CELL BIOLOGY and GENETICS

Level 1 BMLS

Cell Biology

- General structure of **cells** and **tissues**: Cell diversity and classification, ***epithelial***, ***Muscular***, ***Connective***, ***Nervous***
- Ultra-structure and organization of cell organelles.
- Cellular compartments; cyto-skeleton and cell motility; types of cell division; relationship between cells, tissues and organs; cellular communication.
- The application of **microscopy** in cellular biology

Genetics

- Basic genetic principles and mechanisms; Mendelian inheritance; Sex determination.
- Multiple genes and alleles; Gene expression and genetic disorders; Gene regulation of functions;
- Gene and Chromosomal mutation; Introduction to gene basic unit and structure, Chromosomes.

History of Cell Biology

- The scientific study of cells developed gradually from the first description of cells **in the seventeenth century**.

- In **the eighteenth and nineteenth centuries** research expanded to include the study of **cell chemistry** and **physiology**, efforts that proceeded independently from morphological studies.

- The study of ***cell structure***, ***cell chemistry***, and ***cell physiology*** continued as separate fields of experimentation **until the beginning of the twentieth century**, when the rapidly developing field of **biochemistry began to influence cell biology.**

The discovery of cells followed from the ***invention of the microscope***. In 1665, **Robert Hooke** saw a *network of tiny boxlike compartments* that reminded him of a honeycomb. (initially in a section of **cork**, and then in **bones** and **plants**)

- ❑ He called these little compartments "cellulae", a Latin term meaning little room.
- ❑ **It is from this word we get our present-day term cell.**
- ➢ In actual fact, Hook had observed the **empty cell walls of dead plant tissue..**

- In 1824 **Henri Dutrochet** (1776–1847) proposed **that animals and plants had similar cell structures**.
- **Robert Brown** (1773–1858) discovered the **cell nucleus** in **1831**, and **Matthias Schleiden** (1804–1881) named the **nucleolus** (the structure within the nucleus now known to be involved in the production of ribosomes) ***around that same time***.
- Working independently, **Schleiden and Theodor Schwann** (1810–1882) described preliminary forms of the general cell theory in **1839**, the former stating that cells were the **basic unit of plants** and Schwann extending the idea to animals.

- In **1855 Robert Remak** (1815–1865) became the first to describe **cell division**. Shortly after Remak's discovery, **Rudolph Virchow** (1821–1902) stated that **all cells come from preexisting cells**. The work of ***Schleiden*, *Schwann*, and *Virchow*** firmly established the cell theory.
- In 1868 **Ernst Haeckel** (1834–1919) proposed that **the nucleus was responsible for heredity**.
- Chromosomes were named and observed in the nucleus of a **cell in 1888 by Wilhelm von Waldeyen-Hartz (1836–1921).**
- **Walther Flemming.** (1843–1905) was the first individual to **follow chromosomes through the entire process of cell division**.
- Meanwhile, ***Anton van Leeuwenhoek*** was the first to examine a drop of pond water under microscope. He observed the teeming microscopic "**animalcules**" that darted back and forth before his eyes.

- He was also the first to describe **various forms of bacteria**, which he obtained from water in which pepper had been soaked and from scrapings of his teeth.
- It wasn't until the 1830s that the *widespread importance* of cells was realized.
- In **1838**, **Matthias Schleiden**, a German *lawyer turned botanist*, concluded that , despite differences in the structure of various tissues, **plants were made of cells and that the plant embryo arose from a single cell**. But truly what is a cell?
- A cell is a membrane-bound unit that contains **hereditary** material (DNA) and **cytoplasm**; it is the basic structural and functional unit **of life**.
- **Cell theory?**

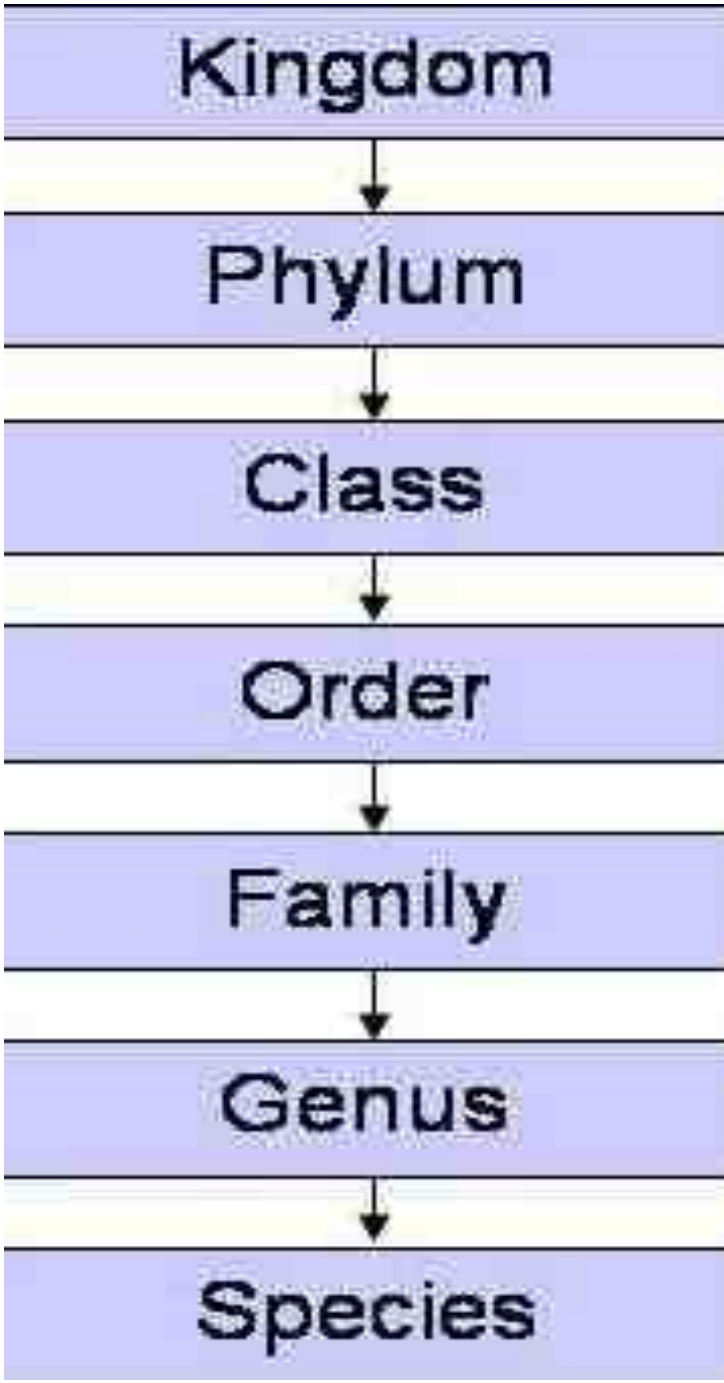
✓ The cell theory is the concept that as all living things are made up of essential units called **cells**, **they are the fundamental components of all life**.

✓ The cell is **the simplest collection of matter that can live**.

- ✓ There are diverse forms of life existing as **single celled organisms.**
- ✓ More complex organisms, including plants and animals, are **multi-cellular cooperatives composed of diverse specialized cells that *could not survive for long on their own***.
- ✓ All cells come **from preexisting cells** and are ***related by division to earlier cells*** that have been modified in various ways during the long evolutionary history of life on Earth.
- ✓ Everything in an organism does occurs fundamentally at the cellular level.

Why do we classify things?

- Classification provides scientists and students a way to sort and group organisms for easier study.
- All living things are placed in one of the five **KINGDOMS**...which are the most general group.
- They are then broken down into smaller groups, then smaller groups, then smaller and so on until there is just one... **SPECIES** is the most specific group...



Organisms are grouped among these five kingdoms by:

- The presence or absence of a nuclear membrane
- Unicellular (one cell) or multicellular (many cells)
- The type of nutrition used by the organism (heterotrophic or autotrophic)

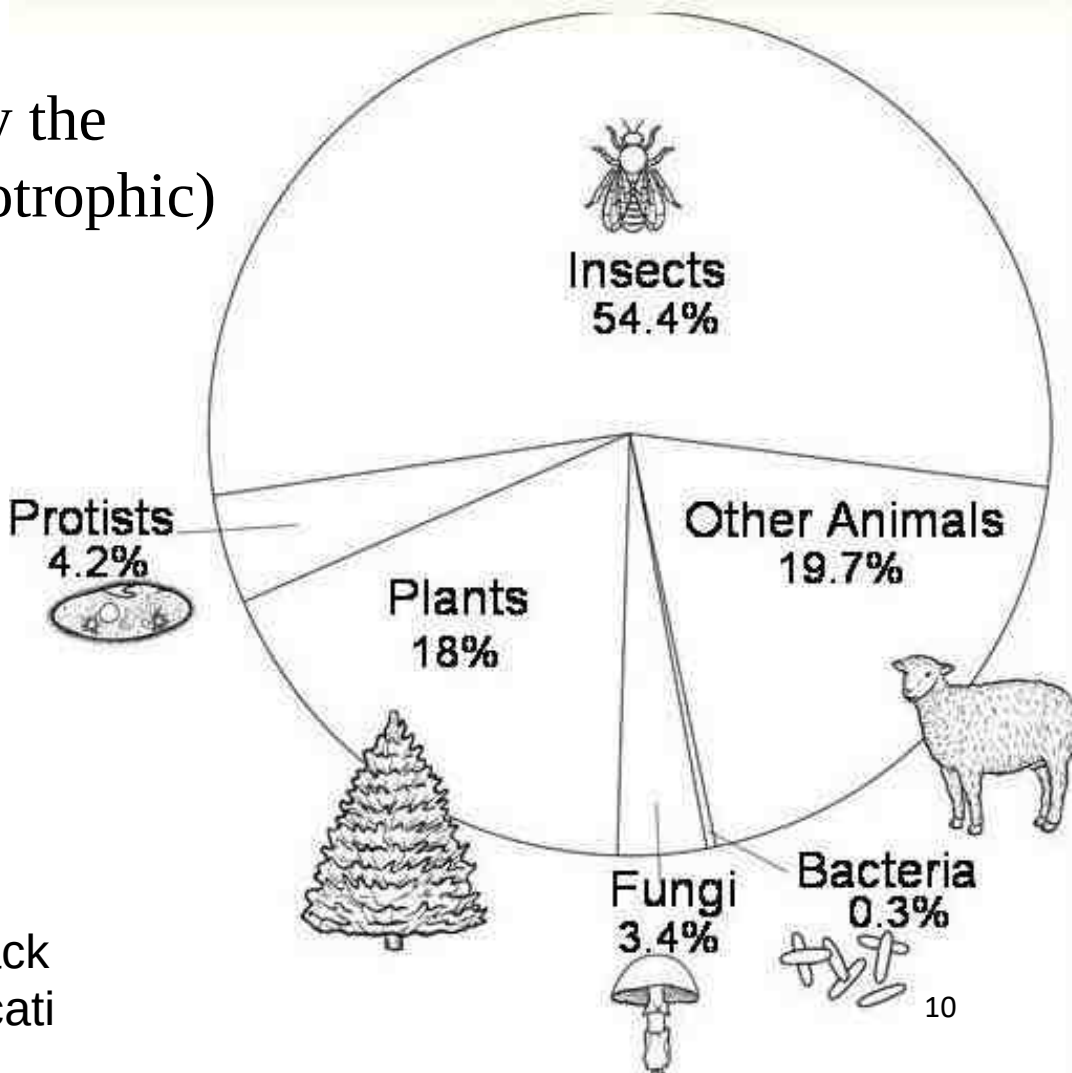
MONERA

PROTISTA

FUNGI

PLANT

ANIMAL



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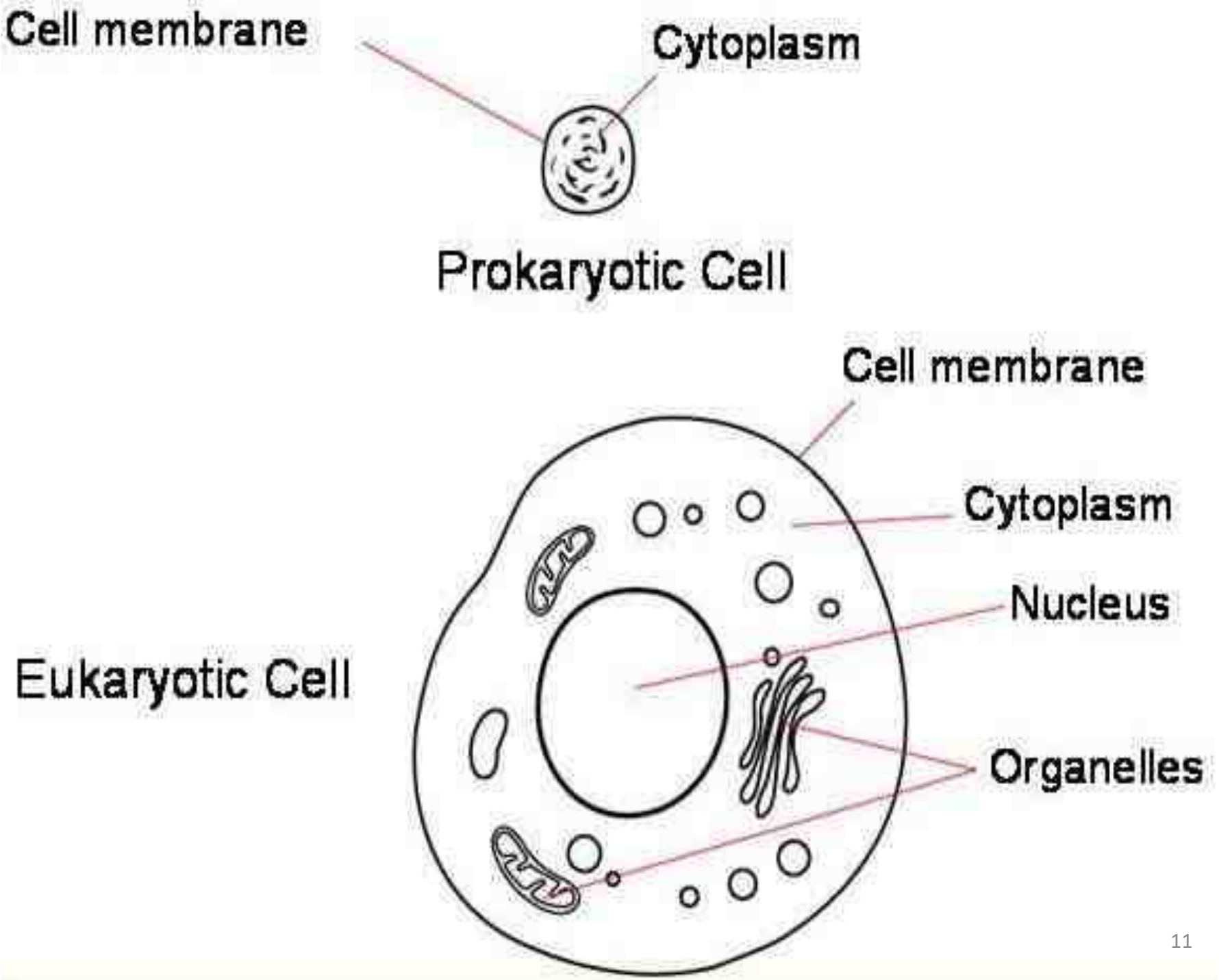

Cell membrane
Cytoplasm
Prokaryotic Cell
Cell membrane
Cytoplasm
Nucleus
Eukaryotic Cell
Organelles

- All human beings belong to a single species and an Adult human body is composed of about 100,000,000,000,000 cells.
- They are about 200 different kind of specialized cells in the human body.
- Some different types of specialized cells in the human body are: Nerve cells, epithelial cells, exocrine cells, endocrine cells, blood cells …
- Many identical cells organized together make a tissue and various tissues organized together for a common purpose make an organ
- Each of those cells has basic requirements to sustain it and the body's organ systems are largely built around providing the many trillions of cells with those basic needs.

Cell Theory

Those early scientists did experiments on living things and developed **CELL THEORY**

Main Ideas of Cell Theory

1) All living things **are made of** one or more cells

2) **Cells are the** basic units of structure & function **of living things**

3) **All cells come** from existing cells

What are cells made of? In terms of molecules

Cells are mostly **water**. **The rest** of the present ***molecules*** are:

- **protein**
- **nucleic acid**
- **carbohydrate**
- **lipid**
- **other**

What are cells made of? (in terms of elements)

By **elements**, a cell is composed

of:

- 60% **hydrogen**
- 25% **oxygen**
- 10% **carbon**
- 5% **nitrogen**

Special Cell Process:

- There are approx. 100 trillion cells in the human body
  - 100,000,000,000,000
- Cells need certain substances to stay alive

QUESTION:
How do they get these substances?

ANSWER:

- ✓ Osmosis
- ✓ Diffusion

PROKARYOTIC AND EUKARYOTIC CELLS

- **The French marine biologist Edouard Chatton (1883–1947) proposed the** terms *procariotique (prokaryotic) and eucariotique (eukaryotic)* ***in 1937***.
- Prokaryotic, meaning "**before nucleus**" was used to describe **bacteria** and eukaryotic meaning "**true nucleus**" was used to describe all other cells.

- Prokaryotes fall into two different domains of the kingdom Monera : **Archaea** and **bacteria.**
- Archaebacteria have ***no peptidoglycan*** *in their cellular walls*. They also have ***odd lipids*** *in their cell walls*. Many are *able to* ***live in extreme places***.

- Eubacteria ***have peptidoglycan*** in their cell walls, and they have ***no unusal lipids***. They have **three shapes**: ***bacilli*** , **cocci** , and ***spirilli***.
- Eubacteria can also have **prefixes** before their names: **strepto**, indicating chains of the shaped bacteria, and **straphylo**, indicating clusters of the shaped bacteria. *Eubacteria are* ***tested in labratories for Gram stains***.

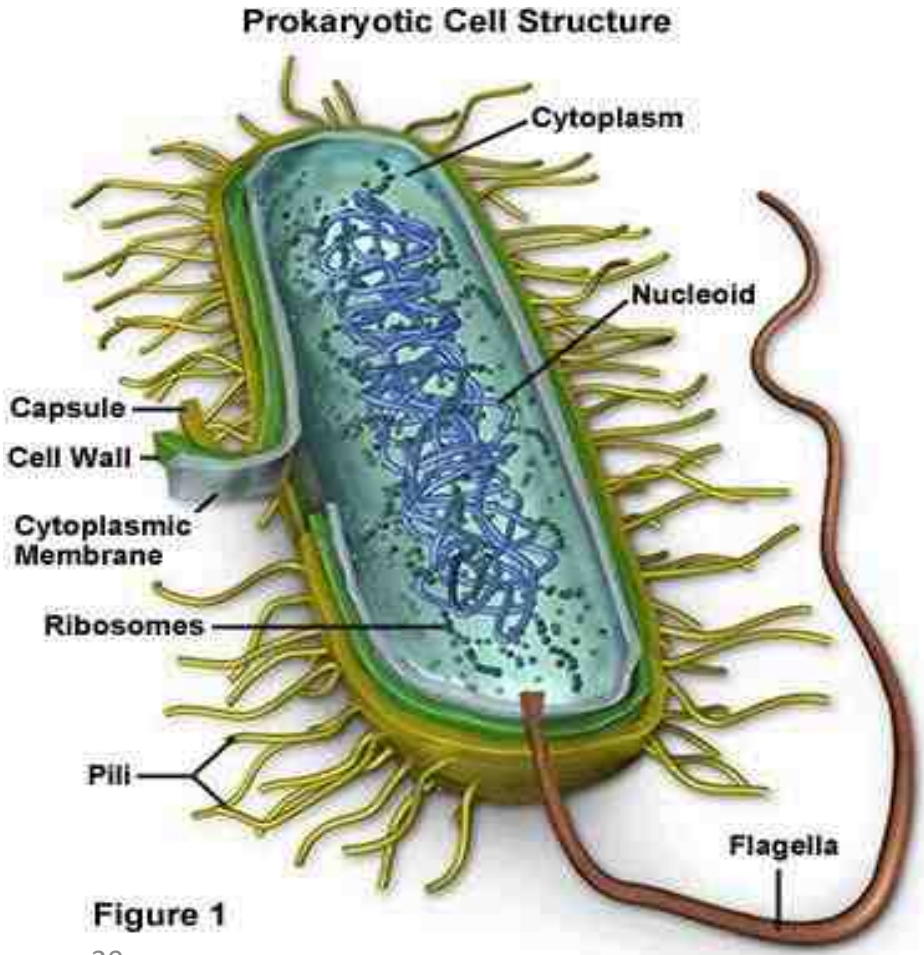
- **Reproduction** is either through **binary fission** (splitting of a cell with **no variety in its genes**) or through several **other forms** that produce genetic variety.

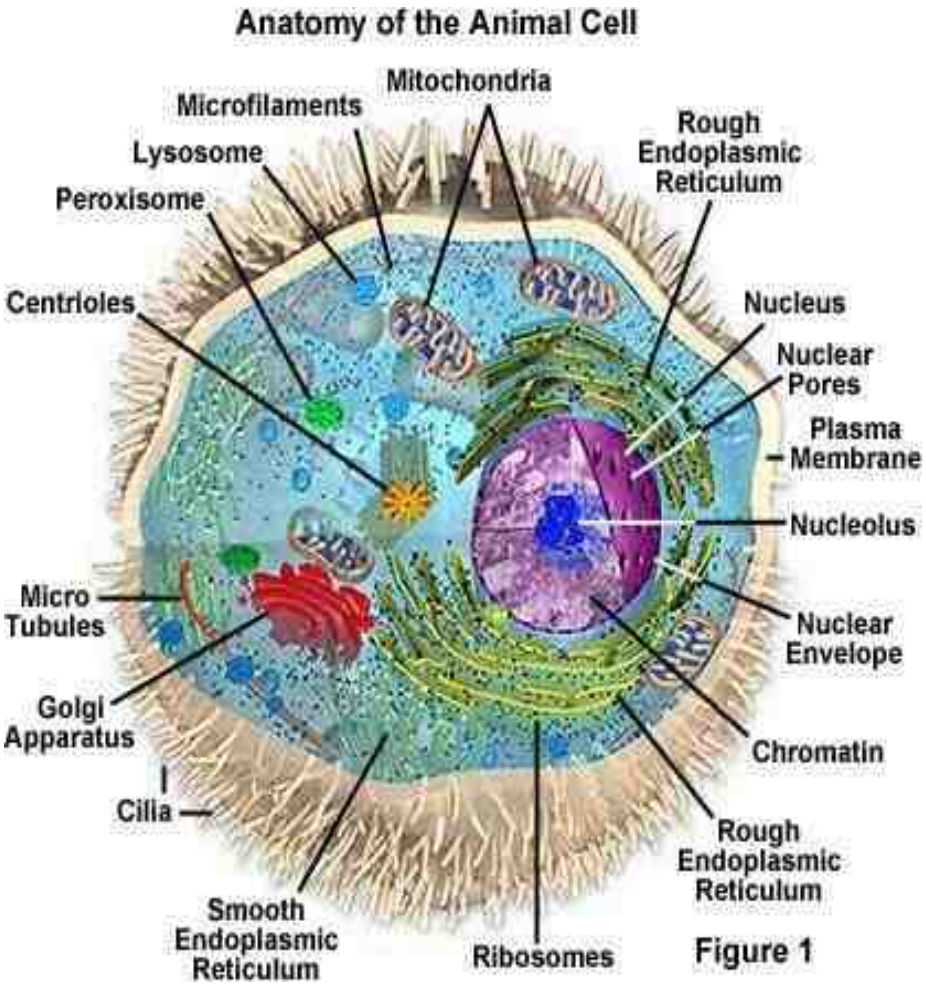
- Bacteria produce **poisons** that can cause sickness: **exotoxins**, which are given off by the Gram positive bacteria, and **endotoxins,** which are given off by Gram negative bacteria as they die.

EUKARYOTES

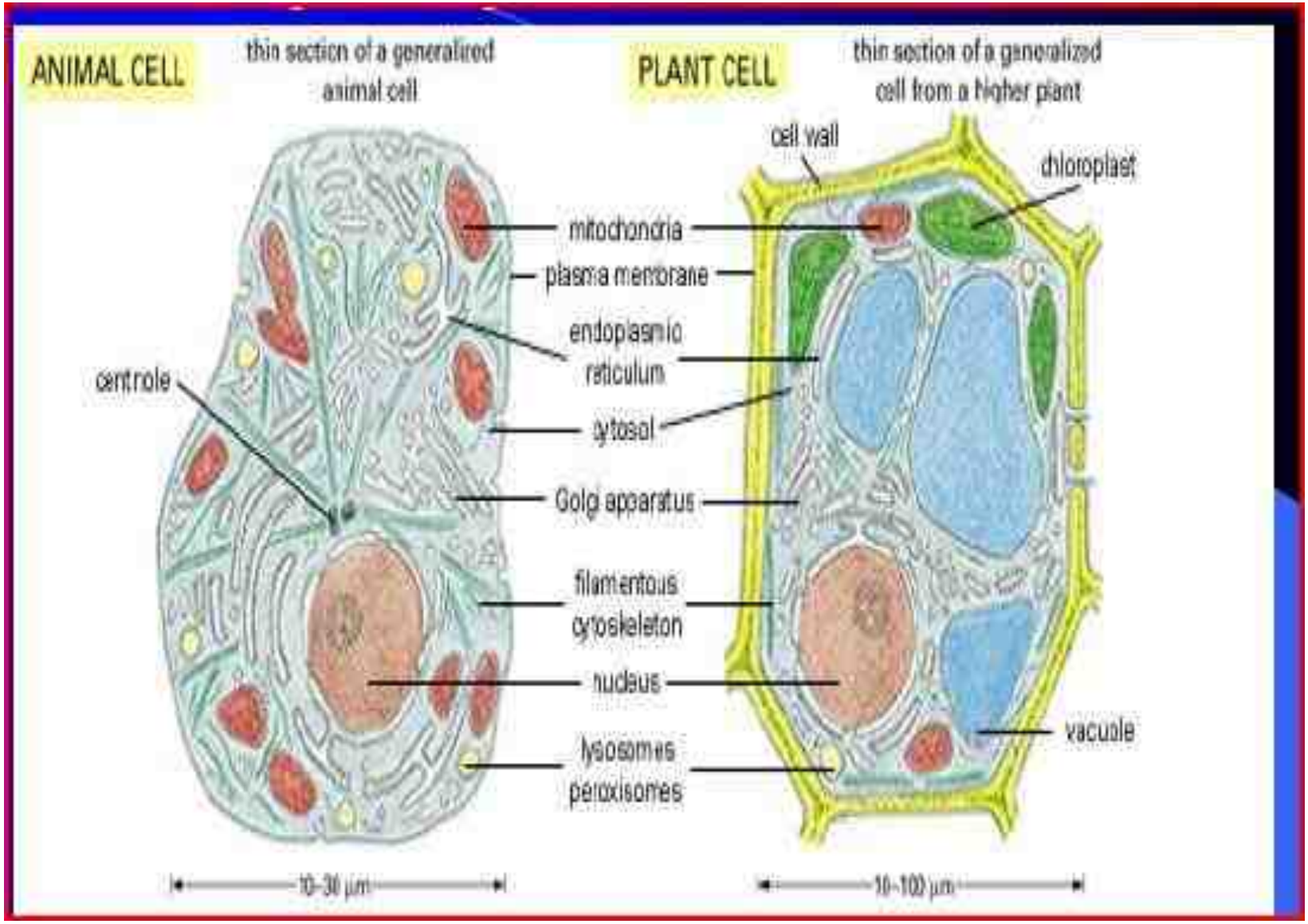
- **Eukaryotes** are cells with a ***distinct nucleus***, a structure in which the genetic material (DNA) is contained, surrounded by a membrane much like the outer cell membrane.

Prokaryotic vs Eukaryotic





ANAMAL VS PLANT CELL



Cell Membrane

OUTLINE

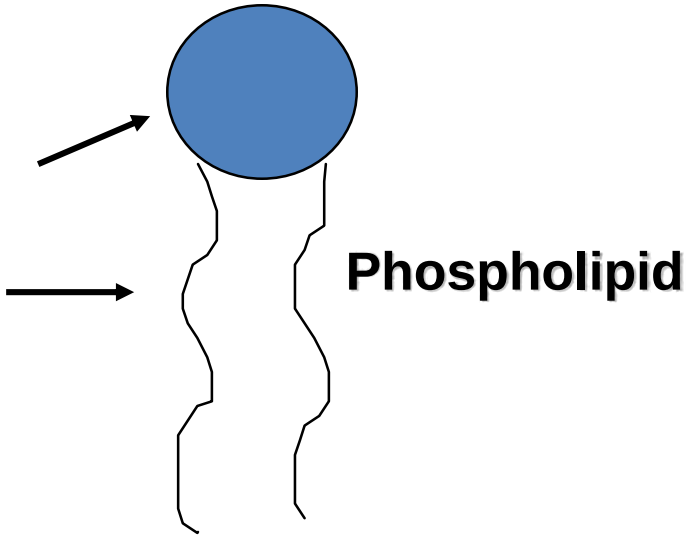
- Phospholipid Bilayer
- Fluid Mosaic Model
- Membrane Proteins
- Diffusion
- Facilitated Diffusion
- Osmosis
- Bulk Transport
- Active Transport

Plasma/Cell Membrane

- Boundary that separates the **living cell** from it's **non-living** surroundings.
- **Phospholipid bilayer**
- **Amphipathic -** having both:

  hydrophilic heads

  hydrophobic tails
- ~8 nm thick
- **Is a dynamic structure**



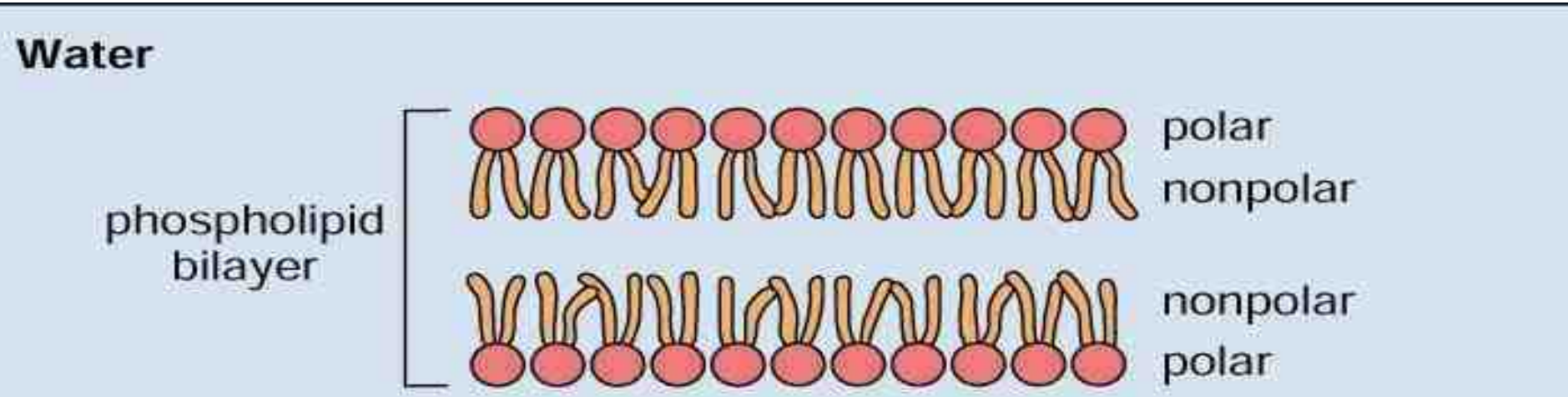
PLASMA MEMBRANE STRUCTURE

- Phosphate group makes the head polar and are hydrophilic.
- The two fatty acid tails are non-polar and hydrophobic.
- The phospholipids are arranged in such a way that the polar heads can be closest to the water molecules and the non-polar tails can be farthest away from the water molecules.

History of the Membrane Idea

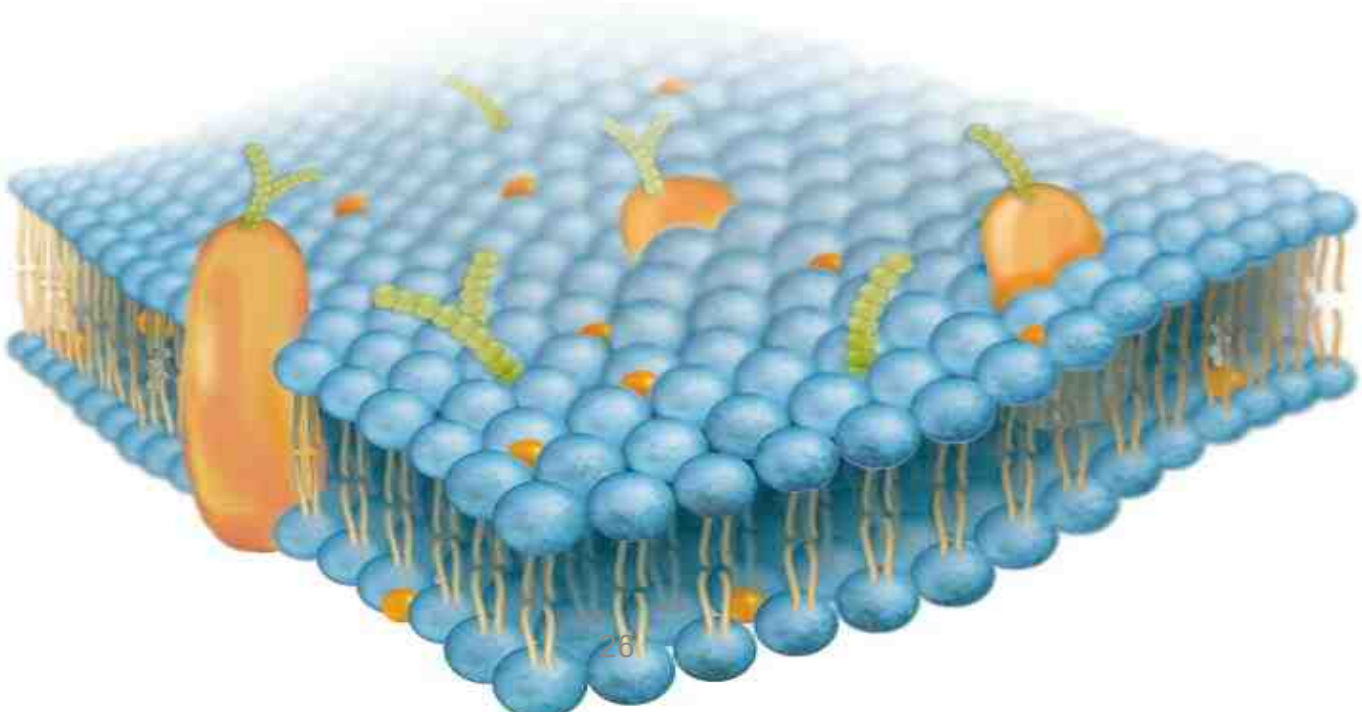
- 1925-Gorter & Grendel-. ***hydrophobic tails inward***
- 1940s-Daniel and Davson-**Sandwich model**:

  (*protein, phospholipid, and protein*.)
- 1972-Singer and Nicholson-**fluid mosaic model.**

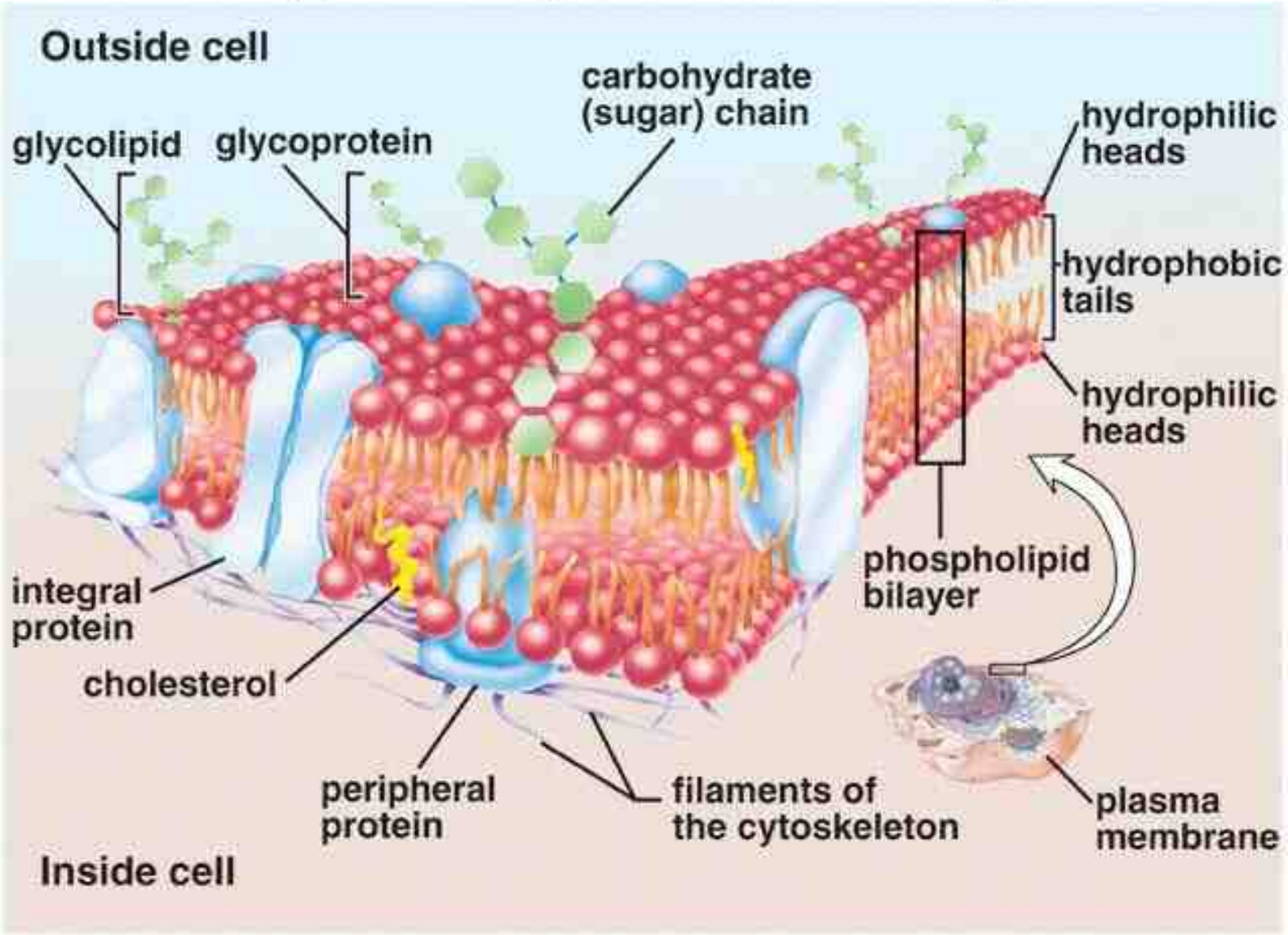


FLUID MOSAIC MODEL

- **The components of the plasma membrane are in constant motion (fluid)**
- **The different substances in the plasma membrane creates a pattern (mosaic) on the surface**

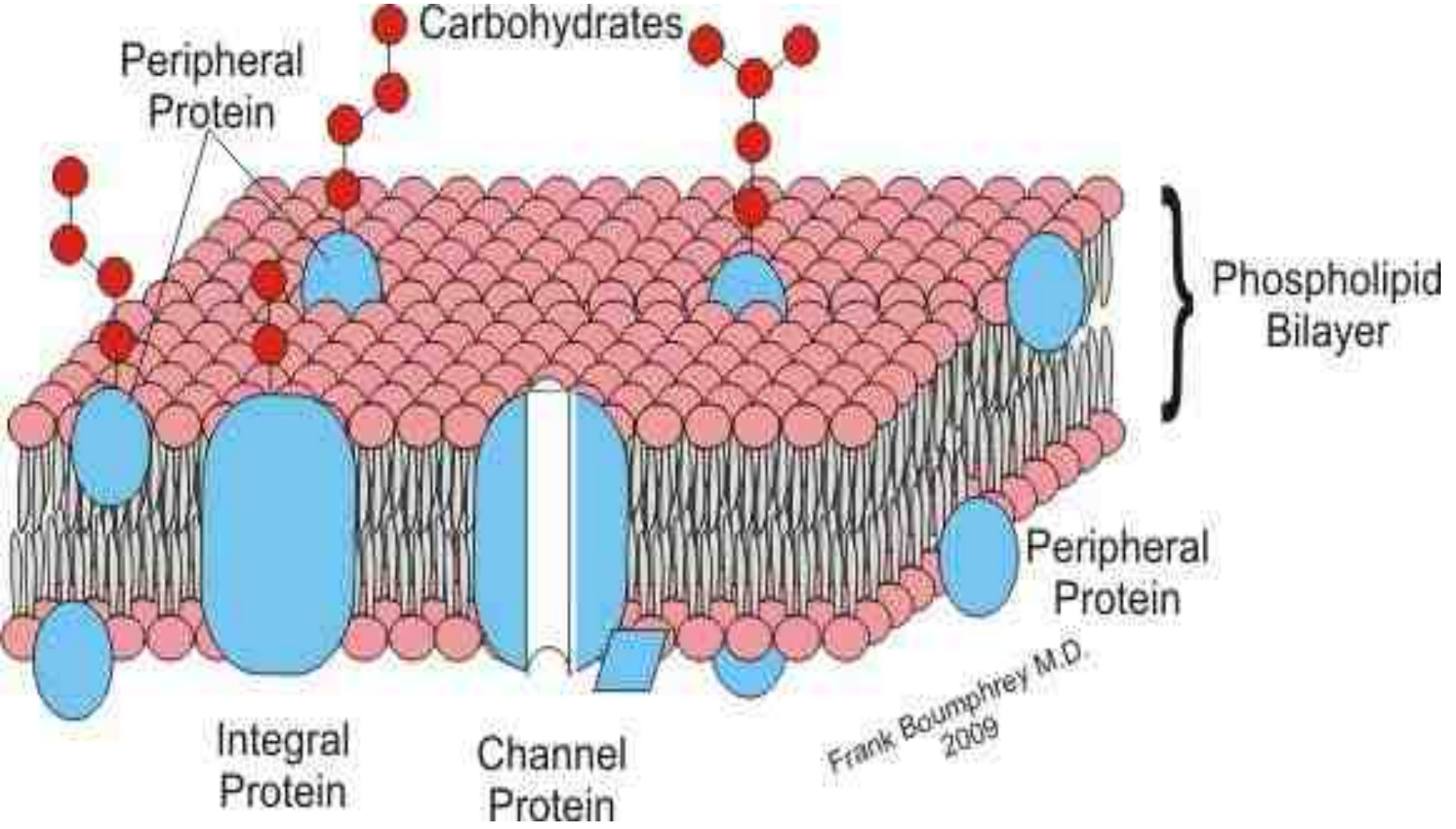


Fluid-Mosaic Model



Plasma Membrane Structure

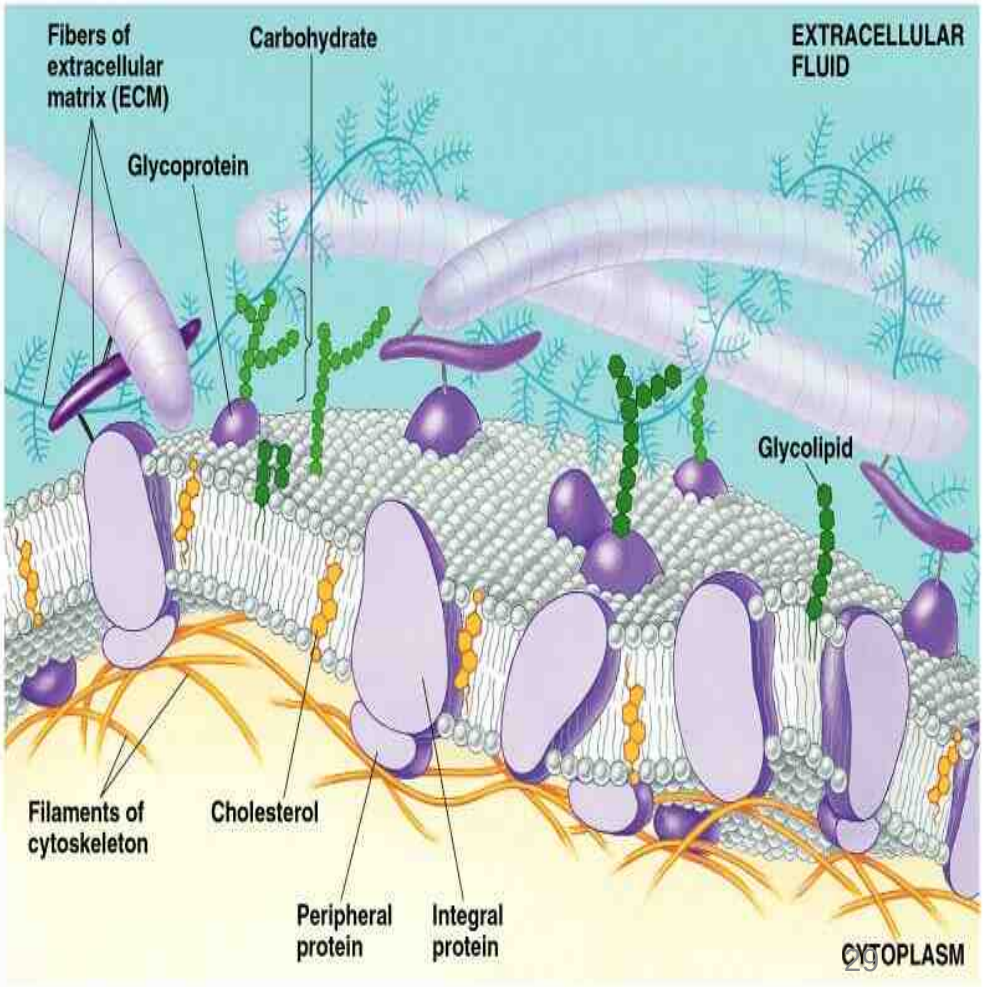
- Proteins may be peripheral or integral.



CARBOHYDRATE CHAINS

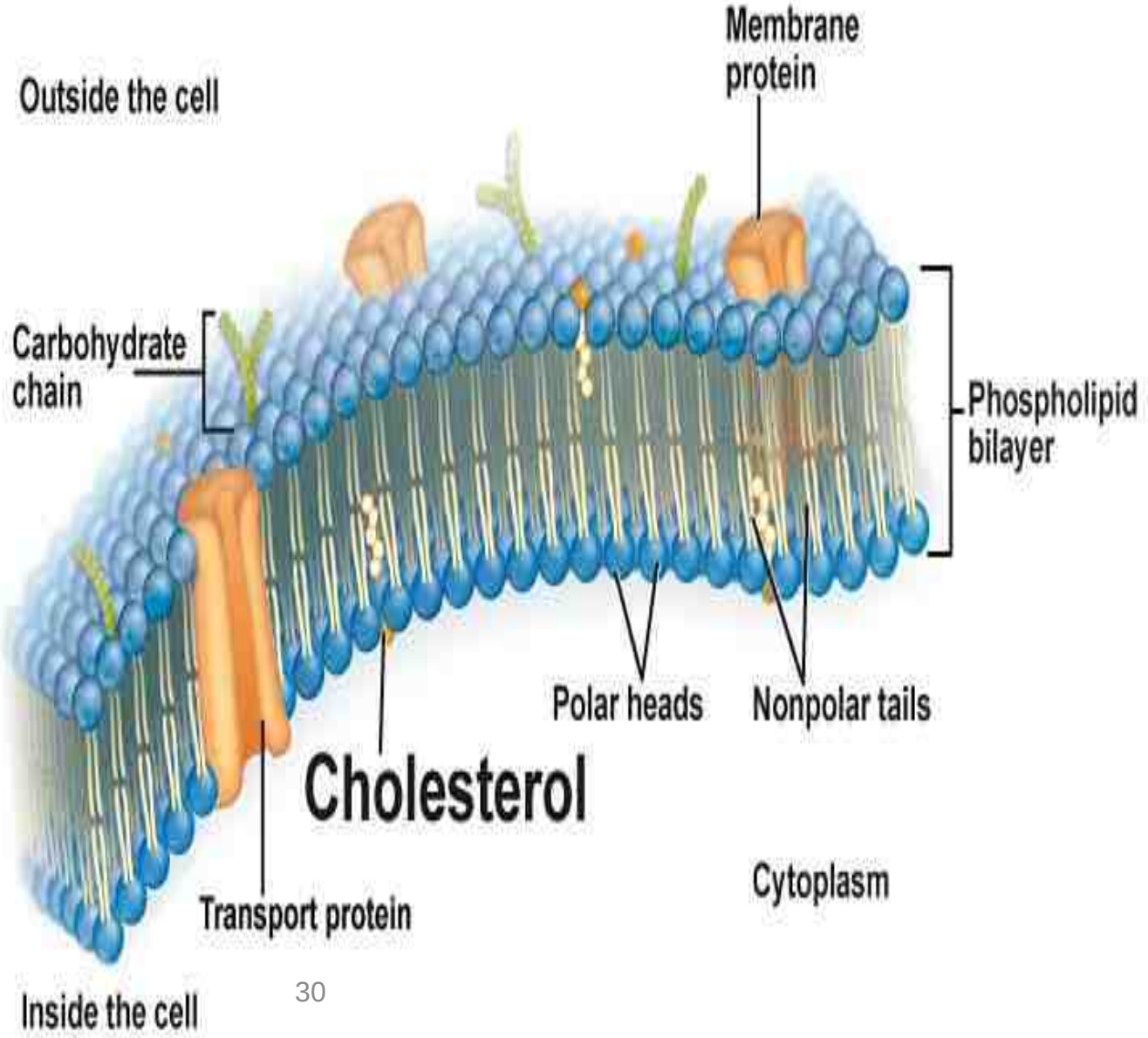
In animal cells, the carbohydrate chains give the cell a "sugar coat," called the **glycocalyx** which helps

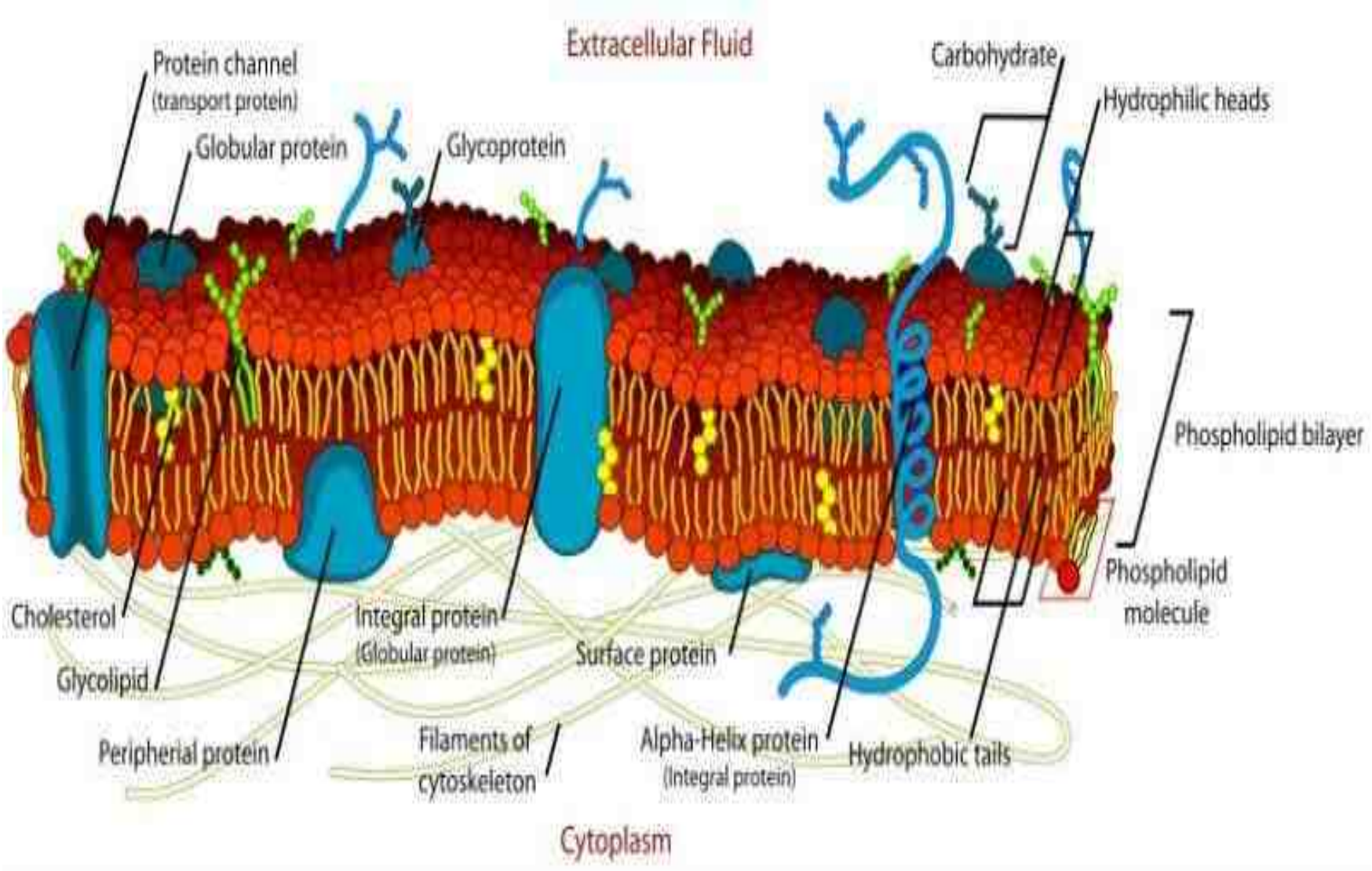
- protect the cell
- adhesion between cells
- in the reception of signal molecules
- cell-to-cell recognition.
- give a "fingerprint" (tissue rejection)
- give rise to A, B, and O blood groups



Cholesterol

- Prevents fatty acid tails of the phospholipid bilayer from sticking together





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MEMBRANE FUNCTIONS

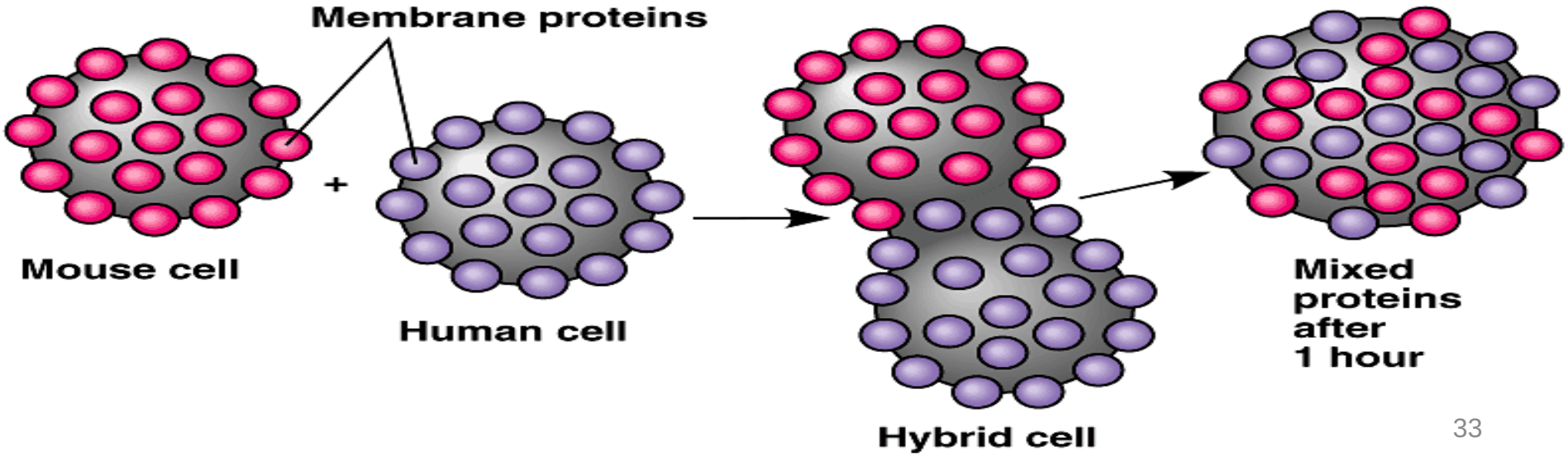
- **Protection**:Protects the cell, helps in cell movement, secretion, and in transmitting impulses.

- **Communication**: Receives chemical messages from other cells, e.g. hormones, growth factors, neurotransmitters.

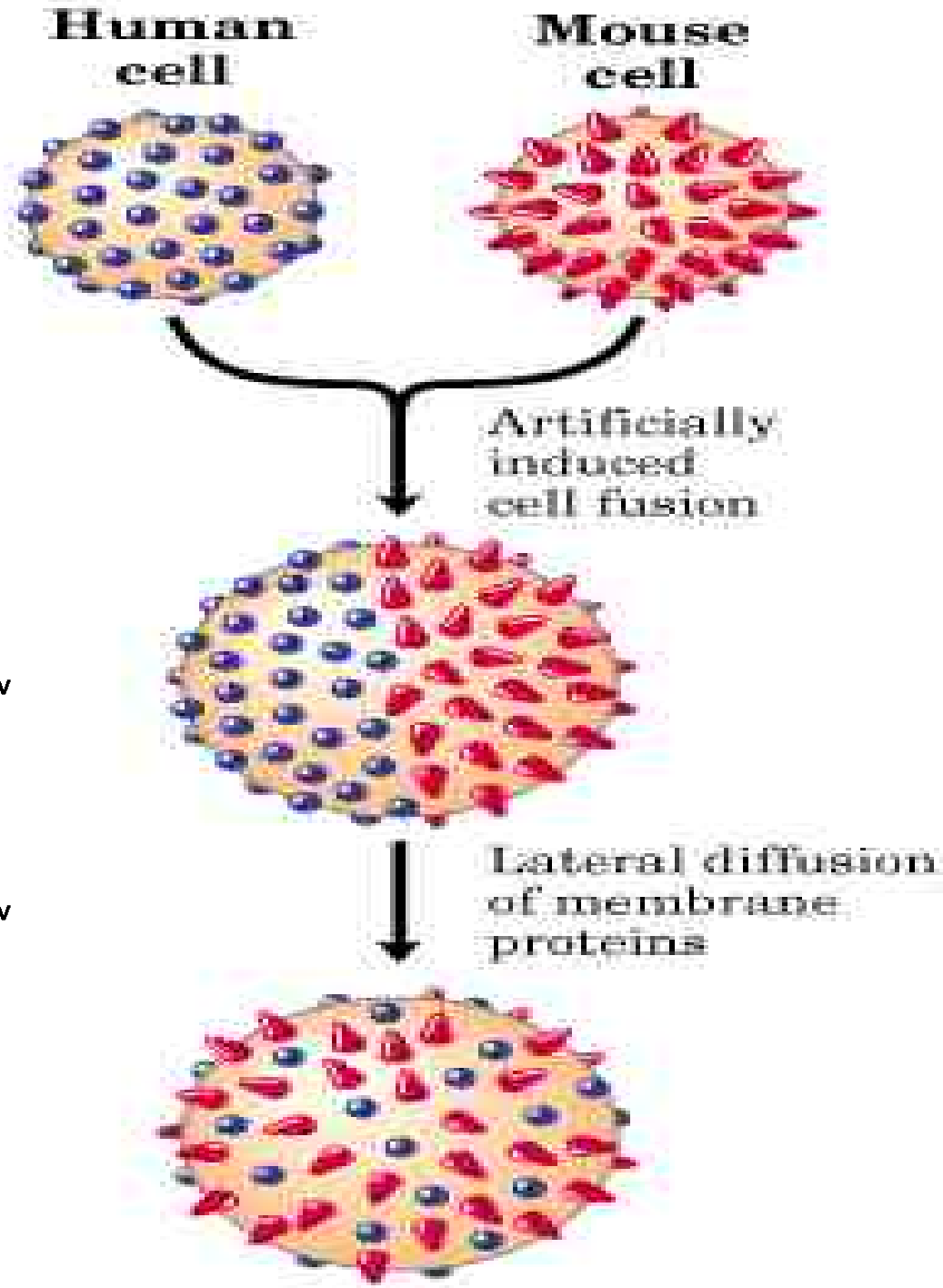
- **Selectively** allow substances in: Regulates the passage of materials into and out of the cell.
- **Respond to environment**:
- Recognition:

PLASMA MEMBRANE AS A FLUID

- At body temperature, **consistency of olive oil**.
- Each phospholipid molecule **can move sideways at ~ 2 mm/s**
- Most **proteins are free to drift along it**.
- Cholesterol **stiffens and strengthens the membrane, helping to regulate fluidity.**



- The lipids and proteins in the cell membrane are not fixed in position but constantly moving.
- The proteins move laterally within the cell membrane – **lateral diffusion**
- While the lipids can move both laterally and rotate 360 degrees – **flip-flop diffusion**



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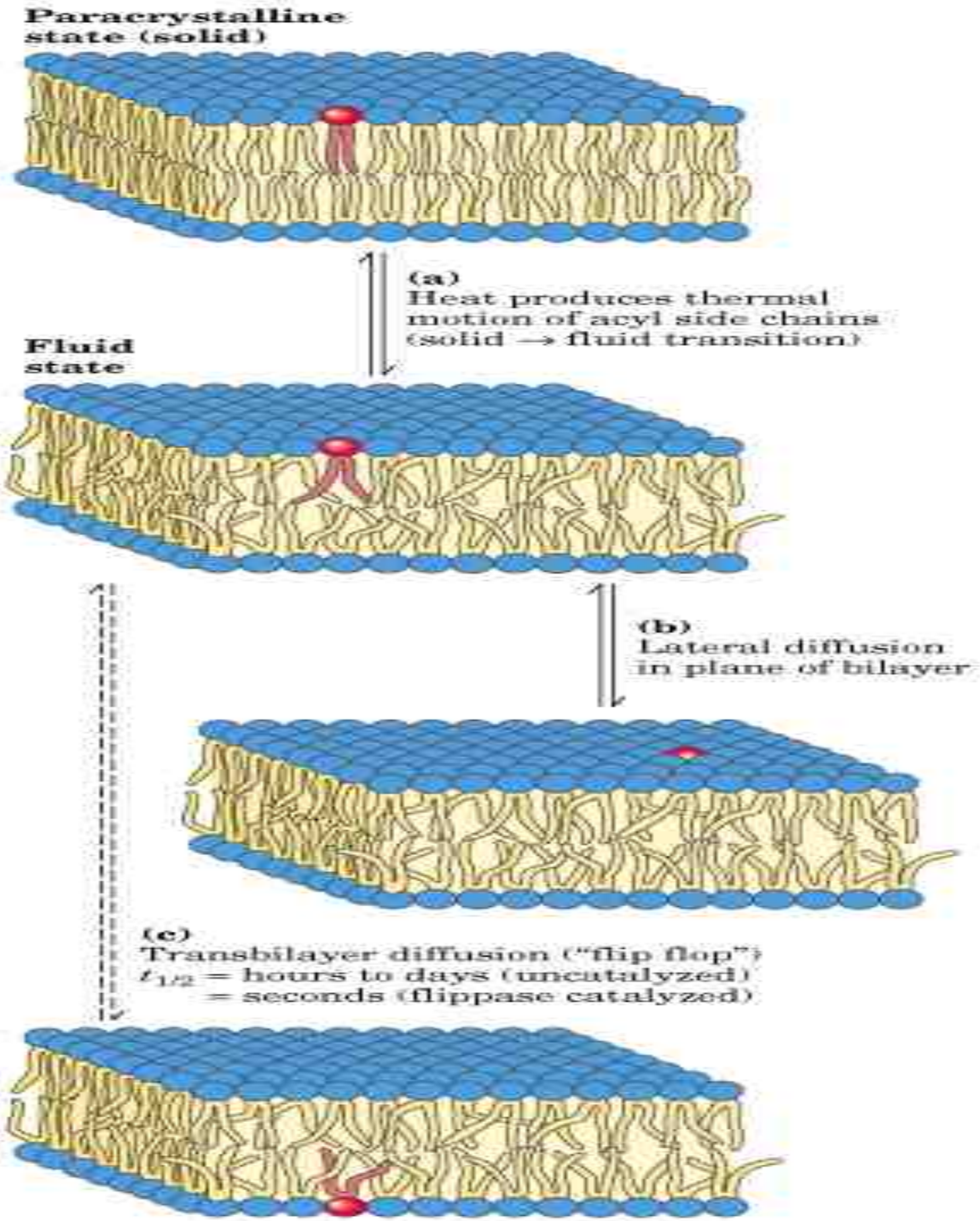
Paracrystalline state (solid)
(a) Heat produces thermal motion of acyl side chains (solid → fluid transition)
Fluid state
(b) Lateral diffusion in plane of bilayer
(c) Transbilayer diffusion ("flip flop")
$t_{1/2}$ = hours to days (uncatalyzed)
= seconds (flippase catalyzed)

PROTEINS—FOR FUNCTION

- Transport
- Receptors
- Enzymes
- Signal Transducers
- Support

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Protein Functions

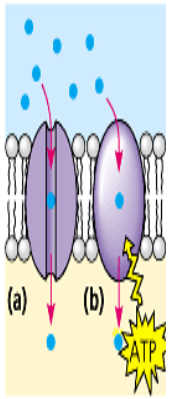
Channel Proteins - pass molecules through

Carrier Proteins - bond with substance to help it through

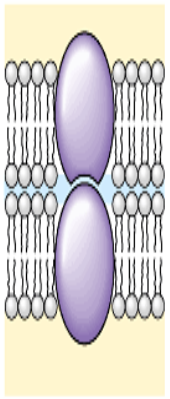
Cell Recognition Proteins - Help body recognize foreign substances and itself.

Receptor Proteins - Protein changes shape to bring about cellular change.

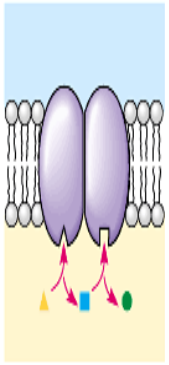
Enzymatic Proteins - Carry out metabolic reactions directly.



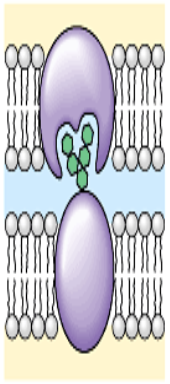
Transport



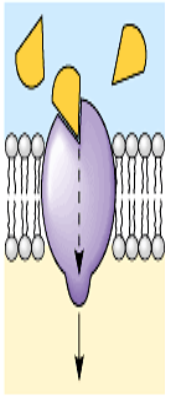
Intercellular joining



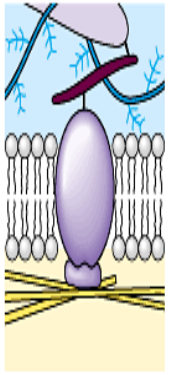
Enzymatic activity



Cell-cell recognition



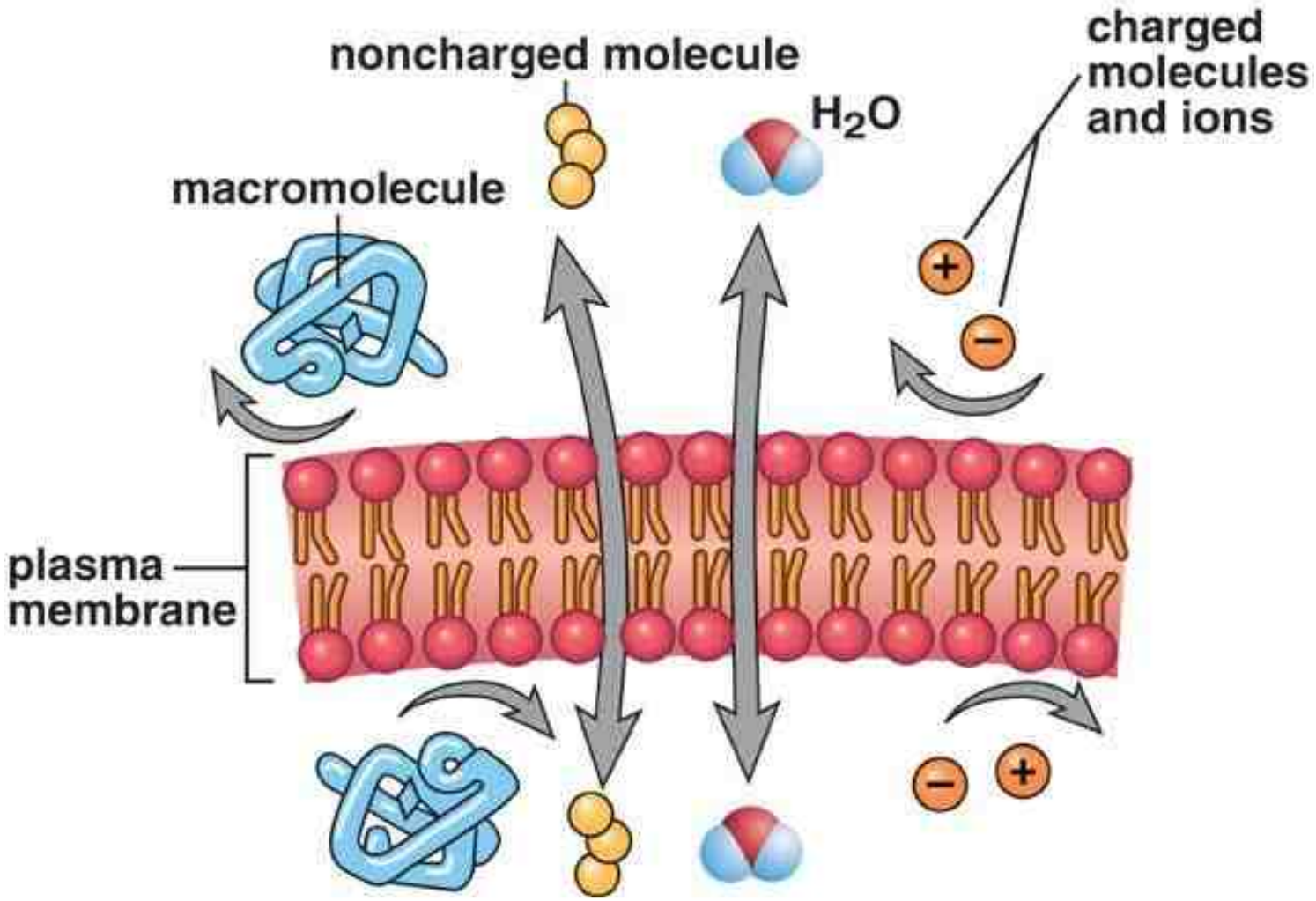
Signal transduction



Attachment to the cytoskeleton and extracellular matrix (ECM)

PERMEABILITY OF THE CELL MEMBRANE-

Differentially Permeable



Permeability of the Cell Membrane

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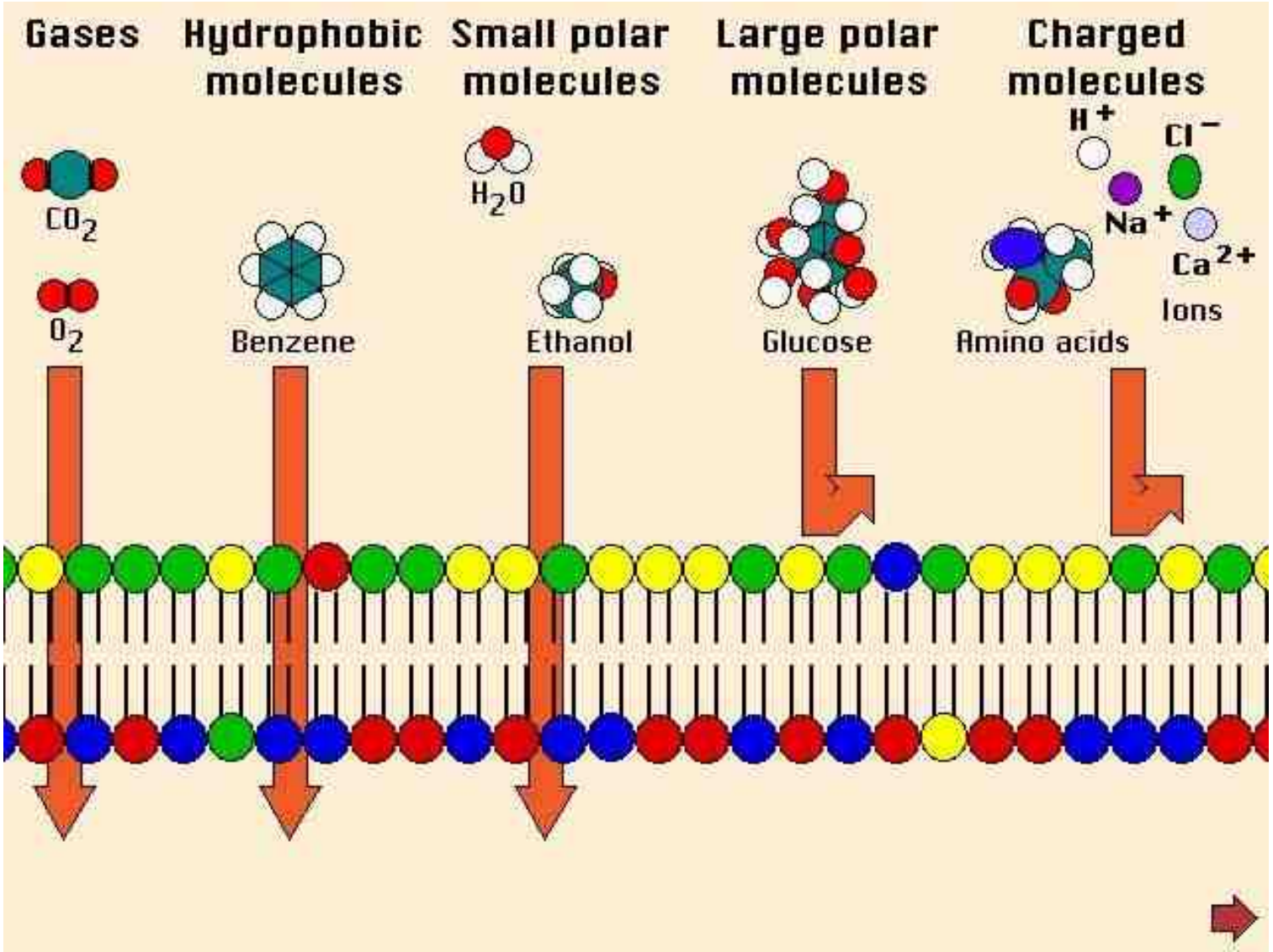
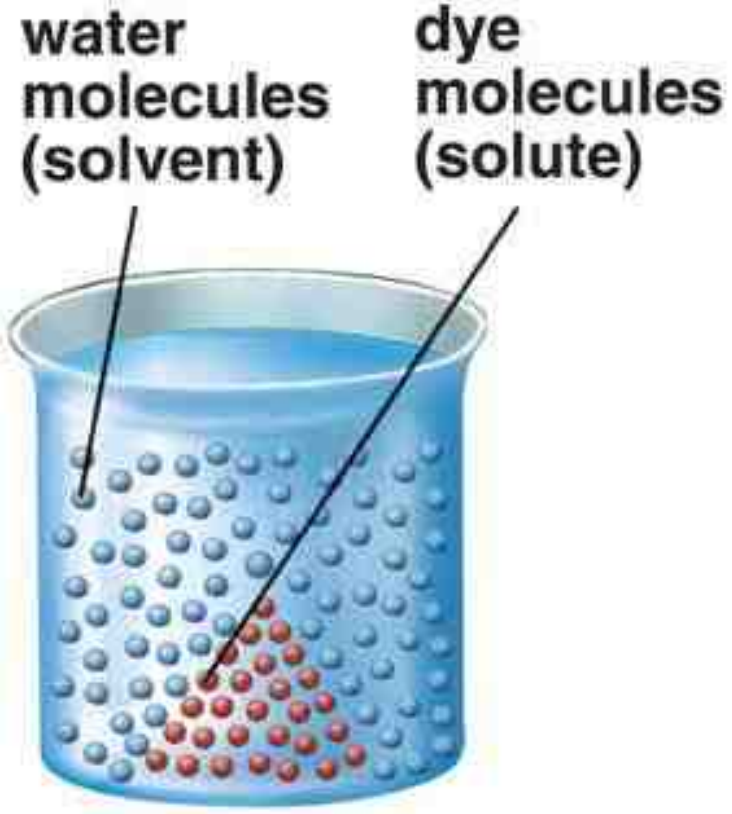


DIFFUSION

- Diffusion
  - the **passive** movement of molecules from a higher to a lower concentration until *equilibrium* is reached.
  - How can we explain diffusion?
  - Gases move through plasma membranes by diffusion.
- Osmosis– A special case of diffusion

Process of diffusion

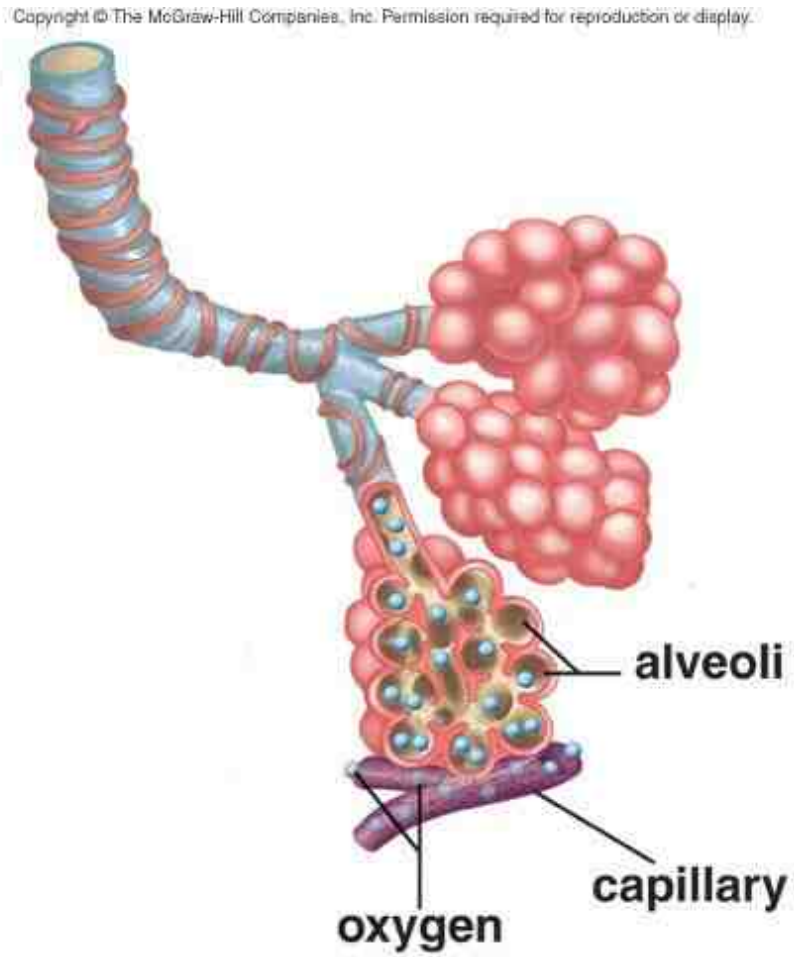


a. Crystal of dye placed in water

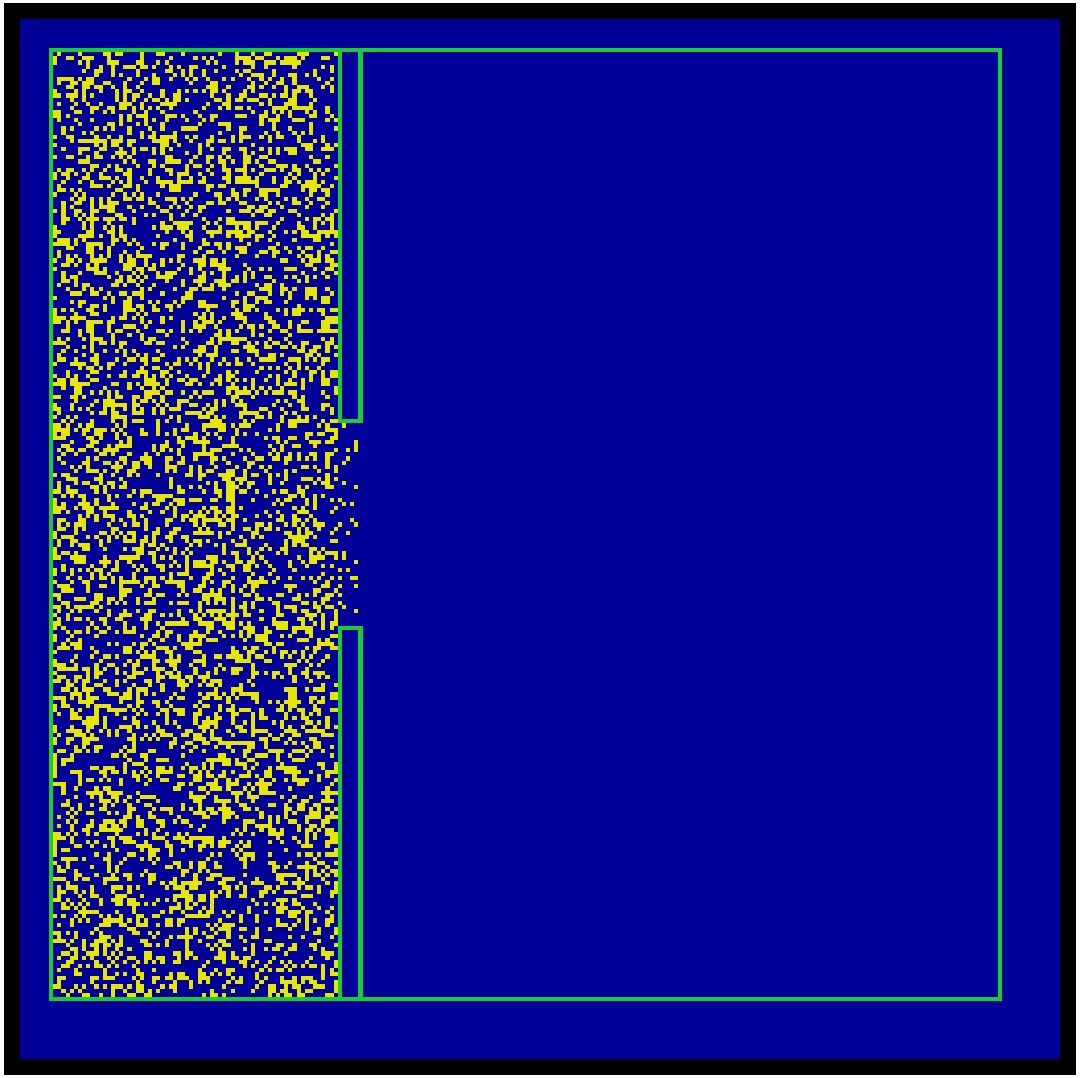
b. Diffusion of water and dye molecules

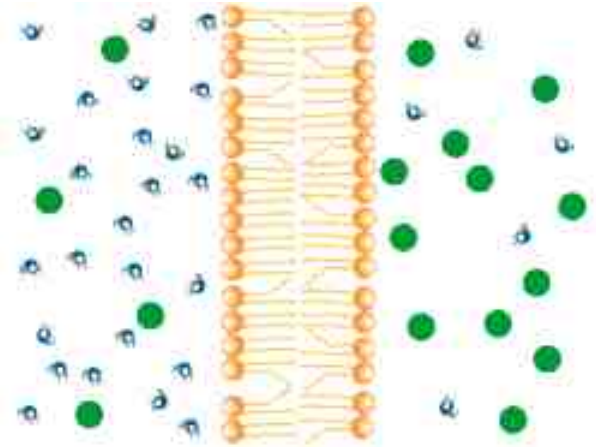
c. Equal distribution of molecules results

Gas exchange in lungs by diffusion

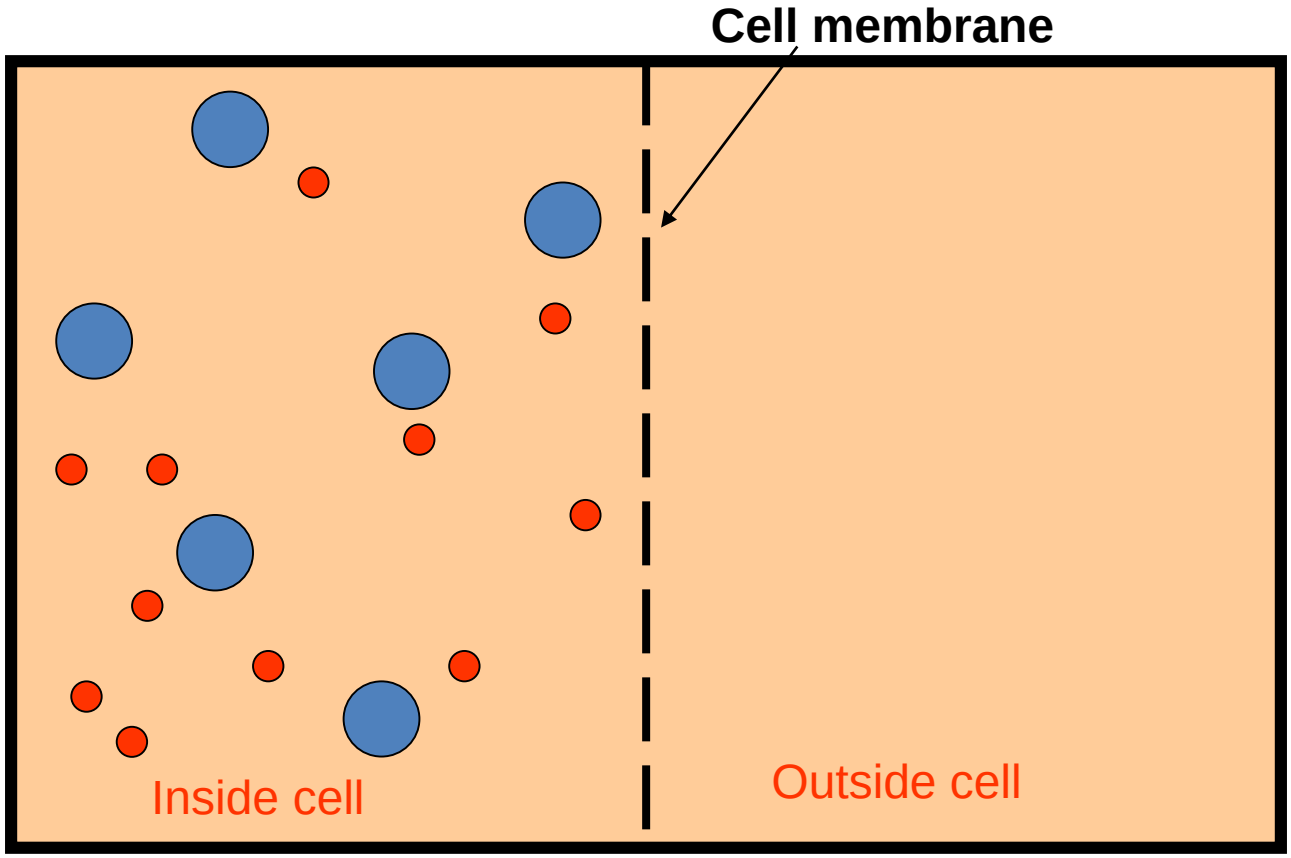


Diffusion Animation

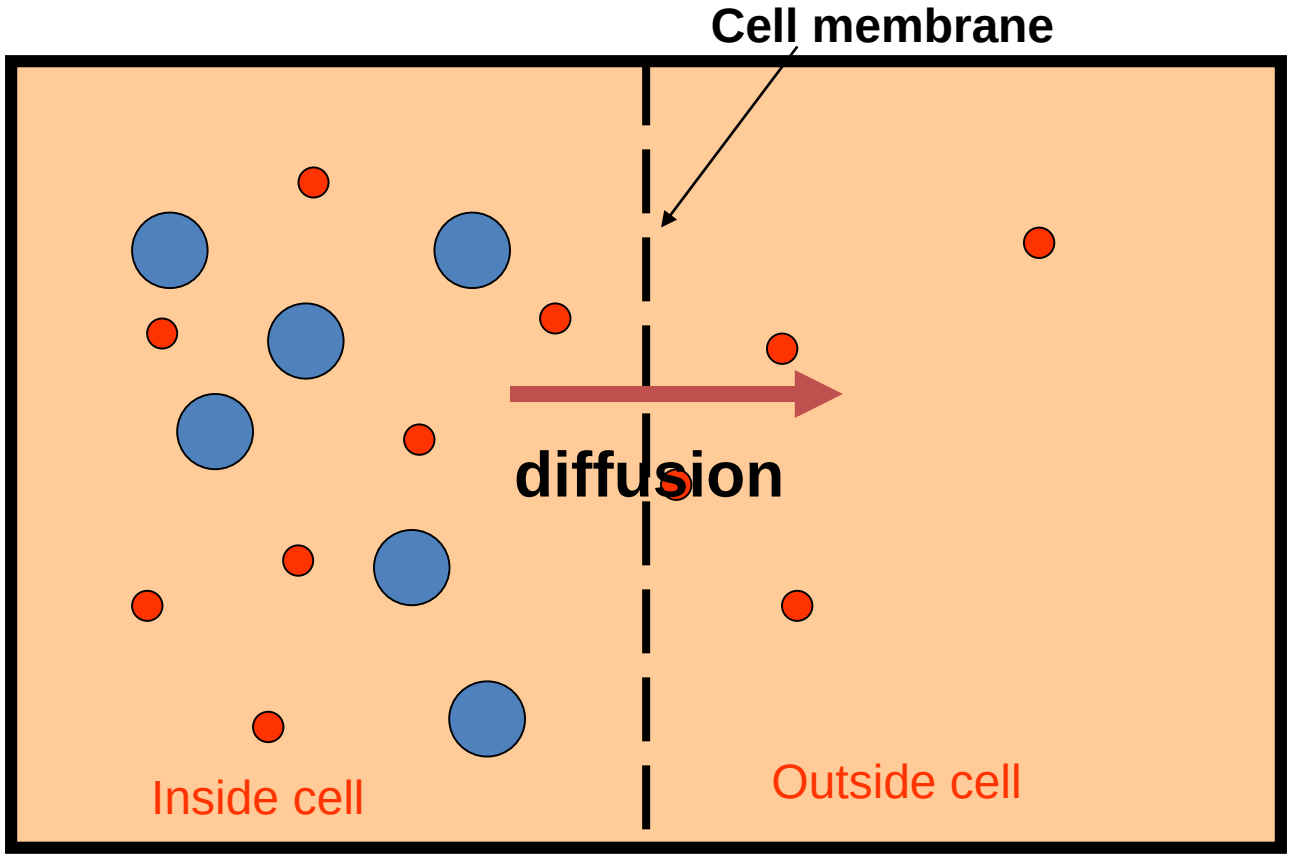




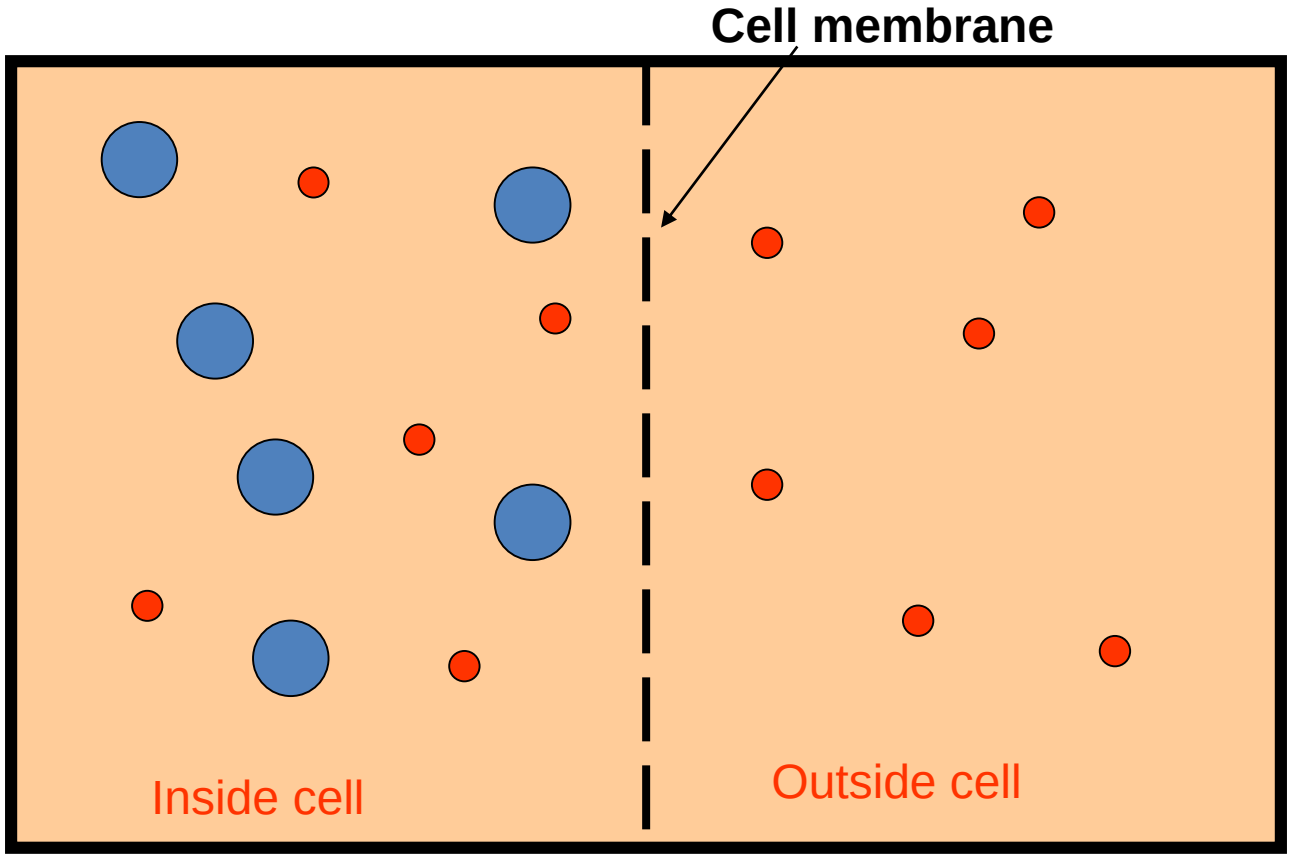
Diffusion through a membrane



Diffusion through a membrane



Diffusion through a membrane

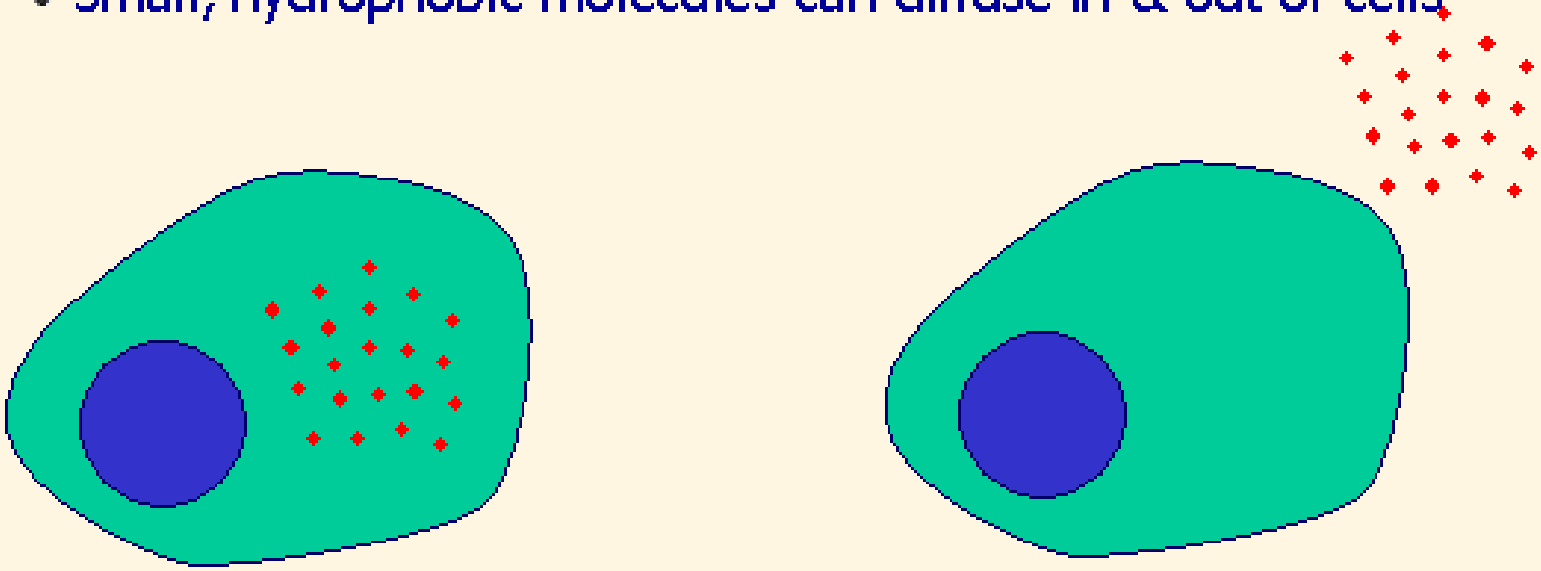


EQUILIBRIUM

How Molecules Cross the Membrane

Diffusion

- Molecules move constantly and randomly
- Over time, they will distribute themselves evenly
- Small, hydrophobic molecules can diffuse in & out of cells



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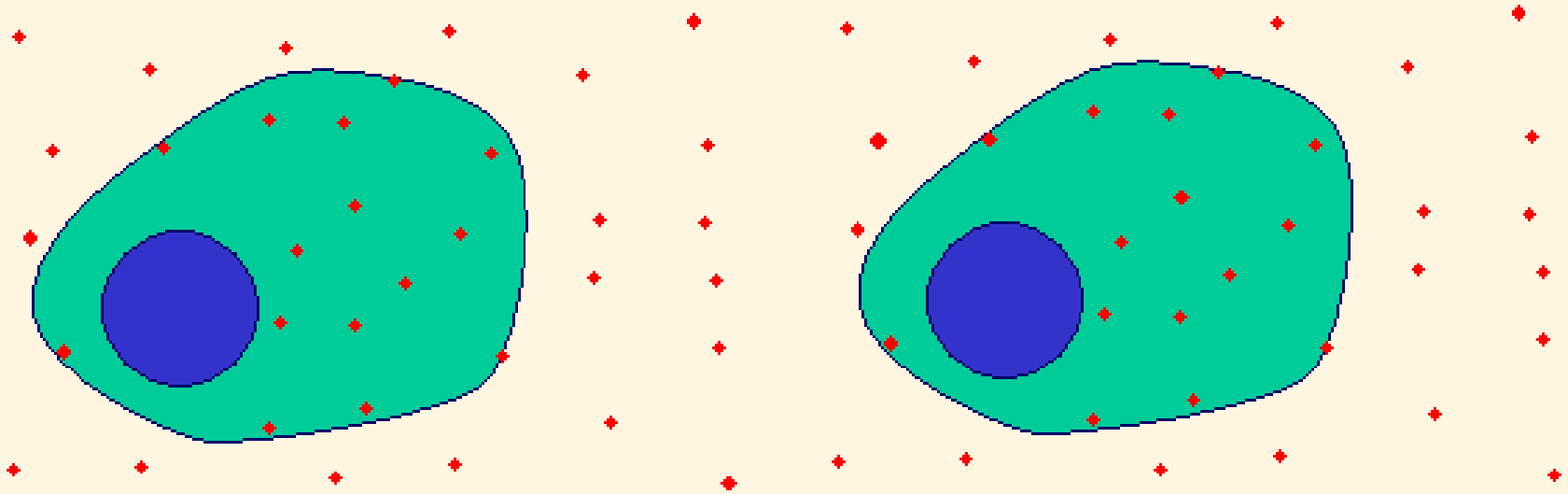


WHAT DETERMINES THE RATE OF DIFFUSION?

THERE 4 FACTORS:

1. **The steepness of the concentration gradient**. The bigger the difference between the two sides of the membrane the quicker the rate of diffusion.

2. **Temperature**. Higher temperatures give molecules or ions more kinetic energy. Molecules move around faster, so diffusion is faster.

3. **The surface area**. The greater the surface area the faster the diffusion can take place. This is because the more molecules or ions can cross the membrane at any one moment.

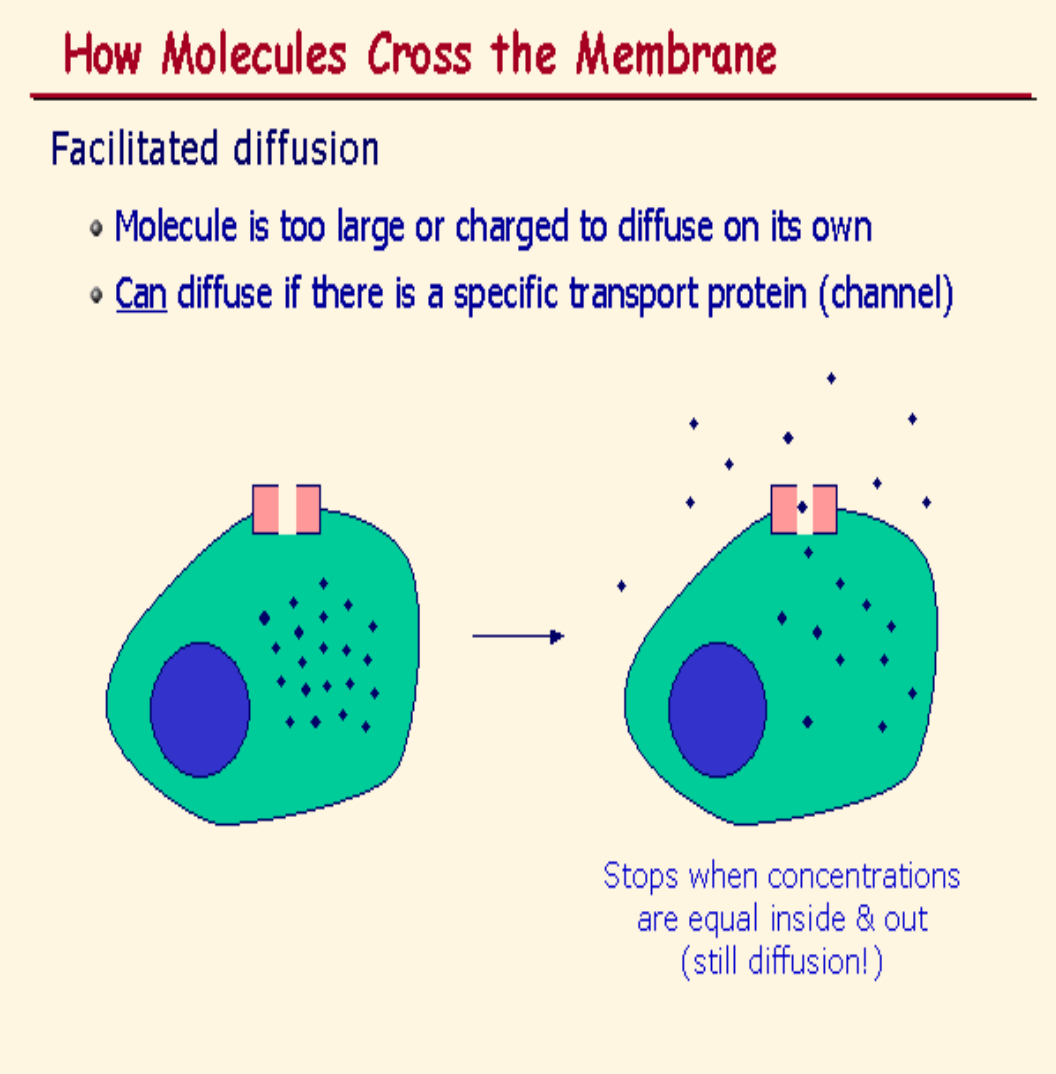
4. **The type of molecule or ion diffusing**. Large molecules need more energy to get them to move so they tend to diffuse more slowly. Non-polar molecules diffuse more easily than polar molecules because they are soluble in the non polar phospholipid tails.

Facilitated diffusion

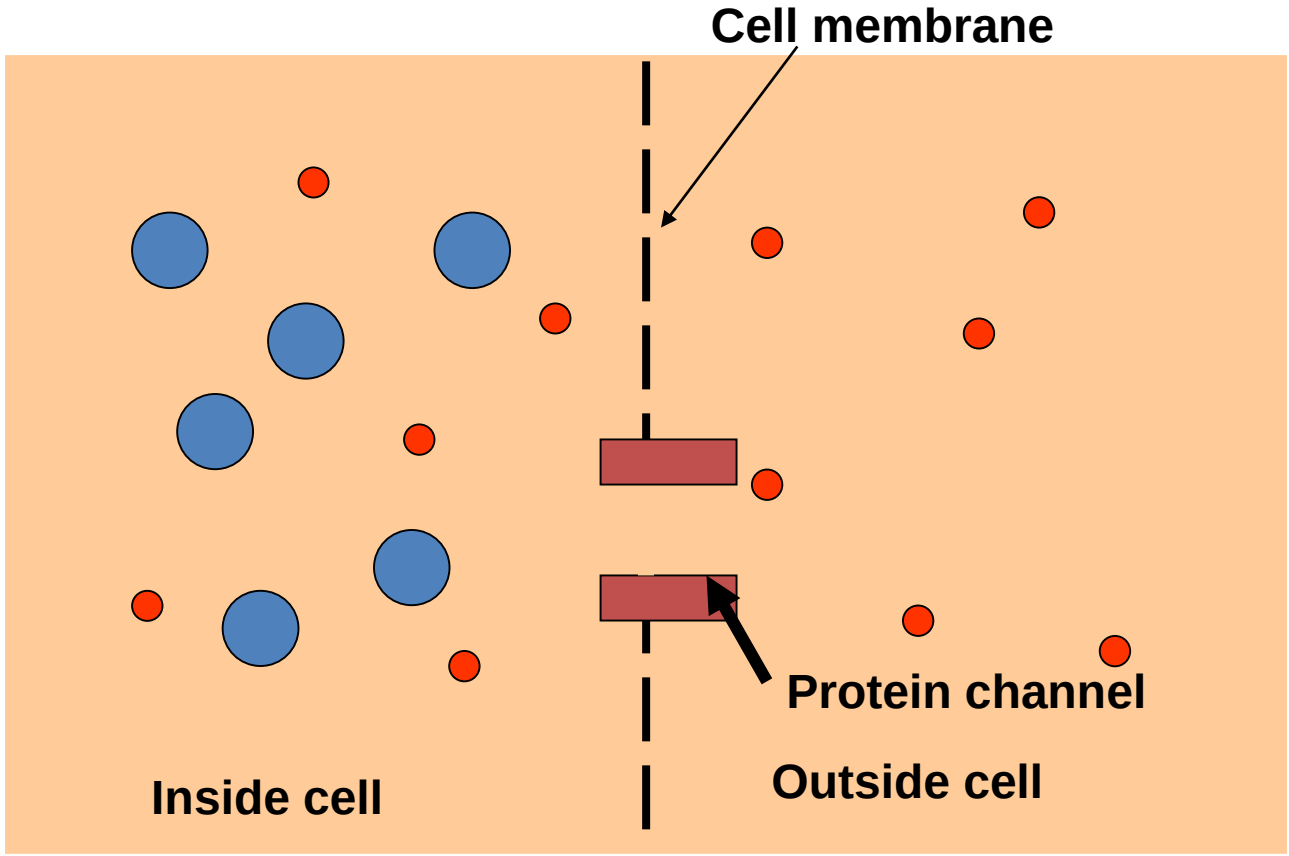
- Large polar molecules such as **glucose** and **amino acids**, cannot diffuse across the phospholipid bilayer. Also ions such as **Na^+** or **Cl^-** cannot pass.

- These molecules pass through **protein channels** instead. Diffusion through these channels is called **FACILITATED DIFFUSION.**

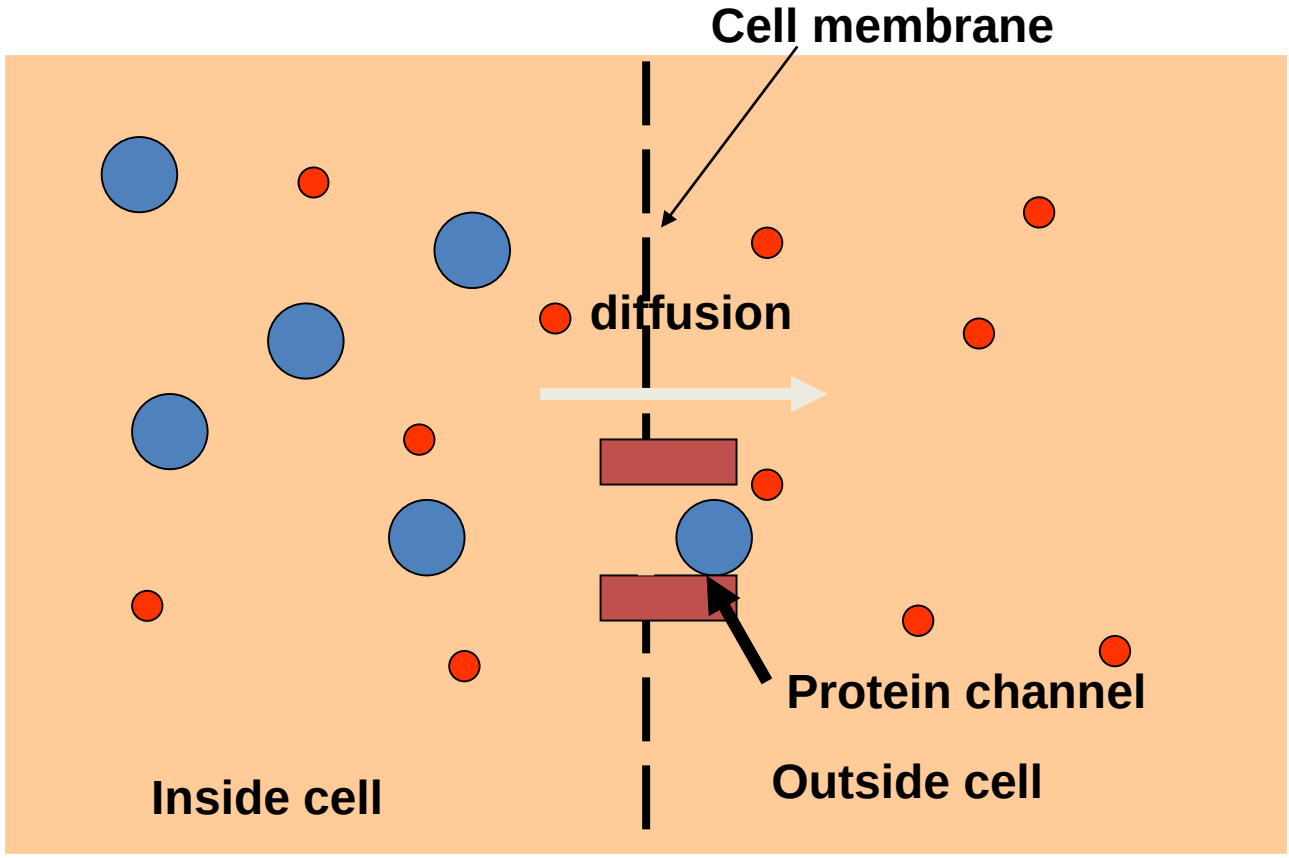
- Movement of molecules is still **PASSIVE** just like ordinary diffusion, the only difference is, the molecules go through a protein channel instead of passing between the phospholipids.



Facilitated Diffusion through a membrane



Facilitated Diffusion through a membrane



Facilitated Diffusion:

Molecules will randomly move through the opening like pore, by diffusion. **This requires no energy, it is a PASSIVE process**. Molecules move from an area of high concentration to an area of low conc.

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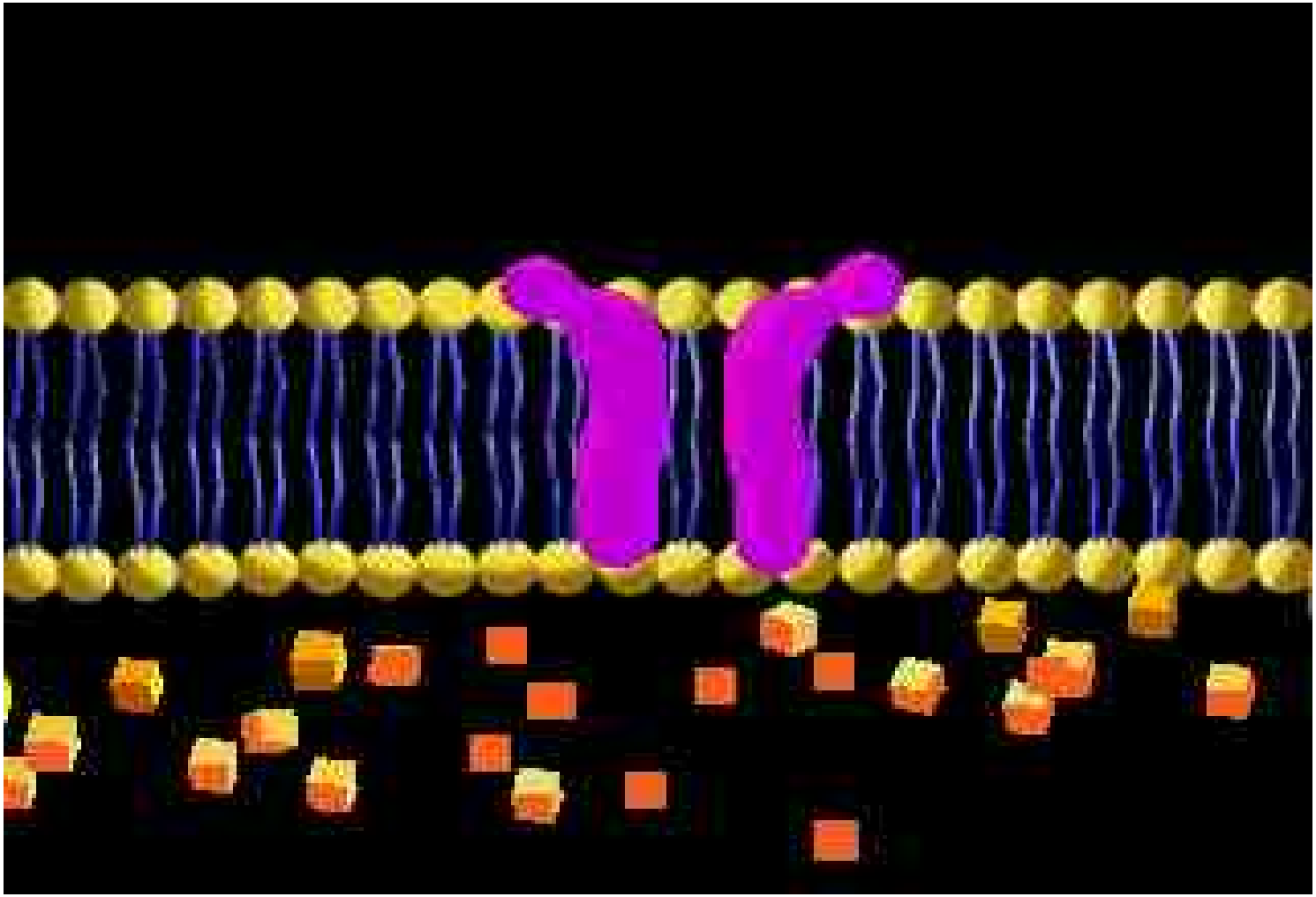
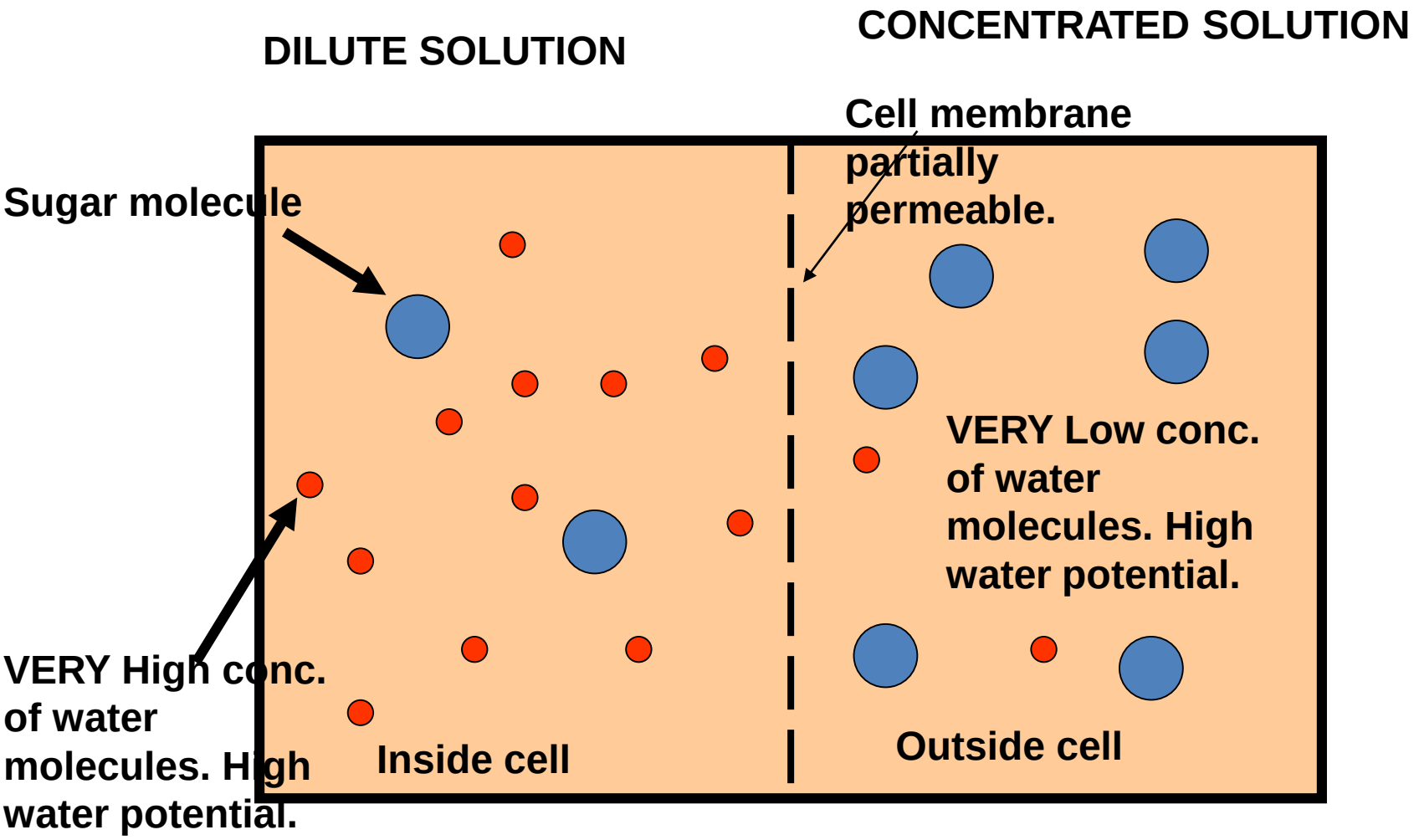


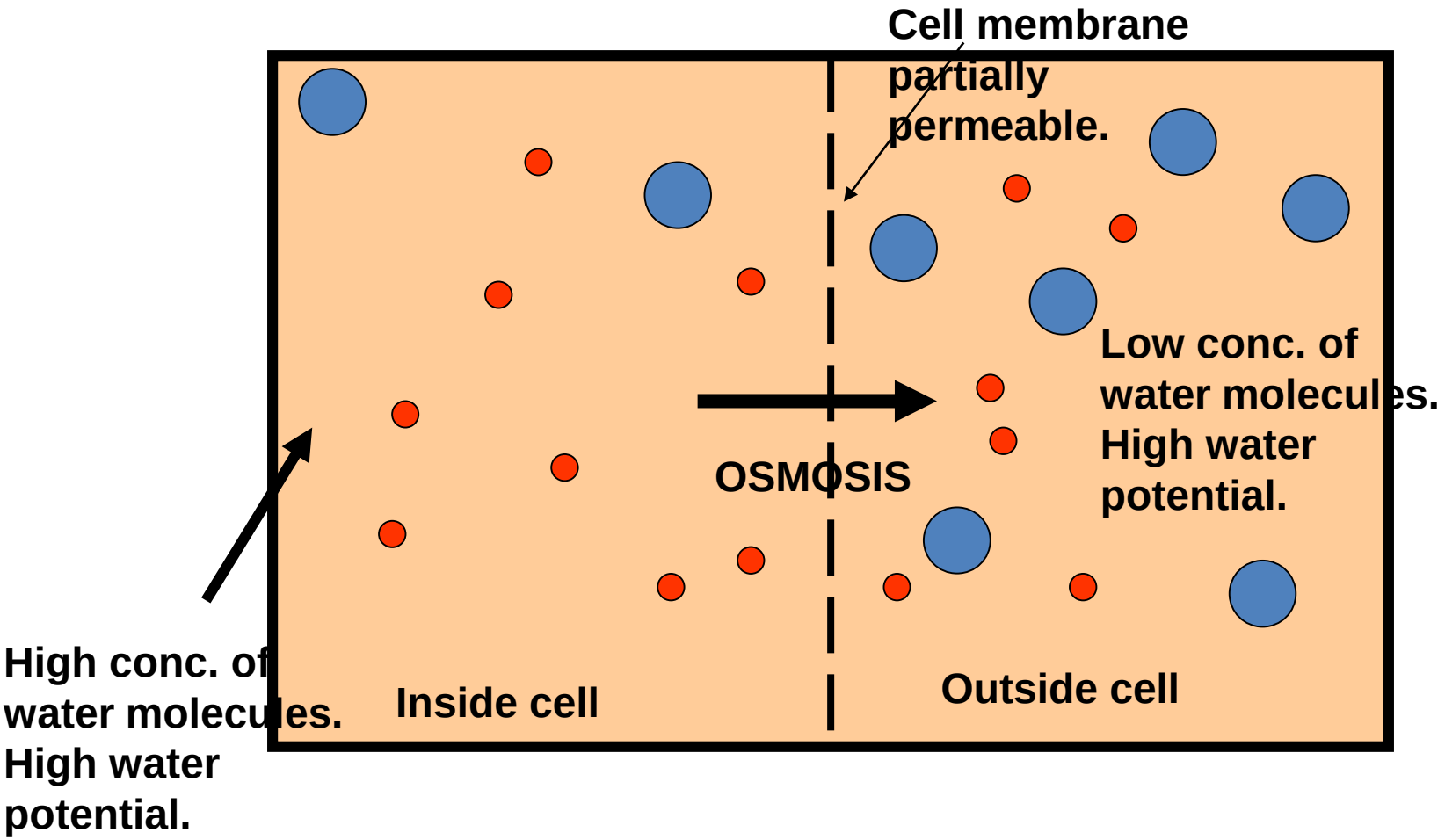
OSMOSIS

The diffusion of **water** across a **differentially permeable membrane due to concentration differences**

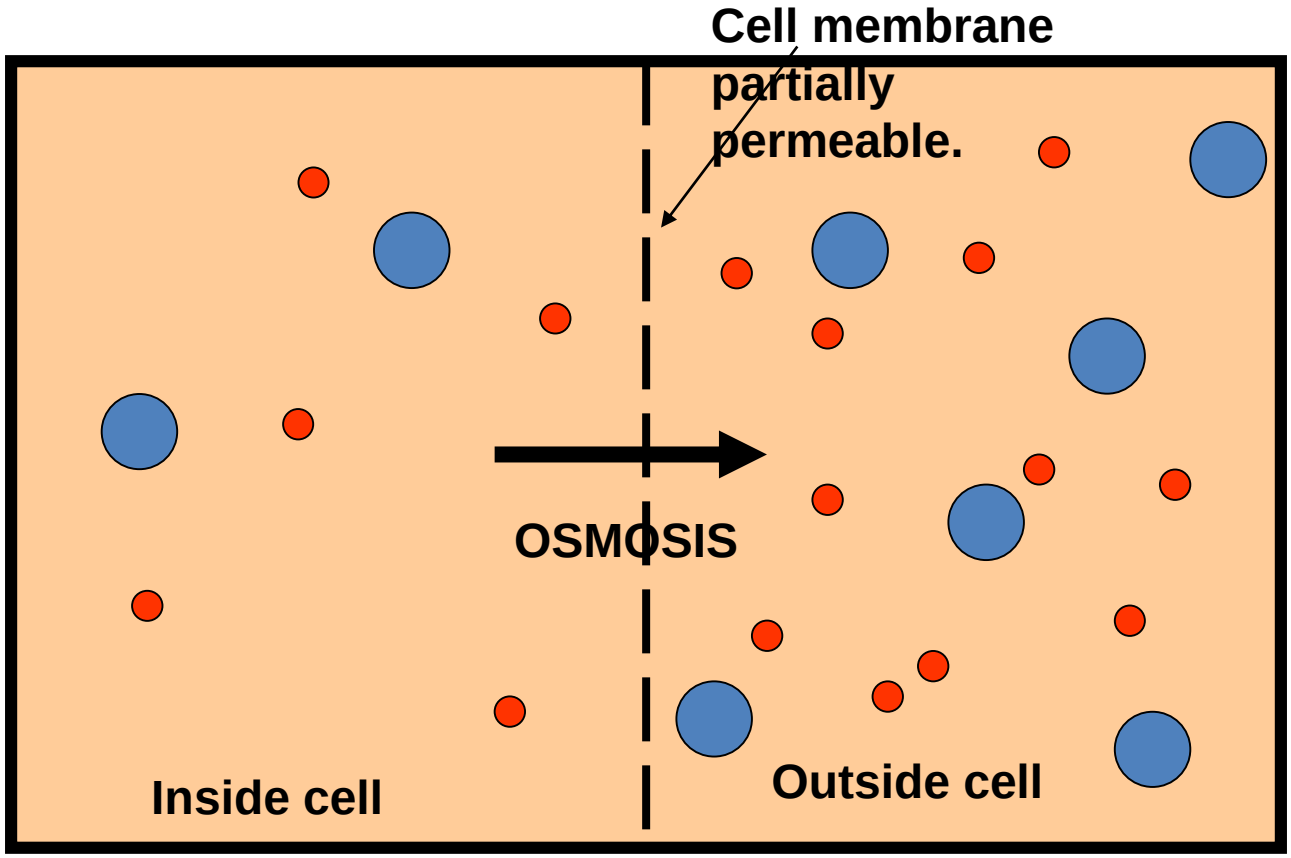
Osmosis


DILUTE SOLUTION
CONCENTRATED SOLUTION
Cell membrane partially permeable.
Sugar molecule
VERY Low conc. of water molecules. High water potential.
VERY High conc. of water molecules. High water potential.
Inside cell
Outside cell

Osmosis


Cell membrane partially permeable.
Low conc. of water molecules. High water potential.
OSMOSIS
High conc. of water molecules. High water potential.
Inside cell
Outside cell

Osmosis

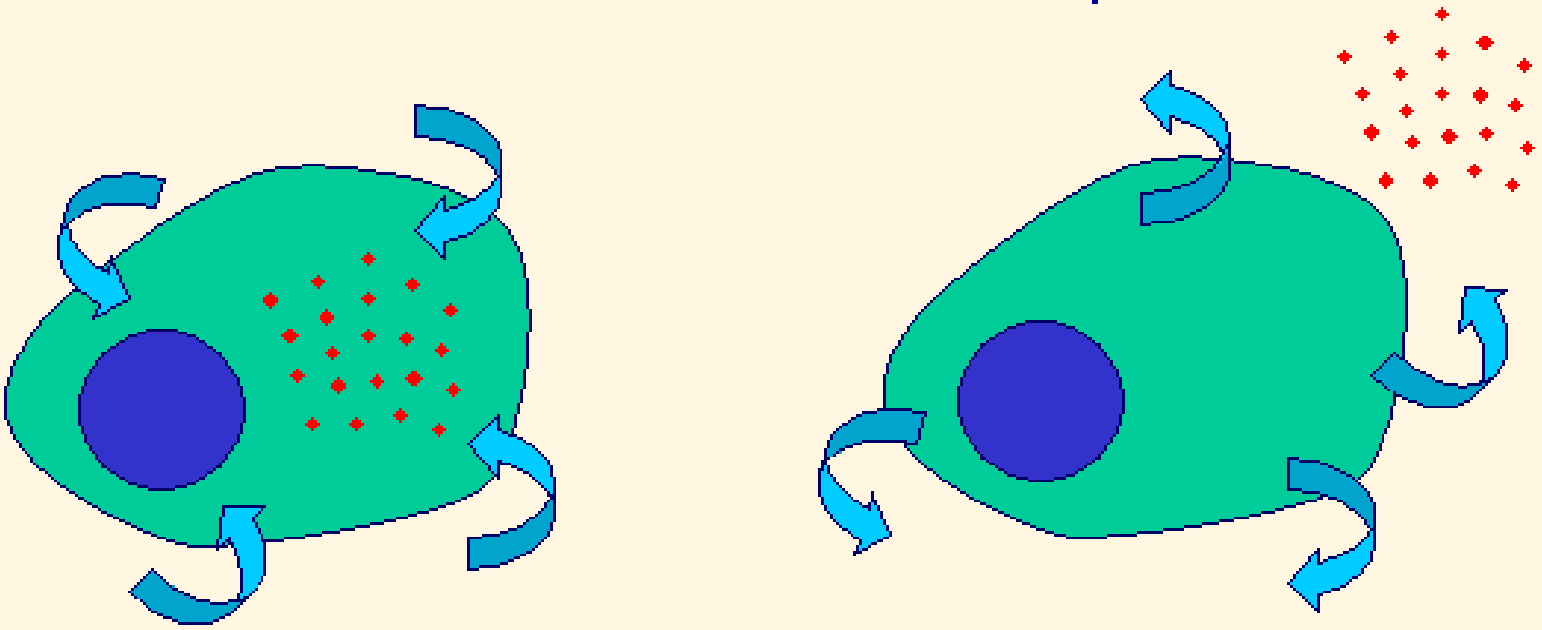


EQUILIBRIUM. Equal water concentration on each side. Equal water potential has been reached. There is no net movement of water

How Molecules Cross the Membrane

Osmosis

- Water can diffuse across a membrane
- Water tries to dilute out molecules that can't move across the membrane until the concentration is equal



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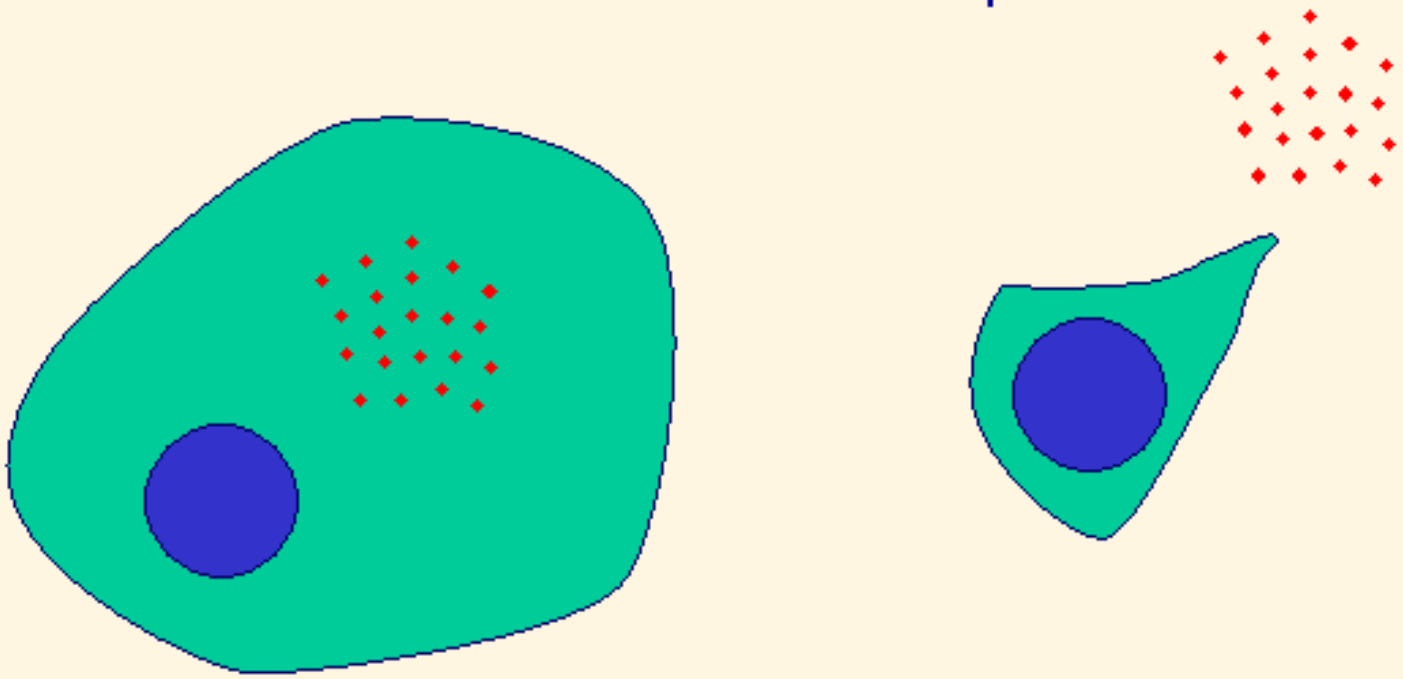


Question:
What's in a Solution?

Answer:

- **solute + solvent $\rightarrow$ *solution***
- **NaCl + H_20 $\rightarrow$ *saltwater***

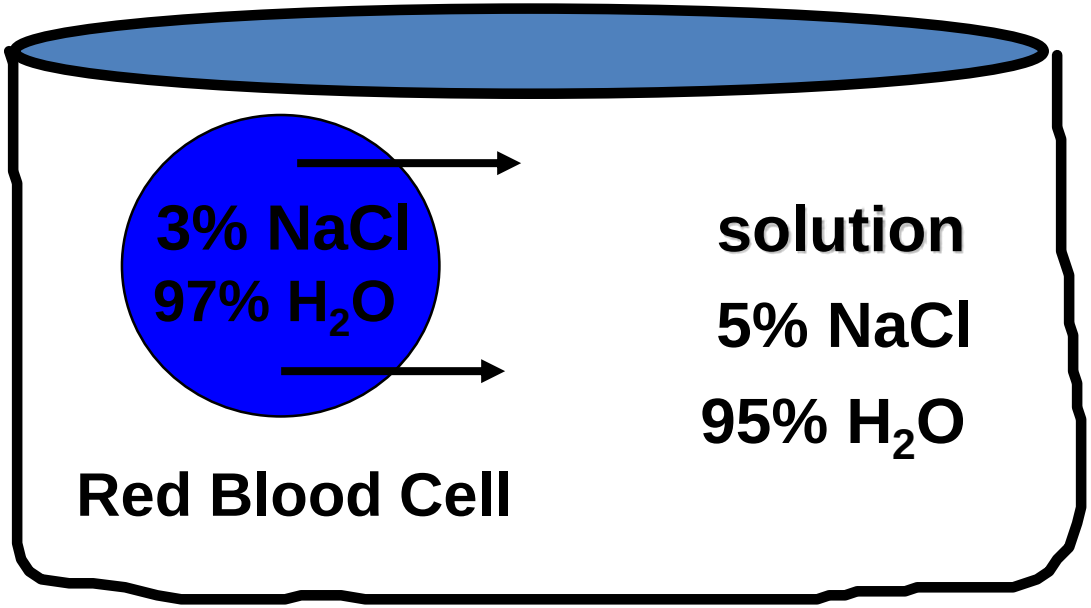
TONICITY

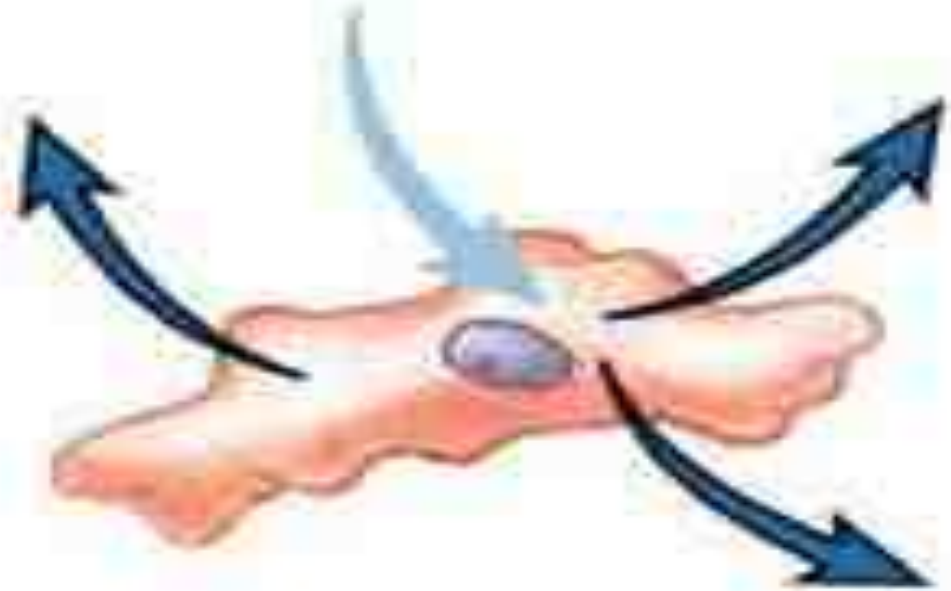
- Refers to the concentration of **SOLUTES**
- Is a **RELATIVE** term, comparing two different solutions
- **Hypertonic**
- **Hypotonic**
- **Isotonic**

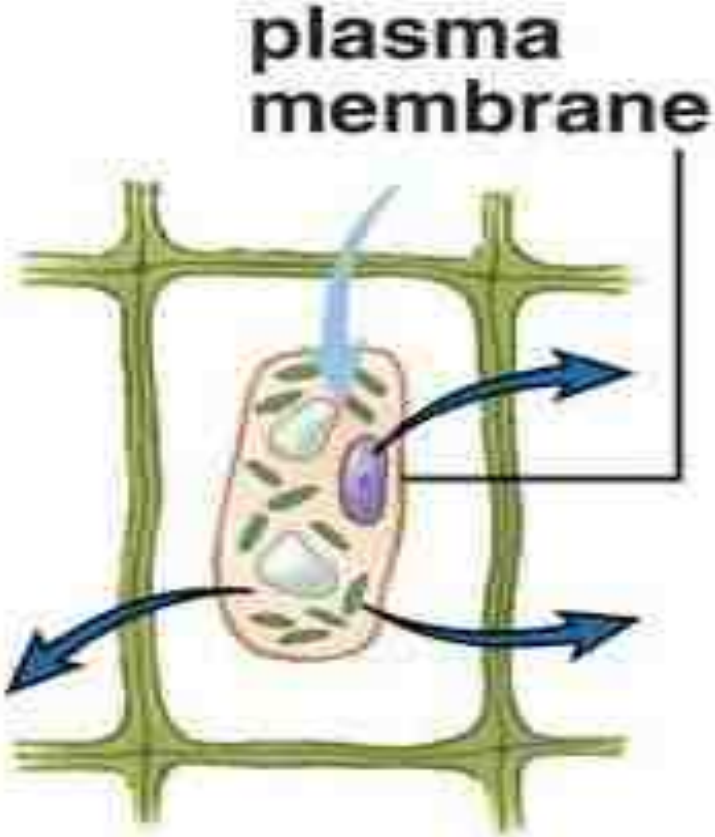
Hypertonic

- A solution with a **greater solute concentration** compared to another **solution**.

Which way will the water move?







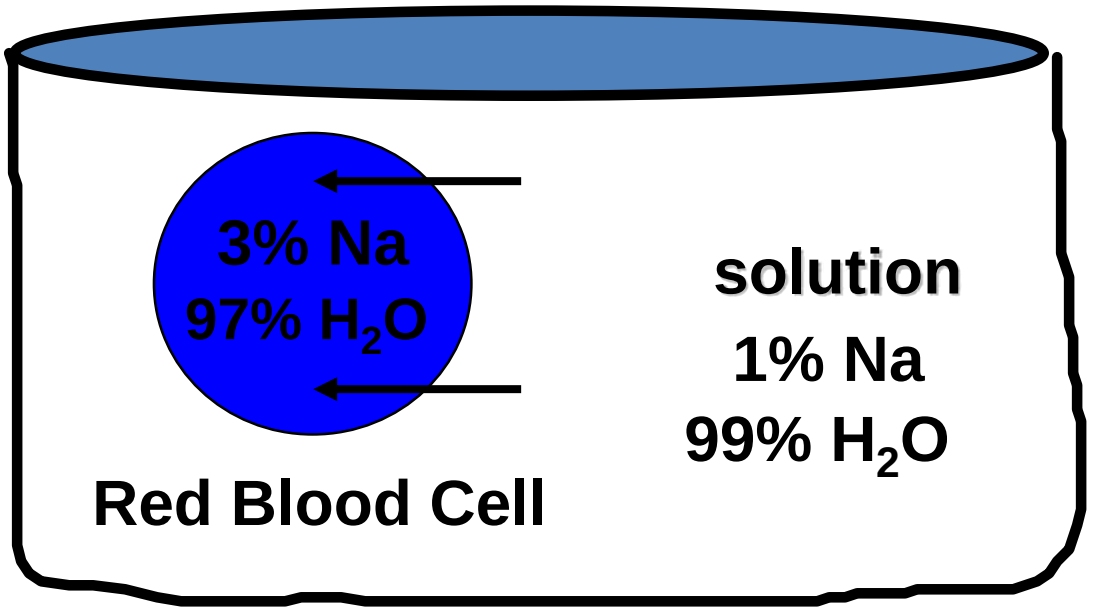
In a hypertonic solution, water leaves the cell, which shrivels (crenation).

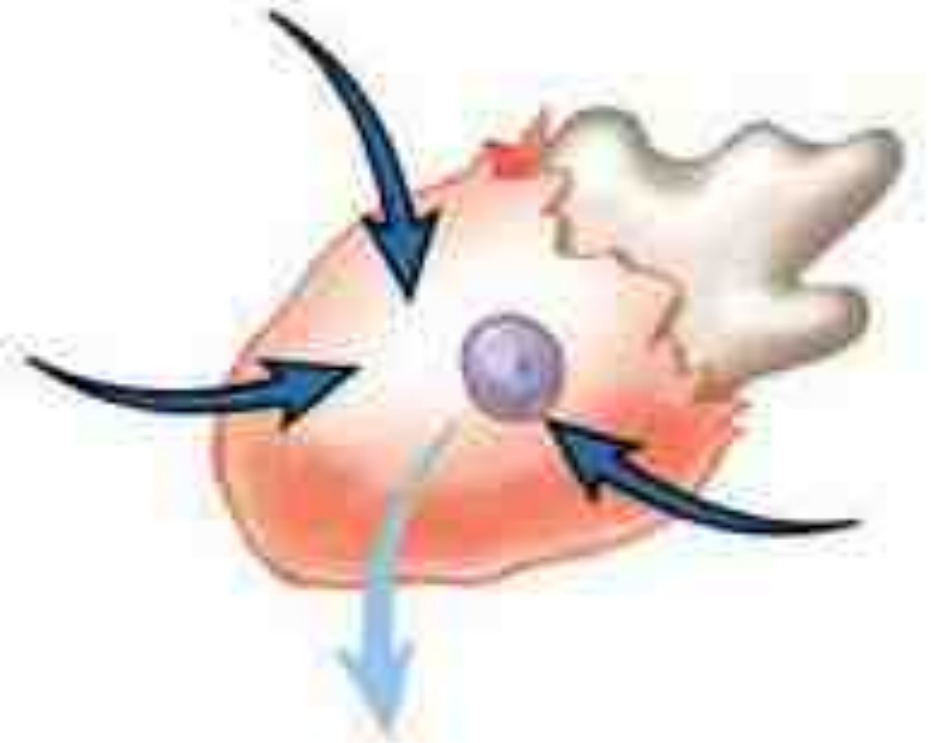
In a hypertonic solution, vacuoles lose water, the cytoplasm shrinks (plasmolysis), and chloroplasts are seen in the center of the cell.

Hypotonic

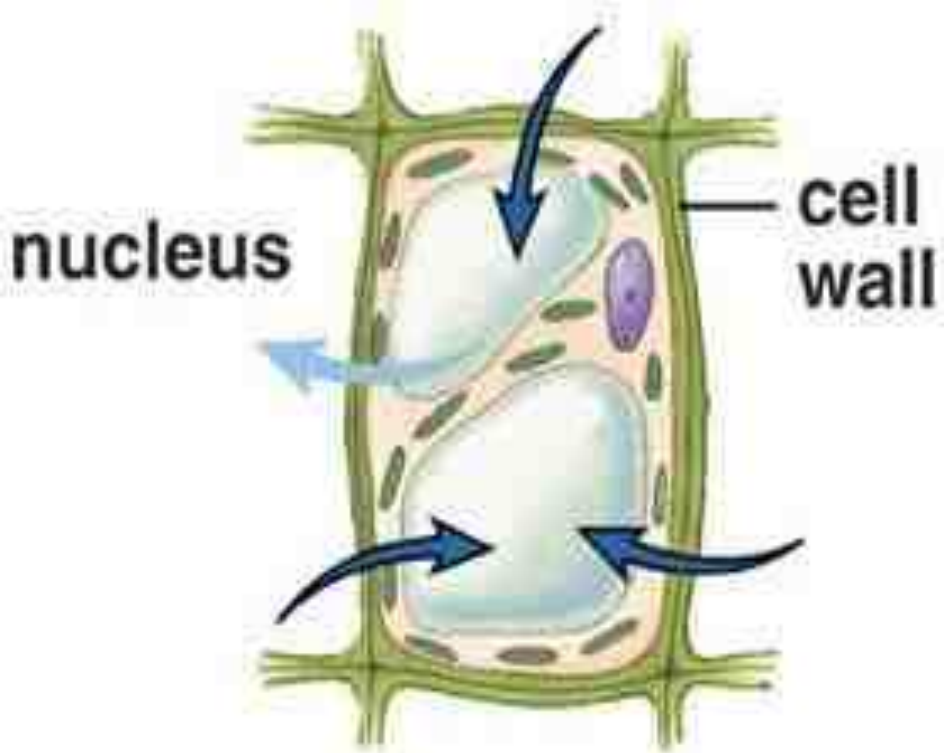
- A solution with a **lower solute concentration** compared to another **solution**.

Which way will the water move?





In a hypotonic solution, water enters the cell, which may burst (lysis).

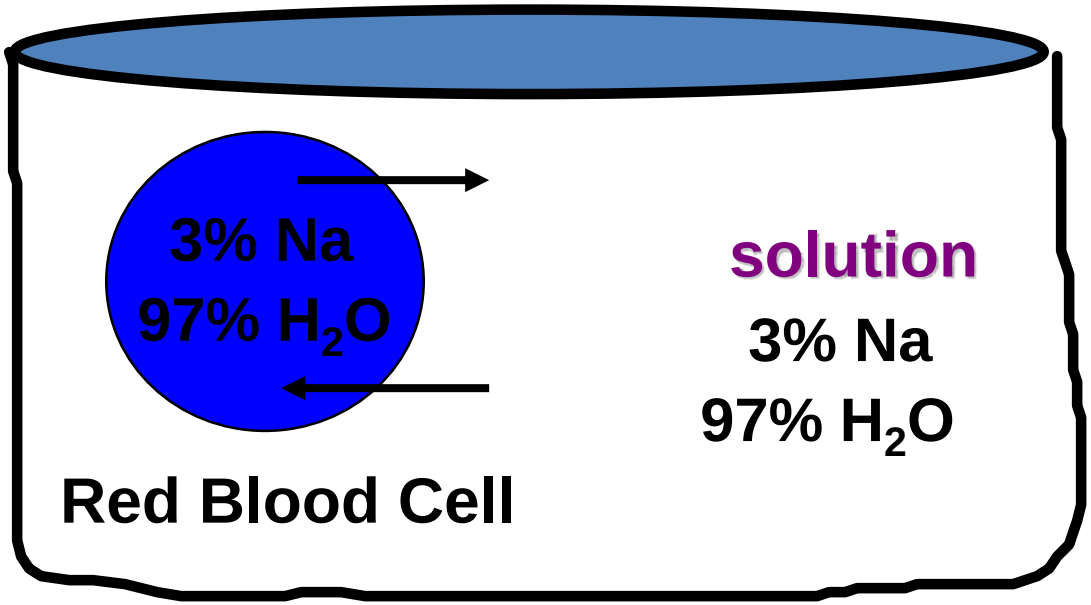


In a hypotonic solution, vacuoles fill with water, turgor pressure develops, and chloroplasts are seen next to the cell wall.

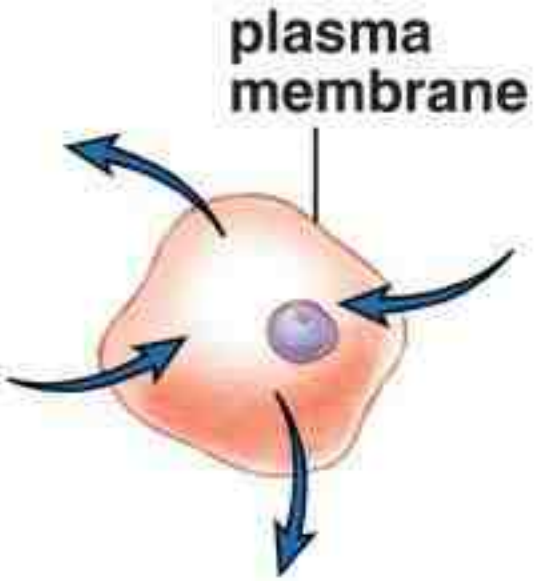
Isotonic

- A **solution** with an **equal solute concentration** compared to another **solution**.

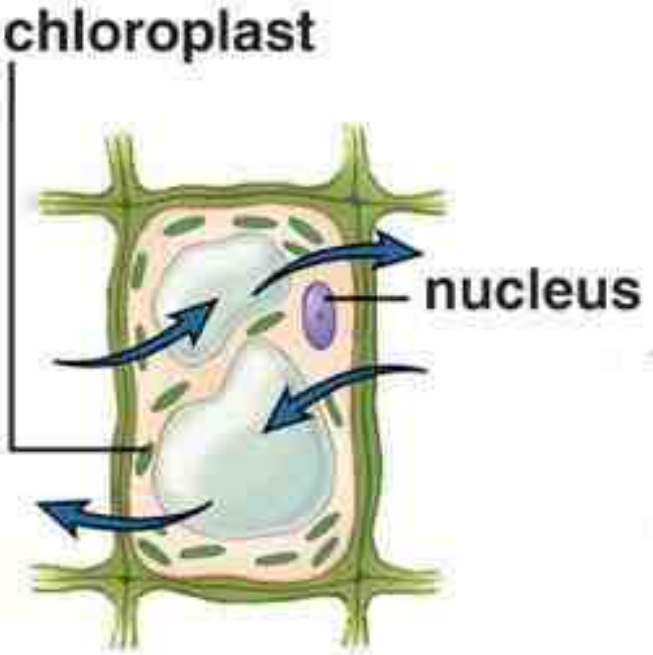
Which way will the water move?



ISOTONIC SOLUTION



In an isotonic solution, there is no net movement of water.

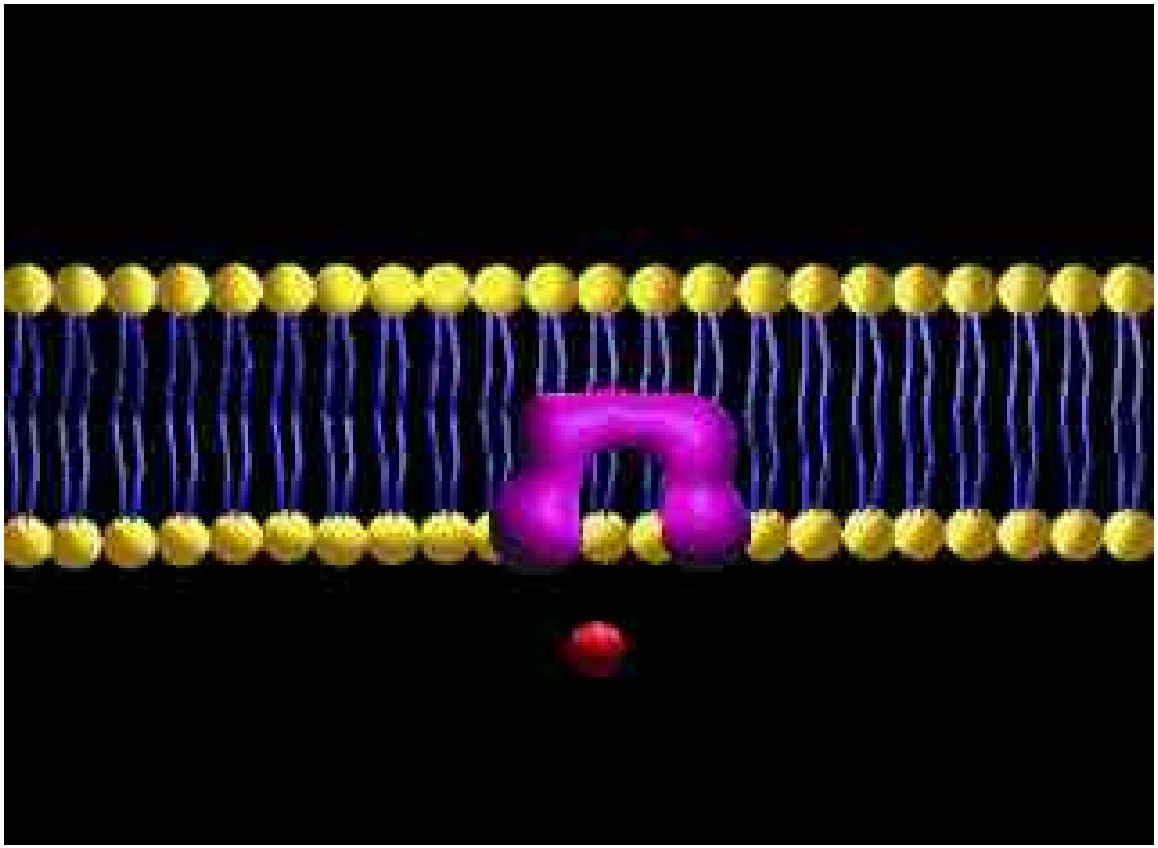


In an isotonic solution, there is no net movement of water.

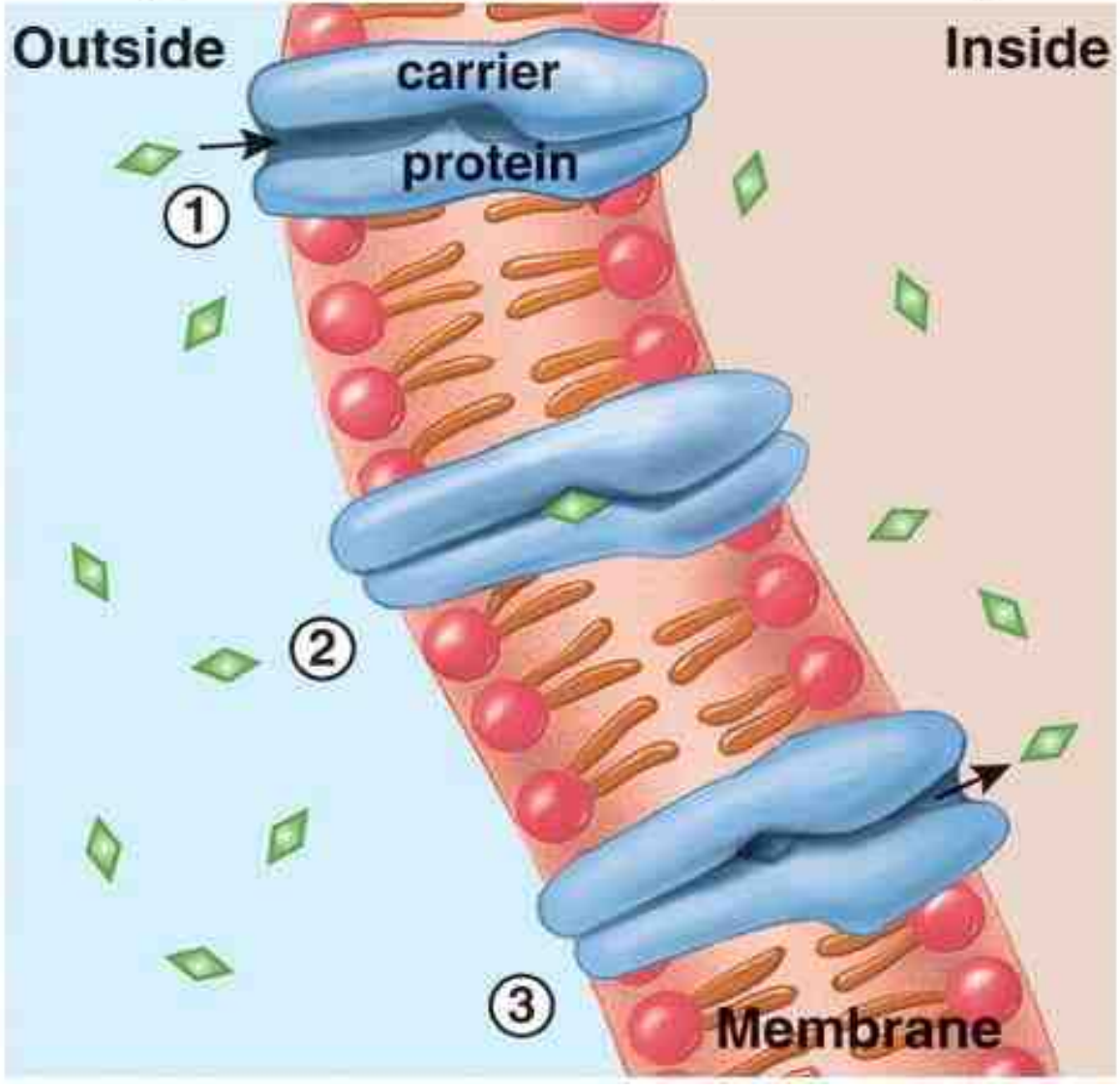
Carrier Proteins

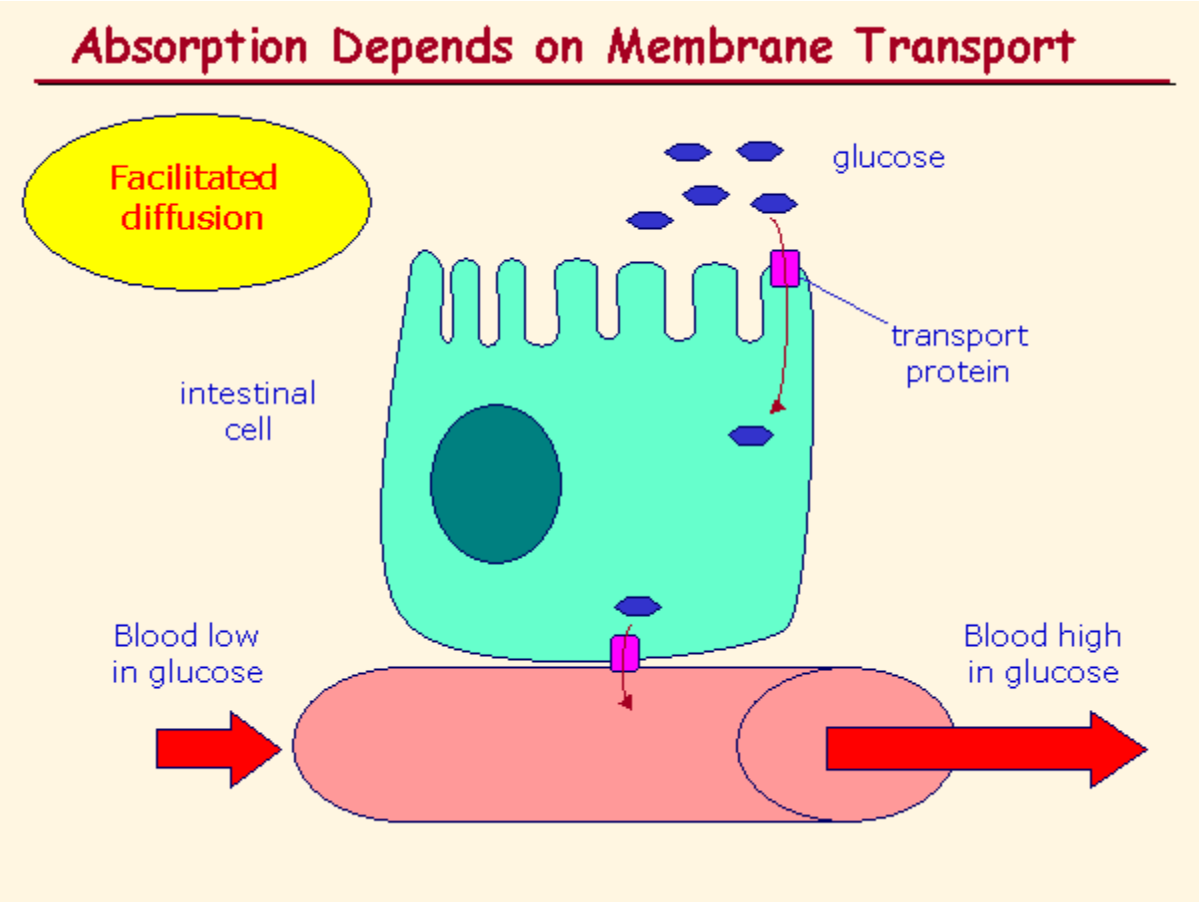
- **Function**—Transport. **Are specific**, combine with only a certain type of molecule.
- **Types**
  - **Facilitated** transport--passive
  - **Active** transport—requires energy

carrier proteins bond and drag molecules through the lipid bilayer and release them on the opposite side.

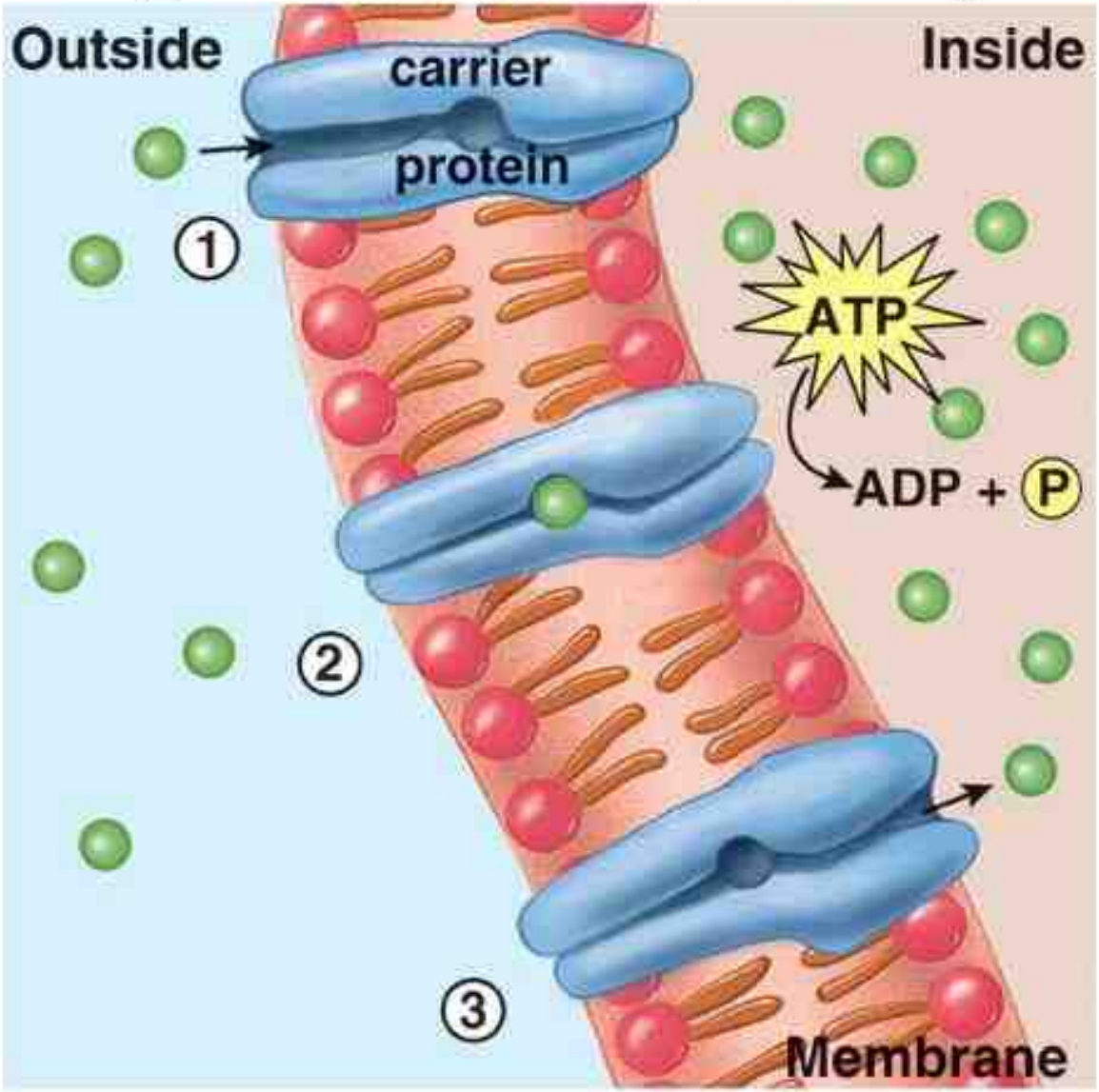


Facilitated Transport



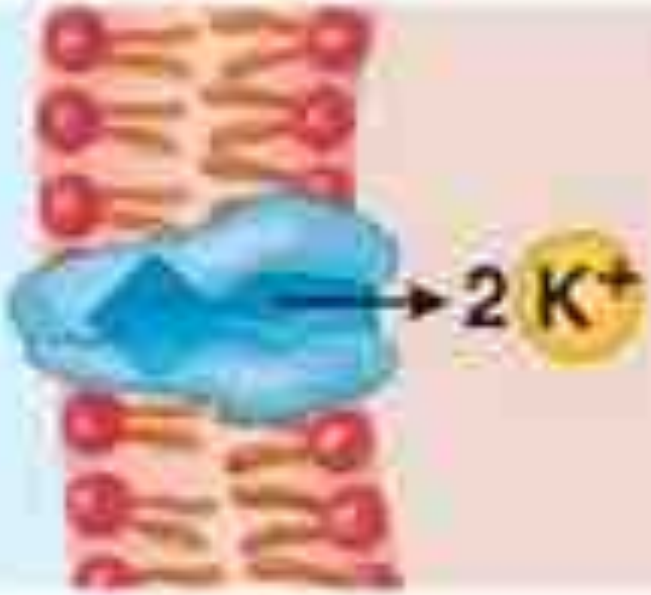

Absorption Depends on Membrane Transport
Facilitated diffusion
glucose
transport protein
intestinal cell
Blood low in glucose
Blood high in glucose

Active Transport



The sodium-potassium pump

Change in shape results that causes carrier to release potassium ions (K^+) inside the cell. New shape is suitable to take up three sodium ions (Na^+) once again.



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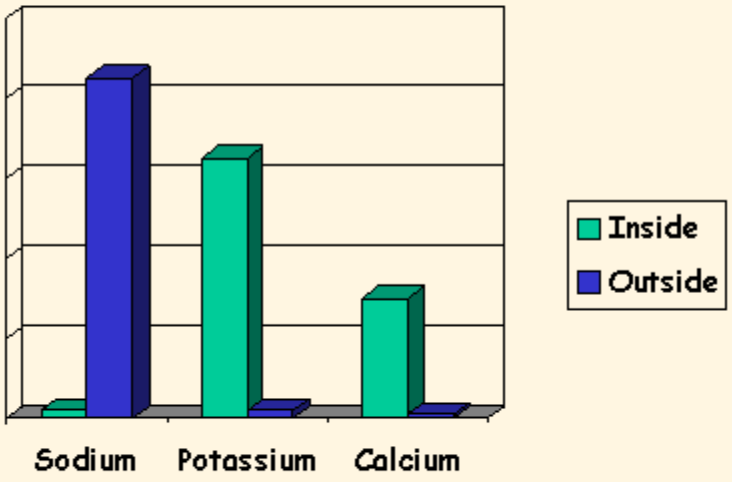
How Molecules Cross the Membrane

Active transport

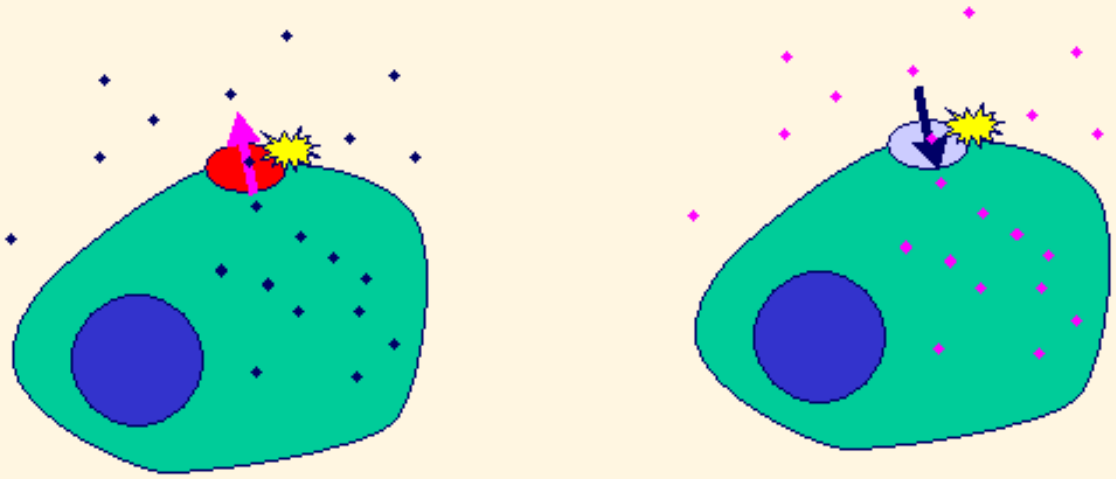
- Cells must maintain very high or low levels of some molecules
  - Passive transport can't do this!



How Molecules Cross the Membrane

Active transport

- Cells must maintain very high or low levels of some molecules
- Active transport proteins use energy to "pump" a molecule in or out of the cell



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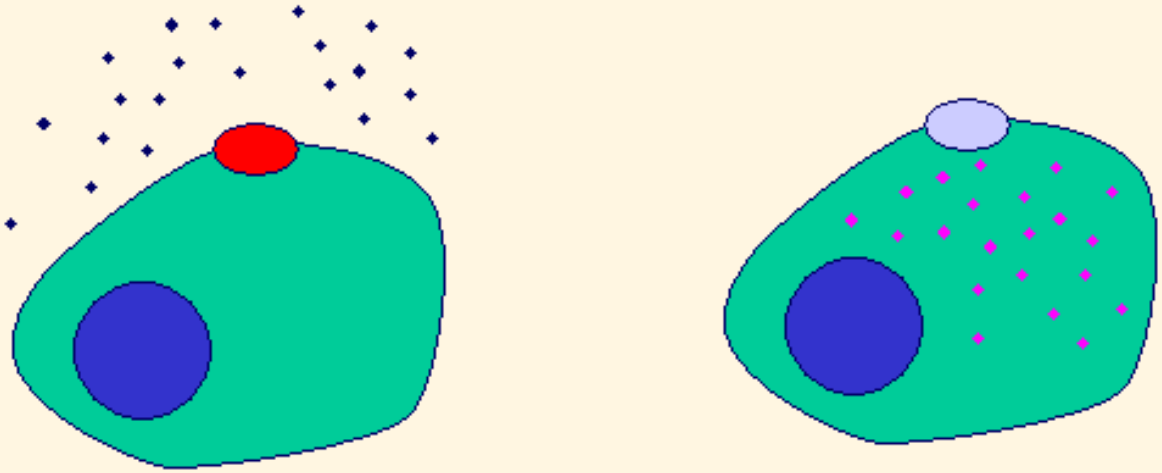
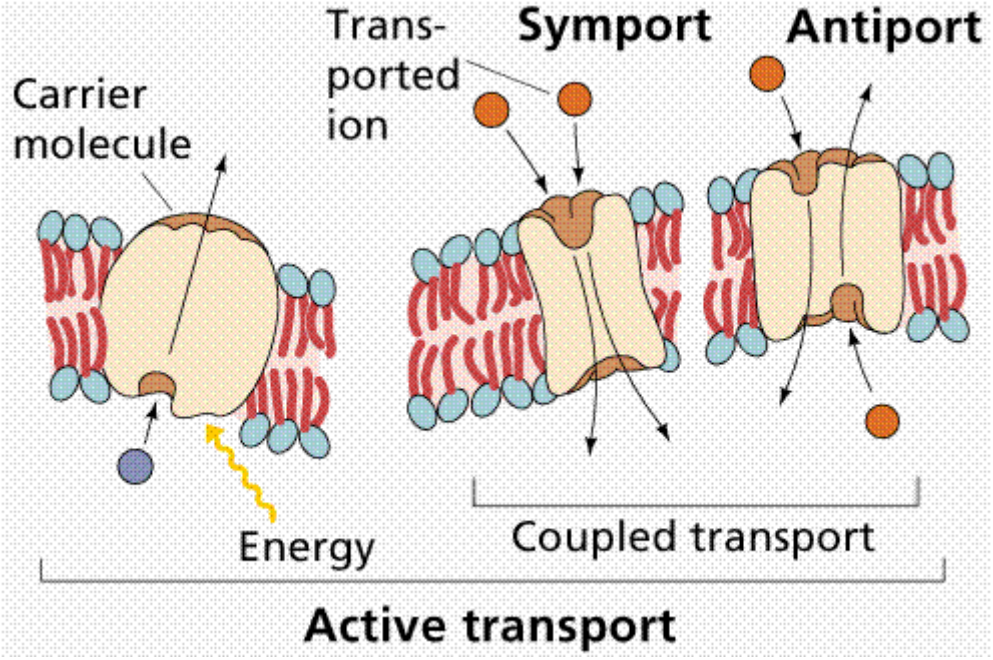
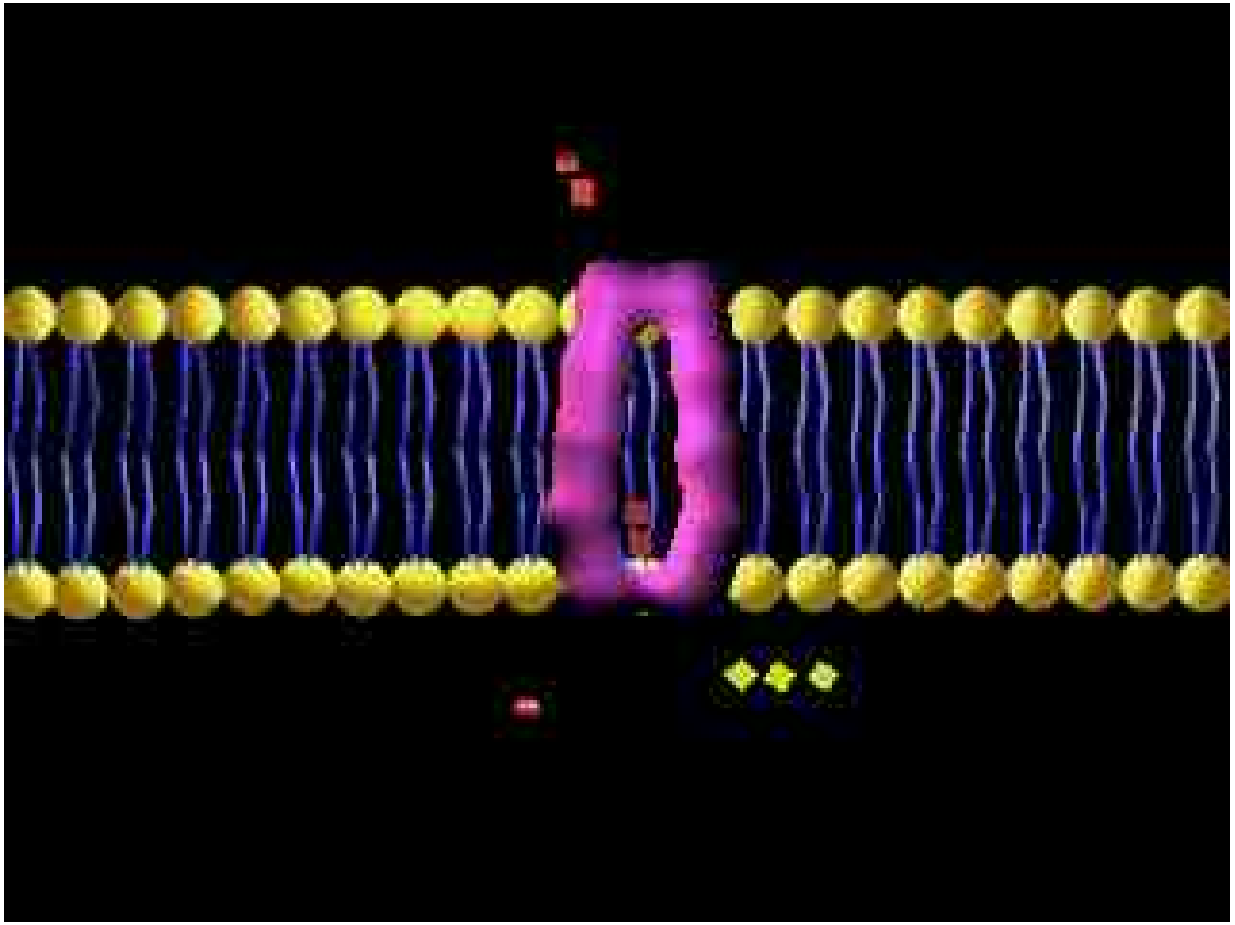
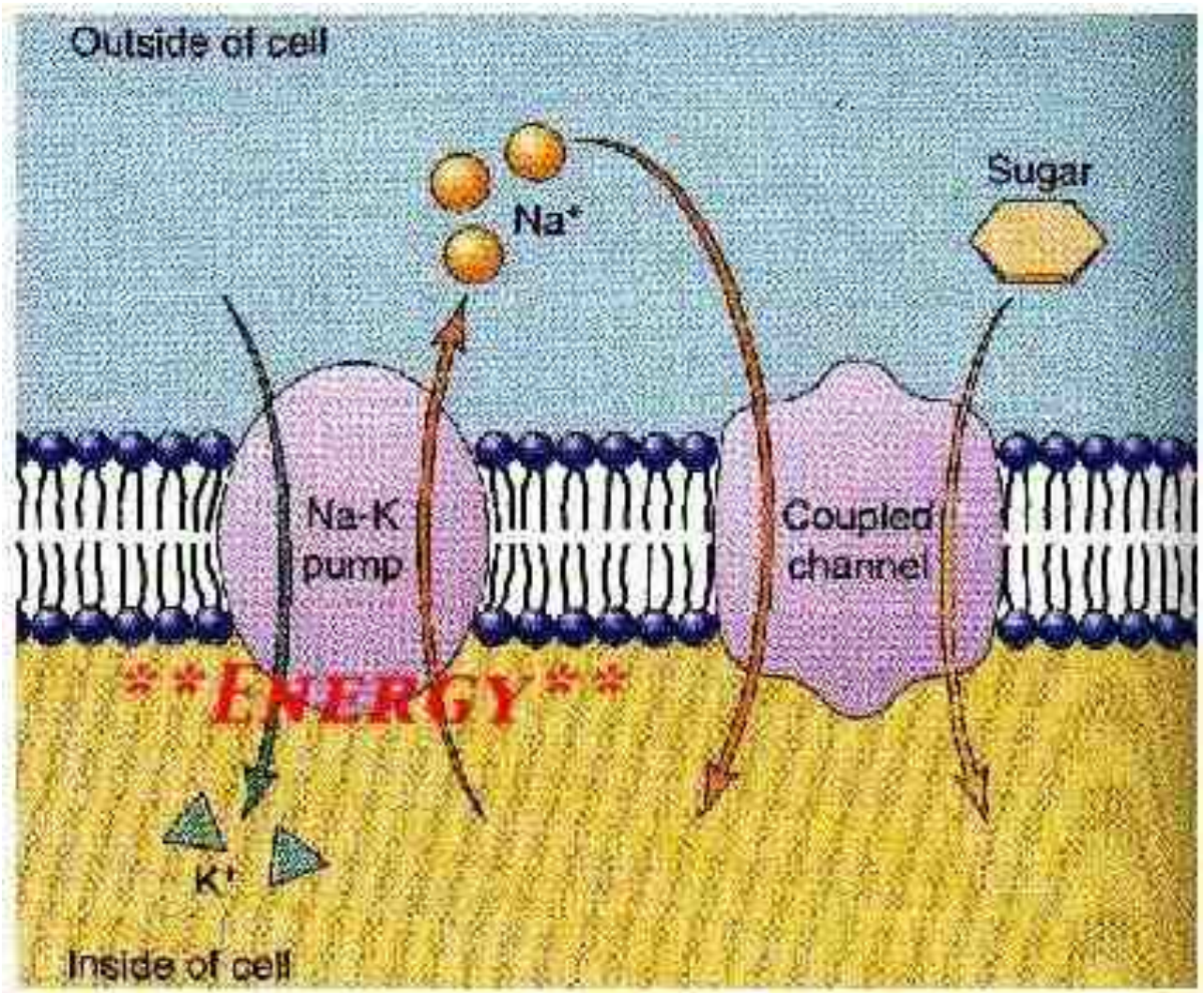


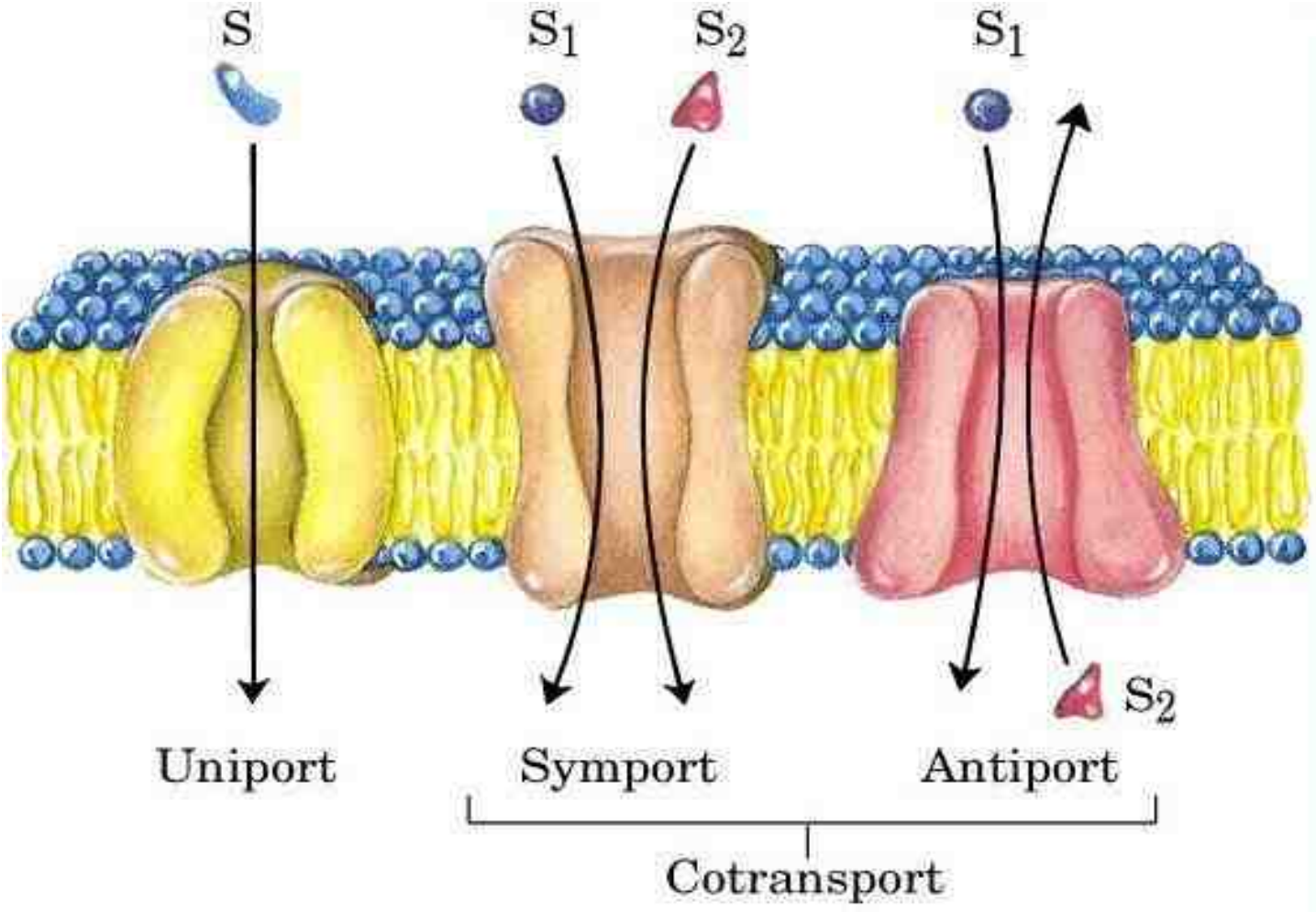

Trans-
ported
ion
Symport
Antiport
Carrier
molecule
Energy
Coupled transport
Active transport

Cotransport also uses the process of diffusion. In this case a molecule that is moving naturally into the cell through diffusion is used to drag another molecule into the cell. In this example **glucose** hitches a ride with **sodium**.





http://science.halleyhosting.com/sci/ibbio/cells/rev/active/a12.htm



http://buffonescience9.wikispaces.com/UNIT+1+-+Basics+of+Life

How Molecules Cross the Membrane

	Active/ Passive	Molecules that Move	Direction	Energy Needed?	Protein Needed?
Diffusion	Passive	small, hydrophobic	down gradient (toward low conc.)	no	no
Osmosis	Passive	water	toward high conc. of solutes	no	no
Facilitated Diffusion	Passive	any (specific transporter)	down gradient (toward low cons.)	no	yes
Active Transport	Active	any (specific transporter)	specific: in or out, dep. on transporter	yes	yes

http://highered.mcgraw-hill.com/novella/MixQuizProcessingServlet

http://highered.mcgraw-hill.com/novella/MixQuizProcessingServlet

http://highered.mcgraw-hill.com/novella/MixQuizProcessingServlet

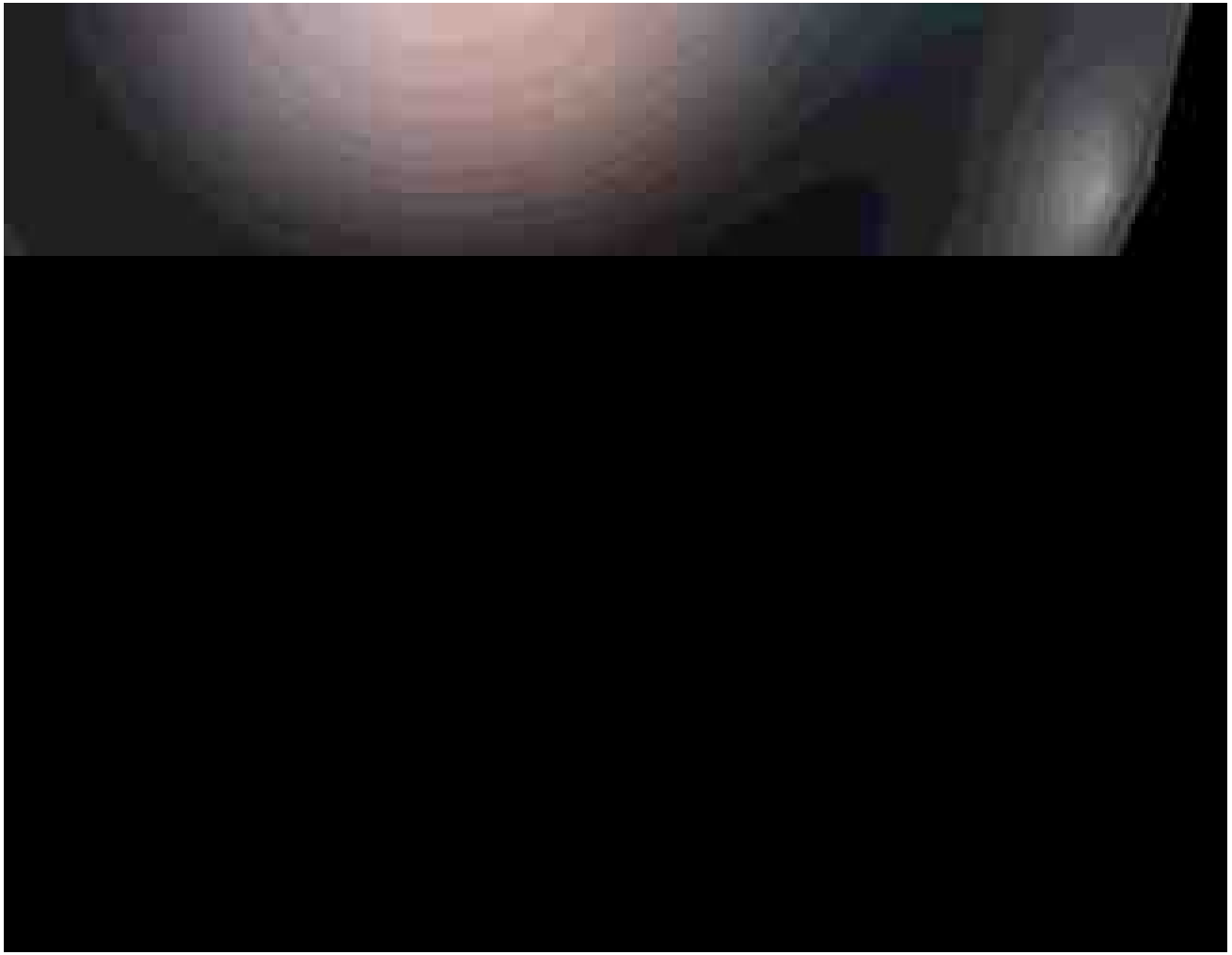
http://highered.mcgraw-hill.com/novella/MixQuizProcessingServlet

Exocytosis and Endocytosis

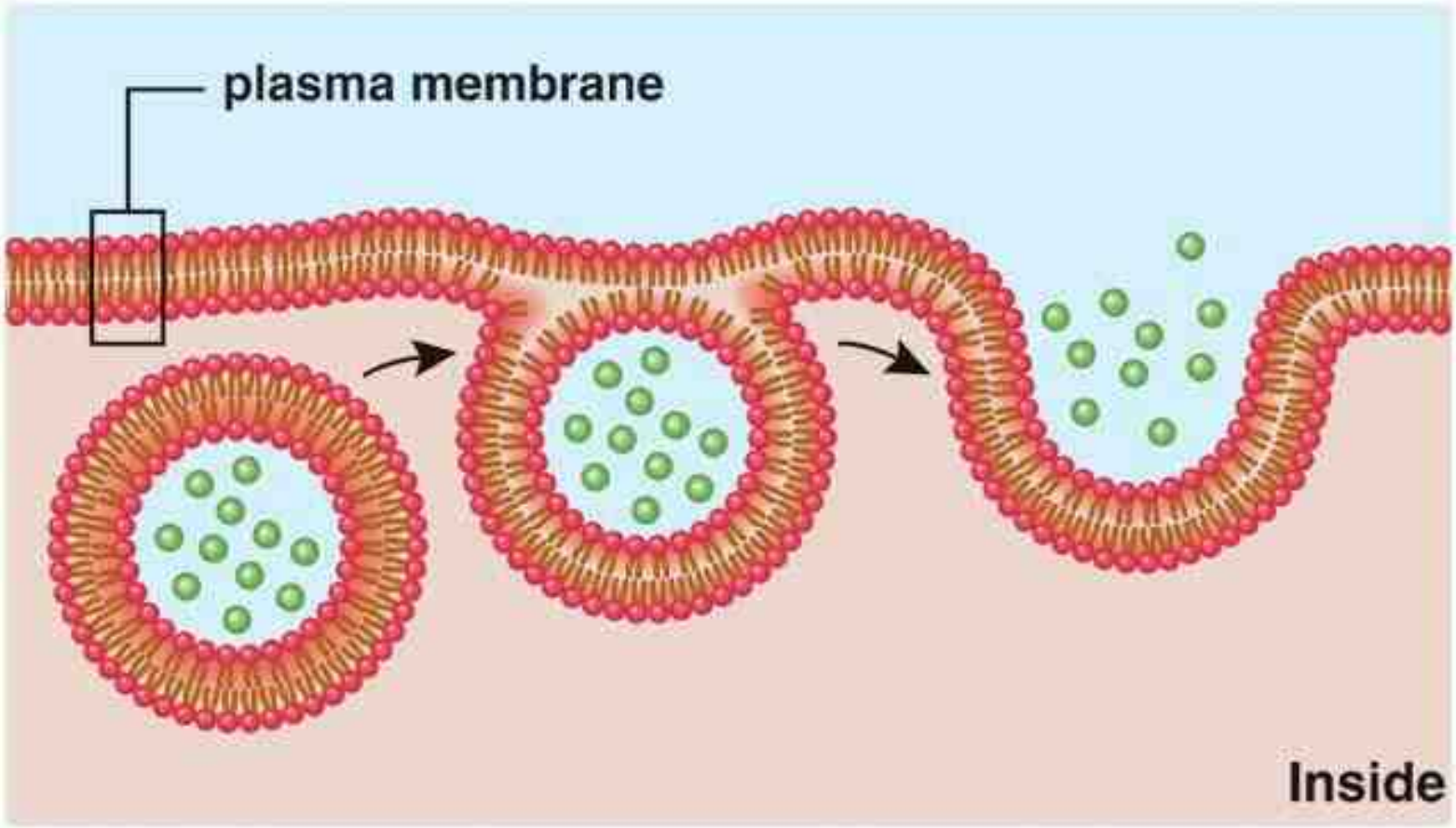
- Exocytosis---**Cellular secretion**
- Endocytosis—
  - –Phagocytosis— "**Cell eating**"
  - –Pinocytosis– "**Cell drinking**"
  - –Receptor-mediated endocytosis- **specific particles, recognition**.

Exocytosis

The opposite of endocytosis is exocytosis. Large molecules that are manufactured in the cell are released through the cell membrane.



Exocytosis



Movement of Large Molecules in Cells

1. Exocytosis: movement out of a cell through the formation of a vesicle
   Ex. Proteins; digestive enzymes; mucus
2. Endocytosis: movement into a cell

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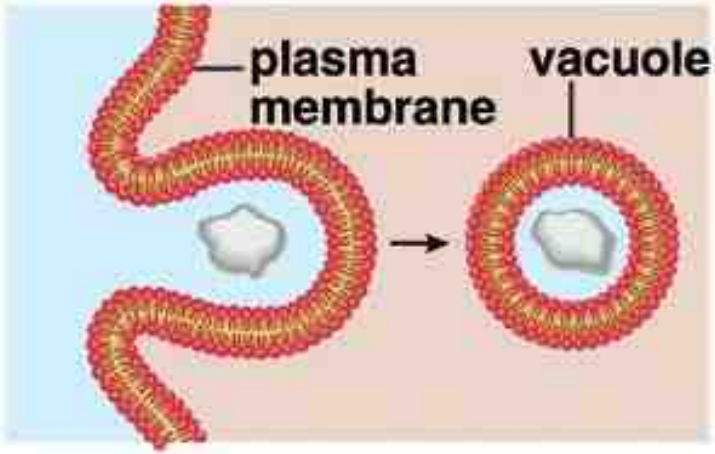
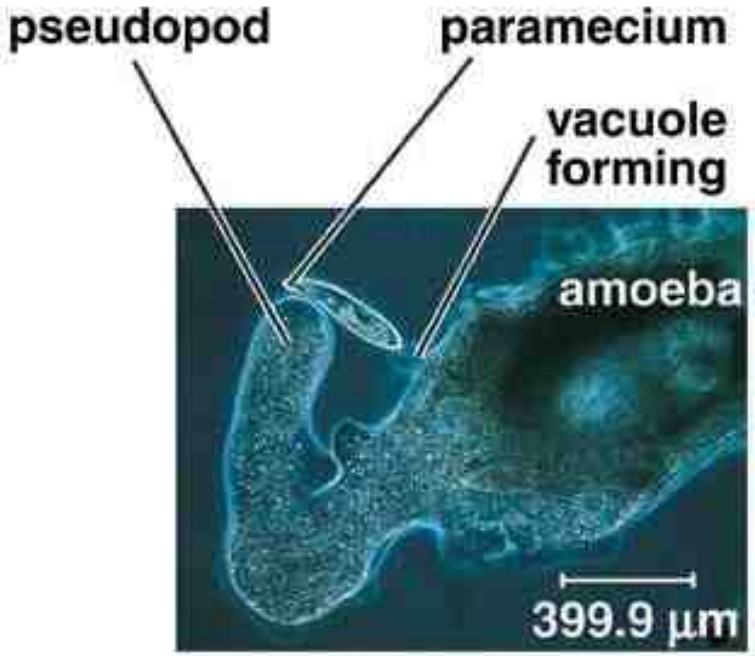
Phagocytosis



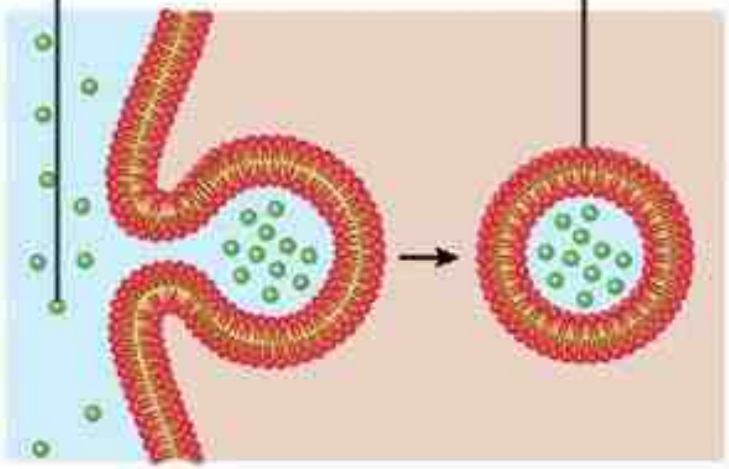
a. Phagocytosis



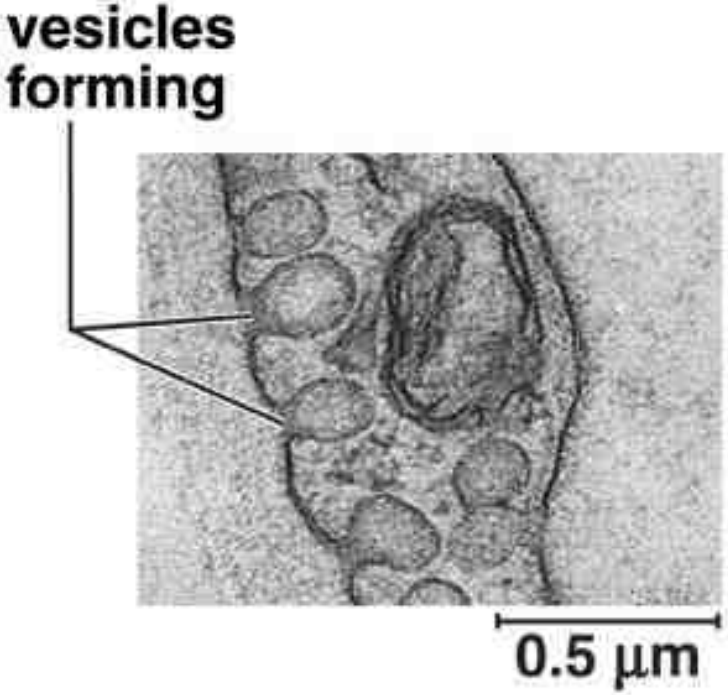
Types of Endocytosis

3. Phagocytosis:
   "cell-eating" because it brings into the cell large materials
   Ex. Bacteria; cell debris

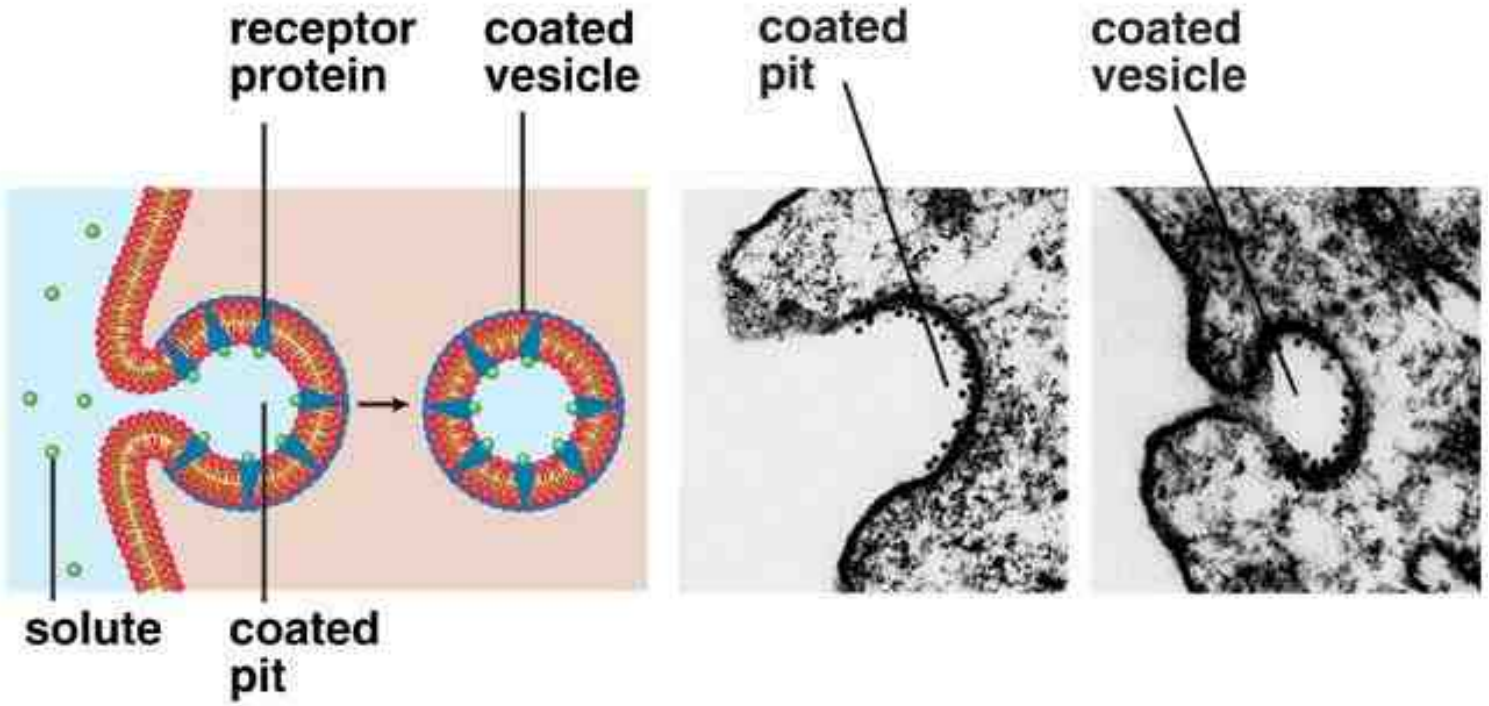
Pinocytosis



b. Pinocytosis



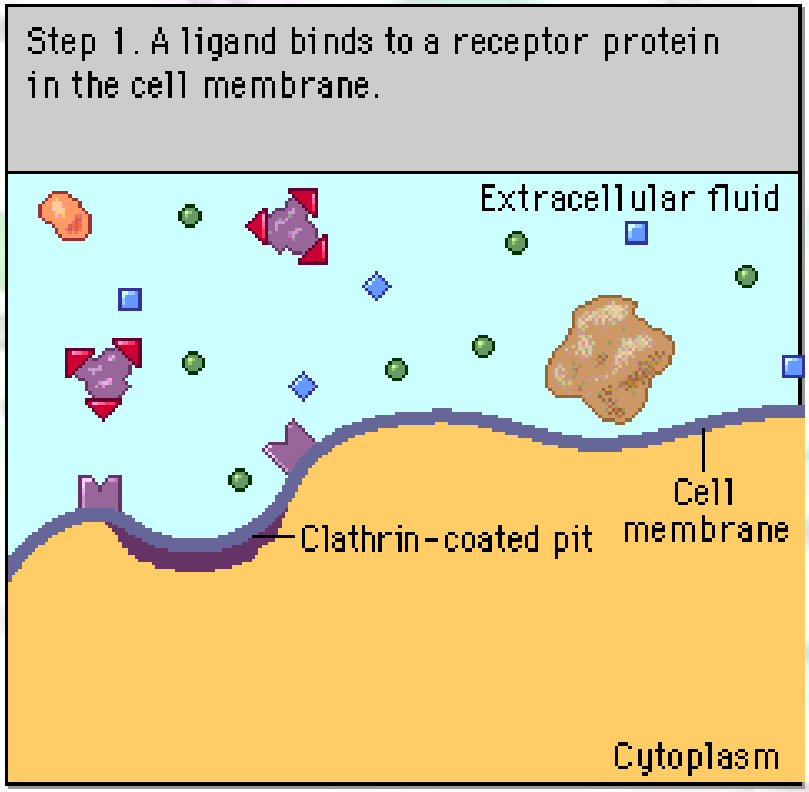
Receptor-mediated Endocytosis

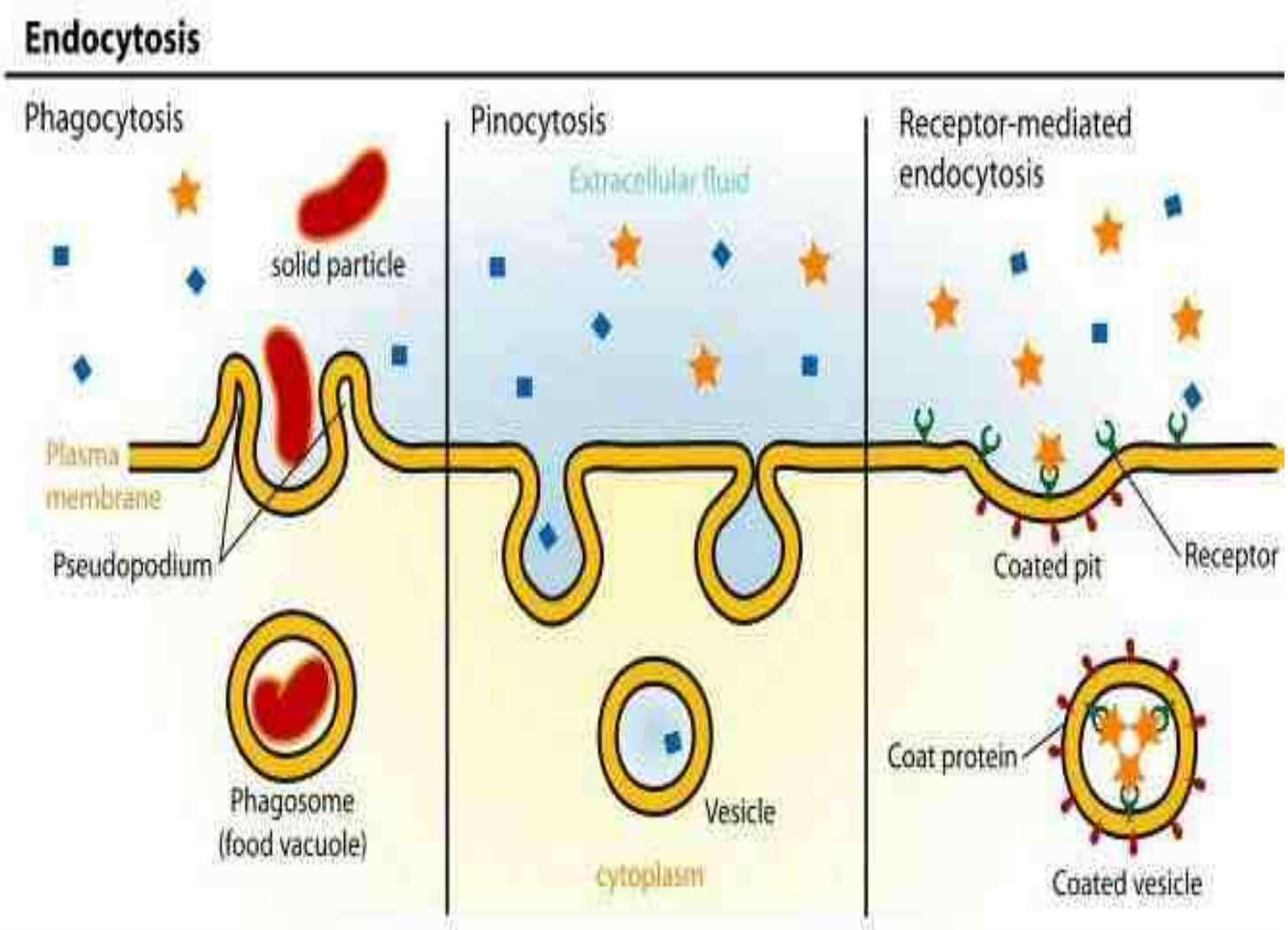


c. Receptor-mediated endocytosis

Types of Endocytosis

2. Receptor-mediated endocytosis:
   specialized cell surface receptors bind to molecules and pulls it into the cell
   Ex. Transport of iron



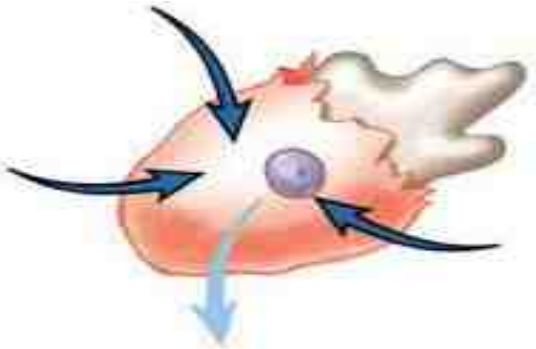

Endocytosis
Phagocytosis
Pinocytosis
Receptor-mediated endocytosis
Extracellular fluid
solid particle
Plasma membrane
Pseudopodium
Coated pit
Receptor
Phagosome (food vacuole)
Vesicle
cytoplasm
Coat protein
Coated vesicle

Test 1

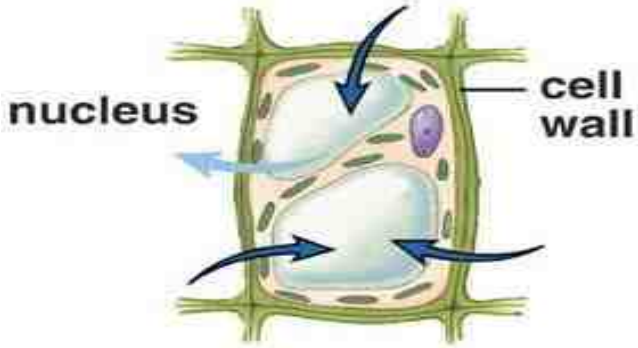
CELL BIOLOGY and GENETICS

Cell walls

- **Plant cells** are *not flaccid like* ***animal cells*** and have a **rigid cell wall around them** made of *fibrils of* ***cellulose*** *embedded in a matrix of several other kinds of polymers such as* ***pectin*** *and* ***lignin***.
- It is the cell wall that is primarily responsible for ***ensuring the cell does not burst in hypotonic surroundings***.
- ***Prokaryotes***, ***algae***, ***fungi*** and ***plant*** **cells** have cell walls.



In a hypotonic solution, water enters the cell, which may burst (lysis).



In a hypotonic solution, vacuoles fill with water, turgor pressure develops, and chloroplasts are seen next to the cell wall.

Function:

- **Protects** the cell,
- Maintains the cell's **shape**,
- **Prevents** excessive uptake of water,
- **On the level of the whole plant**, the strong walls of specialized cells hold the plant up **against the force of gravity.**

Differences in the cell wall between prokaryotes and eukaryotes:

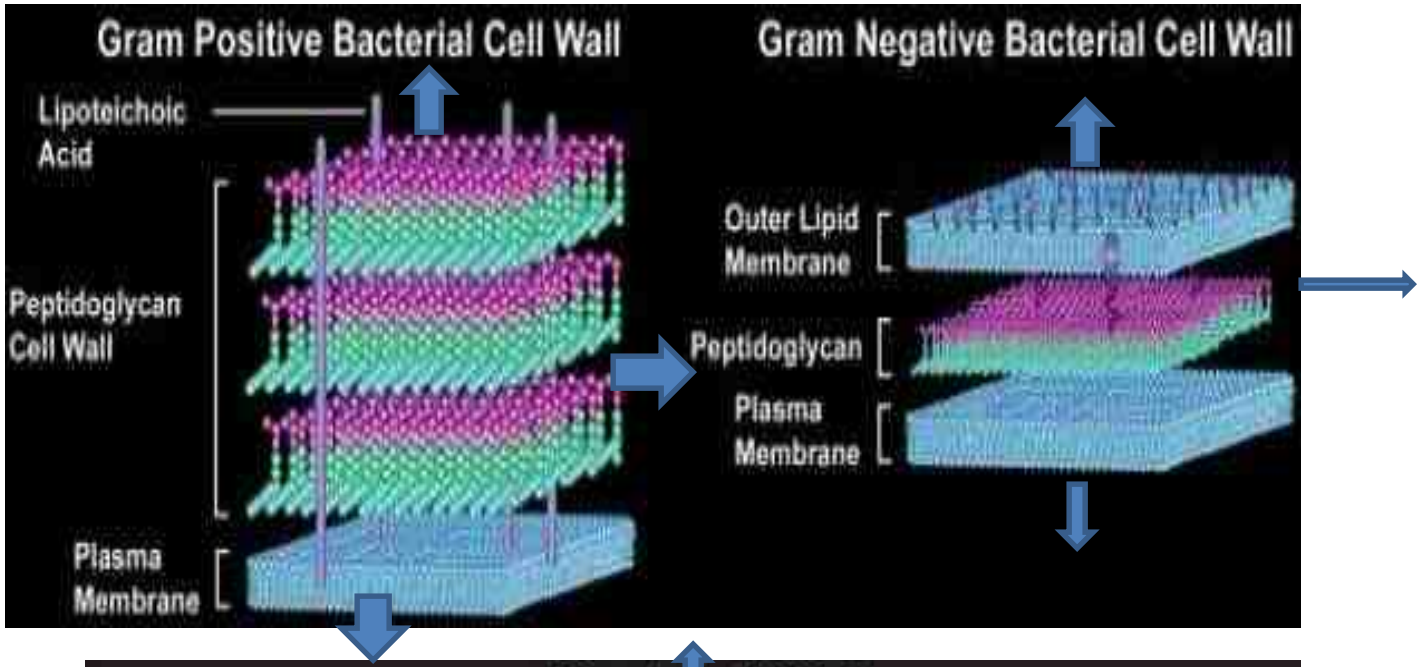
- The cell wall in most bacteria contain a unique material called peptidoglycan which is a polymer of **modified sugars** cross-linked by **short polypeptides**.
- The cell wall in plants is formed from **cellulose**, which are fibers embedded in a **polysaccharide-protein matrix**.

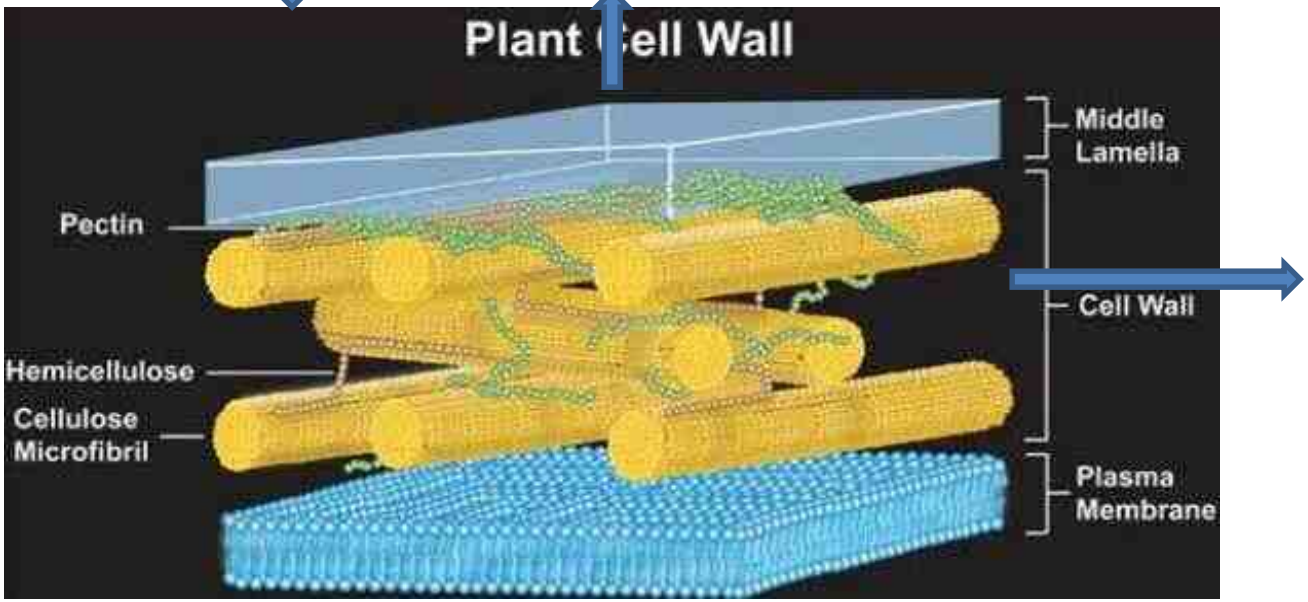
Plant cell wall:

- A young plant cell has **primary cell wall**, which is thin and flexible. *Between primary walls of adjacent cells* is the **middle lamella**, a thin layer of polysaccharide (pectins). Middle lamella **glues the cells together**.

- When the cell matures and stops growing it strengthens its wall by **adding hardening substances into the primary wall.**

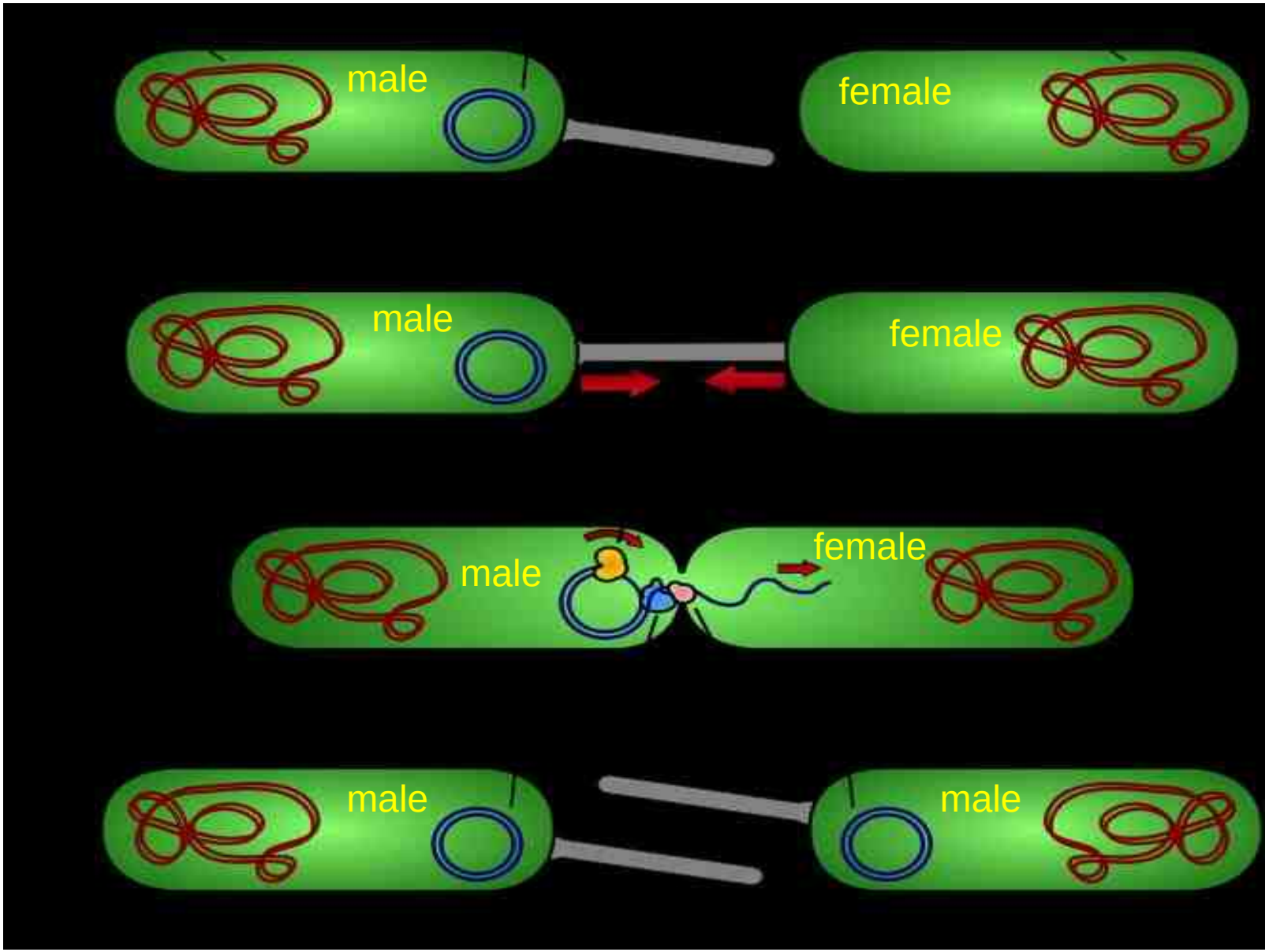
- Other plant cells add **a secondary cell wall *between the plasma membrane and the primary wall***. The secondary wall is strong and more rigid protecting and supporting the cell**. It is also the primary component of wood.**


Gram Positive Bacterial Cell Wall
Lipoteichoic Acid
Peptidoglycan Cell Wall
Plasma Membrane
Gram Negative Bacterial Cell Wall
Outer Lipid Membrane
Peptidoglycan
Plasma Membrane


Plant Cell Wall
Middle Lamella
Pectin
Cell Wall
Hemicellulose
Cellulose Microfibril
Plasma Membrane

PILI, CILIA, FLAGELLA

- **Pili (sing.-Pilus):**
- Found ***on some prokaryote*** *cells*.
- These **long *string-like appendages*** are attached *to the outer surface of the cell*.
- They **allow the cell *to attach itself to other surfaces or other prokaryotic cells*.**
- **Conjugative pili** allow the transfer of DNA between bacteria, in the process of **bacterial conjugation**. They are sometimes called "**sex pili**", in analogy to sexual reproduction, **because they allow for the exchange of genes via the formation of "mating pairs".**


male
female
male
female
male
female
male
male

Cilia(sing.-Cilium) &Flagella(sing.-Flagellum)

- **Similarities:** *Both* of these structures are **used by the cell *in locomotion***.
- Also, they may be used ***to circulate fluid over an area of tissue*, such as the cilia found on the lining of the *human windpipe***. These cilia move *debris trapped in mucus* from the lungs in this manner.
- Cilia and flagella are *both* ***made up of a particular arrangement of microtubules*** *encased in an* ***outgrowth of the plasma membrane.***

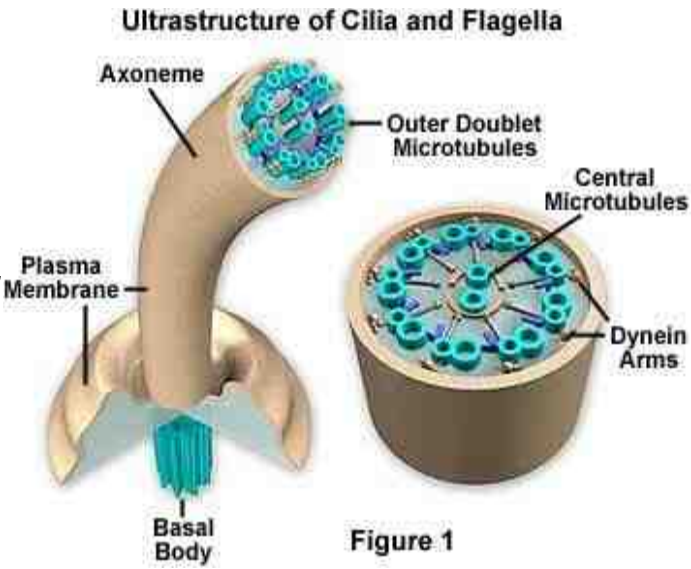


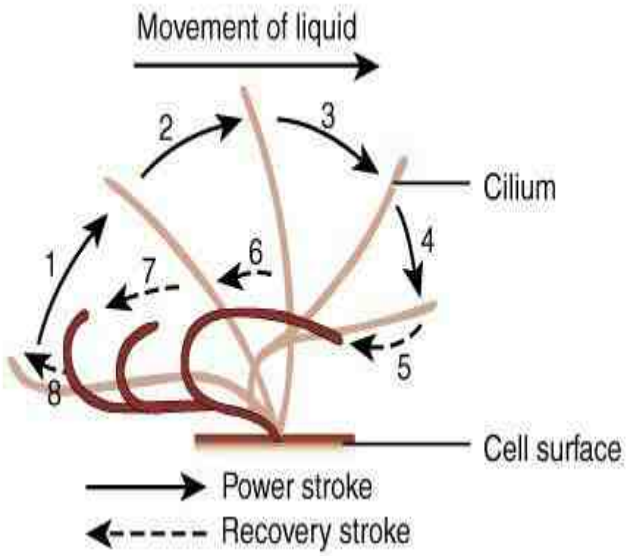
Figure 1

- The microtubules are *set up in a* ***circle of*** ***nine pairs*** *of microtubules* ***with two****, singular microtubules* ***in the center***. This is true for most cilia and flagella found in eukaryotic cells.
- **Radial spokes** reach out from the area near the center pair of microtubules *to each of the outer pairs*.
- In addition to the radial spokes, the outer pairs of microtubules have a ***pair of arms*** *in between each pairs*. These arms ***enable the cilia and flagella to move in a bending motion.***
- The **movement** is made possible by *a large protein molecule known* ***as*** ***dynein***.
- ATP provides the energy required by the dynein. **The basal body**, which has the same composition and structure as the centrioles, *is* ***the anchoring structure of the flagella and cilia***.
- *Some basal bodies* ***turn into centrioles****, such as the sperm's flagellum once it has entered the egg in human gametes.*

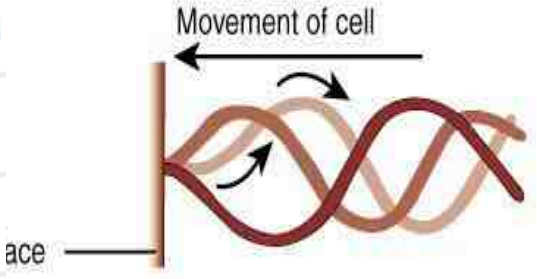
Differences:

- Cells usually contain a ***large amount of cilia***, whereas cells usually **only have one or *a small number of flagella***.
- Cilia, in **diameter**, are approximately *0.25 micrometers and 2-20micrometers long*. Flagella have a **similar diameter** but may range *from* ***10-200 micrometers*** **long**.
- ***Movement*** *is also different* in the flagella and cilia.
- Flagella undulate and propel the cell ***in the same direction of its axis.***
- Cilia move the cell ***perpendicular to it's axis*** using a **propelling** stroke followed by a **recovery stroke**.
- Movement in prokaryotic cells is usually accomplished by flagella.

Definition	Cilia are short, hair like appendages extending from the surface of a living cell.	Flagella are long, threadlike appendages on the surface of a living cell.
Cross section	Nexin arm present.	Nexin arm absent.
Length	Short	Longer than cilia, can vary
Motion	Rotational, like a motor, very fast moving	Wave-like, undulating, sinusoidal, slow movement compared to cilia
Density	Many (hundreds) per cell	Few (less than 10) per cell
Found in	Eukaryotic cells	Eukaryotic and prokaryotic cells
Etymology	Pronounced as 'silly-ah', is the plural of cilium. From Latin word for eyelash.	Pronounced as 'fla-gel-ah', is the plural of flagellum. From Latin word for whip.

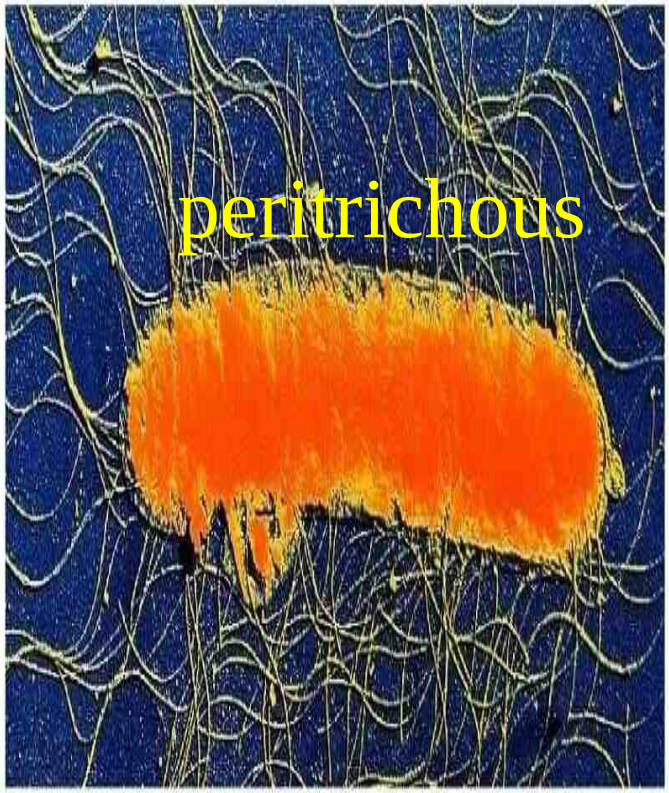


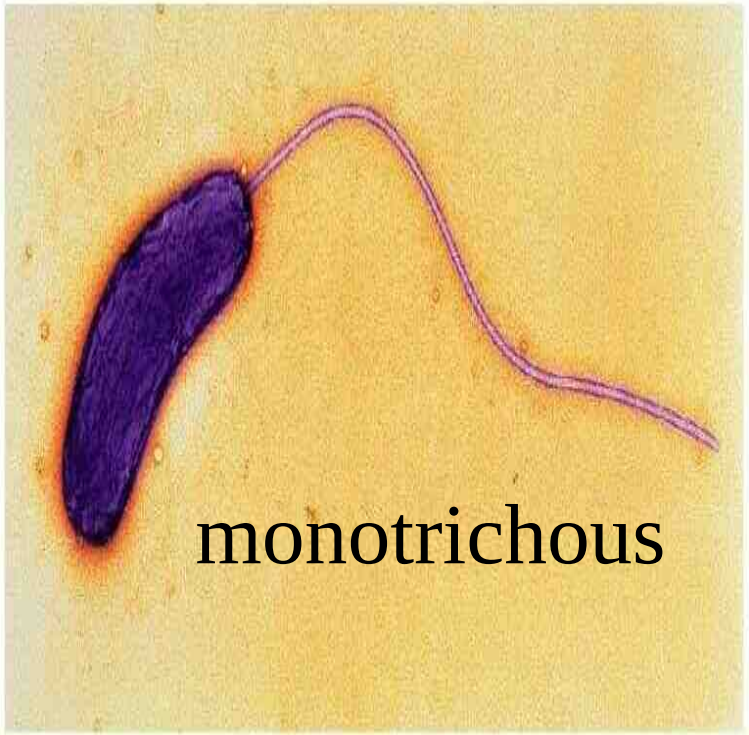
(b) Ciliary movement



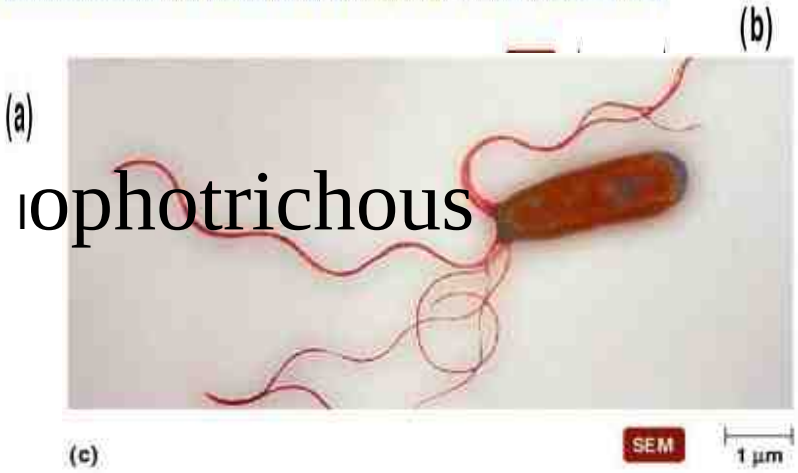
(c) Flagellar movement

Arrangements of Bacterial Flagella





amphitrichous



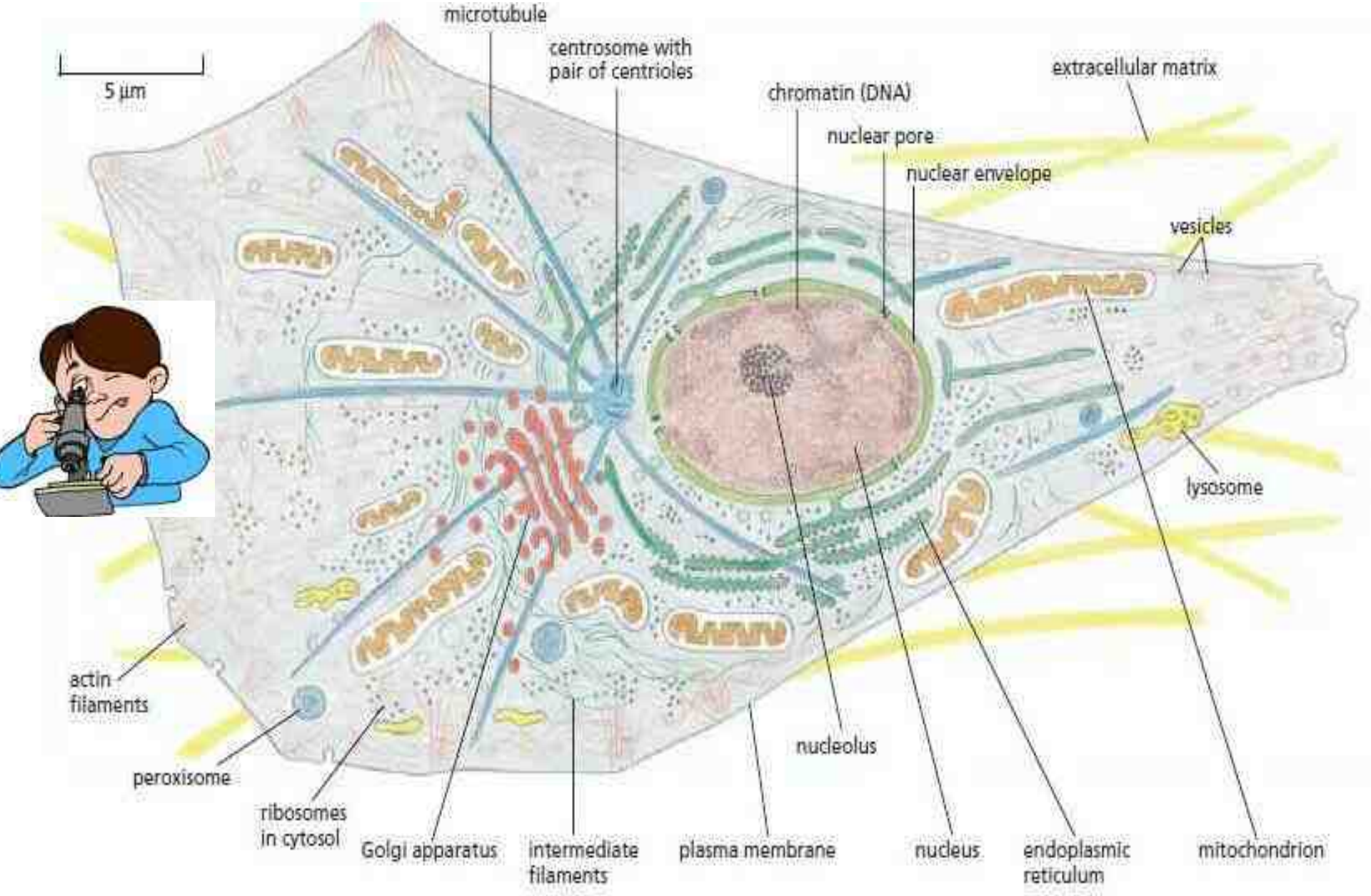
lophotrichous

CYTOPLASM

- Cytoplasm *is* ***everything inside a cell between the plasma membrane and the nucleus***. It is a jelly-like material that is ***eighty percent*** **water** and *usually clear in color*.
- **Cytoplasm**, which *can also be referred to as* ***cytosol***, means **cell substance**. Many tiny structures called organelles are *located in the cytoplasm* **except for the nucleus itself**.
- Among such organelles are *the* ***mitochondria***, which are the sites of energy production. Through ATP (adenosine triphosphate) synthesis,

- *The **endoplasmic reticulum***, the site of **lipid and protein synthesis**;
- The ***Golgi apparatus***, which packages macromolecules into vesicles for transport;
- **Lysosomes** and **peroxisomes**, sacs of digestive enzymes that carry out the **intracellular digestion** of macromolecules such as lipids and proteins;
- ***The cytoskeleton***, a network of protein fibers that give shape and support to the cell.

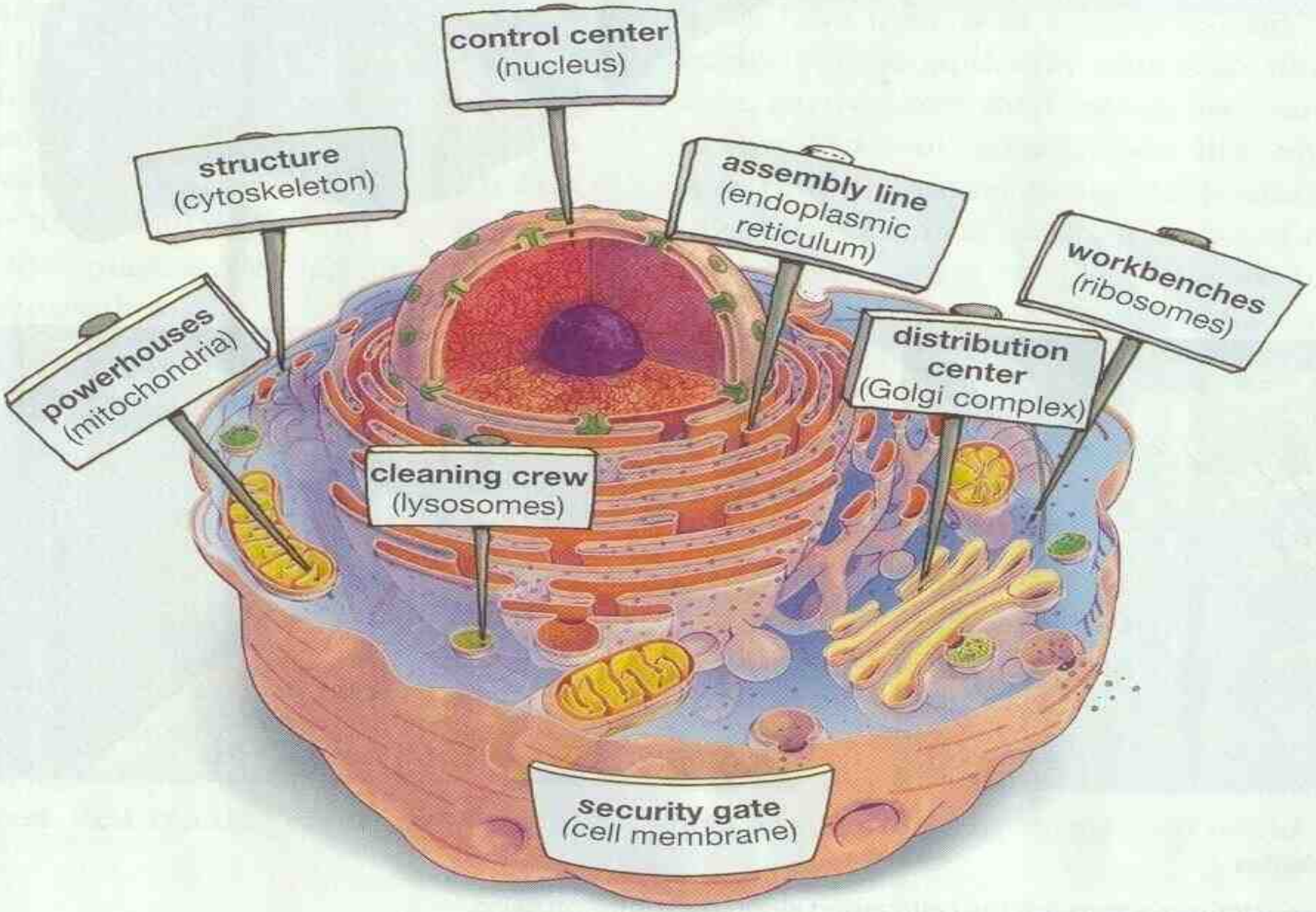
CELL ORGANELLES



- Organelle= "**little organ**"
- Found **only inside eukaryotic cells**
- All the stuff in between the organelles is **cytosol**
- Everything in a cell except the nucleus is **cytoplasm**

Control center, structure, assembly line, workbenches, distribution center, security gate, cleaning crew, powerhouse.

- **Nucleus**
- ER
- Ribosome
- Golgi complex
- Lysosomes
- Mitochondria
- Cytoskeleton
- Cell membrane
- …


control center
(nucleus)
structure
(cytoskeleton)
assembly line
(endoplasmic
reticulum)
workbenches
(ribosomes)
powerhouses
(mitochondria)
distribution
center
(Golgi complex)
cleaning crew
(lysosomes)
security gate
(cell membrane)

THE CELL NUCLEUS:
The BOSS
Brain of the Cell

The Nucleus

- The nucleus is **the headquarters** of the cell.
- It is **the most obvious organelle** in any eukaryotic cell and appears as a large dark spot in EUKARYOTIC cells.
- It **controls all cell activity**.

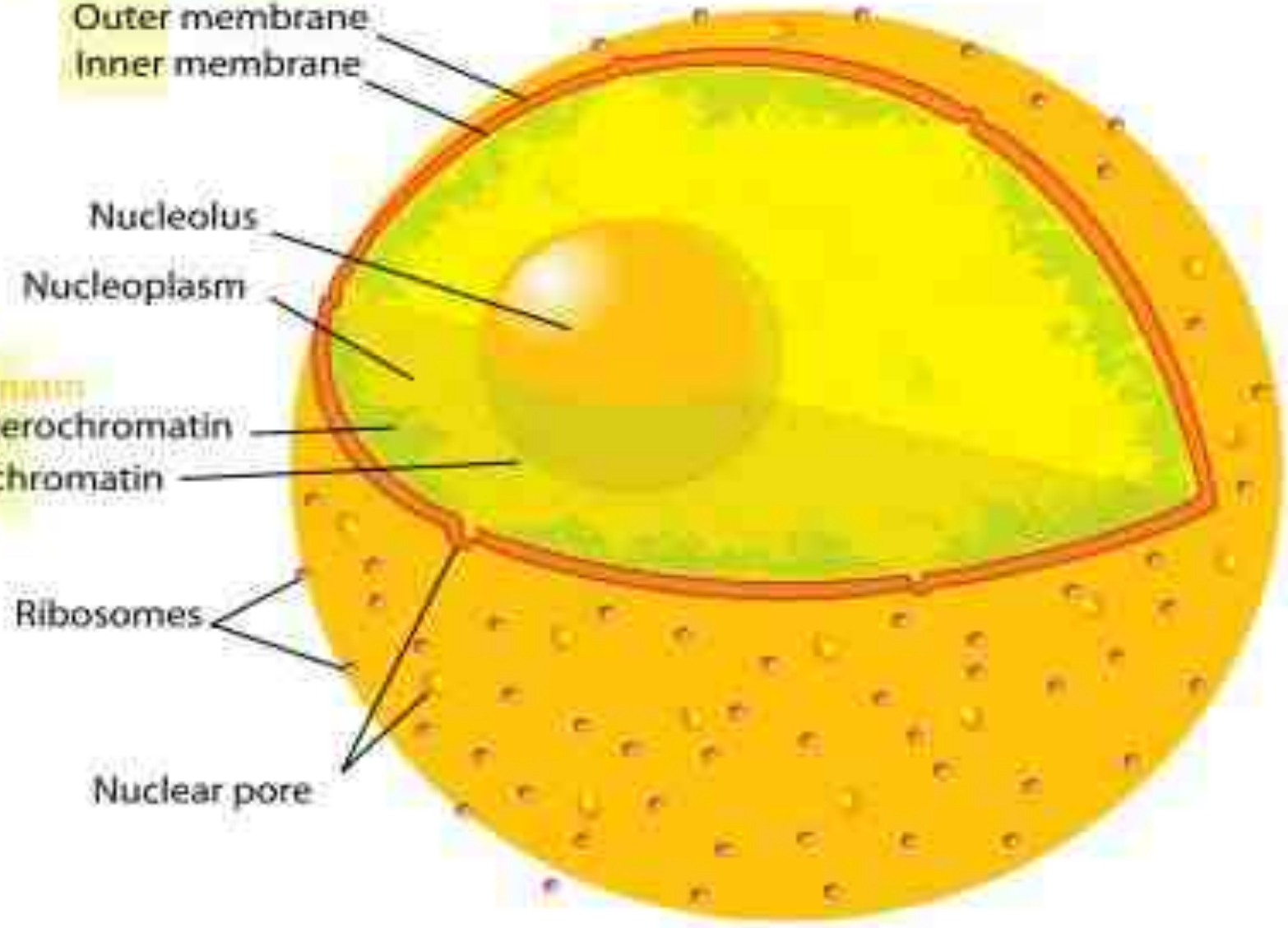
➢ The Nucleus is a membrane-enclosed organelle which **house most of the genetic information** and **regulatory machinery** responsible for providing the cell with its **unique characteristics**.

- It **stores the cell's hereditary material**, or DNA.
- Site of **DNA replication**
- Site of **DNA transcription** to mRNA
- **Ribosomal formation**
- **Nucleolus**: RNA & protein required for ribosomal synthesis
- It **coordinates the cell's activities by regulating gene expression**.

NUCLEUS STRUCTURE

- About **10%** of the cell volume.
- Contains **DNA, condensed and organized with proteins as chromatin.**
- Surrounded by **nuclear envelope** on the exterior.
  - a double membrane, **two leaflets 10-50 nm** apart.
    - This forms an interior space **k/a peri-nuclear space.**
  - Contains ~**3000 nuclear** pores, regulated by a protein structure, the **nuclear pore complex (NPC).**
    - **Small molecules** (<**mw 20,000**) can pass right through, **larger molecules are strongly regulated.**
  - Interior of envelope is **supported by nuclear lamina.**

NUCLEUS



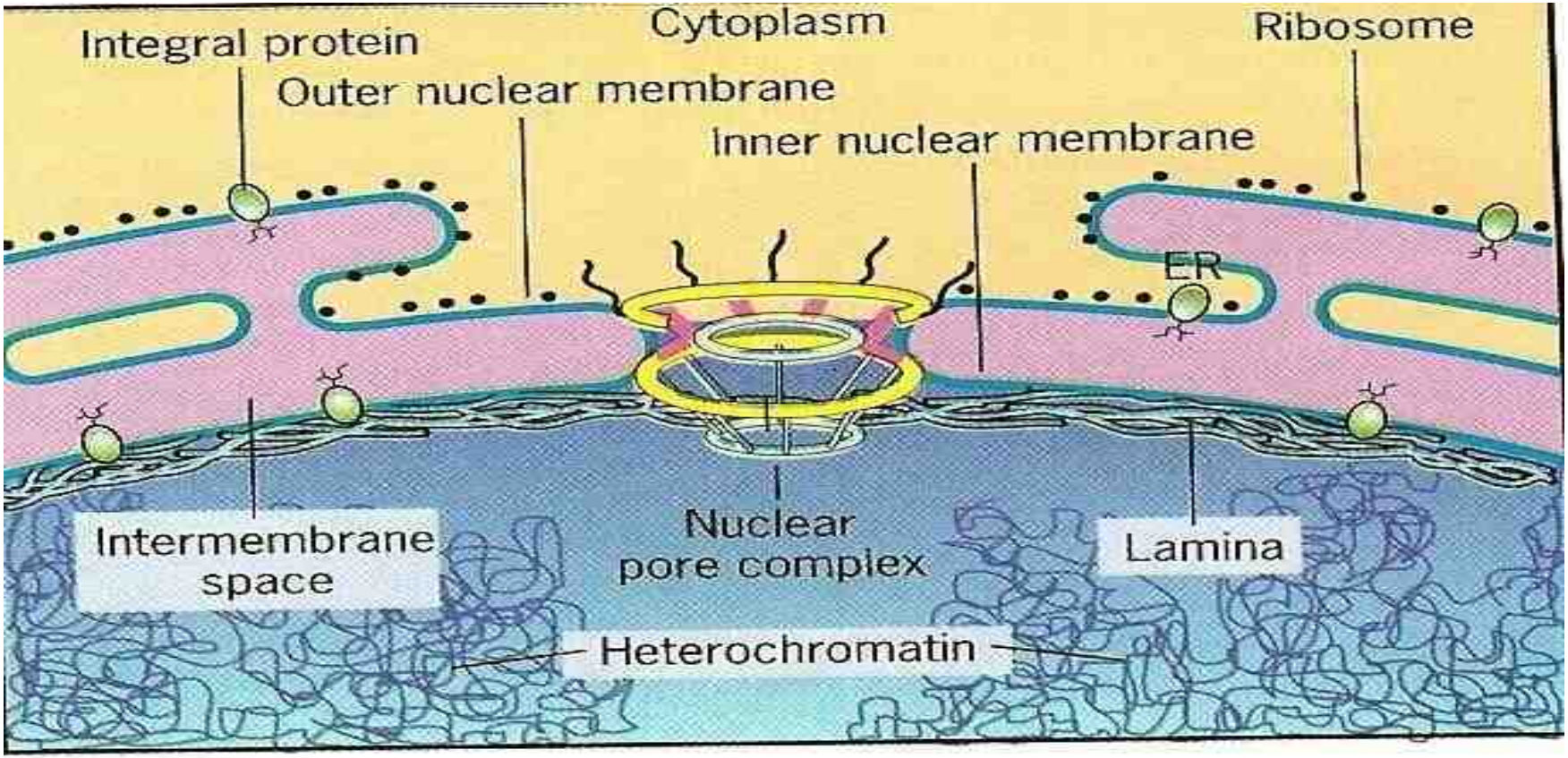
The inside of the nucleus is called the karyoplasm (or nucleoplasm).

THE NUCLEAR ENVELOPE (NE)

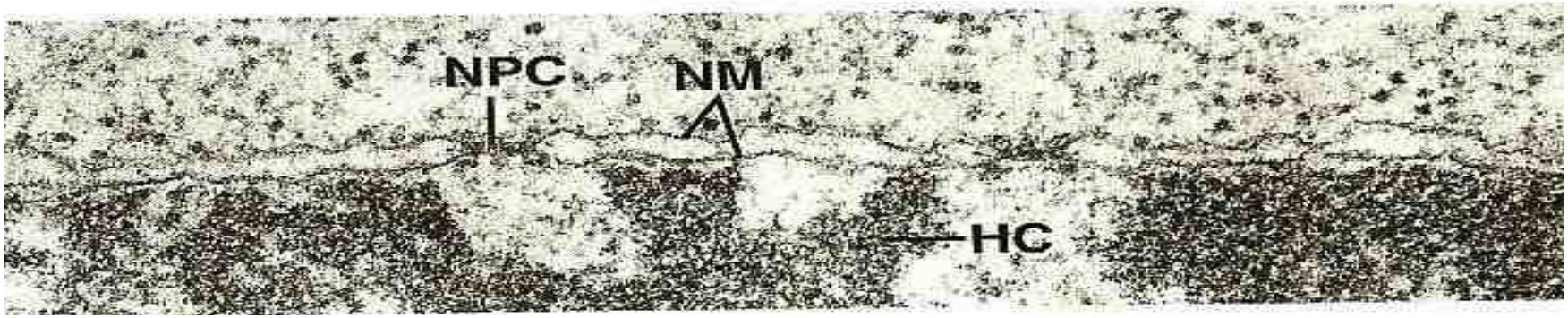
- The nuclear envelope completely encloses the nucleus and separates the cell's genetic material from the surrounding cytoplasm, serving as **a barrier to prevent macromolecules from diffusing freely between the nucleoplasm and the cytoplasm**.

- The outer nuclear membrane is **continuous with the membrane of the rough endoplasmic reticulum (RER), and is similarly studded with ribosomes.**

- The space between the membranes is called the **peri-nuclear space** and is **continuous with the RER lumen**.


Integral protein
Cytoplasm
Ribosome
Outer nuclear membrane
Inner nuclear membrane
ER
Intermembrane space
Nuclear pore complex
Lamina
Heterochromatin

(a)


NPC
NM
HC

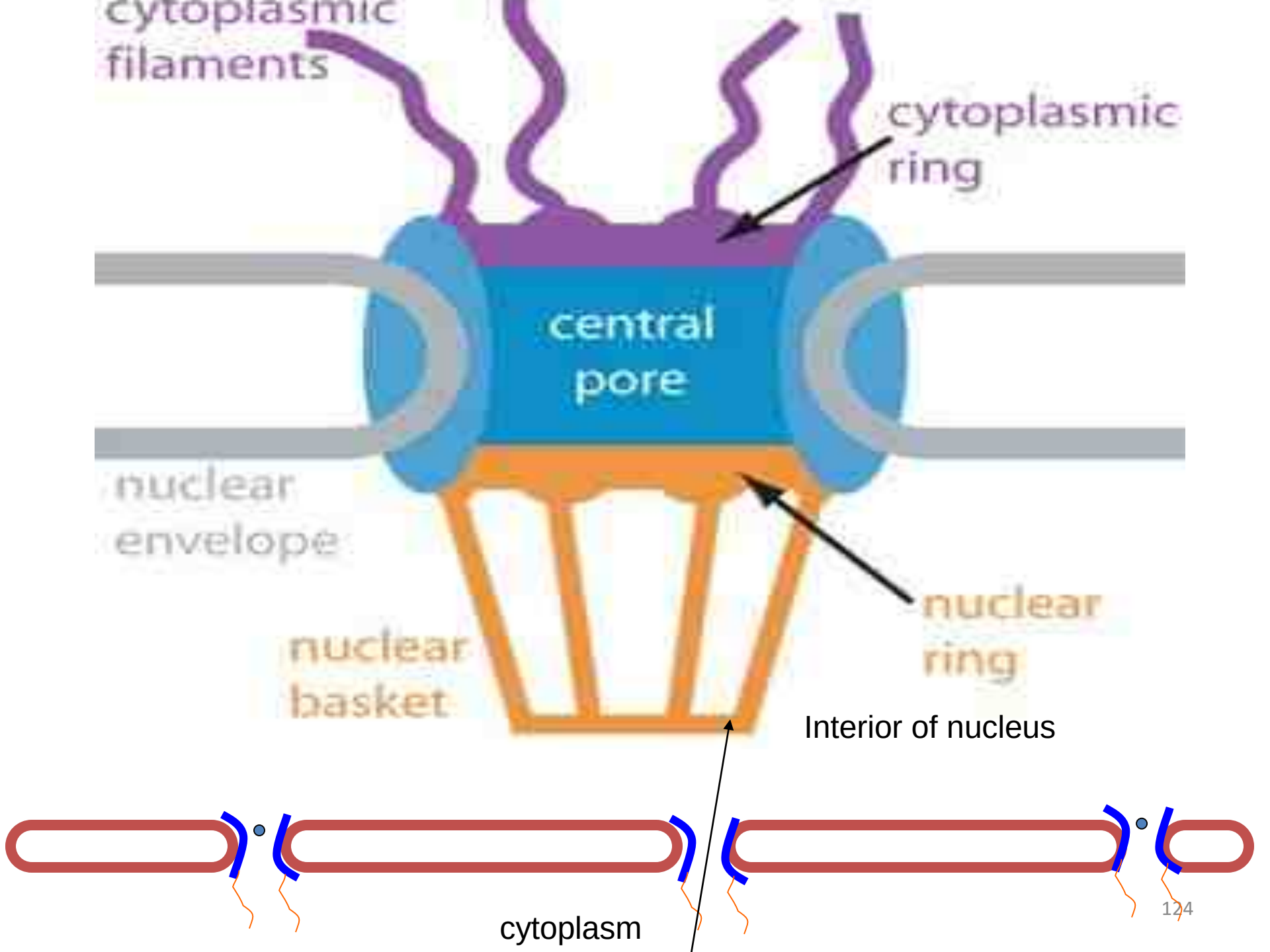
- **The inner surface of the NE** is bound to a *thin filamentous network* (***lamin protein***) called the **nuclear lamina**. It provides mechanical **support to the NE** and serves as **sites for attachment for chromatin fibers**.

- Mutations in the lamin genes are responsible for several distinct human diseases (e.g. a rare form of muscular dystrophy).

THE NUCLEAR PORE

- The nuclear pores are the gateways across which movement of **RNAs and proteins** takes place between the nucleus and cytoplasm ***in both direction***.
- **Proteins** synthesized in the cytoplasm cross the nuclear envelop to initiate replication and transcription of genetic material. Similarly, **mRNA, tRNA and ribosomal subunits** built in the nucleus cross through the nuclear pores to the cytoplasm.

- The pore is **100 nm in total diameter** and consists of around **100 proteins** which allows the free passage of small water-soluble molecules while preventing larger molecules, such as DNA and proteins.
- The nucleus of a typical mammalian cell has about **3000 to 4000 pores throughout its envelope**.
- Each pore contains a donut-shaped, **eight fold-symmetric ring-shaped structure** at a position where the inner and outer membranes fuse.
- Attached to the ring is a structure called the ***nuclear basket*** that extends into the nucleoplasm, and a series of filamentous extensions that reach **into the cytoplasm**.
- Both structures serve to **mediate binding to nuclear transport proteins.**


cytoplasmic filaments
cytoplasmic ring
central pore
nuclear envelope
nuclear ring
nuclear basket
Interior of nucleus
cytoplasm

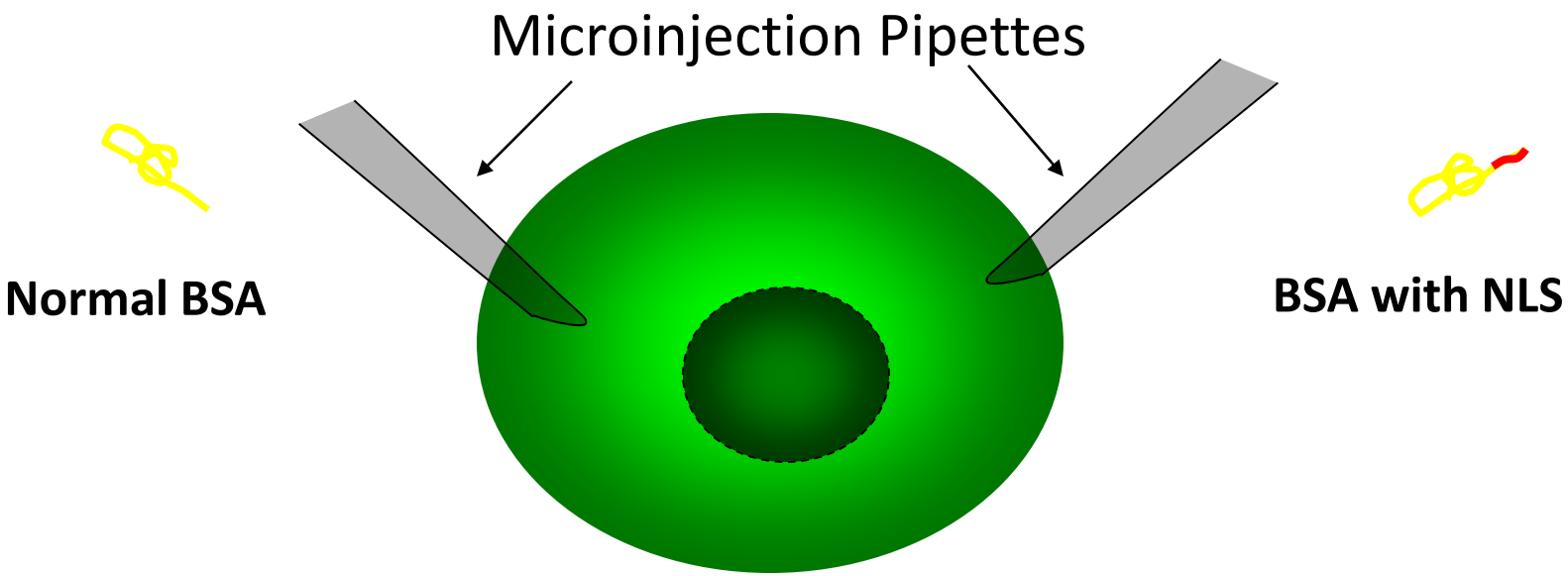
NUCLEAR PORES AND TRAFFIC

Nuclear Pores regulate traffic into and out of the nucleus by means of the Nuclear Location Signal **(*NLS*).**

- Proteins are brought **into the nucleus from the cytoplasm.**
  and can be sent out too
- **RNAs** (messenger RNA, ribosomal RNA and transfer RNAs) are all **transported out of the nucleus**.
  - but only when they are completed
- **Nuclear Location Signal (NLS)**
  - a specific amino acid sequence **marks protein for nuclear entry** (Laskey, 1982)
  - **a series of positively charged amino acids in specific sequence:**
    - pro – lys – lys – lys – arg – lys – val –

Experiment

1. What happens when we use recombinant DNA techniques to add the **NLS** to a dummy protein?
2. Normal or modified **Bovine Serum Albumin** (NLS added) and **injected to the cytoplasm**



- This provided evidence of **nuclear transport receptors**
  - family of proteins associated with the nuclear pore complex
- **Importins** recognize the NLS and bring proteins in
- Another set of proteins, the **exportins,** work in the opposite direction
  - These recognize other signals

(1) Protein binds to a **two-protein complex** (importin a and importin b)

- Importin a is a receptor for the NLS portion of the protein

  i.e. **it recognizes and sticks to this region**.

(2) Complex and protein **stick to cytoplasmic filament**

- mediated by importin b

(3) Complex **moves into nucleoplasm**

- *Not an energy consuming step*, **it can go back at this point unless captured by the Ran- GTP** in next step:

(4) Complex binds to another protein

- This is the Ran-GTP; after binding, **complex dissociates**
- **importin b stays on the Ran-GTP**

https://www.youtube.com/watch?v=rrvTbix4FtQ

(5) **Ran-GTP - importin b complex moves back** to the cytoplasm, down a concentration gradient

(6) Two things happen now

- First, the Ran-GTP is **converted to Ran-GDP** and phosphate by the enzyme **RANGAP.** This causes it to loosen from importin b
- Second, an **exportin molecule binds to importin a, setting it up for transport out of the nucleus**

(7) Ran-GDP diffuses back to the nucleus (1)

- (down its concentration gradient, I.e. from high to low concentration)
- Exportin carries importin a out of the nucleus (2)

(8) Restoration to initial state

- The importin a and importin b complex re-forms.
- Enzyme RCC1 re-forms Ran-GDP to Ran-GTP

How is this type of import controlled?

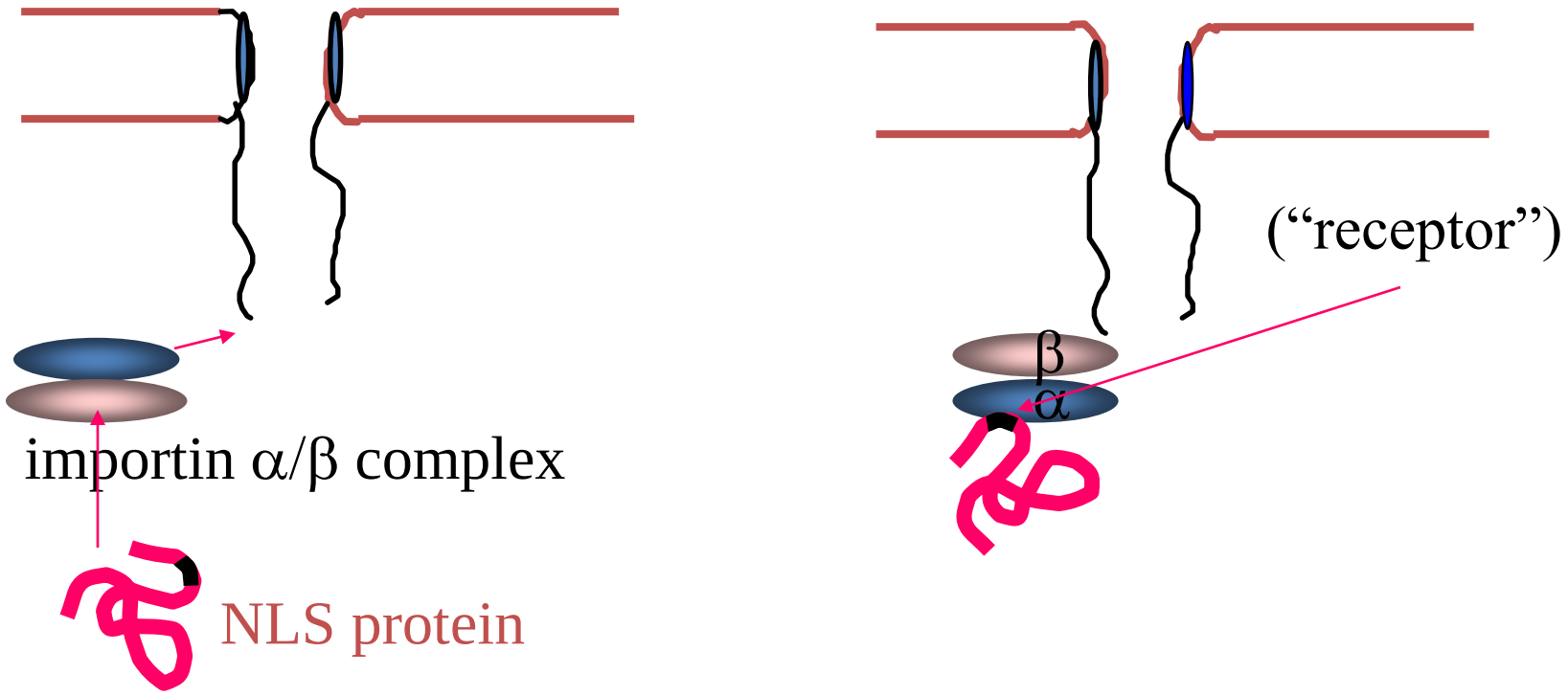
- GDP to GTP conversion is an *energy source and controls the process.*
- Molecules always diffuse from high to low concentration, so if the gradient is maintained, **it can be used to bring importin β back to the cytoplasm**
- ***RCC1 occurs only in the nucleoplasm, RANGAP in cytoplasm***
  - By breaking down Ran-GTP and thereby removing it, ***RANGAP maintains the conc. Gradient*. It can take the other molecule out with it**.
  - By changing Ran-GDP back to Ran-GTP, **RCC1 maintains the gradient helping Ran-GDP to diffuse back into the nucleus**.

Mechanism of protein import through nuclear pore complex

Step 1

Step 2

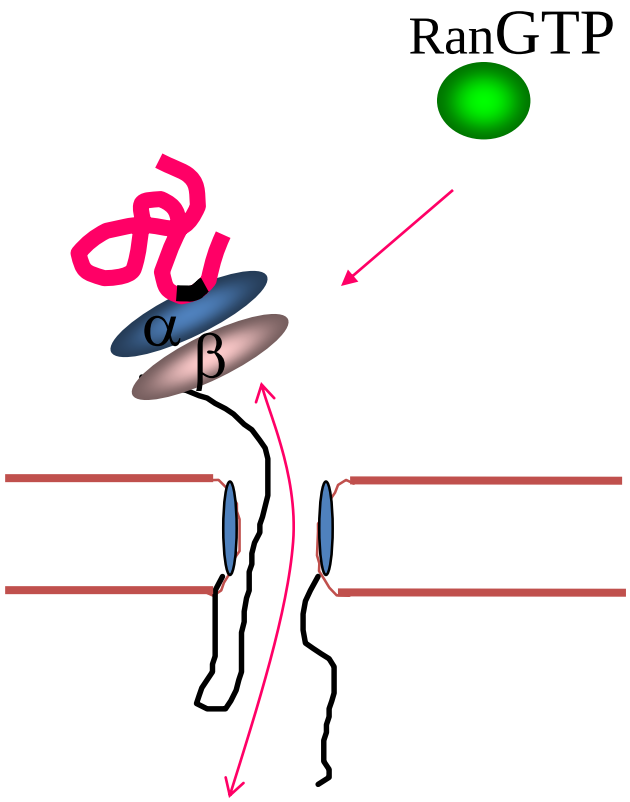
interior of nucleus (select proteins needed here)



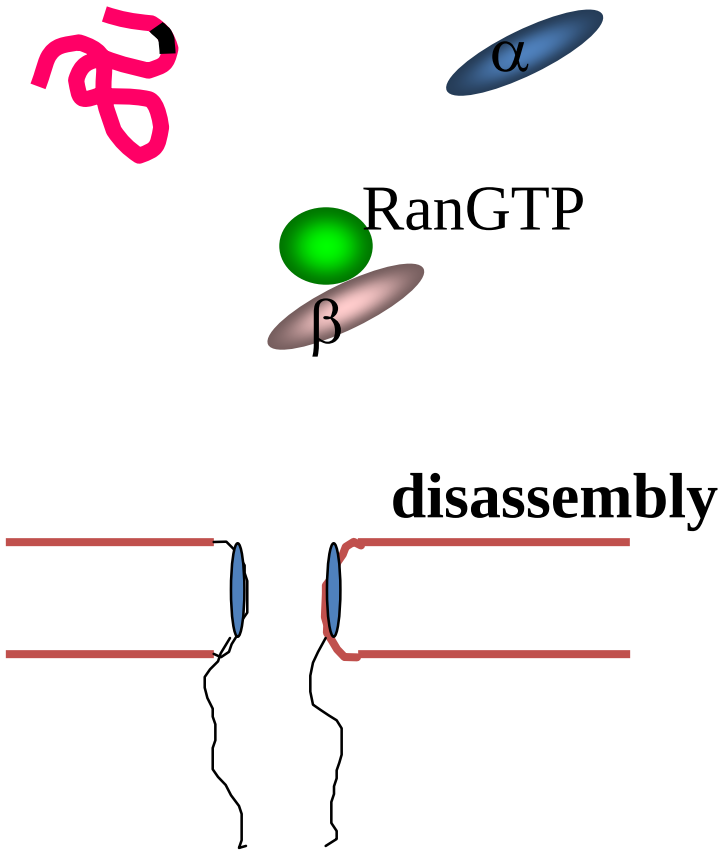
exterior of nucleus (where proteins are made)

Import of proteins to the nucleus, continued

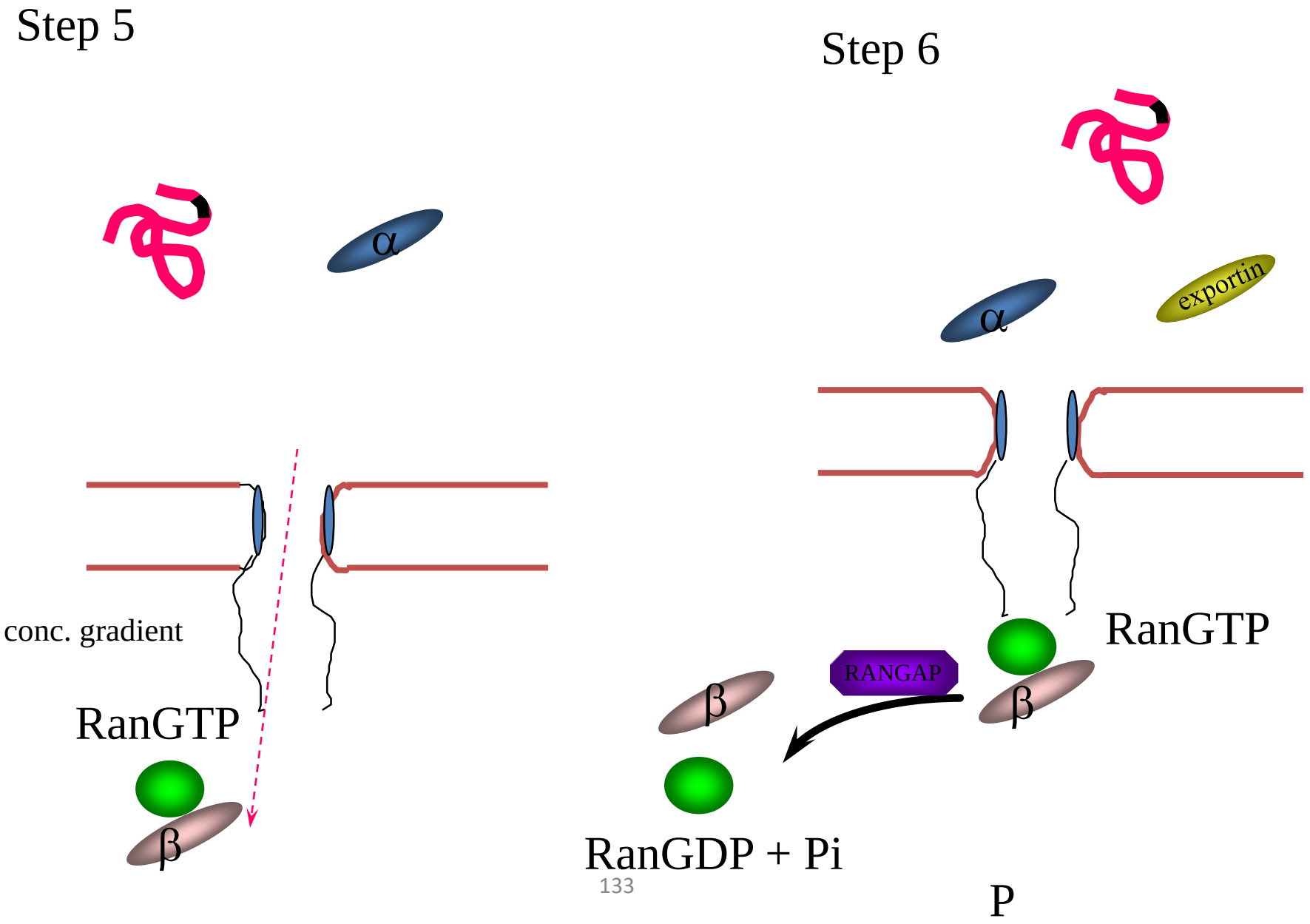
Step 3

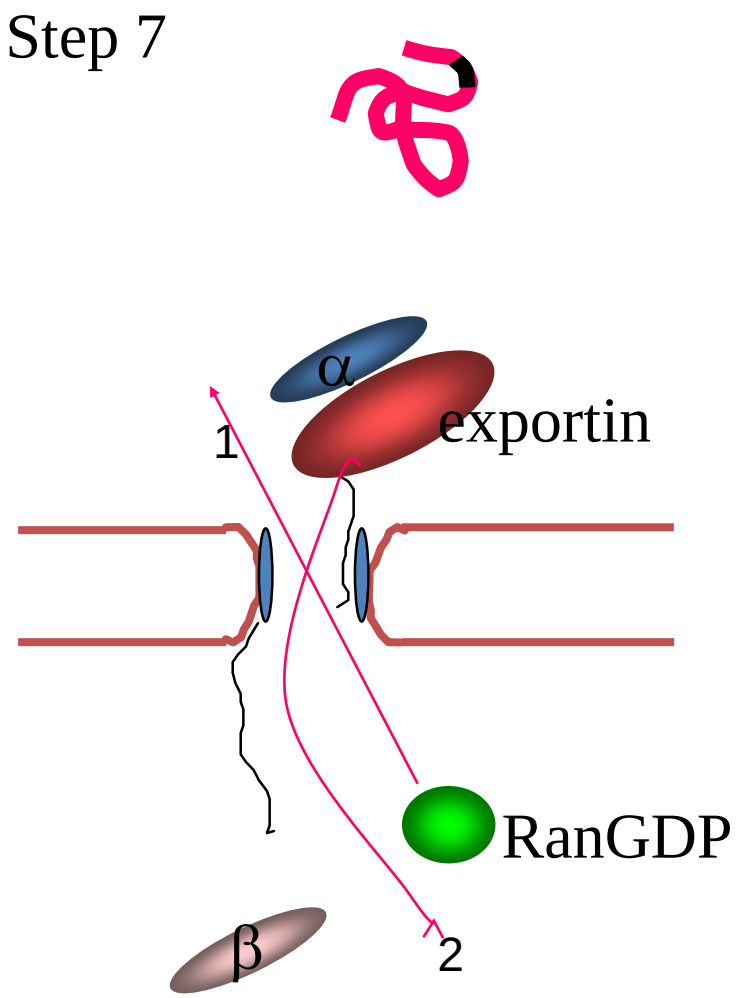


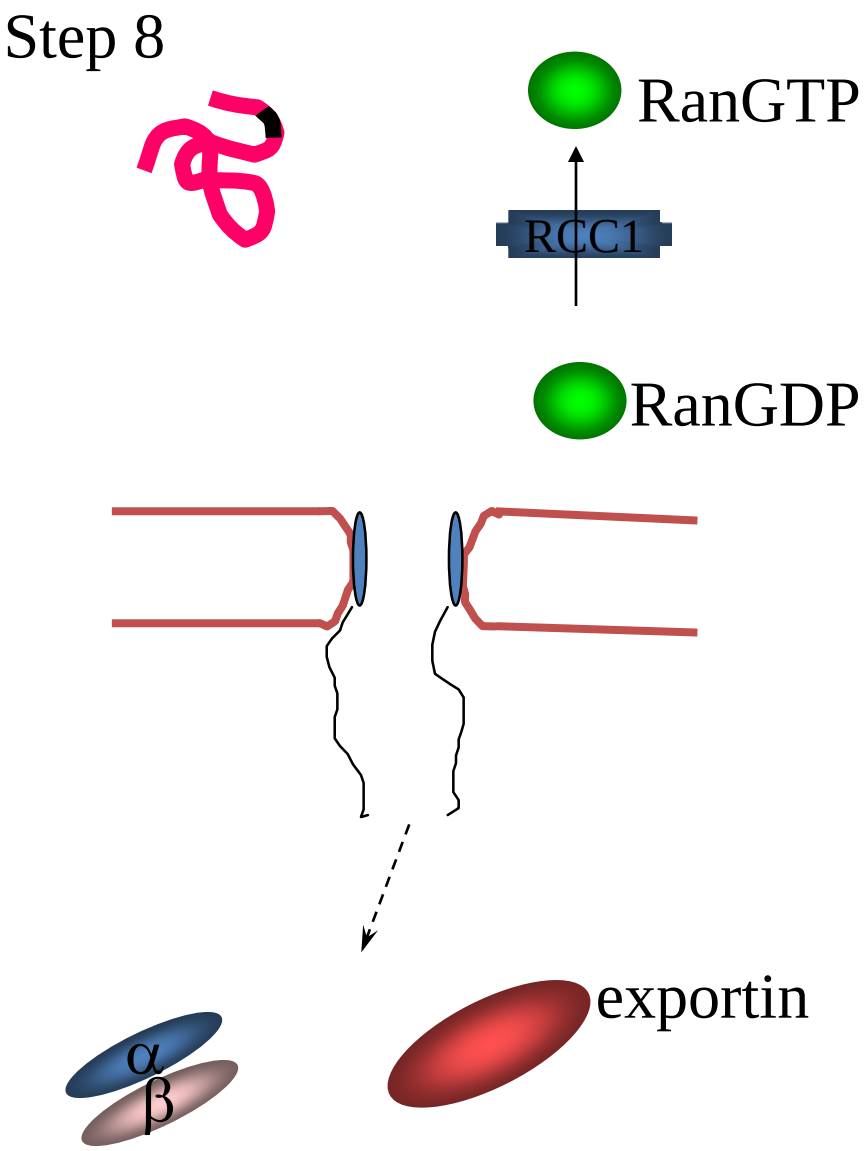
Step 4



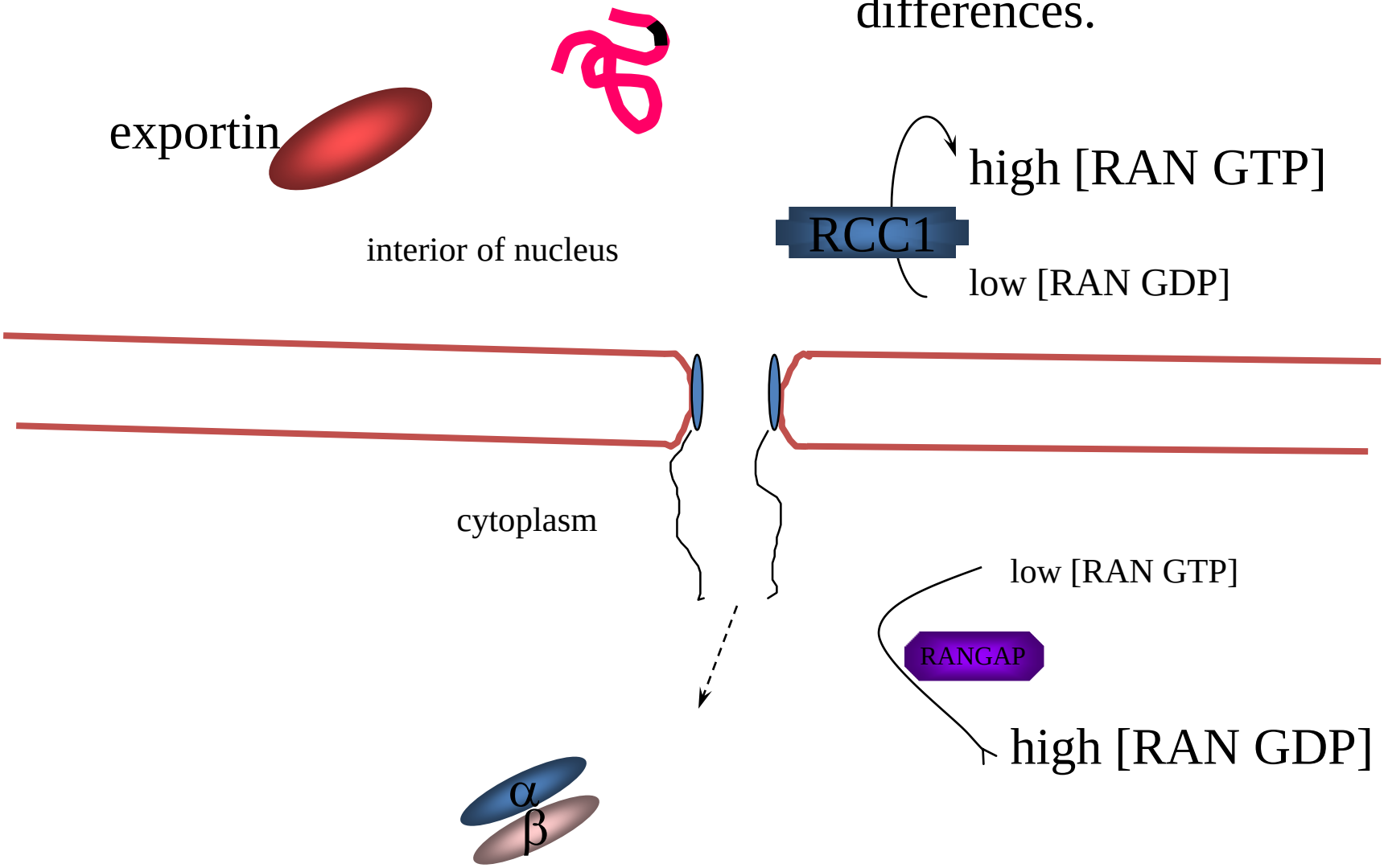
mechanism of import of NLS protein (continued)




Step 7
α
exportin
1
RanGDP
β
2


Step 8
RanGTP
RCC1
RanGDP
exportin
α
β

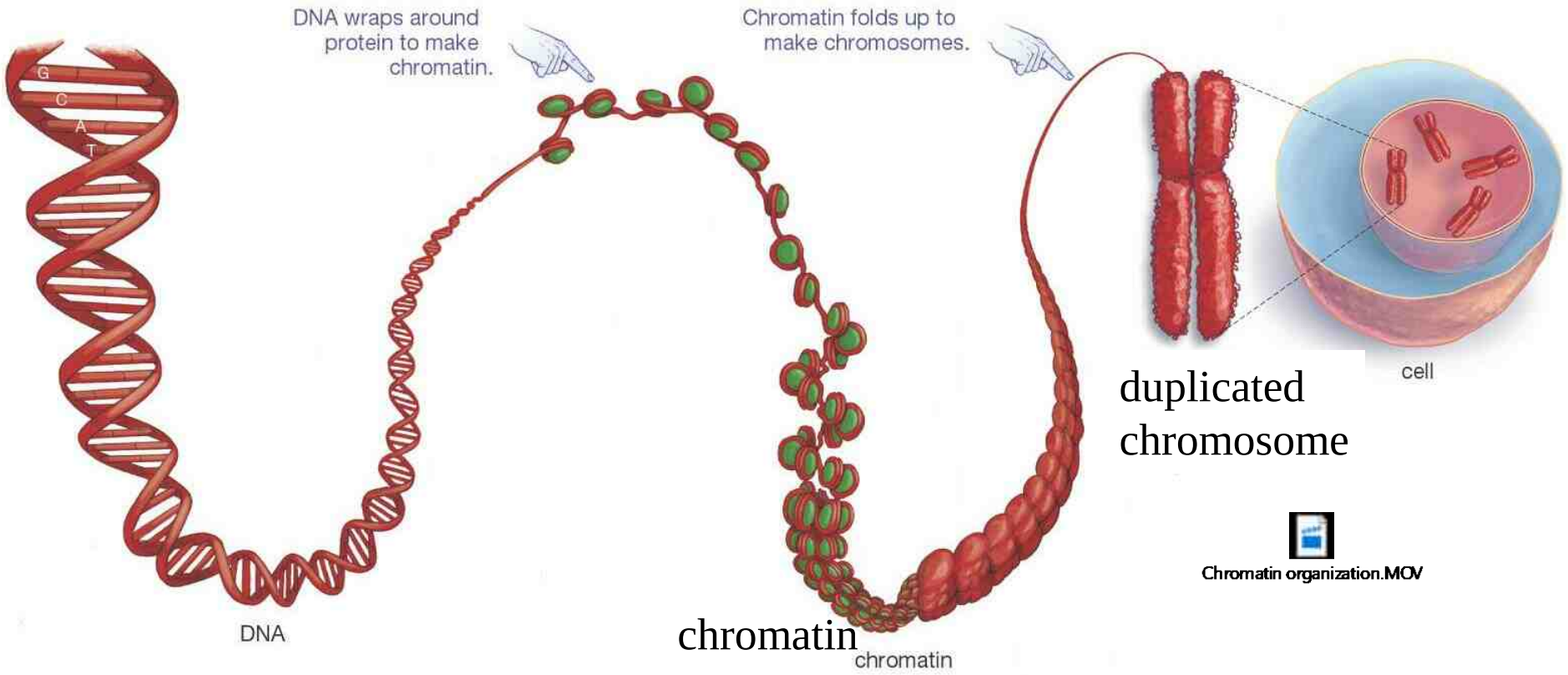
ENERGY SOURCE.
Note concentration differences.



CHROMATIN

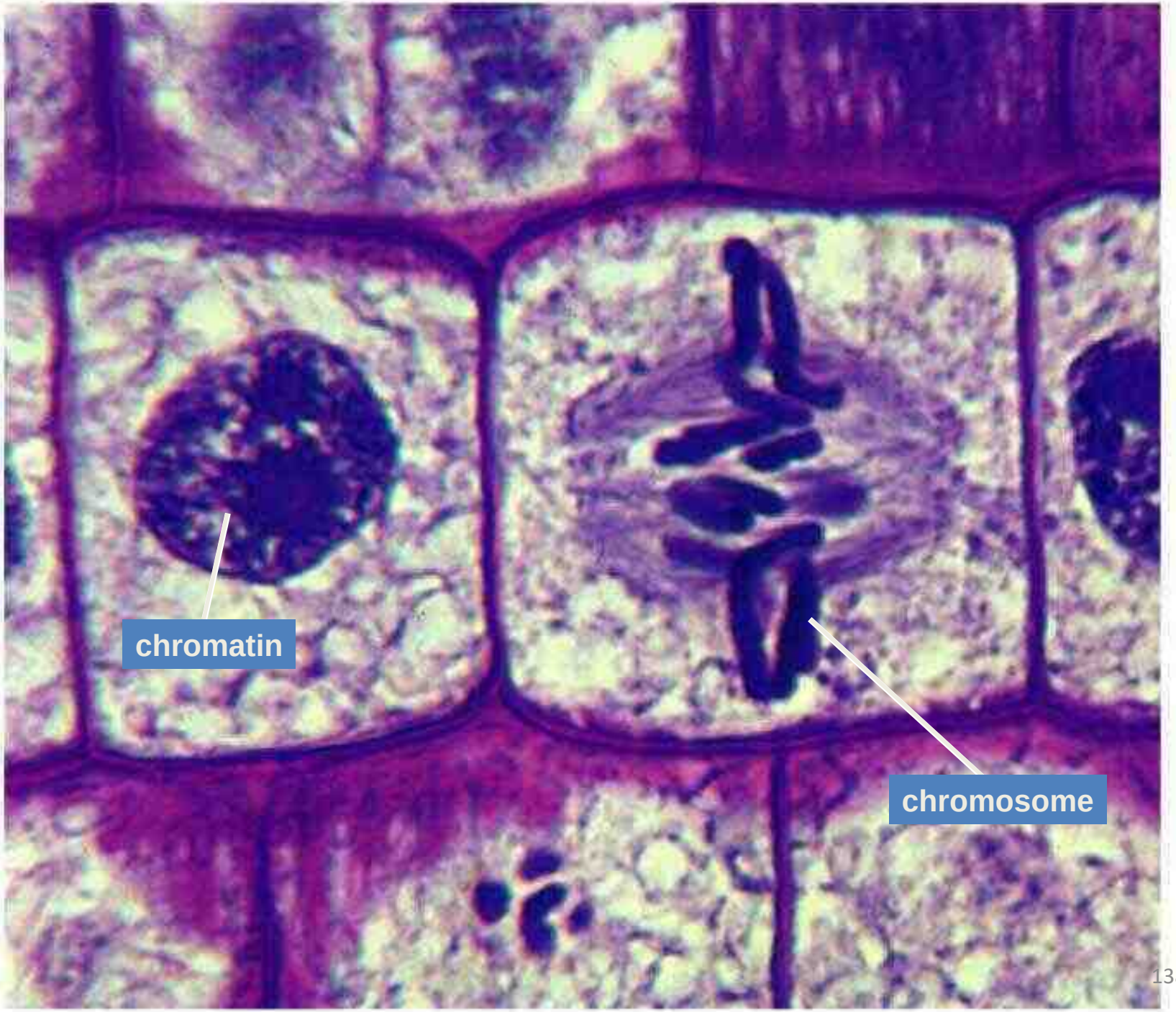
- ***The interphase chromosomes*** **are present in a** ***highly extended nucleoprotein*** *fibers* **called chromatin.**
- **Chromatin is the** ***complex of DNA and protein (Histones)*** **that makes up chromosomes.**
- **Each un-replicated chromosome contains** ***a single continuous DNA molecule.***
- ***The mitotic chromosome*** **represents a highly condensed structure (***10000:1***)**

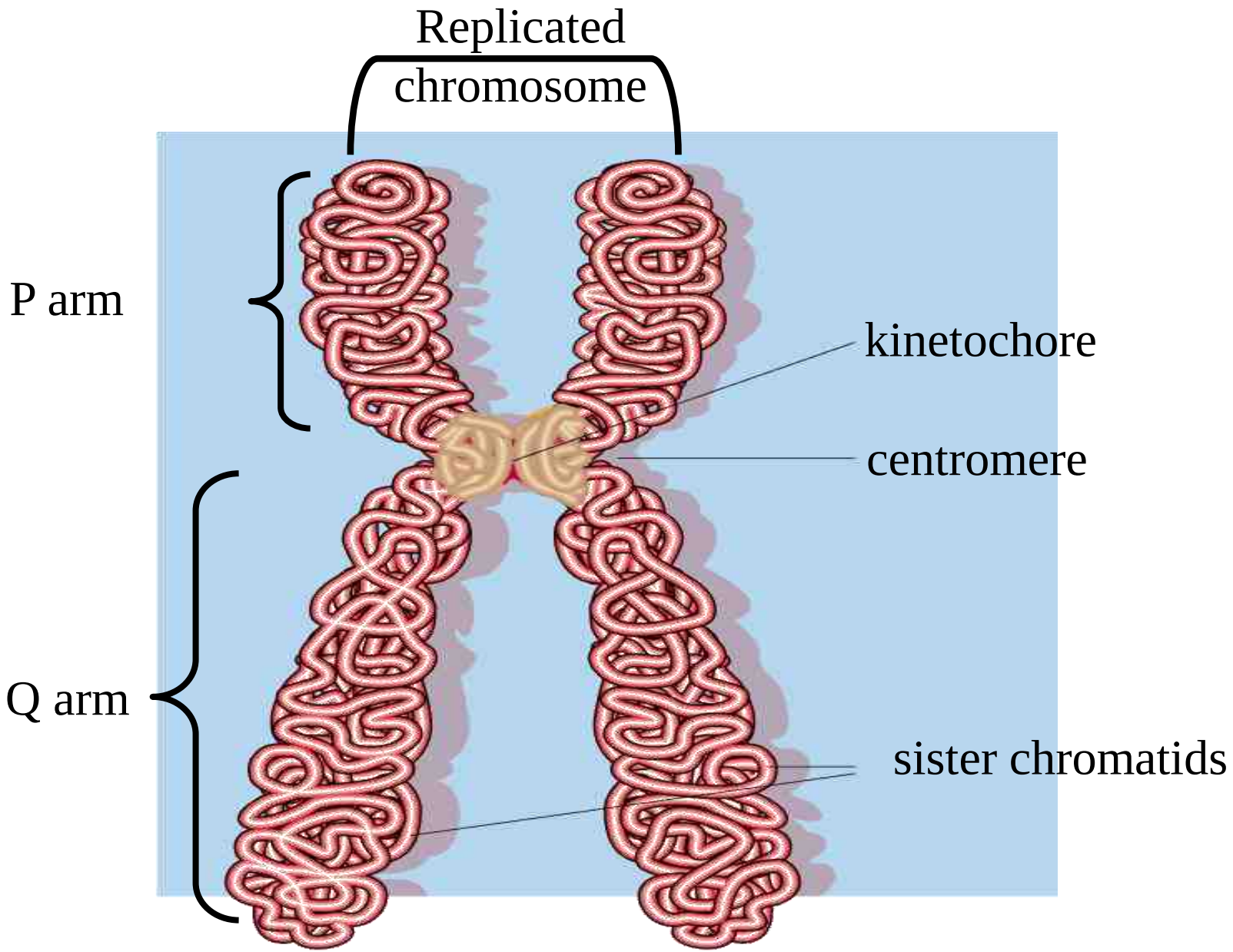
DNA is Packaged into Chromosomes

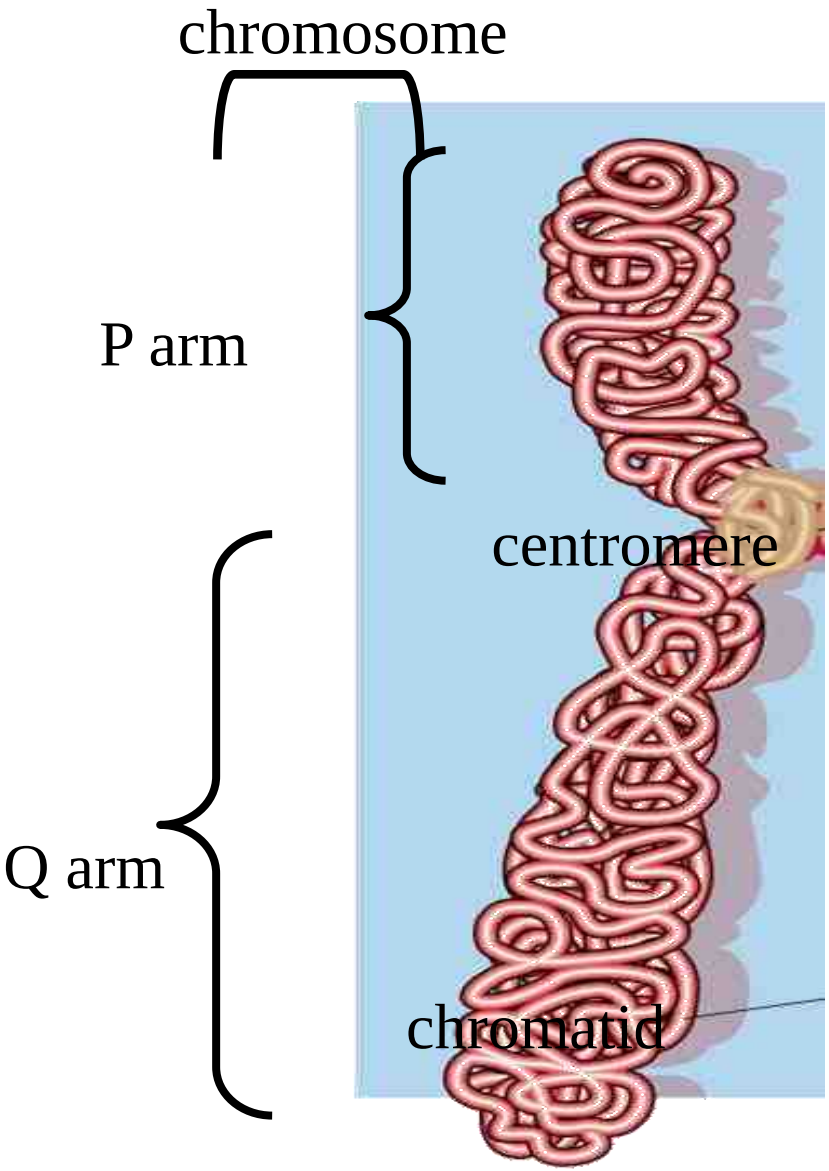


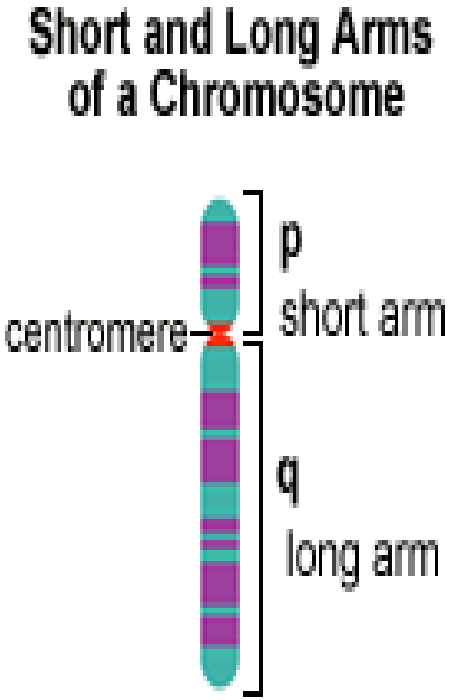
DNA in the cell **is virtually always associated with proteins**.

The packaging is **impressive** ***– 2 meters of human DNA fit into a sphere about 0.000005 meters in diameter.***


chromatin
chromosome


Replicated
chromosome
P arm
kinetochore
centromere
Q arm
sister chromatids


chromosome
P arm
centromere
Q arm
chromatid


Short and Long Arms of a Chromosome
p
short arm
centromere
q
long arm

TYPES OF CHROMATIN

- In non-dividing cells there are two types of chromatin *euchromatin* and *heterochromatin*.

- Euchromatin: is a **lightly packed** form of chromatin that is **rich in gene concentration**, and is often **under *active transcription***. It is found in both eukaryotes and prokaryotes.

- **Heterochromatin**: Heterochromatin is a tightly packed form of DNA.
- Heterochromatin is **inactive** and remains compact during interphase.
- Heterochromatin plays **a role in *gene regulation*** and the protection of the integrity of chromosomes, attributed to the dense packing of DNA, which **makes it less accessible to protein factors that bind DNA or its associated factors**.

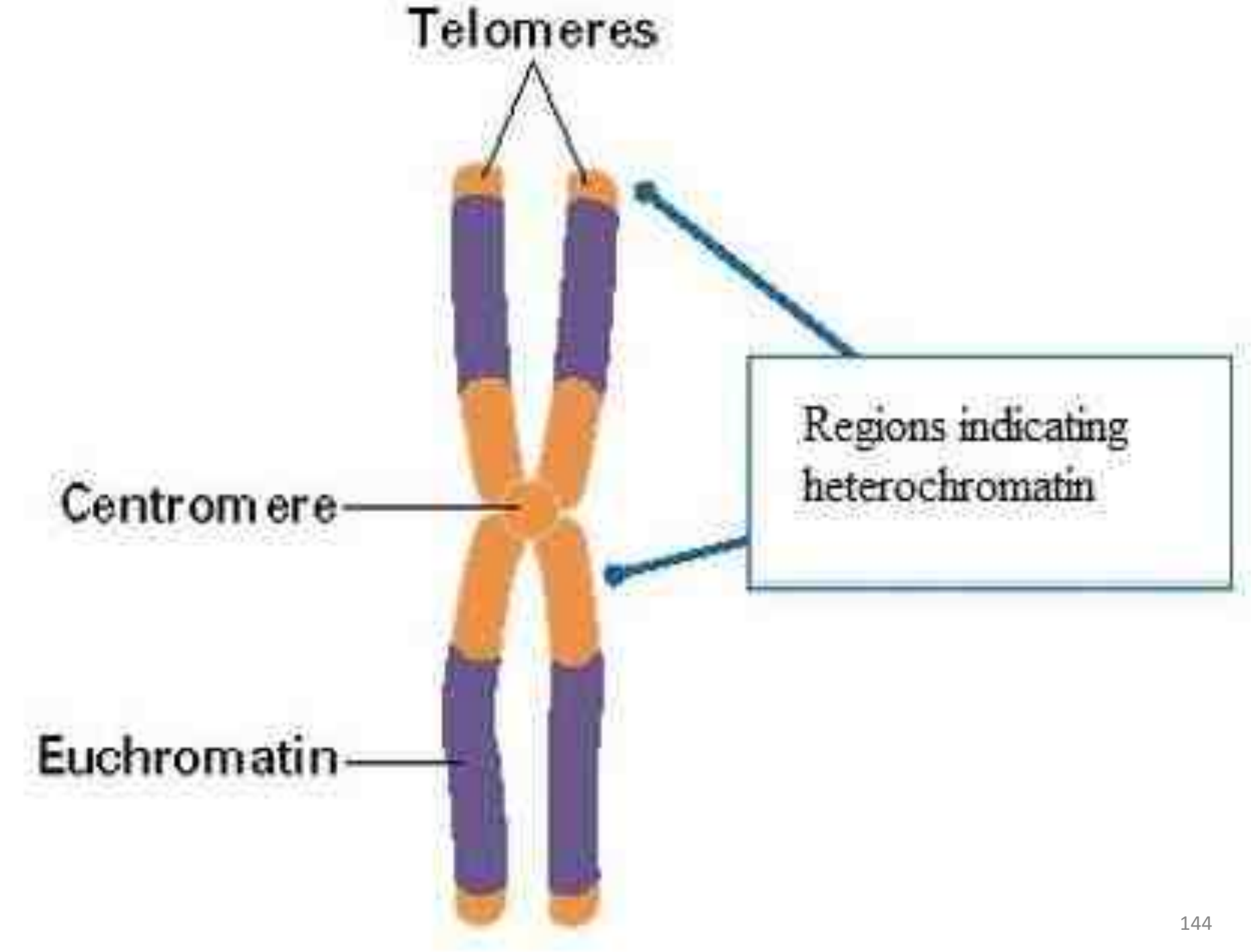
Chromatin Function

- **Package** DNA into a smaller volume to fit in the cell.
- **Strengthen** the DNA to allow mitosis and meiosis
- Serve as a mechanism **to control expression**.
- Changes in chromatin structure are affected mainly by **methylation** (*DNA and proteins*) and ***acetylation*** (*proteins*).
- Chromatin structure is also *relevant to DNA replication and DNA repair.*
- Histones are the proteins closely associated with DNA molecules. They are responsible for the structure of chromatin and play important roles in the regulation of gene expression.

Types of Heterocromatin

Constitutive heterochromatin: **remains compact in all cells and at all times and occurs around the chromosome centromere and near telomeres. It represents the silenced part of DNA.**

Facultative heterochromatin: **is a chromatin that has been inactivated in specific types of differentiated cells. An example of facultative heterochromatin is X- chromosome inactivation in female mammals: one X- chromosome is packaged in facultative heterochromatin and silenced, while the other X chromosome is packaged in euchromatin and expressed.**

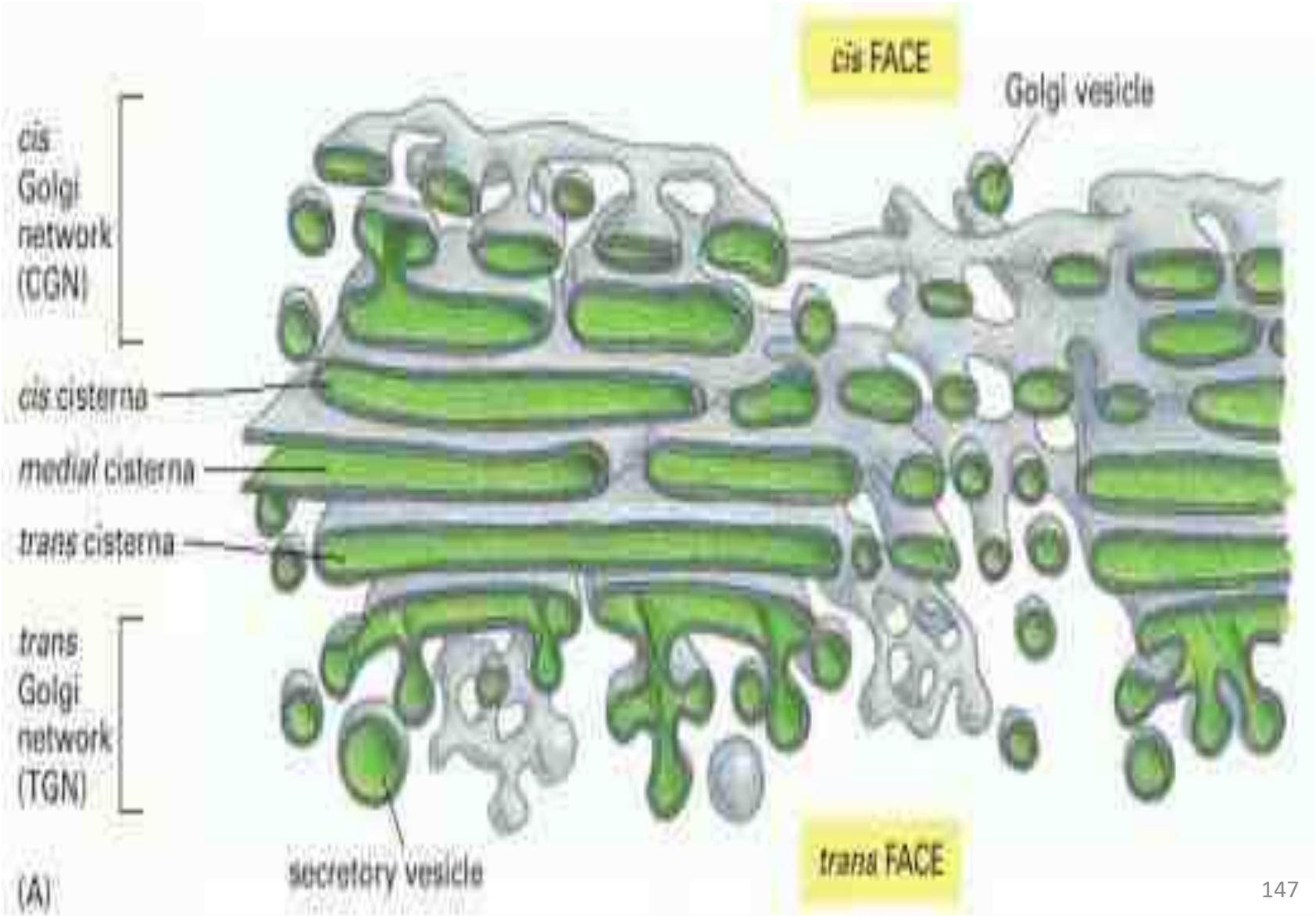

Telomeres
Regions indicating heterochromatin
Centromere
Euchromatin

Golgi Apparatus

- Because of its large and regular structure, the Golgi apparatus was **one of the first organelles described by early light microscopists**.

- It consists of a collection of **flattened, membrane-enclosed cisternae, somewhat resembling a stack of pancakes. Each of these Golgi stacks usually consists of *four to six cisternae***

- Each Golgi stack has **two distinct faces**: a ***cis* face** (or entry face) and a ***trans* face** (or exit face). Both *cis* and *trans* faces are closely **associated with special compartments**, each composed of **a network of interconnected tubular and cisternal structures.**


cis FACE
Golgi vesicle
cis Golgi network (CGN)
cis cisterna
medial cisterna
trans cisterna
trans Golgi network (TGN)
secretory vesicle
trans FACE
(A)

- **The proteins and lipids are modified** as they pass through layers of the Golgi.
- **Molecular tags** are added to the fully modified substances
  - ✓These tags allow the substances to be sorted and packaged appropriately.
  - ✓Tags also **indicate where the substance is to be shipped**.

Modification of proteins in the Golgi apparatus:

- **alteration** of **amino acid side chains**
- addition of **saccharide residues**
- **remodeling** of oligosaccharides
- **specific** proteolytic **cleavages**
- formation of **disulphide bonds**
- **assembly** of multiprotein complexes

Functions of the Golgi Complex

1) Sort proteins and lipids received from the ER;

2) **Modify** certain proteins and glycoproteins; and

3) **Sort and package** these molecules into vesicles for transport to other parts of the cell or secretion from the cell.

4) modification of amino acids (e.g.proline -> hydroxyproline)

5) addition of fatty acids

Structure of Golgi: based on function and morphology

1. **cis-Golgi network**: network of **tubular membranes** closest to ER

   a) Function = **sorting proteins**

   i) **Returns** ER proteins to sender

   ii) **Forwards** remainder to **cis-Golgi cisternae**

2) **Golgi cisternae**: **flattened stacks** of membranes

- subdivided into ***cis***, ***medial***, and ***trans***-cisternae
- **each performs specific functions** involved in processing proteins, has specific enzymes

  i) Many are involved in **glycosylation**

  ii) Also **modify some proteins**

  a) **Remove portions**

  b) **Modify amino acids**, e.g. convert proline to hydroxyproline

3) Trans-Golgi network: network of tubular membranes **farthest from ER**

Function = **sorting proteins, sending to final destination**

Include **ERGIC** (**Endoplasmic Reticulum- Golgi Intermediate Compartment**) between ER and Golgi, as region where RER is morphing into cis-Golgi network.

Transport from RER to Golgi

Proteins (& lipids) move **from site of synthesis to tips of RER.**

COPII-coated vesicles transport materials from tips of RER to cis-Golgi network via ERGIC

ENDOPLASMIC RETICULUM

- Throughout the eukaryotic cell, **especially those responsible for the production of hormones and other secretory products**, is *a vast amount of membrane called the endoplasmic reticulum*, or **ER for short**. The ER membrane is **a continuation of the outer nuclear membrane** .

- When viewed by electron microscopy, some areas of the endoplasmic reticulum **look "smooth"** (smooth ER) and some **appear "rough"** (rough ER).
- The rough endoplasmic reticulum consists of *a system of membranous sacs and tubules known as cisternae*. It derives its name from the fact that it is ***coated with numerous ribosomes***, *which line the cytoplasmic surface of its membrane*

- **The rough ER** has two primary functions; **make *more membrane*** and **convert polypeptide chains into a *variety of functional proteins***.
- **The smooth ER** is a network of **interconnected tubules that lack ribosomes**. *Much of its activity results from enzymes embedded in its membrane*. One of the most important functions of the smooth ER is the ***synthesis of lipids***, which includes fatty acids, phospholipids, and steroids. ***Each of these products is made by particular kinds of cells.***

LYSOSOMES

In 1955 Christian René de Duve discovers and names lysosomes.

- Lysosomes are membrane-bound sacs of ***hydrolytic enzymes***, which the cell uses to ***digest macromolecules***.
- The enzymes that are contained in the lysosomes have varying functions. **Some hydrolyze *proteins*, *polysaccharides*, *fats*, and *nucleic acids***.

- Lysosomes provide **a safe way for the cell to digest products *without having to deal with the destructive possibilities of hydrolytic enzymes*.**
- Lysosomes not only digest food products, but they also ***aid in the recycling of materials from defective or dying cell parts***.
- Lysosomes also ***work closely with food vacuoles***, which basically hold food products waiting for enzymes from lysosomes to come and continue with the cellular digestion of food.

VACUOLES

- Vacuoles are *membranous sacs* that belong to the endomembrane system.
- Plant cells have a large central water-filled vacuole enclosed by a **membranous extension** of the endomembrane system.
- Vacuoles play **many roles *in the maintenance and functioning of the cell*.**
- Vacuoles are primarily *storage bins* that **hold *a variety of substances*, which in turn determine their function.**

- **Food vacuoles** are *common in most **protozoan** and some **algae***.
- ***They form where the surface of the cell contacts a particle of food***.
- The plasma membrane at the surface forms *an in-pocketing to engulf* the food, which is then *detached from the plasma membrane* and **becomes a vacuole in the cytoplasm**.
- Lysosome fuses with the food vacuoles, exposing the nutrients to hydrolytic enzymes that digest them.

- ***Autophagic vacuoles*** is needed for cell to digest portions of itself. This often happens ***in response to starvation***.
- ***Contractile vacuoles*** are common in *protozoan* and are found in some *algae*.
- The *contractile vacuoles is essential only for* ***the removal of excess water from the cytoplasm***.
- Contractile vacuole is vital in *maintaining the cells internal environment.*

PEROXISOMES

- **Unlike lysosomes, peroxisomes do not bud from the endomembrane system.**
- **They are semi-spherical in shape and often have a granular or crystalline core. The core is probably made up of a collection of enzymes.**
- **The enzymes that are found in peroxisomes take hydrogen from various substrates and bind it to oxygen, making the by-product hydrogen peroxide (H202).**
- **In other peroxisomes, oxygen is used to break fatty acids into smaller molecules.**
- Peroxisomes play an **important role in the liver**, where **they *detoxify alcohol* by removing hydrogen to form H_2O_2**. Although, hydrogen peroxide is toxic, ***enzymes do exist in peroxisomes that convert it into water***.

Endomembrane system

- **There are two classes of internal membrane-bound structures in eukaryotic cells.**
- **There are discrete organelles such as mitochondria, chloroplasts, and peroxisomes; then there is the dynamic endomembrane system—nuclear membrane, endoplasmic reticulum, Golgi apparatus, lysosomes, and vacuoles.**
- **The endomembrane system is composed of the different membranes that are suspended in the cytoplasm within a eukaryotic cell.**
- These membranes divide the cell into functional and structural compartments, or organelles.
- The system is defined more accurately as **the set of membranes that form a single functional and developmental unit, either being connected together directly, or exchanging material through vesicle transport .**

ORGANELLES OF THE ENDOMEMBRANE SYSTEM

Plasma Membrane and Nuclear Envelope

Endoplasmic Reticulum (SER, RER)

Golgi Apparatus

Transport, Secretory Vesicles, and

Vacuoles

Lysosomes (only in animal cells)

Central Vacuole (only in plant cells)

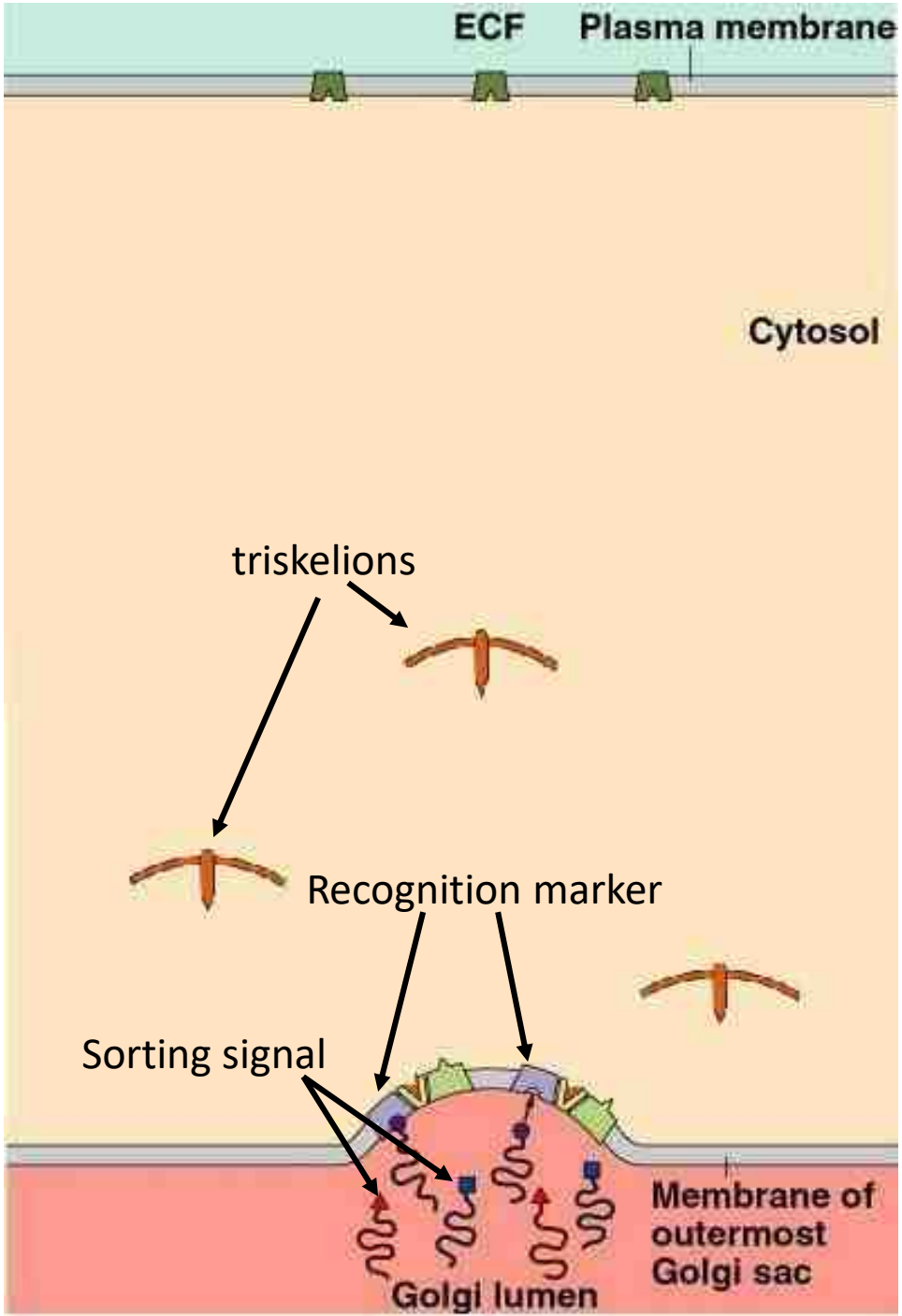
The endomembrane system allows macromolecules to diffuse or be transferred from one of the components of the system to another.

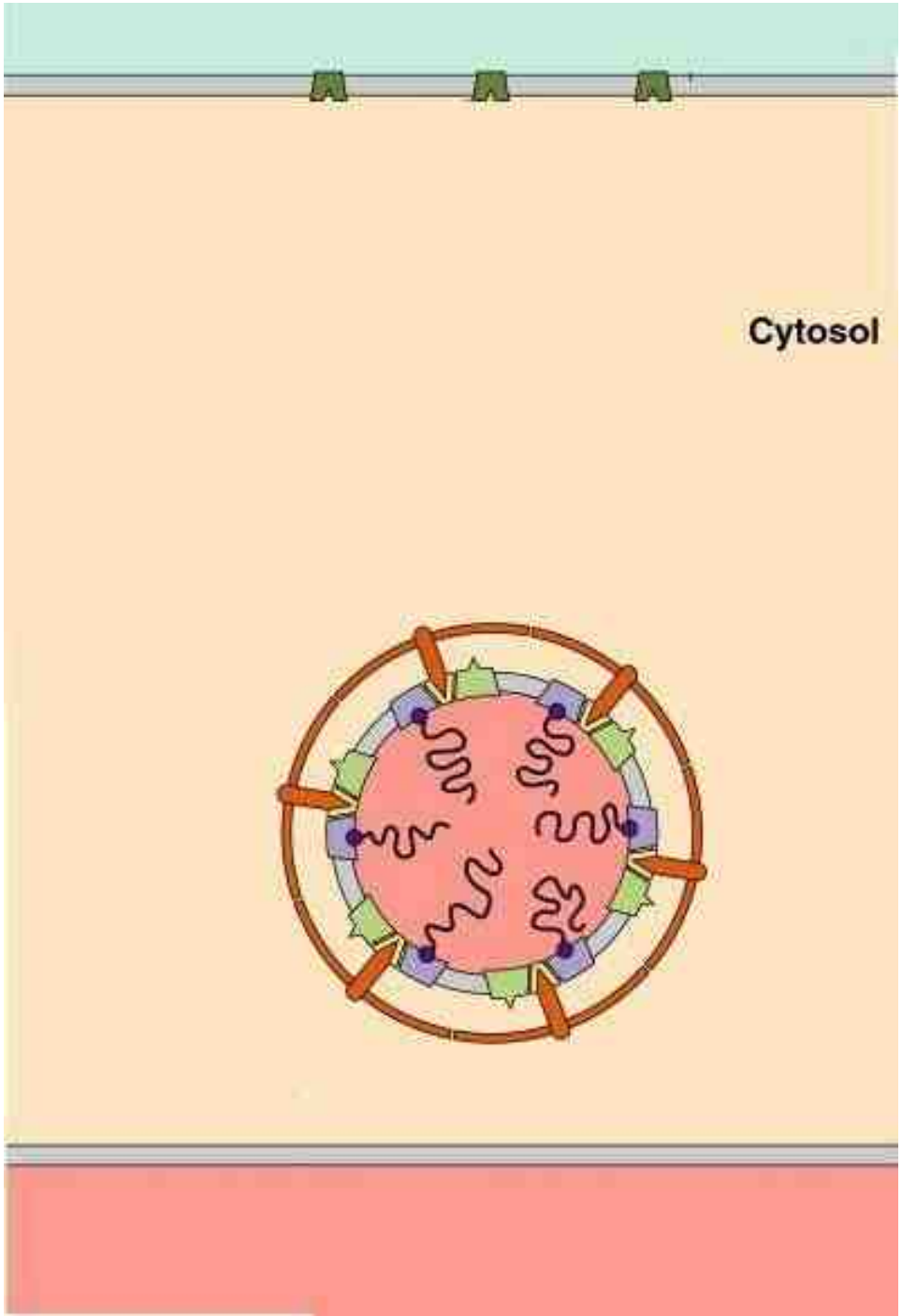
Vesicular Transport between Compartments

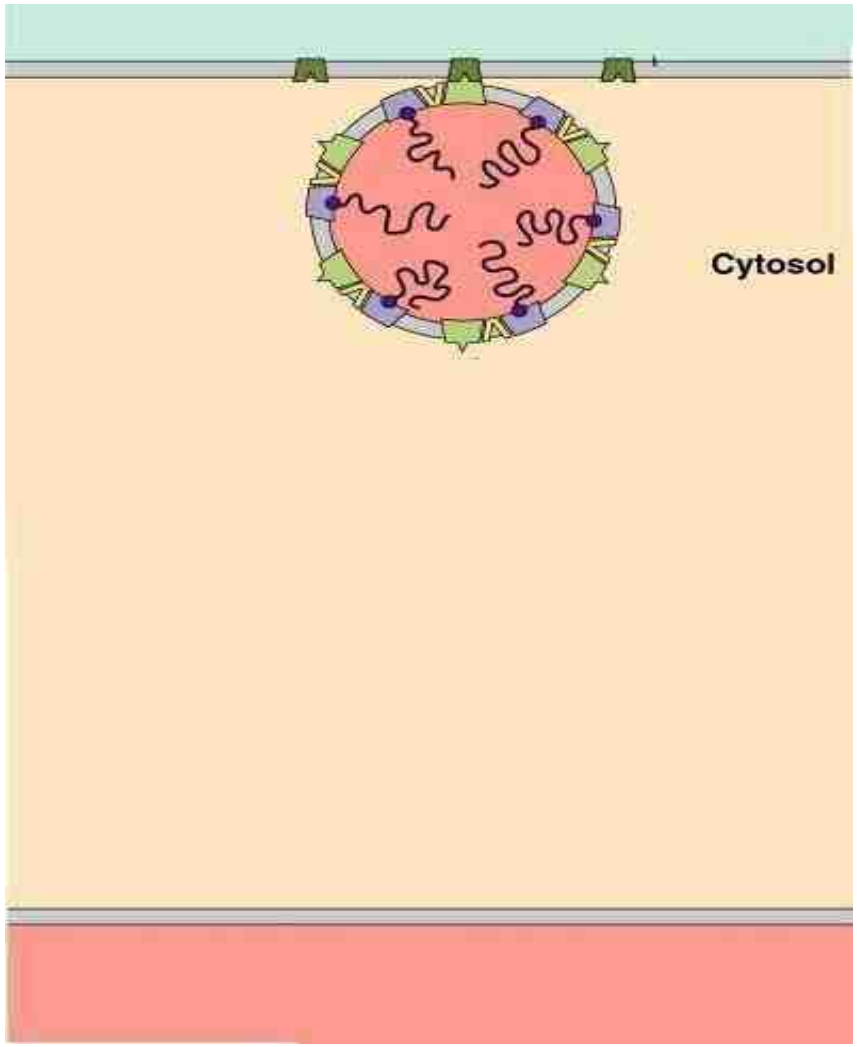
- **Transport vesicles are generally covered with coat proteins:**
- ✓ **COPII-coated vesicles: move proteins from ER to cis-Golgi**
- ✓ **COPI-coated vesicles: move proteins from cis-Golgi to ER; also possibly from ER to Golgi and between Golgi cisternae**
- ✓ **Clathrin-coated vesicles: move proteins from the trans-Golgi to the plasma membrane or lysosomes.**
- **Receptor protein systems (SNAREs) are believed *to target* and *dock* specific vesicles to the correct compartment**
- **At each step in the cytomembrane pathway, proteins that should stay in the previous compartment are retrieved by membrane-bound receptors and sent back to the correct compartment.**

- **Directed binding of proteins to specific markers**
  - **Sorting signal: on the protein to be secreted**
  - **Recognition marker: on golgi-binds the sorting signal**

- **Triskelions (clathrin) or adaptins in cytosol form a "coating" that also causes bulging to form the vesicle.**
- **Coating may (or not) shed, exposing the V-snare**


ECF
Plasma membrane
Cytosol
triskelions
Recognition marker
Sorting signal
Membrane of outermost Golgi sac
Golgi lumen


Cytosol

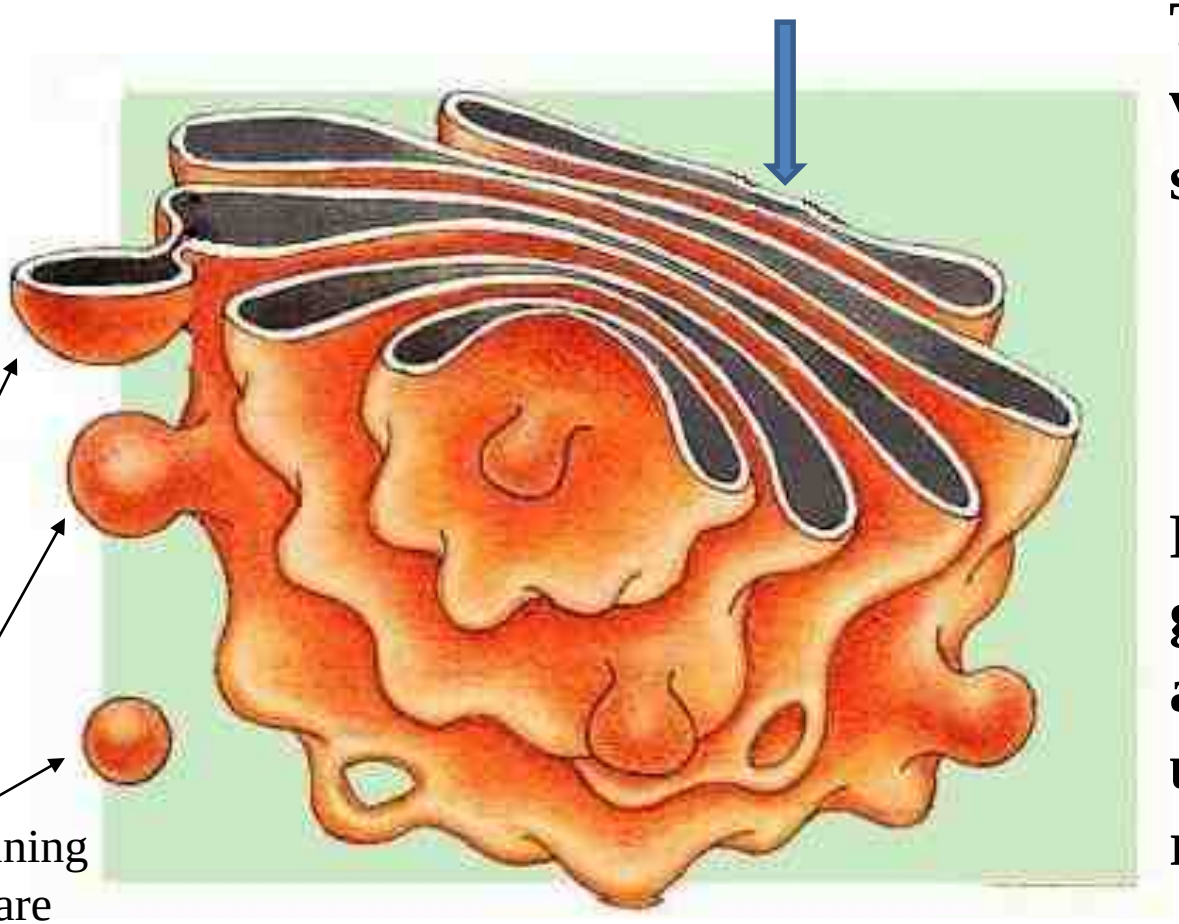


13.1-clathrin.mov

https://www.youtube.com/watch?v=0YUcHET4Z-g

SECRETORY VESICLES

- **Secretory vesicles** (from the trans-Golgi) are targeted to the plasma membrane, with which they fuse.
- The soluble contents of the vesicles are released to the outside, and **the vesicle membrane becomes part of the PM**.



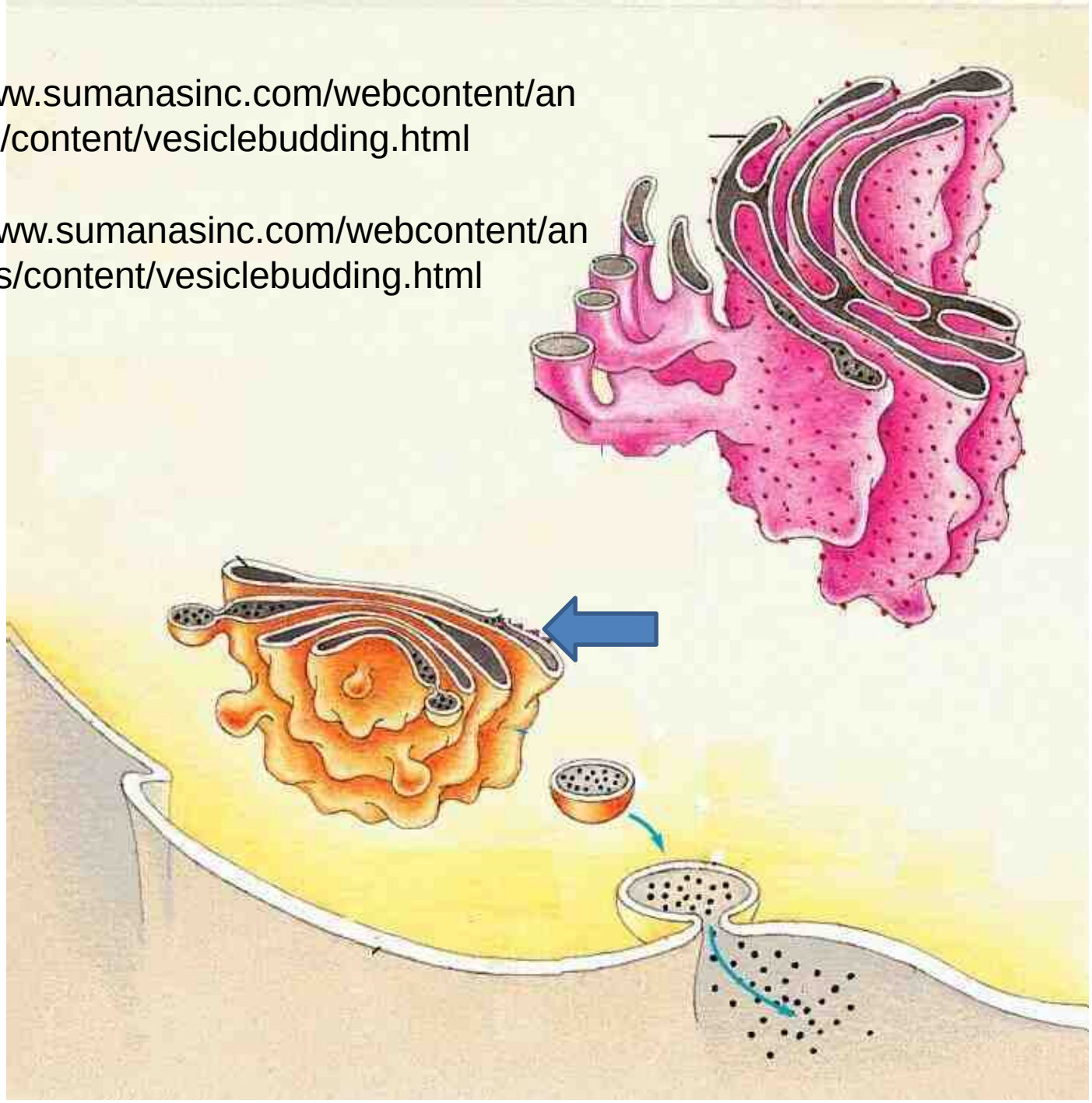
Transport vesicles from smooth ER

Fuse with golgi stack, and proteins undergo refinement

Vesicles containing final products are released from distal stack

http://www.sumanasinc.com/webcontent/animations/content/vesiclebudding.html

http://www.sumanasinc.com/webcontent/animations/content/vesiclebudding.html



The acid hydrolases in the lysosome are sorted in the TGN based on **the chemical marker mannose 6-phosphate.**

Hydrolases are transported **to the late endosome which later matures into a lysosome.**

Adaptins bridge the M6P receptor to clathrin.

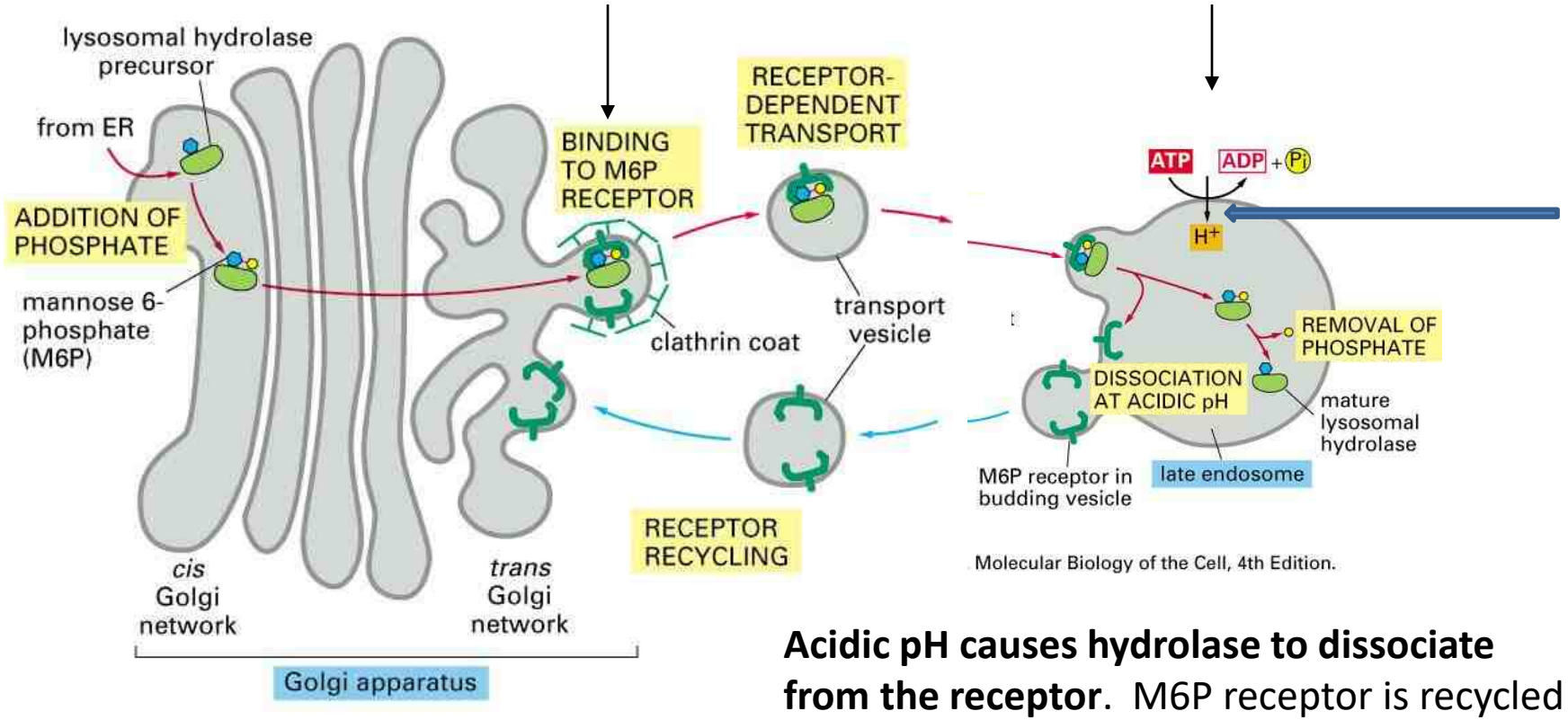
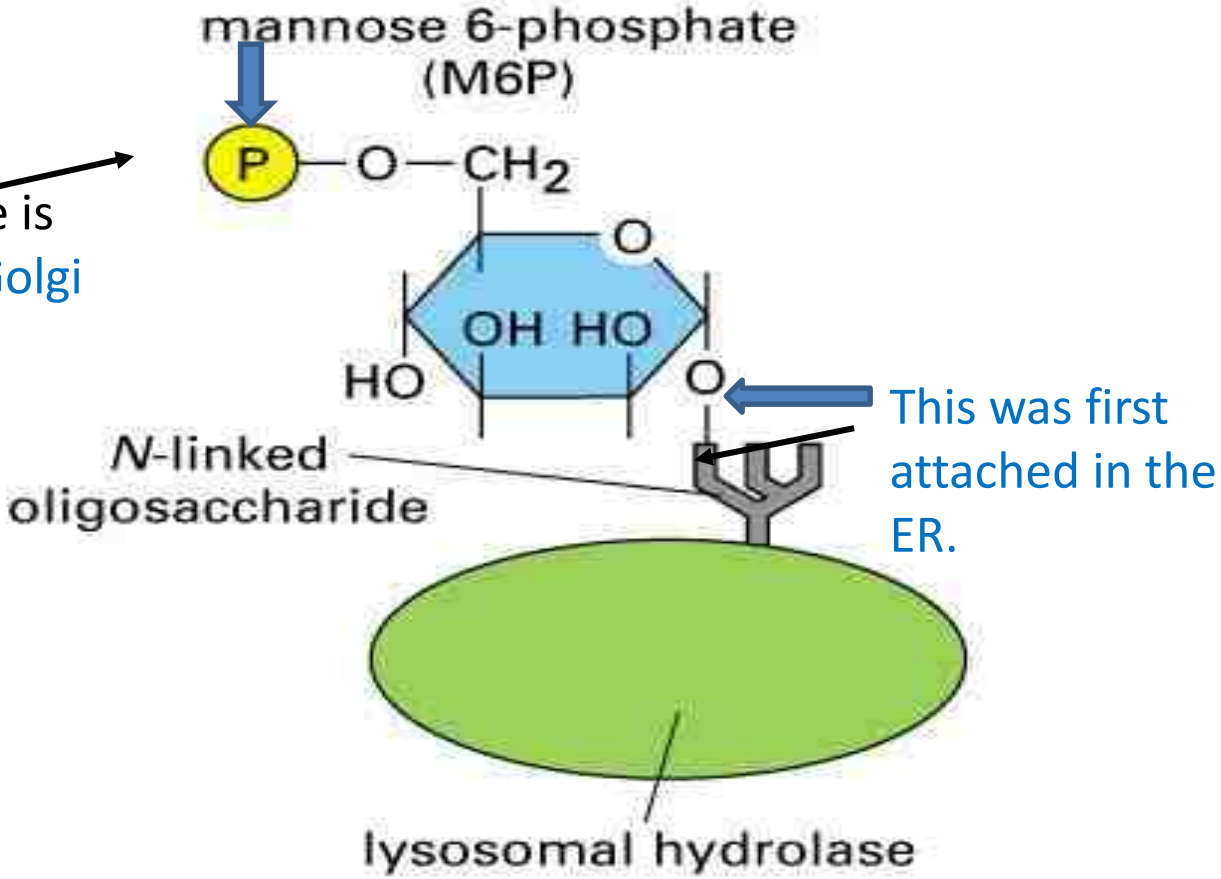


Figure 13–37 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Acidic pH causes hydrolase to dissociate from the receptor. M6P receptor is recycled back to the TGN.

Mannose 6-phosphate tag.

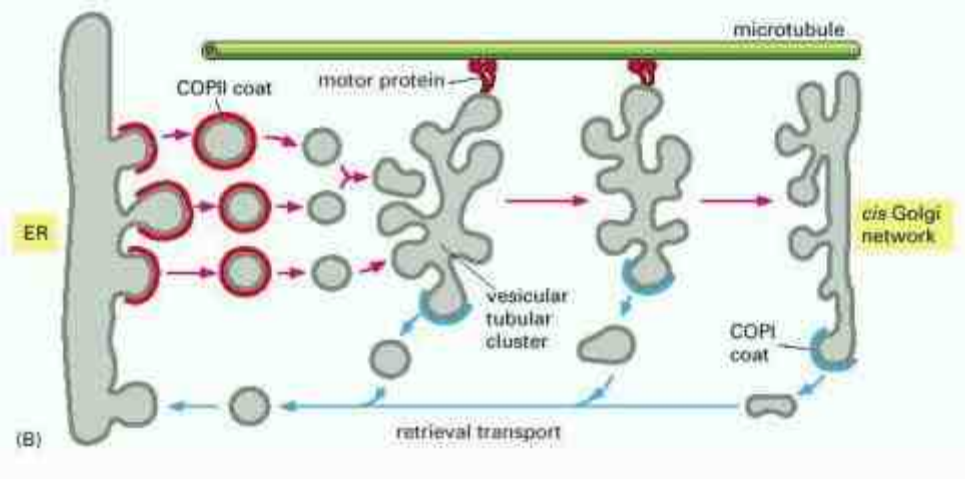


The phosphate is added in the Golgi

This was first attached in the ER.

Figure 13–36. Molecular Biology of the Cell, 4th Edition.

TRANSPORT OF PROTEINS FROM ER TO GOLGI



- Proteins destined for the Golgi, lysosome, PM, or extracellular fluid are packaged into vesicles **at specialized sites** referred to as ER EXIT SITES.

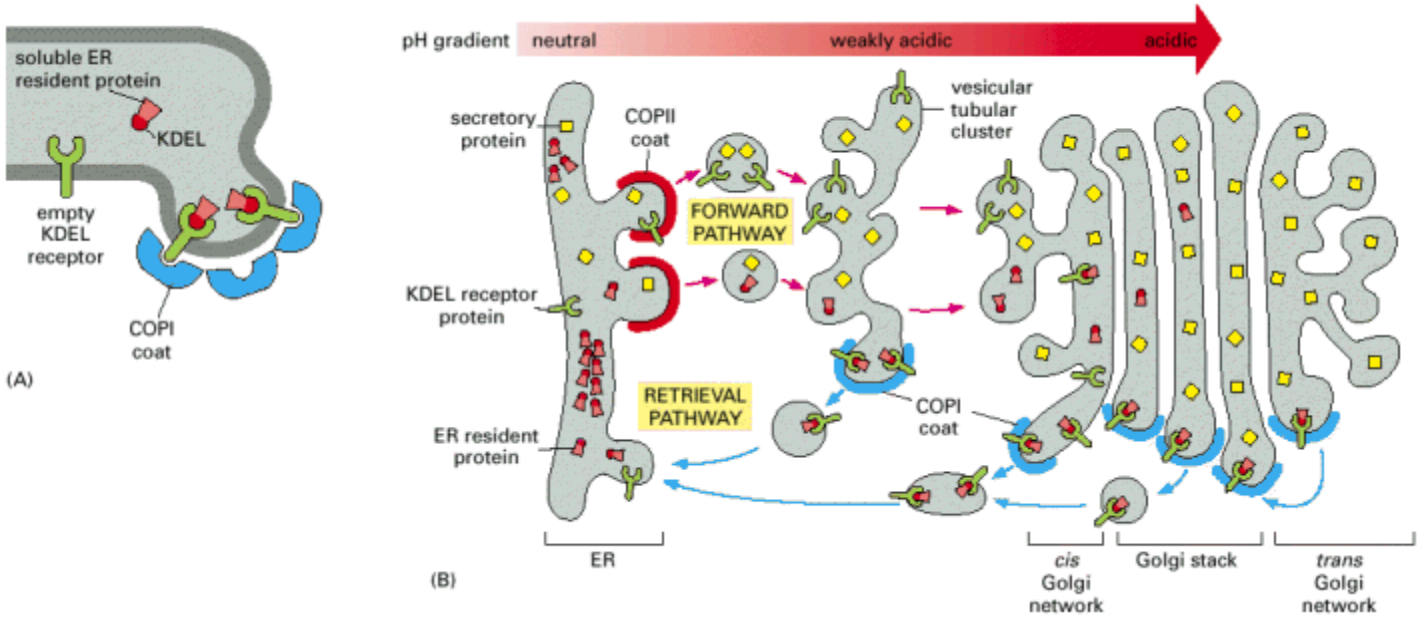
- ER exit sites are **studded with receptors which bind to proteins destined to leave the ER**. Proteins leaving the ER contain **specific amino acid sequences which are bound by these receptors**.

- Binding the receptor **induces vesicle budding** and the transport of the vesicle to the *cis*-Golgi network.

- It is important to note that **only properly folded proteins are transported**.

- Following vesicle budding, **vesicles fuse to form a vesicular tubular cluster** **which is then transferred to the Golgi**.

The ER retrieval pathway



- During the vesicular transport of proteins from the ER to the Golgi, proteins from the ER can be accidently packaged within the vesicles destined for the Golgi.

- Proteins resident to the ER are recovered by the ER RETRIEVAL PATHWAY (RETROGRADE TRANSPORT). ER proteins are packaged in COPI vesicles and transferred back to the ER.

- **Membrane proteins** are easily packaged into the vesicle by a **KKXX sequence**.
- **Soluble proteins**, such as Bip, also contain retrieval signals however the mechanism is slightly different. This signal consists of Lys-Asp-Glu-Leu (**KDEL sequence**)
- Soluble ER proteins which have escaped the lumen of the ER are retrieved by KDEL receptors.
- The affinity of KDEL receptors for KDEL sequences is **dependent on the pH of each organelle**.

- While the KDEL receptor has a high affinity for the KDEL sequence at the more acidic pH of the Golgi lumen, **the neutral pH of the ER lumen decreases the affinity of the receptor for the protein prompting its release**.

- Thus the Retrieval Pathway is pH dependent.

CONSTITUTIVE SECRETORY PATHWAY

- A secretory pathway found in all cells by which transport **vesicles continuously leave the Golgi** apparatus and fuse with the plasma membrane, and **their contents are exported to the extracellular space or used as components of the plasma membrane.**

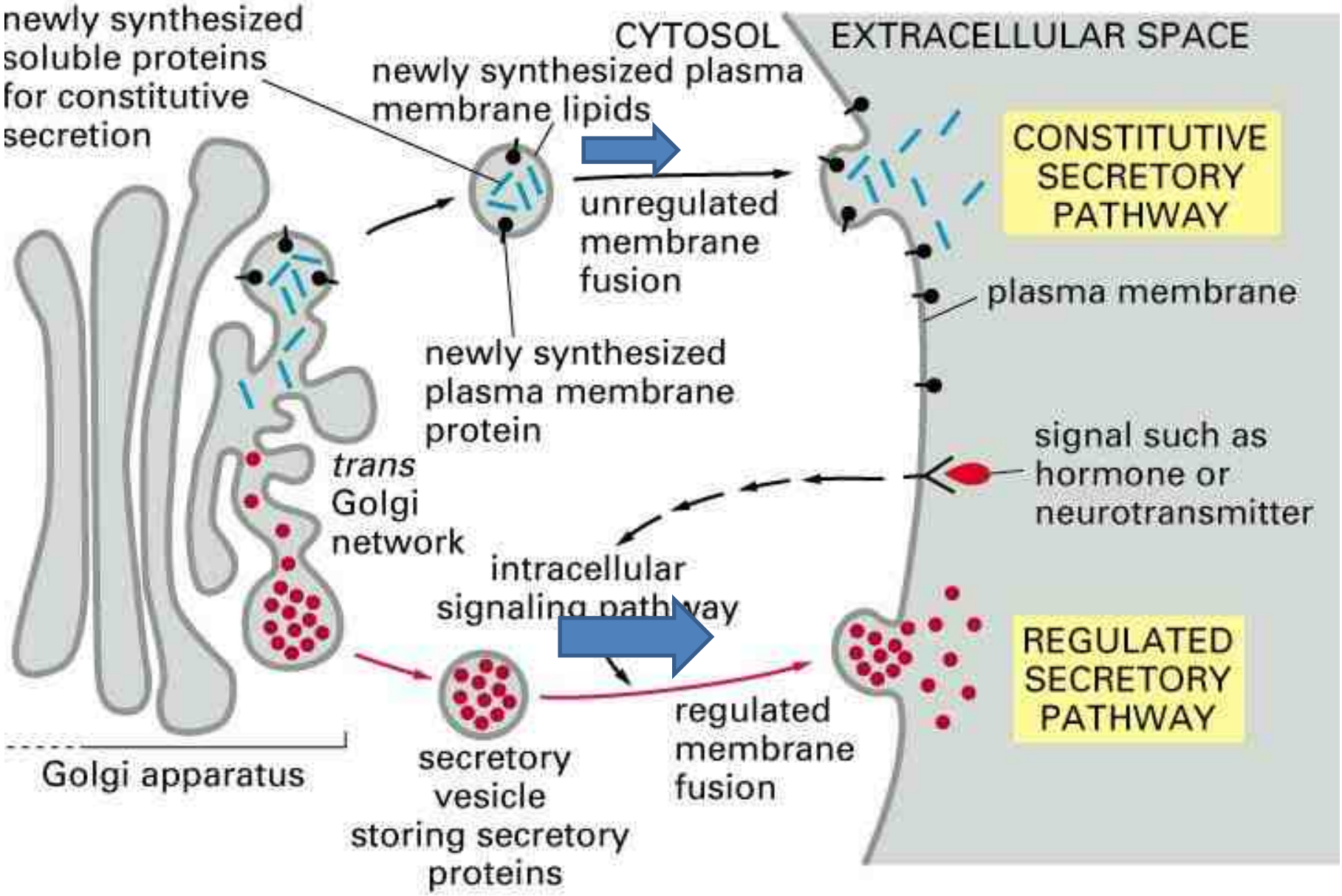


Figure 13–54. Molecular Biology of the Cell, 4th Edition.

HOW COMPLEX IS THE SYSTEM?

- The proteins and lipids synthesized in the ER provide the foundation for **assembly** **and function** of all compartments comprising the **exocytic and endocytic pathways**.
- The process **simultaneously** **moves thousands** of different proteins **efficiently** and **precisely** between different compartments.
- And as if that weren't enough - Intracellular transport must be able to respond to **environmental** and **organismal conditions**!!!

Ribosomes

Not surrounded by a lipid membrane- Amembranous

Composed of protein and ribosomal RNA (rRNA)

Made in the nucleolus

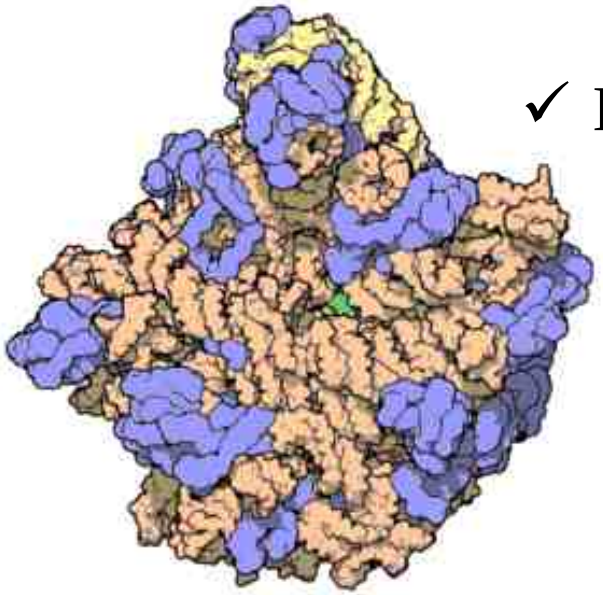
Site of protein synthesis

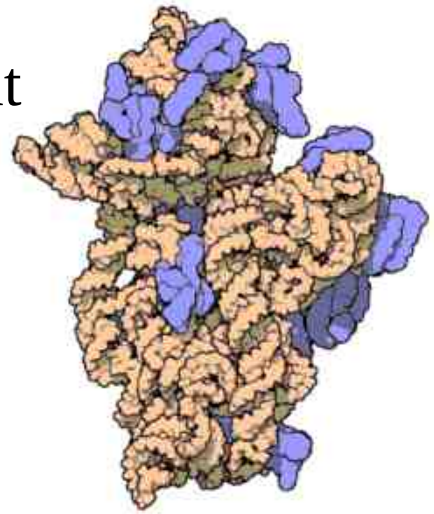
Two major types based on location

- Free ribosomes
  - Synthesize proteins used *intracellularly*
  - Very abundant in embryonic cells
- Membrane-bound ribosomes
  - synthesize proteins that are packaged and secreted from the cell or incorporated into the plasma membrane or membranes of different organelles

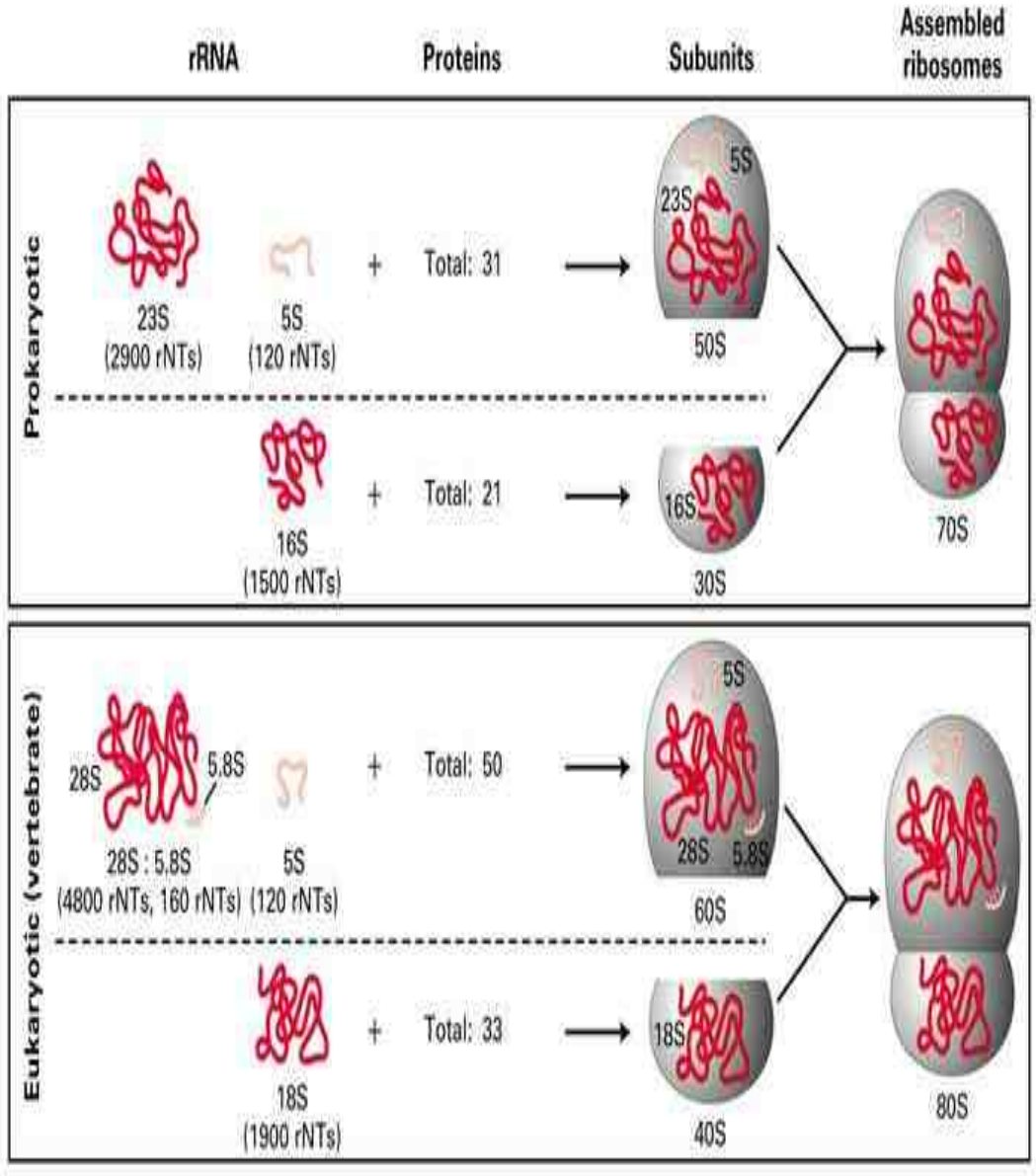
50S and 30S???

- Related to their respective sizes. Numbers actually measures of how quickly each subunit sinks to the bottom of a container of liquid when spun in a centrifuge
- One subunit smaller than other, but both are larger than average protein.
  - ✓ About two-thirds of ribosome's mass made up of RNA
  - ✓ Most important functions of ribosome performed by RNA.



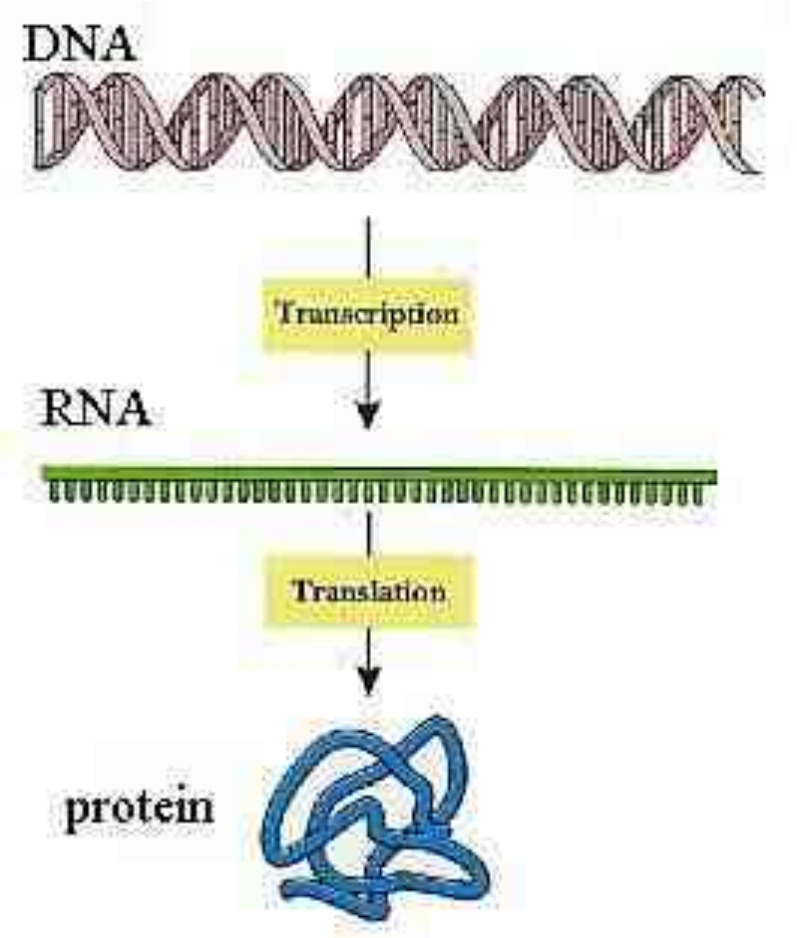


- **Three size rRNA (23S, 16S, 5S) in prokaryotes**
- **Mammalian ribosome contains two nucleoprotein subunits—a 60S and a 40S.**
- **60S subunit contains a 5S, a 5.8S, and a 28S rRNA.**
- **40S subunit smaller and contains a single 18S rRNA.**



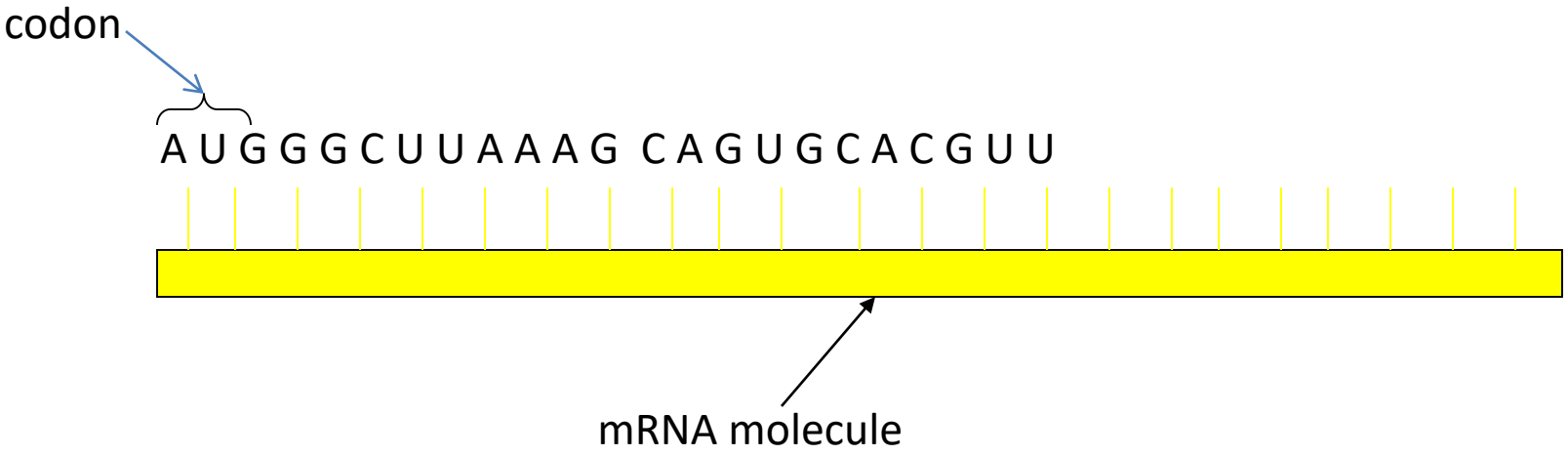
Protein synthesis

- Process starts from DNA through “transcription”
- “Translation” is where ribosome comes in. Translation occurs when protein is formed from code on mRNA.
- Ribosome carries out the translation of the nucleotide triplets

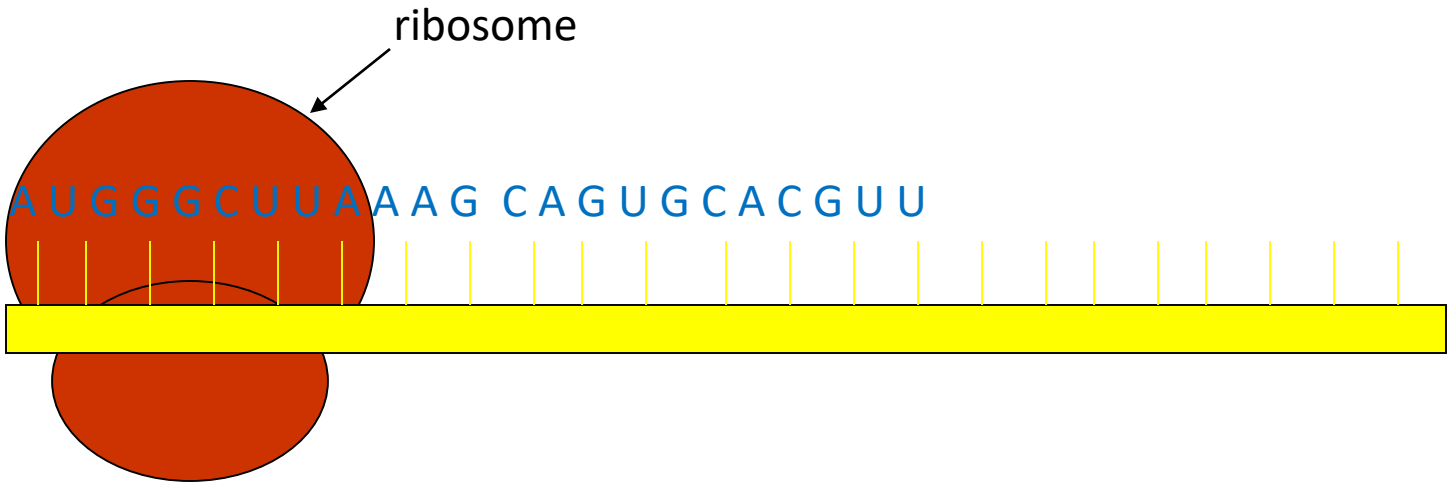


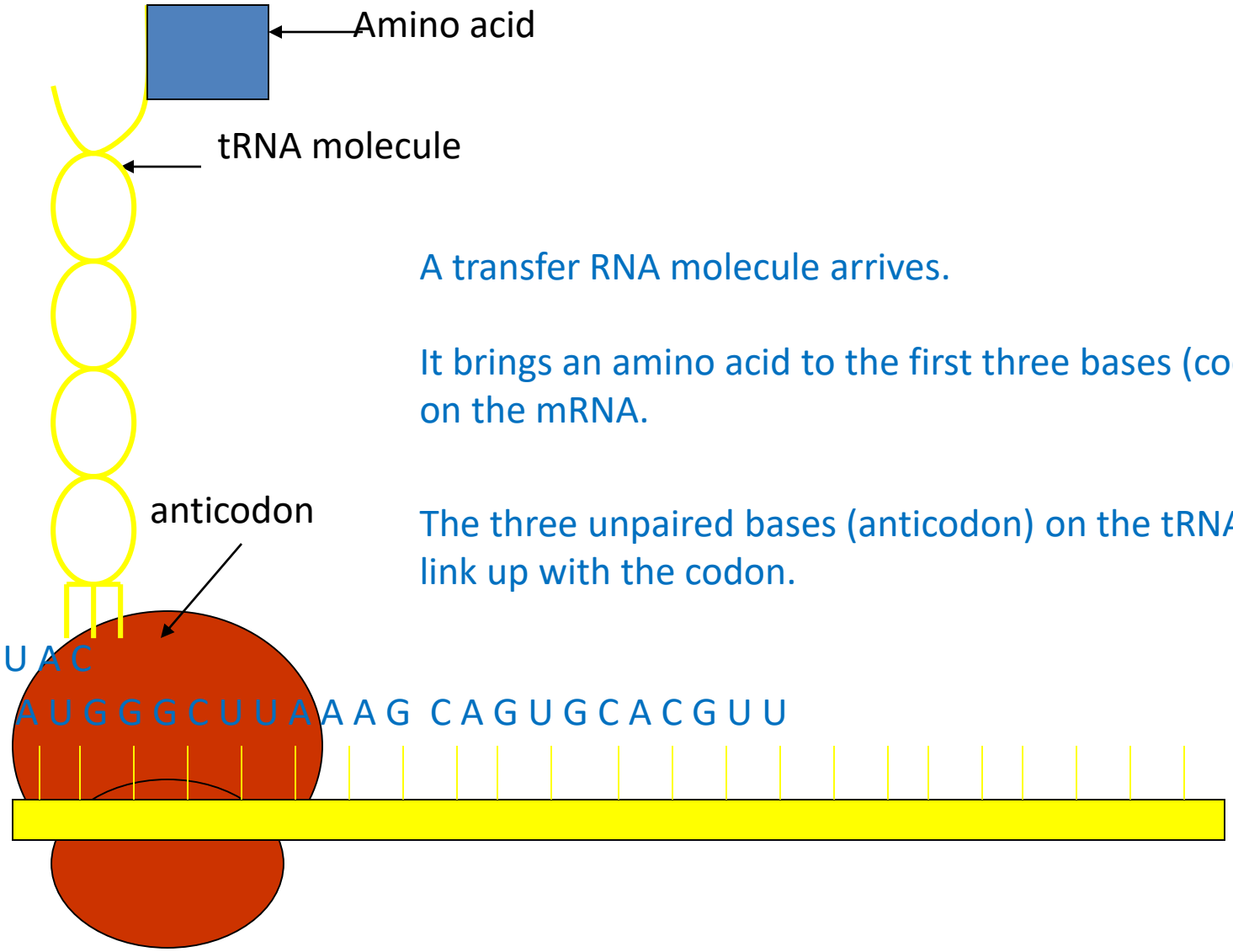
This is a molecule of messenger RNA.

It was made in the nucleus by transcription from a DNA molecule.



A ribosome on the rough endoplasmic reticulum attaches to the mRNA molecule.

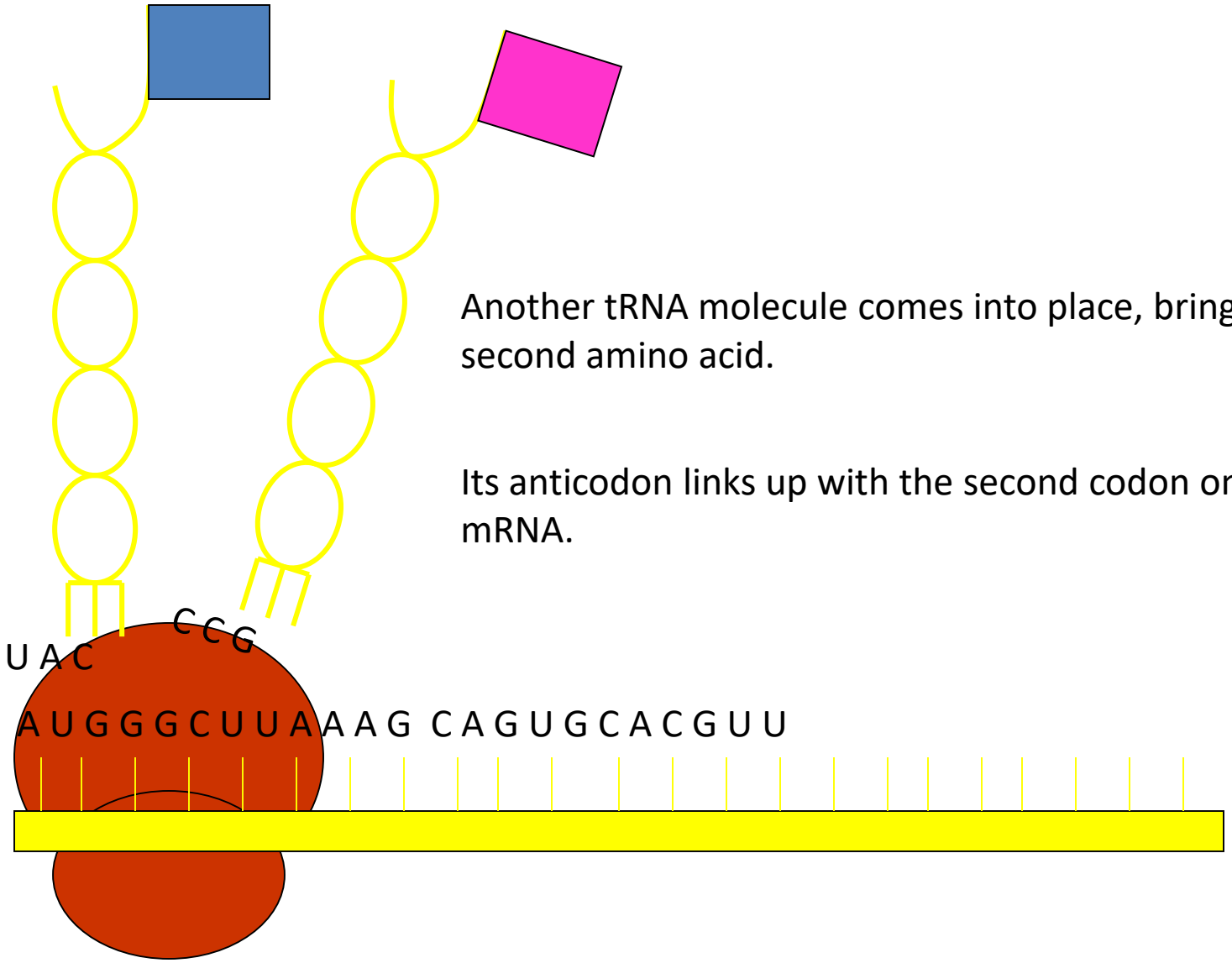




A transfer RNA molecule arrives.

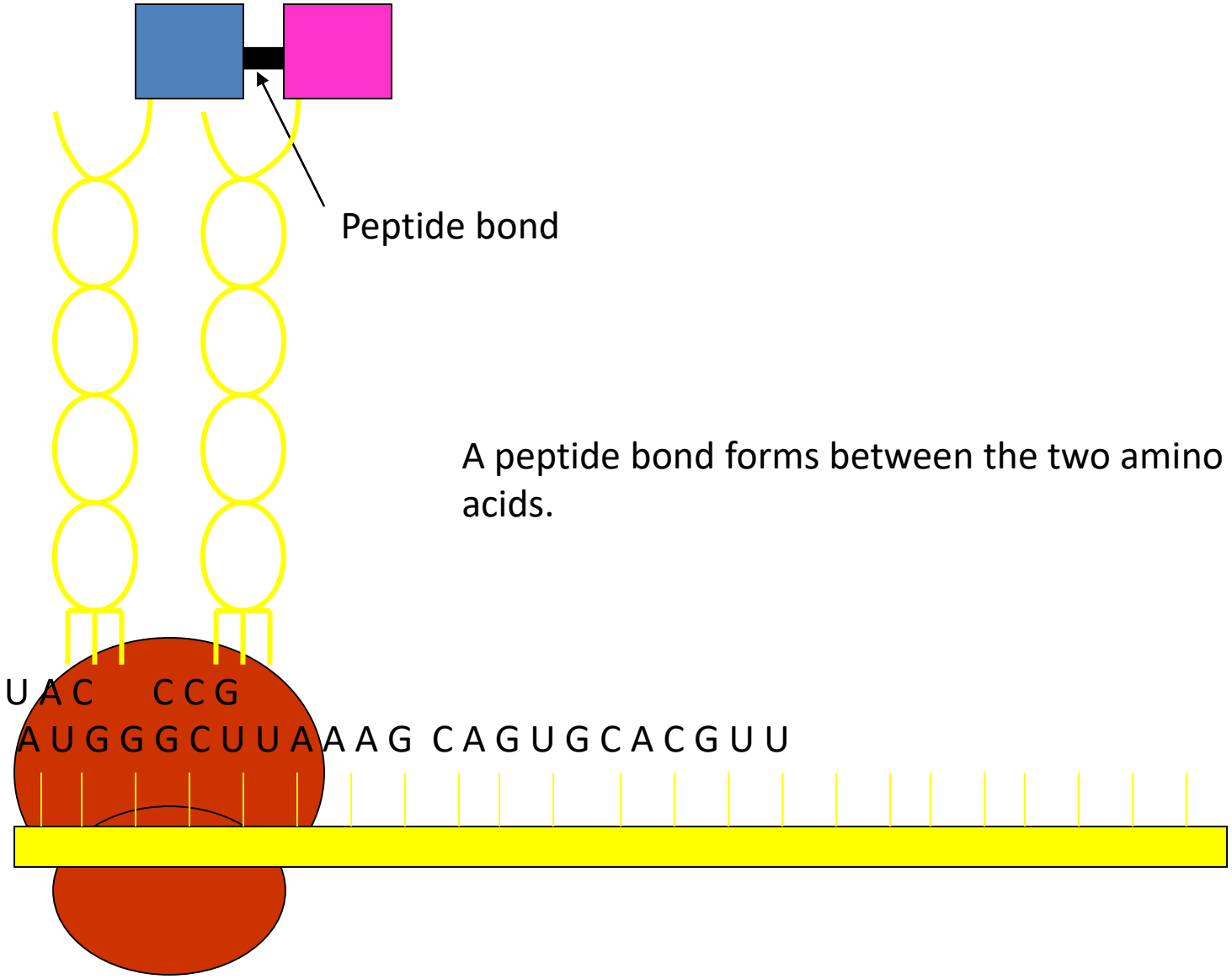
It brings an amino acid to the first three bases (codon) on the mRNA.

The three unpaired bases (anticodon) on the tRNA link up with the codon.

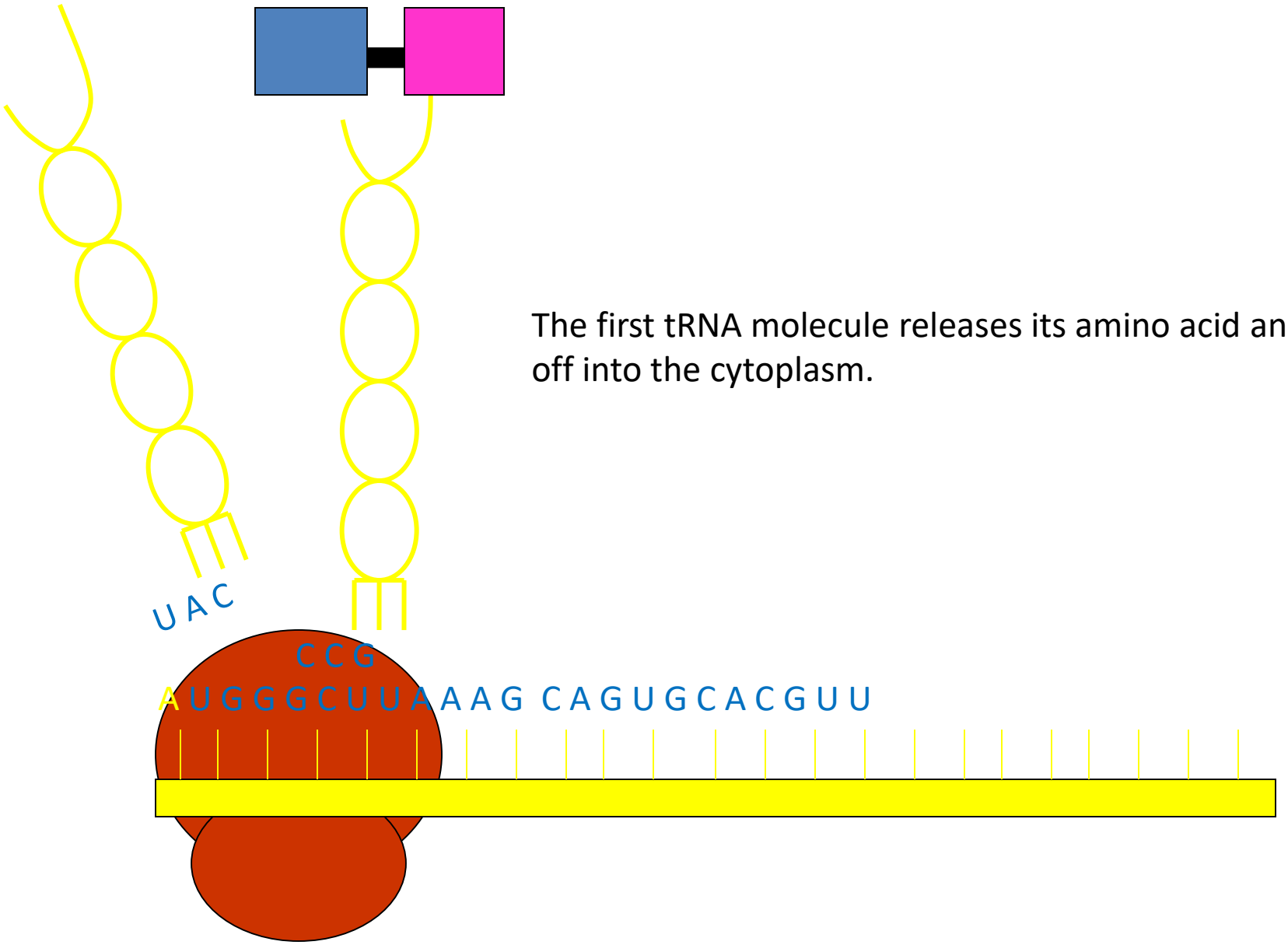


Another tRNA molecule comes into place, bringing a second amino acid.

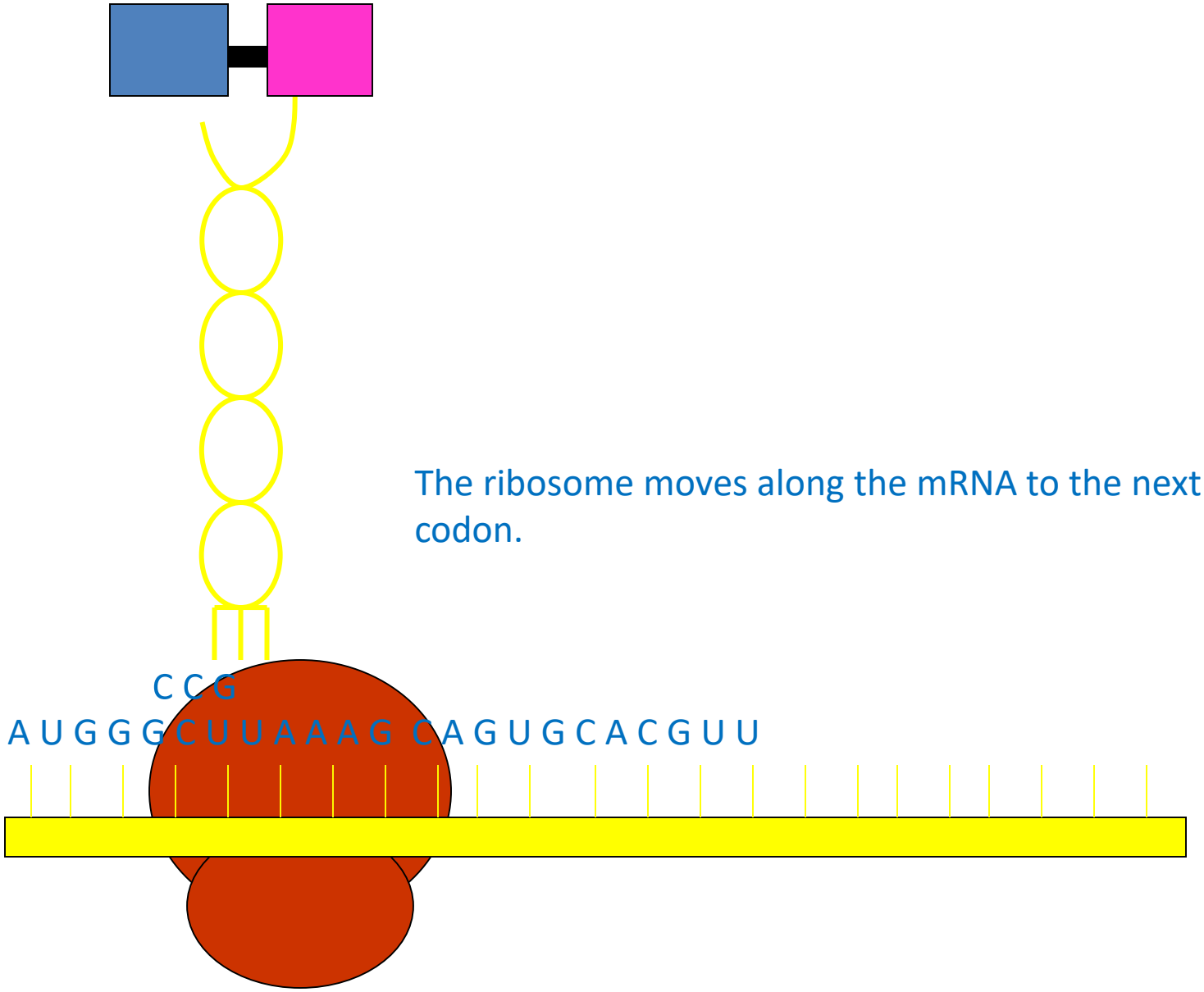
Its anticodon links up with the second codon on the mRNA.



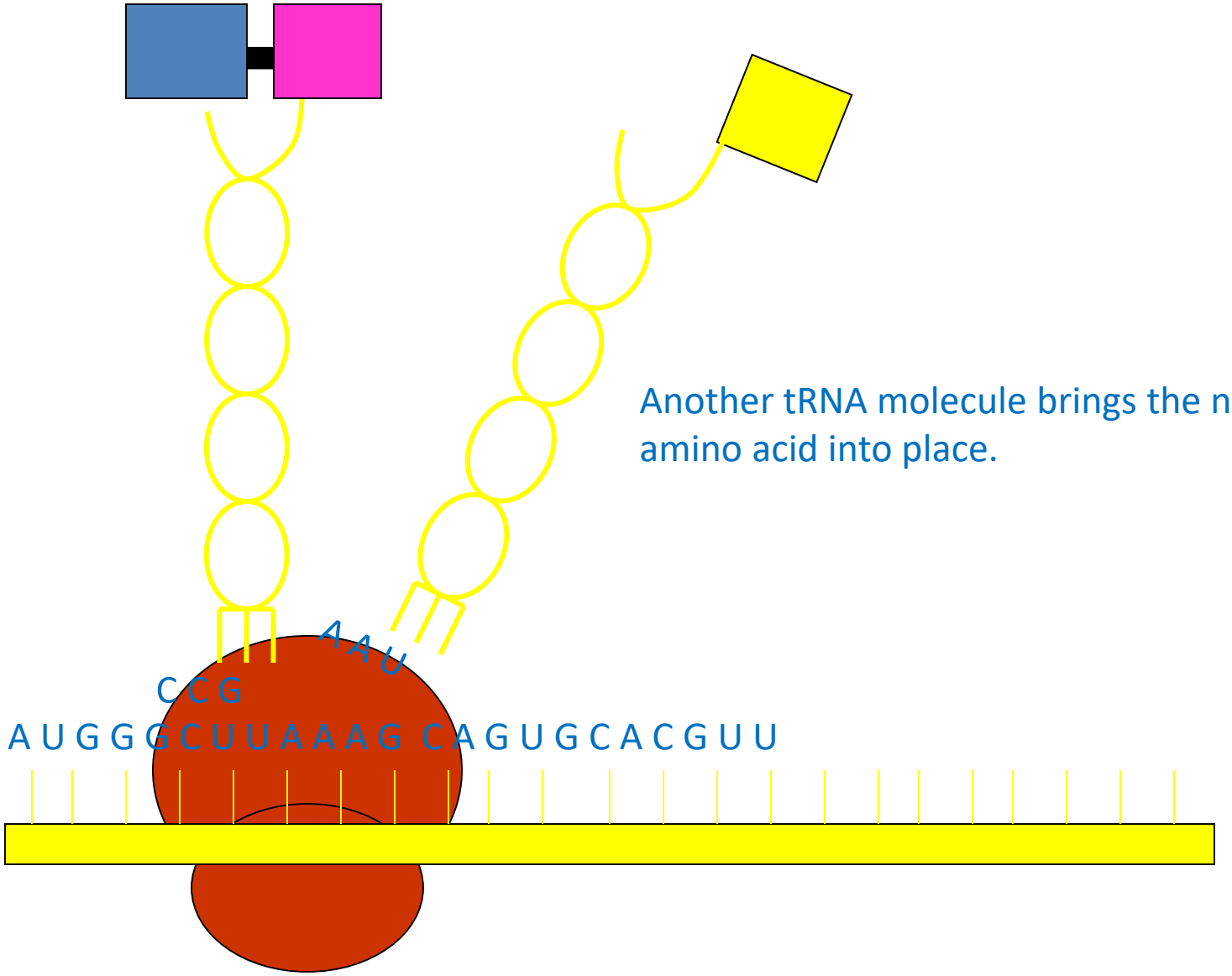
A peptide bond forms between the two amino acids.



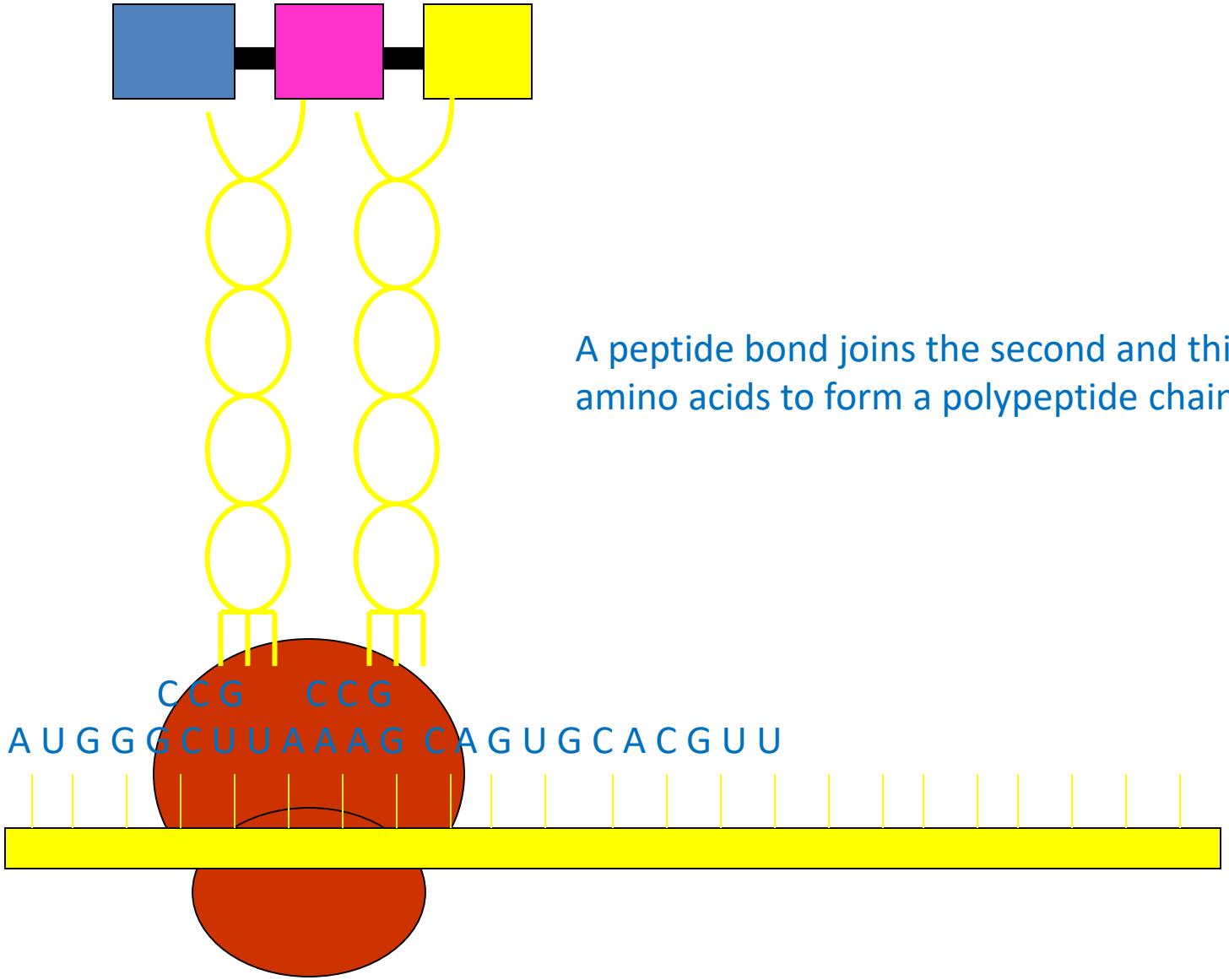
The first tRNA molecule releases its amino acid and moves off into the cytoplasm.



The ribosome moves along the mRNA to the next codon.



Another tRNA molecule brings the next amino acid into place.



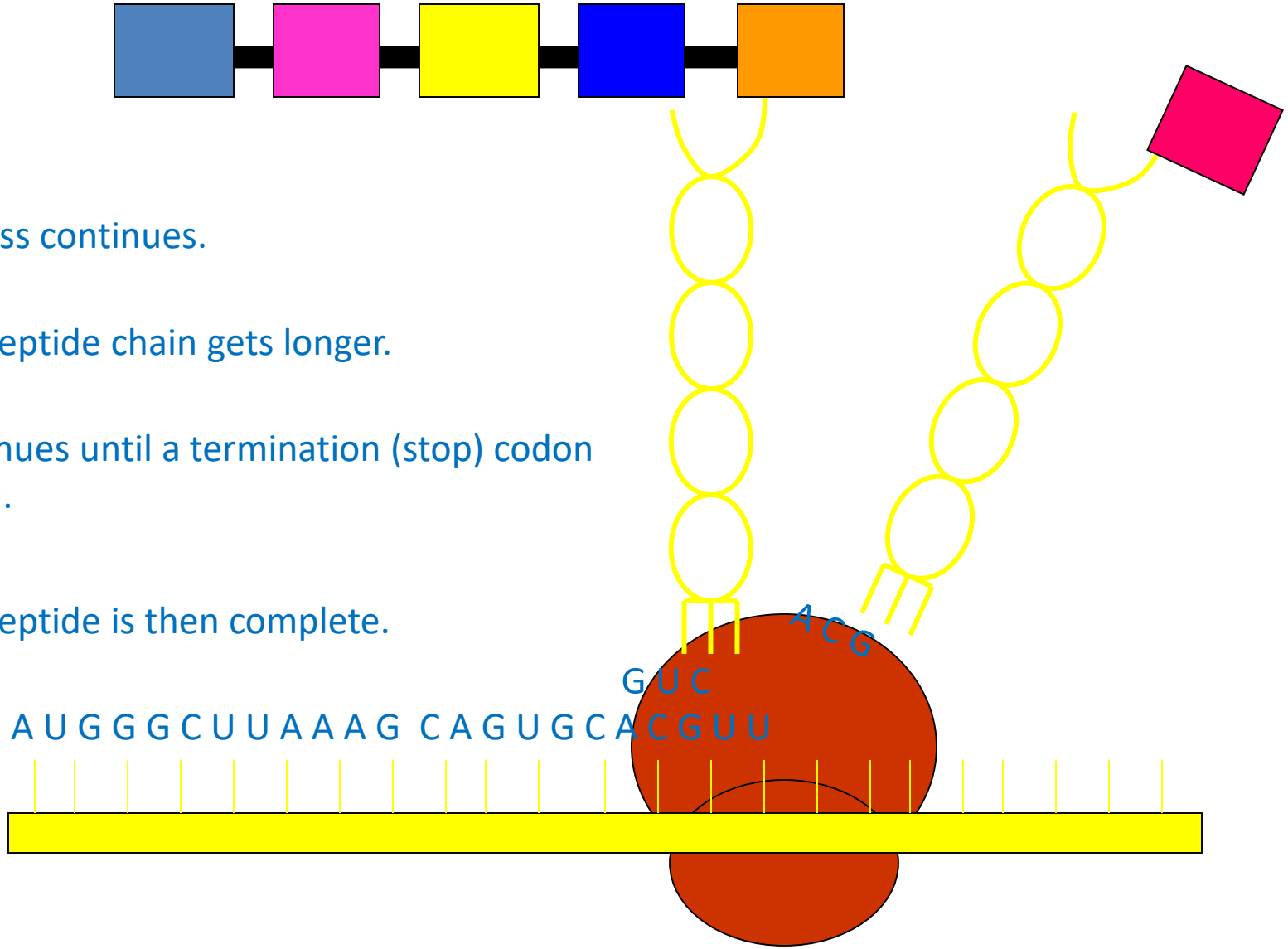
A peptide bond joins the second and third amino acids to form a polypeptide chain.

The process continues.

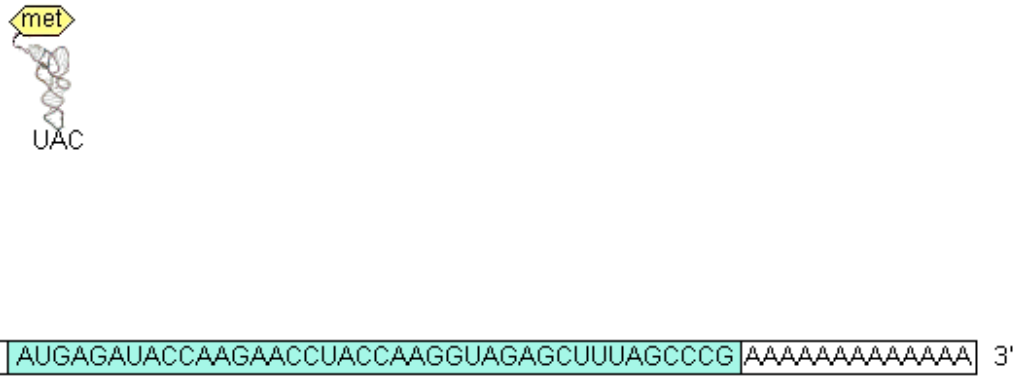
The polypeptide chain gets longer.

This continues until a termination (stop) codon is reached.

The polypeptide is then complete.



Translation



MITOCHONDRIA

Size: about the same **as a bacterium**

0.5 to 1.0 um wide and 3 um long

Location: often where energy requirements are the highest

Number: varies widely **from few to thousands**

1 in *Chlamydomonas*

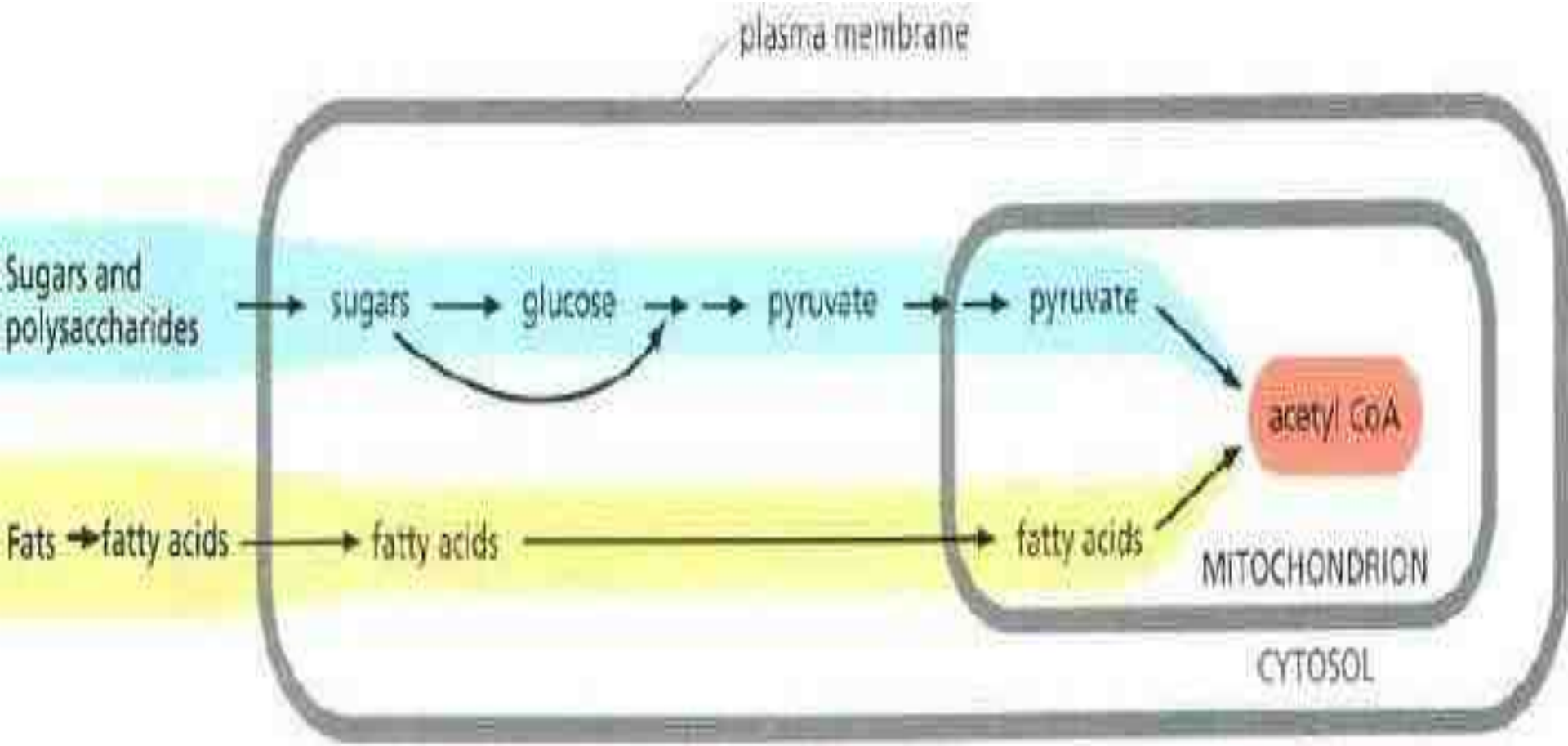
100 + in spinach leaf cell

Number can vary over life time of a cell

Plasticity: *Spin* and *contort* through endless shapes

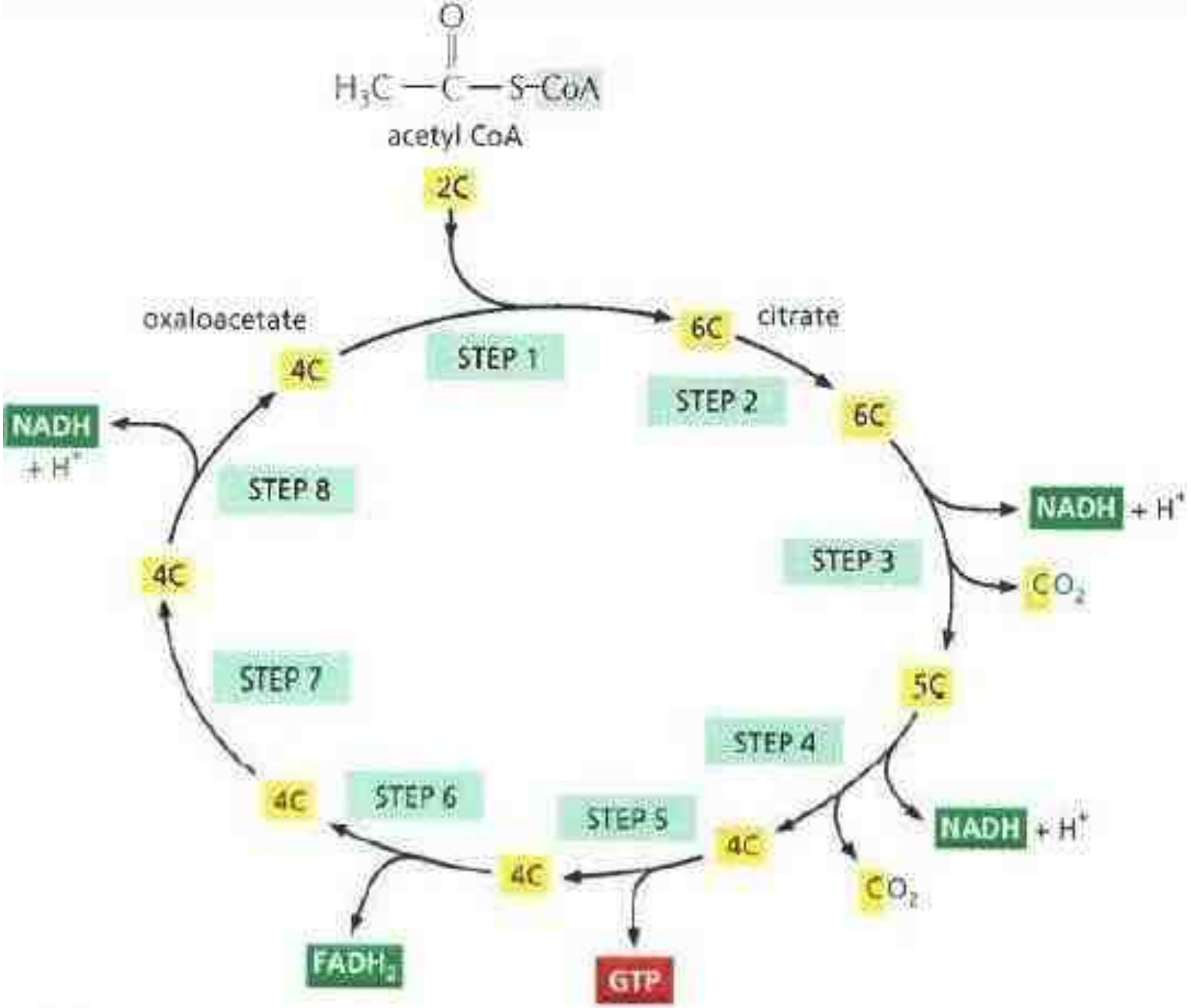
- Structure of the mitochondrion is **long and slender**, or even **bean-shaped**, or **oval** through an electron microscope.
- **The outer compartment**, the area between the two membranes, is filled with liquid.
- The inner membrane is called cristae. It looks like folds and are the ***sites of ATP synthesis***.
- ✓ The structure of cristae is very important. The folds allow more surface area for ATP synthesis to occur.
- ✓ ***Transport proteins*** *are molecules also known as* ***electron transport chains*****.**

- **The enzymes that synthesize ATP are in the folds of the cristae**. Within the cristae is a liquid filled area known as the **inner compartment**, or **matrix**.
- In the inner compartment is **where the enzymes that are used in aerobic respiration are located.**
- The main function of the mitochondria is **to make energy** for cellular activity by the process of **aerobic respiration**.
- During aerobic respiration glucose is broken down in the cell's cytoplasm to make **pyruvic acid, which is transported into the mitochondrion**.

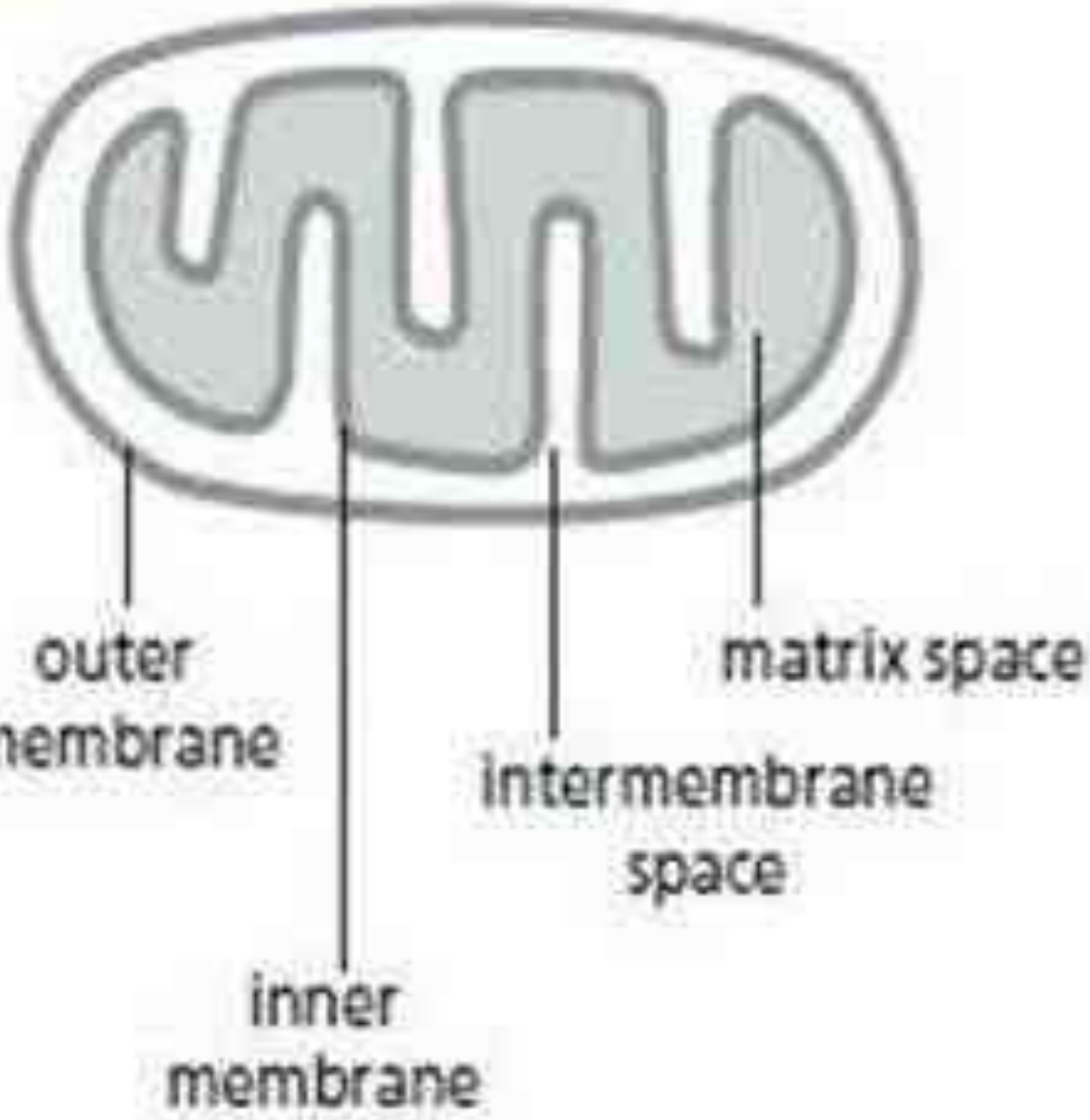

plasma membrane
Sugars and polysaccharides
sugars
glucose
pyruvate
pyruvate
acetyl CoA
Fats
fatty acids
fatty acids
fatty acids
MITOCHONDRION
CYTOSOL

- The citric acid cycle takes place inside mitochondria in eucaryotic cells. It results in **the complete oxidation of the carbon atoms of the acetyl groups in acetyl CoA, converting them into CO2**.
- But the acetyl group is **not oxidized directly**. Instead, this group is transferred from acetyl CoA to a larger, four-carbon molecule, oxaloacetate, to form the six-carbon **tricarboxylic acid**, citric acid, for which the subsequent cycle of reactions is named.
- The citric acid molecule is then **gradually oxidized**, allowing the energy of this oxidation to be harnessed **to produce energy-rich activated carrier molecules**.
- The chain of **eight reactions** forms a cycle because at the end the oxaloacetate is regenerated and enters a new turn of the cycle.

- The energy that is stored in the readily transferred high-energy electrons of **NADH and FADH2** will be utilized subsequently for ATP production through the process of oxidative phosphorylation, **the only step in the oxidative catabolism of foodstuffs that directly requires gaseous oxygen (O2) from the atmosphere.**


H3C — C — S-CoA
acetyl CoA
2C
6C
citrate
STEP 1
6C
STEP 2
NADH + H+
CO2
STEP 3
5C
STEP 4
NADH + H+
CO2
4C
STEP 5
4C
GTP
4C
STEP 6
FADH2
4C
STEP 7
4C
STEP 8
NADH + H+
4C
oxaloacetate

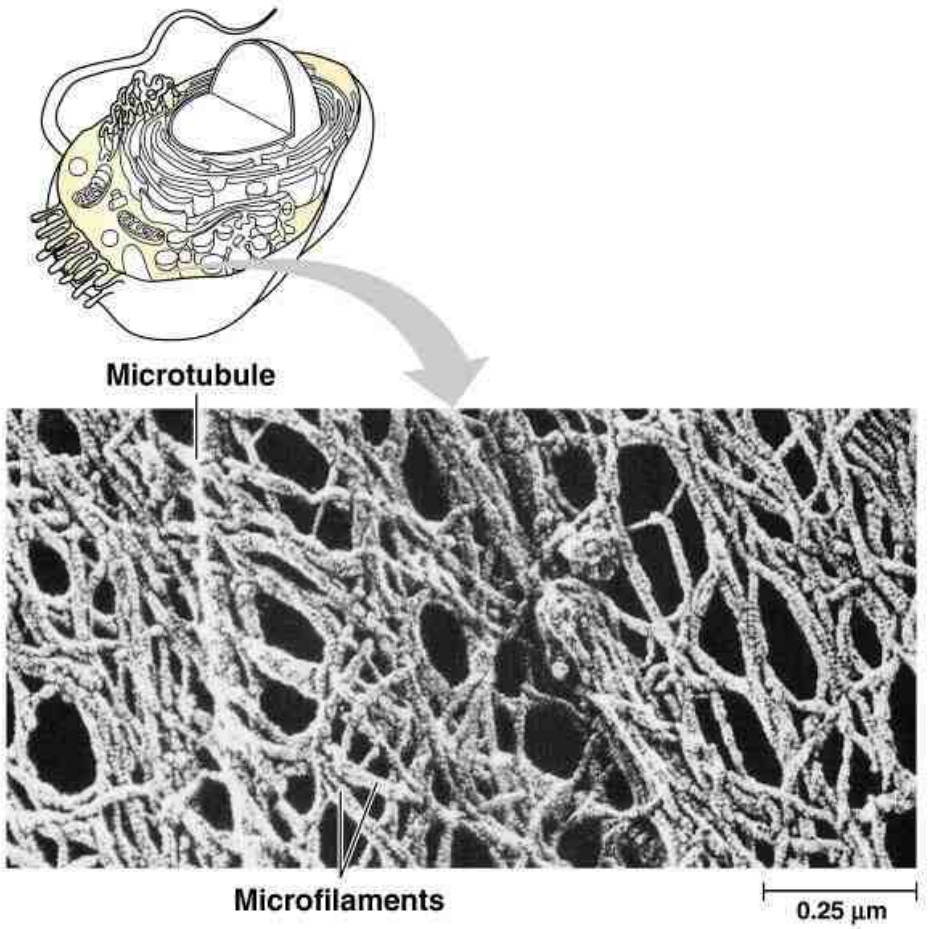
MITOCHONDRION



Cytoskeleton

Introduction

- The **cytoskeleton** is a network of fibers extending throughout the cytoplasm.



There are three main types of fibers in the cytoskeleton:

- **microtubules**,
- **microfilaments**, and
- **intermediate filaments**

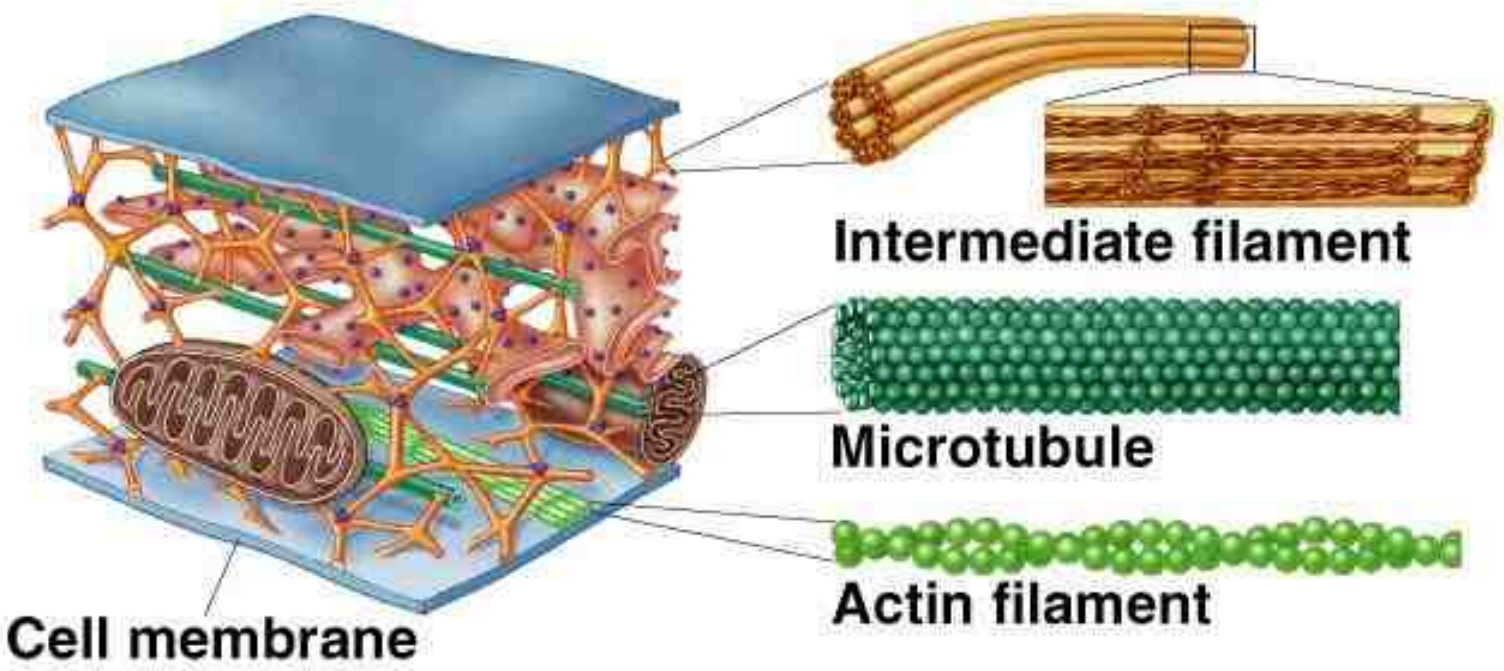
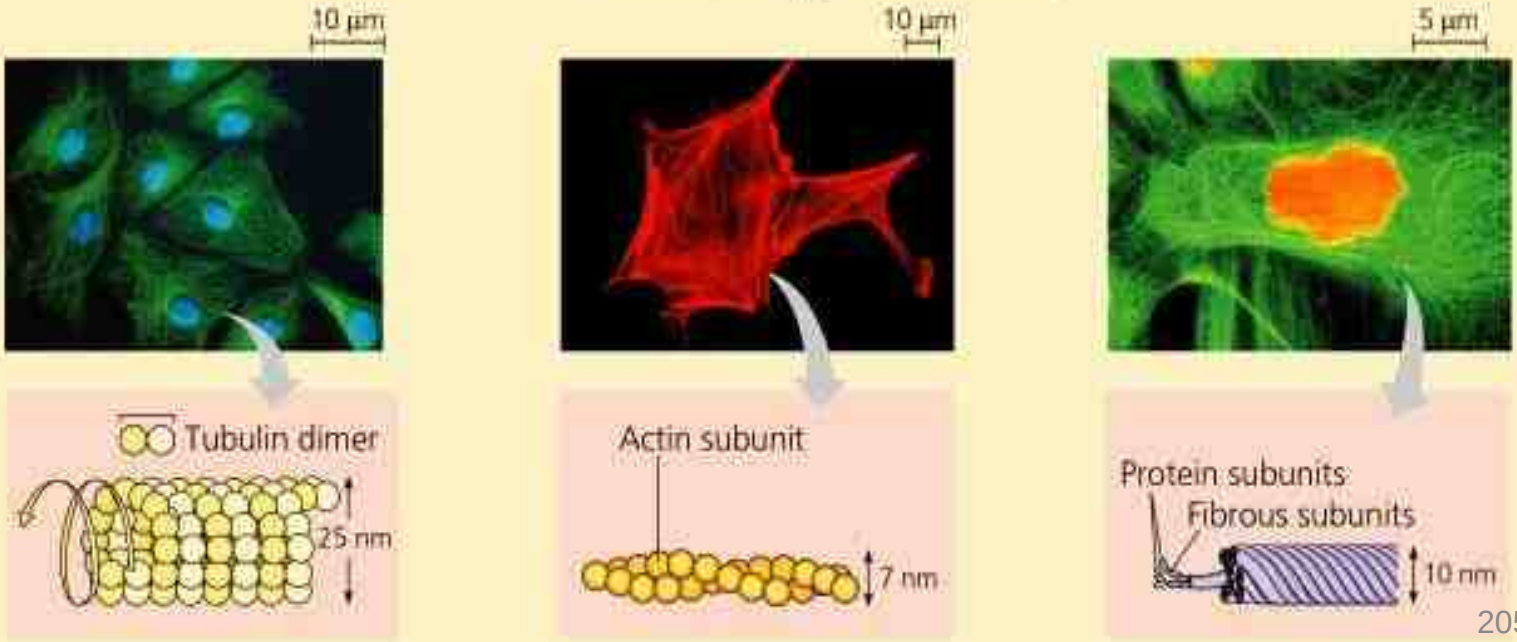


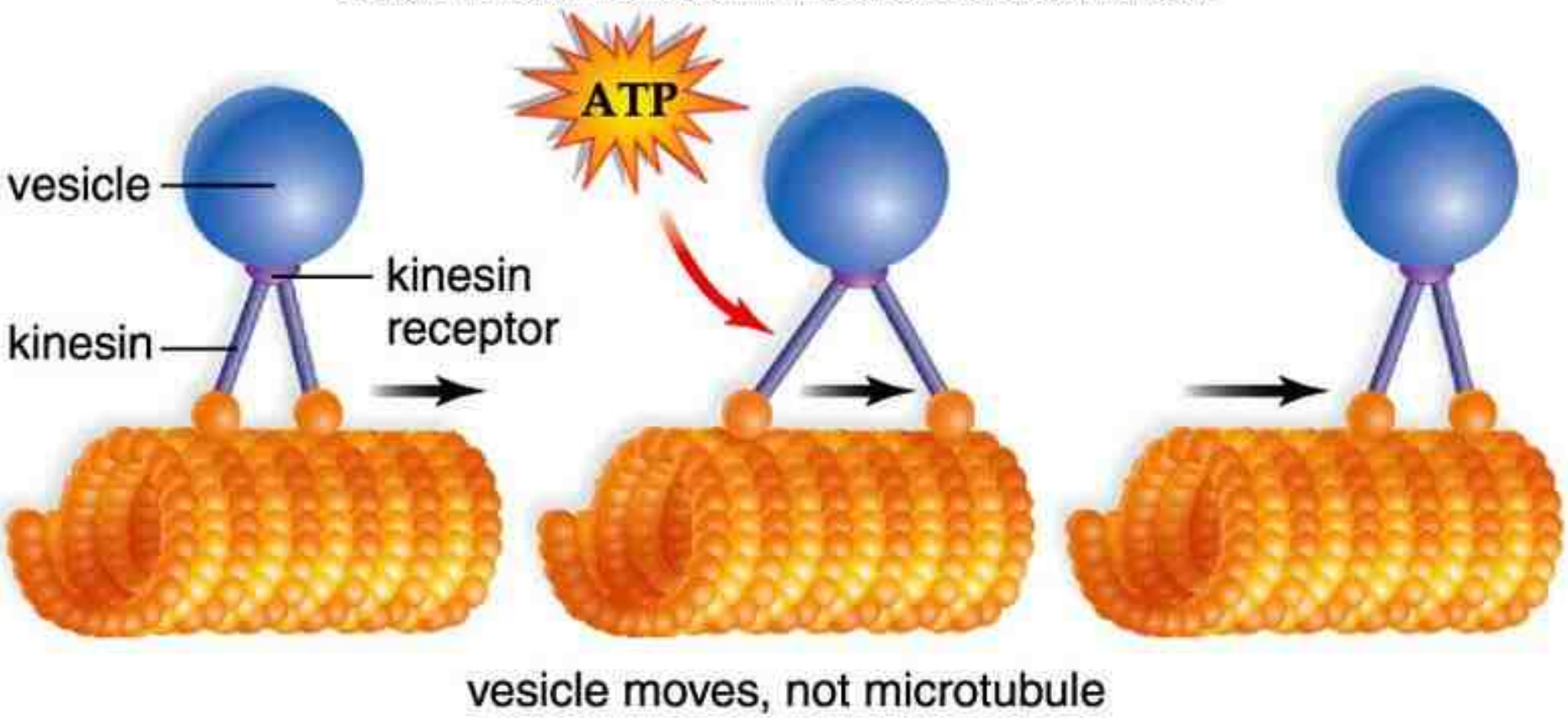
Table 7.2 The Structure and Function of the Cytoskeleton

Property	Microtubules	Microfilaments (Actin Filaments)	Intermediate Filaments
Structure	Hollow tubes; wall consists of 13 columns of tubulin molecules	Two intertwined strands of actin	Fibrous proteins supercoiled into thicker cables
Diameter	25 nm with 15-nm lumen	7 nm	8–12 nm
Protein subunits	Tubulin, consisting of α-tubulin and β-tubulin	Actin	One of several different proteins of the keratin family, depending on cell type
Main functions	Maintenance of cell shape (compression-resisting "girders") Cell motility (as in cilia or flagella) Chromosome movements in cell division Organelle movements	Maintenance of cell shape (tension-bearing elements) Changes in cell shape Muscle contraction Cytoplasmic streaming Cell motility (as in pseudopodia) Cell division (cleavage furrow formation)	Maintenance of cell shape (tension-bearing elements) Anchorage of nucleus and certain other organelles Formation of nuclear lamina



SOURCE: Adapted from W. M. Becker, L. J. Kleinsmith, and J. Hardin, *The World of the Cell*, 4th ed. (San Francisco, CA: Benjamin Cummings, 2000), p. 753.

The Cytoskeleton:Microtubule Operation



http://upload.wikimedia.org/wikipedia/commons/1/1c/Kinesin_walking.gif

- A flagellum has an undulatory movement.
  - Force is generated parallel to the flagellum's axis.

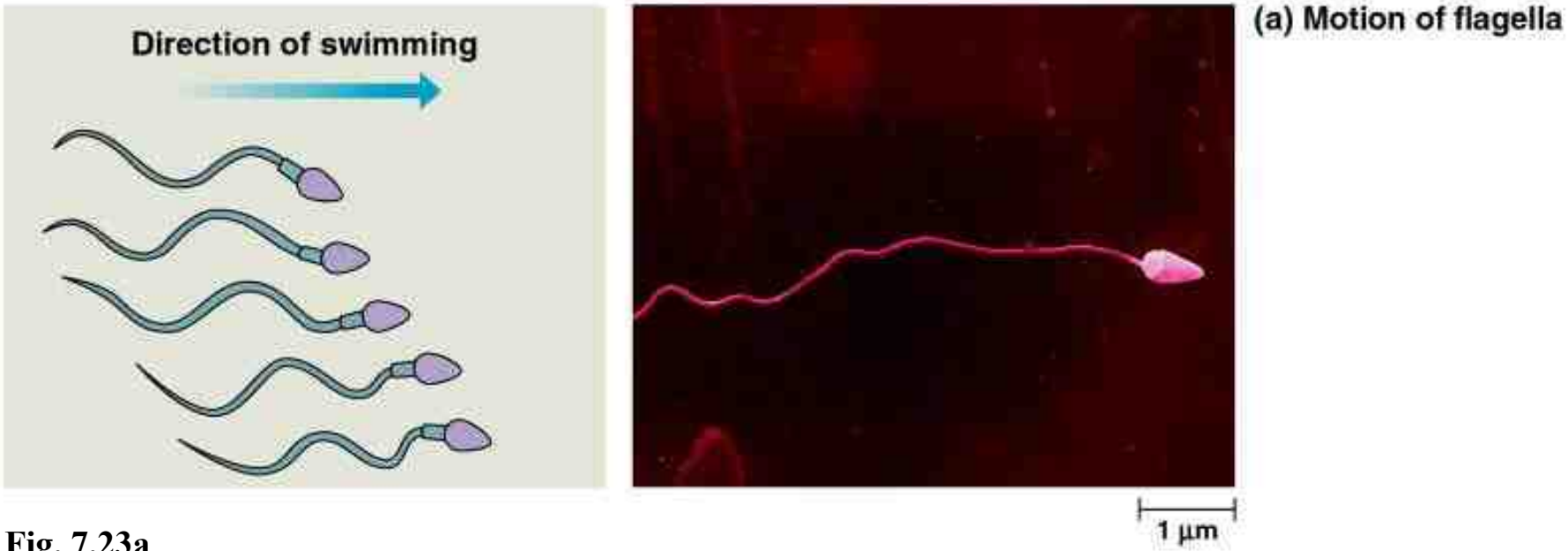
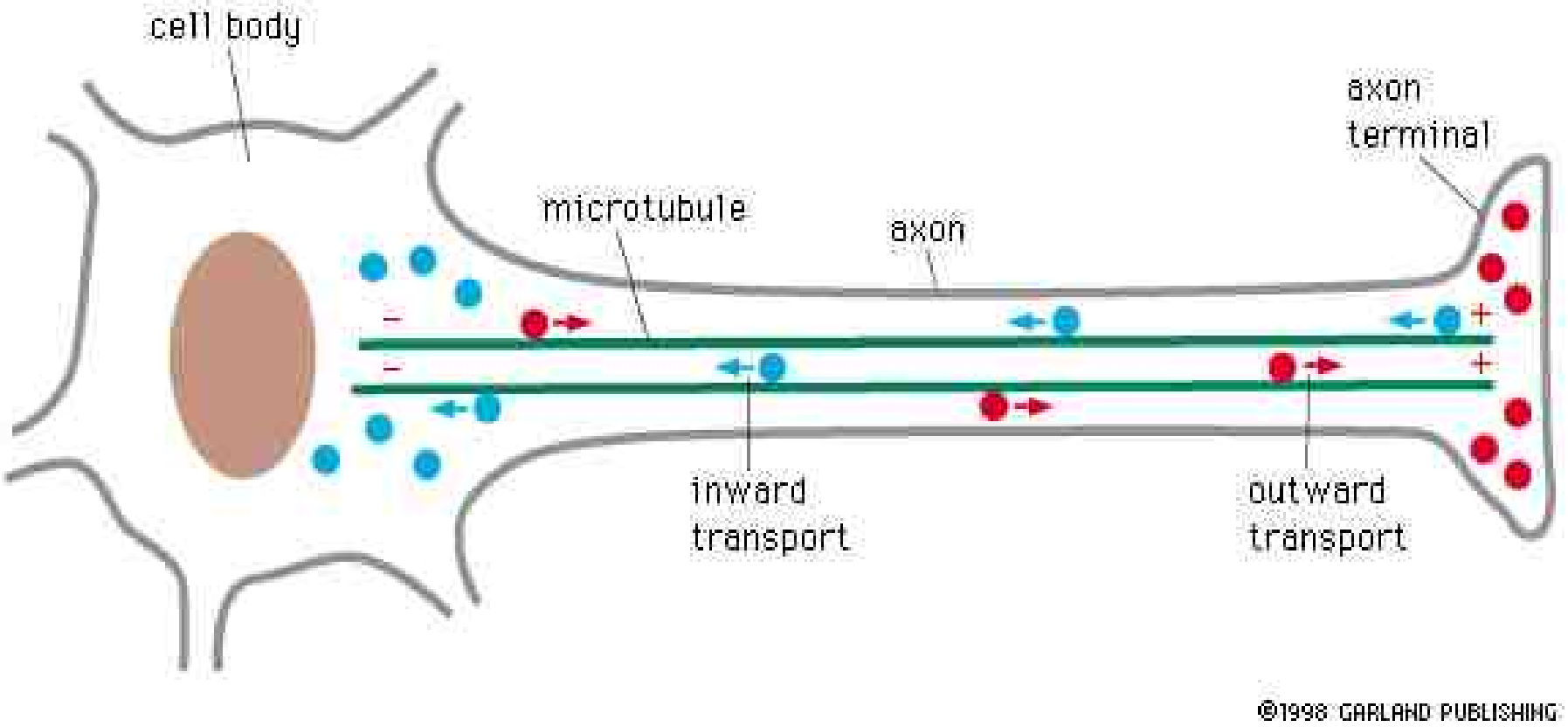
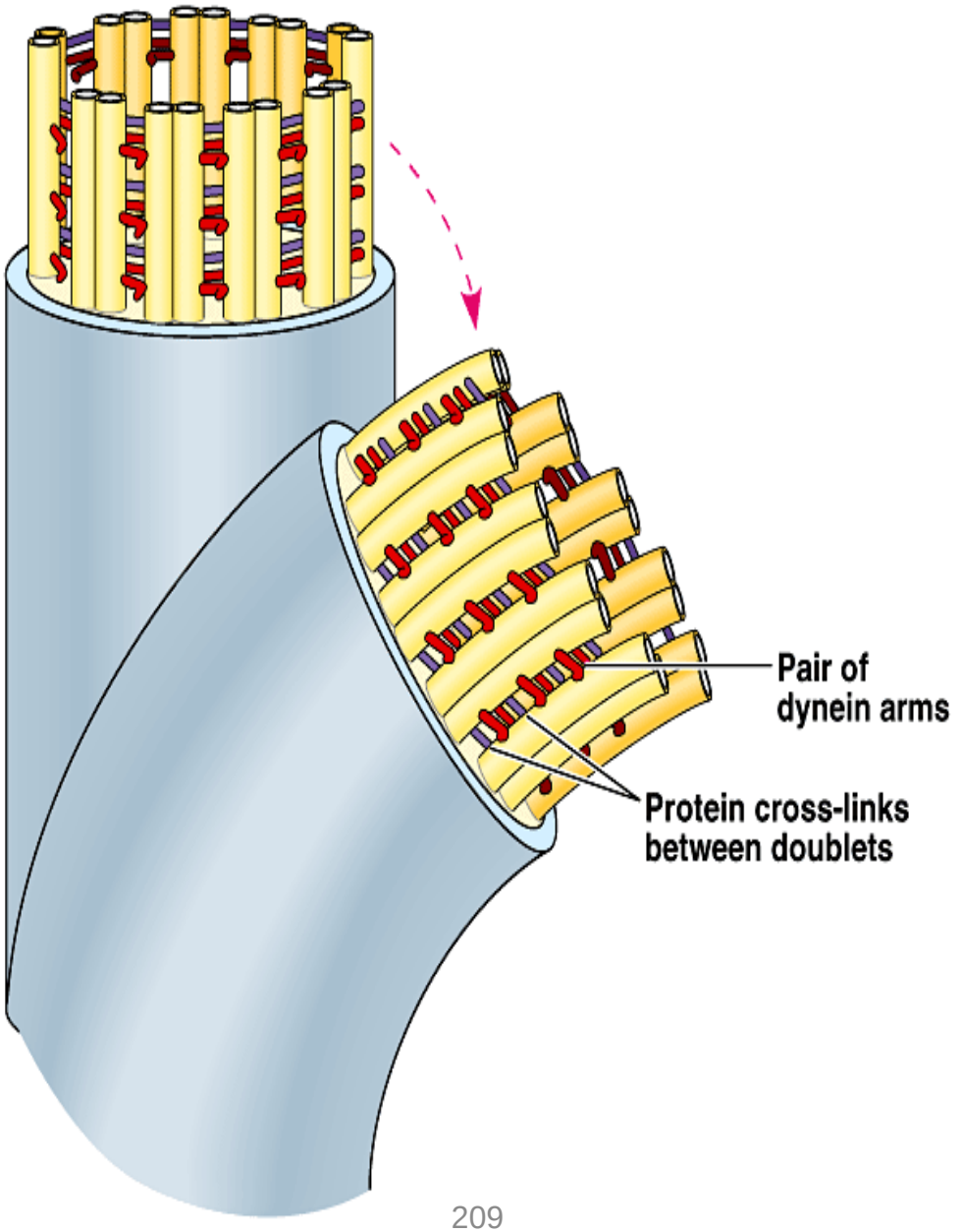
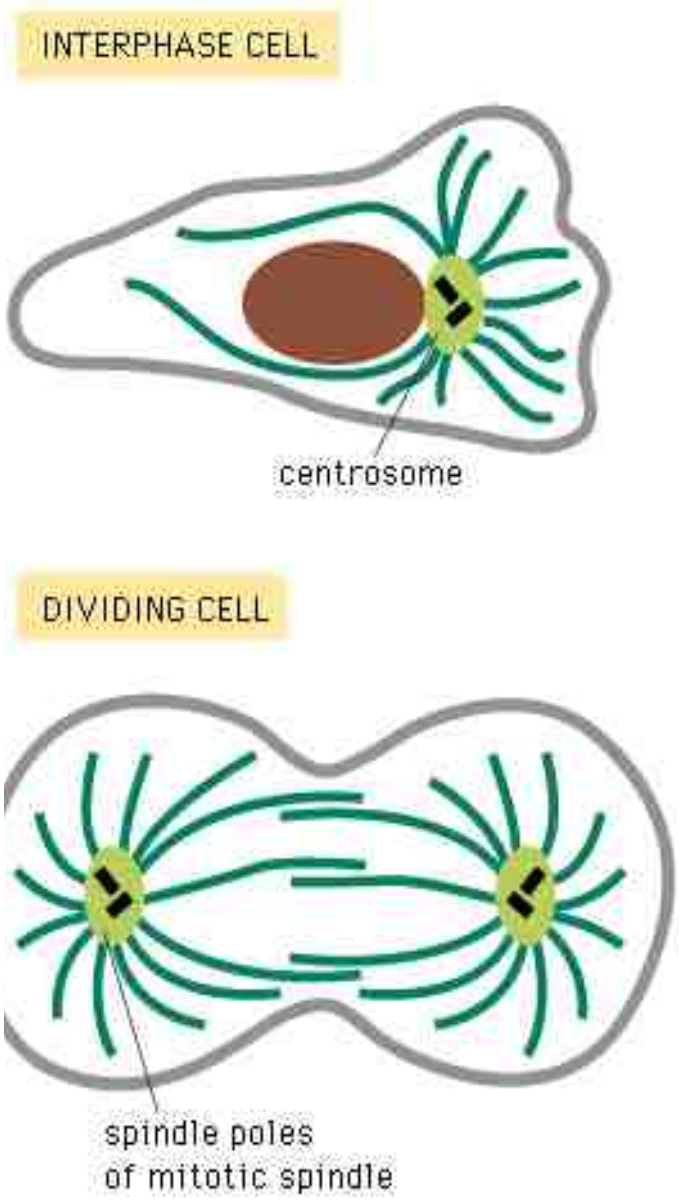


Fig. 7.23a

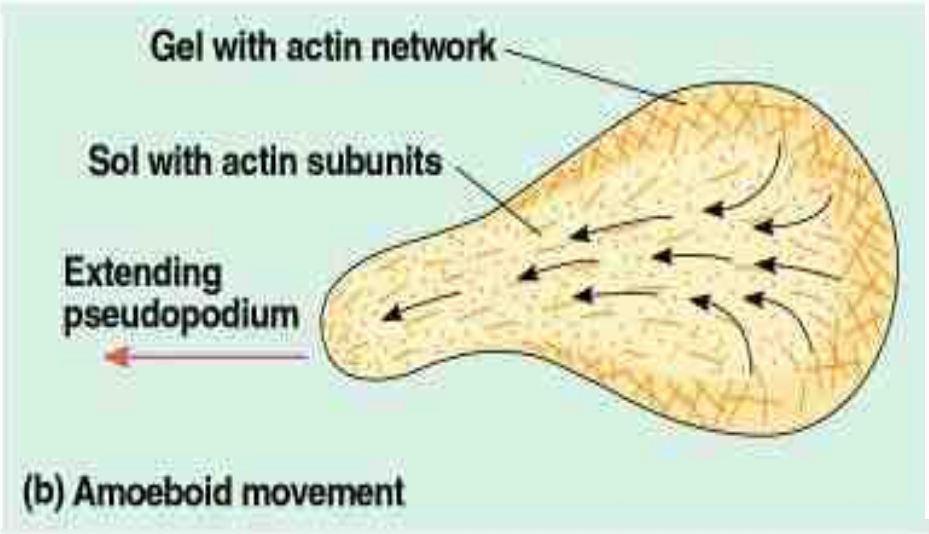
Microtubules Provide Tracks for Transport

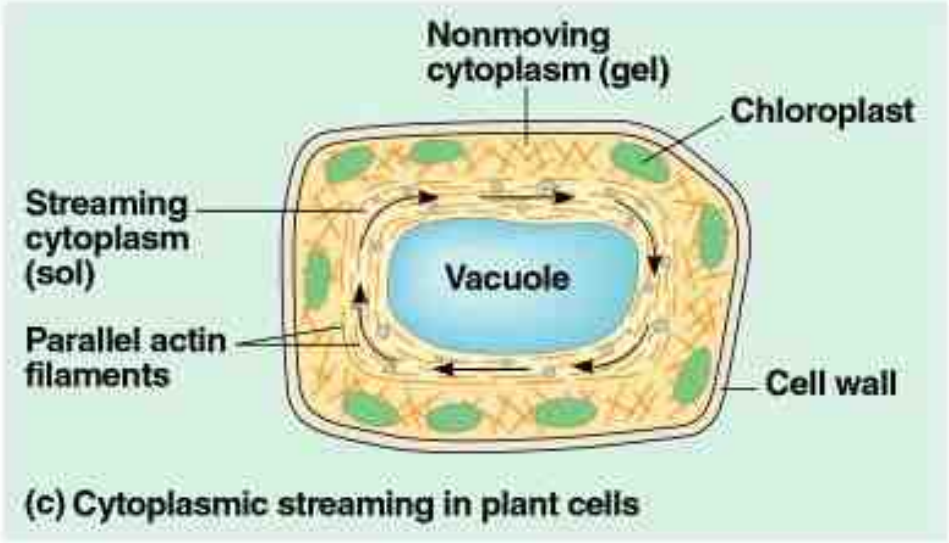


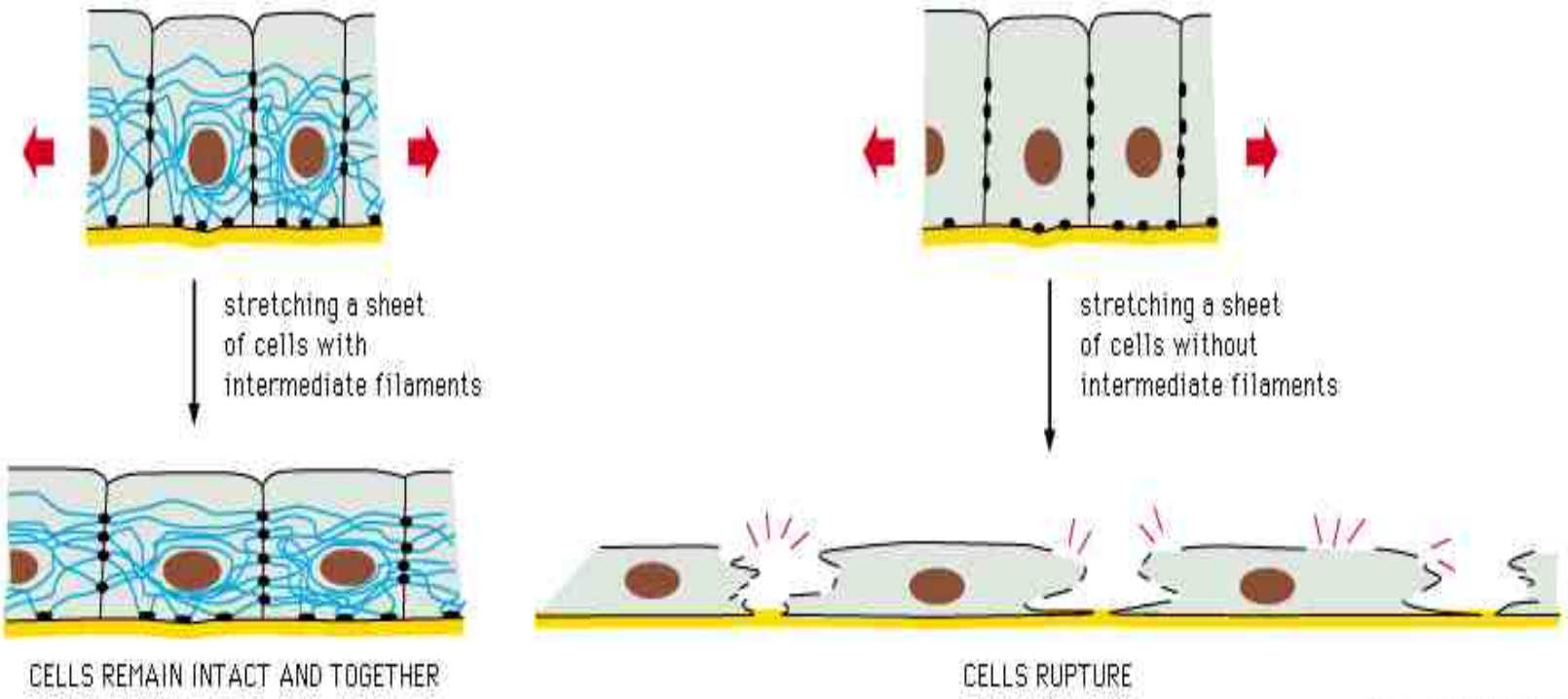

Pair of
dynein arms
Protein cross-links
between doublets


INTERPHASE CELL
centrosome
DIVIDING CELL
spindle poles
of mitotic spindle

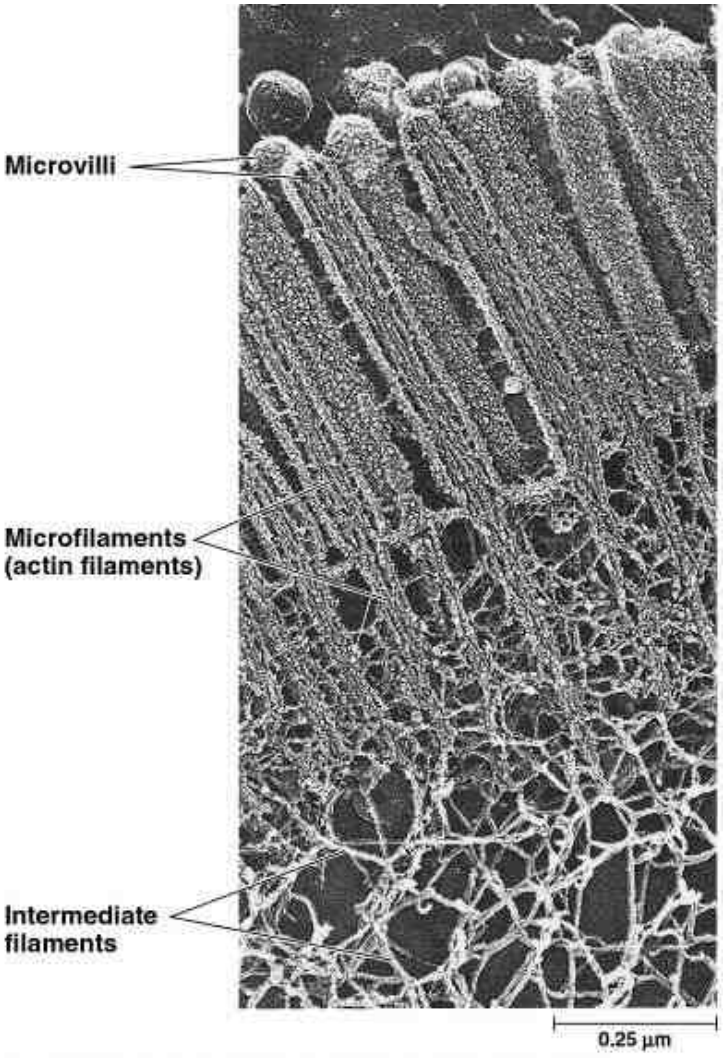
ACTIN AND INTERMEDIATE FILAMENT


Gel with actin network
Sol with actin subunits
Extending pseudopodium
(b) Amoeboid movement


Nonmoving cytoplasm (gel)
Chloroplast
Streaming cytoplasm (sol)
Vacuole
Parallel actin filaments
Cell wall
(c) Cytoplasmic streaming in plant cells


stretching a sheet of cells with intermediate filaments
stretching a sheet of cells without intermediate filaments
CELLS REMAIN INTACT AND TOGETHER
CELLS RUPTURE
©1998 GARLAND PUBLISHING

- Intermediate filaments, intermediate in size at 8 - 12 nanometers, are specialized for bearing tension.
  - Intermediate filaments are built from a diverse class of subunits from a family of proteins called keratins.
- Intermediate filaments are more permanent features of the cytoskeleton than are the other two classes.
- They reinforce cell shape and fix organelle location.

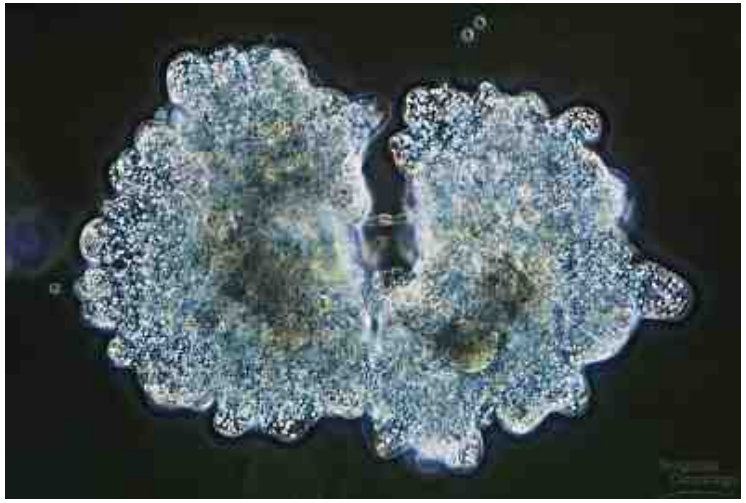


CELL BIOLOGY and GENETICS

CELL DIVISION

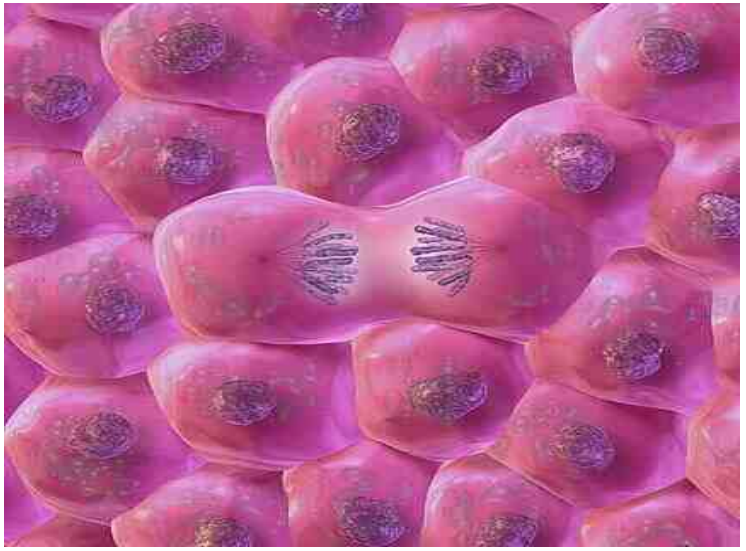
“Every cell from a cell”

120101.swf



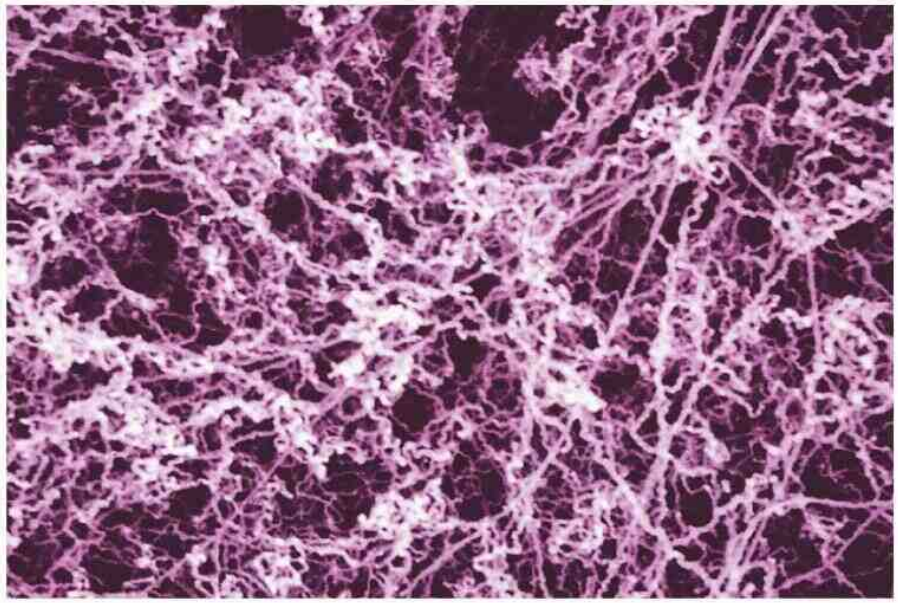
- Why do cells divide?
  - Reproduction
  - Growth and Development
  - Tissue Renewal and repair

120102.swf



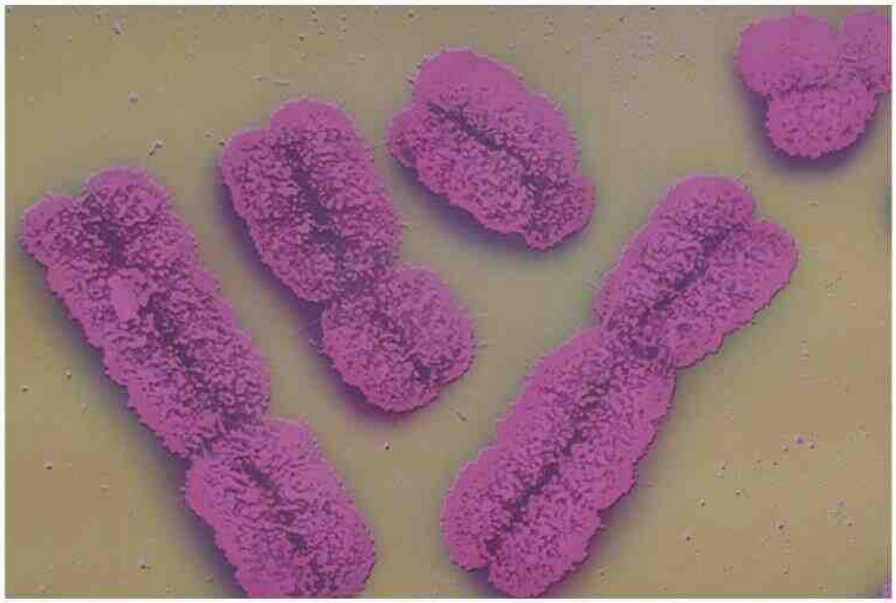
DNA is Condensed into Visible Chromosomes Only For Brief Periods in the Life of a Cell

(a) DNA in uncondensed form



95% of the time, chromosomes are like this.

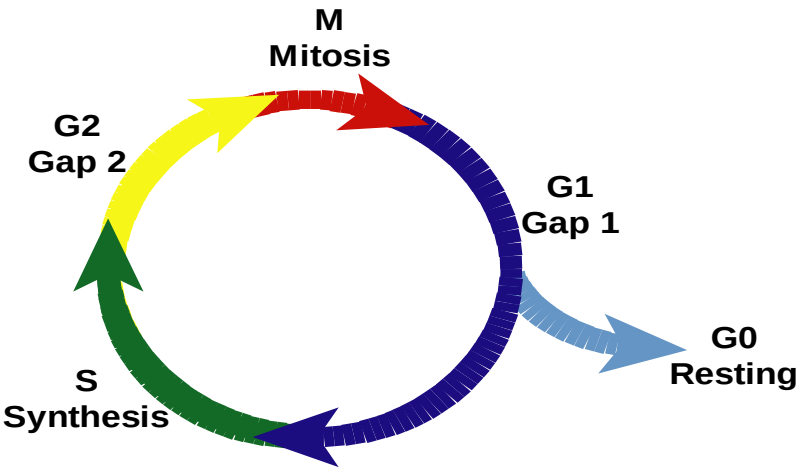
(b) DNA condensed into duplicated chromosomes



Easily visible chromosomes are apparent perhaps 5% of the time in an actively growing cell and less in a non-growing cell.

Cell cycle

- Cell has a "*life cycle*"



cell is formed from a mitotic division

cell grows & matures to divide again

cell grows & matures to never divide again

G_1, S, G_2, M

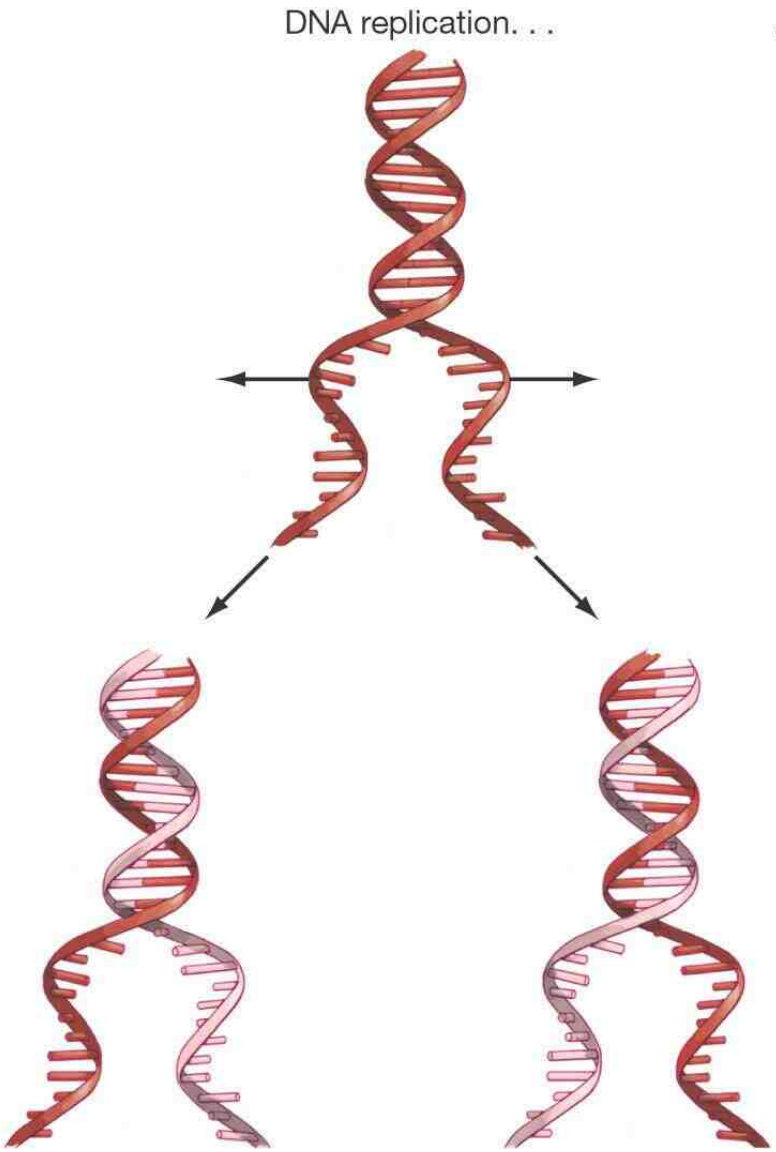
liver cells

G_0

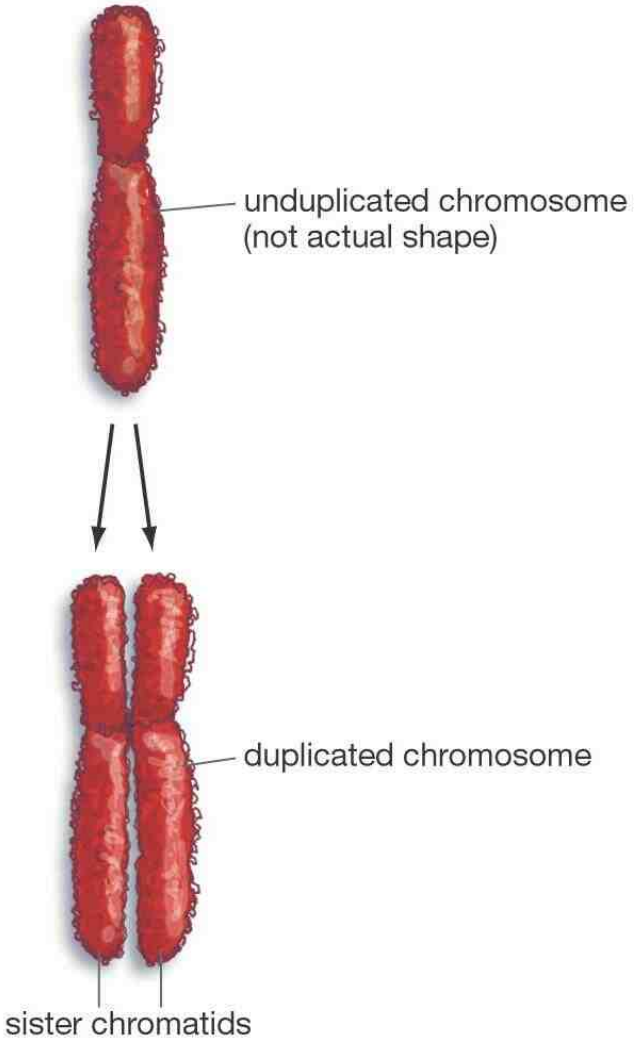
epithelial cells, blood cells, stem cells

brain nerve cells

The Link Between DNA Replication and Chromosome Duplication



. . has this effect at the chromosomal level.



➢**Mitosis** occurs **exclusively in eukaryotic cells**.

➢In multicellular organisms, the **somatic** (body cells) **cells** undergo mitosis, while **germ cells** (cells destined to become **sperm** in males or **ova** in females) divide by a related process called **meiosis**.

➢Prokaryotic cells, which lack a nucleus, divide by a process called **binary fission**.

➢Cell division consists of **TWO** steps (Mitosis and Cytokinesis)

❖**Mitosis**: process by which a cell separates its duplicated genome into two identical halves. **Mitosis only separates the newly replicated chromosomes**; DNA replication does **not** occur during mitosis.

Mitosis is broken down into four phases: (PMAT)

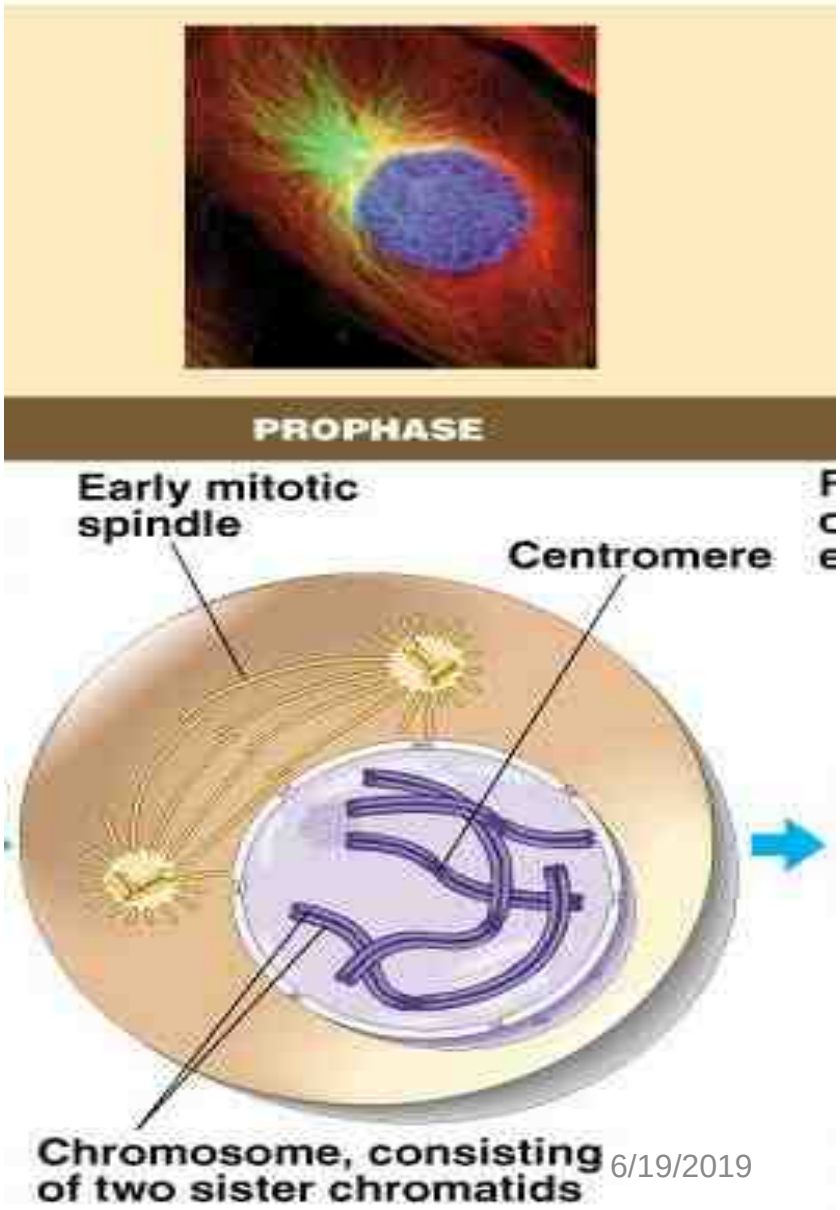
Prophase, Metaphase, Anaphase, Telophase.

❖**Cytokinesis** which divides the cytoplasm and cell membrane.

MITOSIS → PROPHASE

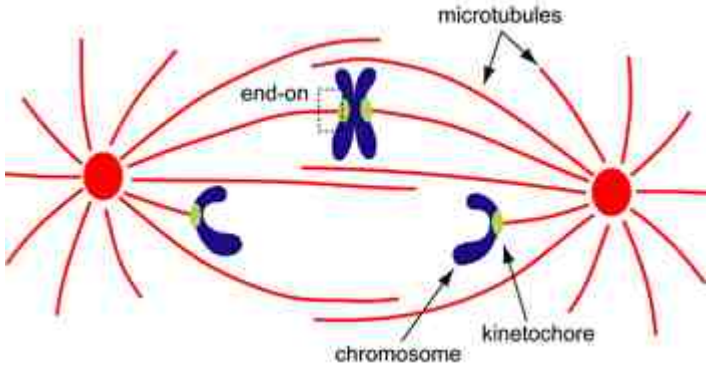
- Longest phase of mitosis

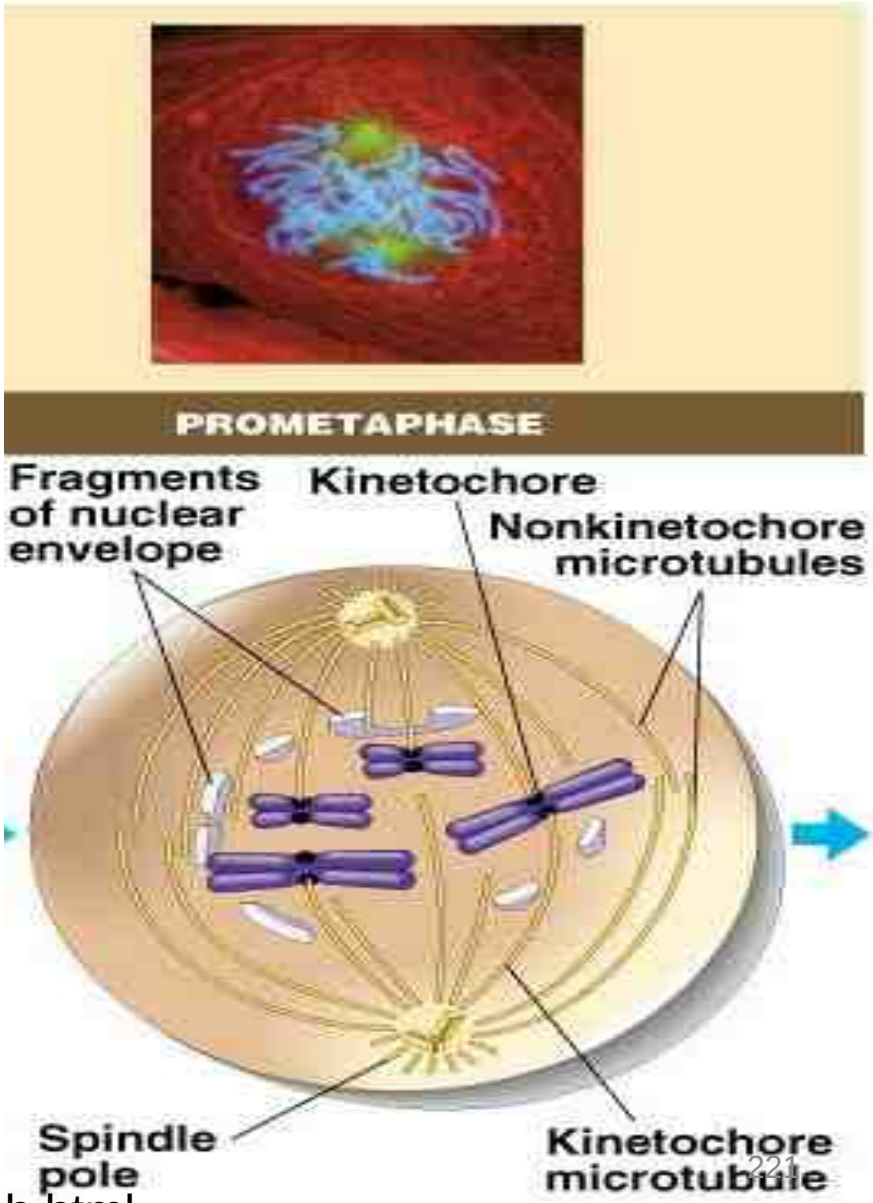
1. Chromosomes condense (become visible)
2. Centrioles (in cytoplasm) separate and move to opposite sides of cell
3. Nuclear membrane breaks-down
4. Microtubule structure called the spindle develops (attaches from centrioles to chromosomes).



PROMETAPHASE

1. *Proteins attach to centromeres*
   - creating kinetochores
2. Microtubules attach at kinetochores
   - connect centromeres to centrioles
3. Chromosomes begin moving

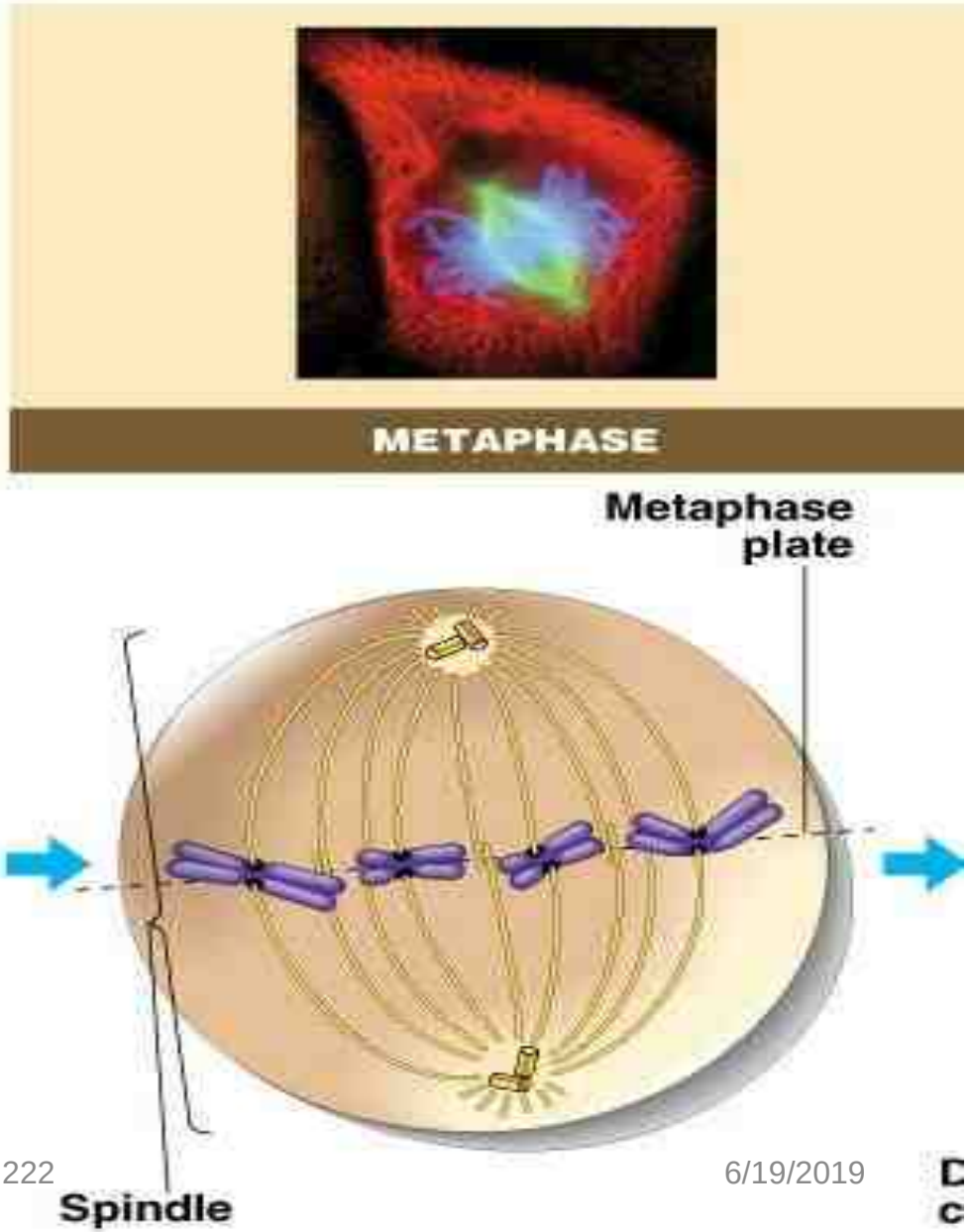




http://faculty.washington.edu/casbury/research.html

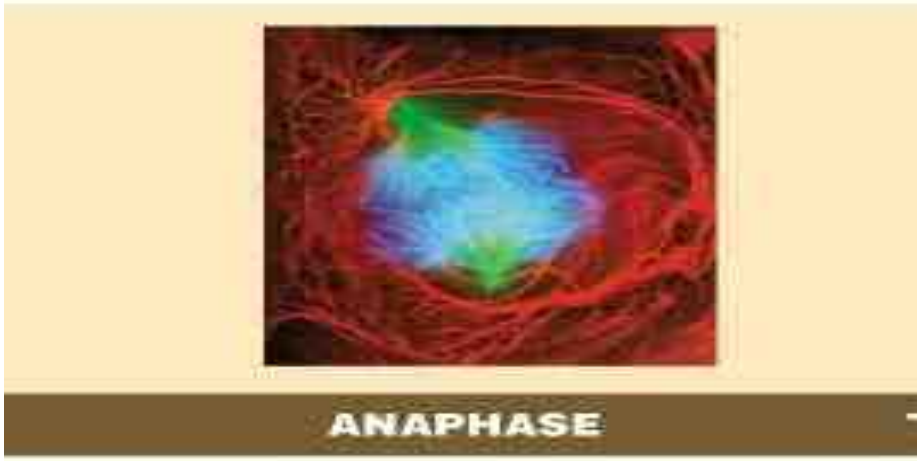
MITOSIS → METAPHASE

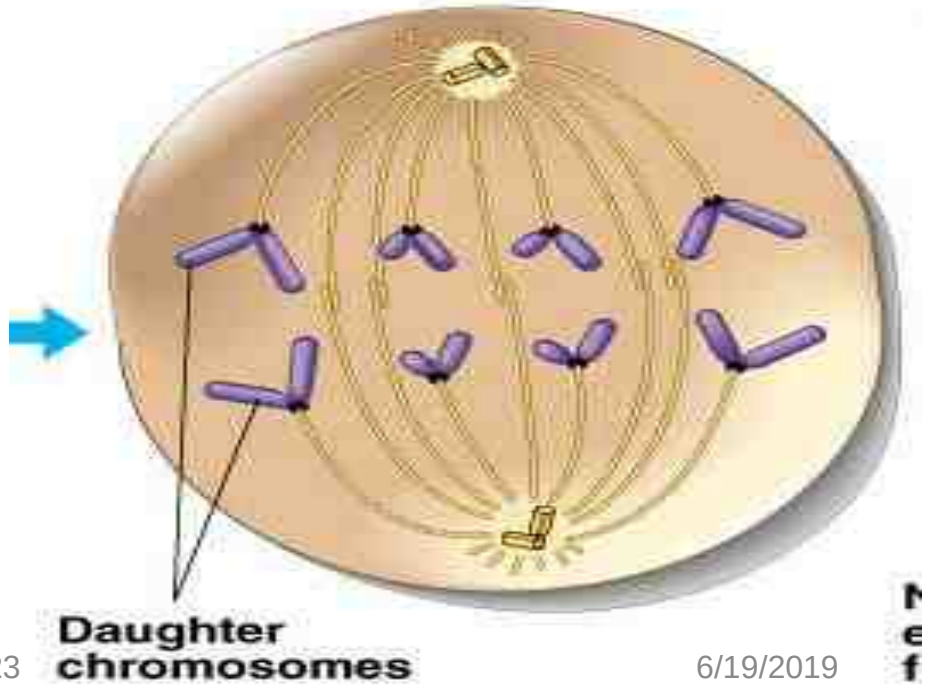
- Chromosomes line-up along center of cell (metaphase plate)



MITOSIS → ANAPHASE

1. Sister chromatids separate into separate chromosomes.
2. Separated chromosomes pulled to opposite sides.

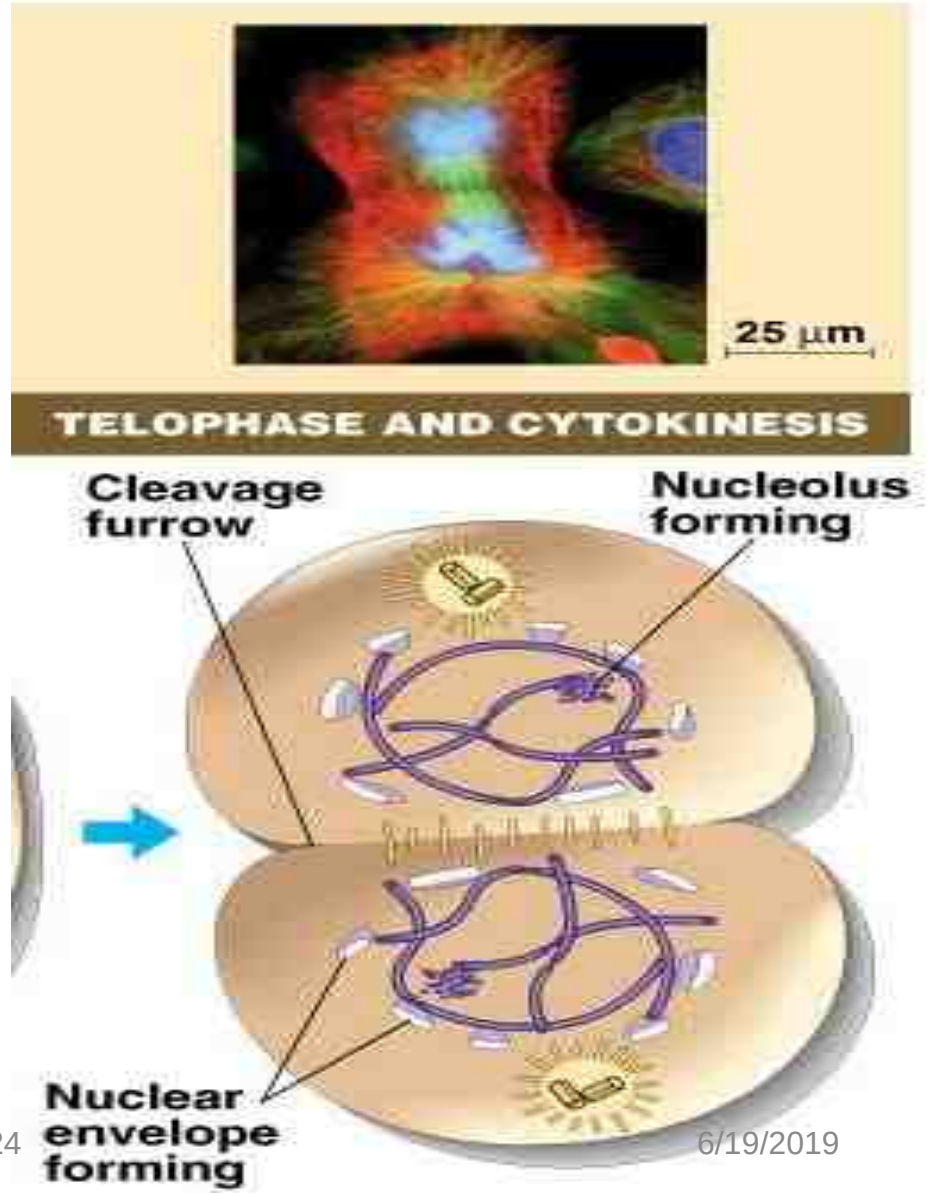




MITOSIS → TELOPHASE

1. Chromosomes move together at opposite ends of the cell and become less condensed.
2. Spindle breaks apart
3. Two new nuclear membrane form

➢ Result is one cell with 2 nuclei!

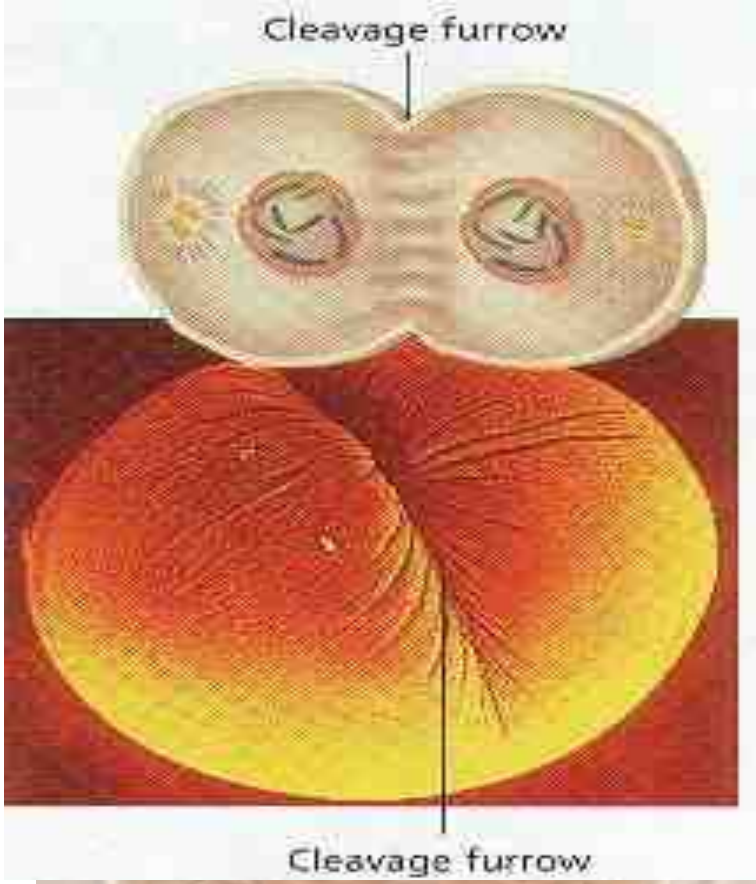


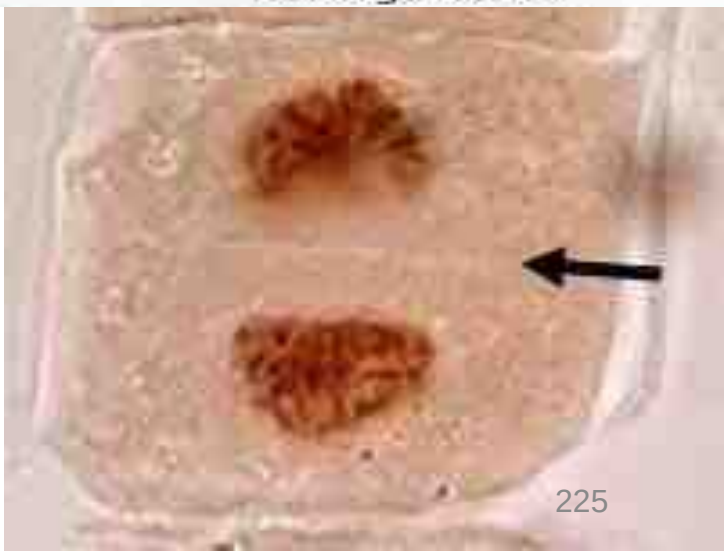
CYTOKINESIS

- Remember, NOT part of mitosis

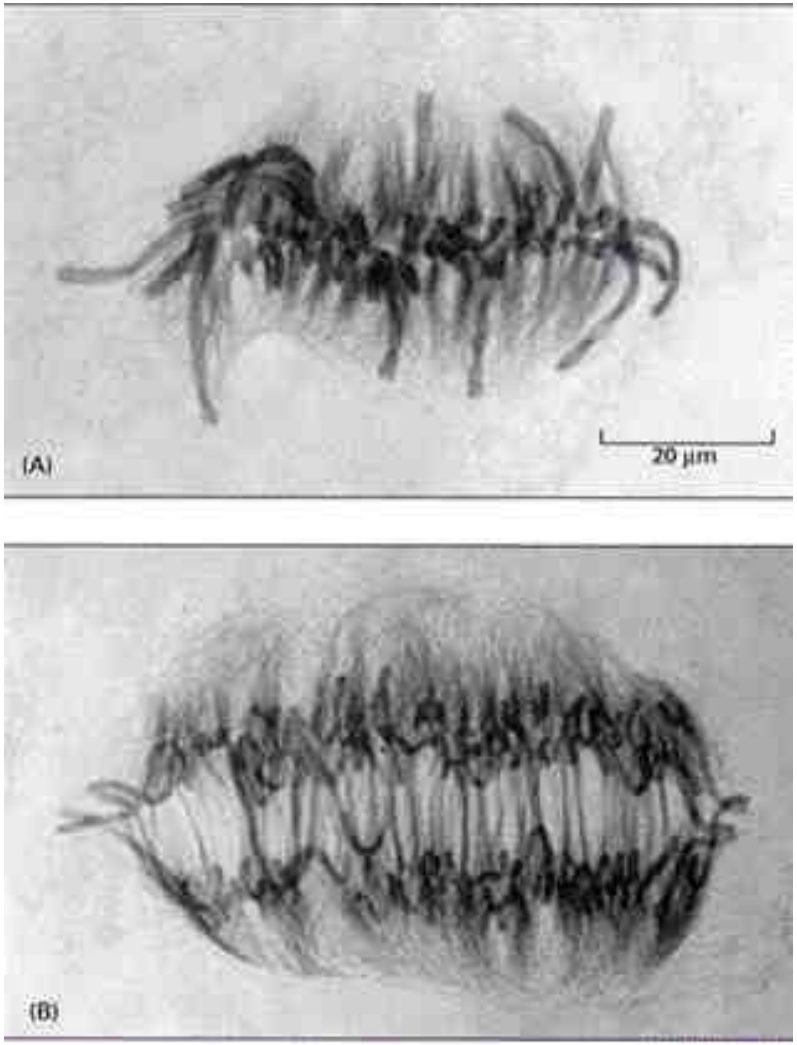
- Animals
  - Cell membrane pinches off cytoplasm into two equal parts at a region called the ***cleavage furrow***

- Plants
  - Cell Plate develops between two new nuclei which grows into a separating membrane and ultimately a separating cell wall

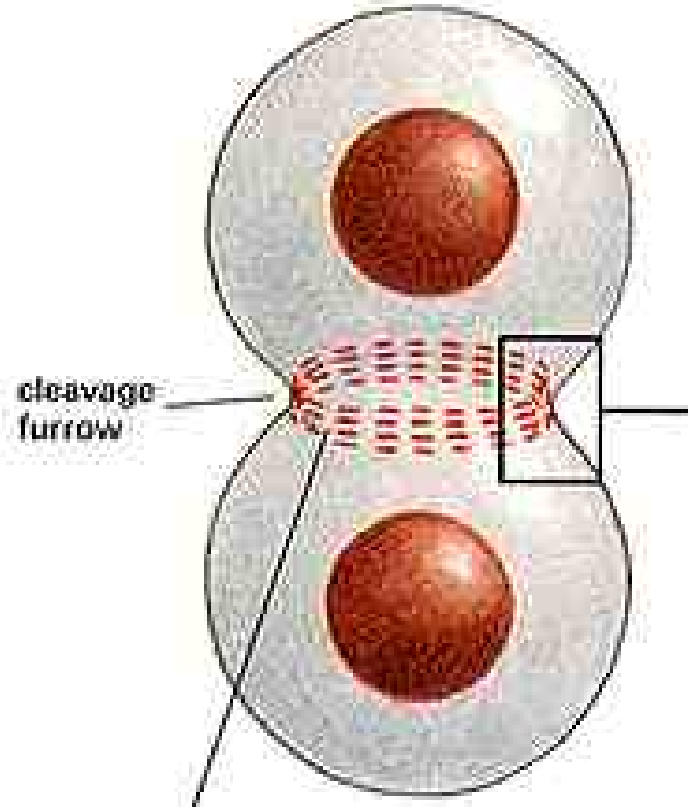




Cell division requires coordinated division of chromosomes (mitosis) …..



…… and division of the cytoplasm (cytokinesis).



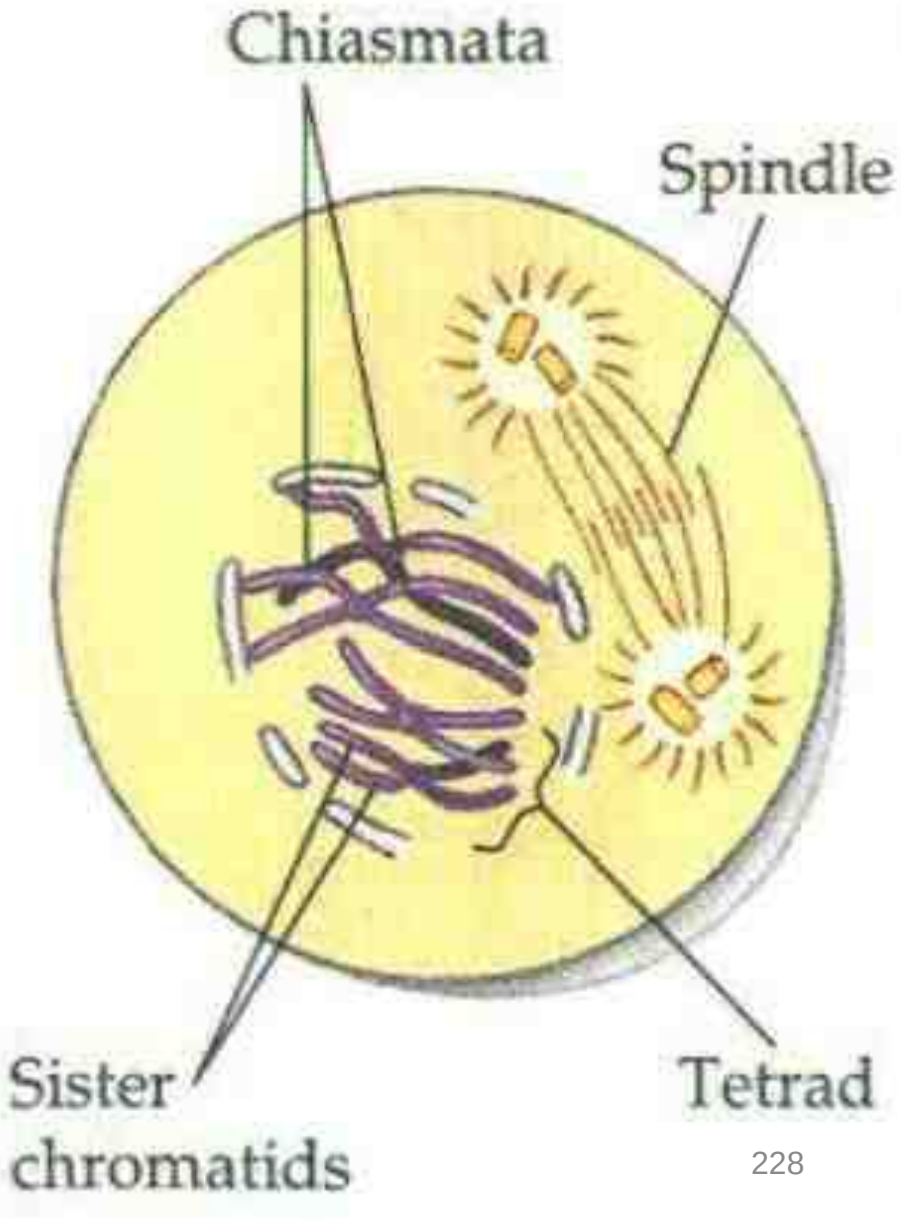
MEIOSIS

- Divided into two distinct stages
  - Meiosis I
  - Meiosis II
- Starts with **one diploid cell** and ends with **4 haploid daughter cells.**
- Before meiosis begins, DNA undergoes replication just like in mitosis!

- We know that regular somatic (body) cells contain two sets of chromosomes (diploid/ 2N)
- When a sexually reproducing organism produces gametes (sex cells) they must somehow separate these pairs of chromosomes so **gametes only get one set**.
- Why?

MEIOSIS I: PROPHASE I

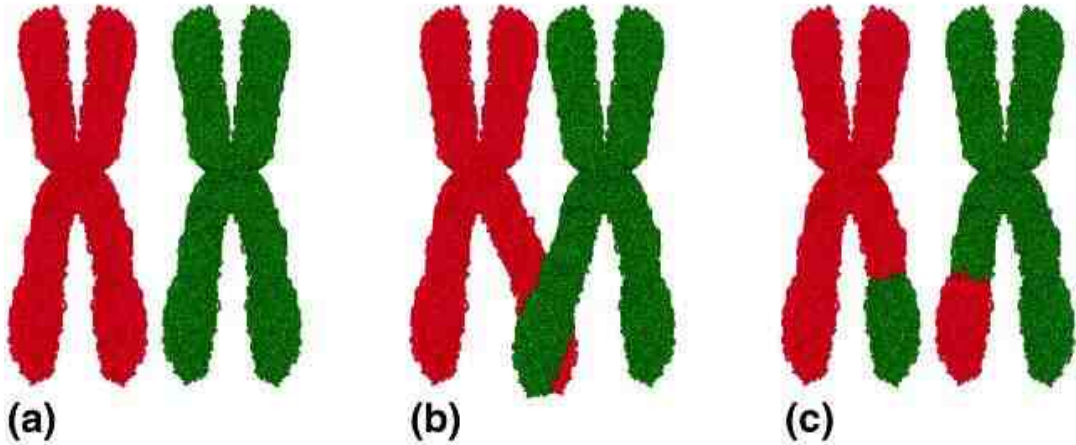
- Appearance of the chromosomes, the development of the spindle, and the breakdown of the nuclear membrane (envelope).
- Each **replicated chromosome pairs up with its corresponding homologous chromosome**
  - Paired chromosomes (4 chromatids) form a tetrad



Chromatid arms may overlap and temporarily fuse (chiasmata, or synapsis), resulting in crossovers.

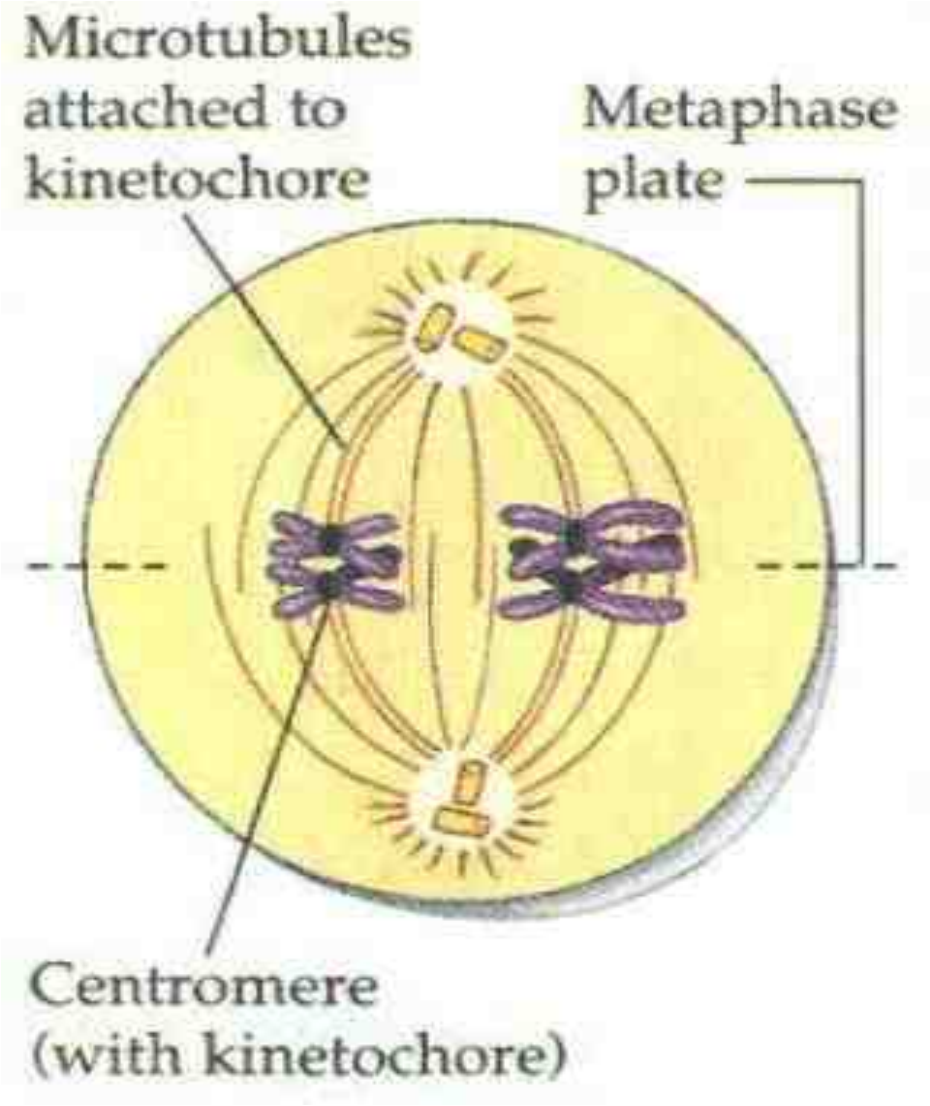
What is Crossing Over?

- Paired-up homologous chromosomes, may exchange portions of their chromatids
- Advantage?



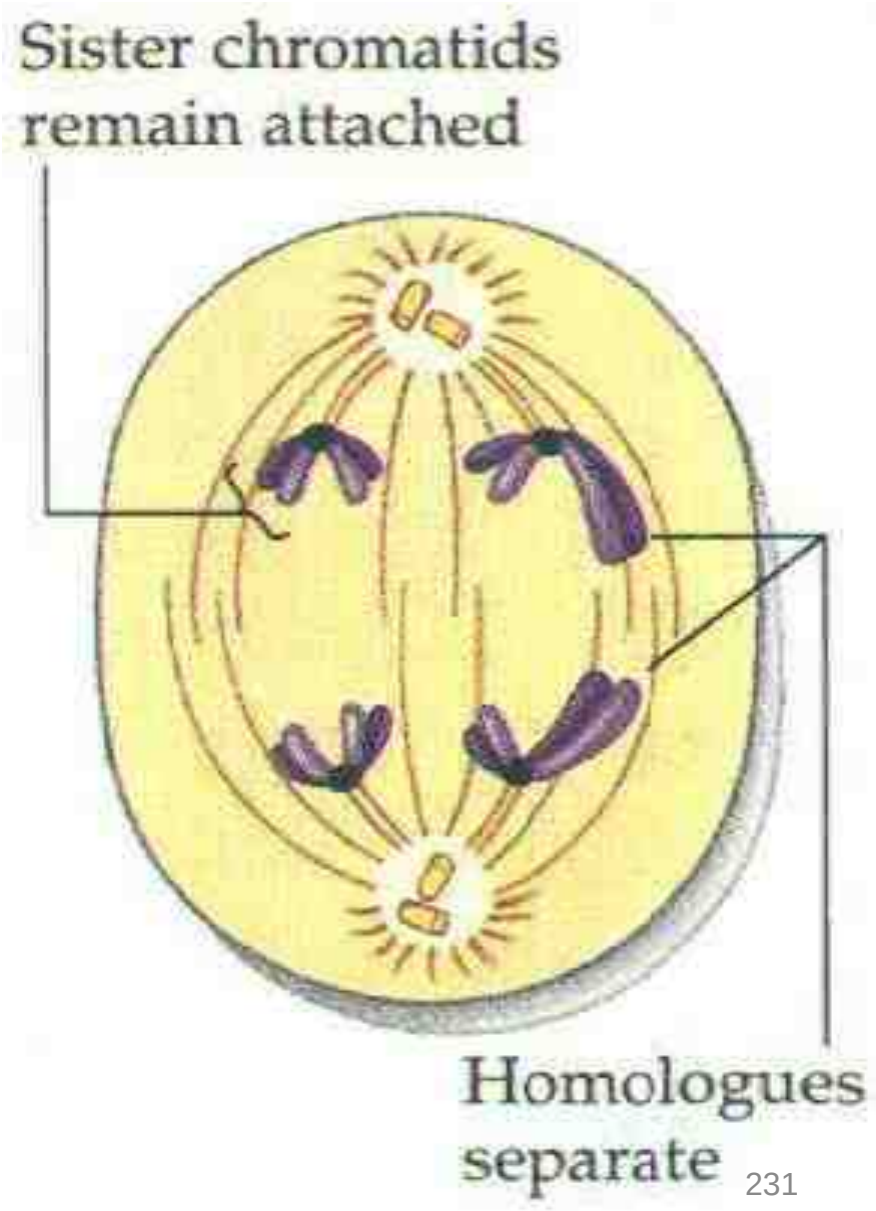
MEIOSIS I: METAPHASE I

- Here is where the critical difference occurs between Metaphase I in meiosis and metaphase in mitosis. In the latter, all the chromosomes line up on the metaphase plate in **no particular order**. In Metaphase I, the chromosome pairs are aligned **on either side of the metaphase plate.**



MEIOSIS I: ANAPHASE I

- During Anaphase I the spindle fibers contract, pulling the homologous pairs away from each other and toward each pole of the cell.



MEIOSIS II

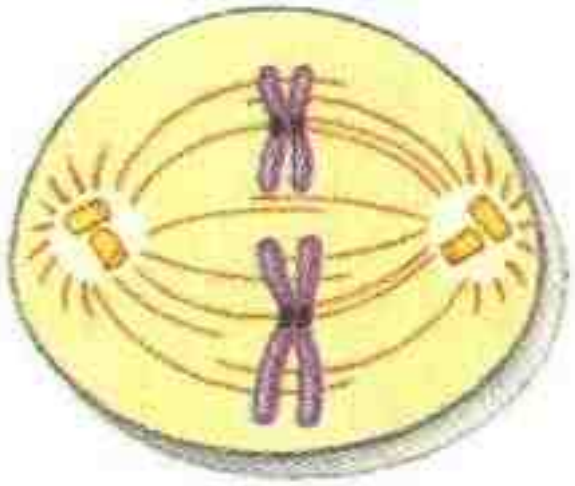
- Meiosis II is quite simple in that it is simply a mitotic division of each of the haploid cells produced in Meiosis I.
- There is no Interphase between Meiosis I and Meiosis II

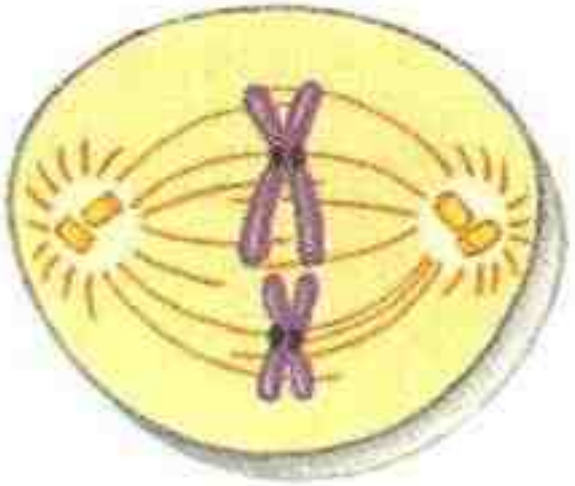
MEIOSIS II: PROPHASE II

- A new set of spindle fibers forms and the chromosomes begin to move toward the equator of the cell.

MEIOSIS II: METAPHASE II

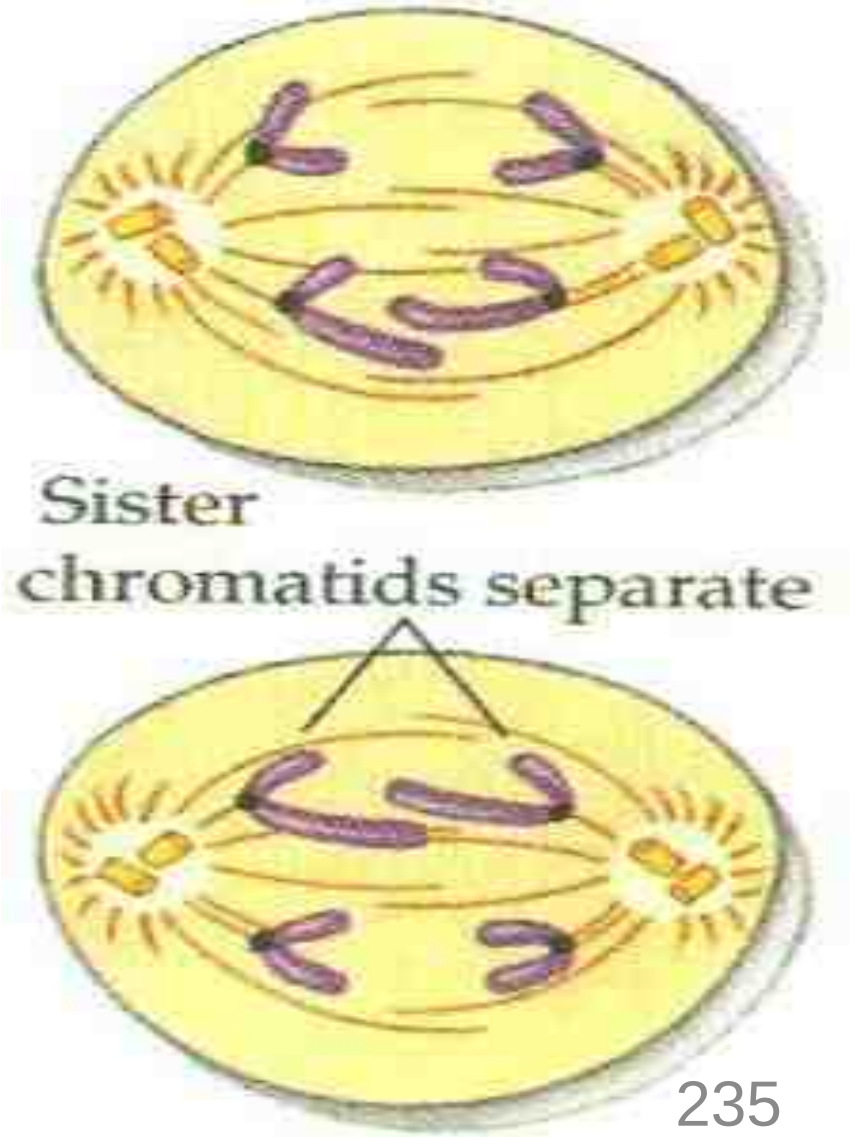
- All the chromosomes in the two cells align with the metaphase plate.





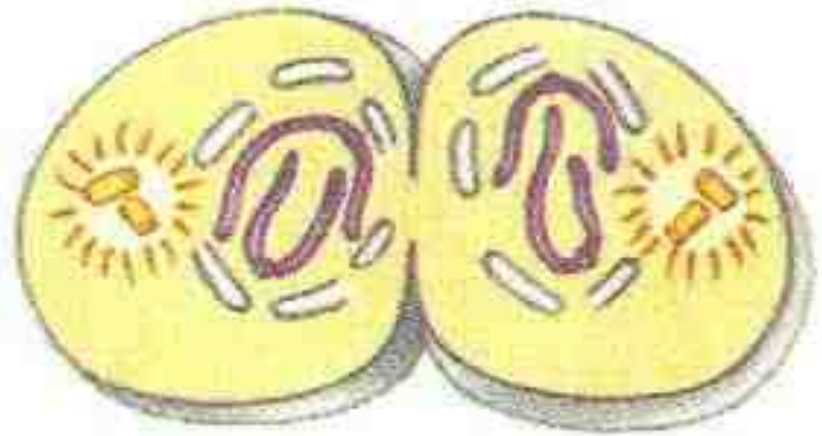
MEIOSIS II: ANAPHASE II

- Sister chromatids separate as they are pulled by spindle fibers.

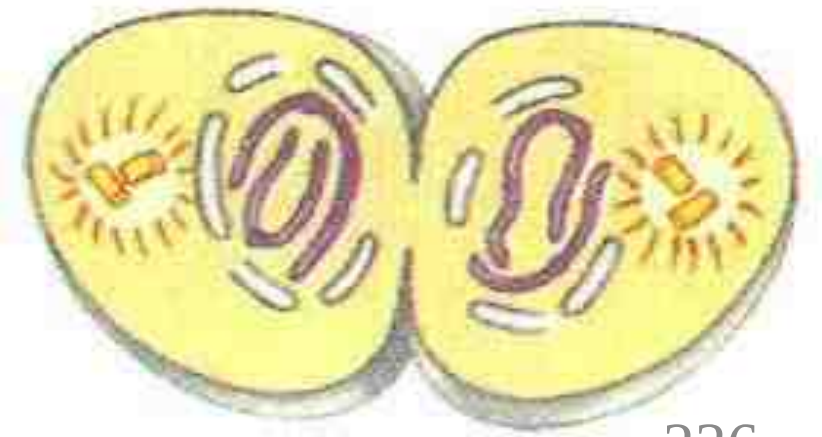


MEIOSIS II: TELOPHASE II

- A cleavage furrow develops, followed by cytokinesis and the formation of the nuclear membrane (envelope). The chromosomes begin to fade, replaced by the granular chromatin characteristic of interphase.
- When Meiosis II is complete, there will be a total of four daughter cells, each with half the total number of chromosomes as the original cell.



Haploid daughter cells



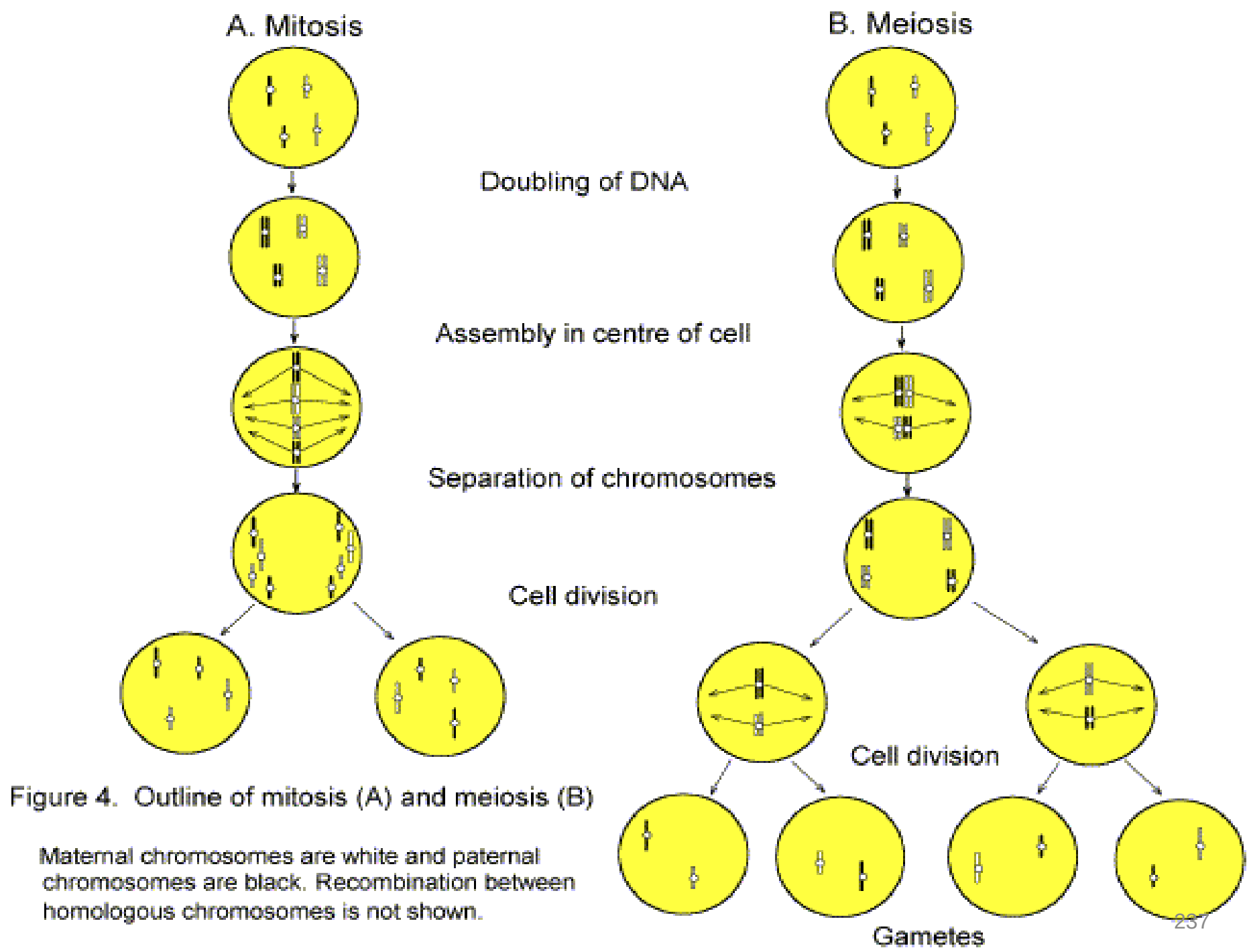


Figure 4. Outline of mitosis (A) and meiosis (B)

Maternal chromosomes are white and paternal chromosomes are black. Recombination between homologous chromosomes is not shown.

ADVANTAGES OF SEXUAL REPRODUCTION?

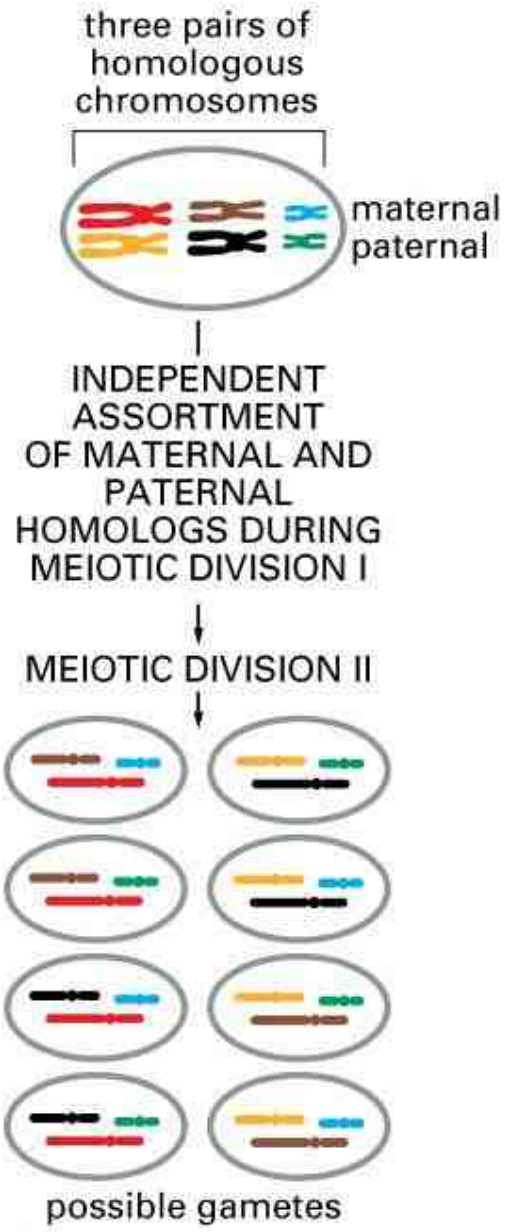
- Recombination of maternal and paternal chromosomes in the gamete results in genetic variation among the offspring.
- In an environment which changes, this allows the process of natural selection to occur.

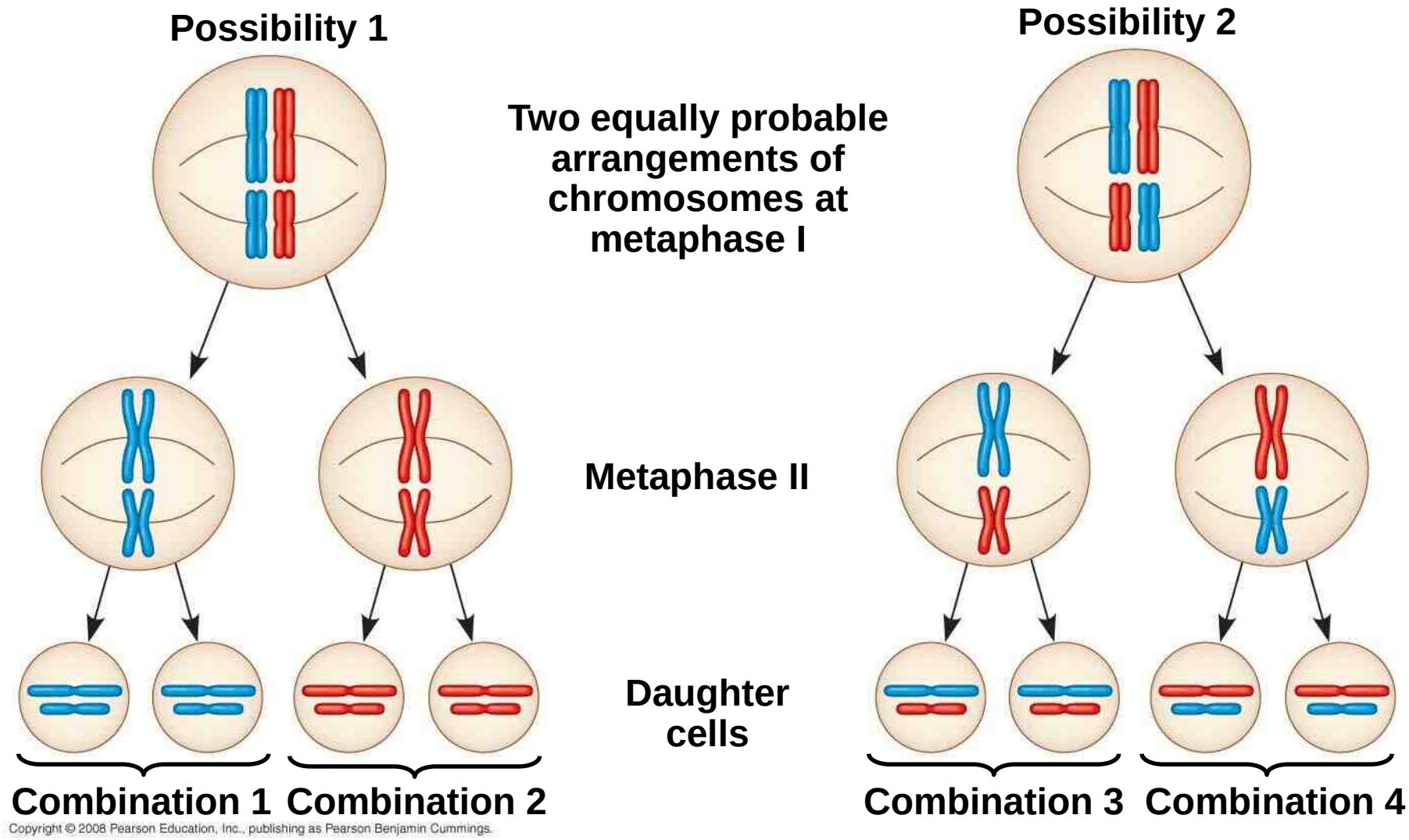
One Way Meiosis Makes Lots of Different Sex Cells (Gametes) – Independent Assortment

Independent assortment produces 2^n distinct gametes, where *n* = the number of unique chromosomes.

In humans, n = 23 and $2^{23} \approx$ 8,000,0000.

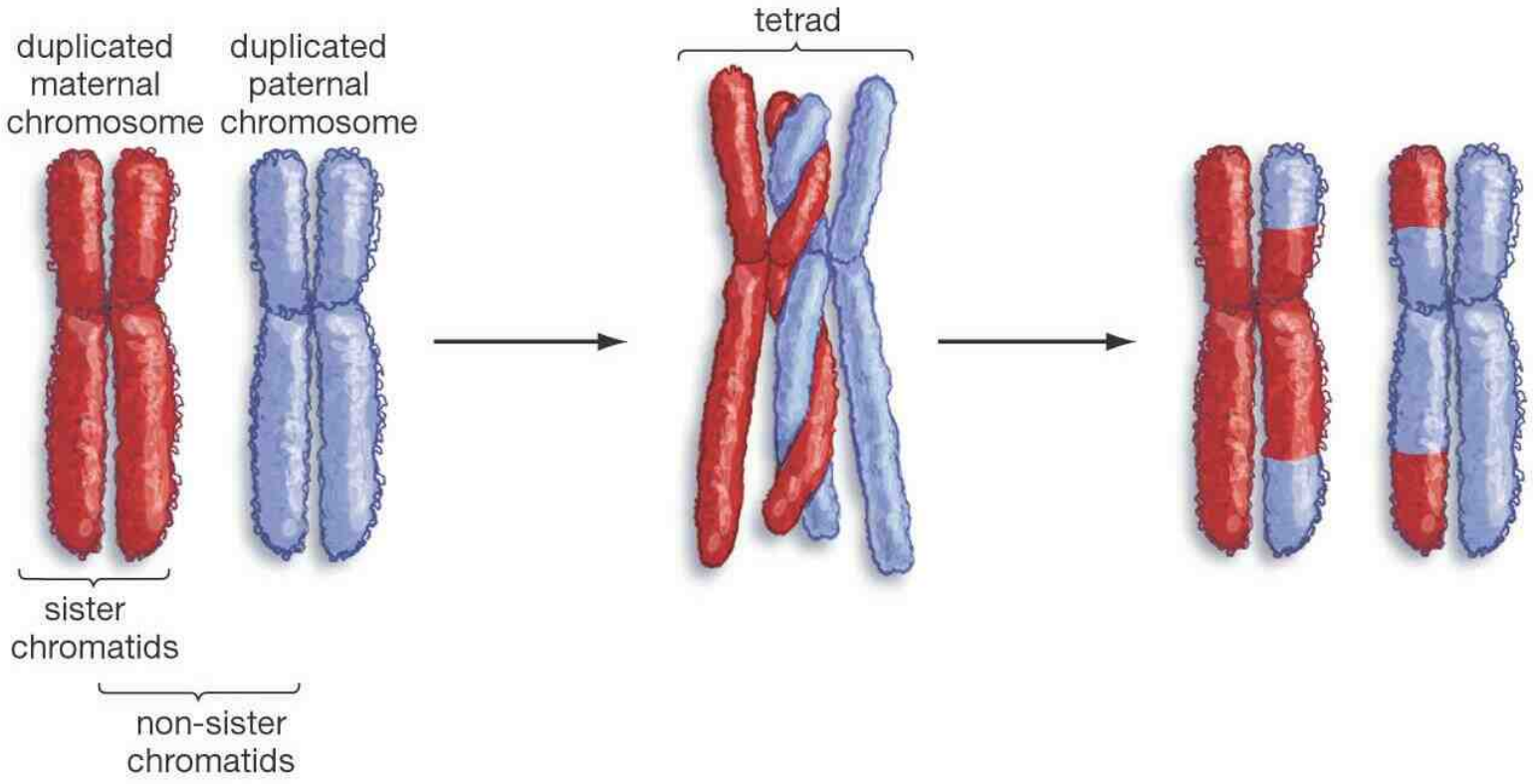
That's a lot of diversity by this mechanism alone.





Another Way Meiosis Makes Lots of Different Sex Cells – Crossing-Over

Exchange of parts of non-sister chromatids.



Crossing-over multiplies the already huge number of different gamete types produced by independent assortment.

REGULATION OF CELL CYCLE

The cell cycle varies among different cell types

- In multicellular organisms **generation time varies markedly among cell type** depending in their role in the organism.
  - Divide continuously (sperm formation, stem cells, Bone marrow cells, skin cells)
  - Slow growing tissues
  - Do not divide at all (mature nerve or muscle tissue)
  - Induced to start dividing (liver, white blood cells).

Most of these variations in generation time **are based on differences in the length of G1**, although S and G2 can also vary.

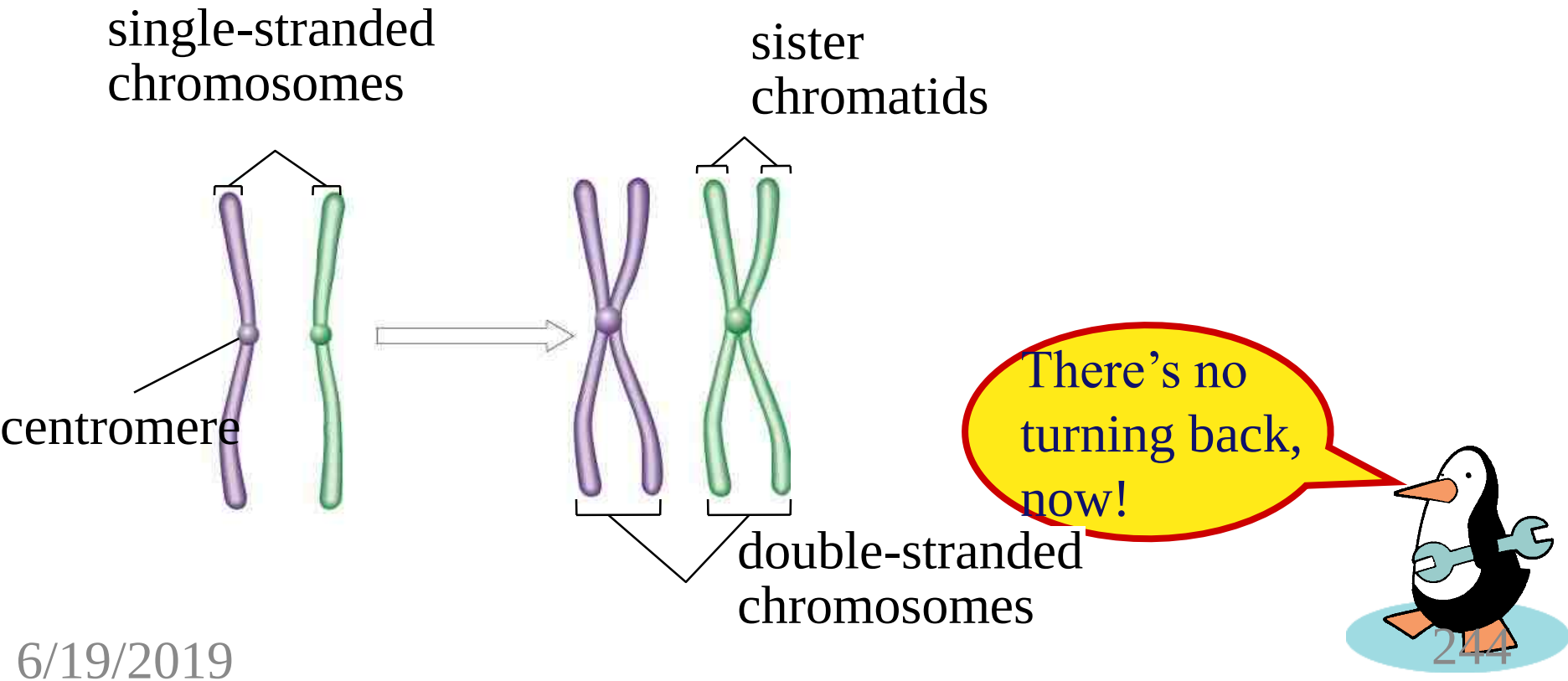
CYCLE REGULATORS

- The cell cycle is regulated by special proteins called ***cyclins*** and ***cyclin-dependent kinases*****.**
- **High concentrations of *cyclin*** influences a cell to divide.
- ✓ **Internal Regulators** → proteins that respond to internal stimuli
  - Ex. **Cell will not enter mitosis** until all chromosomes are replicated.
- ✓ **External Regulators** → proteins that respond to external stimuli
  - Ex. **Cell will begin to divide rapidly after injury**
  - Ex. When dividing cells come in **contact** with adjacent cells, division will slow

20.2-contact_inhibition.mov

CELL CYCLE CONTROL

- **Two irreversible points** in cell cycle
  - Replication of genetic material
  - Separation of sister chromatids
- Cell can be put on hold at specific **checkpoints**



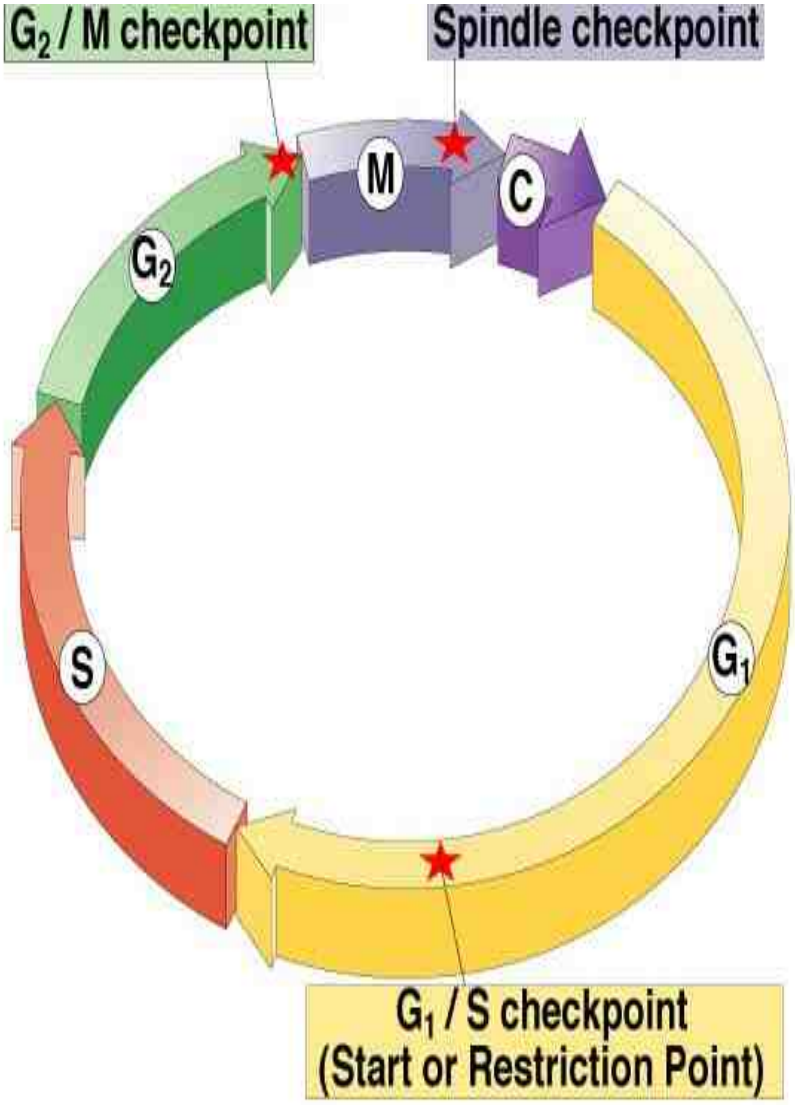
- Progression through the cell cycle is controlled at **several key transition point.**
- **The first** control point occurs during **late G1**(size, nutrients).
- **A second** important transition point occurs at the **G2-M boundary**, where the commitment is made to inter into mitosis.
- A **third** key transition point occurs during M phase **at the jonction between metaphase and anaphase**, where ***commitment is made to move the two sets of chromosomes*** into the newly forming daughter cells.

CHECKPOINT CONTROL SYSTEM

3 major checkpoints:

- **G_1**
  - **can** DNA synthesis begin?
- G_2
  - has DNA synthesis been **completed correctly?**
  - commitment to mitosis
- M phases
  - spindle checkpoint
  - can sister chromatids **separate correctly?**

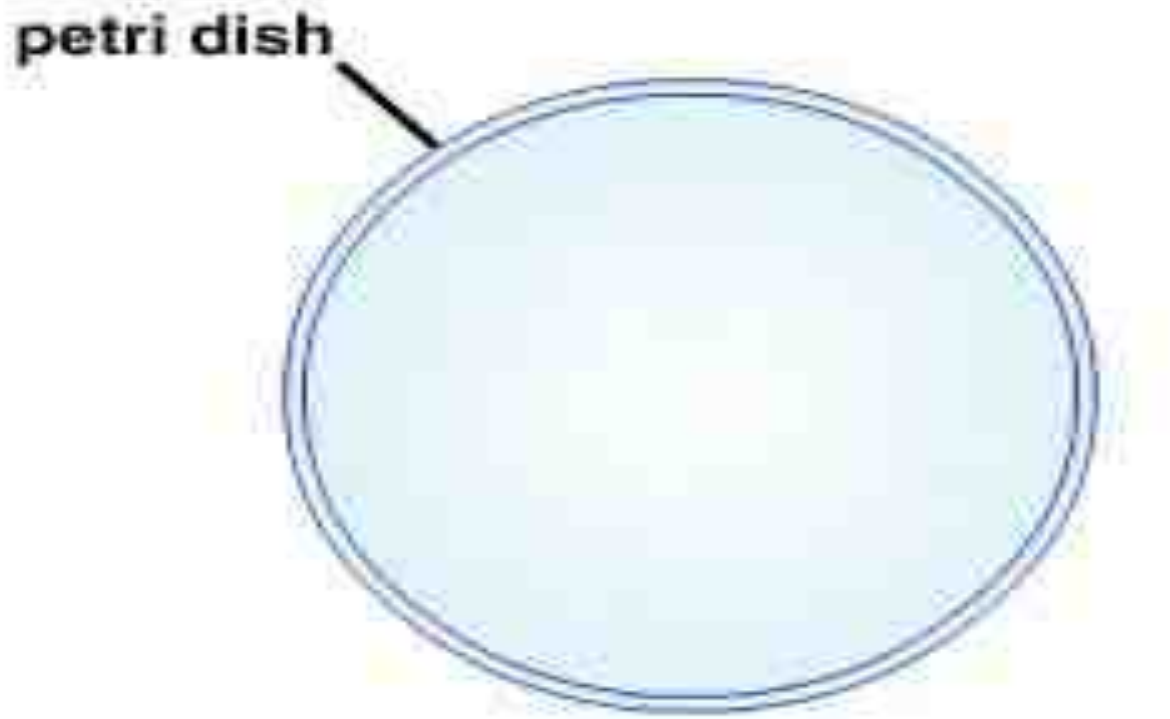
Failed control system can result in cancer



- Cancer is defined as **a combination of two properties**: The ability of cells to proliferate in an **uncontrolled way** and their ability to **spread** throughout body.
- The crucial issue is not the **rate** of cell division but rather the **balance between cell division and cell differentiation**.
- As dividing cells accumulates, **the normal organization and function of the tissue gradually become disrupted**.
- Tumor are classified as either **benign** or **malignant.**


Cell cycle.MOV

Failed control system can result in cancer



CELL DEATH

- Cells that are damaged by injury, such as by Mechanical damage, Exposure to toxic chemicals undergo a characteristic series of changes:
- They (and their organelles like mitochondria) swell (because the ability of the plasma membrane to control the passage of ions and water is disrupted) .
- **The cell contents leak out**, leading to inflammation of surrounding tissues.
- The pattern of events in death by suicide is so ordered that the process is often called **programmed cell death** or PCD.
- Programmed cell death is also called **apoptosis.**

Why should a cell commit suicide?

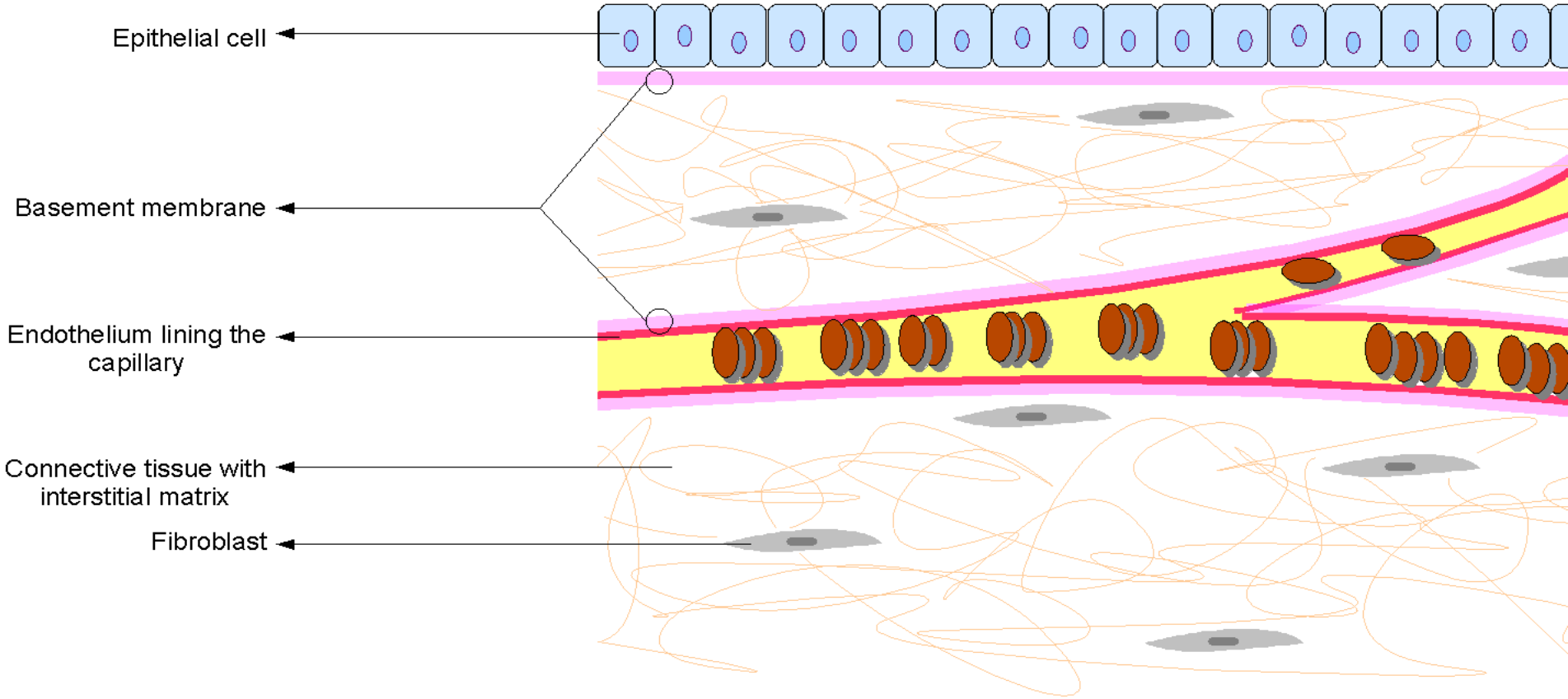
- Programmed cell death is as needed for **proper development of multicellular organisms.**
- Programmed cell death is needed **to destroy cells that represent a threat** to the integrity of the organism.

EXTRACELLULAR MATRIX

- The extracellular matrix (ECM) is the extracellular part of animal tissue that usually provides **structural support** to the animal cells in addition to performing various other important functions.
- The extracellular matrix is the **defining feature of connective tissue in animals.**
  The constituent substances are secreted by cells in the vicinity, especially ***fibroblasts*.**

- The extracellular matrix, also called **ground substance**, **holds the cells together** and provides a **porous pathway for the diffusion of nutrients** and oxygen to individual cells.
- The extracellular matrix is composed of an **interlocking meshwork** of heteropolysaccharides and fibrous proteins such as **collagen**, **elastin**, **fibronectin**, and **laminin**.

Illustration depicting extracellular matrix in relation to epithelium, endothelium and connective tissue



CELL JUNCTION

- Every animal has four levels of hierarchical organization: **cell**, **tissue**, **organ**, and **organ system**.
- Each level in the hierarchy is of increasing complexity, and all organ systems work together to form an **organism**.
- The four major types of tissue are **epithelial**, **connective**, **muscle,** and **nerve.**
- **Cell junctions** are the specialized **connections between** the plasma membranes of adjoining cells.

- The three general types of cell junctions are **tight** junctions, **anchoring** junctions, and **communicating** junctions.
- **Tight junctions** **bind cells together**, forming a barrier that **is leak-proof**. For example, tight junctions form **the lining of the digestive tract**, preventing the contents of the intestine from entering the body.
- **Anchoring** (or adhering) junctions **link cells together**, enabling them to function as a unit and forming tissue, such as heart muscle or the epithelium that comprises skin.
- **Communicating** (or gap) junctions allow rapid **chemical** and **electrical** communication between cells. They consist of **channels** that connect the cytoplasm of adjacent cells.

TYPES OF CELL JUNCTIONS

ANCHORING JUNCTIONS

Actin filament attachment sites

1. cell–cell junctions (adherens junctions)
2. cell–matrix junctions (actin-linked cell–matrix adhesions)

Intermediate filament attachment sites

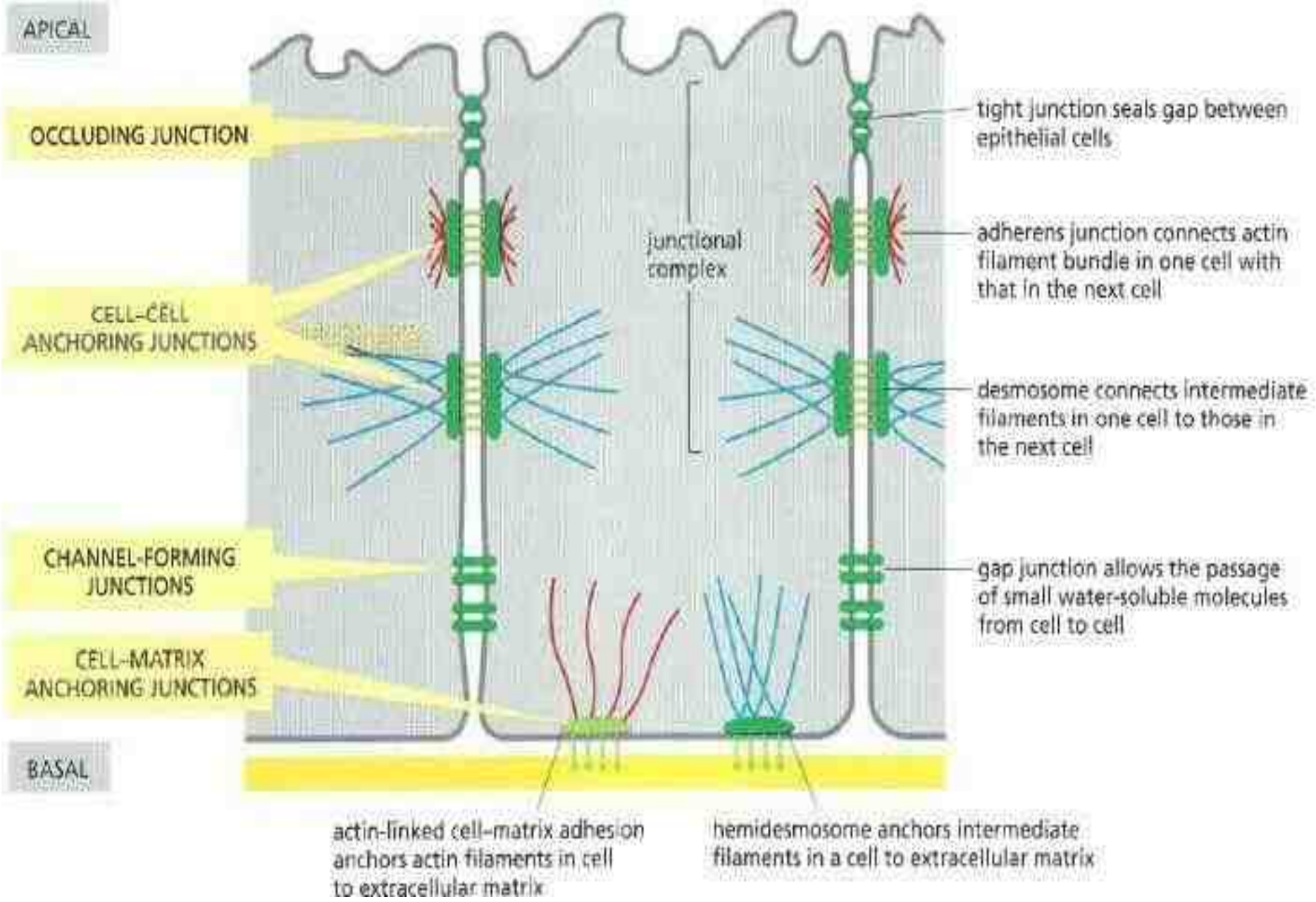
1. cell–cell junctions (desmosomes)
2. cell–matrix junctions (hemidesmosomes)

OCCLUDING JUNCTIONS

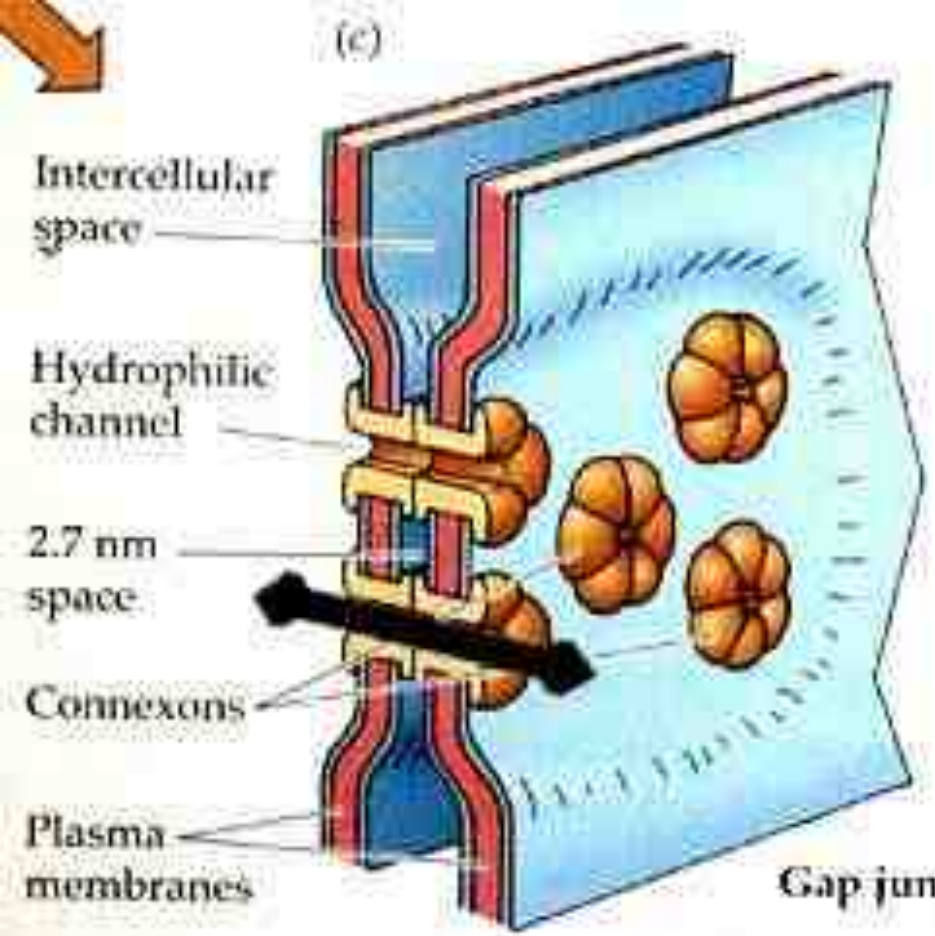
1. tight junctions (in vertebrates)
2. septate junctions (in invertebrates)

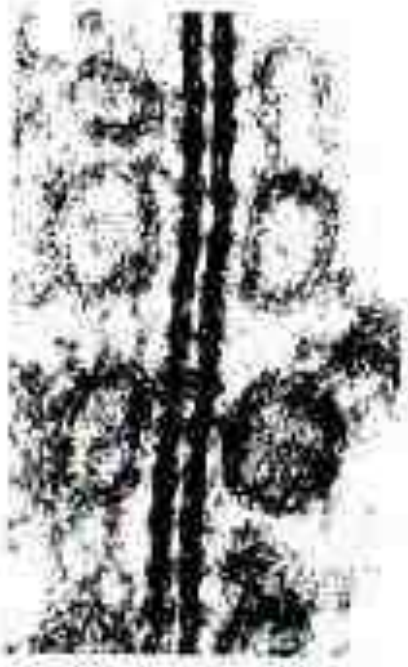
CHANNEL-FORMING JUNCTIONS

1. gap junctions (in animals)
2. plasmodesmata (in plants)


APICAL
OCCLUDING JUNCTION
CELL–CELL ANCHORING JUNCTIONS
CHANNEL-FORMING JUNCTIONS
CELL–MATRIX ANCHORING JUNCTIONS
BASAL
junctional complex
tight junction seals gap between epithelial cells
adherens junction connects actin filament bundle in one cell with that in the next cell
desmosome connects intermediate filaments in one cell to those in the next cell
gap junction allows the passage of small water-soluble molecules from cell to cell
actin-linked cell–matrix adhesion anchors actin filaments in cell to extracellular matrix
hemidesmosome anchors intermediate filaments in a cell to extracellular matrix

(c)





0.1 μm

Gap junction

MULTICELLULARITY

Integrating Cells into Tissues:
Cell-Cell Adhesion and Communication

- A key event in multicellularity is the **ability for cells to adhere to one another and be able to communicate with each other.**
- *CAMs* (***cell-adhesion molecules)*** allow interaction **with each other** and **with the surrounding extracellular matrix** (ECM).

-This results in coordinated functioning of tissues.

HOW??

- These interactions result in the **activation of specific signal transduction cascades** eventually resulting in the desired cellular effect.

-Therefore the physical interaction of CAMs with the ECM can turn pathways on or off – cellular effect.

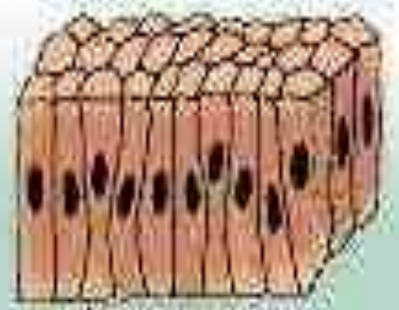
Types of tissues

- ❖ 4 primary tissues types interweave to form the body
- ✓ - Epithelial: lining and covering
- ✓ - Connective: support
- ✓ - Muscle: movement
- ✓ - Nervous: control
- ❖ Each tissue has numerous subclasses or varieties

Types of Epithelium

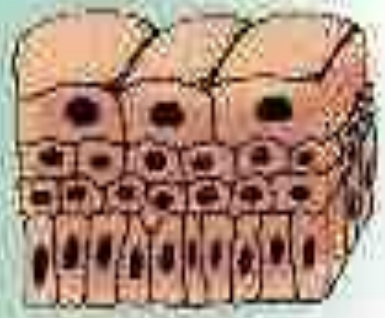
Simple squamous

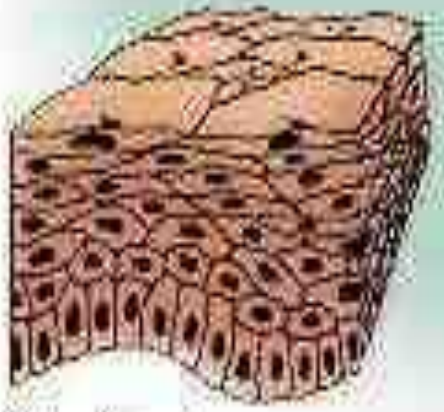
Simple cuboidal



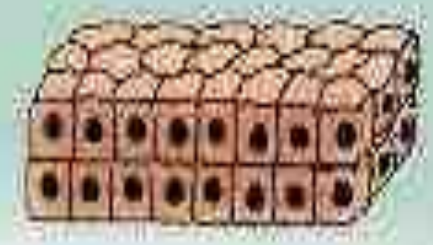
Simple columnar

Transitional

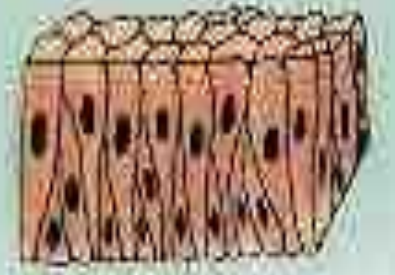




Stratified squamous



Stratified cuboidal



Pseudostratified columnar

Connective Tissue

- Most diverse and abundant tissue
- Main classes
  - Connective tissue proper
  - Blood – Fluid connective tissue
  - Cartilage
  - Bone tissue

  } Supporting connective tissues
- Components of connective tissue:
  - **Cells** (varies according to tissue)
  - **Matrix**
    - Protein fibers (varies according to tissue)
    - Ground substance (varies according to tissue)

4. Muscle Tissue

- Three types of muscle tissue occur in animals (the only taxonomic kingdom to have muscle cells):

- Skeletal (striated)
- Smooth
- Cardiac

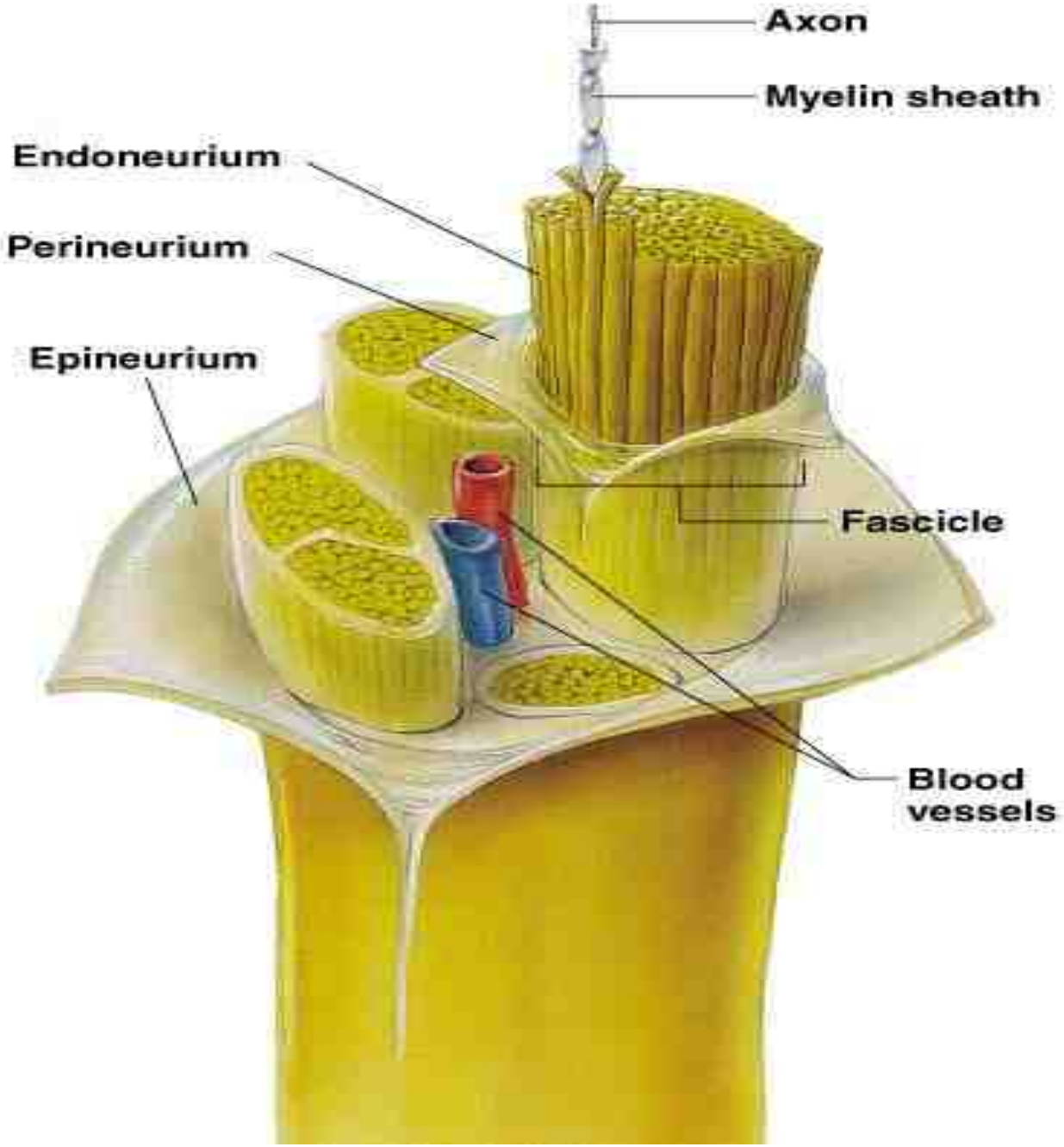
Types of Muscle Tissue - Classified by **location**, **appearance**, and by the type of nervous system control or innervation.

- Skeletal muscle
  - Located throughout the body connected to bones and joints
  - Striated in appearance
  - Under voluntary nervous control.
- Smooth or visceral muscle
  - Located in the walls of organs
  - No striations
  - Under involuntary or unconscious nervous control.
- Cardiac muscle
  - Located only in the heart
  - Striated in appearance
  - Under involuntary or unconscious nervous control.

NERVOUS TISSUE

- Although nerve and neuron may sound similar to most people, they are, in fact, two different components of the body.
- There are three main types of nerves: Afferent nerves, efferent nerves and mixed nerves.
- Afferent nerves transmit signals from sensory neurons to the central nervous system;
- Efferent nerves transmit signals from the central nervous system to the muscles and glands, and
- Mixed nerves are responsible for receiving sensory information, and for sending information to the muscles.
- Nerves are also classified as spinal nerves and cranial nerves.
- The spinal nerves connect the spinal column to the spinal cord, and transmit signals to most of the body,
- while cranial nerves are found in the brainstem, and they are responsible for the signals to the brain.

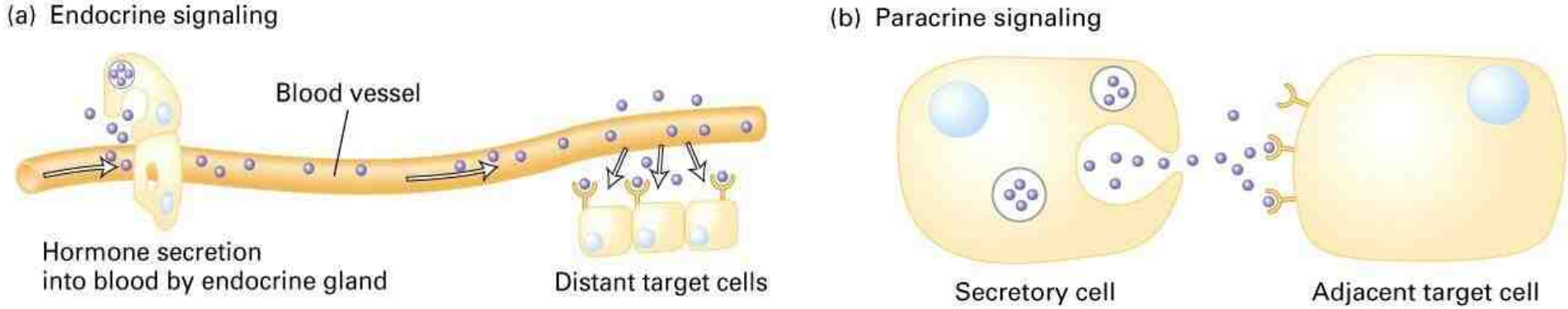
- Nerves are **found in the peripheral nervous system**. Each nerve is covered by three layers, starting with
- the inner **endoneurium**, which covers the nerve fibres;
- the middle layer called the **perineurium**, and
- the outer layer over the perineurium, called the **epineurium**.
- On the other hand, **neurons are found in the brain, spinal cord and peripheral nerves**. Neurons are also named as neurone, or as nerve cells.
- There are two types of neurons ‘‘ the **sensory** neurons and the **motor neurons**.
- Sensory neurons send signals to the brain and the spinal cord, while
- Motor neurons receive signals from the brain and spinal cord.


Axon
Myelin sheath
Endoneurium
Perineurium
Epineurium
Fascicle
Blood vessels

CELL SİGNALİNG

- Steps involved are:
  - **Synthesis**
  - **Release** from signaling cells
  - **Transport** to target cells
  - **Binding** to receptor and activation
  - **Signal transduction** by activated receptor
  - **Specific changes**
  - Removal of signal (termination)

Signaling molecules operate over various distances in animals



extracellular signaling can occur over:

1. Large distances or **endocrine signaling** –

signaling molecules are **called hormones**

act on target cells distant from their site of synthesis usually carried through the bloodstream

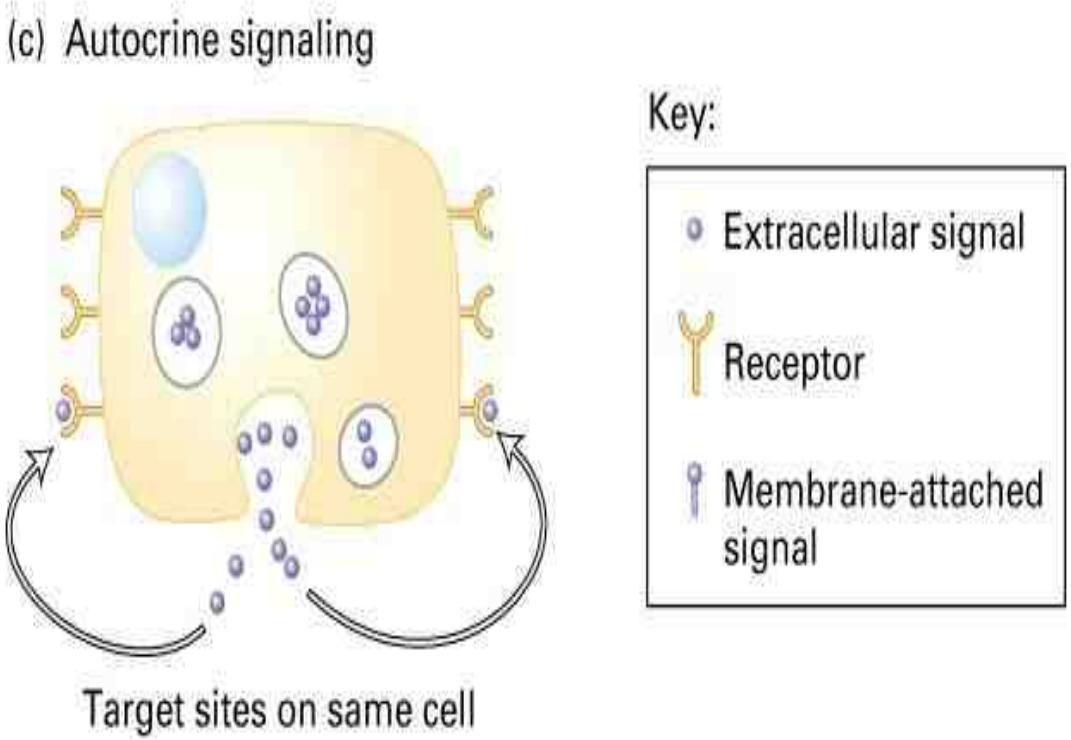
2. Short distances or paracrine signaling –

affects target cells within proximity to the cell that synthesized the molecule .

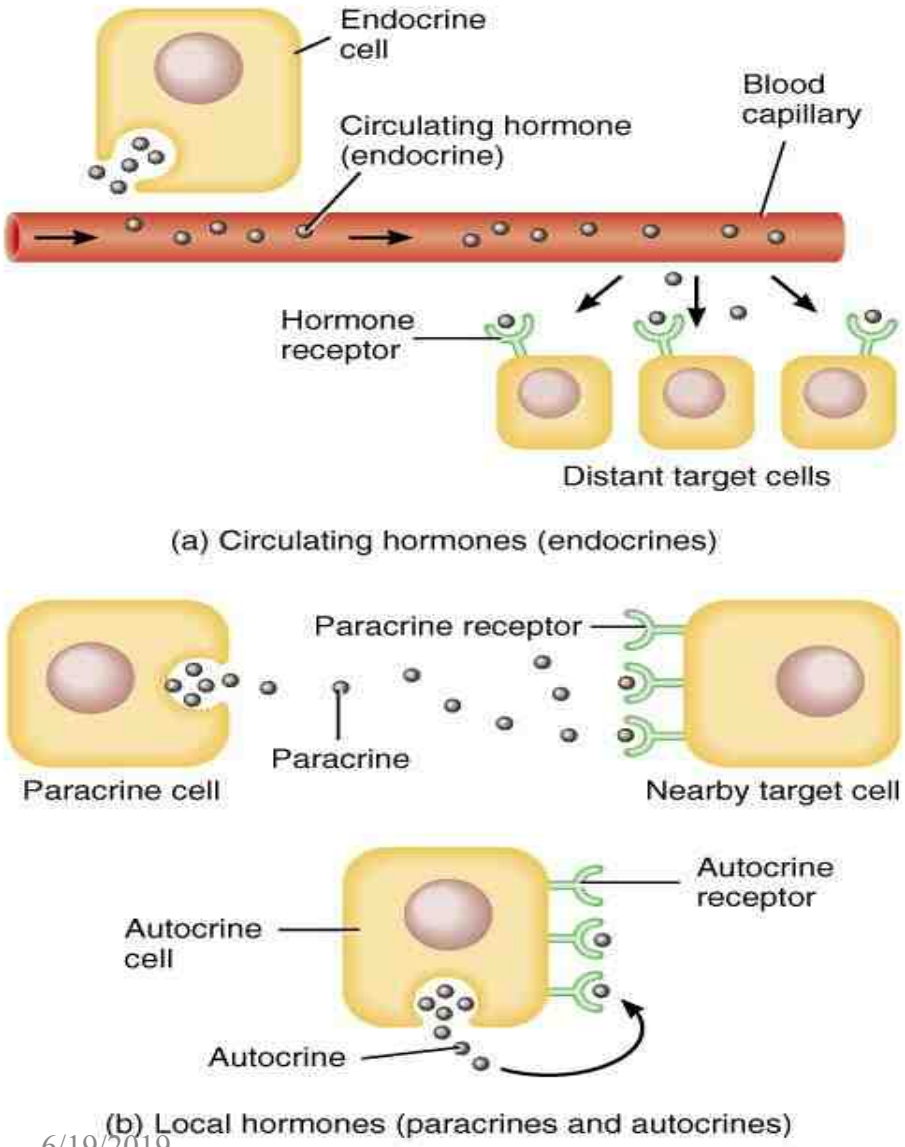
3. *No distance or* **autocrine signaling.**

these compounds generally act on themselves to regulate proliferation

seen frequently in tumor cells

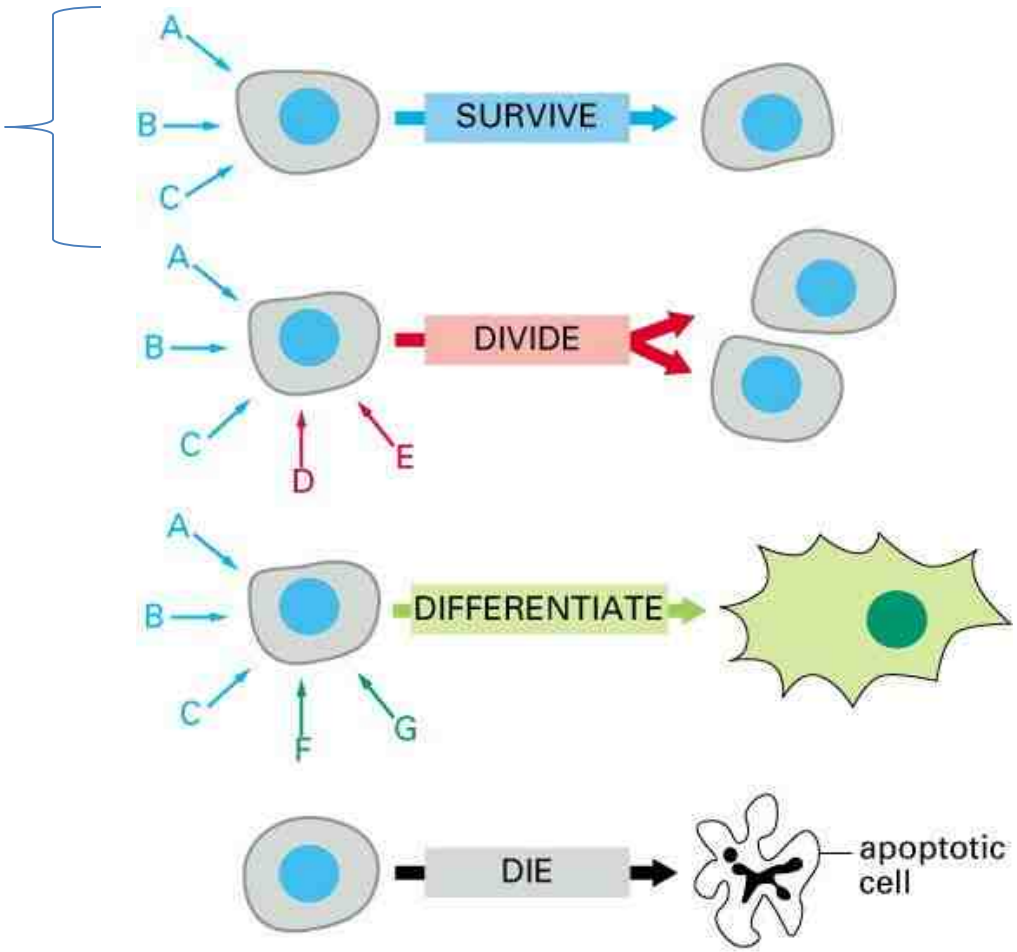


Circulating & Local Hormones

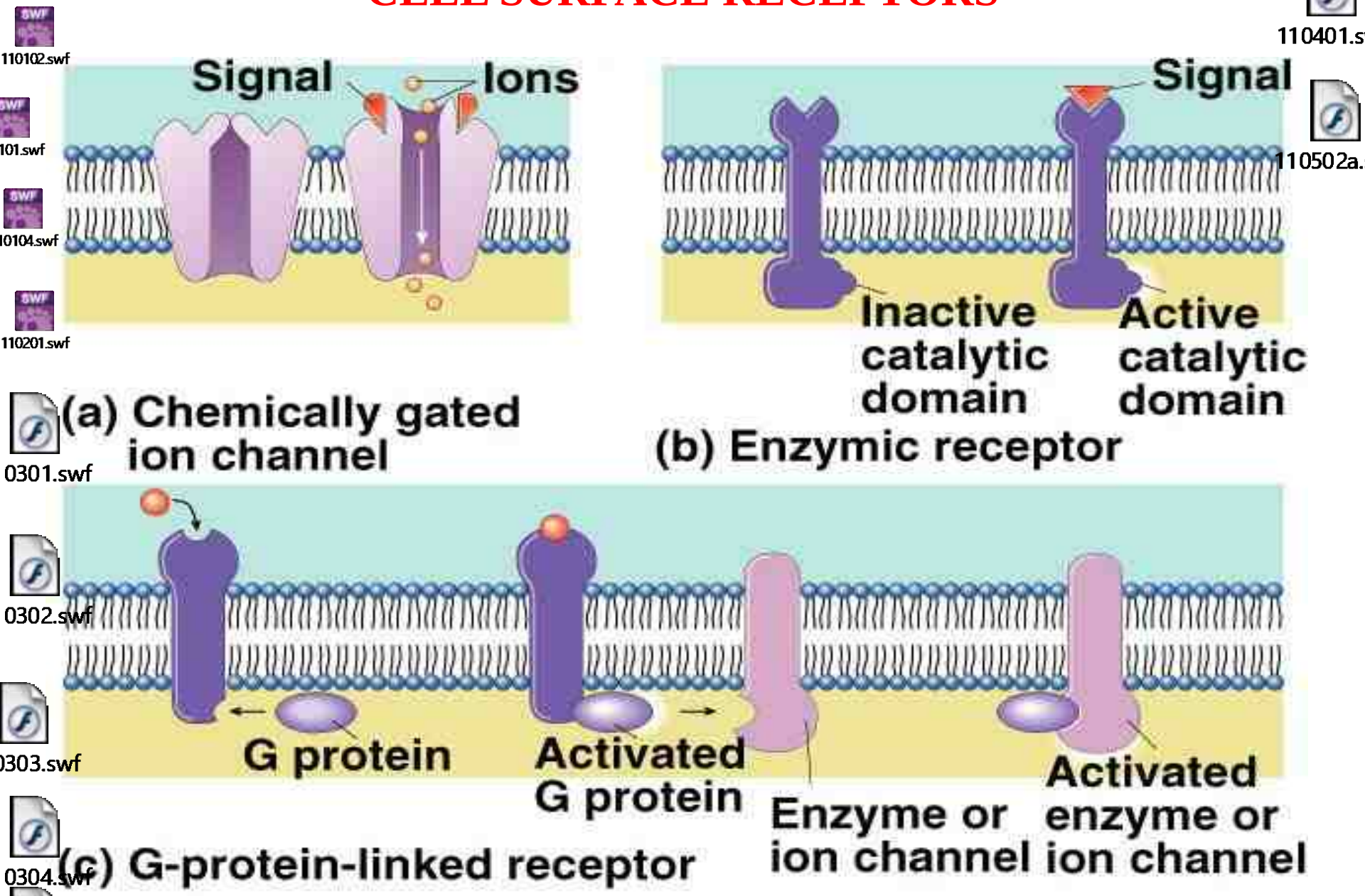


- **Circulating *hormones***
  - act on distant targets
  - travel in blood
  - endocrine hormones
- **Local hormones**
  - paracrine hormones & autocrine hormones

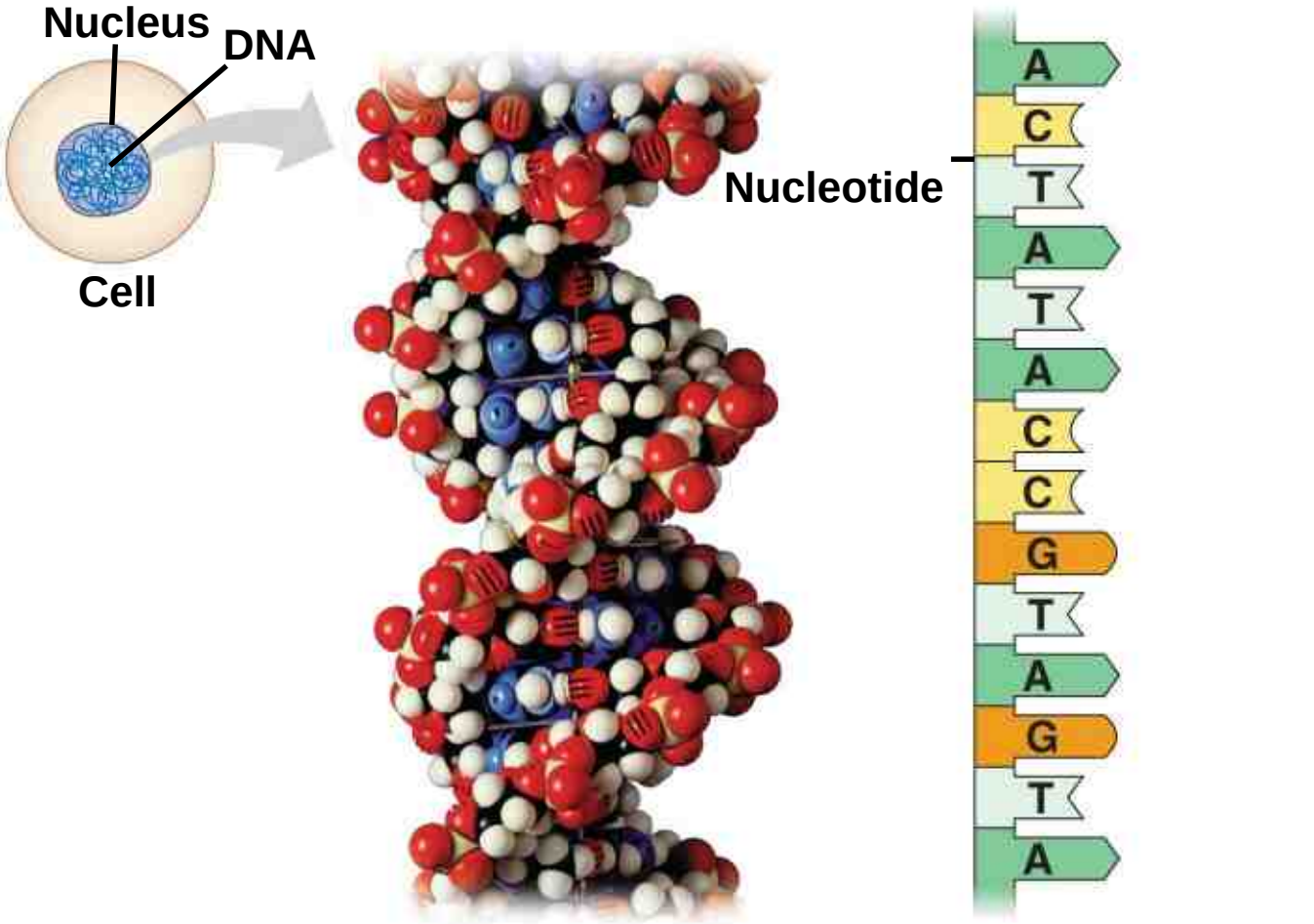
signal processing



CELL SURFACE RECEPTORS



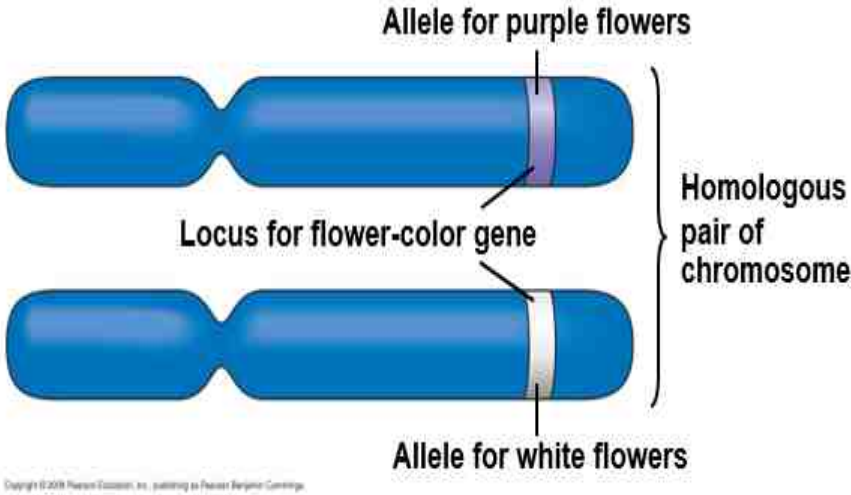
Introduction to Heredity and Genetics



(a) DNA double helix (b) Single strand of DNA

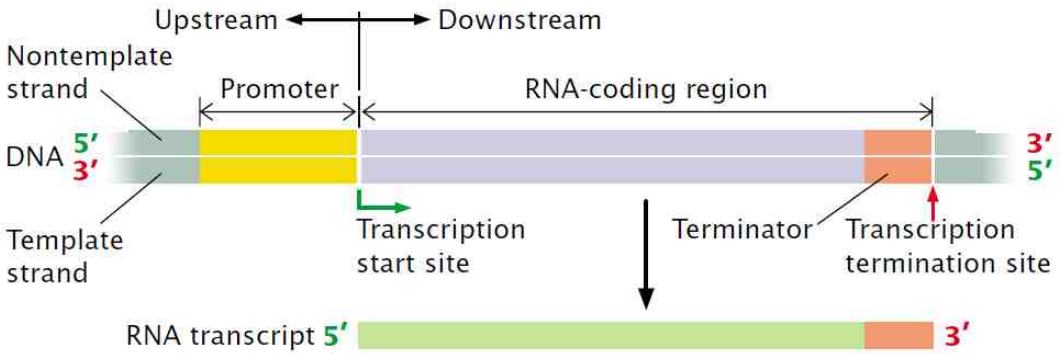
- **Genetics** is the scientific study of heredity and hereditary variation.
- An offspring acquires genes from parents by inheriting chromosomes.
- What are the biological mechanisms leading to the hereditary similarity and variation that we call a "family resemblance"? Then what can be inherited? We inherit thousands of **genes** (fragments of DNA which is a polymer of 4 nucleotides) from both parents and these genes form the **genome.**
- Thus, **our genetic link to our parents accounts for family resemblance.**
- The transmission of hereditary traits has its molecular basis in the precise replication of DNA, which produces copies of genes that can be passed along from parents to offspring.
- The cellular vehicles that transmit genes from one generation to the next are **sperm** and **ova** (unfertilized eggs).
- Offspring of sexual reproduction vary genetically from their siblings and both parents.
- What mechanisms generate this genetic variation?

- The two chromosomes composing a pair have the same length, centromere position, and staining pattern: These are called **homologous chromosomes**, or **homologs**.
- Both chromosomes of each pair carry genes controlling the same inherited characters.
- For example, if a gene for eye color is situated at a particular locus on a certain chromosome, then the homolog of that chromosome will also have a gene specifying eye color at the equivalent locus.
- The genetic variation is the result of 3 mechanisms: (i) independent assortment of chromosomes, (ii) Cross-over and (iii) Random fertilization.

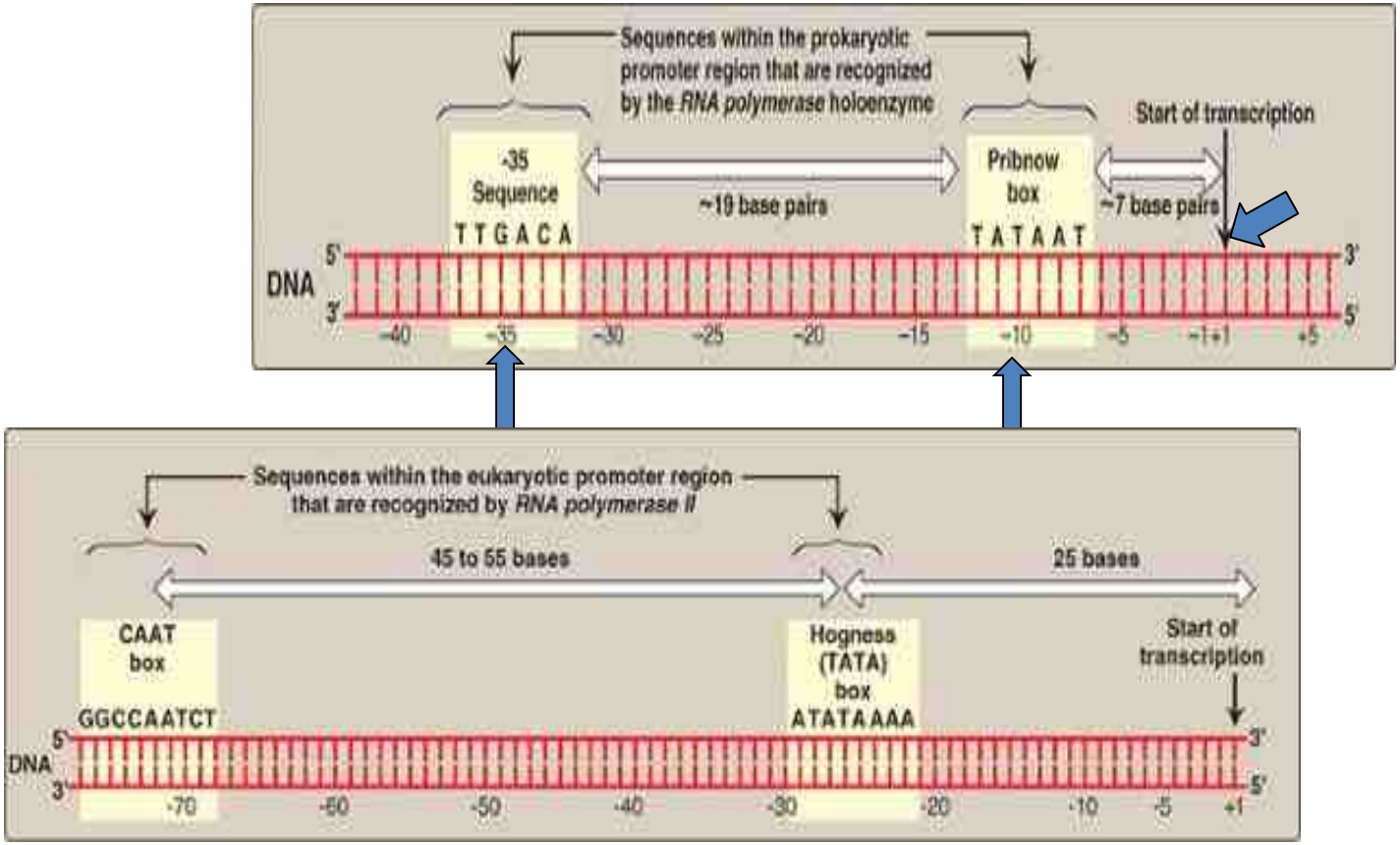


The Transcription Unit

- **Stretch of DNA that codes for an RNA molecule and the sequences necessary for transcription**
  - **3 critical regions:**
- **PROMOTER**
- **RNA CODING REGION**
- **TERMINATOR**

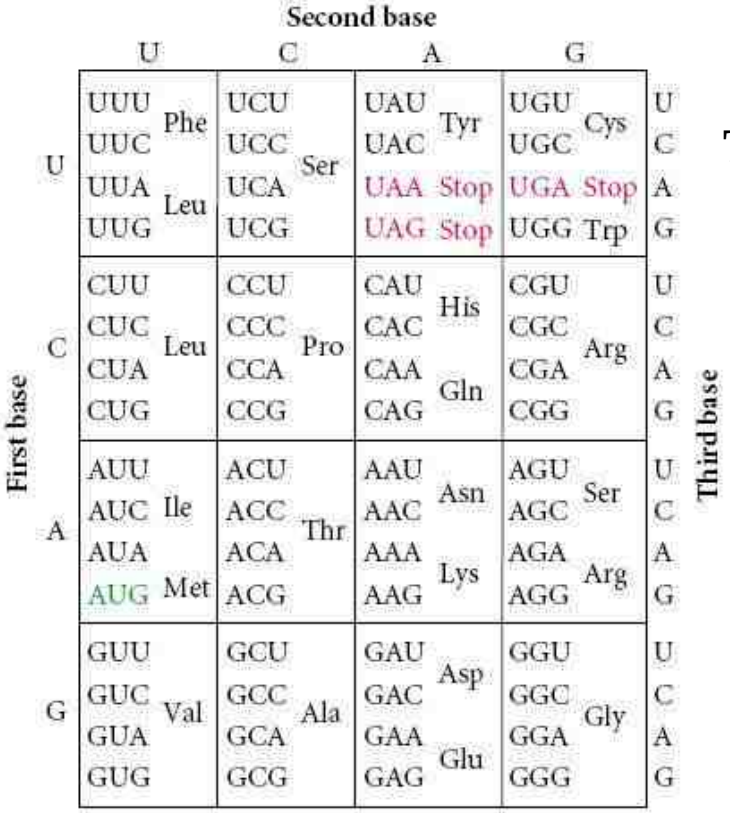


Promoters and Consensus Sequences



- **A Consensus Sequence is a short stretch of DNA that is conserved among promoters of different genes.**

One amino acid is encoded by three consecutive nucleotides in mRNA, and each nucleotide can have one of four possible bases (A, G, C, and U) at each nucleotide position thus permitting **$4^3 = 64$ possible codons** (see next Figure).



First base	Second base: U	Second base: C	Second base: A	Second base: G	Third base
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

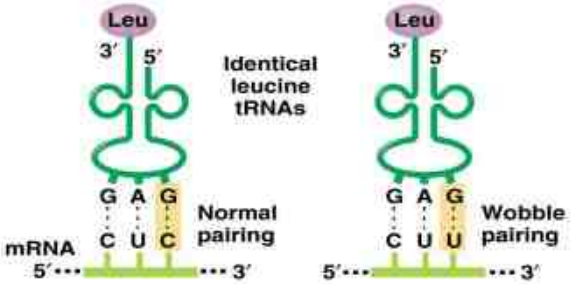
THE GENETIC CODE

The genetic code consists of 64 codons and the amino acids specified by these codons. The codons are written 5′→3′, as they appear in the mRNA. AUG is an initiation codon; UAA, UAG, and UGA are termination codons.

Table

The wobble rules, indicating which bases in the third position (3′ end) of the mRNA codon can pair with bases at the first (5′ end) of the anticodon of the tRNA

First Position of Anticodon	Third Position of Codon	Pairing
C	G	Anticodon 3′–X—Y—C–5′ / 5′–Y—X—G–3′ Codon
G	U or C	Anticodon 3′–X—Y—G–5′ / 5′–Y—X—U–3′ C Codon
A	U	Anticodon 3′–X—Y—A–5′ / 5′–Y—X—U–3′ Codon
U	A or G	Anticodon 3′–X—Y—U–5′ / 5′–Y—X—A–3′ G Codon
I (inosine)	A, U, or C	Anticodon 3′–X—Y—I–5′ / 5′–Y—X—A–3′ U C Codon



WOBBLE

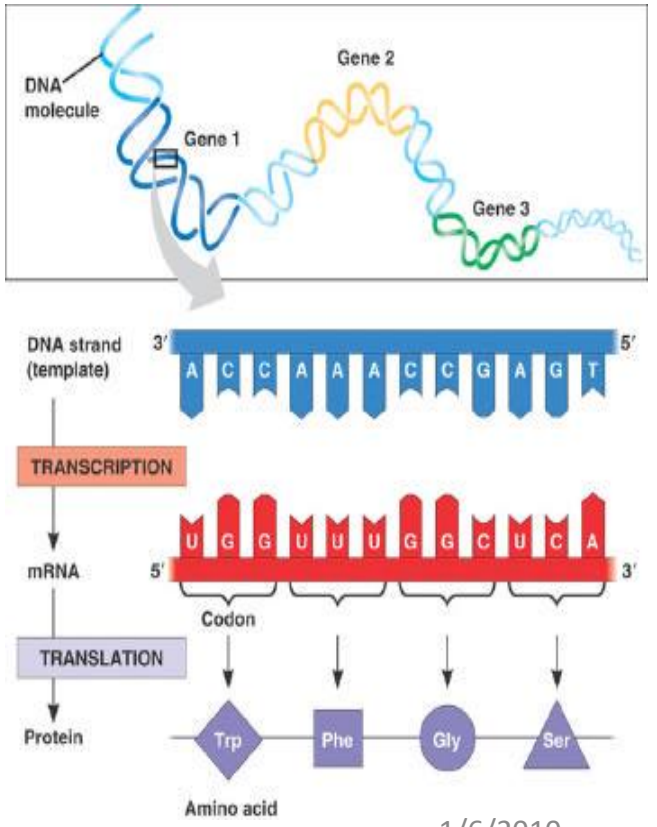
Occurs when the third base (5’end) of the tRNA anticodon has some play or wobble, so that it can hydrogen bond with more than one kind of a base in the third position (3’ end) of the codon.

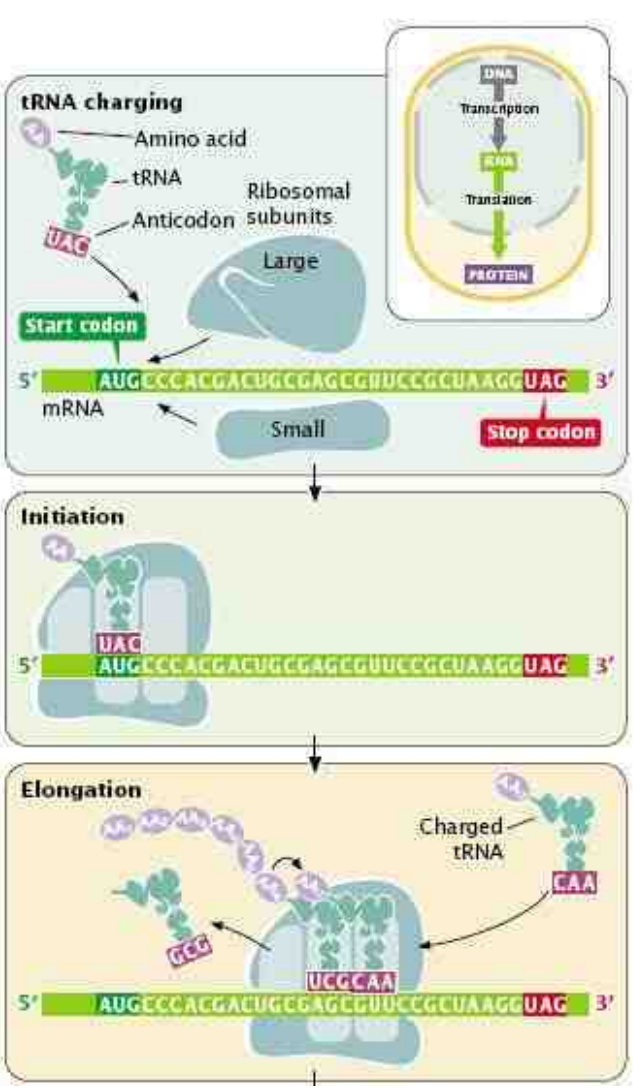
Concepts

The genetic code consists of 61 sense codons that specify the 20 common amino acids; the code is degenerate and some amino acids are encoded by more than one codon. Isoaccepting tRNAs are different tRNAs with different anticodons that specify the same amino acid. Wobble exists when more than one codon can pair with the same anticodon.

PROTEIN SYNTHESIS: FROM GENE TO PROTEIN

- **Genes are stretches of nucleotides organized in *triplets***
- **Different arrangements or DNA triplets encode for each one of the 20 amino acids that make proteins**
- **During transcription, a DNA triplet will produce an mRNA *codon.***
- **During translation, a codon will constitute an amino acid**

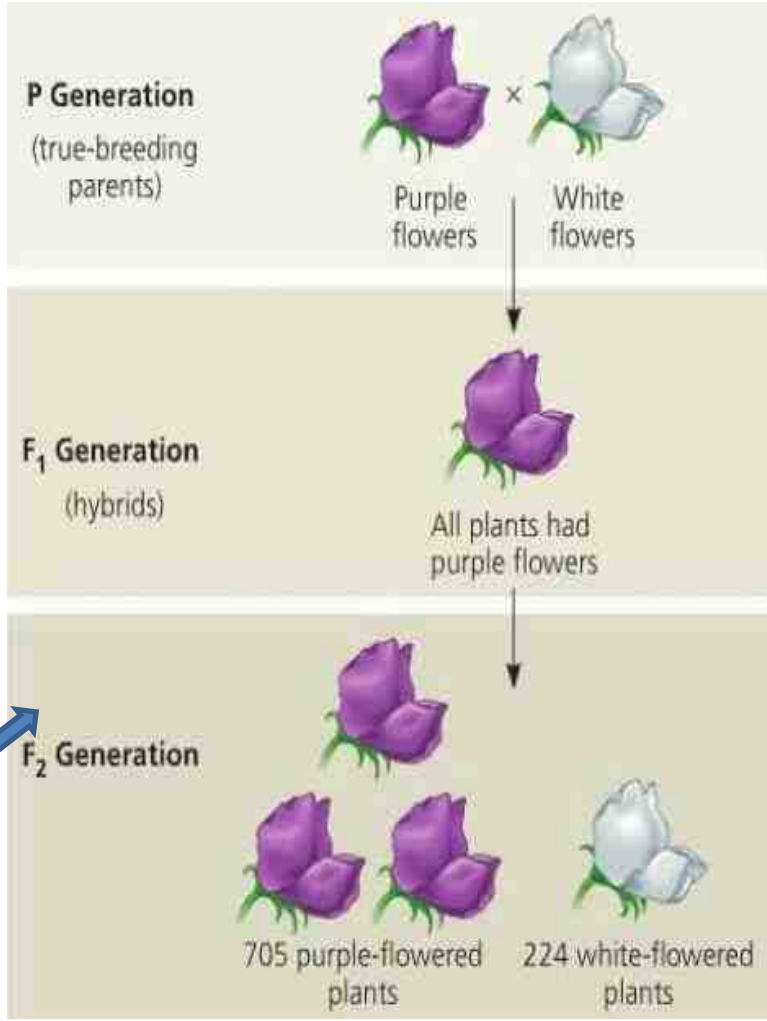




The four steps involved in translation are tRNA charging (the binding of amino acids to tRNAs), initiation, elongation, and termination. In this process, amino acids are linked together in the order specified by the mRNA to create a polypeptide chain. A number of **initiation**, **elongation**, and **release factors** take part in the process, and **energy** is supplied by ATP and GTP.

Mendel's work

- Mendel discovered the basic principles of heredity by breeding garden peas in carefully planned experiments.
- Genetics use the term character for a heritable feature (flower color) each variant for a **character**, such as purple or white color for flowers, is called a **trait.**
- He decided to work with peas because they were available in many varieties.
- Mendel also made sure he started his experiments with varieties that are true-breeding.
- When pollen from a white flower was transferred to a purple flower, the first-generation hybrids all had purple flowers.
- The result was the same for the reciprocal cross, which involved the transfer of pollen from purple flowers to white flowers.



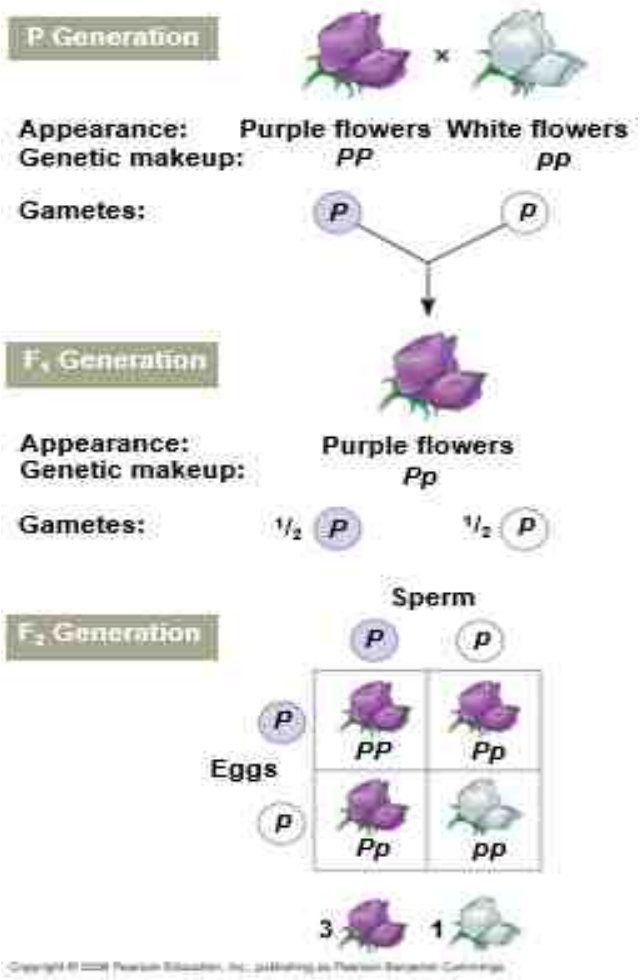
- **Hybridization** is a crossing or mating of 2 varieties (purple flowered plants and white-flowered plants for example) while a **monohybrid cross** is a cross that tracks the inheritance of a single character (flower color).
- Mendel's quantitative analysis of F2 plants revealed the **2 fundamental principles of heredity** that are now known as the **law of segregation** and the **law of independent assortment**

The **law of segregation**

- All the F_1 offspring had flowers just as purple as the purple-flowered parents.(See slide 10)
- What happened to the white-flowered plants' genetic contribution to the hybrids?
- If it were lost, then the F_1 plants could produce only purple-flowered offspring in the F2 generation, but when Mendel allowed the F_1 plants to self-pollinate and planted their seeds, the white-flower trait reappeared in the F2 generation.(Slide 10)
- Mendel reasoned that the *heritable factor for white flowers did not disappear in the F_1 plants, but was somehow **hidden or masked when the purple-flower factor was present***.
- Mendel's model has four related concepts, the 4th of which is the law of segregation.
- The 4 concepts are:

1. ***Alternative versions of genes** account for variations in inherited characters.*
2. *For each character, **an organism inherits two alleles**, one from each parent.*
3. ***If the two alleles at a locus differ**, then one, the dominant allele, determines the organism's appearance; the other, the recessive allele, has no noticeable effect on the organism's appearance.*
4. *The two alleles for a heritable character **segregate (separate) during gamete formation** and end up in different gametes*

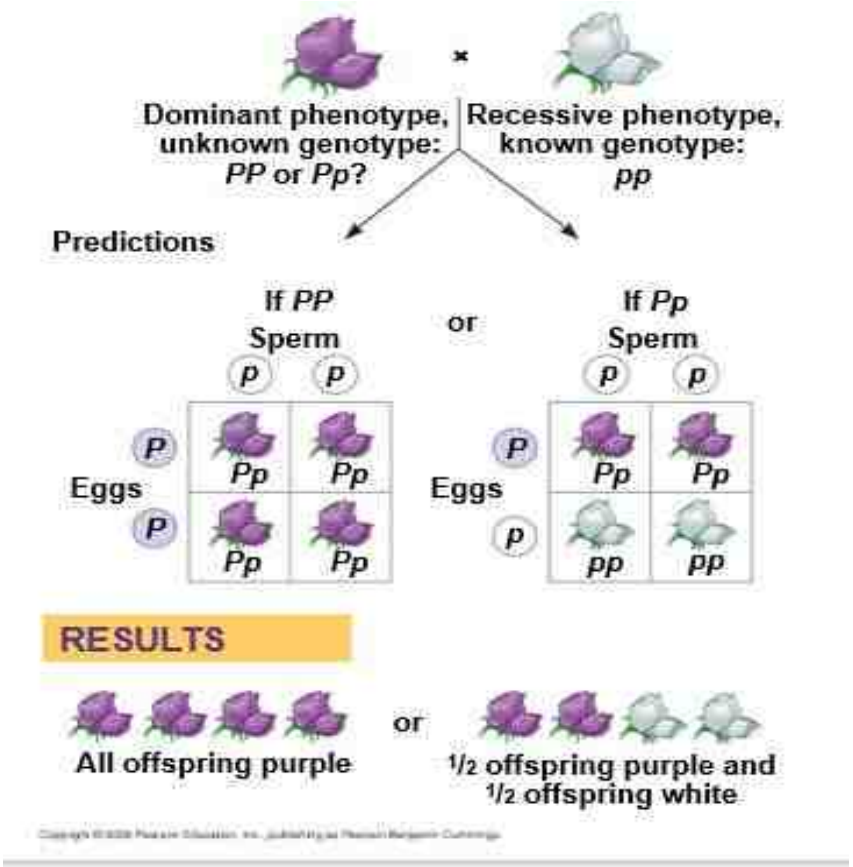
- Thus, an egg or a sperm gets only one of the two alleles that are present in the somatic cells of the organism making the gamete.
- In terms of chromosomes, this segregation corresponds to the distribution of the two members of a homologous pair of chromosomes to different gametes in meiosis.



- Suppose we have a pea plant that has purple flowers.
- **We cannot tell** from its flower color if this plant is homozygous or heterozygous because both genotype ***PP*** and *Pp* result in the same phenotype.

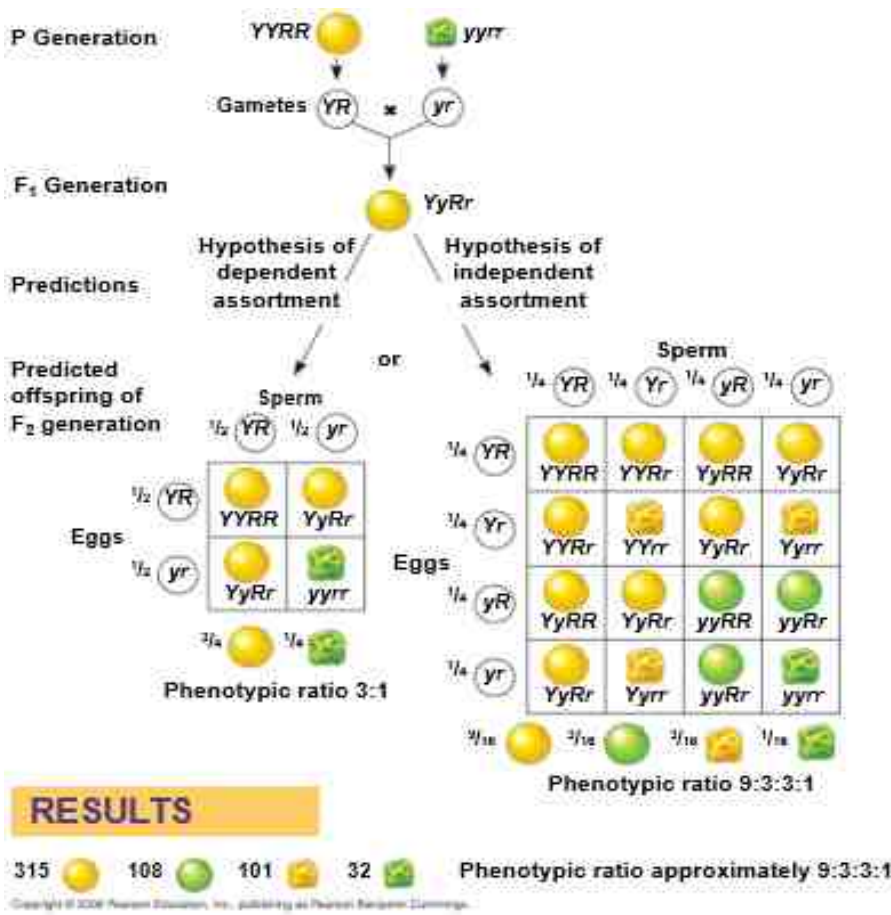
- The breeding of a recessive homozygote with an organism of dominant phenotype, but unknown genotype, is called a testcross.
- It was devised by Mendel and continues to be an important tool of geneticists.

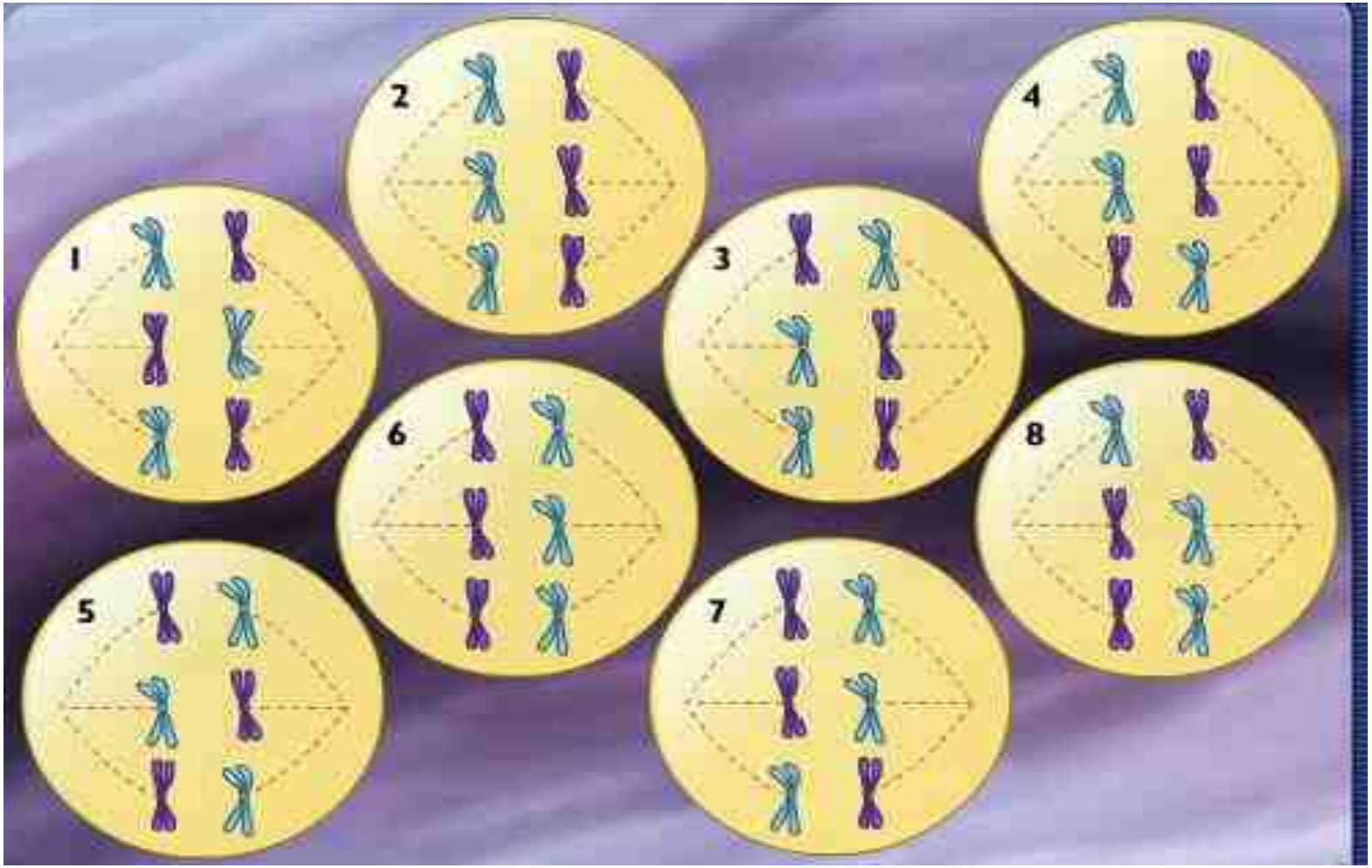
The testcross



The law of independent assortment of chromosomes

- What would happen in a mating of parental varieties differing in 2 characters (a **dihybrid cross**)?
- For eg. Mendel studied the seed color (yellow or green) and seed shape (round or wrinkled).
- Conclusion: **Only the hypothesis of independent** assortment predicts the appearance of two of the observed phenotypes: **green-round** seeds and **yellow-wrinkled** seeds.
- The alleles for seed color and seed shape sort into gametes independently of each other.
- The results of Mendel's dihybrid experiments are the basis for what we now call the law of independent assortment, which states that *each pair of alleles segregates independently of each other pair of alleles during gamete formation.*



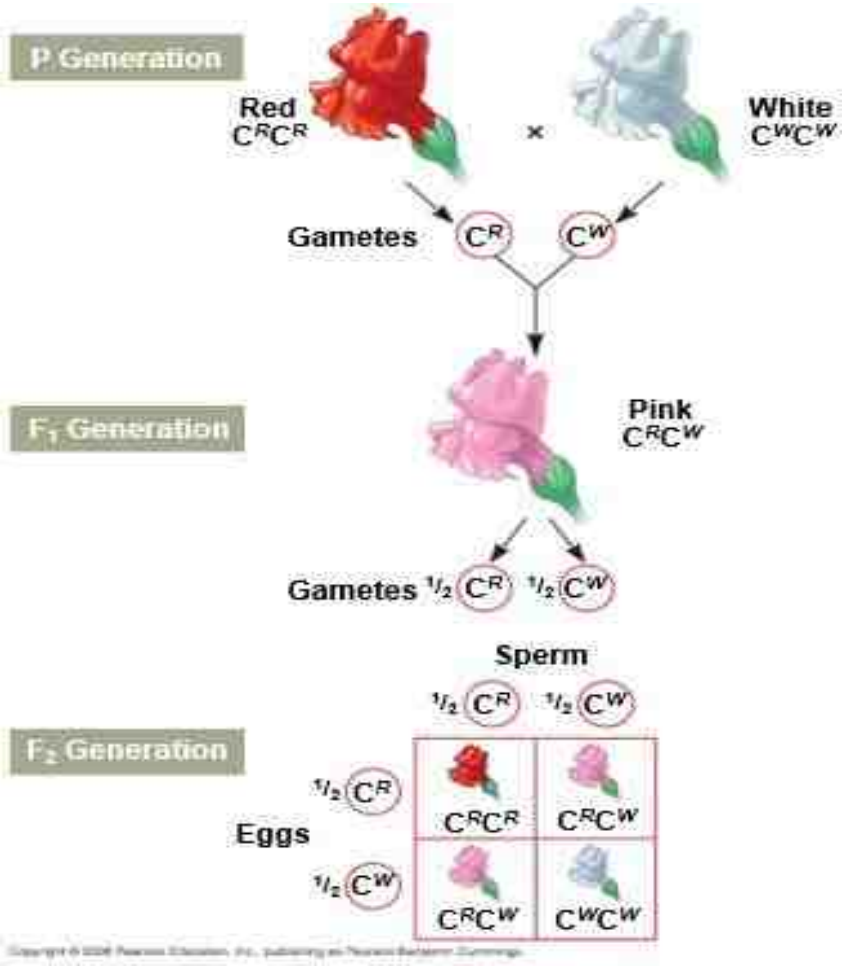

1
2
3
4
5
6
7
8

Exercises

1. For any gene with a dominant allele *C* and recessive allele *c*, what proportions of the offspring from a *CC x Cc* cross are expected to be homozygous dominant, homozygous recessive, and heterozygous?
2. An organism with the genotype *BbDD* is mated to one with the genotype *BBDd*. Assuming independent assortment of these two genes, write the genotypes of all possible offspring from this cross .

Extending Mendelian Genetics

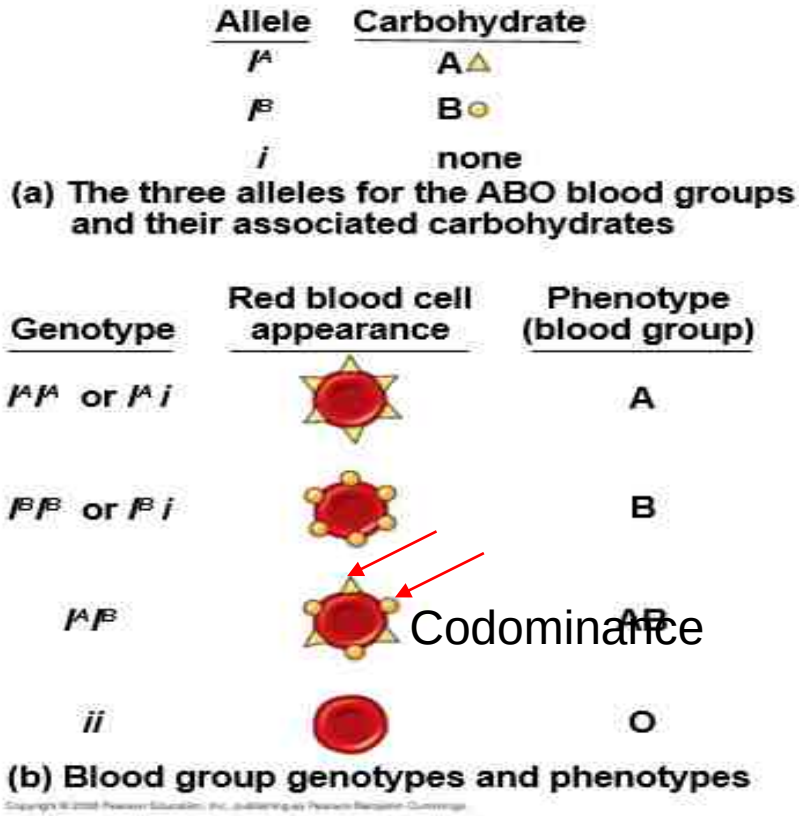
- For some genes, there is **incomplete dominance**, where the F1 hybrids have an appearance somewhere in between the phenotypes of the 2 parental varieties.
- eg., When red snapdragons are crossed with white snapdragons, all the F1 hybrids have pink flowers. This **3rd phenotype** results from flowers of the heterozygotes having **less red pigment than the red homozygotes.**
- Breeding the F1 hybrids produces F2 offspring with a phenotypic ratio of 1 red to 2 pink to 1 white.
- The alleles for flower color are heritable factors that **maintain their identity in the hybrids**; i.e., **inheritance is particulate**.



Codominance

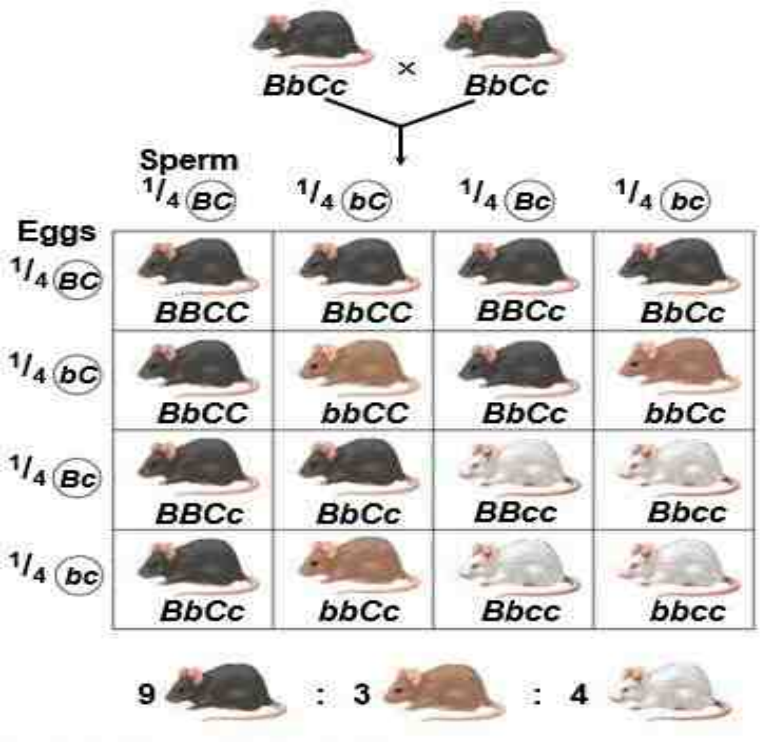
The **four** phenotypes of the ABO blood group in humans are determined by three alleles for the enzyme (I) that attaches A or B carbohydrates to red blood cells: I^A, I^B, and *i*.

The enzyme encoded by the I^A allele adds the A carbohydrate, whereas the enzyme encoded by the I^B allele adds the B carbohydrate; the enzyme encoded by the ***i* allele adds neither**.



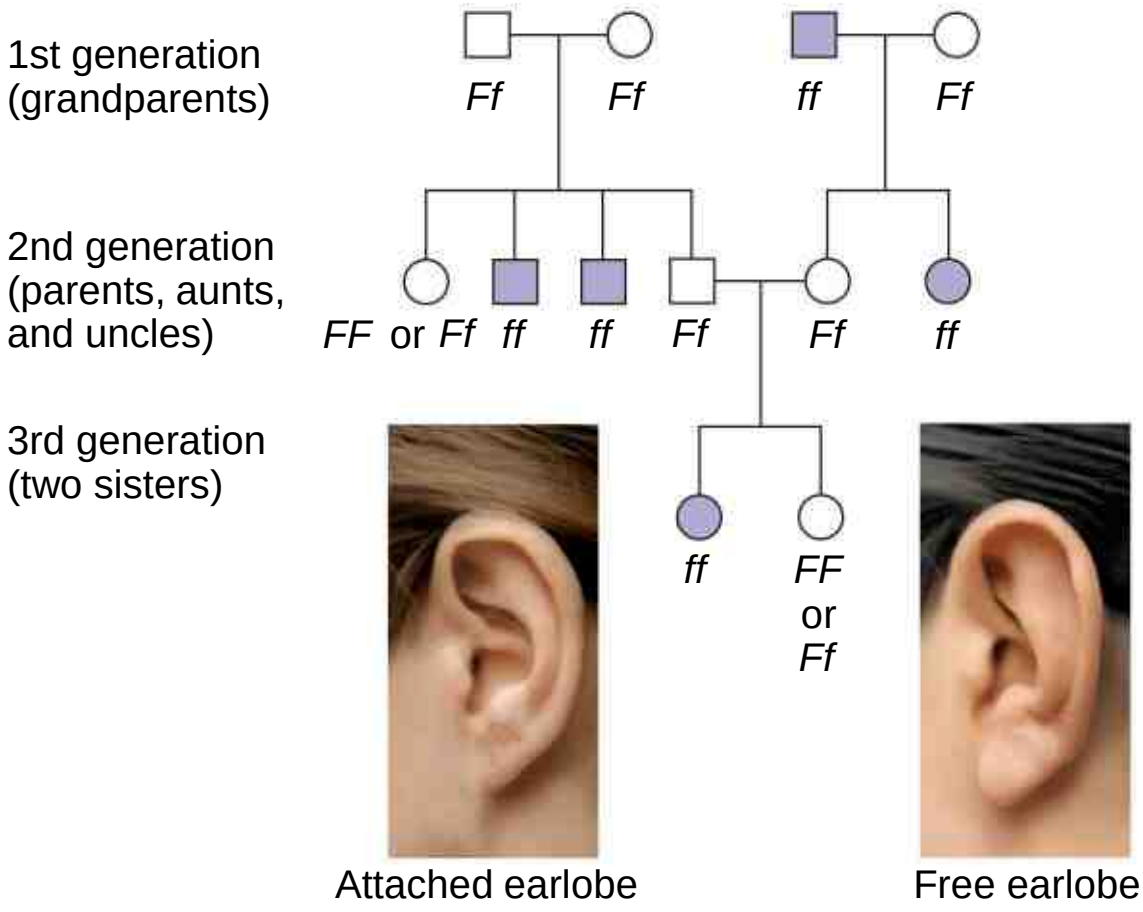
- **Pleiotropy** is the ability of a gene to affect an organism in many ways.
- For example, alleles that are responsible for certain hereditary diseases in humans, such a sicke-cell anemia, usually cause multiple symptoms.
- **Epistasis** is the result of a gene at one locus altering the phenotypic expression of a gene at a 2nd locus.
- In epistasis, the rule followed is the independent assortment of chromosomes but modified because the ratio 9:3:3:1 is changed into 9:3:4

Epistasis



B(black), b(brown), C(color), c (no color)

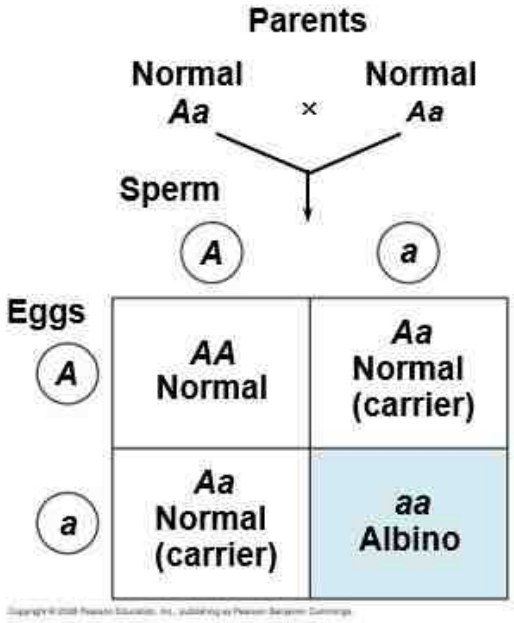
- A **family pedigree** is a family tree describing the interrelationships of parents and children across generations.
- The pedigree is used to trace a trait occurring in a family like breast cancer.



Is an attached earlobe a dominant or recessive trait?

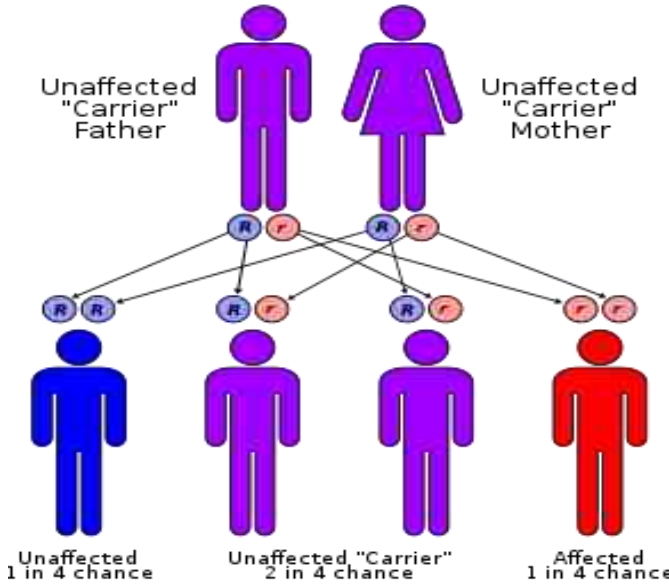
Recessively inherited disorders

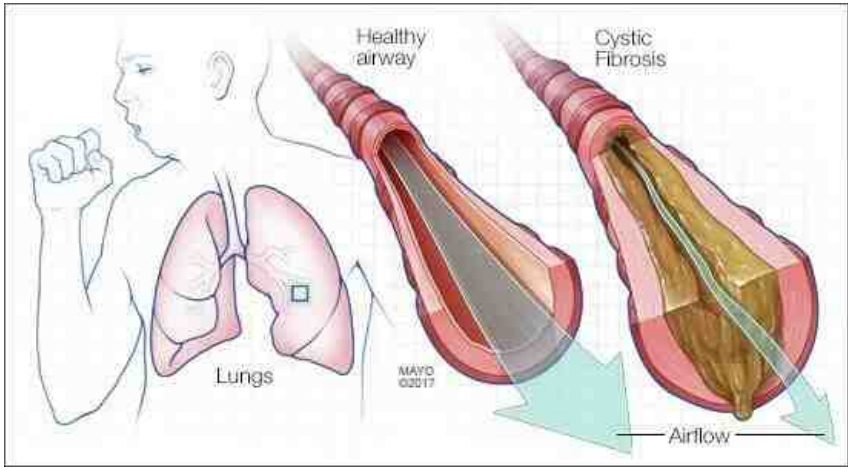
- Thousands of genetic disorders are known to be inherited as simple recessive traits.
- These disorders range in severity from traits that are relatively harmless, such as **albinism** (lack of skin pigmentation), to life threatening conditions (**cystic** fibrosis).
- Heterozygotes are normal in phenotype because one copy of the normal allele produces a sufficient amount of the specific protein.
- People without the disorder are either *AA* or *Aa*. Hererozygotes (Aa) who are phenotypically normal are called **carriers** of the disorder because they may transmit the recessive allele to their offspring
- If the disorder is lethal before reproductive age or results in sterility, no *aa* individuals will reproduce.
- Even if recessive homozygotes are able to reproduce, such individuals will still account for a much smaller % of the population than heterozygous carriers.



Cystic fibrosis (CF)

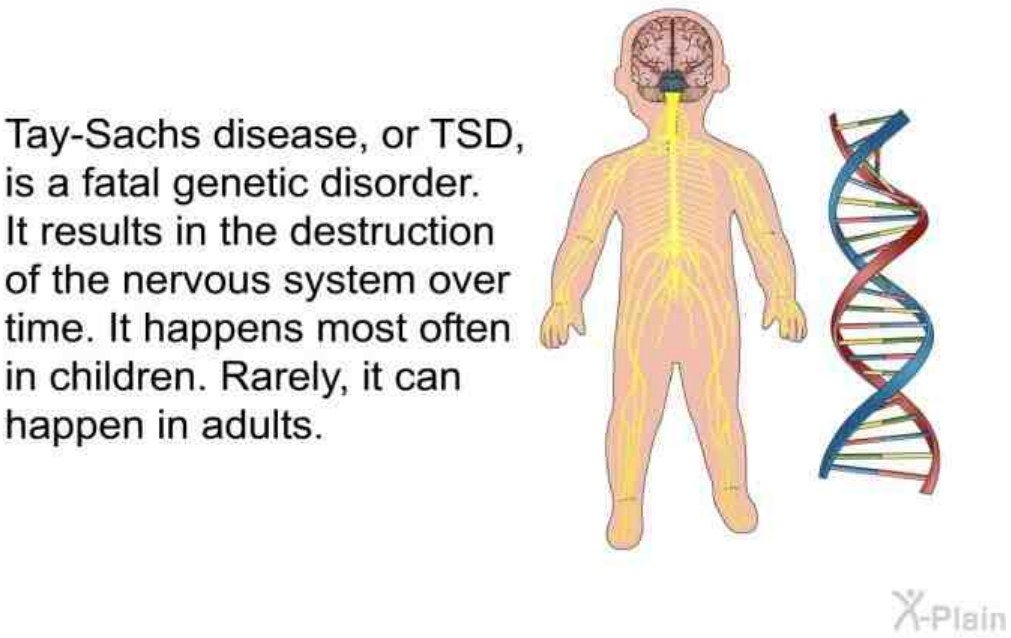
- It is a lethal genetic disease (death before 5 years if untreated).
- The normal allele for this gene codes for **a membrane protein** that functions in Cl^- ion transport between **certain cells** and the Extra cellular fluid.
- These Cl^- channels are defective or absent in the plasma membranes of children who have inherited 2 of the recessive alleles that cause cystic fibrosis.
- The disease results in more extra cellular Cl^- causing the mucus that coats certain cells to become thicker and stickier than normal.
- The mucus builds up in the **pancreas**, **lungs**, **digestive tract** and **other organs**, a condition that favors bacterial infections.
- This Cl^- also favors infections by **disabling a natural antibiotic made by some body cells**.
- When the immune cells come to the rescue, their remains add to the mucus creating a vicious cycle.





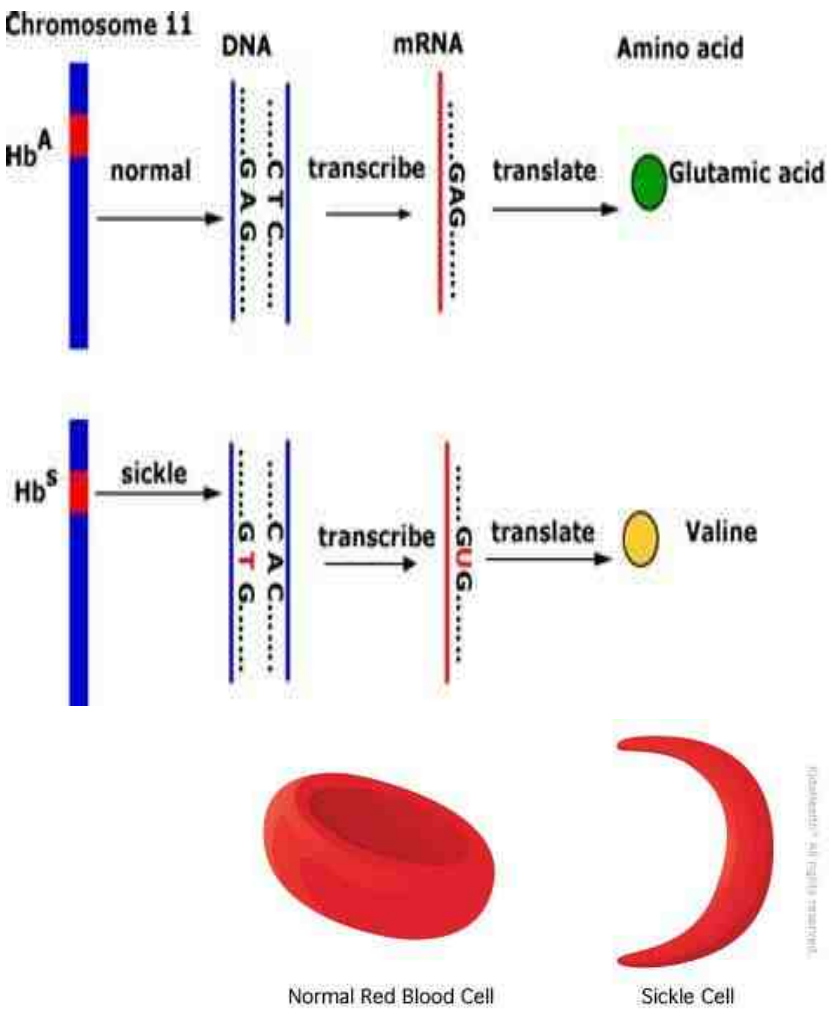
Tay-Sachs disease

- It is also lethal as CF, inherited as a recessive allele.
- It is caused by a dysfunctional enzyme that fails to break down brain lipids of a certain class.
- Symptoms (seizures, blindness, and degeneration of **motor** and **mental** performance) occur few months after birth.
- The disease is common among Ashkenazic Jews. In that population, the frequency of this disease is 1/3600 births, about 100 times greater than the incidence among non-jews.



Sickle-cell anemia

- It is a common inherited disease among blacks affecting 1/400 african-americans.
- It is caused by the substitution of a single amino acid in the Hb protein of RBCs.
- When the oxygen content of an affected individual is low (at **high altitude** or under physical stress), the **sicke cell Hb deforms the RBCs to a sickle shape.**
- Individuals who are heterozygous for the sickle-cell allele are said to have sickle-cell trait and
- Carry a normal life but suffer some symptoms of sickle-cell disease **when there is an extended reduction of blood oxygen**.
- The sickle-cell trait (heterozygous) is **sometimes considered as an advantage**. People who are heterozygous (having a single copy of the allele) are **resistant to malaria**.
- Thus, in tropical Africa, where malaria is common, the sickle-cell allele is both boon and bane.



- It is unlikely that 2 carriers of the same rare harmful allele will meet and mate. The probability increases greatly **if the man and woman are close relatives (siblings or 1st cousins).**
- Most societies and cultures have laws and taboos forbidding marriages between close relatives due to genetic defects and diseases resulting from such marriages.

Dominantly inherited disorders

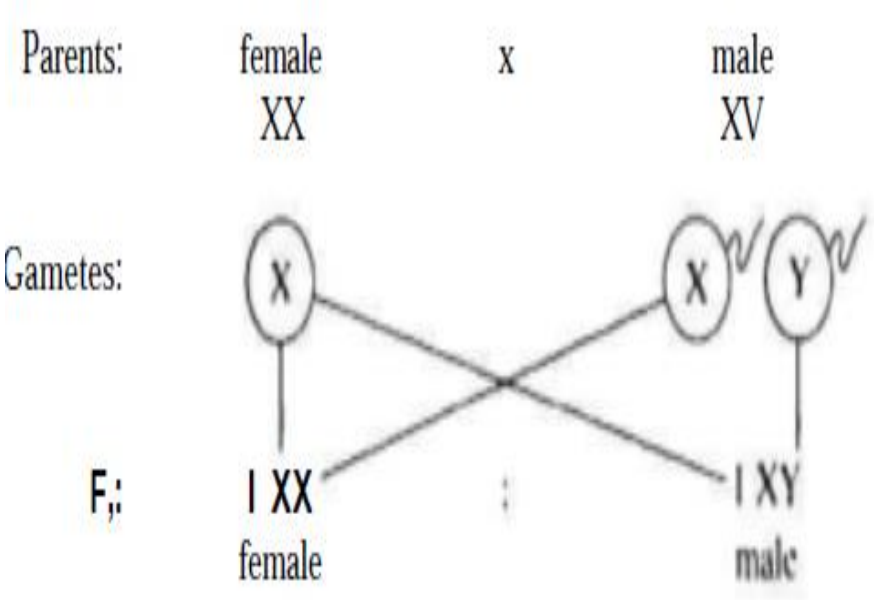
- Although most harmful alleles are recessive, many human disorders are due to dominant alleles.
- Lethal dominant alleles are **much less common** than lethal recessives.
- Many lethal dominant alleles are the result of **new mutations** (changes) in a gene of the sperm or egg that subsequently **kill the developing offspring**.
- An individual who does not survive to reproductive maturity will not pass on the new form of the gene.
- **Lethal recessive mutations are perpetuated** from generation to generation by the reproduction of heterozygous carriers who have normal phenotypes.
- A lethal dominant allele can **escape elimination if it is late-acting**: Causing death at a relatively advanced age.
- By the time the symptoms appear, the individual may have already transmitted the lethal allele to his or her children.
- Huntington's disease, a degenerative disease of the nervous system (NS), is caused by a lethal dominant allele that has no obvious phenotypic effect until the individual is about **35 to 45 years old**.
- Once degeneration of the NS begins, it is **irreversible and inevitably fatal**.

- For those with a family of Huntington's disease, the availability of test poses an **agonizing dilemma**: Under what circumstances is it beneficial for a presently healthy person to find out whether he or she has inherited a fetal and not yet curable disease?
- **Technology is providing new tools for genetic testing and counseling.**
- Tests used to identify alleles for **Tay-Sachs disease**, **sickle-cell disease**, and most forms of **cystic fibrosis** are available.
- On one hand, these tests enable people with family histories of genetic disorders **to make informed decisions about having children.**
- On the other hand, these new methods for genetic screening could be abused.
- If confidentiality is breached, will carriers be stigmatized? Will they be denied health or life insurance, **even though they are themselves healthy**? Will misinformed employers equate carrier with disease?
- And will sufficient genetic counseling be available to help a large number of individuals understand their test results?
- Fetal testing involves different techniques including amniocentesis (uterus) and chorionic villus sampling (CVS) done on placenta, ultrasound, etc.

Sex-determining mechanisms in human

Sex chromosome mechanisms

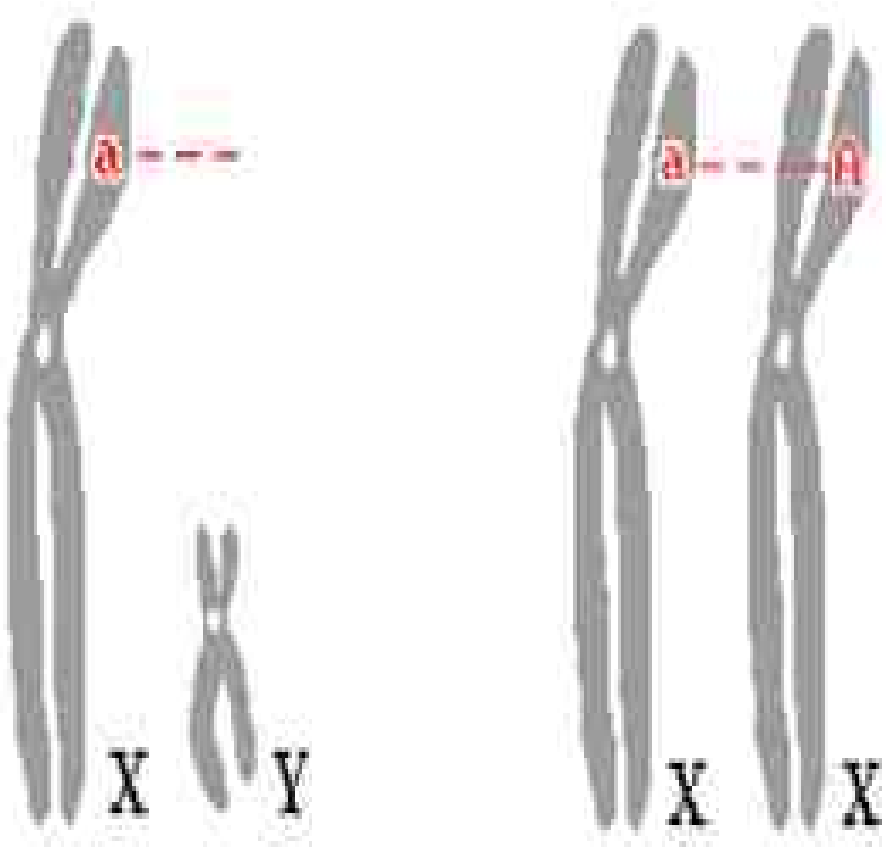
- Normal males are **chromosomally XY** and females are XX.
- This produces a 1:1 sex ratio in each generation.
- Since the **male produces two kinds of gametes** as far as the sex chromosomes are concerned, he is said to be the **heterogametic** sex.
- The female, producing only one kind of gamete is **the homogametic** sex.
- This mode of sex determination is commonly referred to as **the XY method**



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312213/

Sex linked genes

- X and Y sex chromosomes **not only carry the genes that determine male and female traits** but also those for some other characteristics as well.
- Genes that are carried by either sex chromosome are said to be **sex linked**.
- There are **about 1,098 human X-linked genes**.
- Most of them code for something **other than female anatomical traits.**
- Many of the non-sex determining X-linked genes are responsible for abnormal conditions such as **hemophilia**, **fragile-X syndrome** , some high **blood pressure**, **congenital night blindness**, etc.
- X-linked genes are also responsible for a common form of baldness referred to as "male pattern baldness" related to hair loss



Exercise

1. In humans, hemophilia is a sex linked trait. Females can be normal, carriers, or have the disease. Males will either have the disease or not (but they won't ever be carrier).

a) Show the cross of a man who has hemophilia with a woman who is a carrier.

b) What is the probability that their children will have the disease?

2. **A woman who is a carrier** of hemophilia marries **a normal man**. Show the cross.

What is the probability that their children will have hemophilia? What sex will a child in the family with hemophilia be?

3. A woman who has hemophilia marries a normal man. How many of their children will have hemophilia, and what is their sex?

4. A human female "carrier" who is heterozygous for the recessive, sex-linked trait causing red-green color blindness (or alternatively, hemophilia), marries a normal male.

What proportion of their male progeny will have red-green color blindness (or alternatively, will be hemophiliac)?

MULTIPLE GENES AND ALLELES

- In classical Mendelian genetics, each gene has two possible alleles. However, **some genes have more than two alleles.**
- The gene for the blood type protein has three alleles (A, B, and O). One eye color gene in fruit flies has many alleles.
- Human blood types are determined by proteins on the surface of the red blood cells.
- Alleles A and B, for A type and B-type glycoprotiens, are co-dominant; that is, a person who inherits a A allele from one parent and a B allele from the other parent will have type AB blood. The o allele is recessive.

- The o allele produces no glycoproteins. Thus a person with the genotype Ao will make some type A glycoproteins, and have type A blood.
- A person with the genotype oo will make neither the A-type nor the B-type glycoproteins, and will have type O blood.
- Most human traits are controlled by several genes. Some, such a skin color, eye color, and hair color, are controlled by multiple copies of the same gene.
- In skin color, for example there are **several pairs of genes that code for the pigment melanin**. **The more copies of the dominant allele** a person has, **the darker their skin**.
- Some traits, such as human height, are **controlled by the activities of many different genes**.

QUESTIONS

1. Mr. and Mrs. Smith have a daughter, Samantha. Mr. Jones, their neighbor, is suing for custody of the child, claiming that he had an affair with Mrs. Smith and that Samantha is his daughter. The judge in the case orders blood tests to determine blood types of all the people involved. The results are:

- Mr. Smith: Type AB; Mrs. Smith: Type B; Mr. Jones: Type A; Samantha: Type O.
- Is it possible that Mr. Jones could be Samantha's father?

2. What if Samantha had type AB blood? Who could be her father in that case?

3. Lethal dominant alleles are **much less common** than lethal recessives

4.Explain what you do understand by non-sex determining X-linked genes

Rh Factor

- Each of the four blood types is additionally classified according to the presence of another protein on the surface of RBCs that indicates **the Rh factor**. If you carry this protein, you are Rh positive. If you don't carry the protein, you are Rh negative.
- Most people **about 85% are Rh positive**. But if a woman who is Rh negative and a man who is Rh positive conceive a baby, there **is the potential for a baby to have a health problem**.

LETHAL GENE

- Cuénot and Baur discovered first recessive lethal genes because they altered Mendelian inheritance ratios.
- **Recessive lethal genes can code for either dominant or recessive traits**, but they do not actually cause death unless an organism carries two copies of the lethal allele.
- Examples of human diseases caused by recessive lethal alleles include cystic fibrosis, sickle-cell anemia, and achondroplasia

- Conditional lethal genes are expressed under certain conditions.

CONDITIONAL LETHAL GENES

- Favism is a sex-linked, when affected individuals eat fava beans, they develop hemolytic anemia.
- Affected individuals may also develop anemia when administered therapeutic doses of antimalarial medications and other drugs.
- They are resistant to malaria, because it is more difficult for malaria parasites to multiply in cells with deficient amounts of **glucose-6-phosphate dehydrogenase**.
- A mutant protein may be genetically engineered to be **fully functional at 30°C** and completely **inactive at 37°C**.
- By developing a conditional lethal version of a dominant lethal gene, scientists can study and maintain organisms carrying dominant lethal alleles.

Dominant Lethal Genes

- Dominant lethal genes are expressed in both homozygotes and heterozygotes. But how can alleles like this be passed from one generation to the next if they cause death.
- One example of a disease caused by a dominant lethal allele is Huntington's disease, a neurological disorder in humans, which reduces life expectancy. Because the onset of Huntington’s disease is slow, individuals carrying the allele can pass it on to their offspring. This allows the allele to be maintained in the population.

SYNTHETIC LETHAL GENES

- Some mutations are only lethal when paired with a second mutation. These genes are called synthetic lethal genes.
- Synthetic lethality can also indicate that:

1. two genes **function in parallel pathways** that **share information with one another**. Each of the two pathways could compensate for a defect in the other, but when both pathways have a mutation, the combination results in synthetic lethality.
2. **Two affected genes have the same role**, and therefore, lethality only results when both copies are nonfunctional and one gene cannot substitute for the other.
3. **Both genes may function in the same essential pathway**, and the pathway's function may be diminished by each mutation.

- When an allele causes lethality, this is evidence that the gene must have a critical function in an organism.
- The discoveries of many lethal alleles have provided information on the functions of genes during development.
- Additionally, scientists can use conditional and synthetic lethal alleles to study the physiological functions and relationships of genes under specific conditions.

Mutations

A **stable change** of a gene such that the changed condition is **inherited** by offspring cells.

The altering of one DNA sequence to another .

The rate of naturally occurring mutations, is quite low and varies widely between individual genes and organisms. Mutational changes are passed from generation to generation as the cells divide. This is known as **traditional mutagenesis**.

Mutations within DNA generally fall into one of two categories.

- **Point mutations**
- **Frame shift mutations**

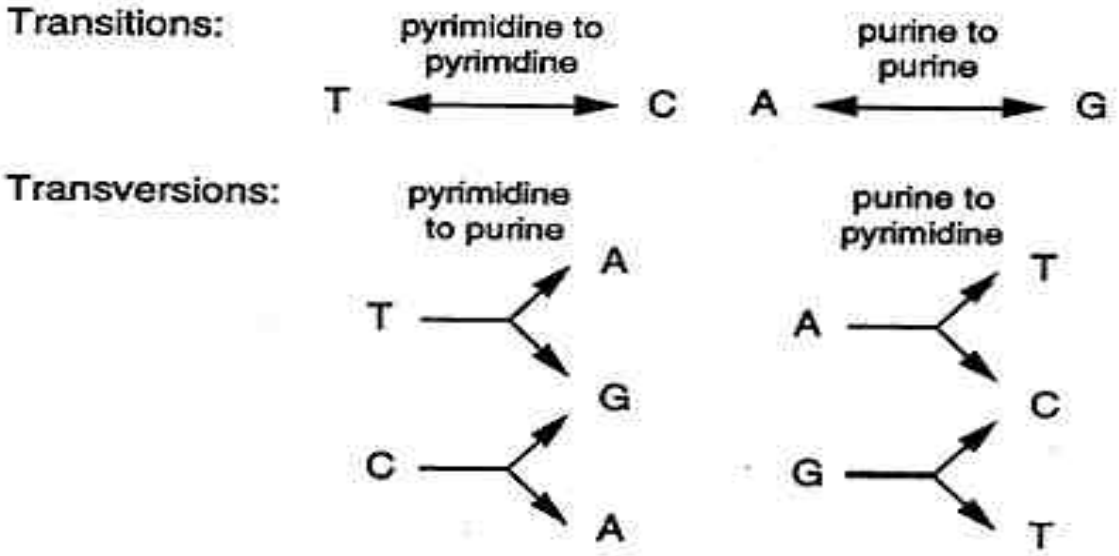
POINT MUTATION

- A point mutation is a type of mutation that causes the **replacement of a single base nucleotide with another nucleotide of the genetic material**. It is of two types:

1**) Transition mutations**

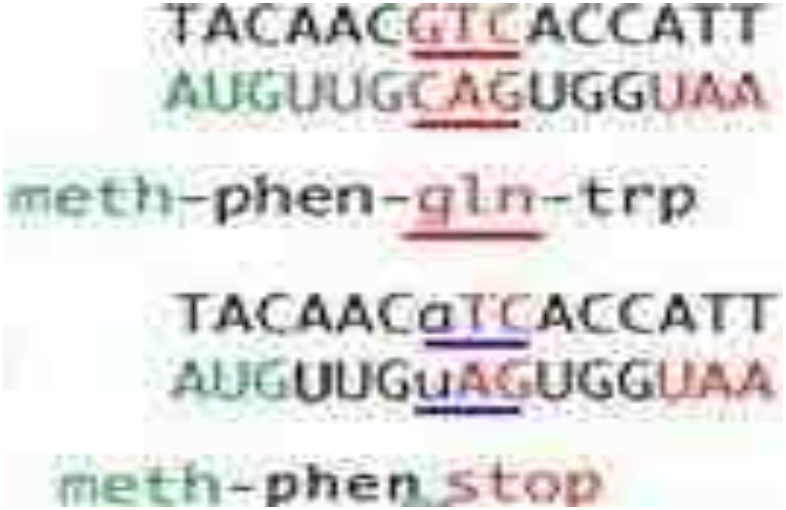
2) Transversions

- **Transition mutations**:-The replacement of a purine base with another purine or replacement of a pyrimidine with another pyrimidine.
- **Transversions**: - replacement of a purine with a pyrimidine or vice versa. Transition mutations are more frequent than transversion mutations.



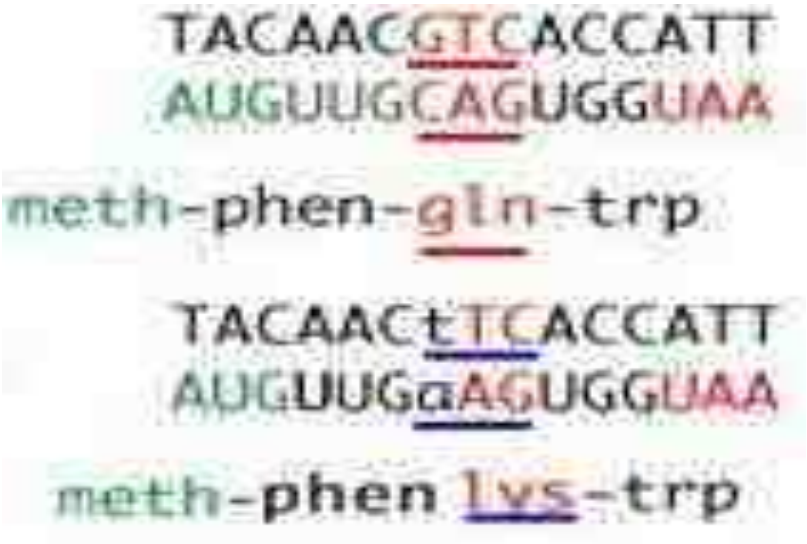
- Point mutations can also be categorized functionally:
  - Nonsense mutations
  - Mis-sense mutations
  - Silent mutations

➢A mutation results in a formation of a **new stop codon.** Therefore translation is stopped prematurely and a shortened protein is made.



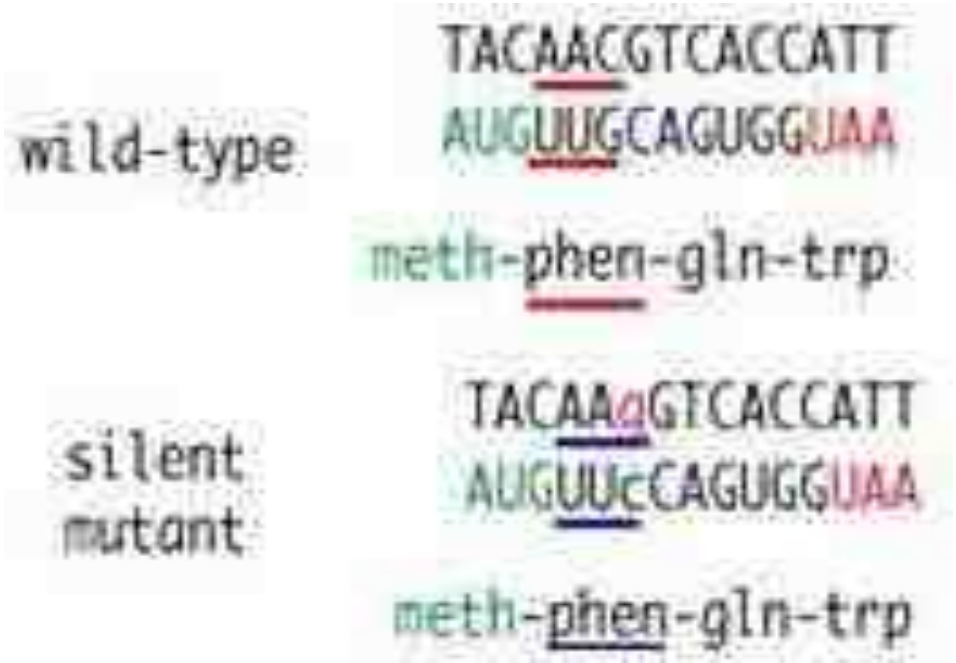
Mis sense mutation

- A mutation results a change in an **amino acid**, where the new amino acids has a different property than the old amino acid.



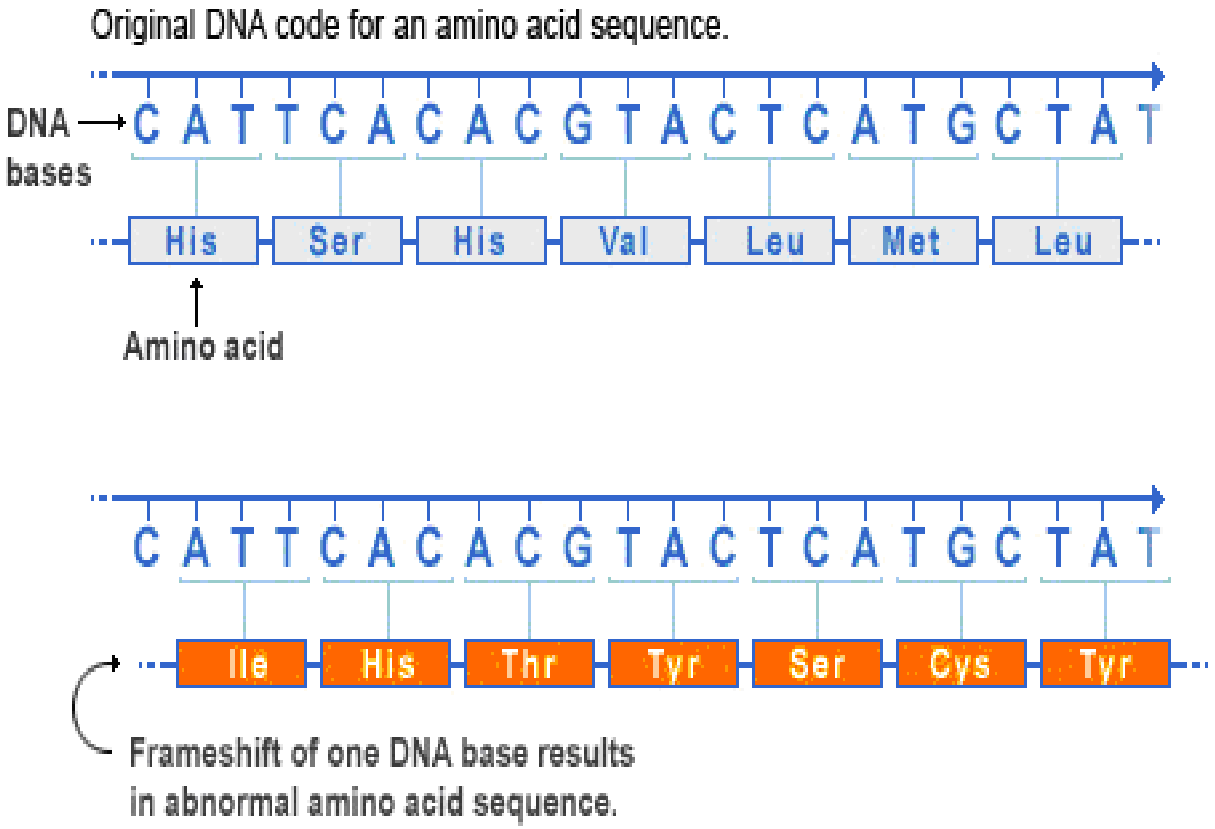
Silent mutation

- A change in a base pair does not result in a change of amino acid.



Frame shift mutation

- Results due to **deletion or insertion** of nucleotides in DNA structure.
- During translation, it shifts the reading frame beyond the mutation thus forms a different set of codons.
- As the result of this lot of amino acids in sequence are changed..


Original DNA code for an amino acid sequence.
DNA bases
C A T T C A C A C G T A C T C A T G C T A T
His Ser His Val Leu Met Leu
Amino acid
C A T T C A C A C G T A C T C A T G C T A T
Ile His Thr Tyr Ser Cys Tyr
Frameshift of one DNA base results in abnormal amino acid sequence.

MUTAGENESIS

- The genetic information of an organism is changed in a stable manner, either in a natural way or experimentally by the use of chemicals or radiations called **mutagens.**

Mutagens

- Mutagens are chemical, physical or biological agents that increase the mutation rate.

These are of 3 types:

1) CHEMICAL MUTAGENS
2) PHYSICAL MUTAGENS
3) BIOLOGICAL MUTAGENS

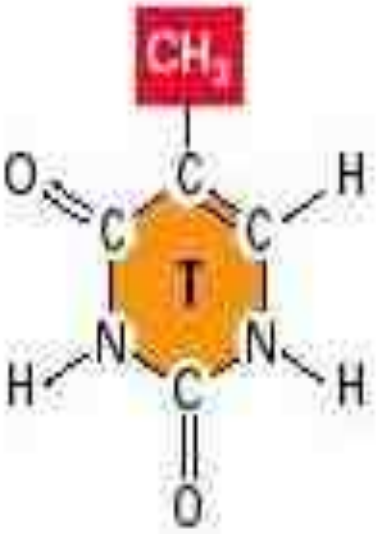
Chemical mutagens

- **Base analogs**: - molecules which are similar to the one of the bases of DNA.

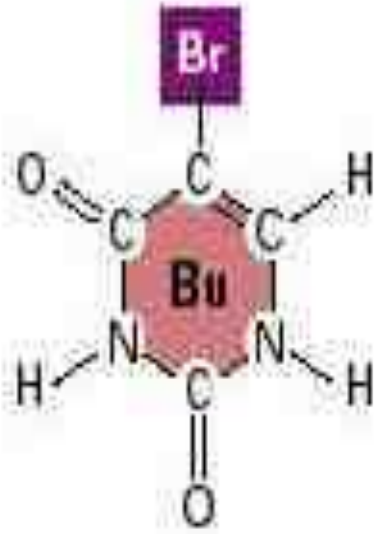
  e.g. 5 bromo uracil instead of thymine.

- **alkylating agents** :- add alkyl group to other molecules eg addition of methyl group with guanine. **it pairs with thymine.**

- **deaminating agents**:- removes amino group e.g. deamination of adenine make it resembles to guanine.



Thymine

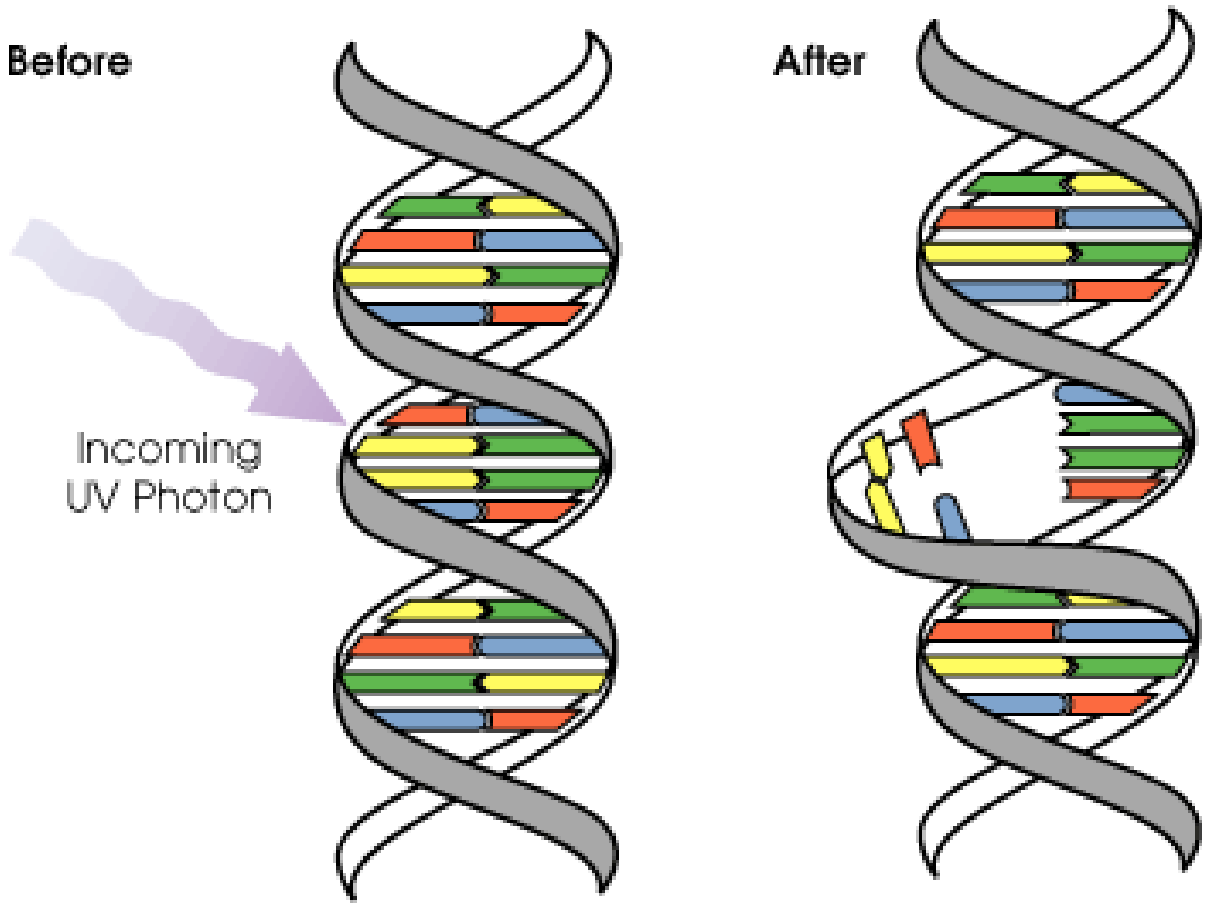


5-Bromouracil (keto form)

PHYSICAL MUTAGENS

- **Ultraviolet radiations: -** UV rays leads to formation of pyrimidine dimers i.e. bonding of two pyrimidine. So, **no base paring occur during replication and gap forms** and thus transcription **stops at gap**.

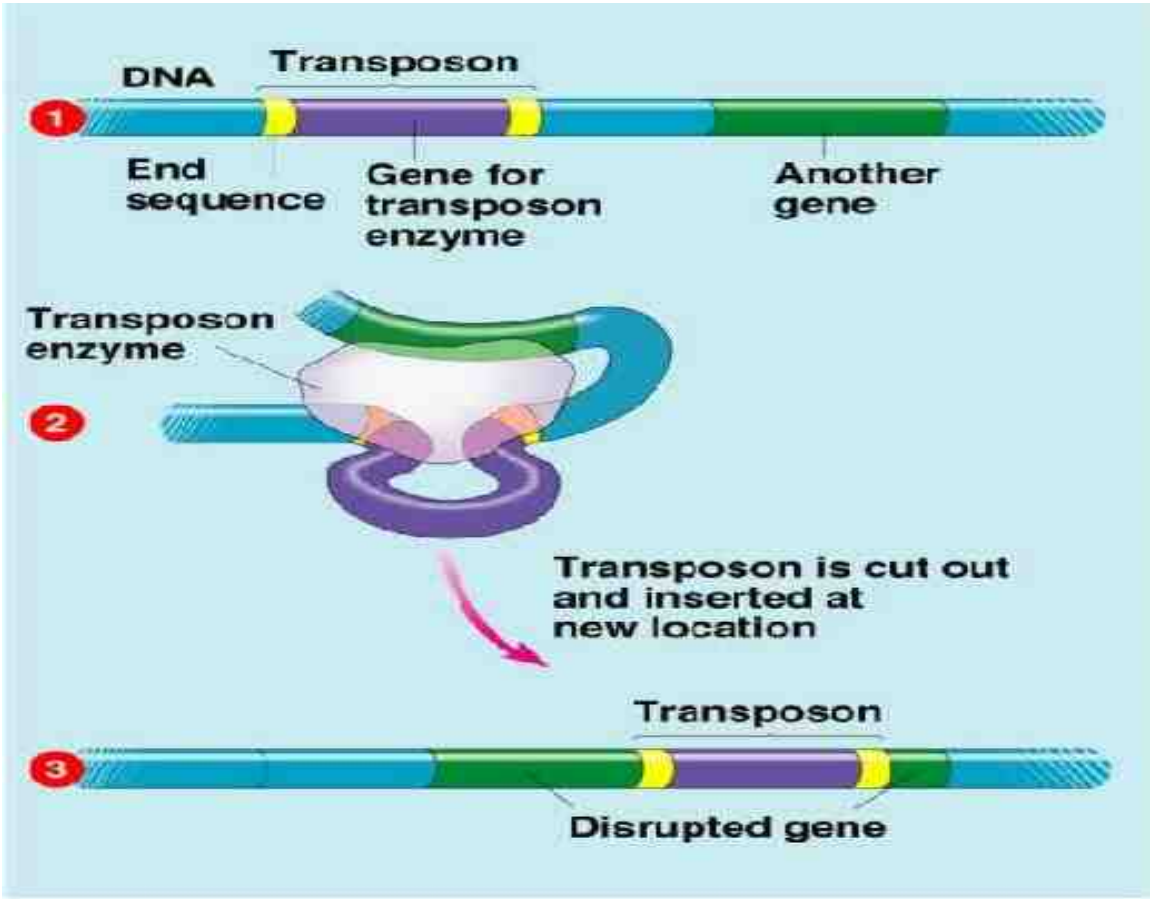
- **X rays and gamma rays: -** Easily breaks chemical bonds in DNA therefore generates free radicals. Free radicals are very reactive and thus attack other molecules and cause errors in DNA replecation


Before
Incoming
UV Photon
After

BIOLOGICAL MUTAGENS

- It includes **transposons**. Also known as **jumping genes** or insertional mutants.

- Transposons may not be able to replicate independently


DNA
Transposon
1
End sequence
Gene for transposon enzyme
Another gene
Transposon enzyme
2
Transposon is cut out and inserted at new location
Transposon
3
Disrupted gene

Chromosomal mutations

- A chromosome mutation is any change in the **structure** or **arrangement of the chromosomes**.
- Mutations to chromosomes happen most frequently **during the crossing over stage of meiosis.**
- There are many different types of mutation that can change the chromosome structure resulting in detrimental changes to the genotype and phenotype of the organism.
- Chromosomal mutations effecting essential parts of the DNA can result **in the abortion of the fetus before birth**.

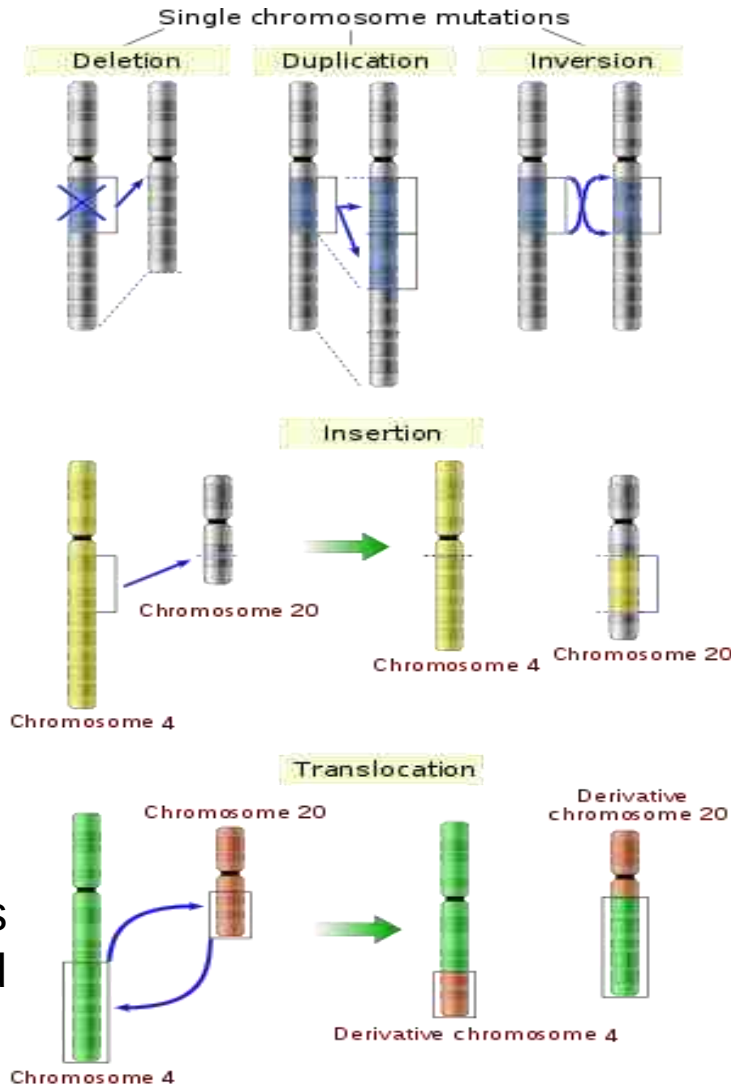
1.Deletions

2.Duplications

3.Inversion

4.Translocations

5.Chromosome non-disjunction



Search for publications written on mutation(s) above and highlight its (their) consequences in 2 pages

Search for articles talking about XX males persons and XY females persons and write a summary note on one page.

THANKS