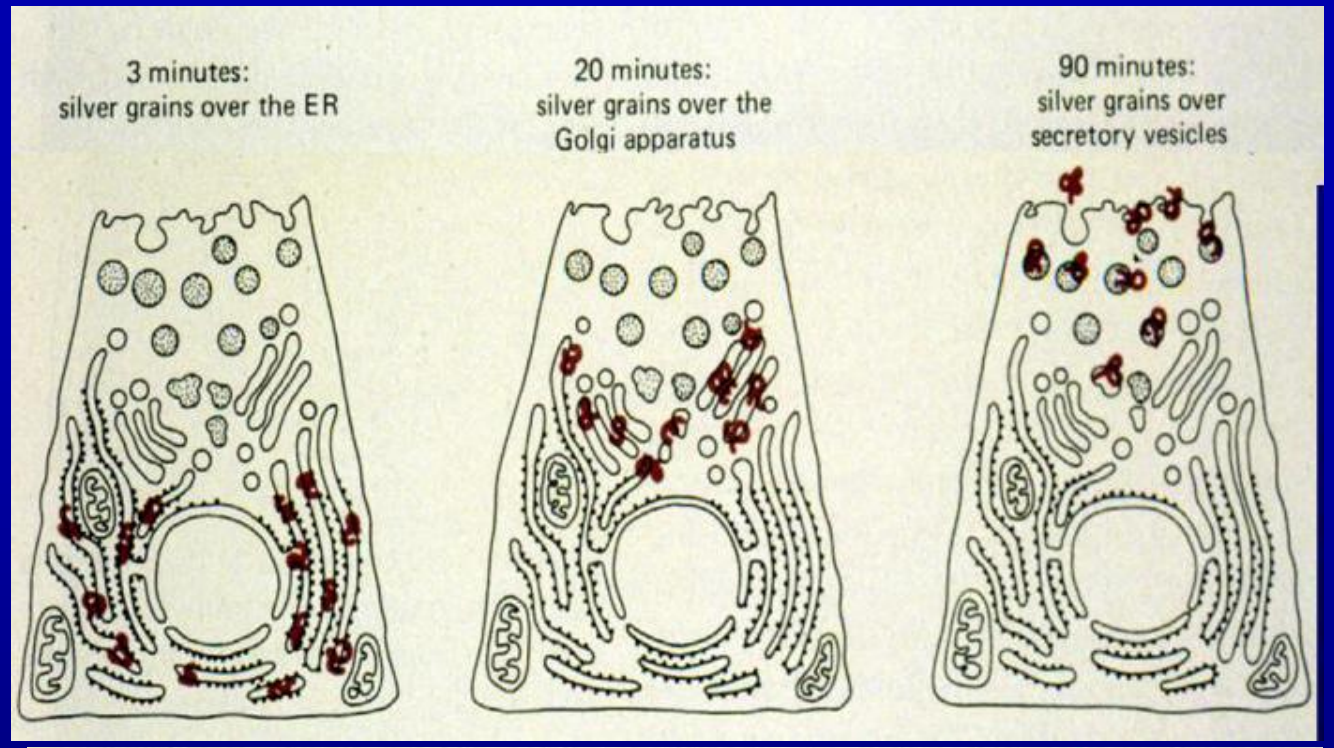


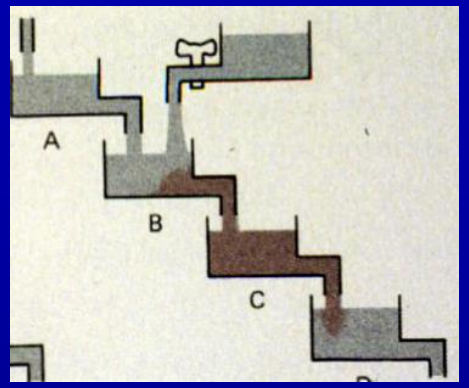
Figure 4–41 Schematic diagram outlining the logic of a typical pulse-chase experiment using radioisotopes. The chambers labeled A, B, C, and D represent either different compartments in the cell (detected by autoradiography or by cell fractionation experiments) or different chemical compounds (detected by chromatography or other chemical methods).

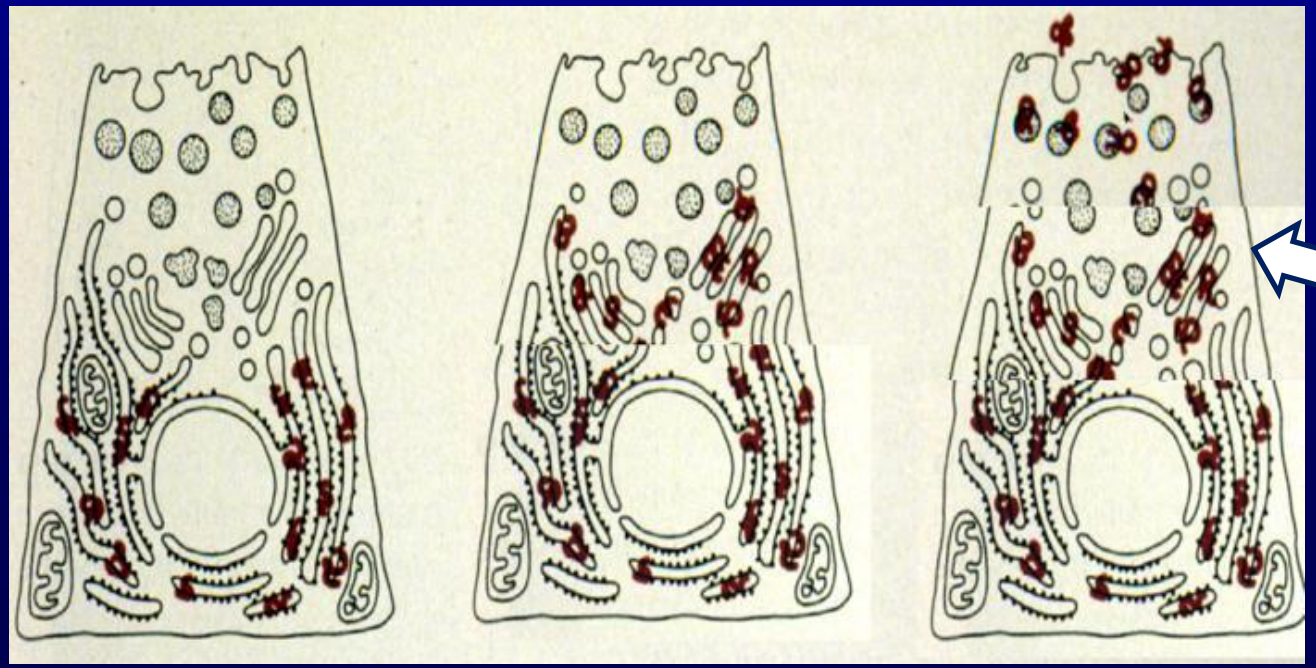
Temporal appearance = sequence / timing of occurrence

When compared to a cell: B = RER, B/C = Golgi,
C/D = Secretory granules, and D = Secretory products



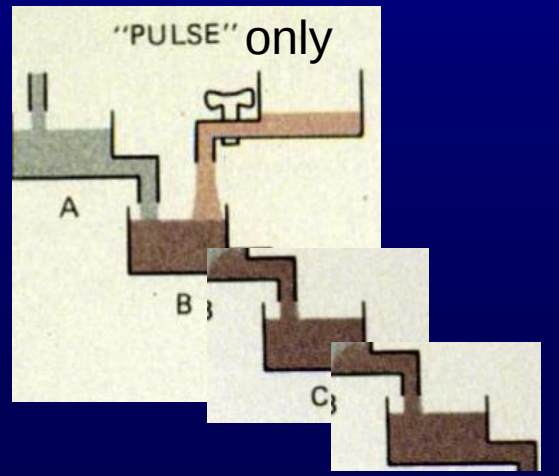
Pulse followed with a chase

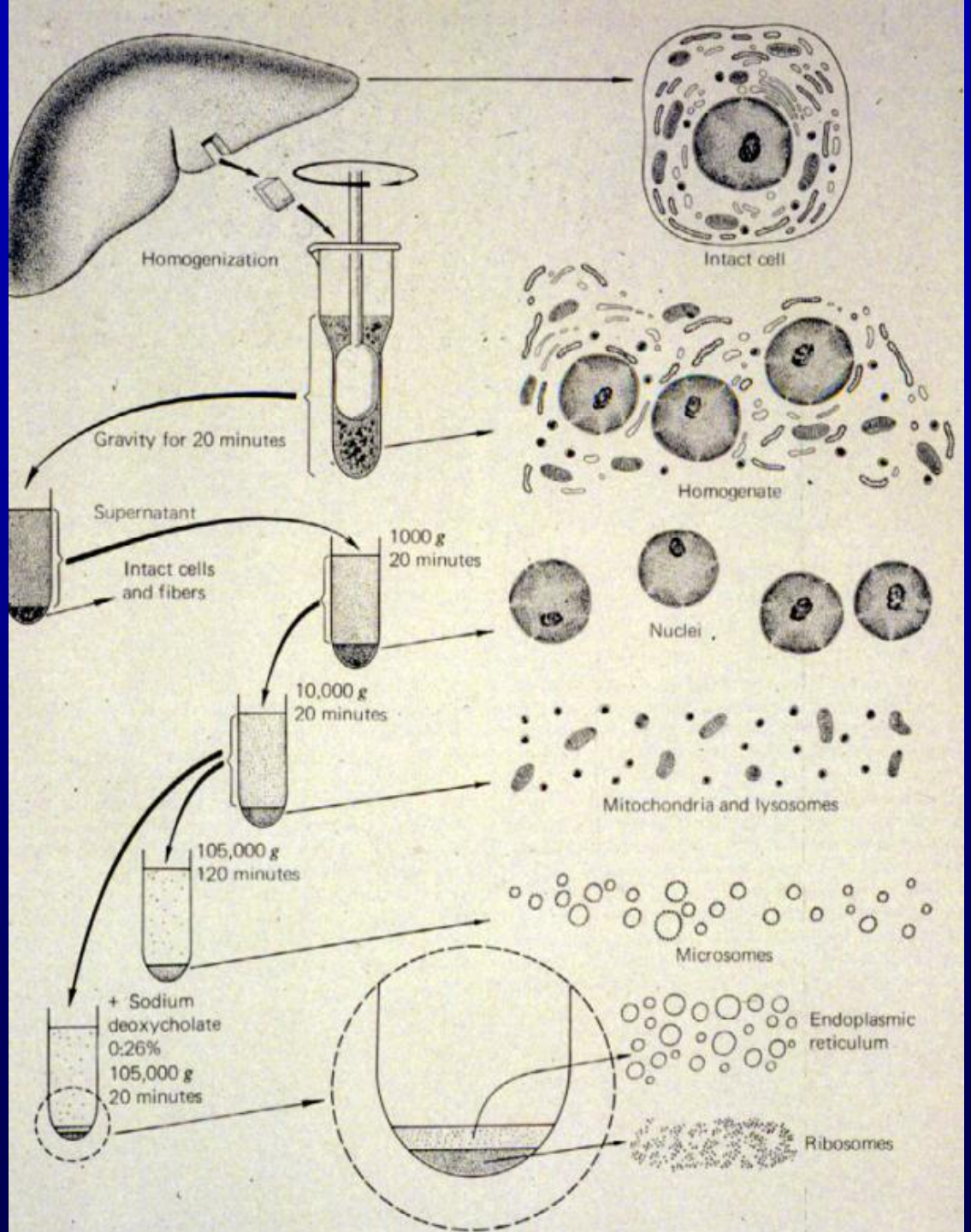




Pulse followed with continued pulse (i.e., no chase)

Results are more difficult to follow (interpret)

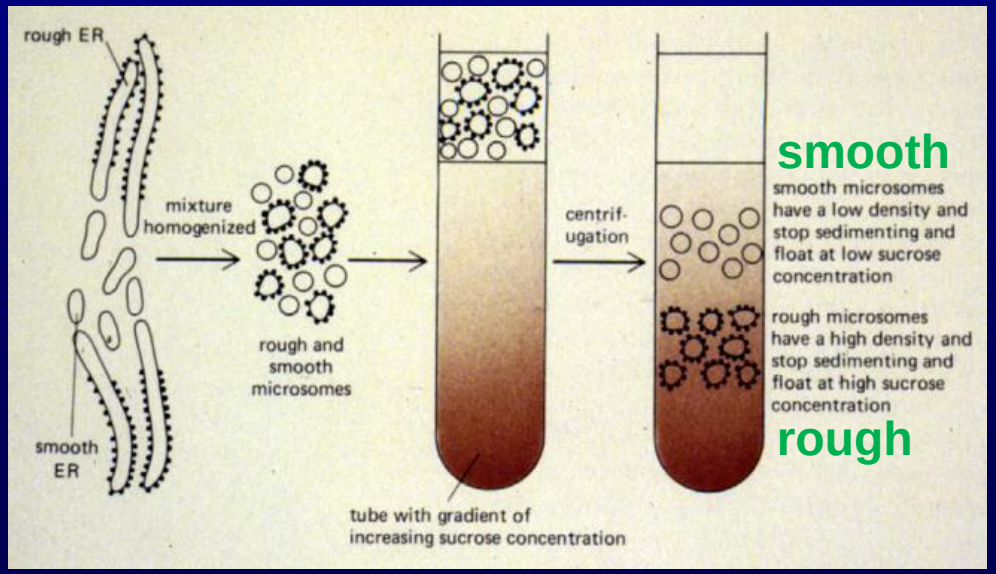




Note: Good science uses different methods to answer the same question.

Cell fractionation

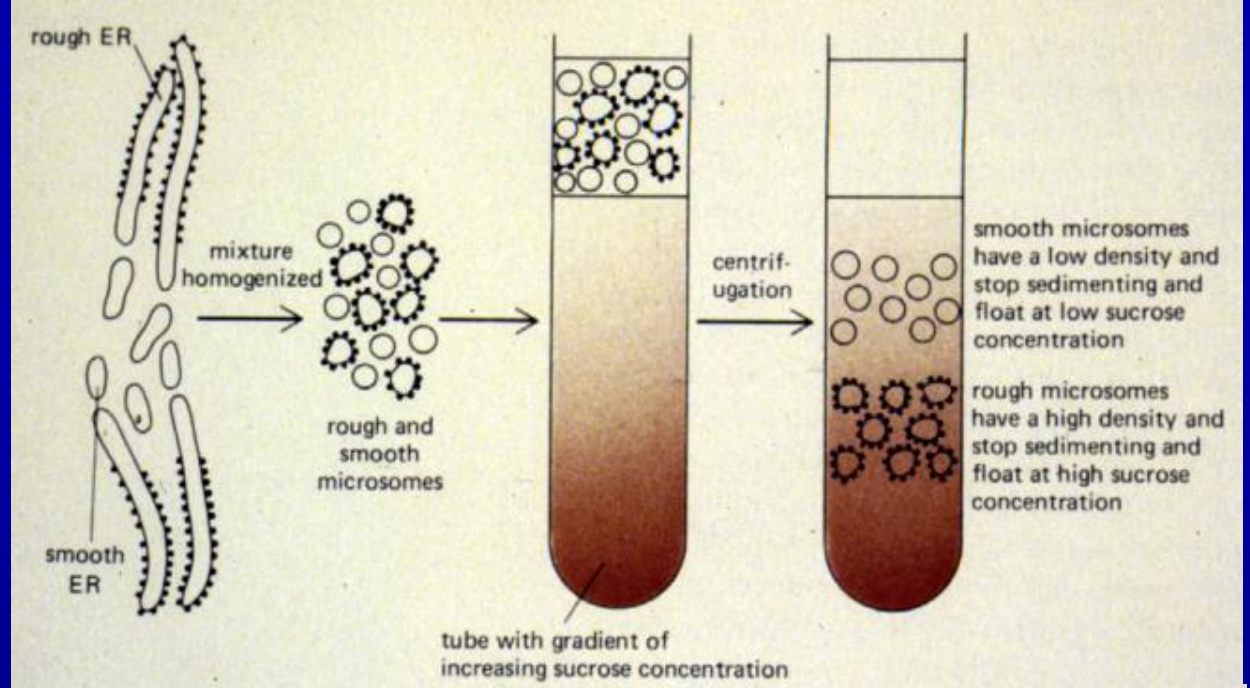
Grind cell into components, separate components on sucrose gradient by ultra centrifugation, and analyze components for radioactivity. Separate smooth (Golgi) and rough (RER) vesicles



Temporal appearance of radioactive proteins in different organelles with smooth or rough membranes

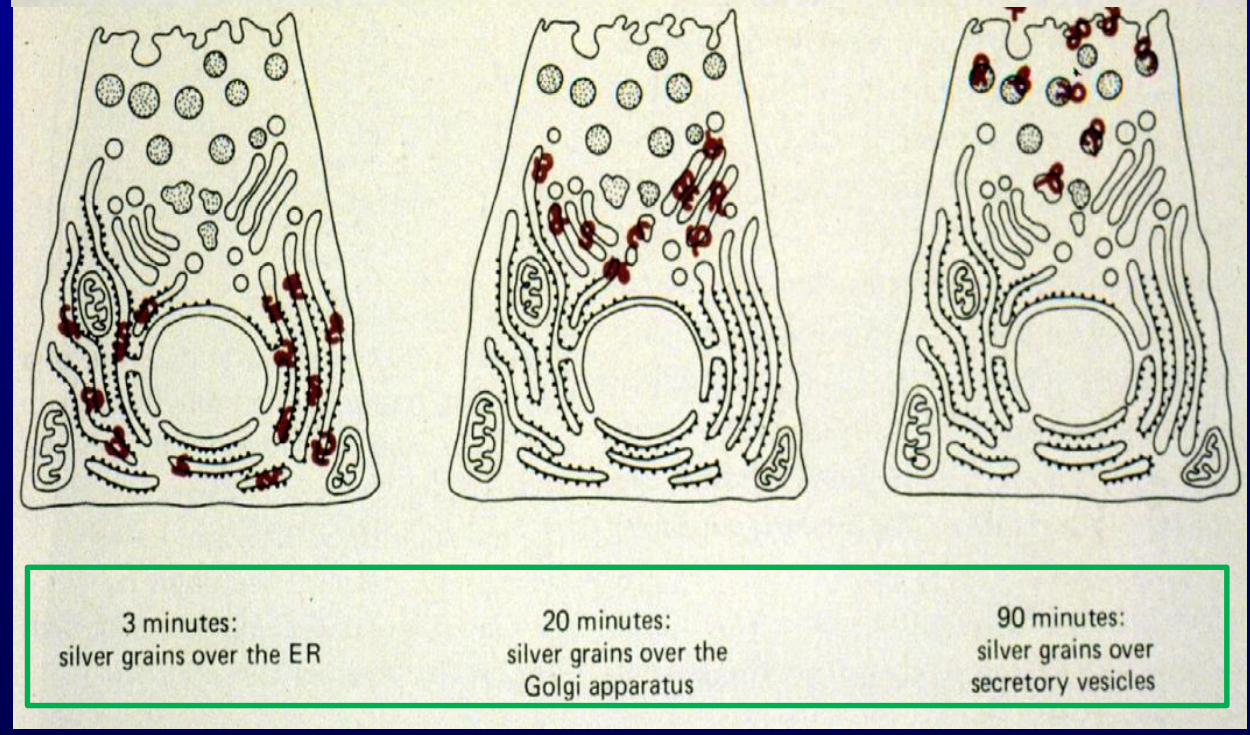
Seen by:

cell fractionation



Golgi

RER



Temporal differences = changes with time

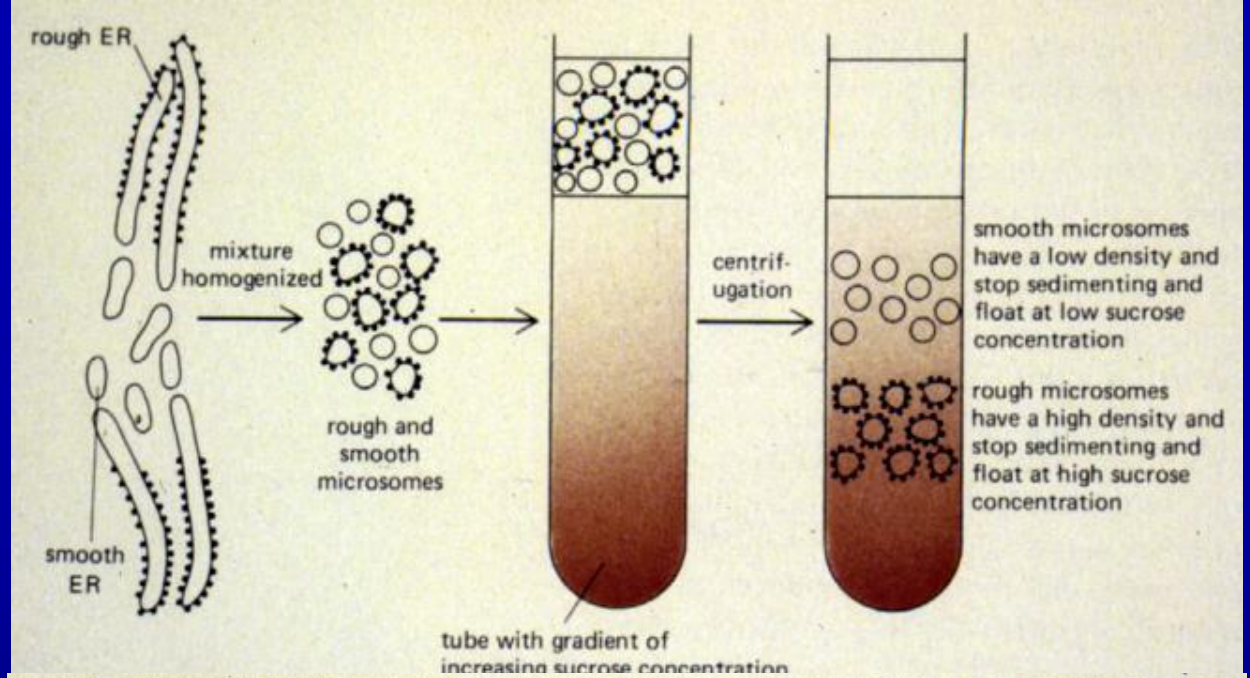
Temporal appearance of radioactive proteins in different organelles with smooth or rough membranes

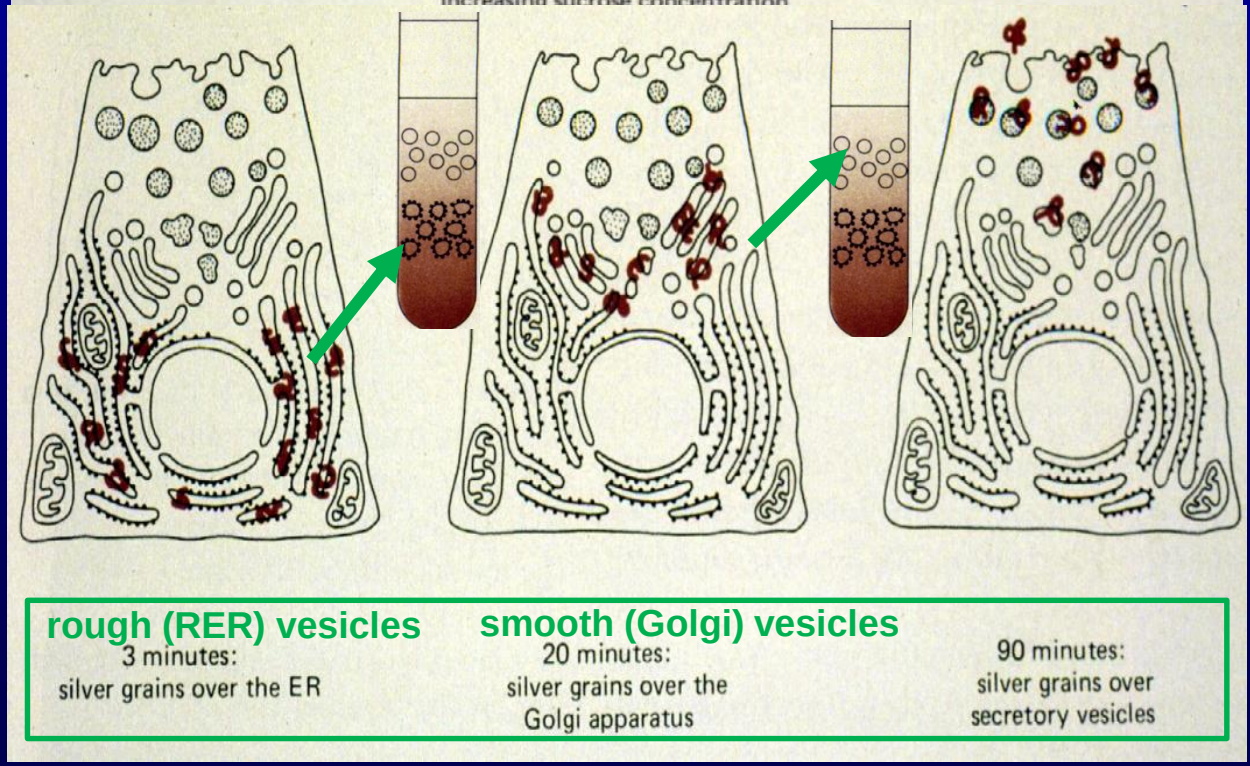
Seen by:

cell fractionation

autoradiography

Temporal differences = changes with time



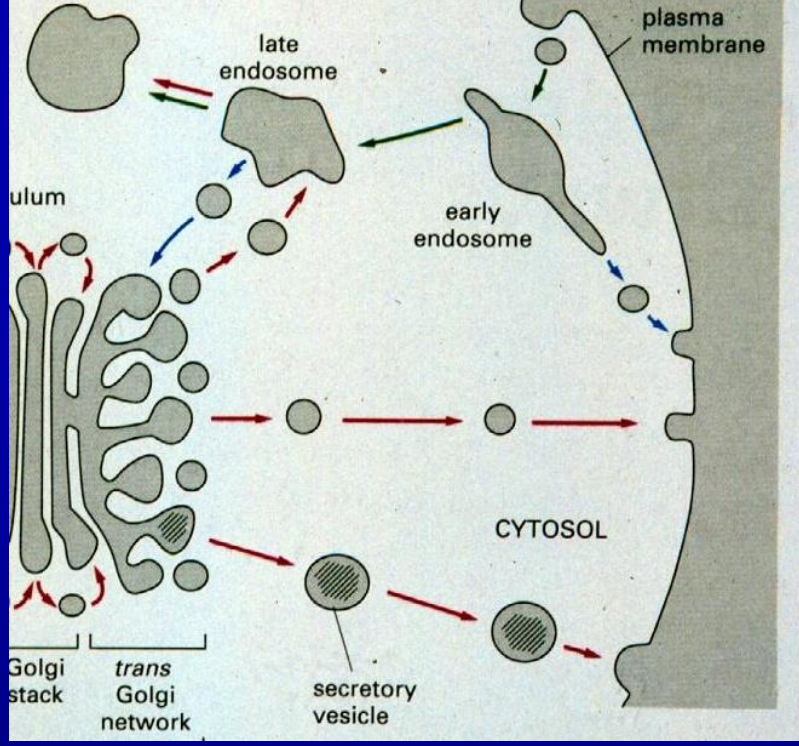


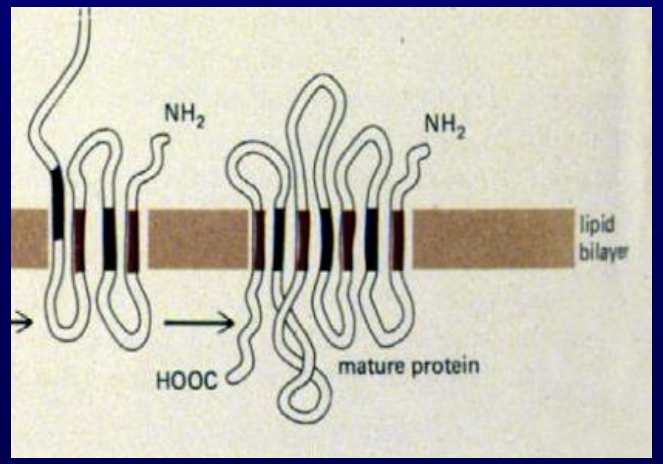
Golgi

RER

Protein sorting?

1. How does a cell segregate cytoplasmic proteins from those for secretion?
2. What signals direct vesicles to a specific organelle?
3. How are proteins designated to be inserted into the membrane or not?
4. How do proteins loop in the membrane?

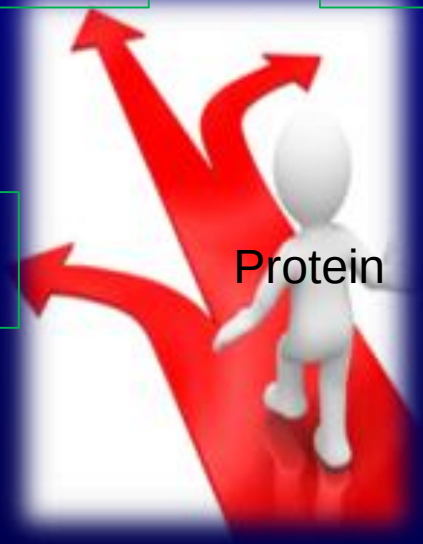


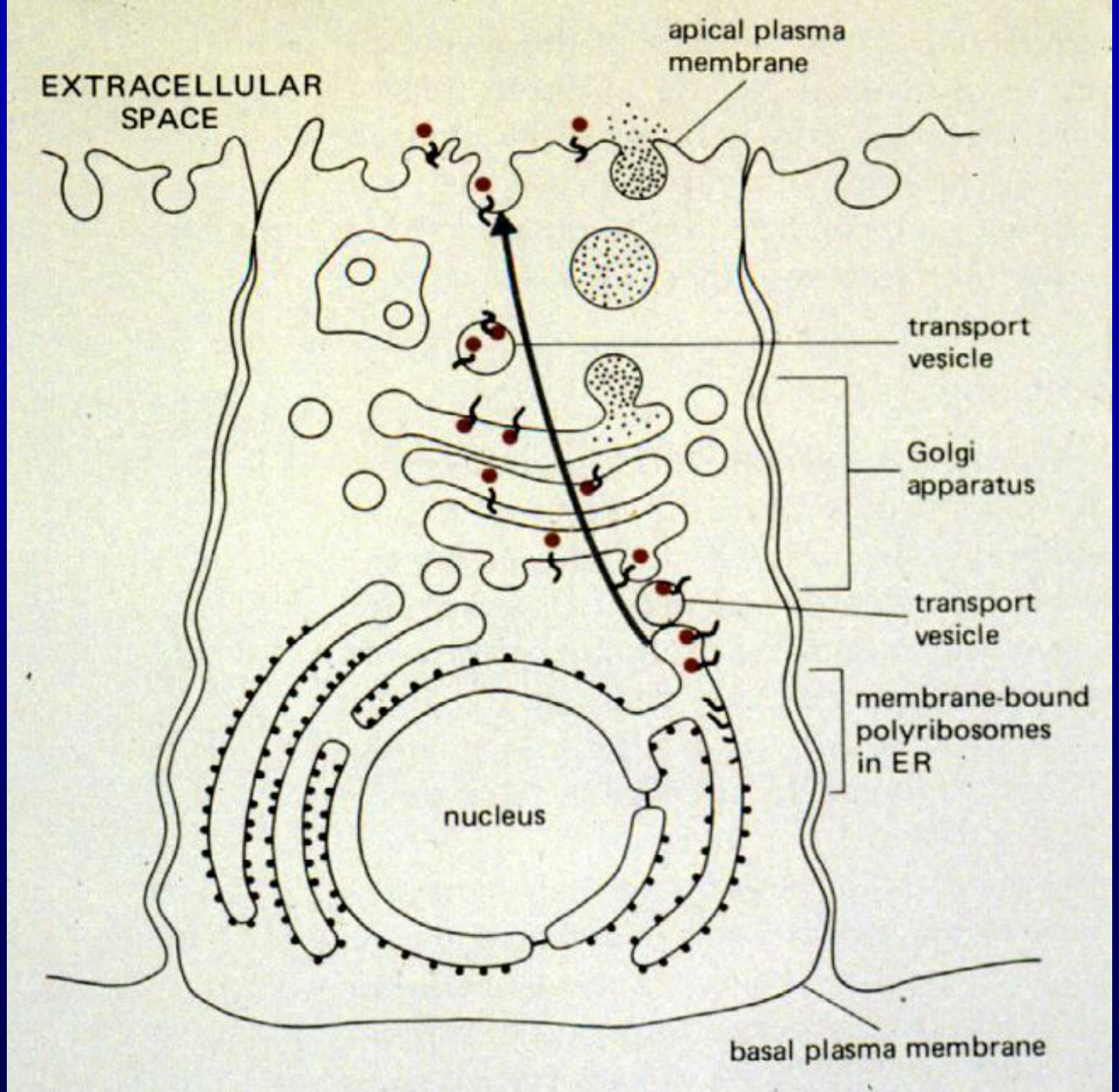


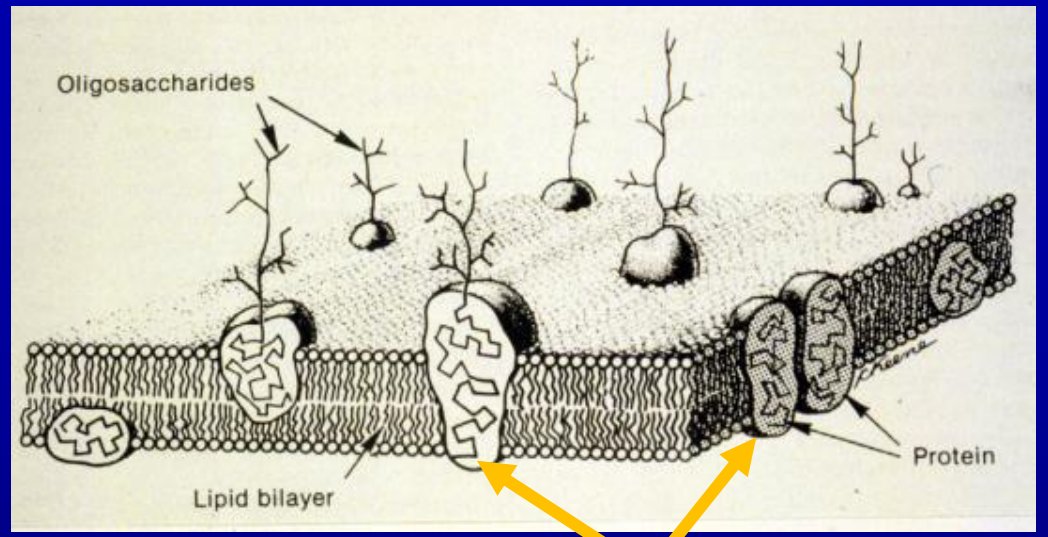
Cell membrane

Lysosome vesicle

Secretory vesicle







No sugar on this side
of these membrane proteins

Sugars are on membrane proteins out side of the cell but not on proteins inside of the cell.
Membrane proteins inside of the cell were never exposed to Golgi enzymes that add sugars.

Protein sorting

In vitro **vs.** ***In situ*** **translation systems for protein production**
(*in vitro* translation yielded proteins with 20 hydrophobic AAs more)

1. **Signal peptide (~20 hydrophobic AAs)**
2. **Signal recognition particle**
3. **Ribophorin - on RER, binds ribosome to RER**
4. **Stop transfer sequence**
5. **Hydrophobic amino acid sequence – inserted that portion of the protein into middle of membrane** (lipid bilayer)

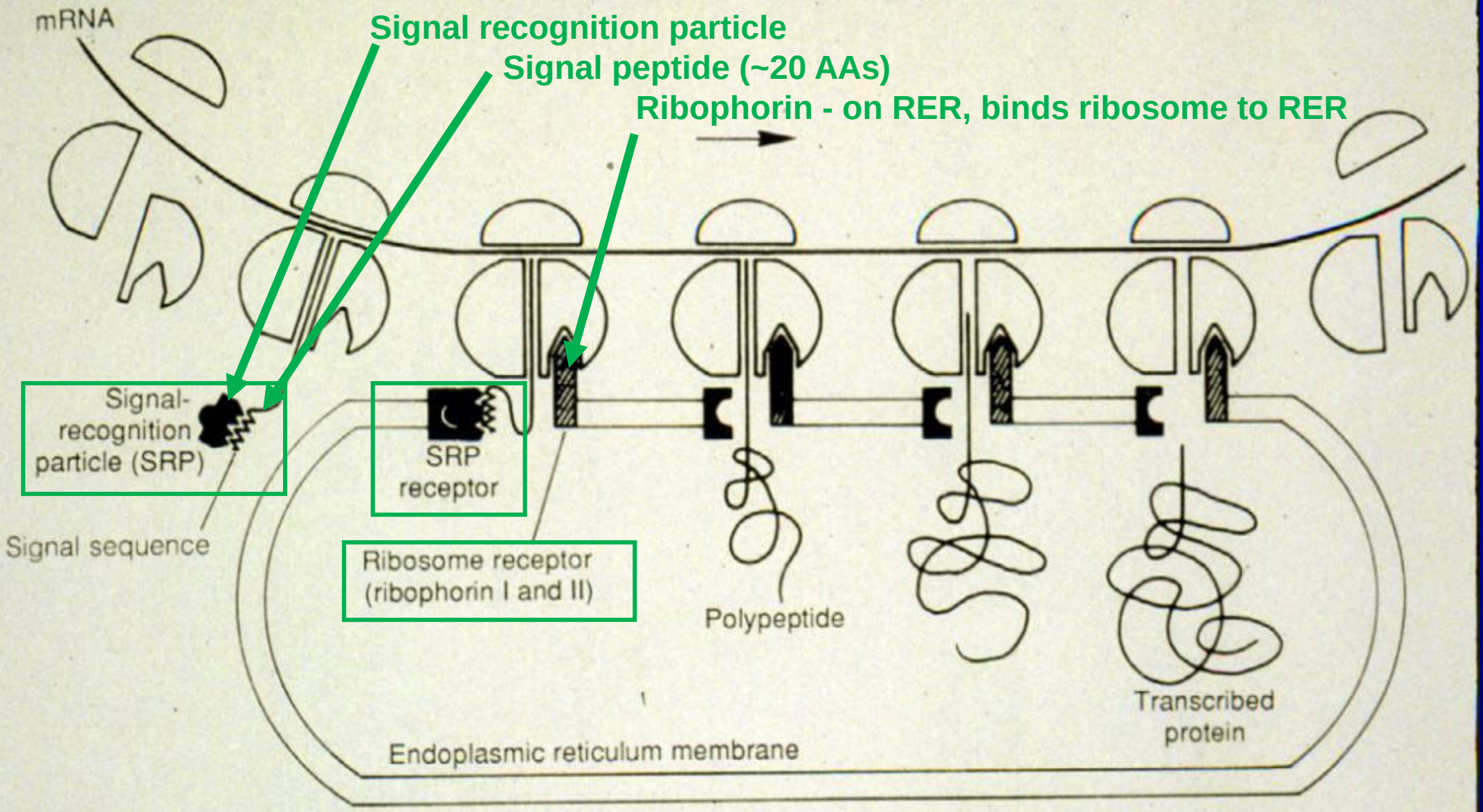
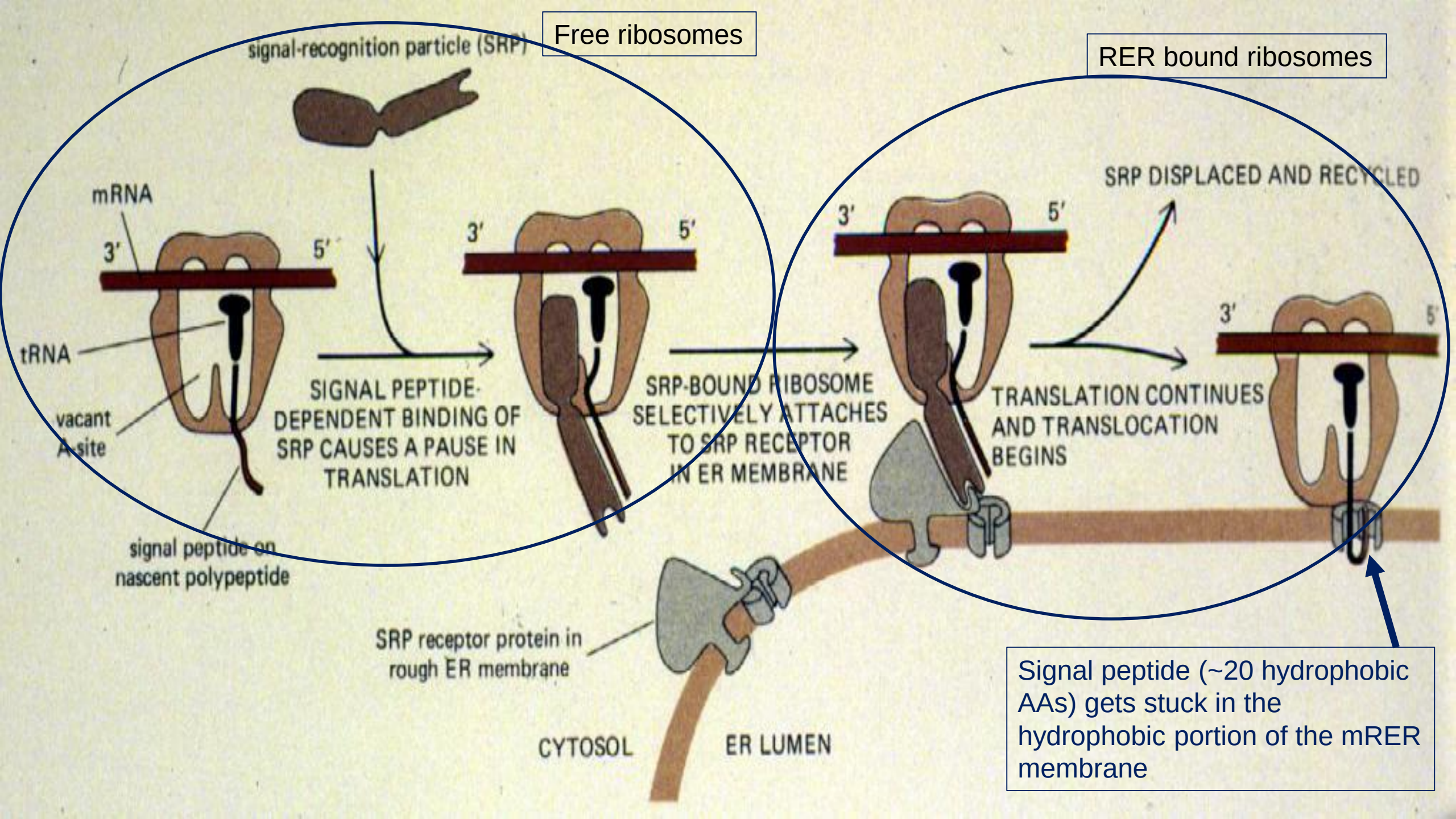
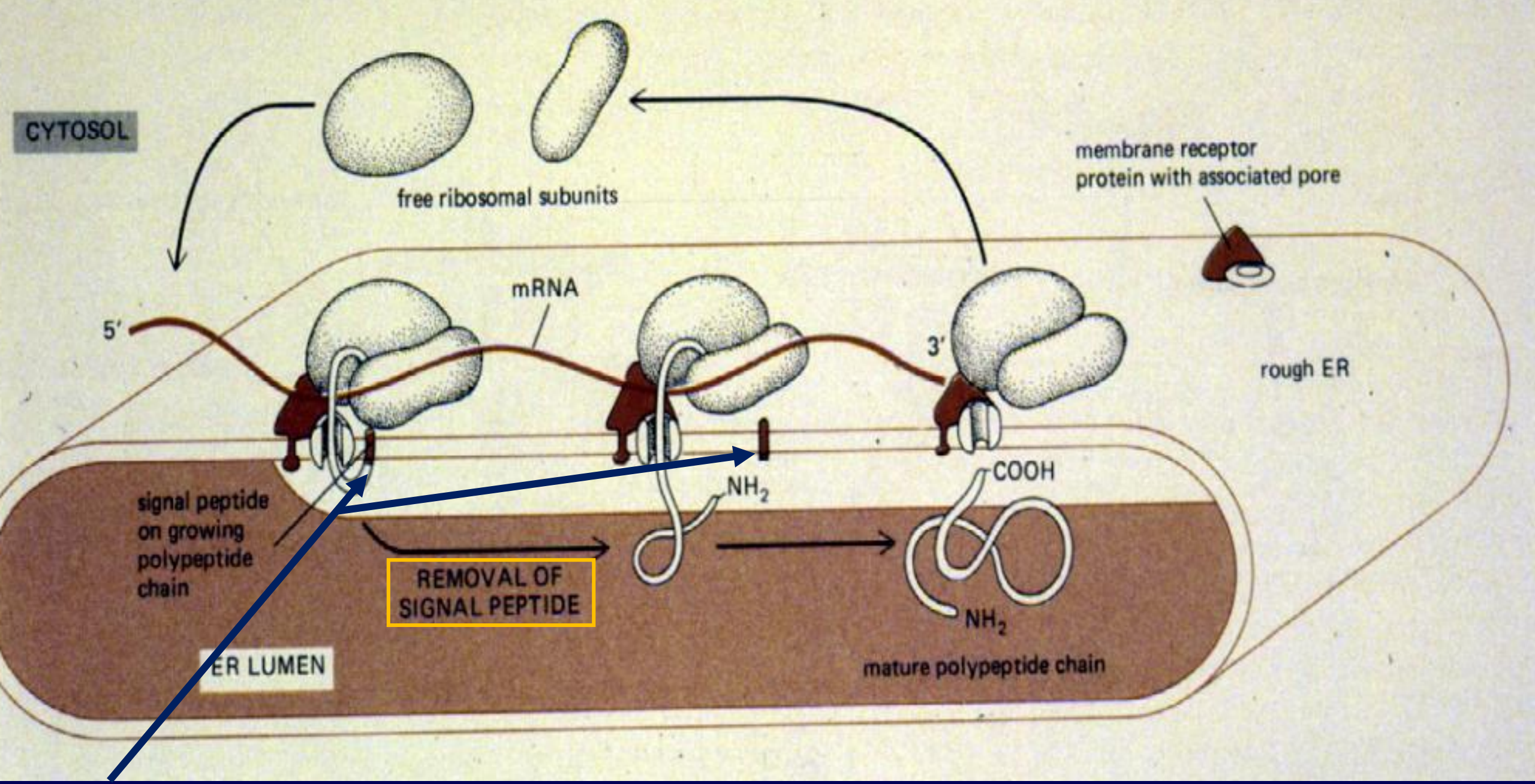
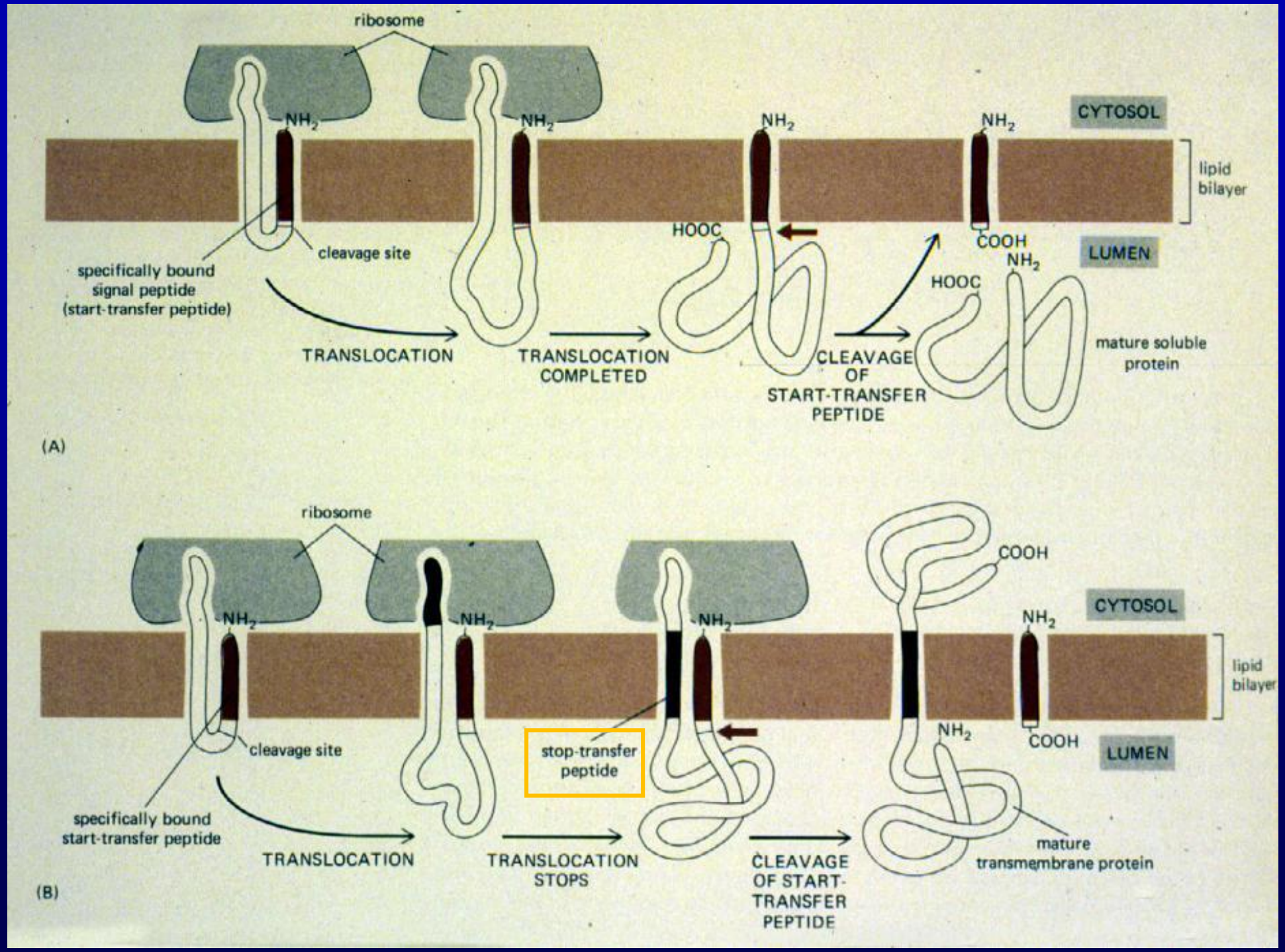


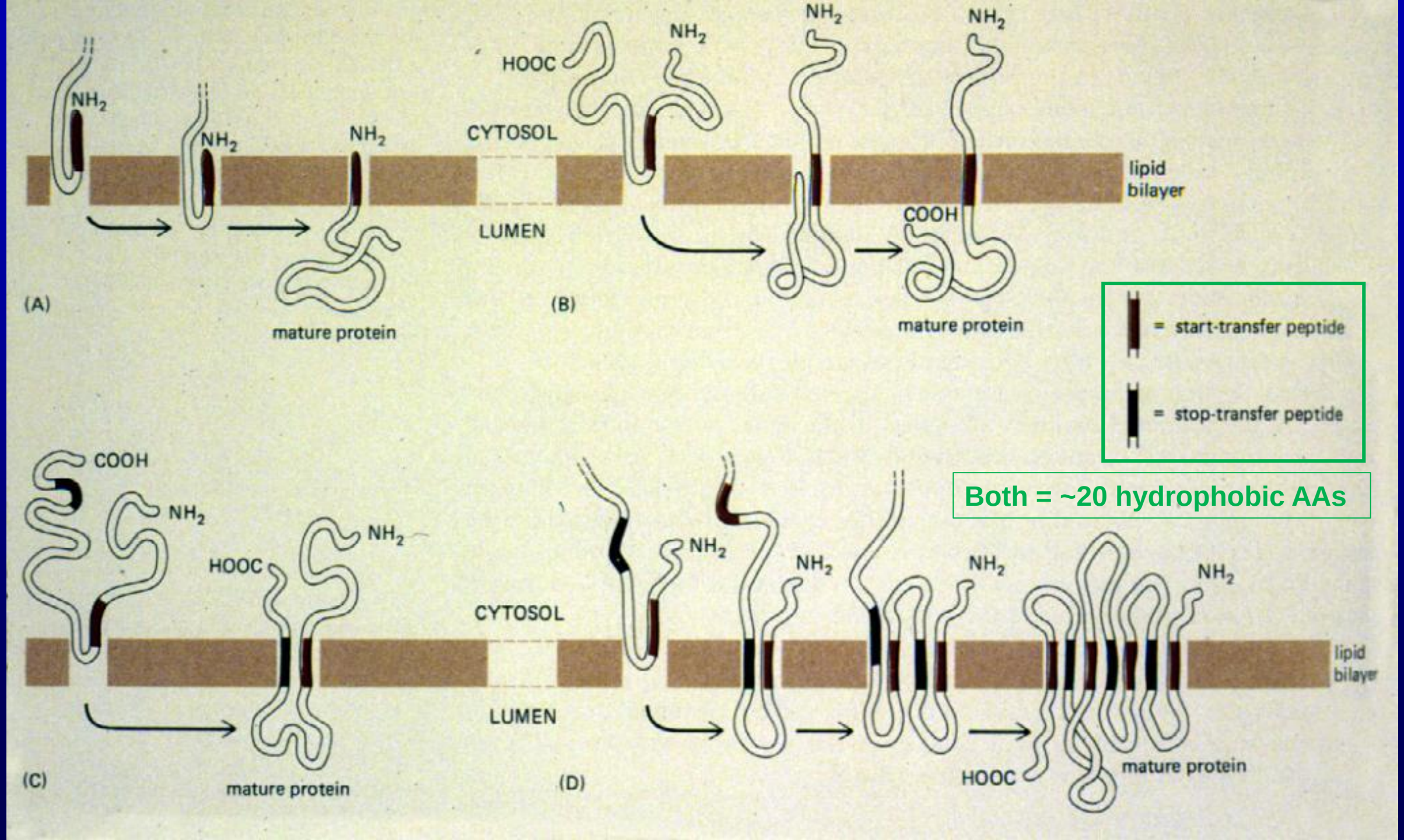
Figure 3–9. Diagram illustrating the transport of proteins across the membrane of the endoplasmic reticulum. The ribosomes bind to mRNA, and the signal peptide is initially bound to a signal-recognition particle (SRP). Ribosomes bind to the ER by interacting with the SRP and a ribosomal receptor. The signal peptide is then removed by a signal peptidase (not shown). These interactions cause the opening of a pore through which the protein is extruded into the endoplasmic reticulum.

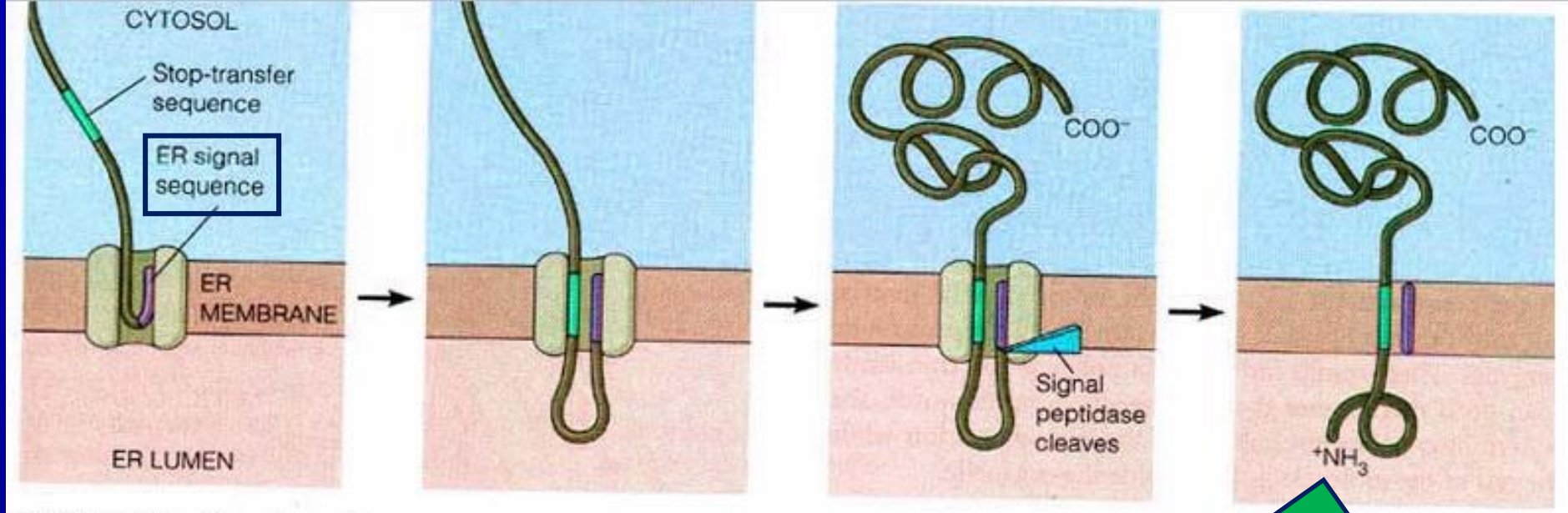

Free ribosomes
RER bound ribosomes
signal-recognition particle (SRP)
mRNA
3'
5'
tRNA
vacant A-site
signal peptide on nascent polypeptide
SIGNAL PEPTIDE-DEPENDENT BINDING OF SRP CAUSES A PAUSE IN TRANSLATION
SRP-BOUND RIBOSOME SELECTIVELY ATTACHES TO SRP RECEPTOR IN ER MEMBRANE
SRP DISPLACED AND RECYCLED
TRANSLATION CONTINUES AND TRANSLOCATION BEGINS
SRP receptor protein in rough ER membrane
CYTOSOL
ER LUMEN
Signal peptide (~20 hydrophobic AAs) gets stuck in the hydrophobic portion of the mRER membrane



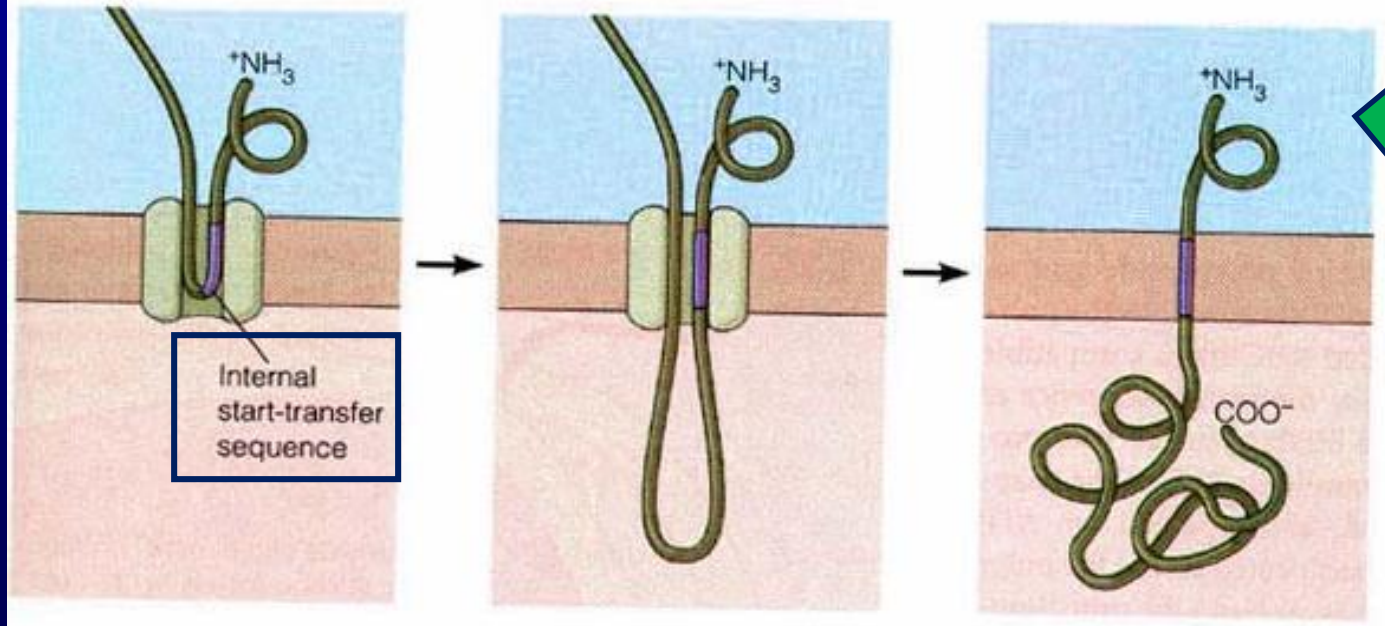
Signal peptide (~20 hydrophobic AAs) gets stuck in the hydrophobic portion of the mRER membrane


ribosome
NH2
NH2
NH2
NH2
CYTOSOL
lipid bilayer
cleavage site
specifically bound signal peptide (start-transfer peptide)
HOOC
COOH
NH2
LUMEN
HOOC
TRANSLOCATION
TRANSLOCATION COMPLETED
CLEAVAGE OF START-TRANSFER PEPTIDE
mature soluble protein
(A)
ribosome
COOH
NH2
NH2
NH2
CYTOSOL
NH2
lipid bilayer
cleavage site
stop-transfer peptide
NH2
COOH
LUMEN
specifically bound start-transfer peptide
TRANSLOCATION
TRANSLOCATION STOPS
CLEAVAGE OF START-TRANSFER PEPTIDE
mature transmembrane protein
(B)


NH2
NH2
NH2
CYTOSOL
LUMEN
(A)
mature protein
HOOC
NH2
NH2
NH2
lipid bilayer
COOH
(B)
mature protein
= start-transfer peptide
= stop-transfer peptide
Both = ~20 hydrophobic AAs
COOH
NH2
HOOC
NH2
CYTOSOL
LUMEN
(C)
mature protein
NH2
NH2
NH2
NH2
HOOC
mature protein
lipid bilayer
(D)

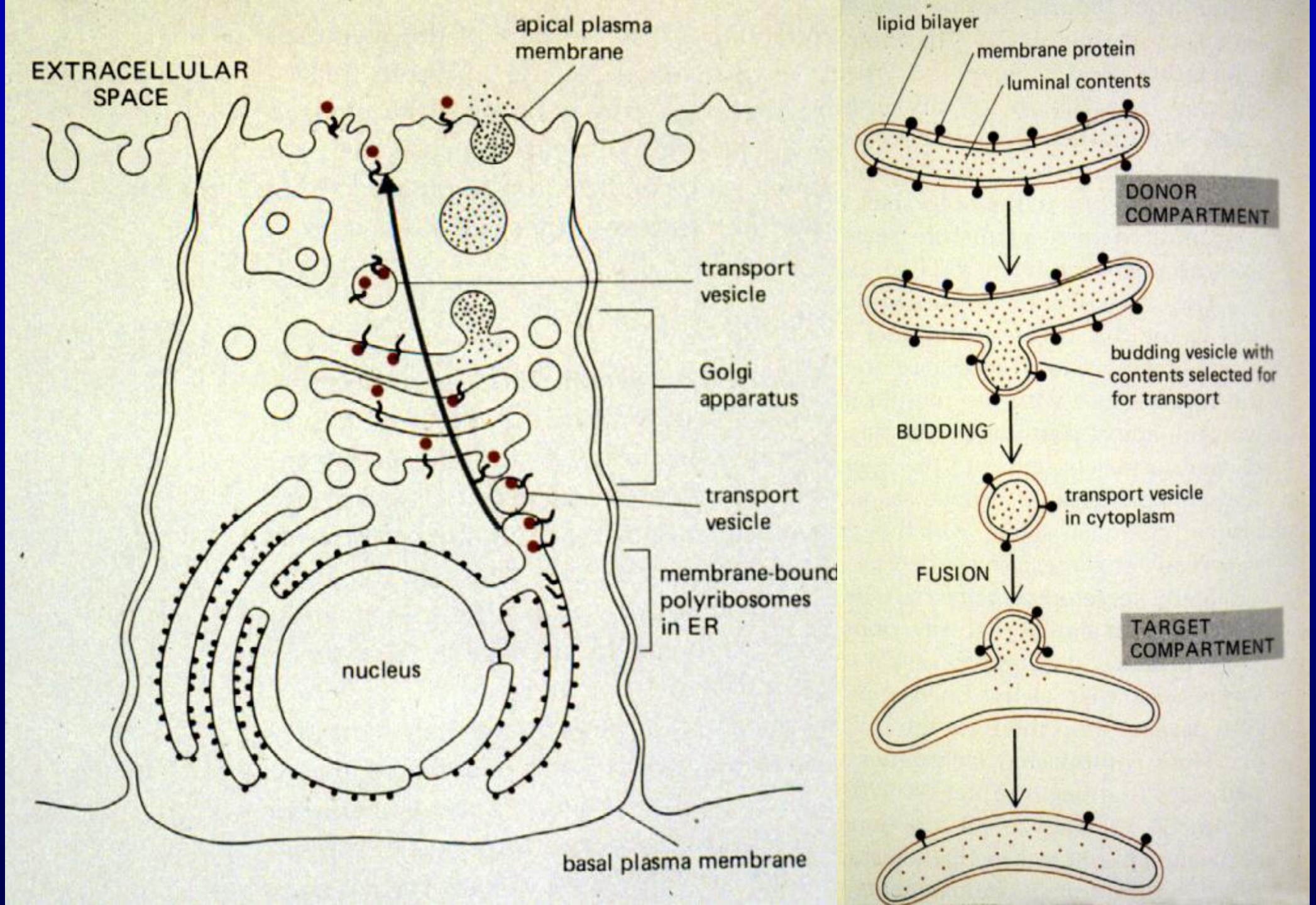


(a) Polypeptide with an internal stop-transfer sequence and a terminal ER signal sequence



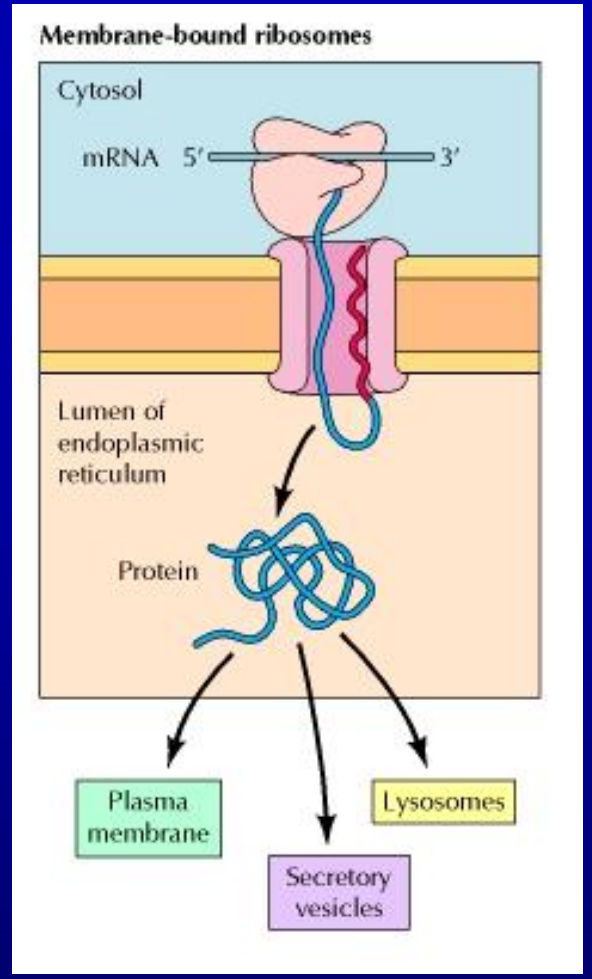
(b) Polypeptide with an internal start-transfer sequence

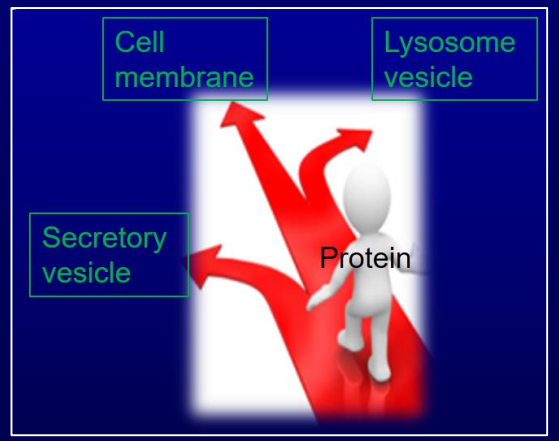
Location of amino terminus

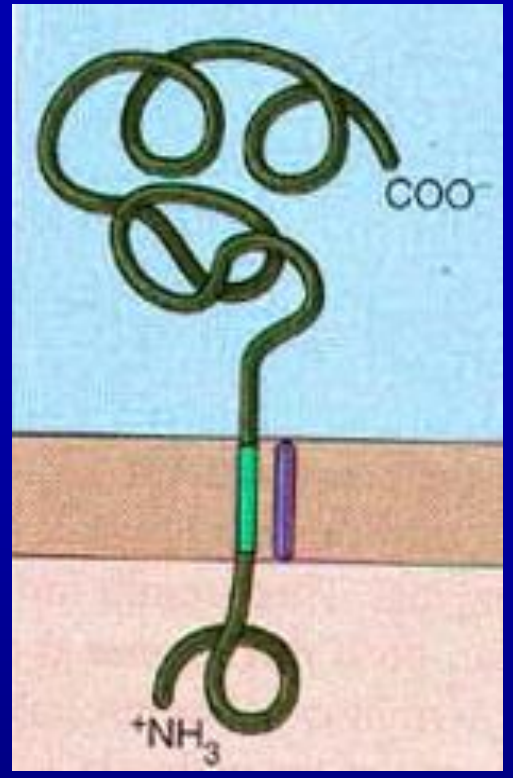

apical plasma membrane
EXTRACELLULAR SPACE
transport vesicle
Golgi apparatus
transport vesicle
membrane-bound polyribosomes in ER
nucleus
basal plasma membrane
lipid bilayer
membrane protein
luminal contents
DONOR COMPARTMENT
budding vesicle with contents selected for for transport
BUDDING
transport vesicle in cytoplasm
FUSION
TARGET COMPARTMENT

Protein sorting summary

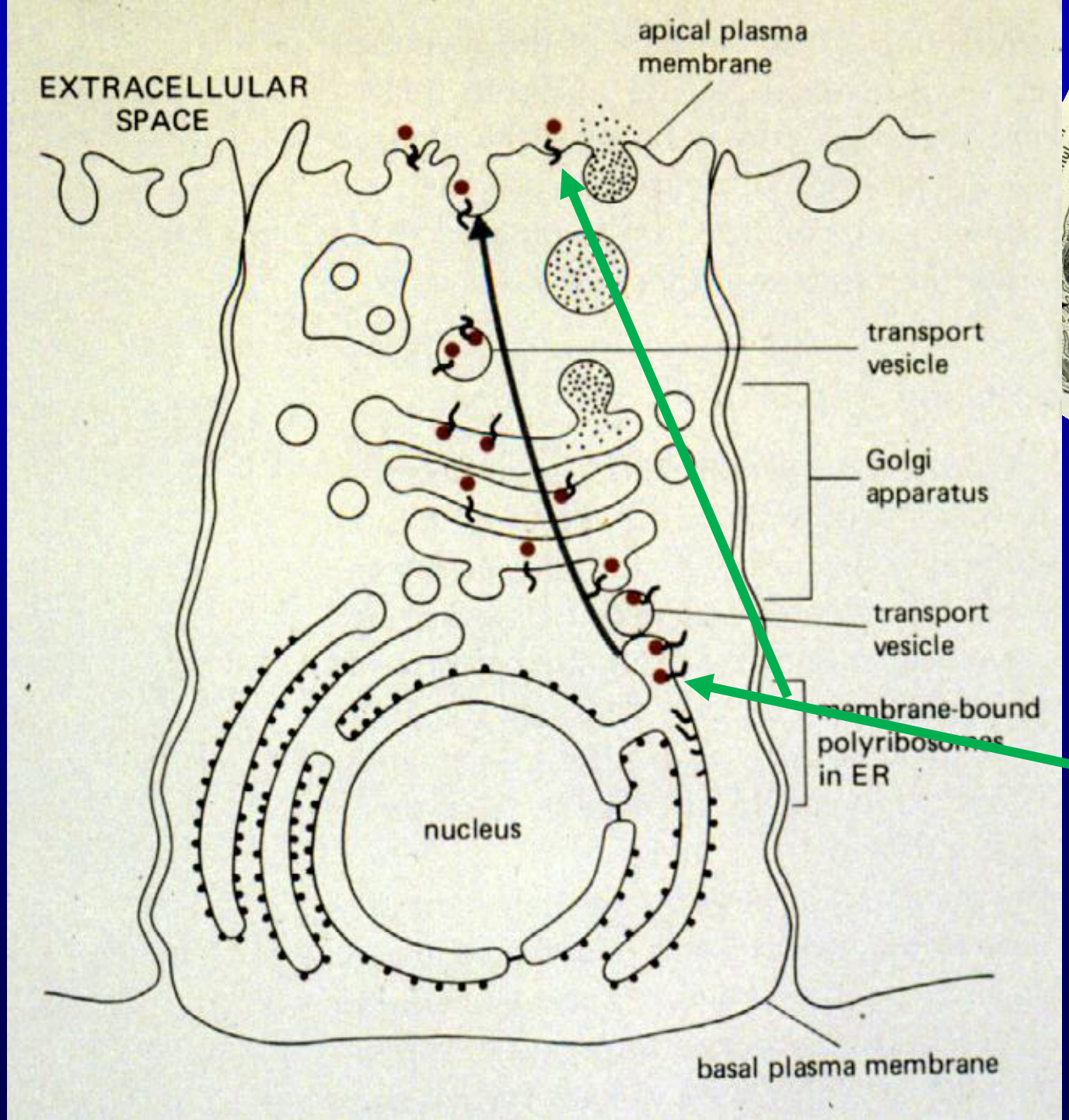
1. If Signal peptide, it goes to RER and start transfer
2. Signal recognition particle
3. Ribophorin on RER,
   binds ribosome and
   attaches ribosome to RER
4. Stop transfer
5. Hydrophobic amino acid sequence –
   inserted into membrane

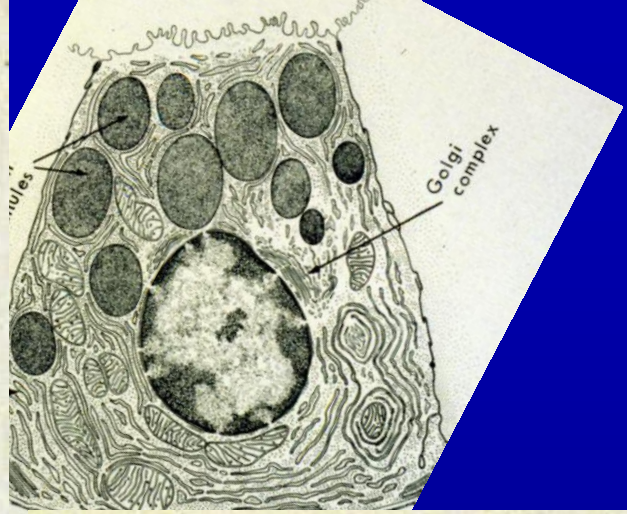


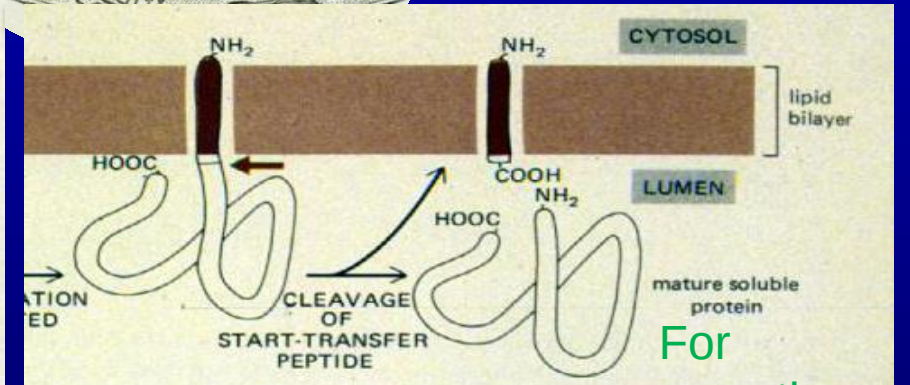




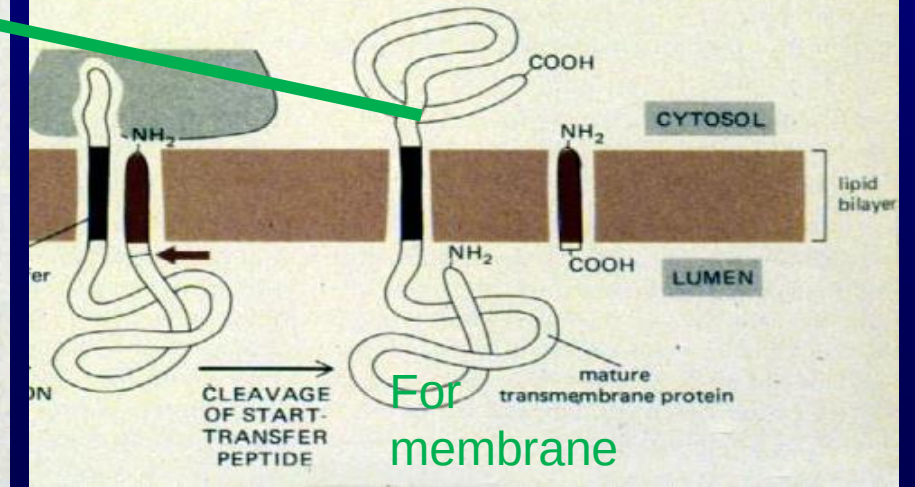
Another option is for the protein to stay in the membrane and become a cell membrane protein



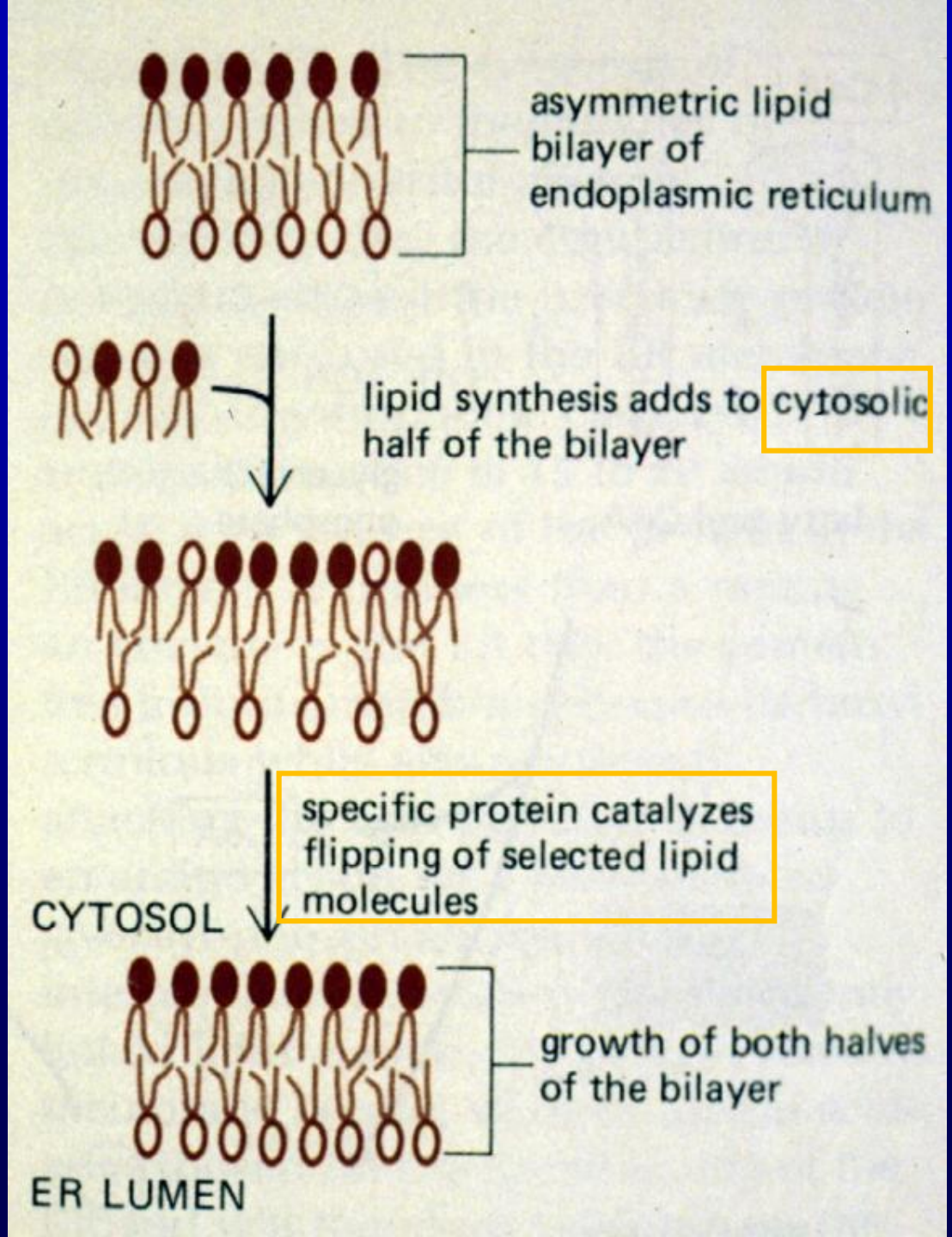




For secretion



For membrane



Membranes are made in the endoplasmic reticulum

Membranes

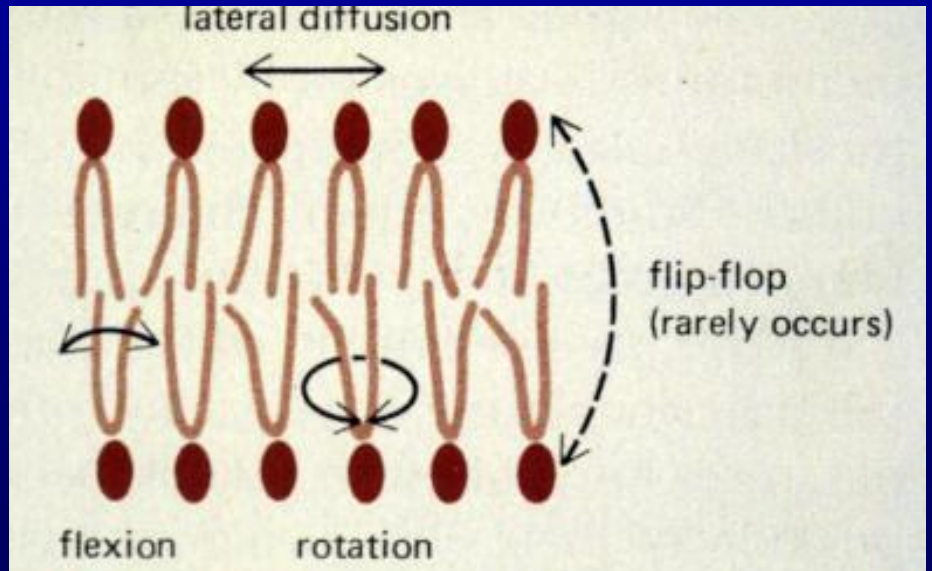
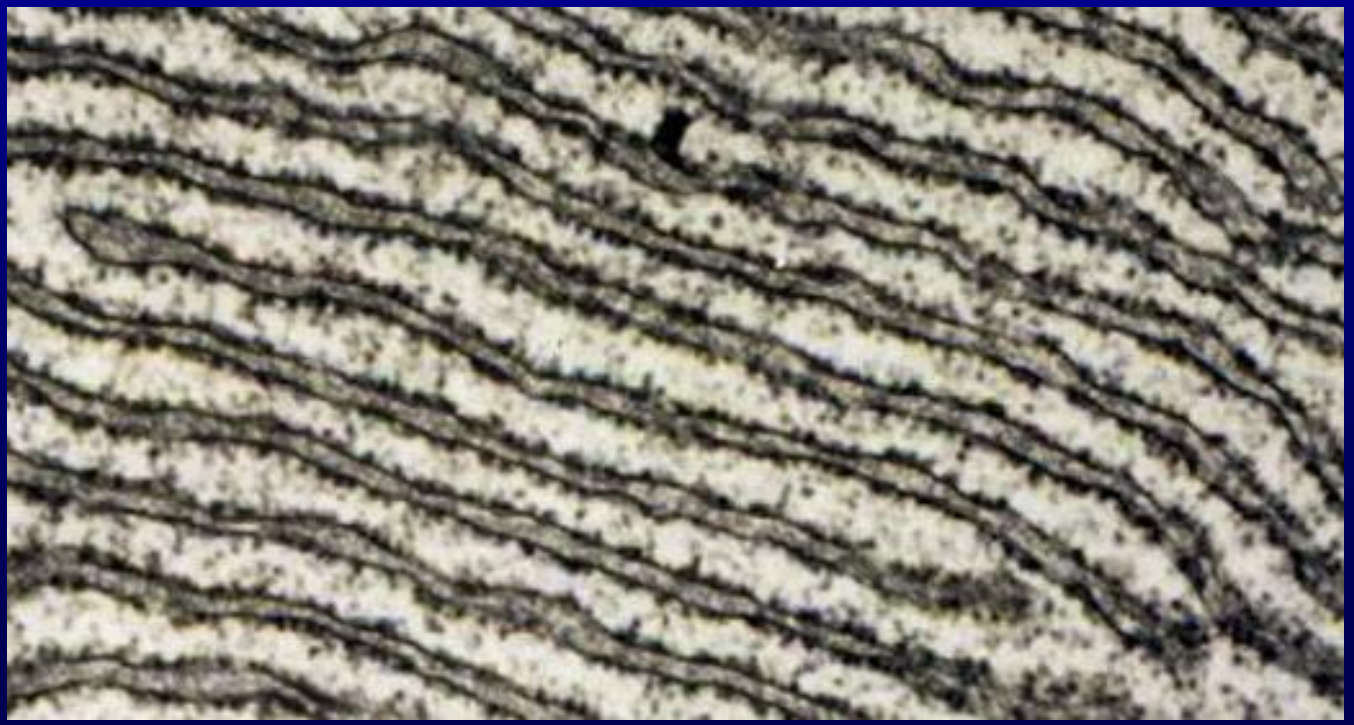


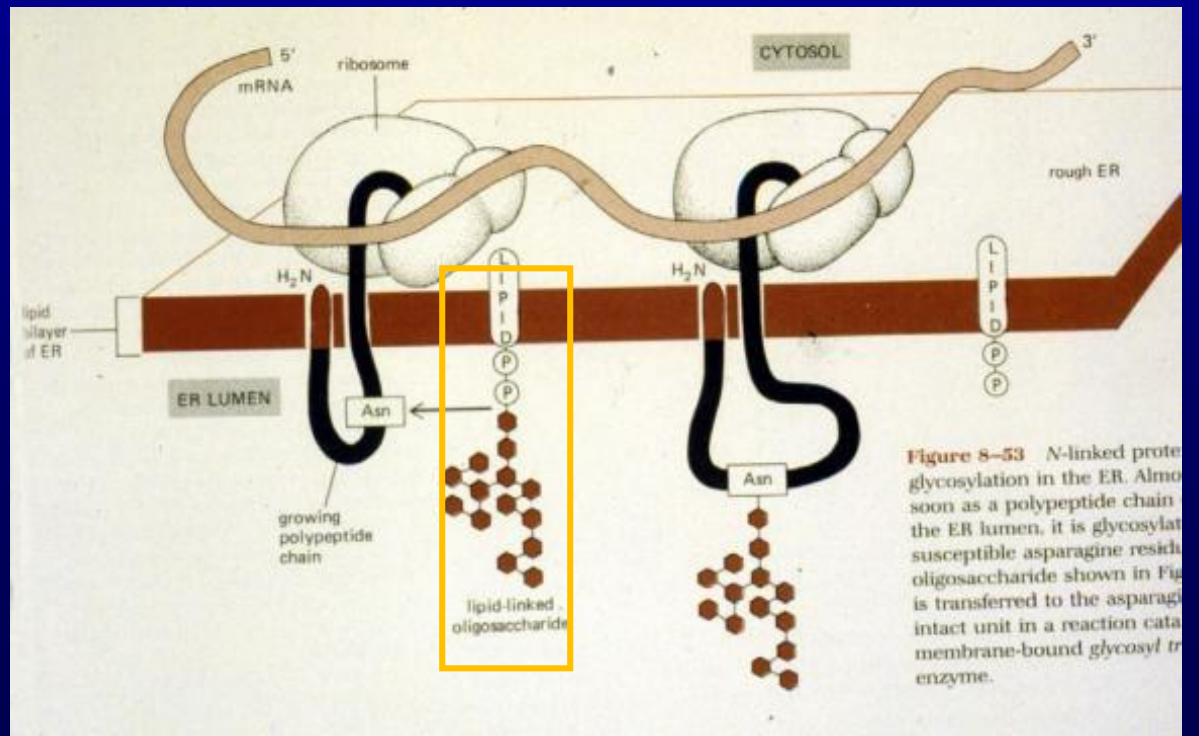
Figure 6–6 Different types of movement possible for phospholipid molecules in a lipid bilayer.

Post-translational modifications

RER

- Initial glycosylation & trim glucose
- Add chains of sugars first synthesized on a dolichol [lipid linked (through phosphate groups) oligosaccharide]

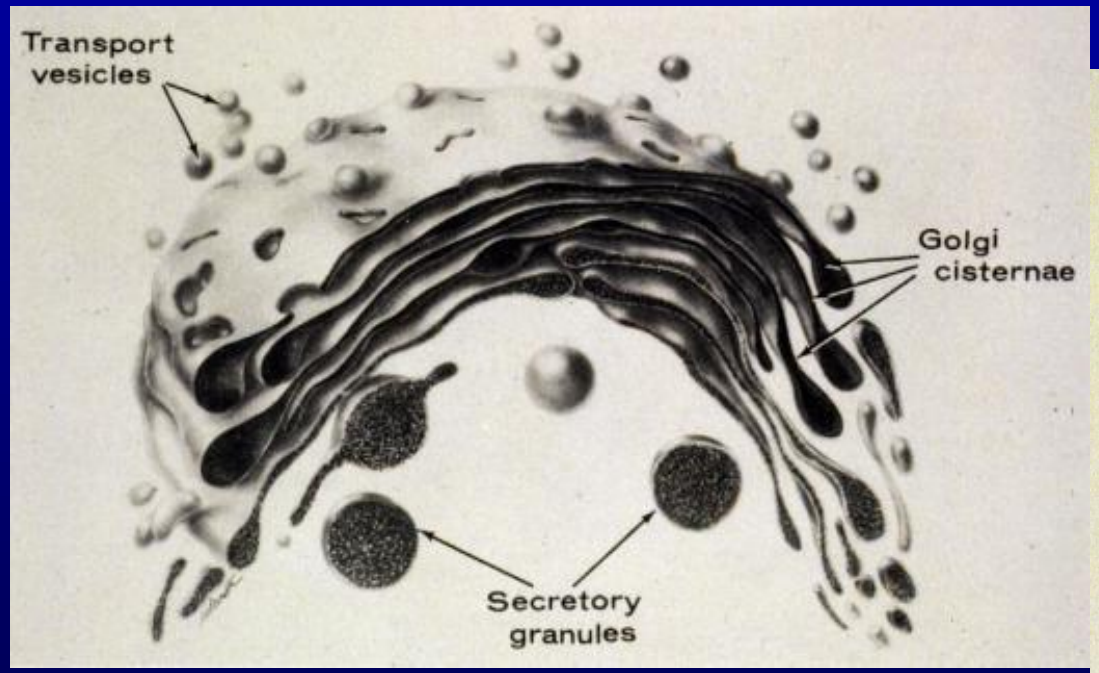


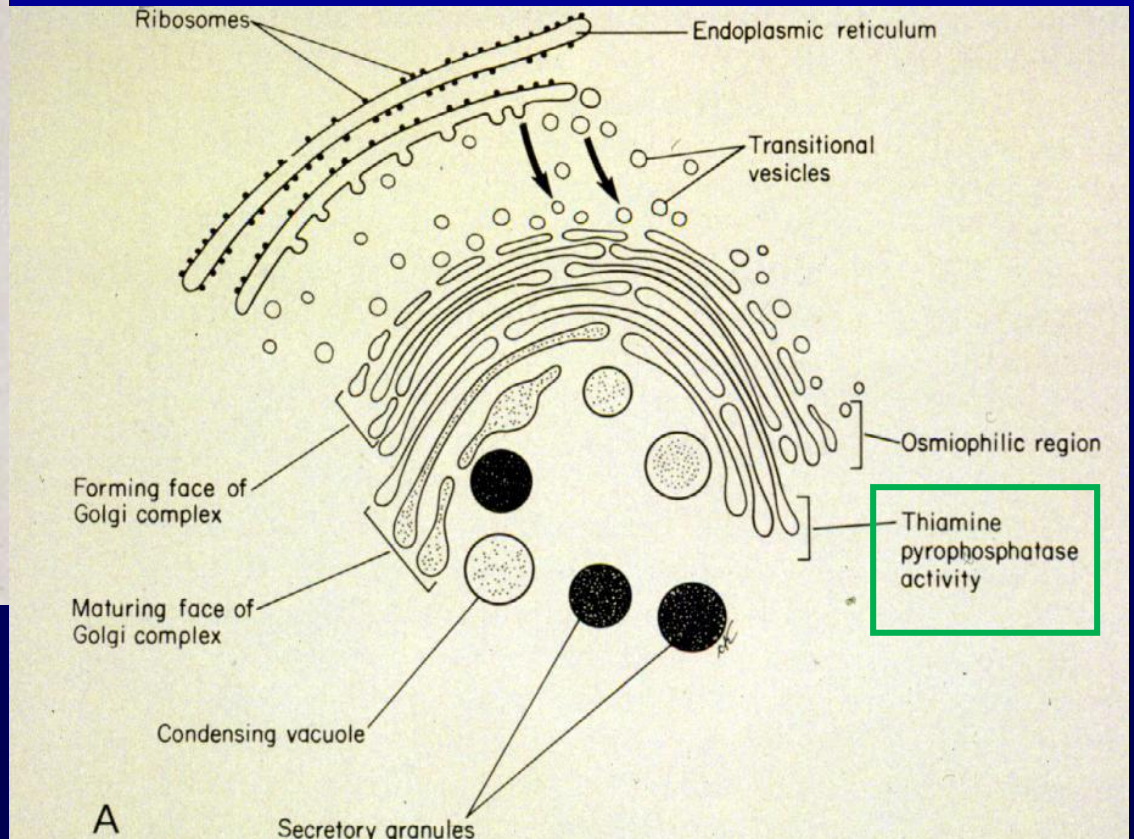


Post-translational modifications

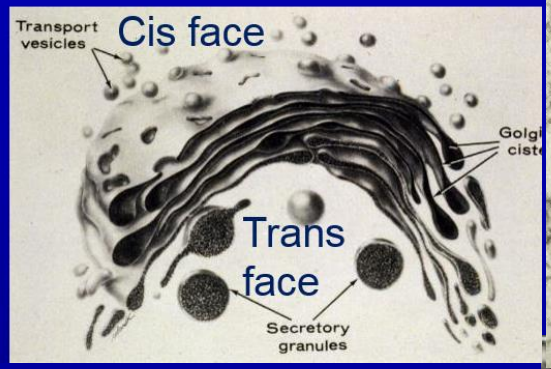
Golgi

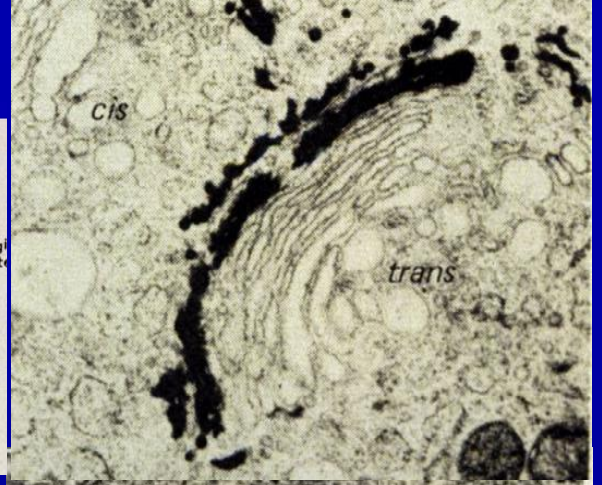
- Trim glucose & some mannose added by RER

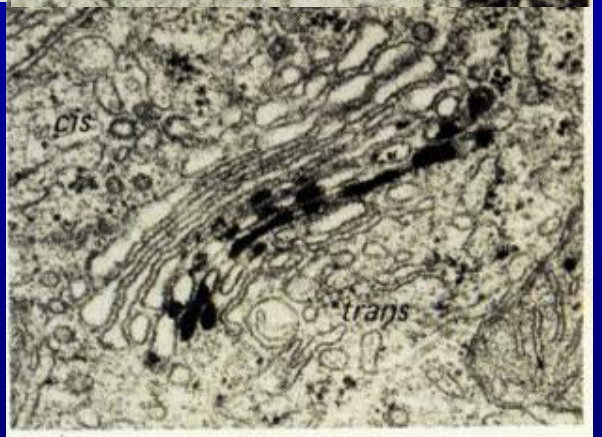




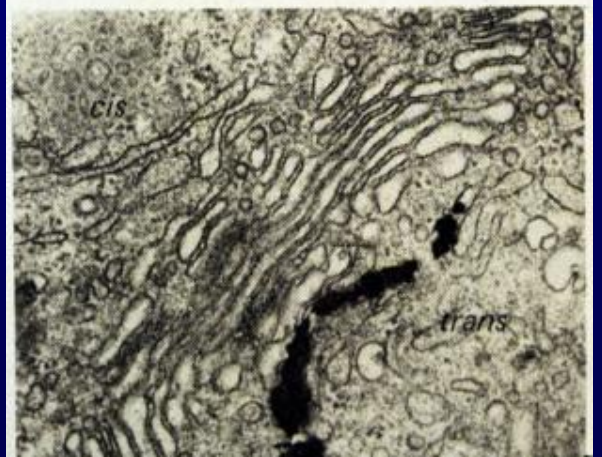
Golgi – polarized shape and function







(C)



Cis

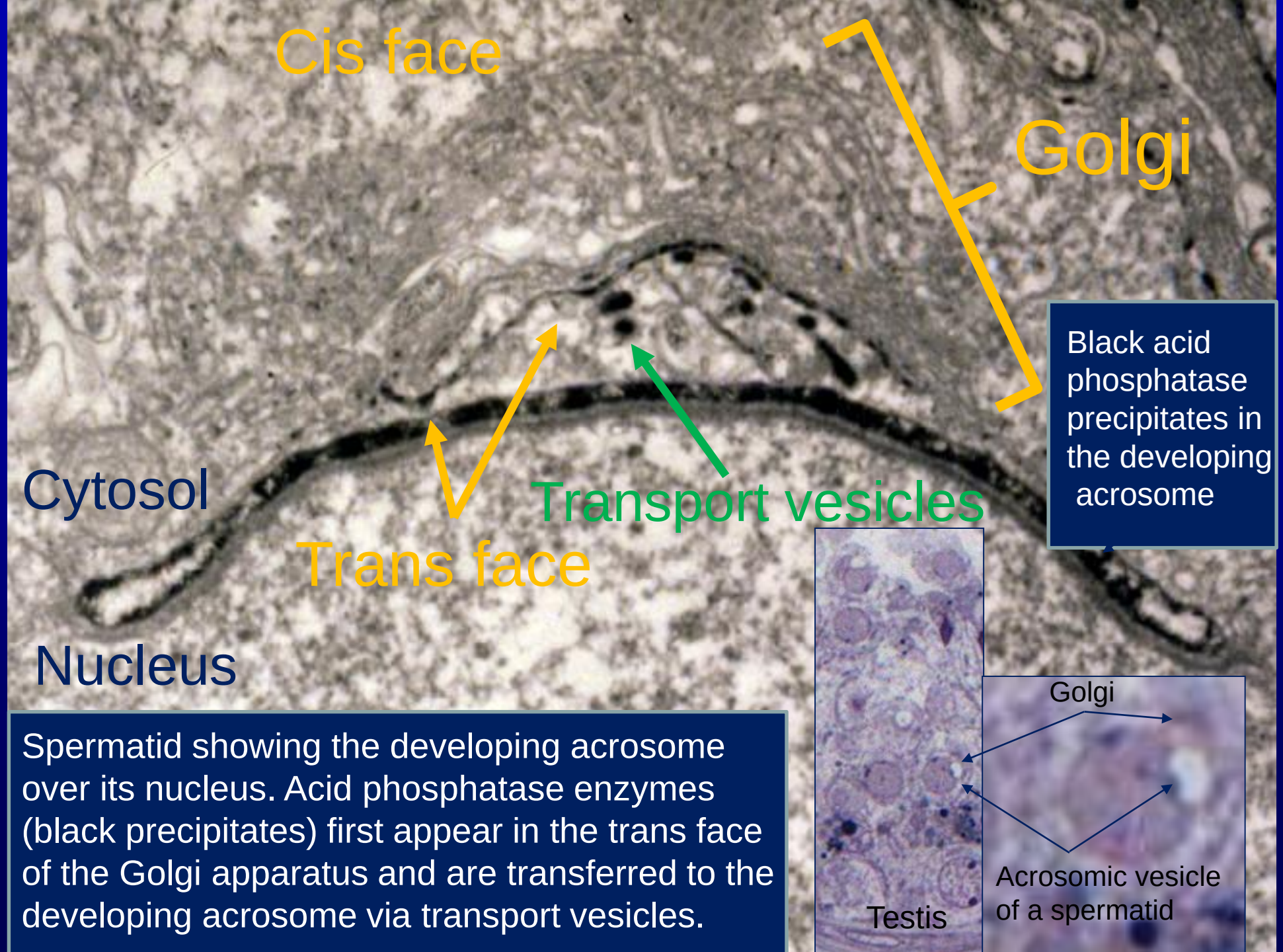
- Convex region - phosphate groups added

Middle

- Mannose removed

Trans

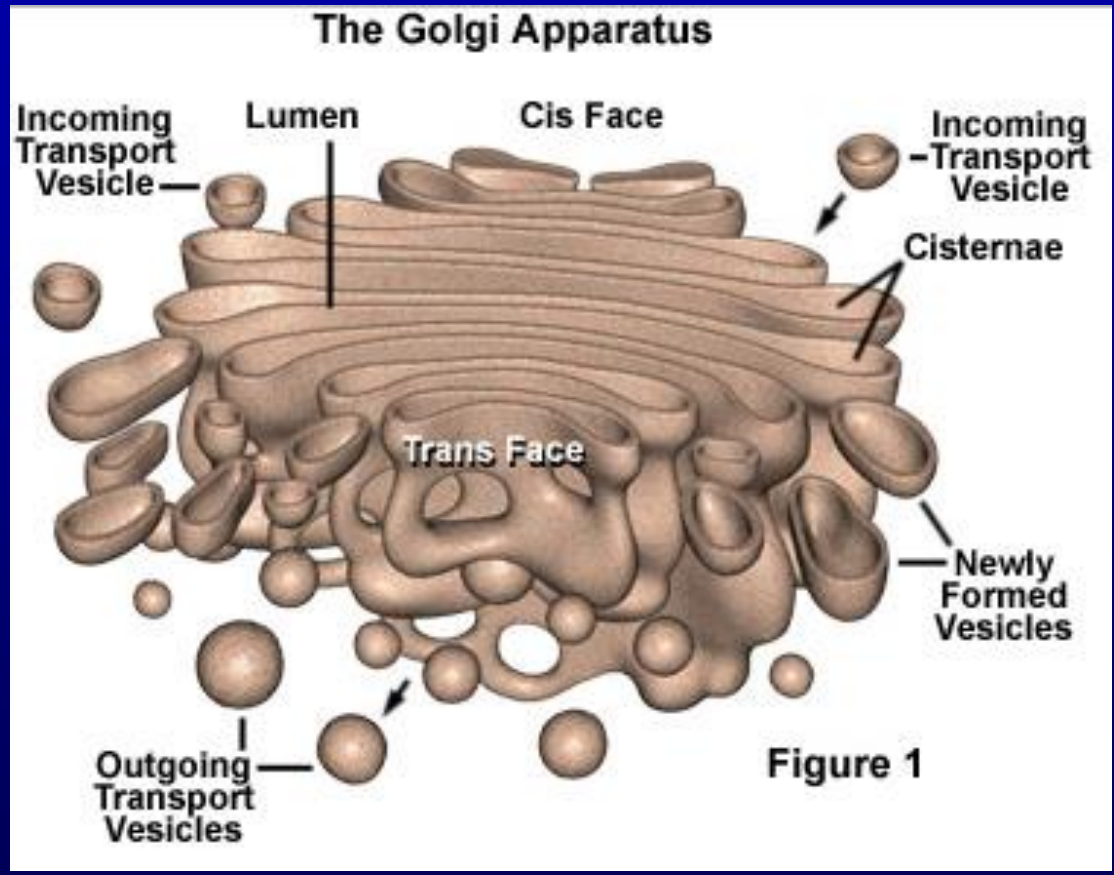
- Concave region – sialic acid, galactose added



Spermatid showing the developing acrosome over its nucleus. Acid phosphatase enzymes (black precipitates) first appear in the trans face of the Golgi apparatus and are transferred to the developing acrosome via transport vesicles.

Golgi - polarized shape and function

- Cis
  - Convex region - phosphate groups added
- Middle
  - Mannose removed
  - N-acetylglucosamine
- Trans
  - Concave region – sialic acid, galactose added

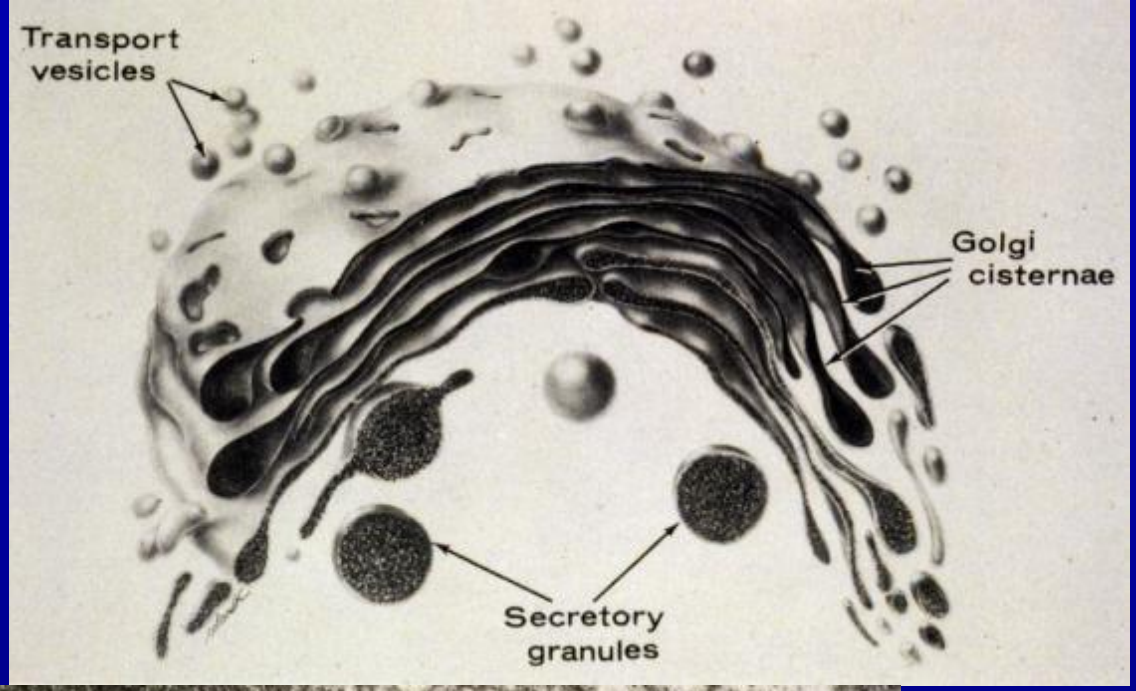


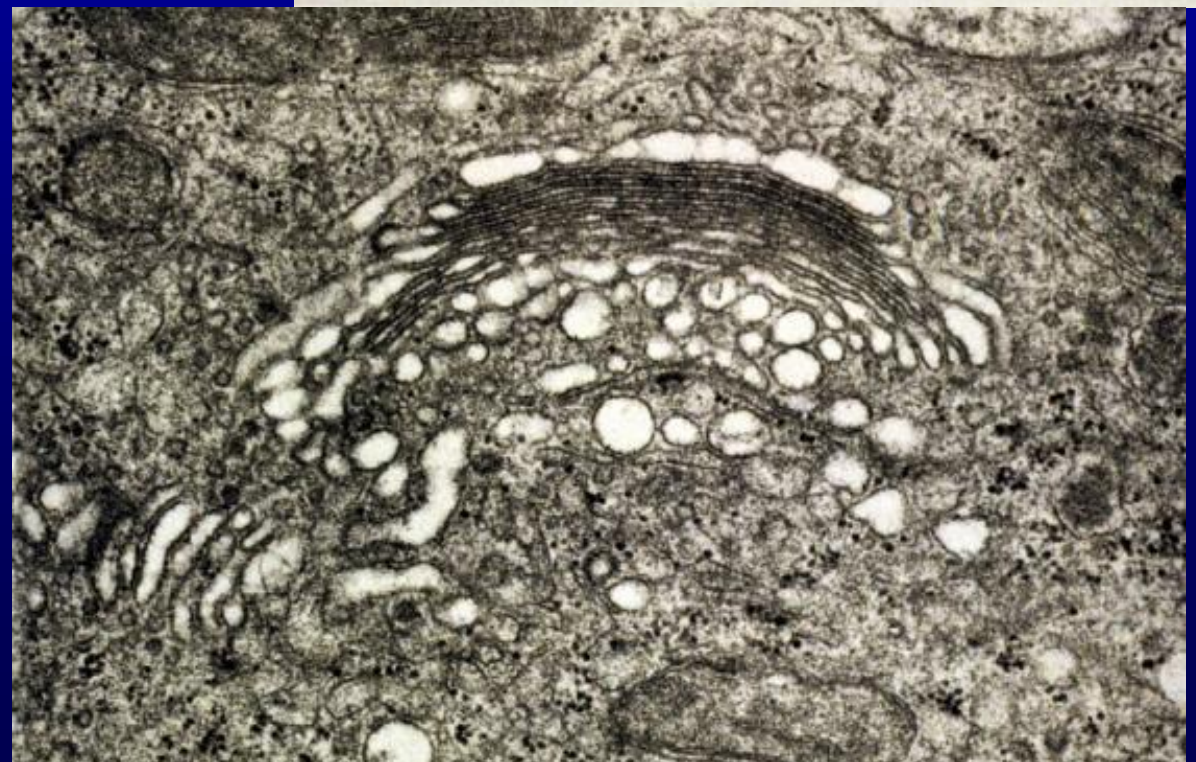
Golgi

Also adds

fatty acids, sulfate groups

Recycling of membrane of transport vesicles from Golgi to RER; however, the cargo does not recycle

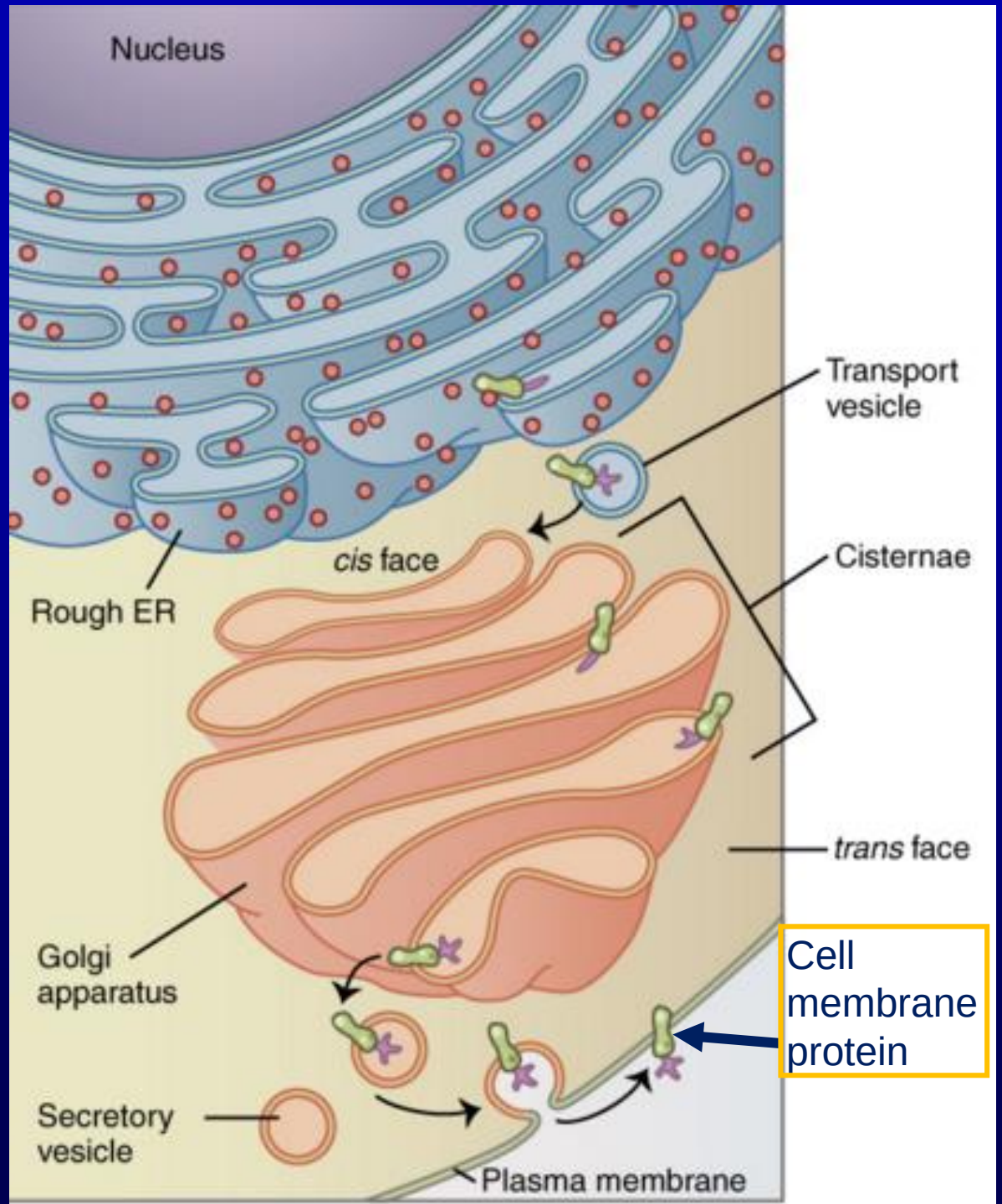




Golgi
and plasma membrane proteins

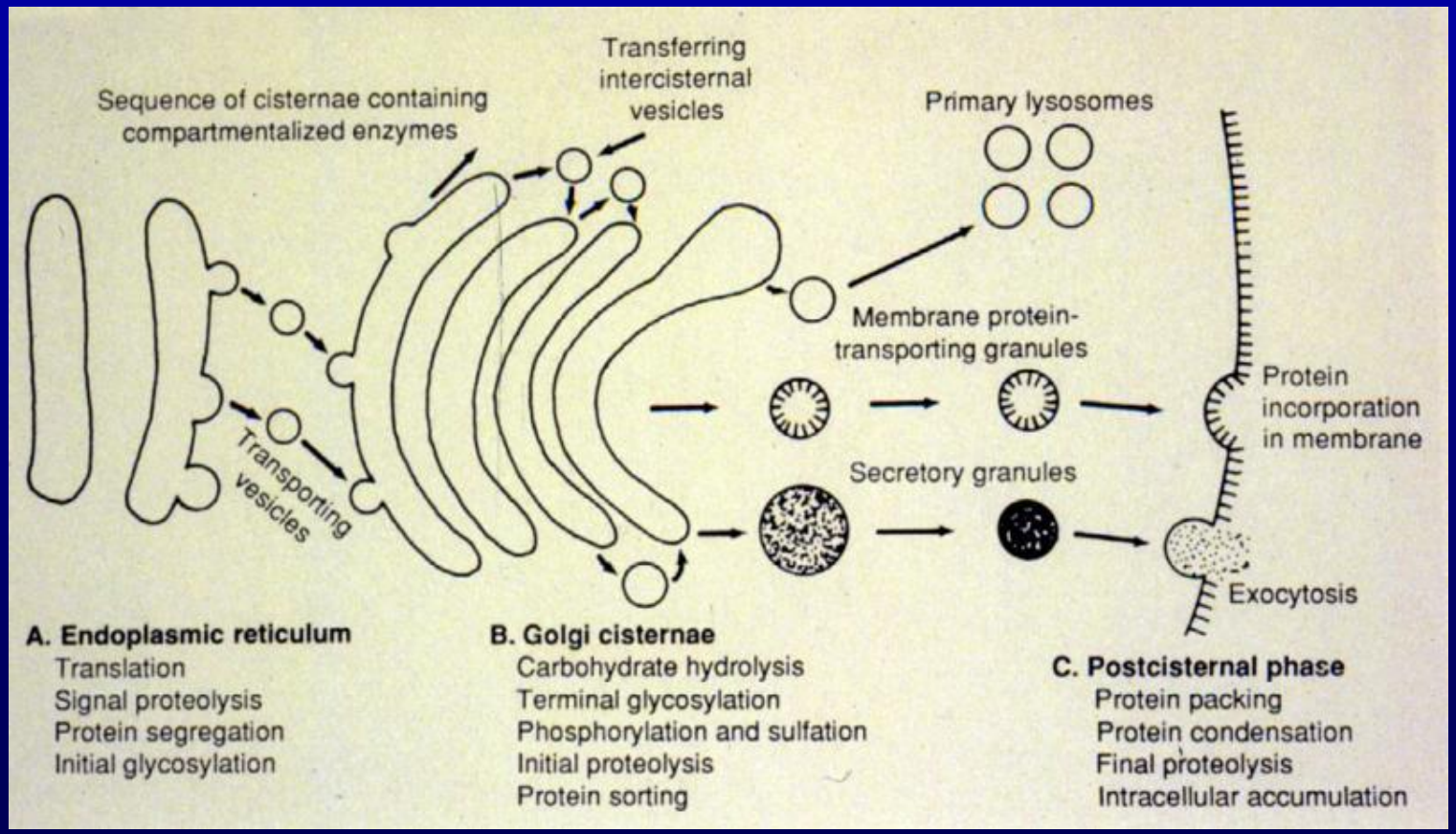
Cell membrane proteins are gylcolasolated only on the out side as that is the only part of the protein that had access to Golgi enzymes that add sugars

https://en.wikipedia.org/wiki/Golgi_apparatus



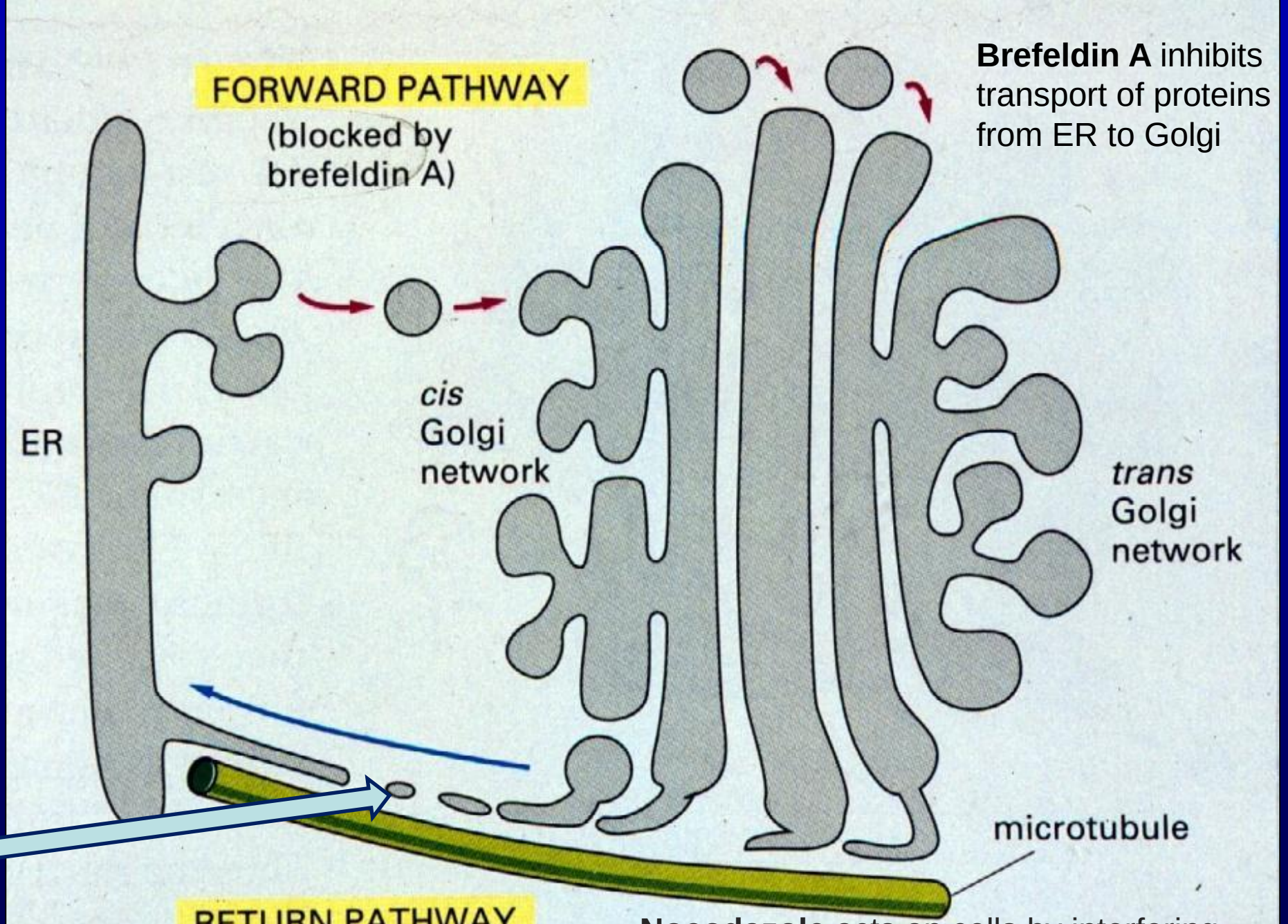
Lysosomal pathway

- **Mannose-6-PO_4 directs vesicles with polypeptide to lysosomes**



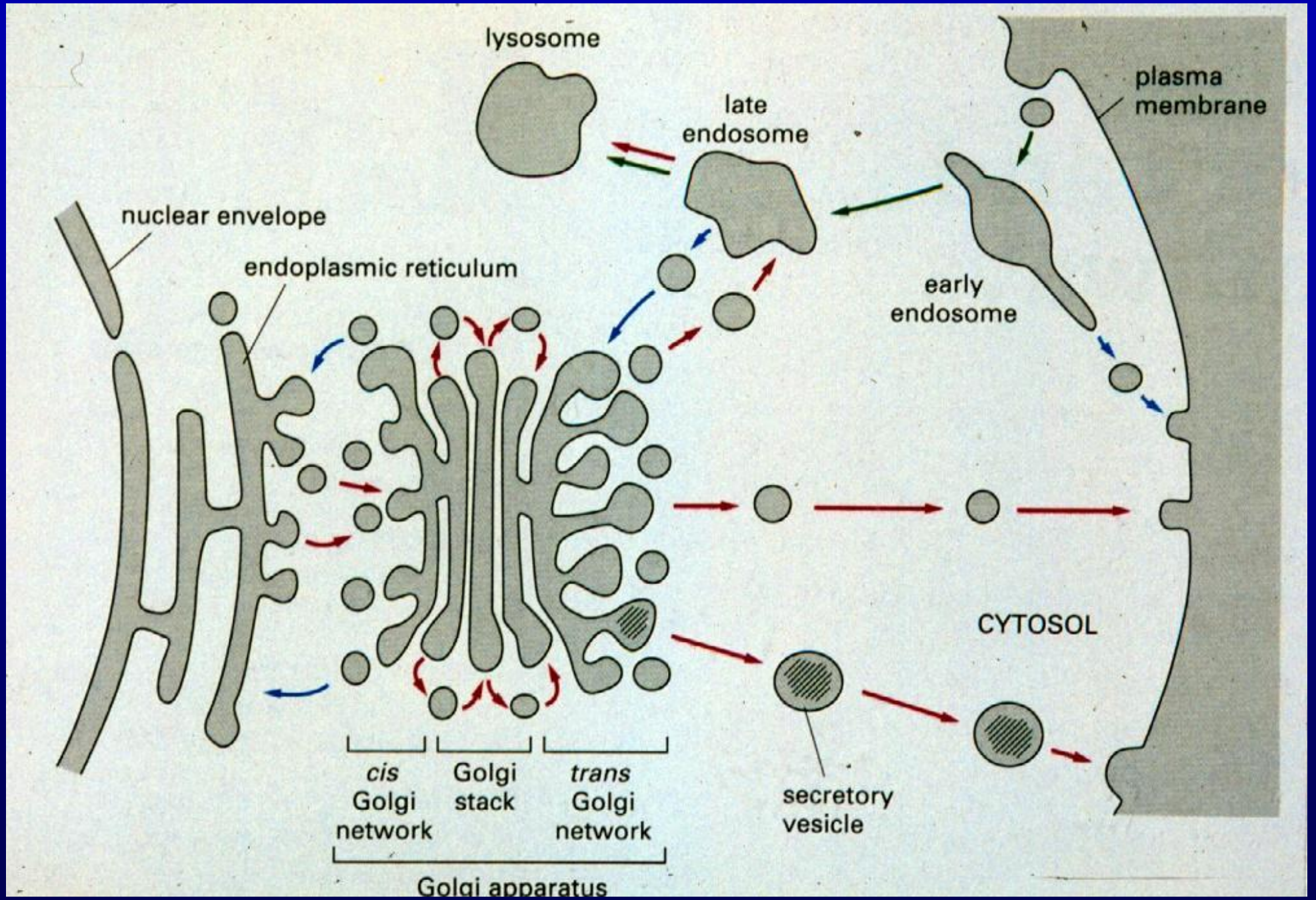
Cisternal and postcisternal phases of secretion?

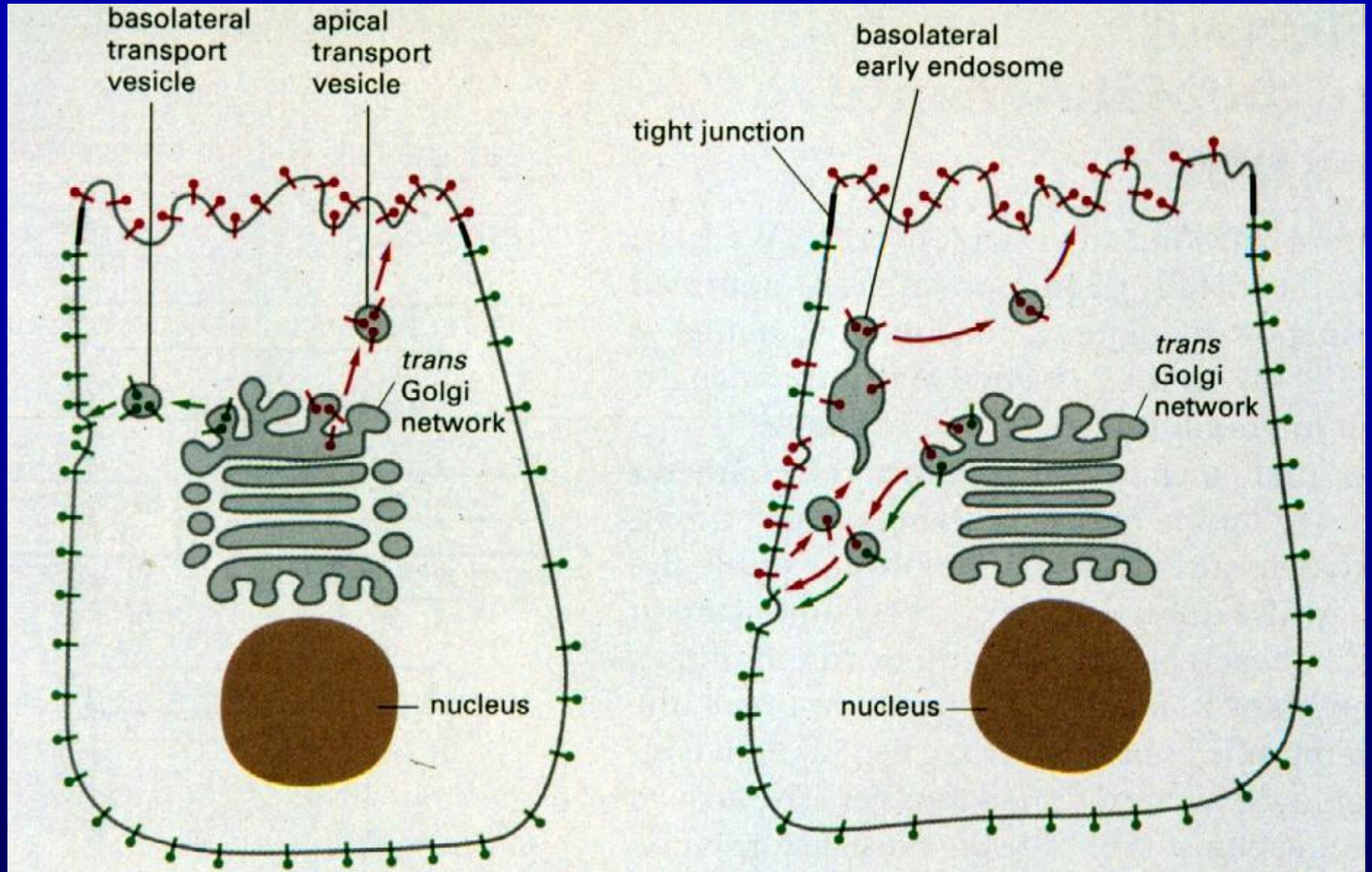
Brefeldin A inhibits transport of proteins from ER to Golgi



Golgi recycling membrane to RER

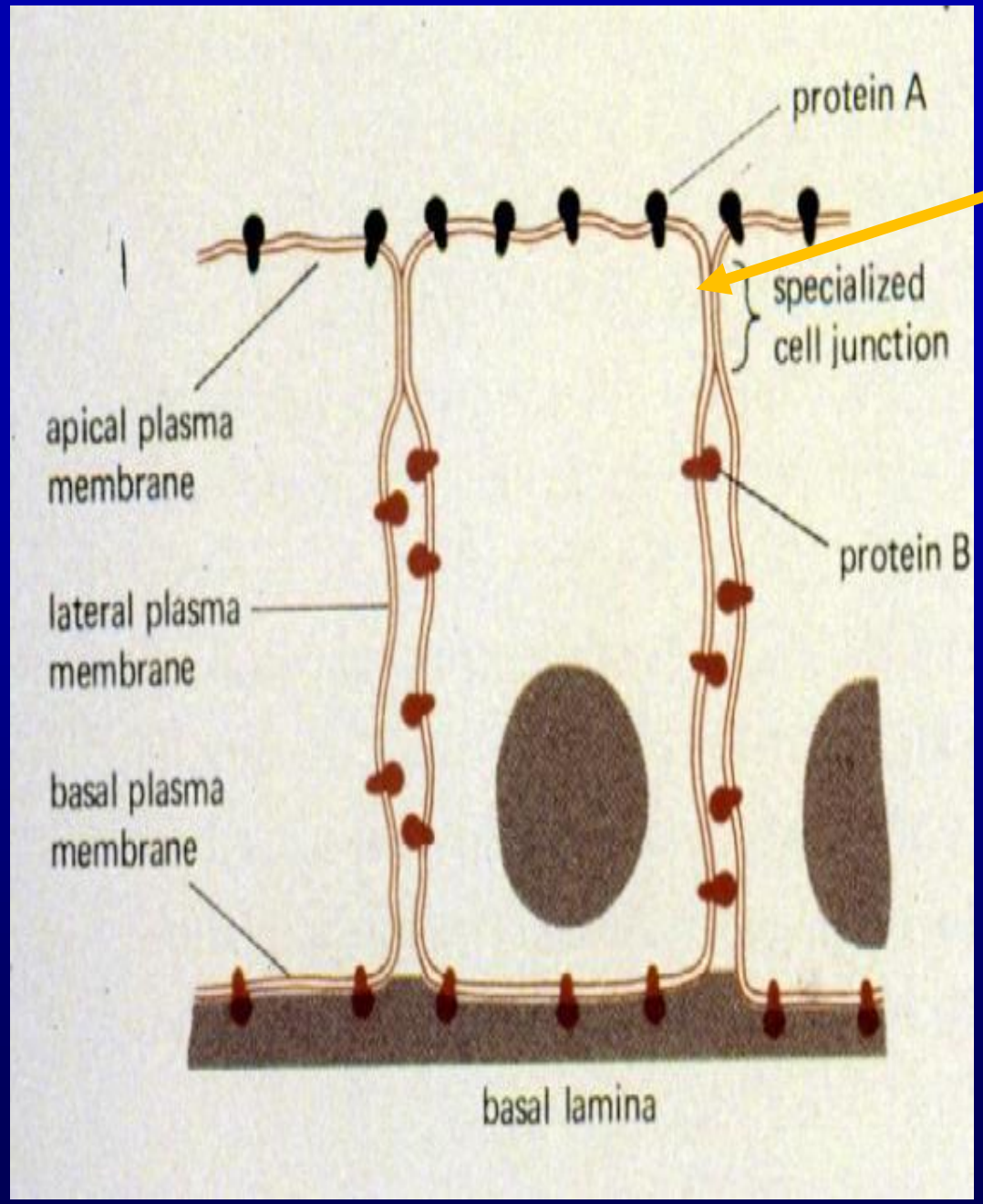
Nocodazole acts on cells by interfering with the polymerization of microtubules.


lysosome
late endosome
plasma membrane
nuclear envelope
endoplasmic reticulum
early endosome
CYTOSOL
cis Golgi network
Golgi stack
trans Golgi network
secretory vesicle
Golgi apparatus

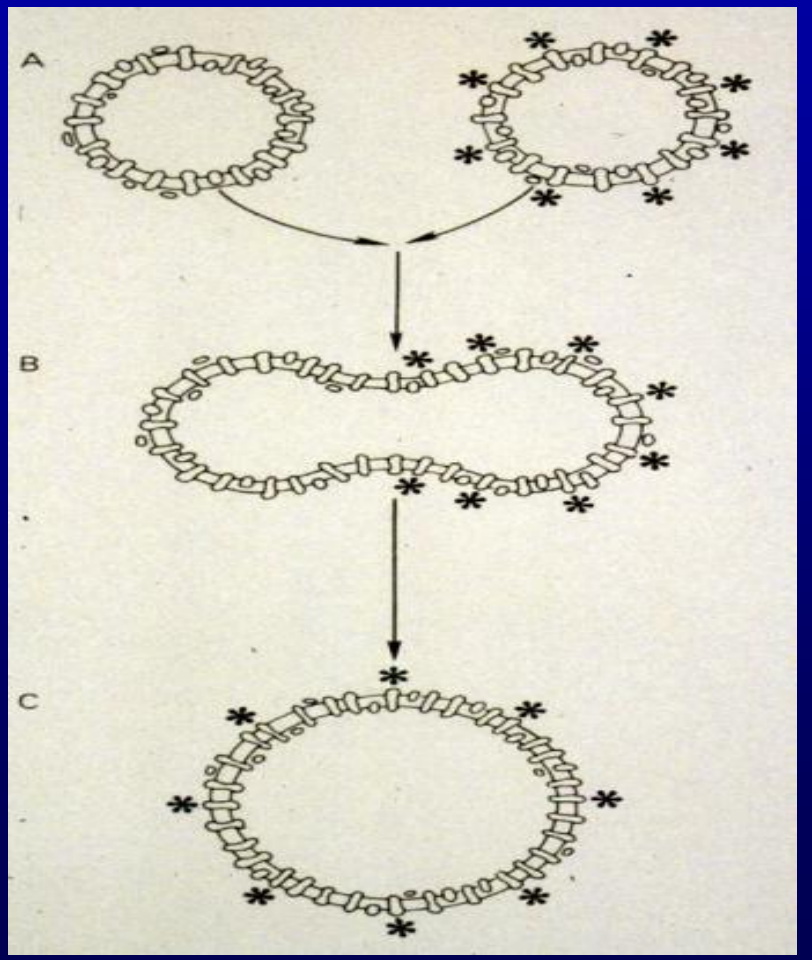


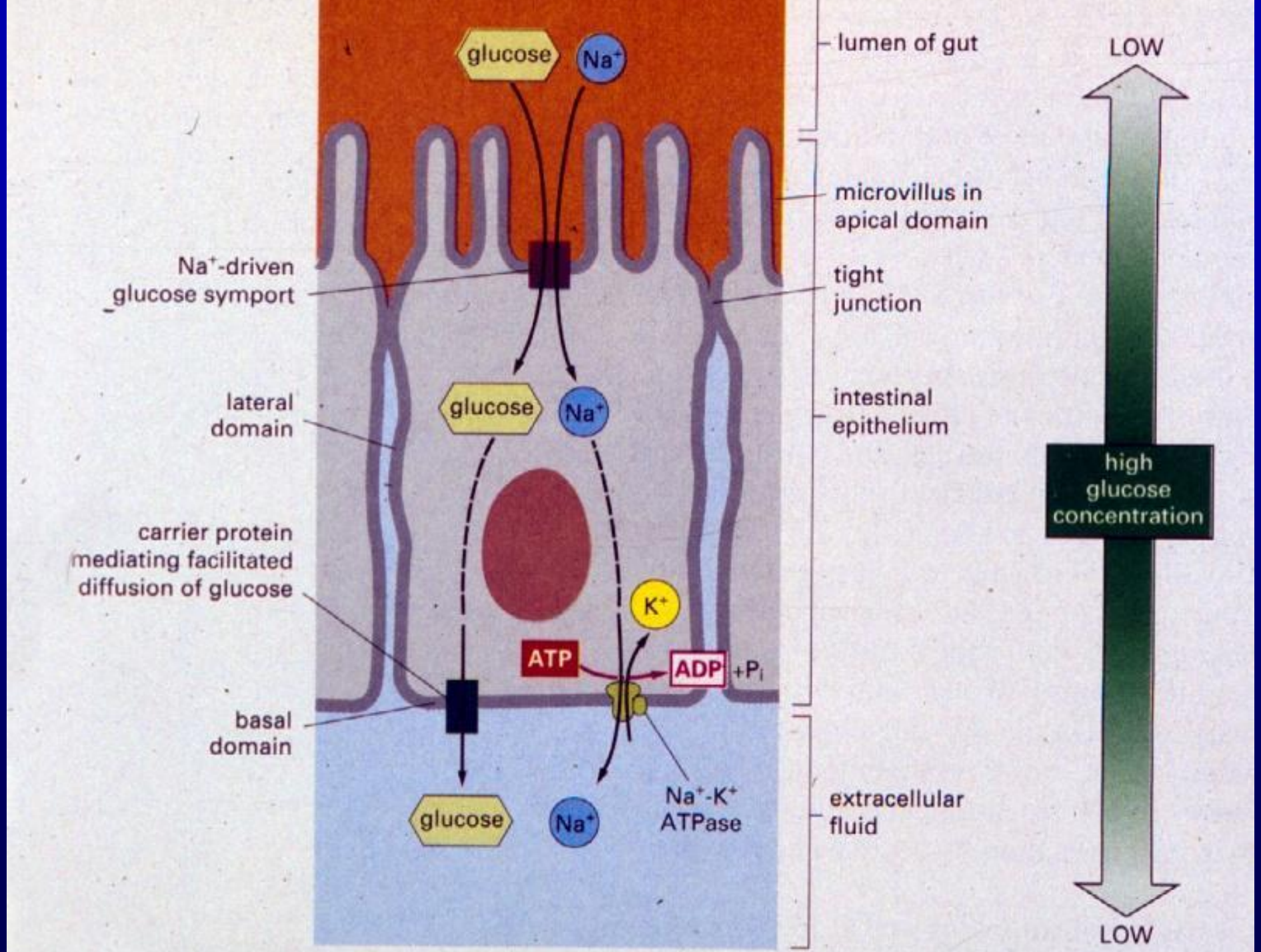
(A) DIRECT SORTING OF MEMBRANE PROTEINS IN THE *TRANS* GOLGI NETWORK

(B) INDIRECT SORTING VIA ENDOSOMES



Specialized cell junctions (tight junctions) isolate the membrane fluidity to luminal or basal/lateral domains of the cell membrane



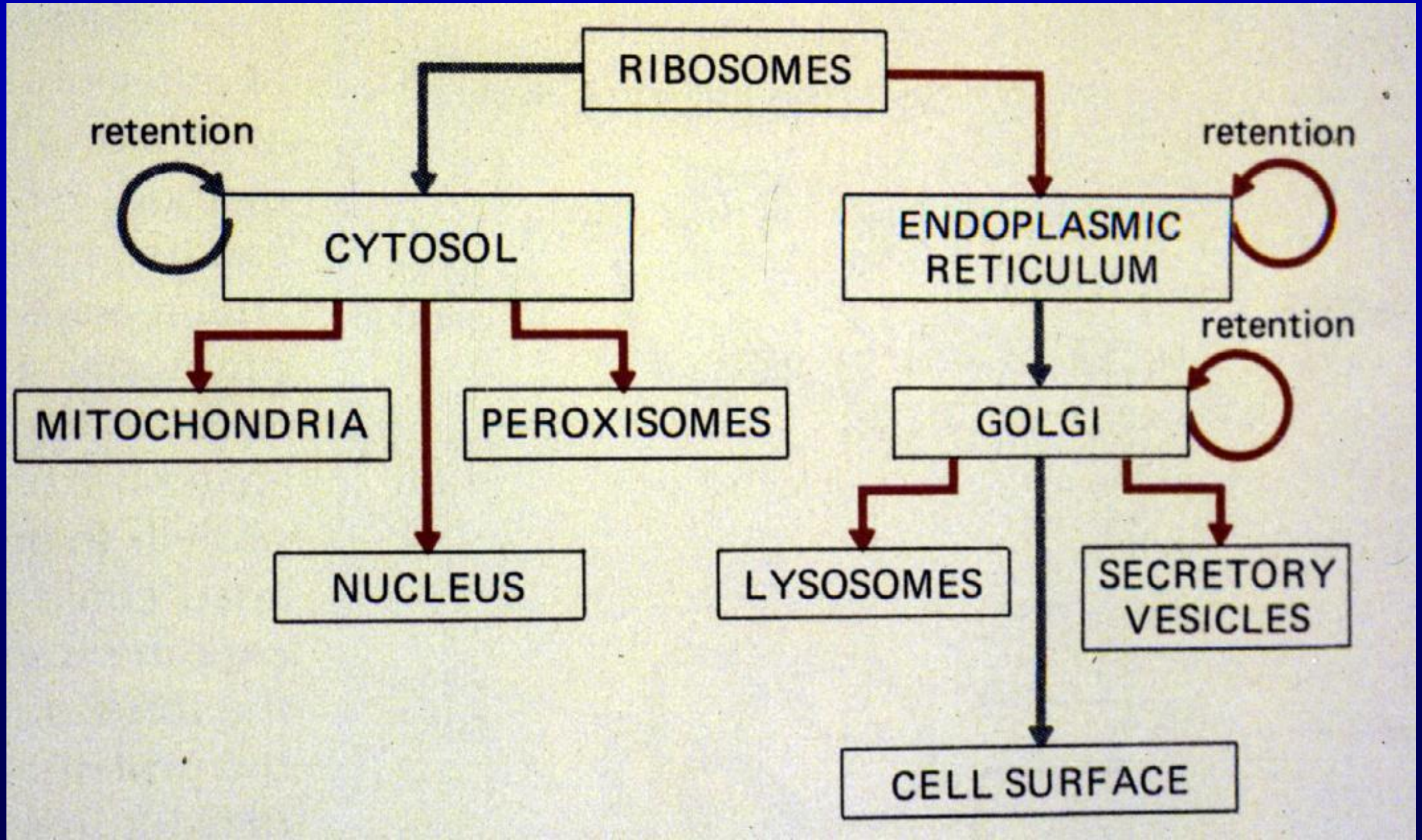

glucose
Na+
lumen of gut
LOW
microvillus in apical domain
Na+-driven glucose symport
tight junction
lateral domain
intestinal epithelium
high glucose concentration
carrier protein mediating facilitated diffusion of glucose
K+
ATP
ADP
+Pi
basal domain
Na+-K+ ATPase
extracellular fluid
LOW

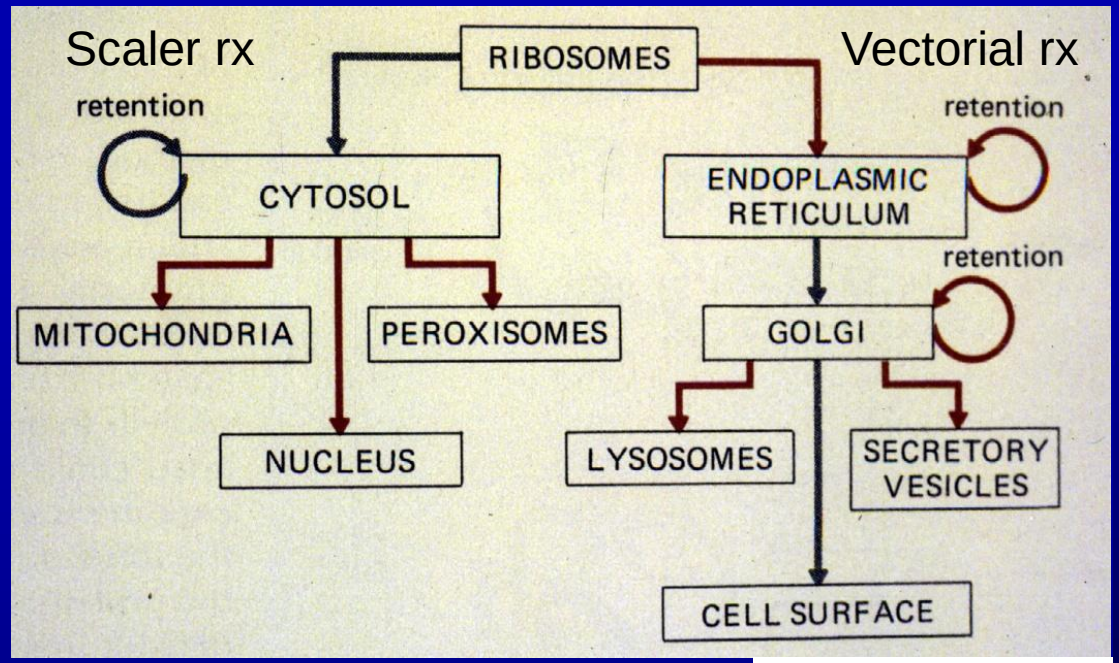
Voyage inside the Cell: Membrane

organelles

https://www.youtube.com/watch?v=yKW4F0Nu-UY

https://www.youtube.com/watch?v=FzcTgrxMzZk


RIBOSOMES
retention
retention
CYTOSOL
ENDOPLASMIC RETICULUM
retention
MITOCHONDRIA
PEROXISOMES
GOLGI
NUCLEUS
LYSOSOMES
SECRETORY VESICLES
CELL SURFACE



Reactions

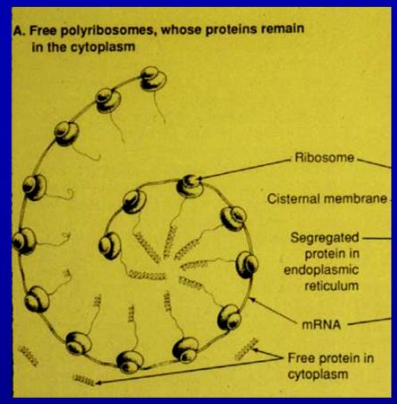
- **Scaler reactions**

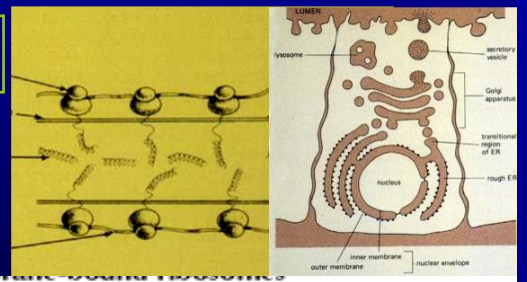
$$a + b = c$$

- **Vectorial reactions**

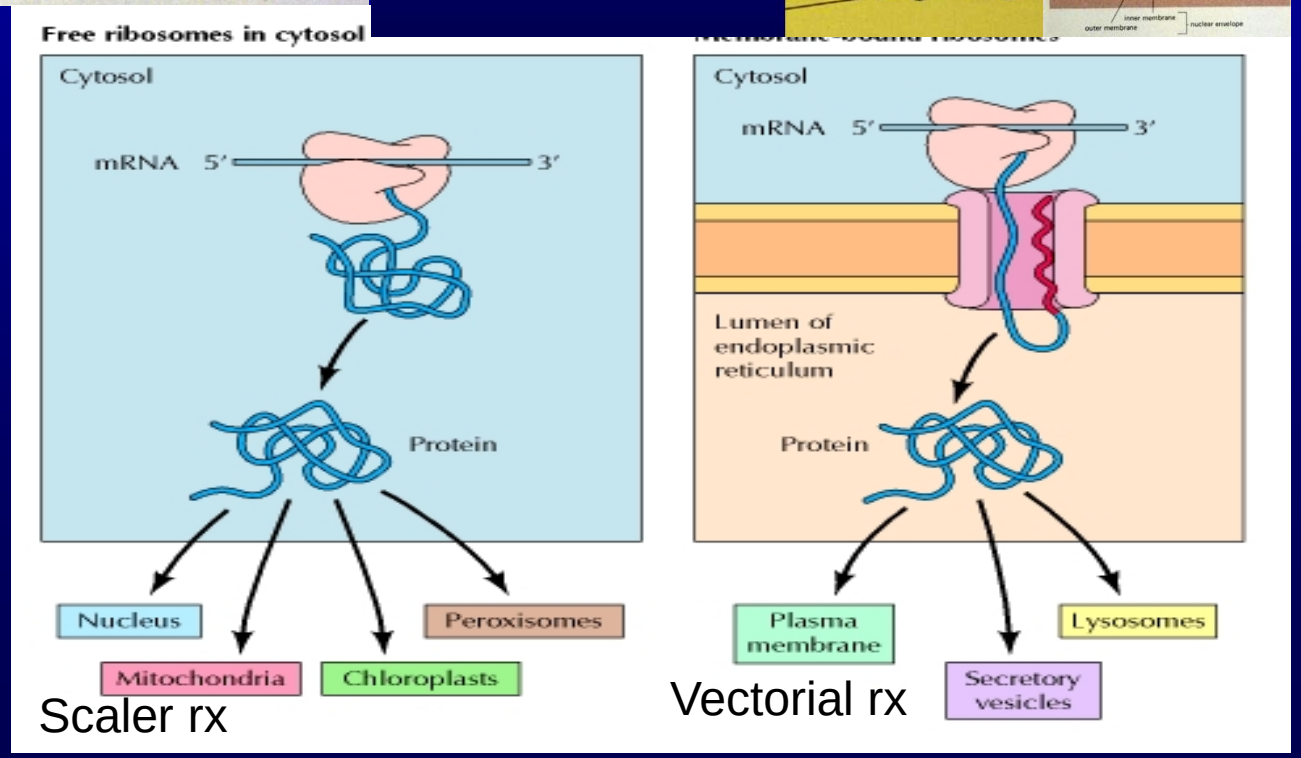
$$a + b = c$$

membranes





Signal Peptide on newly synthesizes protein being produced directs free ribosome to RER



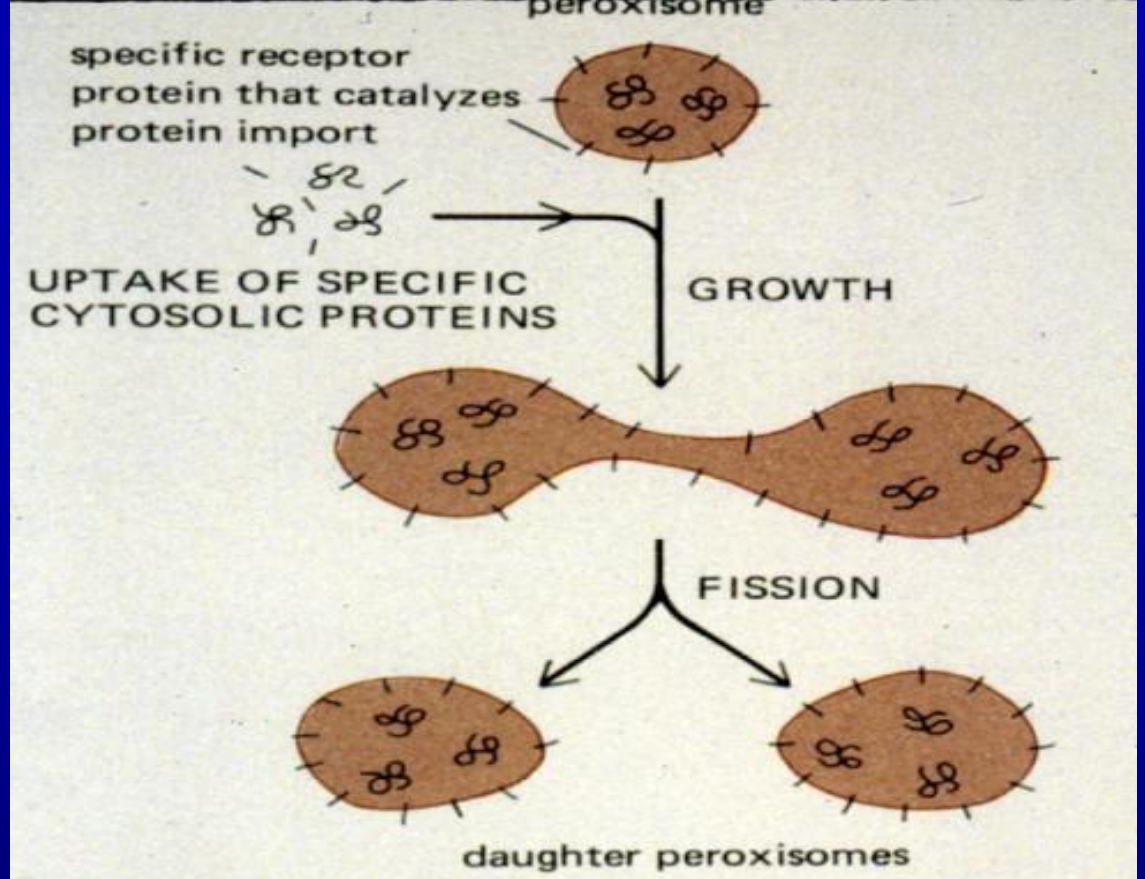


Figure 8–34 A model for how peroxisomes are assembled. The peroxisome membrane contains specific import receptor proteins. All peroxisomal proteins, including new copies of the import receptor, are synthesized by cytosolic ribosomes and then imported from the cytosol. Thus peroxisomes form only from preexisting peroxisomes by a process of growth and fission; like mitochondria and chloroplasts, they continually import

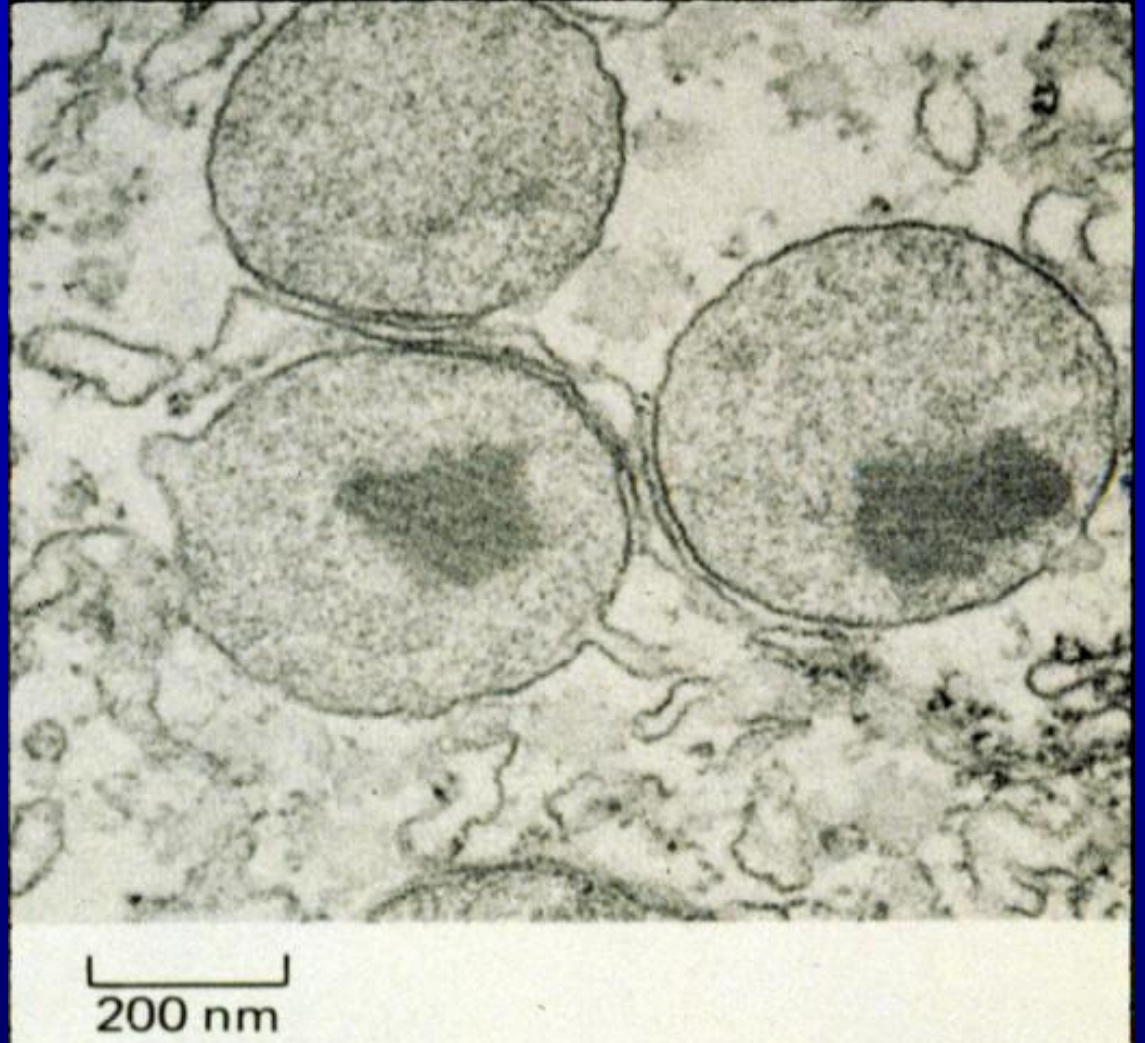


Figure 8–32 Electron micrograph of three peroxisomes in a rat liver cell. The paracrystalline electron-dense inclusions are the enzyme urate oxidase. (Courtesy of Daniel S. Friend.)

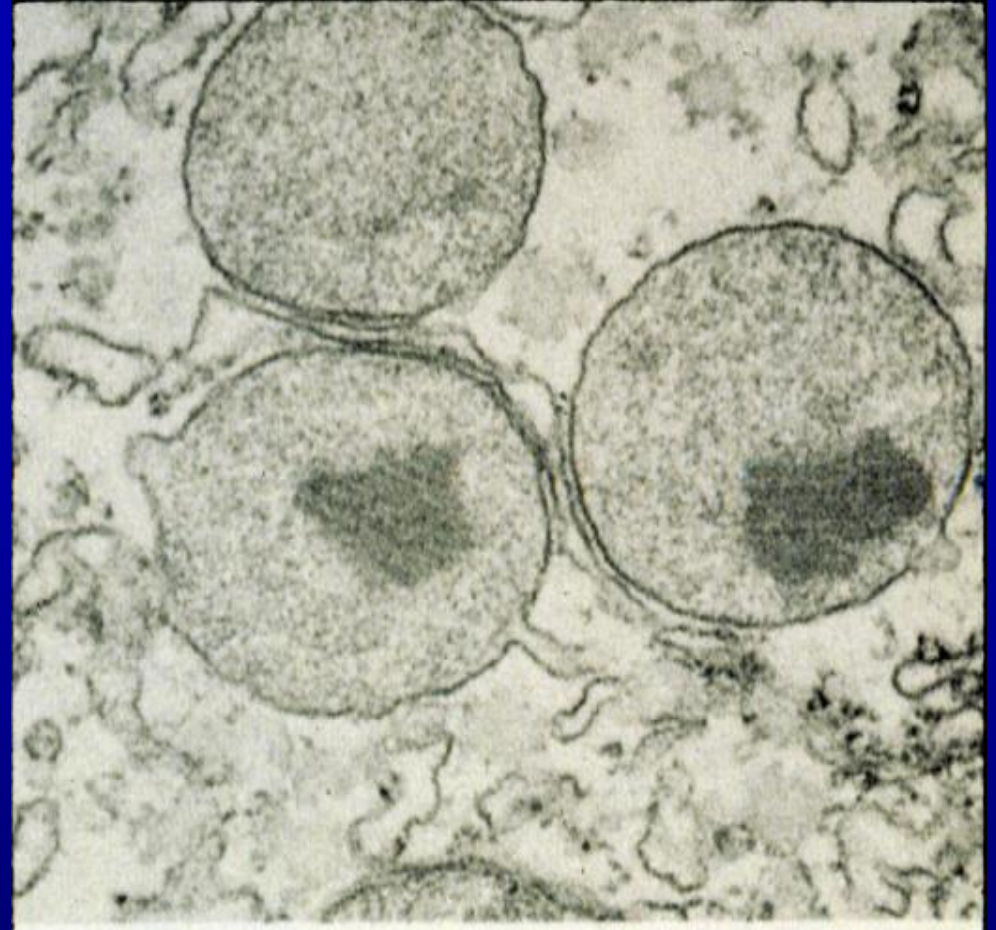


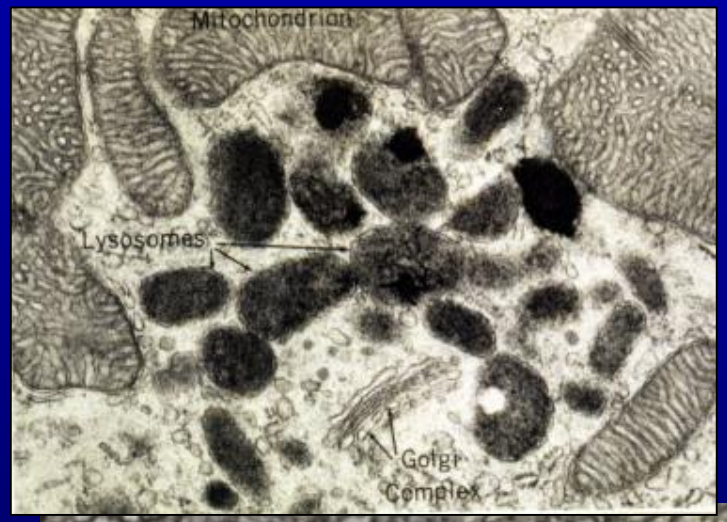
Figure 8–32 Electron micrograph of three peroxisomes in a rat liver cell. The paracrystalline electron-dense inclusions are the enzyme urate oxidase. (Courtesy of Daniel S. Friend.)

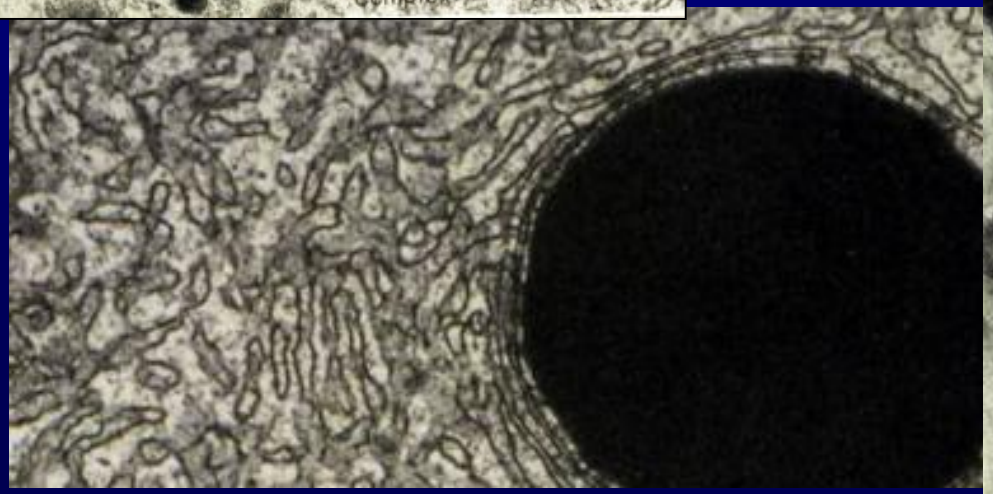
Peroxisomes

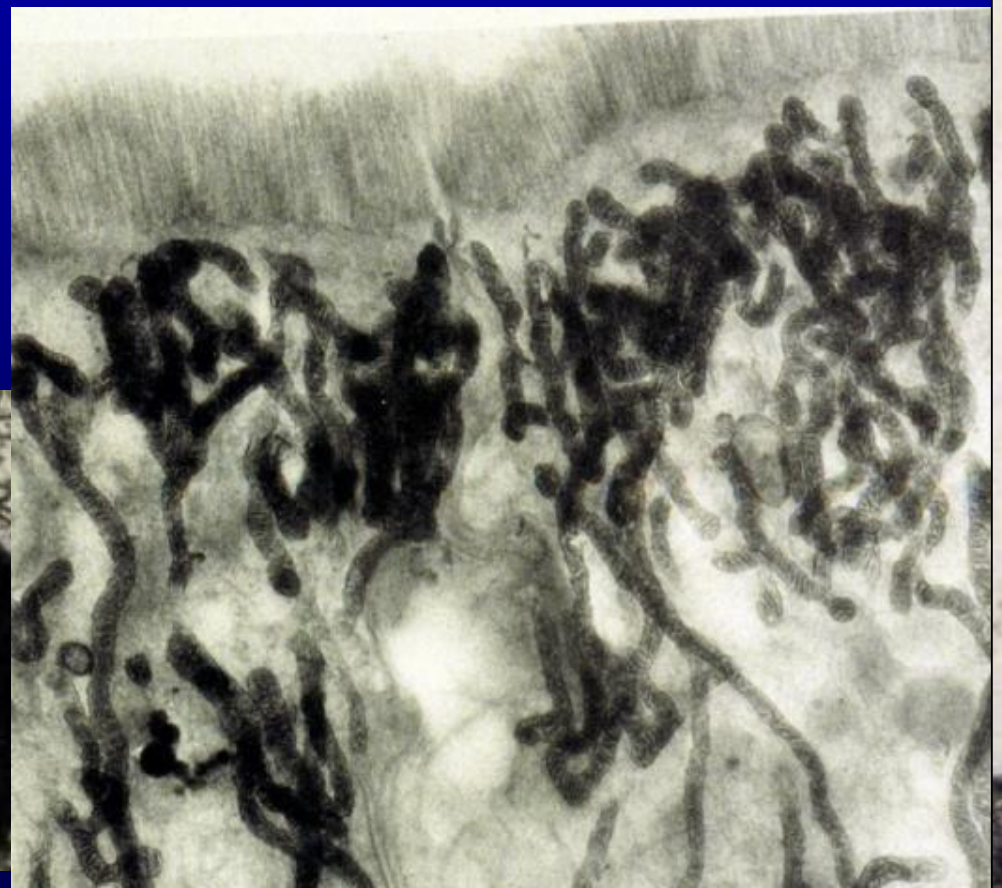
1. O_2 metabolism
2. Detoxification of harmful substances in fatty acid metabolism
3. Crystalline core

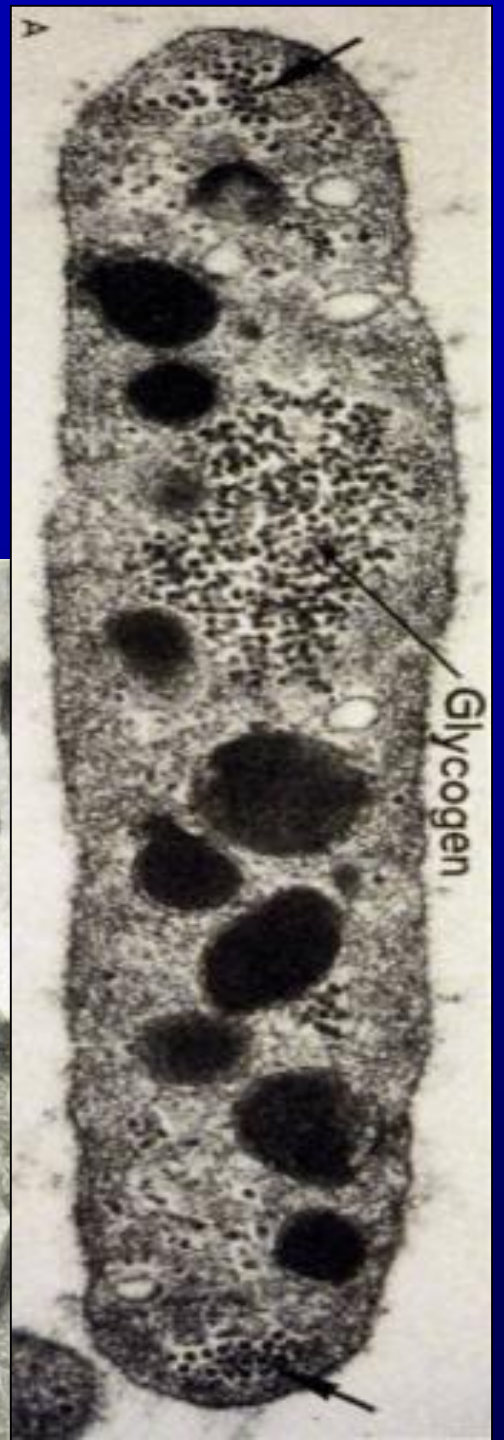
Next time, but do not go yet lesson on taking the quizzes

Lysosomes, smooth ER, mitochondria, and inclusions









Approach for studying for quizzzes part A

basic tissues

Epithelium

Connective tissue

Protein production / secretion – structure/process

Ribosome

Ribophorin

Dolichol

Post-translational modification

Protein sorting

classes of cellular structures

Non-membranous organelles

Membranous organelles

Approach for studying for quizs part A con't

Characteristic of membranes
Cellular compartmentalization
Chemical heterogeneity of the cell
Amphipathic molecules

Organelles
Nuclear envelope
Peroxisome

Microsopy
Resolution

Procedures in cell biology
Autoradiography
Cell fractionation
SDS gel electrophoresis

Part B

8. Based on the following characteristics, name the basic type of tissue and give one function of the stated characteristic:

Characteristic	Tissue Type	Function
a. Gap junction	*Epithelium*	*Allows cell-to-cell communication*
b. Avascular	*Epithelium*	*Blood vessels don't interfere in function*
c. Histologic glue	*Connective tissue*	*Attach tissues*
d. Myelin sheath	*Nervous tissue*	*Aid in impulse conduction*

Part B con't

9. List the corresponding cellular organelle and the function of the following structures or distinct structural characteristics.

Characteristic	Organelle	Function
a. Phospholipid bilayer	*Membrane*	*Compartmentalization*
b. Functions in decoding	*Ribosomes*	*Produce proteins*
c. Signal proteolysis	*RER*	*Separate signal from secretory protein*
d. Phosphorylation & sulfation	*Golgi*	*Post translational modifications of proteins*

Part B con’t

10 Contrast light (bright field) with conventional transmission electron (TEM) or scanning electron (SEM) microscopy.

Microscope Type of Observation	Light Source	Lens Type	Method
a. Light			
b. TEM			
c. SEM			

Part C

13. What is a distinguishing feature of this cell? *(Neutrophil) Granular, light staining cytoplasm, lobulated nucleus.*

14. What would eosin stain in these cells? *(Apical cytoplasm pancreatic acinar cells) secretory granules, protein in cytoplasm.*

15. Name two functions of this organelle. *(Mitochondrium) (a) ATP production; (b) Ca++ storage; or cholesterol-side chain cleavage.*

16. Which is greatest? The thickness of a plasma membrane *(7-10 nm)*, thickness of a microtubule *(25 nm)*, or diameter of a ribosome *(15 nm)*?

Microtubule

Many illustrations in these VIBS Histology YouTube videos were modified from the following books and sources: Many thanks to original sources!

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- Bruce Alberts, et al. 1994. Molecular Biology of the Cell. Garland Publishing, Inc., New York, NY.
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- Nature (http://www.nature.com), Vol. 414:88,2001.
- A.L. Mescher 2013 Junqueira's Basis Histology text and atlas, 13th ed. McGraw
- Douglas P. Dohrman and TAMHSC Faculty 2012 Structure and Function of Human Organ Systems, Histology Laboratory Manual - Slide selections were largely based on this manual for first year medical students at TAMHSC